Cytokinetics Announces Progression of REDWOOD-HCM to Cohort 2

December 9, 2020 12:30 PM EST

Interim Analysis of Data from Cohort 1 Demonstrate Substantial Effects of CK-274 to Reduce LVOT Gradient in Patients with Obstructive Hypertrophic Cardiomyopathy with No Dose Interruptions Due to Left Ventricular Ejection Fraction Below 50%

SOUTH SAN FRANCISCO, Calif., Dec. 09, 2020 (GLOBE NEWSWIRE) -- Cytokinetics, Incorporated (Nasdaq: CYTK) today announced the progression of REDWOOD-HCM following the conduct of an interim analysis of data from Cohort 1. REDWOOD-HCM (**R**andomized **E**valuation of **D**osing **W**ith CK-274 in **O**bstructive **O**utflow **D**isease in **HCM**) is an ongoing Phase 2 clinical trial of CK-3773274 (CK-274), a next-generation cardiac myosin inhibitor in development for the potential treatment of hypertrophic cardiomyopathy (HCM).

The interim analysis of data from Cohort 1 of REDWOOD-HCM showed patients experienced substantial reductions in the average resting left ventricular outflow tract gradient (LVOT-G) as well as the post-Valsalva LVOT-G (defined as resting gradient <30 mmHg and post-Valsalva gradient <50 mmHg). These clinically relevant decreases in pressure gradients were achieved with only modest decreases in average left ventricular ejection fraction (LVEF); there were no dose interruptions due to LVEF falling below 50%, the prespecified safety threshold. Pharmacokinetic data were similar to those observed in Phase 1. In addition, the safety and tolerability data were supportive of continued dose escalation with no serious adverse events attributed to study treatment reported by the investigators.

Based on these results from Cohort 1, the Steering Committee and the Data Monitoring Committee of REDWOOD-HCM have recommended that the trial proceed to Cohort 2. The second cohort is open for enrollment in centers in North America and Europe. Enrollment in Cohort 2 of REDWOOD-HCM is expected to complete in Q1 2021 and full results from REDWOOD-HCM across both Cohort 1 and Cohort 2 are expected in mid-2021.

“We are encouraged that clinically relevant reductions in the LVOT gradient were achieved within four to six weeks in the majority of patients of Cohort 1 in this interim analysis,” said Fady I. Malik, M.D., Ph.D., Cytokinetics’ Executive Vice President of Research & Development. “Given the observed safety profile and opportunity to achieve further reductions of the LVOT-G in some patients, we are pleased to dose escalate in Cohort 2. We hope to rapidly enroll Cohort 2 with the goal of sharing results from REDWOOD-HCM in the middle of 2021 as may support progression of CK-274 to a planned Phase 3 by the end of next year.”

REDWOOD-HCM: Interim Analysis

In Cohort 1, 21 patients were randomized 2:1 in double-blind fashion to escalating doses of CK-274 (5, 10, and 15 mg. once daily) or placebo. Two weeks after initiation of treatment in each patient at the starting dose of 5 mg (or placebo), an echocardiogram was performed and, if escalation criteria were met (LVEF >50% and resting LVOT-G >30 mmHg or post-Valsalva LVOT-G >50 mmHg), the patient was up-titrated to receive 10 mg (or placebo) for two weeks; similarly, if escalation criteria were met at four weeks, the patient up-titrated again to receive 15 mg (or placebo) and continued study drug until 10 weeks. If escalation criteria were not met at Week 2 or 4, the patient continued at the same dose for the rest of the trial.

At the cut-off date for this interim analysis, echocardiographic core lab data were available from 11 patients through Week 6 for review while all 21 patients contributed safety data. Following a review of the aggregate, unblinded dataset, the Data Monitoring Committee of REDWOOD-HCM endorsed the recommendation jointly made by Cytokinetics and the Steering Committee of REDWOOD-HCM to proceed to Cohort 2 with doses of 10 mg, 20 mg, and 30 mg, once-daily. Screening of patients for Cohort 2 of REDWOOD-HCM has commenced.

REDWOOD-HCM: Clinical Trial Design

REDWOOD-HCM is a multi-center, randomized, placebo-controlled, double-blind, dose finding clinical trial of CK-274 in patients with symptomatic obstructive HCM (oHCM). The primary objective of the trial is to determine the safety and tolerability of CK-274. The secondary objectives are to describe the concentration-response relationship of CK-274 on the resting and post-Valsalva left ventricular outflow tract gradient as measured by echocardiography during 10 weeks of treatment, to describe the dose response relationship of CK-274, and to evaluate the plasma concentrations of CK-274 in patients with oHCM.

The trial will enroll two sequential cohorts, with an option for a third cohort. Within each cohort, approximately 18 patients will be randomized 2:1 to active or placebo treatment and receive up to three escalating doses of CK-274 or placebo based on echocardiographic guidance. Patients receive an echocardiogram after two weeks of treatment at each dose to determine whether they will be up-titrated. Overall, the treatment duration will be 10 weeks with an echocardiogram to confirm reversibility of effect 2-weeks after the last dose. REDWOOD-HCM is expected to enroll patients in approximately 20 investigative sites in North America and Europe. Additional information can be found on www.clinicaltrials.gov.

About CK-274

CK-274 is a novel, oral, small molecule cardiac myosin inhibitor that company scientists discovered independent of its collaborations. CK-274 arose from an extensive chemical optimization program conducted with careful attention to therapeutic index and pharmacokinetic properties that may translate into best-in-class potential in clinical development. CK-274 was designed to reduce the hypercontractility that is associated with hypertrophic cardiomyopathy (HCM). In preclinical models, CK-274 reduces myocardial contractility by binding directly to cardiac myosin at a distinct and selective allosteric binding site, thereby preventing myosin from entering a force producing state. CK-274 reduces the number of active actin-myosin cross bridges during each cardiac cycle and consequently reduces myocardial contractility. This mechanism of action may be therapeutically effective in conditions characterized by excessive hypercontractility, such as HCM.

In preclinical models of cardiac function, CK-274 reduced cardiac contractility in a predictable dose and exposure dependent fashion. In preclinical models of disease, CK-274 reduced compensatory cardiac hypertrophy and cardiac fibrosis. The preclinical pharmacokinetics of CK-274 were characterized, evaluated and optimized for potential ease-of-use in the clinical setting.

A Phase 1 study demonstrated that CK-274 was safe and well tolerated in healthy participants. The pharmacokinetics of CK-274 were generally dose linear, and steady-state appeared evident within 14 days of dosing. Left ventricular ejection fraction decreased in an exposure dependent manner and

the PK/PD relationship for CK-274 observed in humans was similar to that observed preclinically when adjusted for differences in protein binding. Specifically, the shallow exposure-response relationship observed preclinically appears to translate to humans and thereby may enable flexible dose optimization in humans.

The overall development program will assess the potential of CK-274 to improve exercise capacity and relieve symptoms in patients with hyperdynamic ventricular contraction due to HCM.

About Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disorder, affecting approximately 1 in 500 individuals worldwide. HCM is a disease in which the heart muscle (myocardium) becomes abnormally thick (hypertrophied). The thickening of cardiac muscle leads to the inside of the left ventricle becoming smaller and stiffer, and thus the ventricle becomes less able to relax and fill with blood. This ultimately limits the heart's pumping function, resulting in symptoms including chest pain, dizziness, shortness of breath, or fainting during physical activity. A subset of patients with HCM are at high risk of progressive disease which can lead to atrial fibrillation, stroke and death due to arrhythmias. There are no current medical treatments that directly address the hypercontractility that underlies HCM.

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 for regulatory interactions for *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). Cytokinetics is conducting REDWOOD-HCM, a Phase 2 clinical trial of CK-274 in patients with obstructive HCM. Cytokinetics is also developing *reldesemtiv*, a fast skeletal muscle troponin activator for the potential treatment of ALS and other neuromuscular indications following conduct of FORTITUDE-ALS and other Phase 2 clinical trials. The company is considering potential advancement of *reldesemtiv* to Phase 3 pending ongoing regulatory interactions. 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 2 clinical trial of CK-274; the potential benefits of CK-274; the ability to complete enrollment of Cohort 2 of REDWOOD-HCM in Q1 2021 and the impact of the COVID-19 pandemic on such enrollment (for further information regarding the historical and potential prospective impact of the COVID-19 pandemic on our business operations and clinical trials, please refer to Cytokinetics' Form 10-Q for the quarterly period ended September 30, 2020); 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.

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

Cytokinetics

Source: Cytokinetics, Incorporated