Cytokinetics Announces Additional Results From SEQUOIA-HCM Presented in Late Breaking Clinical Trial Session at the European Society of Cardiology Heart Failure 2024 Congress

May 13, 2024 1:33 PM EDT

Analyses of SEQUOIA-HCM Elaborate on Dosing and Measures of Safety During Treatment with Aficamten

Results from Cardiopulmonary Exercise Testing Showed Improvement in Exercise Performance were Strongly Correlated to Other Measures of Clinical Improvement

Company to Host Investor Event and Webcast Today at 4:00 PM Western European Summer Time (11:00 AM Eastern Time)

SOUTH SAN FRANCISCO, Calif., May 13, 2024 (GLOBE NEWSWIRE) -- Cytokinetics, Incorporated (Nasdaq: CYTK) today announced that additional results from SEQUOIA-HCM (**S**afety, **E**fficacy, and **Q**uantitative **U**nderstanding of **O**bstruction **I**mpact of ***A**ficamten* in **HCM**), the pivotal Phase 3 clinical trial of *aficamten* in patients with symptomatic obstructive hypertrophic cardiomyopathy (HCM), elaborating on dosing and safety data as well as the effect of *aficamten* on exercise performance were presented at Heart Failure 2024, an International Congress of the European Society of Cardiology. The primary results from SEQUOIA-HCM were also presented in the same Late Breaking Clinical Trial session at the Congress and simultaneously published in the *New England Journal of Medicine*.[1]

"These additional analyses from SEQUOIA-HCM further illuminate the positive impact of treatment with *aficamten* on measures of dosing, safety, efficacy and impact on quality of life beyond the primary and secondary endpoints of the trial," said Stuart Kupfer, M.D., SVP, Chief Medical Officer. "Notably, the dosing and safety data support dose down-titration in cases of low left ventricular ejection fraction (LVEF), potentially enabling ease of individualized dosing for patients treated with *aficamten* and also may inform a tailored risk mitigation approach."

***Aficamten* Demonstrates Predictable Dosing with No Dose Interruptions Due to LVEF <50%**

Results from prespecified analyses from SEQUOIA-HCM on dosing and measures of safety during treatment with *aficamten* were presented by Caroline Coats, M.D., Ph.D., Lead Clinician, West of Scotland Inherited Cardiac Conditions Service, Honorary Senior Lecturer, School of Cardiovascular and Metabolic Health, University of Glasgow. In SEQUOIA-HCM, there were no major adverse cardiovascular events associated with treatment with *aficamten*. Serious adverse events occurred in 8 (5.6%) patients in the *aficamten* group and 13 (9.3%) patients in the placebo group, none of which were determined to be related to study drug. There was no difference in the incidence of adverse events by dose strength. Over the duration of the 24-week double-blind treatment period, patients treated with *aficamten* had a placebo-corrected average change in left ventricular ejection fraction (LVEF) of -4.8% (95% CI -6.3 to -3.2). This modest reduction in LVEF in patients treated with *aficamten* resulted in large reductions in left ventricular outflow tract gradient (LVOT-G).

Titration of patients to their individually determined target dose of *aficamten* resulted in dose-related increases in plasma drug concentrations with the majority of patients achieving one of the two highest doses (15 mg in 35.0% and 20 mg in 48.6%). Following the completion of dose titration, during the maintenance phase, plasma drug concentrations of *aficamten* remained stable with low variability for the duration of the treatment.

Overall, there was a low frequency of LVEF <50% in SEQUOIA-HCM. LVEF determined by the core laboratory was the prespecified analysis; 5 patients (3.5%) on *aficamten* compared to 1 patient (0.7%) on placebo had LVEF <50%. One of the 5 patients on *aficamten* had LVEF <40% following infection with COVID-19 but did not interrupt treatment as the site-read LVEF remained greater than 40% and the patient did not have symptoms of heart failure due to systolic dysfunction. Overall, there were no instances of worsening heart failure or treatment interruptions due to low LVEF.

To enable same-day dose adjustments, the dosing algorithm in SEQUOIA-HCM used site-interpreted LVEF and LVOT gradients for dose adjustments per protocol as implemented by the interactive Web-response system. There were 7 (4.9%) patients treated with *aficamten* who underwent per-protocol dose reductions for site-read LVEF <50%. Only one patient treated with *aficamten* had both core laboratory and site-read LVEF <50%. There were no dose interruptions and none of the patients treated with *aficamten* experienced symptoms of heart failure due to systolic dysfunction.

"The pharmacological properties that were designed into *aficamten* appear to translate into the intended clinical benefits. In SEQUOIA-HCM patients underwent dose titration as early as two-weeks and achieved the maximal therapeutic effect in the majority of patients while the occurrence of adverse event was similar to placebo," said Caroline Coats, M.D., Ph.D., Lead Clinician, West of Scotland Inherited Cardiac Conditions Service, Honorary Senior Lecturer, School of Cardiovascular and Metabolic Health, University of Glasgow. "The favorable safety and tolerability data from SEQUOIA-HCM affirm *aficamten* as a promising potential treatment for obstructive HCM."

***Aficamten* Improved Novel Integrated Exercise Performance Metric; Improvements in Exercise Performance Correlated with Improvements in Cardiac Structure and Function**

Results from a prespecified analysis of cardiopulmonary exercise testing (CPET) metrics in SEQUOIA-HCM were presented by Gregory Lewis, M.D., Jeffrey and Mary Ellen Jay Chair and Section Head, Heart Failure Medical Director, Cardiopulmonary Exercise Testing Laboratory, Professor of Medicine, Harvard Medical School. In addition to significantly improving peak oxygen uptake (pVO_2), this prespecified analysis demonstrated that treatment with *aficamten* for 24 weeks improved a novel integrated exercise performance metric. Additionally, improvements in pVO_2 were highly correlated with improvements in other clinically important measures.

To capture both maximal and submaximal exercise performance (pVO_2 and ventilatory efficiency [V_E/VCO_2], respectively) an integrated CPET Z-score metric was developed that combines the two measurements into a composite endpoint. It integrates the effect of *aficamten* on exercise across the entire test, representing a more complete view of the therapeutic effect of *aficamten* on functional capacity. *Aficamten* substantially improved overall performance of the integrated CPET Z-score by a placebo-adjusted difference of 0.35 (95% CI, 0.25, 0.46; p<0.001). Additionally, of patients

treated with *aficamten*, 72.2% experienced an improvement in pVO_2, compared to 43.8% of patients treated with placebo. Among the patients treated with *aficamten,* 27.8% had a large improvement (≥3.0 mL/kg/min) in pVO_2, 21.8% had a moderate improvement (≥1.5 to <3.0 mL/kg/min) and 22.6% had a small improvement (0 to <1.5).

Furthermore, enhanced exercise performance was shown to be correlated with improvements in clinically important measures including Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) (p=0.001), New York Heart Association (NYHA) Functional Class (p<0.001), resting LVOT-G (p=0.003), Valsalva LVOT-G (p=0.001), NT-proBNP (p<0.001) and high-sensitivity cardiac troponin I (p=0.010). Importantly, these correlations demonstrate that the therapeutic effects of *aficamten* manifest broadly and are interrelated.

"Measuring changes in peak oxygen uptake only tells part of the story in HCM. Through this analysis we've developed a novel integrated exercise performance metric that, in addition to pVO_2, is designed to take into account submaximal exercise performance, which may represent patient exertion in day-to-day activities," said Gregory Lewis, M.D., Jeffrey and Mary Ellen Jay Chair and Section Head, Heart Failure Medical Director, Cardiopulmonary Exercise Testing Laboratory, Professor of Medicine, Harvard Medical School. "Using this metric, which is designed to assess the impact of *aficamten* across a range of exercise intensities, we saw that the therapeutic effect of *aficamten* spanned the range associated with meaningful daily activity. By positively impacting cardiac function, *aficamten* enhanced overall exercise performance, which is closely correlated with improvements in several important measures of disease including cardiac structure, function and symptoms, underscoring the potential clinical significance of the beneficial effects of *aficamten*."

Investor Event and Webcast Information

Cytokinetics will host an investor event and conference call on May 13, 2024 at 4:00 PM Western European Summer Time (11:00 AM Eastern Time). The event will be held at the Pestana Palace Lisboa Hotel in Lisbon, Portugal in the Lusitano II room. The event will be simultaneously webcast and will be accessible in the Investors & Media section of Cytokinetics' website. Interested parties must register to attend in person or online at https://cytokinetics-SEQUOIA-HCM-investor-event.open-exchange.net/registration. Registered attendees may access the virtual event platform by visiting the Investor & Media section of the Cytokinetics website at www.cytokinetics.com. A link to the webcast replay will be archived on the Cytokinetics website until November 13, 2024.

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 showed that treatment with *aficamten* for 24 weeks significantly improved exercise capacity compared to placebo, increasing peak oxygen uptake (pVO_2) measured by cardiopulmonary exercise testing (CPET) by 1.8 ml/kg/min compared to baseline in patients treated with *aficamten* versus 0.0 ml/kg/min in patients treated with placebo (least square mean (LSM) difference [95% CI] of 1.74 mL/kg/min [1.04 - 2.44]; 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 5.6% and 9.3% of 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. Overall, there were no instances of worsening heart failure or treatment interruptions due to low LVEF.

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, and 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. *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 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. 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, 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, and the labeling or post-marketing conditions that FDA or another regulatory body may require in connection with the approval of *aficamten.* 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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Source: Cytokinetics, Incorporated