Cytokinetics Announces Start of COMET-HF, a Confirmatory Phase 3 Clinical Trial of Omecamtiv Mecarbil in Patients with Symptomatic Heart Failure with Severely Reduced Ejection Fraction

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SOUTH SAN FRANCISCO, Calif., Dec. 03, 2024 (GLOBE NEWSWIRE) -- Cytokinetics, Incorporated (Nasdaq: CYTK) today announced that COMET-HF (**C**onfirmation of ***O**mecamtiv **M**ecarbil* **E**fficacy **T**rial in **H**eart **F**ailure), a confirmatory Phase 3 clinical trial of *omecamtiv mecarbil* in patients with symptomatic heart failure (HF) with severely reduced ejection fraction, is open to enrollment. *Omecamtiv mecarbil* is a novel investigational selective cardiac myosin activator in development for the potential treatment of heart failure with severely reduced ejection fraction. COMET-HF is being conducted in collaboration with Duke Clinical Research Institute (DCRI), a leading academic research organization.

"We are pleased to be starting COMET-HF to evaluate *omecamtiv mecarbil* in patients with severe heart failure who have limited treatment options and remain at high risk after failing guideline-directed medical therapy," said Stuart Kupfer, M.D., Senior Vice President, Chief Medical Officer. "The design of COMET-HF is informed by encouraging data from GALACTIC-HF as well as extensive discussions with FDA and the heart failure community. This confirmatory trial has pragmatic features intended to improve the efficiency of study conduct and reduce patient burden. We hope to generate additional evidence of the potential treatment benefit of *omecamtiv mecarbil* among these heart failure patients with high unmet need."

"Heart failure, and especially more severe forms of heart failure, is an area of major unmet need despite recent progress in developing more effective treatments," said DCRI faculty member Michael Felker, M.D., M.H.S, Professor of Medicine and Cardiovascular Research Therapeutic Area Lead, and Principal Investigator for COMET-HF. "These patients are at high risk of heart failure hospitalization and death despite existing therapies, highlighting the critical need for new treatments. Through DCRI's collaboration with Cytokinetics, we expect to leverage our decades of expertise in conducting cardiovascular clinical trials and advance our shared commitment to innovation in service of patients."

COMET-HF is a Phase 3 multinational, multi-center, double-blind, randomized, placebo-controlled trial designed to assess the efficacy and safety of *omecamtiv mecarbil* in patients with symptomatic heart failure with severely reduced ejection fraction. The primary endpoint of COMET-HF is the time to first event in the primary composite endpoint of cardiovascular death, first heart failure event, left ventricular assist device (LVAD) implantation or cardiac transplantation, or stroke. Secondary endpoints will evaluate the risk of individual components, including heart failure hospitalization, cardiovascular death, and stroke, as well as the risk of irreversible morbidity/mortality based on the composite endpoint of cardiovascular death, LVAD or cardiac implantation, or stroke.

COMET-HF is expected to randomize approximately 1,800 patients on a 1:1 basis to receive *omecamtiv mecarbil* or placebo. At screening, patients enrolled in COMET-HF must have symptomatic heart failure with severely reduced ejection fraction defined as left ventricular ejection fraction <30%, NT-proBNP ≥1,000 pg/mL, and a heart failure event within the preceding six months.

Eligible patients will enter a two-week run-in period. Patients who are intolerant to *omecamtiv mecarbil*, are non-adherent, or have either undetectable or excessive plasma concentrations of *omecamtiv mecarbil* will not be eligible for randomization. Following the two-week run-in period, all patients will undergo a two-week washout period before being randomized to receive *omecamtiv mecarbil,* up to a maximum dose of 50 mg twice daily based on the plasma concentration of *omecamtiv mecarbil* during the run-in period, or placebo. Patients will continue to receive *omecamtiv mecarbil* or placebo twice daily until at least 850 primary composite endpoint events have occurred in the trial.

About *Omecamtiv Mecarbil*

Omecamtiv mecarbil is an investigational, selective, small molecule cardiac myosin activator, the first of a novel class of myotropes[1] designed to directly target the contractile mechanisms of the heart, binding to and recruiting more cardiac myosin heads to interact with actin during systole. In doing so, *omecamtiv mecarbil* augments the impaired contractility that is associated with heart failure with reduced ejection fraction (HFrEF). Preclinical research has shown that *omecamtiv mecarbil* increases cardiac contractility without increasing intracellular myocyte calcium concentrations or myocardial oxygen consumption.[2-4]

The development program for *omecamtiv mecarbil* assessed its potential for the treatment of HFrEF. Positive results from GALACTIC-HF, the first Phase 3 clinical trial of *omecamtiv mecarbil*, demonstrated a statistically significant effect of treatment with *omecamtiv mecarbil* to reduce risk of the primary composite endpoint of cardiovascular death or heart failure events (heart failure hospitalization and other urgent treatment for heart failure) compared to placebo in patients treated with standard of care. No reduction in the secondary endpoint of time to cardiovascular death was observed. In general, the overall rates of myocardial ischemia, ventricular arrhythmias, and death were similar between treatment and placebo groups. Adverse events and treatment discontinuation of study drug were balanced between treatment arms.[5] The magnitude of the treatment effect in a pre-specified subgroup of more than 4,500 patients with heart failure with severely reduced ejection fraction (<30%) was observed to be greater than in the overall drug treated population of GALACTIC-HF.[6] *Omecamtiv mecarbil* is now the subject of COMET-HF (**C**onfirmation of ***O**mecamtiv **M**ecarbil* **E**fficacy **T**rial in **H**eart **F**ailure), a confirmatory Phase 3 clinical trial in patients with symptomatic heart failure with severely reduced ejection fraction.

About Heart Failure with Severely Reduced Ejection Fraction

Heart failure is a grievous condition that affects more than 64 million people worldwide[5], about half of whom have reduced left ventricular function.[8,9] HF is the leading cause of hospitalization and readmission in people age 65 and older.[10,11] By 2029, is it estimated that 2.8 million people in the U.S. will have heart failure with severely reduced ejection fraction[12], characterized as heart failure with reduced ejection fraction (HFrEF) <30%, and 840,000 people will have severely reduced ejection fraction with other features indicative of high-risk heart failure.[13] Patients with high-risk heart failure with severely reduced ejection fraction account for approximately 60% of all HFrEF hospitalizations, with 35% of patients re-hospitalized within

a year. [14,15]

About Cytokinetics

Cytokinetics is a late-stage, specialty cardiovascular biopharmaceutical company focused on discovering, developing and commercializing muscle biology-directed drug candidates 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. Following positive results from SEQUOIA-HCM, the pivotal Phase 3 clinical trial evaluating *aficamten,* a next-in-class cardiac myosin inhibitor, in obstructive hypertrophic cardiomyopathy (HCM), Cytokinetics is progressing regulatory submissions for *aficamten* for the treatment of obstructive HCM in the US, Europe, and China. *Aficamten* is also currently being evaluated in MAPLE-HCM, a Phase 3 clinical trial of *aficamten* as monotherapy compared to metoprolol as monotherapy in patients with obstructive HCM, ACACIA-HCM, a Phase 3 clinical trial of *aficamten* in patients with non-obstructive HCM, CEDAR-HCM, a clinical trial of *aficamten* in a pediatric population with obstructive HCM, and FOREST-HCM, an open-label extension clinical study of *aficamten* in patients with HCM. Cytokinetics is also developing *omecamtiv mecarbil*, a cardiac muscle activator, in patients with heart failure with severely reduced ejection fraction (HFrEF), CK-586, a cardiac myosin inhibitor with a mechanism of action distinct from *aficamten* for the potential treatment of heart failure with preserved ejection fraction (HFpEF), and CK-089, a fast skeletal muscle troponin activator (FSTA) for the potential treatment of a specific type of muscular dystrophy.

For additional information about Cytokinetics, visit www.cytokinetics.com and follow us on X, LinkedIn, Facebook and YouTube.

About the Duke Clinical Research Institute

The DCRI, part of the Duke University School of Medicine, is the largest academic clinical research organization in the world. Our mission is to develop, share, and implement knowledge that improves global health through innovative clinical research. The institute conducts multinational clinical trials, manages major national patient registries, and performs landmark outcomes research. The DCRI is a pioneer in cardiovascular and pediatric clinical research and conducts groundbreaking clinical research across multiple other therapeutic areas, including infectious disease, neuroscience, respiratory medicine, and nephrology.

For additional information about DCRI, visit dcri.org and follow us on X, LinkedIn, 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 the Company's development plans for *omecamtiv mecarbil* in the United States, including its ability to full enroll COMET-HF by any particular date, if at all. 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.

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