Cytokinetics Announces Start of ACACIA-HCM, a Pivotal Phase 3 Clinical Trial of Aficamten in Patients With Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy

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Expanding Development Program to Assess Potential of Aficamten in Additional Patient Population to Inform Increased Utility of Cardiac Myosin Inhibition

SOUTH SAN FRANCISCO, Calif., Sept. 06, 2023 (GLOBE NEWSWIRE) -- Cytokinetics, Incorporated (Nasdaq: CYTK) today announced that ACACIA-HCM (**A**ssessment **C**omparing ***A**ficamten* to Placebo on **C**ardiac Endpoints **I**n **A**dults with Non-Obstructive **HCM**), a Phase 3 clinical trial of *aficamten* in patients with symptomatic non-obstructive hypertrophic cardiomyopathy (nHCM), is open to enrollment. *Aficamten* is a next-in-class cardiac myosin inhibitor in development for the potential treatment of HCM.

"As the first Phase 3 clinical trial of *aficamten* in non-obstructive hypertrophic cardiomyopathy, ACACIA-HCM represents an important advancement in the development program for *aficamten* alongside our two ongoing Phase 3 clinical trials in obstructive HCM," said Fady I. Malik, M.D., Ph.D., Cytokinetics' Executive Vice President of Research & Development. "ACACIA-HCM builds on the encouraging findings from Cohort 4 of REDWOOD-HCM, the Phase 2 clinical trial which demonstrated that treatment with *aficamten* resulted in statistically significant improvements in heart failure symptoms and cardiac biomarkers in patients with non-obstructive HCM. In ACACIA-HCM we look forward to assessing the impact of *aficamten* in patients with non-obstructive HCM on symptoms and quality of life as well as on other measures of disease burden, including exercise capacity, functional class, cardiac structure and function and cardiovascular outcomes."

ACACIA-HCM: Clinical Trial Design

ACACIA-HCM is a Phase 3, multi-center, randomized, double-blind, placebo-controlled clinical trial designed to evaluate the effect of *aficamten* compared to placebo on health-related quality of life in participants with symptomatic nHCM. The primary endpoint is the change in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score from baseline to Week 36. Secondary endpoints include the change from baseline to Week 36 in maximal exercise performance (peak VO_2) and sub-maximal exercise performance (Ve/VCO_2), the proportion of patients with ≥1 class improvement in New York Heart Association (NYHA) functional class, changes in left atrial volume index (LAVI) and NT-proBNP. After the primary analysis at 36 weeks, patients will continue treatment with *aficamten* or placebo for up to 72 weeks to evaluate additional secondary and exploratory analyses including the time to first cardiovascular event.

ACACIA-HCM is expected to enroll 420 patients, randomized on a 1:1 basis to receive *aficamten* or placebo. Randomization will be stratified by persistent atrial fibrillation and presence of intracavitary obstruction. At screening, patients enrolled in ACACIA-HCM must have a resting left ventricular outflow tract gradient (LVOT-G) < 30 mmHg and post-Valsalva LVOT-G < 50 mmHg in addition to left ventricular ejection fraction (LVEF) ≥ 60%, respiratory exchange ratio (RER) ≥ 1.00 and peak VO_2 ≤ 90% predicted, NT-proBNP ≥ 300 pg/mL or ≥ 900 pg/mL if atrial fibrillation or atrial flutter are present at screening, NYHA functional class II or III and KCCQ Clinical Summary Score ≥ 30 and ≤ 85.

ACACIA-HCM will consist of two parts, with Part 1 comprising Day 1 to Week 36 and Part 2 comprising Week 36 to Week 72. All participants will complete Part 1. At the end of Part 1, participants will continue into Part 2 until the last randomized participant has completed Part 1. Each patient will receive up to four escalating doses of *aficamten* or placebo based on echocardiographic guidance. Patients receiving *aficamten* will begin with 5 mg dosed once daily. At weeks 2, 4 and 6 patients will receive an echocardiogram to determine if they will be up-titrated to escalating doses of 10, 15 or 20 mg. Dose escalation will occur only if a patient has an LVEF ≥ 60%. Patients who do not meet escalation criteria will continue to receive their current dose or may be down-titrated if their LVEF is < 50%. Patients who complete ACACIA-HCM will be eligible to participate in an open-label extension clinical trial. Additional information can be found on www.clinicaltrials.gov.

About *Aficamten* and the Broad Phase 3 Clinical Trials Program

Aficamten is an investigational selective, small molecule cardiac myosin inhibitor discovered following an extensive chemical optimization program that was conducted with careful attention to therapeutic index and pharmacokinetic properties and as may translate into next-in-class potential in clinical development. *Aficamten* was designed to reduce the number of active actin-myosin cross bridges during each cardiac cycle and consequently suppress the myocardial hypercontractility that is associated with hypertrophic cardiomyopathy (HCM). In preclinical models, *aficamten* reduced 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.

The development program for *aficamten* is assessing its potential as a treatment that improves exercise capacity and relieves symptoms in patients with HCM as well as its potential long-term effects on cardiac structure and function. *Aficamten* is currently the subject of SEQUOIA-HCM (**S**afety, **E**fficacy, and **Q**uantitative **U**nderstanding of **O**bstruction **I**mpact of ***A**ficamten* in **HCM**), a pivotal Phase 3 clinical trial in patients with symptomatic obstructive hypertrophic cardiomyopathy (HCM), MAPLE-HCM (***M**etoprolol* vs ***A**ficamten* in **P**atients with **L**VOT Obstruction on **E**xercise Capacity in **HCM**), a Phase 3 clinical trial evaluating *aficamten* as monotherapy compared to metoprolol as monotherapy in patients with obstructive HCM, and ACACIA-HCM (**A**ssessment **C**omparing ***A**ficamten* to Placebo on **C**ardiac Endpoints **I**n **A**dults with Non-Obstructive **HCM**), a pivotal Phase 3 clinical trial in patients with symptomatic non-obstructive HCM. Results from SEQUOIA-HCM are expected by the end of 2023. *Aficamten* received Breakthrough Therapy Designation for the treatment of symptomatic obstructive HCM from the U.S. Food & Drug Administration (FDA) as well as the National Medical Products Administration (NMPA) in China.

About Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (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 reduced exercise capacity and symptoms including chest pain, dizziness, shortness of breath, or fainting during physical activity. HCM is the most common monogenic inherited cardiovascular disorder, with approximately 280,000 patients diagnosed in the U.S., however, there are an estimated 400,000-800,000 additional patients who remain undiagnosed.[1,2,3] Two-thirds of patients with HCM have obstructive HCM (oHCM), where the thickening of the cardiac muscle leads to left ventricular outflow tract (LVOT) obstruction, while one-third have non-obstructive HCM (nHCM), where blood flow isn't impacted, but the heart muscle is still thickened. People

with HCM are at high risk of also developing cardiovascular complications including atrial fibrillation, stroke and mitral valve disease.[4] People with HCM are at risk for potentially fatal ventricular arrhythmias, and it is one of the leading causes of sudden cardiac death in younger people or athletes.[5] A subset of patients with HCM are at high risk of progressive disease leading to dilated cardiomyopathy and heart failure necessitating cardiac transplantation.

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 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 express or implied relating to the properties or potential benefits of *aficamten* or any of our other drug candidates and our ability to fully enroll ACACIA-HCM. 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 the risks related to Cytokinetics' business outlines in Cytokinetics' filings with the Securities and Exchange Commission. Forward-looking statements are not guarantees of future performance, and Cytokinetics' actual results of operations, financial condition and liquidity, and the development of the industry in which it operates, may differ materially from the forward-looking statements contained in this press release. Any forward-looking statements that Cytokinetics makes in this press release speak only as of the date of this press release. Cytokinetics assumes no obligation to update its forward-looking statements whether as a result of new information, future events or otherwise, after the date of this press release.

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