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

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

Cytokinetics Inc. 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.

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