Cytokinetics Presents Additional 48-Week Data From FOREST-HCM, the Open Label Extension Clinical Study of Aficamten, at The American College of Cardiology 73rd Annual Scientific Session

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Treatment with Aficamten for 48 Weeks is Associated with Improvements in Clinical Efficacy Endpoints, NYHA Class and Cardiac Biomarkers, Structure and Function

SOUTH SAN FRANCISCO, Calif., April 05, 2024 (GLOBE NEWSWIRE) -- Cytokinetics, Incorporated (Nasdaq: CYTK) today announced additional 48-week data from FOREST-HCM (**F**ollow-up, **O**pen-Label, **R**esearch **E**valuation of **S**ustained **T**reatment with *Aficamten* in **HCM**), the open label extension clinical study of *aficamten* in patients with hypertrophic cardiomyopathy (HCM), at the 73rd Annual American College of Cardiology (ACC) Scientific Session taking place from April 6, 2024 –April 8, 2024 in Atlanta, GA.

FOREST-HCM enrolled 213 patients with obstructive HCM from May 28, 2021 through October 31, 2023. Previously presented data from 17 patients who had been enrolled through 48 weeks in FOREST-HCM showed that prolonged treatment with *aficamten* was associated with significant and sustained reductions in left ventricle outflow tract gradient (LVOT-G), and improvements in symptoms and cardiac biomarkers. The updated data set presented at ACC in Atlanta focuses on 46 patients from FOREST-HCM that had completed 48 weeks of follow-up at the time of the current interim analysis.

At Week 48, 75% of these patients were receiving the 15 mg or 20 mg dose of *aficamten*. Treatment with *aficamten* for 48 weeks resulted in substantial and sustained reductions in average resting LVOT-G (mean change from baseline (SD) = -39.6 mmHg (34), p<0.0001) and Valsalva LVOT-G (mean change from baseline (SD) = -53.2 mmHg (38.6), p<0.0001). Statistically significant improvements in New York Heart Association (NYHA) Functional Class from baseline were observed, with 82.2% of patients improving by ≥1 NYHA class with no instances of worsening NYHA class. Additionally, there were significant improvements in NT-proBNP, a biomarker of cardiac wall stress, with an average decrease of 63% from baseline to week 48 (p<0.001). Treatment with *aficamten* also resulted in statistically significant improvements in measures of cardiac structure and function including decreases in maximum wall thickness (mean change from baseline (SE) = -0.12 cm (0.02), p<0.0001), left atrial volume index (mean changes from baseline (SE) = -3.5 mL/m^2 (0.98), p=0.0008) and lateral E/e' (mean change from baseline (SE) = -2.2 (0.92), p=0.02). While 19 of these 46 patients in FOREST-HCM met guideline eligibility criteria for septal reduction therapy (SRT) at baseline, only one patient remained eligible for SRT after six months of treatment with *aficamten,* representing a 94% reduction in SRT-eligibility.

In FOREST-HCM, *aficamten* appears to be well-tolerated, with no treatment-related serious adverse events (SAEs). There was a modest reduction in left ventricular ejection fraction (LVEF) from baseline to Week 48 (mean change from baseline (SD) = -5.1 mg (5.9), p<0.0001). As has been previously reported, three patients underwent dose down-titration due to LVEF <50%. Two patients were asymptomatic, and one dose down-titration occurred due to recurrent alcohol-induced atrial fibrillation.

"These data from FOREST-HCM continue to reinforce the efficacy and safety of longer-term treatment with *aficamten* for patients with obstructive HCM, demonstrating significant improvements in patient symptom burden and cardiac function while also improving the overall architecture of the heart," said Fady I. Malik, M.D., Ph.D., Cytokinetics' Executive Vice President of Research & Development. "In light of the positive results from SEQUOIA-HCM, the pivotal Phase 3 clinical trial of *aficamten*, we are pleased to see this additional clinical evidence that reinforces our intended next-in-class profile and that may enable *aficamten* to become the cardiac myosin inhibitor of choice among physicians and patients with HCM."

About *Aficamten*

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 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.

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

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.

SEQUOIA-HCM (**S**afety, **E**fficacy, and **Q**uantitative **U**nderstanding of **O**bstruction **I**mpact of ***A**ficamten* in **HCM**), was the pivotal Phase 3 clinical trial in patients with symptomatic obstructive hypertrophic cardiomyopathy (HCM). The results from SEQUOIA-HCM show that treatment with *aficamten* significantly improved exercise capacity compared to placebo, increasing peak oxygen uptake (pVO_2) measured by cardiopulmonary exercise testing (CPET) by a least square mean difference (95% CI) of 1.74 (1.04 - 2.44) mL/kg/min (p=0.000002). The treatment effect with *aficamten* was consistent across all prespecified subgroups reflective of patient baseline characteristics and treatment strategies, including patients receiving or not receiving background beta-blocker therapy. Statistically significant (p<0.0001) and clinically meaningful improvements were also observed in all 10 prespecified secondary endpoints. *Aficamten* was well-tolerated with an adverse event profile comparable to placebo. Treatment emergent serious adverse events occurred in 8 (5.6%) and 13 (9.3%) patients on *aficamten* and placebo, respectively. Core echocardiographic left ventricular ejection fraction (LVEF) was observed to be <50% in 5 patients (3.5%) on *aficamten* compared to 1 patient (0.7%) on placebo. There were no instances of worsening heart failure or treatment interruptions due to low LVEF.

Aficamten is currently the subject of two ongoing Phase 3 clinical trials: MAPLE-HCM (***M**etoprolol* vs ***A**ficamten* in **P**atients with **L**VOT Obstruction on **E**xercise Capacity in **HCM)**, 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)**, evaluating *aficamten* in patients with symptomatic non-obstructive HCM. *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. Cytokinetics is preparing for regulatory submissions for *aficamten*, its next-in-class cardiac myosin inhibitor, following positive results from SEQUOIA-HCM, the pivotal Phase 3 clinical trial in obstructive hypertrophic cardiomyopathy. *Aficamten* is also currently being evaluated in two ongoing Phase 3 clinical trials: 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-586, a cardiac myosin inhibitor with a mechanism of action distinct from *aficamten* for the potential treatment of HFpEF, and 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.

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 the properties or potential benefits of *aficamten* or any of our other drug candidates and our ability to obtain regulatory approval for *aficamten* for the treatment of obstructive hypertrophic cardiomyopathy or any other indication from FDA or any other regulatory body in the United States or abroad. 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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