Cytokinetics Presents New Data at CMR 2024 From FOREST-HCM, the Open Label Extension Clinical Trial of Aficamten

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New Data Show Treatment with Aficamten in Patients with Obstructive Hypertrophic Cardiomyopathy Resulted in Favorable Structural Remodeling, Improvements in Cardiac Function and Stabilization of Fibrosis

SOUTH SAN FRANCISCO, Calif., Jan. 25, 2024 (GLOBE NEWSWIRE) -- Cytokinetics, Incorporated (Nasdaq: CYTK) today announced new data at CMR 2024 demonstrating favorable effects on cardiac structure, function and fibrosis related to treatment with *aficamten* in 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 trial of *aficamten* in patients with hypertrophic cardiomyopathy (HCM).

In many patients with HCM, the left ventricular hypertrophy that characterizes the disease results in elevated cardiac mass, and left ventricular outflow tract (LVOT) obstruction is often accompanied by mitral valve regurgitation. Patients with HCM may also present with myocardial fibrosis, a strong predictor of abnormal cardiac rhythm and sudden death, and other cardiac structural abnormalities such as increased left atrial volume. Previously presented data from FOREST-HCM showed that prolonged treatment with *aficamten* was associated with sustained reductions in LVOT gradients with no treatment interruptions for low left ventricular ejection fraction (LVEF) due to *aficamten,* as well as sustained reductions in cardiac biomarkers and improved symptoms.

New data presented today from the cardiac magnetic resonance (CMR) sub-study in FOREST-HCM show that treatment with *aficamten* for 48 weeks resulted in favorable cardiac structural remodeling, improvements in cardiac function, and stabilization of myocardial fibrosis. At the time of this analysis, 16 patients in FOREST-HCM had completed a CMR at baseline and at Week 48. Baseline characteristics of the CMR cohort were comparable to the overall patient population in FOREST-HCM. In this trial, treatment with *aficamten* for 48 weeks resulted in statistically significant improvements in measures of cardiac structure and function including left ventricular mass index (-11.4 g/m^2 ±19.4, p=0.03), maximum left ventricular septal wall thickness (-1.3 mm ±1.8, p=0.02), left atrial volume (-16.3 ml/m^2 ±26.4, p=0.05), and mitral regurgitant volume (-12.9 ml ±15.1, p=0.01) and fraction (-9.5% ± 15.1, p=0.05). Additionally, treatment with *aficamten* stabilized interstitial and replacement myocardial fibrosis, with no increase in the fibrosis mass, as measured by absolute mass of late gadolinium enhancement (-0.6 g ± 5.0, p=0.64).

“These are the first long-term CMR data to emerge from FOREST-HCM, and they demonstrate potential disease modifying effects of *aficamten* in patients with obstructive HCM,” said Fady I. Malik, M.D., Ph.D., Cytokinetics’ Executive Vice President of Research & Development. “Added to the existing body of evidence from both FOREST-HCM and SEQUOIA-HCM, the pivotal Phase 3 clinical trial of *aficamten* in oHCM, these data further support the profile of *aficamten* as a potential next-in-class cardiac myosin inhibitor that is not only associated with statistically significant and clinically meaningful improvements to hemodynamics and symptoms, but that improves the architecture of the heart. We look forward to expanding on these data in the future.”

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 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.

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 (**As**sessment **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 interactions 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-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.

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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