Cytokinetics Presents Results From COURAGE-ALS at the 34th International Symposium on ALS/MND

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As Previously Announced, Reldesemtiv Had No Effect on the Primary Endpoint of Change from Baseline in ALSFRS-R or Key Secondary Endpoints

Trial Discontinued in March 2023 Due to Futility Following Second Planned Interim Analysis

Survey Reveals Site Personnel and Patients Have Favorable View of Trial Features to Reduce Burden of Participation

SOUTH SAN FRANCISCO, Calif., Dec. 07, 2023 (GLOBE NEWSWIRE) -- Cytokinetics, Incorporated (Nasdaq: CYTK) today announced that the full results of COURAGE-ALS (**C**linical **O**utcomes **U**sing ***R**eldesemtiv* on **A**LSFRS-R in a **G**lobal **E**valuation in **ALS**), were presented at the 34th International Symposium on ALS/MND by Jeremy Shefner, M.D., Ph.D., Lead Investigator of COURAGE-ALS, Professor of Neurology, Barrow Neurological Institute, University of Arizona College of Medicine Phoenix.

COURAGE-ALS was designed with two planned interim analyses of unblinded data by the Data Monitoring Committee. At the second interim analysis the Data Monitoring Committee recommended the discontinuation of the clinical trial due to futility. Subsequently, the Company concluded study conduct in March 2023 and discontinued treatment with *reldesemtiv* in all patients including those in the open-label extension study, COURAGE-ALS OLE. Development of *reldesemtiv* has been terminated.

At the time of the discontinuation of COURAGE-ALS, 486 patients had started treatment with *reldesemtiv* or placebo and 276 had completed dosing through 24 weeks. Treatment with *reldesemtiv* for 24 weeks had no effect on the primary efficacy endpoint measure of change from baseline up to Week 24 in the ALS Functional Rating Scale Revised (ALSFRS-R) (joint rank test p=0.11). Patients treated with *reldesemtiv* declined 5.3 points per month (SD=5.3) while patients treated with placebo declined 4.8 points per month (SD=4.4). No pre-defined patient subgroup favored treatment with *reldesemtiv*. Patients with a faster disease progression rate did not experience a greater treatment effect from *reldesemtiv,* contrary to analyses conducted post hoc from FORTITUDE-ALS, the Phase 2 clinical trial of *reldesemtiv*, which had suggested that treatment effects were more evident in patients with a faster disease progression rate. *Reldesemtiv* also demonstrated no effect on key secondary endpoints including change from baseline to Week 24 in in-clinic percent predicted forced vital capacity (FVC), ALS Questionnaire 40 (ALSAQ-40) and handgrip strength.

"ALS is a grievous, fatal disease for which there are few effective treatments, and we have been steadfastly pursuing a potential new treatment for patients with ALS for more than a decade," said Fady I. Malik, M.D., Ph.D., Cytokinetics' Executive Vice President of Research & Development. "We are disappointed that *reldesemtiv* did not demonstrate an effect to slow the decline of the disease; however, we hope the design and conduct of COURAGE-ALS, a trial designed to reduce the burden of participation among site personnel and patients, will contribute to the design and conduct of future trials in ALS. We thank all the people with ALS, caregivers, investigators and site personnel who participated in this trial and hope that by engaging in high-quality, patient-centric clinical research we may continue to lead by example, not only in ALS but in other diseases of high unmet need."

The incidence of serious adverse events in COURAGE-ALS was similar between the placebo group and the *reldesemtiv* group. The most common treatment-emergent adverse events (TEAEs) were in system organ classes including respiratory, thoracic and mediastinal disorders, gastrointestinal disorders and infections and infestations. Overall, non-serious TEAEs also occurred at similar frequency between the placebo group and the *reldesemtiv* group. The only non-serious TEAE that differed between the placebo and *reldesemtiv* groups was abnormal laboratory investigations driven primarily by elevated transaminases, which occurred in 18.8% of patients treated with *reldesemtiv* and 11.8% of patients treated with placebo.

The main cause of death for patients in COURAGE-ALS was respiratory failure/arrest, assisted suicide/euthanasia, ALS and infections. Mortality rates were similar between treatment groups; no deaths were assessed as related to treatment with *reldesemtiv.*

Site and Patient Perspectives on Participating in an ALS Trial Designed to Reduce Burden

COURAGE-ALS was designed with features intended to reduce the burden of participating in a clinical trial for both patients with ALS and site personnel including remote visits. All participants were provided with a mobile device to complete the ALSAQ-40 and portable home spirometer to measure FVC at home. Additionally, during in-clinic visits fewer muscles were tested with hand-held dynamometry (HHD) compared to previous trials. Upon the discontinuation of the clinical trial, a survey was conducted of site personnel and, as embedded in the original trial design, qualitative interviews were held with a subset of trial participants to assess their experience. Survey responses were received from 141 site personnel in North America, Europe and Australia, including study coordinators, investigators, ALSFRS-R trained evaluators, HHD/grip evaluators, and FVC trained evaluators.

The survey results showed that site personnel viewed remote visits favorably when considering whether to participate as a site in COURAGE-ALS. Sites believed the remote visits favorably influenced a participant's decision regarding the trial and the ability to convert an in-clinic visit to a remote visit resulted in patients being more willing or able to remain in the trial despite disease progression. Site personnel reported that 60% of their patients converted an in-clinic visit to a remote visit, citing reasons including disease progression, transportation limitations, caregiver availability, weather and COVID-19 restrictions. COURAGE-ALS was also deemed less time and labor intensive than a traditional clinic-based trial by 55% of site personnel. Patients with ALS responded positively to having labs collected at home, however, patients reported difficulty in conducting FVC remotely and challenges completing the ALSAQ-40 on the mobile device. There were more missed FVC assessments when conducted remotely than when done in-clinic, and approximately half of the time the ALSAQ-40 assessment was completed on paper rather than in the mobile app. Variability in technological skills and degree of weakness may have impacted use with the portable home spirometer and the mobile device. Despite certain limitations related to remote visits, implementing methods to reduce patient and site burden remains an important consideration in patient-centric clinical trial design.

COURAGE-ALS & COURAGE-ALS OLE: Trial Design

COURAGE-ALS was a Phase 3, multi-center, double-blind, randomized, placebo-controlled trial of *reldesemtiv* designed to enroll approximately 555 patients with ALS. Patients were 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 received 300 mg of *reldesemtiv* twice daily. Eligible patients were within the first two years of their first symptom of muscle weakness, had a vital capacity of ≥65% predicted, and a screening ALS Functional Rating Scale – Revised (ALSFRS-R) ≤44. Patients taking stable doses of *edaravone* and/or *riluzole* were permitted to enroll, and randomization was stratified accordingly. The primary efficacy endpoint was change from baseline to 24 weeks in ALSFRS-R. Secondary endpoints included 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. COURAGE-ALS was discontinued due to futility at the second planned interim analysis.

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 the troponin complex, make the actin-myosin interaction dependent on changes in intracellular calcium levels. *Reldesemtiv* is an investigational, selective, small molecule fast skeletal muscle troponin activator (FSTA) arising from Cytokinetics' skeletal muscle contractility program. *Reldesemtiv* was designed to slow 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.

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 two to four years 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, specialty cardiovascular 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 cardiac muscle performance is compromised. As a leader in muscle biology and the mechanics of muscle performance, the company is developing small molecule drug candidates specifically engineered to impact myocardial muscle function and contractility. *Aficamten* is a next-in-class cardiac myosin inhibitor, currently the subject of three Phase 3 clinical trials: SEQUOIA-HCM, evaluating *aficamten* in patients with obstructive hypertrophic cardiomyopathy (HCM), MAPLE-HCM, evaluating *aficamten* as monotherapy compared to metoprolol as monotherapy in patients with obstructive HCM and ACACIA-HCM, evaluating *aficamten* in patients with non-obstructive HCM. Cytokinetics is also developing *omecamtiv mecarbil*, a cardiac muscle activator, in patients with heart failure. Additionally, Cytokinetics is developing CK-136, a cardiac troponin activator for the potential treatment HFrEF and other types of heart failure, such as right ventricular failure, resulting from impaired cardiac contractility, and CK-586, a cardiac myosin inhibitor with a mechanism of action distinct from *aficamten* for the potential treatment of HFpEF. In 2023, Cytokinetics is celebrating its 25-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 X, 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, express or implied, relating to our future plans for our neuromuscular development programs. 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; Cytokinetics' drug candidates may have adverse side effects or inadequate therapeutic efficacy; the FDA or foreign regulatory agencies may delay or limit Cytokinetics' ability to conduct clinical trials; Cytokinetics may be unable to obtain or maintain patent or trade secret protection for its intellectual property; standards of care may change, rendering Cytokinetics' drug candidates obsolete; and competitive products or alternative therapies may be developed by others for the treatment of indications Cytokinetics' drug candidates and potential drug candidates may target. For further information regarding these and other risks related to Cytokinetics' business, investors should consult Cytokinetics' filings with the Securities and Exchange Commission.

Contact:
Cytokinetics
Diane Weiser
Senior Vice President, Corporate Communications, Investor Relations
(415) 290-7757

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