NEWS RELEASE

Cytokinetics Announces Five Presentations at the American College of Cardiology Annual Scientific Session & Expo

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New Analyses Related to Aficamten Expand on its Metabolism Pathways, Treatment Effect Associated with Combination Therapy with Disopyramide and Longer-Term Effect on Cardiac Structure and Function

SOUTH SAN FRANCISCO, Calif., March 17, 2025 (GLOBE NEWSWIRE) -- Cytokinetics, Incorporated (Nasdaq: CYTK) today announced five presentations related to *aficamten*, an investigational cardiac myosin inhibitor, and hypertrophic cardiomyopathy (HCM), at the American College of Cardiology (ACC) Annual Scientific Session & Expo taking place from March 29, 2025–March 31, 2025 in Chicago, IL.

"We are pleased to be sharing several new analyses relating to *aficamten* at the upcoming ACC Scientific Session & Expo," said Stephen Heitner, M.D., Vice President, Head of Clinical Research. "The presentations describe the drug metabolism of *aficamten*, the safety of combination therapy with the standard of care medication *disopyramide*, and the effect of longer-term use of *aficamten*. Together these analyses add to the strong and growing evidence base supporting the potential for *aficamten* in patients with obstructive HCM and inform how it may be used in clinical practice."

Evaluation of Cytochrome P450 2C9, 2C19, and 2D6 Inhibition on the Pharmacokinetics of *Aficamten* in Healthy Participants (1091-139)
Poster Presentation, March 29, 2025, 2:00-3:00 PM CT, South Hall. Neha Maharao, Ph.D., Senior Clinical Pharmacologist, Cytokinetics.

Data from an open-label, fixed-sequence drug-drug interaction (DDI) study of *aficamten* in healthy participants will be presented in a poster presentation. A previous study showed that *aficamten* is metabolized, in part, by the cytochrome P450 (CYP) enzyme 3A4[1]. To further characterize its metabolic pathways, *aficamten* was evaluated with concomitant administration of three strong inhibitors of one or more of the CYP pathways: *fluconazole* (inhibitor of 2C9, 2C19, and 3A4), *paroxetine* (inhibitor of 2D6) and *fluoxetine* (inhibitor of 2C19 and 2D6). The data show that *aficamten* was eliminated by multiple CYP pathways, primarily by CYP2C9 (fraction metabolized [fm]=50%), with contributions from CYP3A (fm=26%), CYP2D6 (fm=21%) and CYP2C19 (fm=3%).

Safety and Outcomes of Concomitant *Aficamten* and *Disopyramide* Use and Withdrawal in Patients with Obstructive Hypertrophic Cardiomyopathy: An Analysis of REDWOOD-HCM Cohort 3, SEQUOIA-HCM, and FOREST-HCM Trials (411-06)
Oral Presentation, March 31, 2025, 9:11-9:18 AM CT, S406b. Ahmad Masri, M.D., MS, Director of the Hypertrophic Cardiomyopathy Center at Oregon Health & Science University.

Data from an analysis of concomitant treatment with *aficamten* and disopyramide from completed and ongoing clinical trials of *aficamten* in patients with obstructive HCM will be presented in an oral presentation. The analysis included 50 participants from Cohort 3 of REDWOOD-HCM (**R**andomized **E**valuation of **D**osing **W**ith CK-274 in **O**bstructive **O**utflow **D**isease in **HCM**), SEQUOIA-HCM (**S**afety, **E**fficacy, and **Q**uantitative **U**nderstanding of **O**bstruction **I**mpact of ***A**ficamten* in **HCM**) and FOREST-HCM (**F**ollow-up, **O**pen-Label, **R**esearch **E**valuation of **S**ustained **T**reatment with *Aficamten* in **HCM**) who were receiving disopyramide at baseline. Participants were separated into four groups: those on disopyramide who underwent withdrawal of *aficamten* due to end of treatment in Cohort 3 of REDWOOD-HCM or SEQUOIA-HCM (n=29), patients on disopyramide receiving placebo in SEQUOIA-HCM (n=20), patients on *aficamten* who underwent disopyramide withdrawal in FOREST-HCM (n=17) and patients on *aficamten* who maintained treatment with disopyramide in FOREST-HCM (n=27). Combination therapy with *aficamten* and disopyramide was well-tolerated; the analysis suggests that combination of disopyramide with *aficamten* did not result in lower left ventricular outflow tract (LVOT) gradients compared to treatment with *aficamten* alone. The analysis suggests that withdrawal of disopyramide while receiving *aficamten* did not reduce the efficacy of *aficamten* and further that withdrawal of *aficamten* while on disopyramide resulted in the return of LVOT obstruction and symptoms, with an increase in NT-proBNP. There were no safety events reported with either *aficamten* or disopyramide withdrawal, and no episodes of atrial fibrillation after disopyramide withdrawal were reported.

Effect of *Aficamten* Treatment for Up to 72 Weeks on Cardiac Structure and Function in Patients with Obstructive Hypertrophic Cardiomyopathy: The SEQUOIA-HCM and FOREST-HCM CMR Sub-studies (964-09)
Moderated Poster Presentation, March 30, 2025, 12:06-12:13 PM CT, Theater 5. Ahmad Masri, M.D., MS, Director of the Hypertrophic Cardiomyopathy Center at Oregon Health & Science University.

New data from the cardiac magnetic resonance (CMR) imaging sub-studies of FOREST-HCM and SEQUOIA-HCM will be presented in a moderated poster presentation. At the time of the current analysis, 64 patients had completed a baseline CMR, including 36 patients who had completed a follow-up CMR at 72 weeks, and 28 patients who had completed a follow-up CMR at 48 weeks. Longer-term treatment with *aficamten* resulted in statistically significant improvements (mean ±SD) in measures of cardiac structure and function including left ventricular mass index (-9.8 g/m2 ±18.1, $p<0.0001$), maximum left ventricular septal wall thickness (-2.4 mm ±2.3, $p<0.0001$), left atrial volume (-17.9 ml ±28.3, $p<0.0001$) and mitral regurgitant volume (-18.1 ml ±19.2, $p<0.0001$) and fraction (-14.2% ±15.6, $p<0.0001$). These changes were accompanied by stable replacement fibrosis (late gadolinium enhancement mass = -0.3 g ±5.0, $p=0.51$) and reduced interstitial fibrosis (global extracellular volume (ECV) = -1.2 % ±2.8, $p = 0.002$; Native T1 = -36.6 ms ±55.7, $p<0.0001$).

Understanding the Impact of Placebo on Patient-Reported Health Status: An Analysis from SEQUOIA-HCM (1029-176)
Poster Presentation, March 29, 2025, 9:30-10:30 AM CT, South Hall. Charles F. Sherrod, M.D., M.Sc., Cardiology Fellow, UMKC Healthcare Institute for Innovations in Quality, Saint Luke's Mid America Heart Institute.

A new analysis from SEQUOIA-HCM of the placebo effect on Kansas City Cardiomyopathy Questionnaire Overall Summary Scores (KCCQ-OSS) will be presented in a poster presentation. In

patients randomized to placebo in SEQUOIA-HCM, the change in KCCQ-OSS was evaluated from baseline to Week 24 and following blinded treatment withdrawal from Week 24 to Week 28. Among the 140 (47%) patients on placebo, the median KCCQ-OSS at baseline was 67.2 (95% CI: 62.9, 71.5) and the median improvement at Week 24 was 5.7 points (95% CI: 3.2, 8.3; p<0.01). After withdrawal from Week 24 to Week 28, the median score decreased by only 2.1 points (95% CI: -3.5, -0.7; p<0.01). These results suggest that about one-third of the improvement observed in KCCQ-OSS in patients receiving placebo was due to a placebo effect, further suggesting that other changes in health status following treatment with placebo may be due to other factors involved in clinical trial participation, such as receiving treatment at expert centers and changes in patient behavior.

Association Between Race/Ethnicity and Outcomes in Patients with Non-Obstructive Hypertrophic Cardiomyopathy (1251-173)
Poster Presentation, March 31, 2025, 10:30-11:30 AM CT, South Hall. Nosheen Reza, M.D., Assistant Professor of Medicine, Division of Cardiovascular Medicine, the Hospital of the University of Pennsylvania.

Data from a new health economics and outcomes research (HEOR) analysis of the association between race/ethnicity and outcomes in non-obstructive HCM patients will be presented in a poster presentation. This retrospective cohort study included adult patients diagnosed with non-obstructive HCM from January 1, 2013 to December 31, 2021. Of the 9,842 patients included, 74.2% were non-Hispanic white, 19.5% were non-Hispanic Black/African American, 4.2% were Hispanic and 2.1% were non-Hispanic Asian. White patients had greater rates of atrial fibrillation and cardiovascular hospitalization compared to Asian and Hispanic patients. Compared to white patients, Black patients had increased rates of stroke (risk ratio [RR] 1.76), heart failure (RR 1.73), ventricular tachycardia (RR 1.24), sudden cardiac arrest (RR 1.90), cardiovascular hospitalization (RR 1.42) and cardiovascular rehospitalization (RR 1.31) and a lower rate of atrial fibrillation (RR 0.74; all p<0.001). All-cause mortality was highest among Black patients (p<0.001). Compared to white patients, non-Hispanic Black patients had the highest rate of adverse cardiovascular outcomes and all-cause mortality, while Asian and Hispanic patients experienced lower rates. These results highlight an urgent need to address drivers of race/ethnicity-based disparities in patients with nHCM.

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 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 as measured by peak oxygen uptake (pVO_2) and relieves symptoms in patients with HCM. *Aficamten* was evaluated in SEQUOIA-HCM, a positive pivotal Phase 3 clinical trial in patients with symptomatic obstructive hypertrophic cardiomyopathy (HCM). *Aficamten* received Breakthrough Therapy Designation for the treatment of symptomatic obstructive HCM from the U.S. Food & Drug Administration (FDA) and from the National Medical Products Administration (NMPA) in China.

Aficamten is currently under regulatory review in the U.S, where the FDA is reviewing a New Drug Application (NDA) for *aficamten,* which was assigned standard review and a Prescription Drug User Fee Act (PDUFA) target action date of September 26, 2025. Additionally, the European Medicines

Agency (EMA) is reviewing a Marketing Authorization Application (MAA) for *aficamten*, and The Center for Drug Evaluation (CDE) of the China National Medical Products Administration (NMPA) is reviewing an NDA for *aficamten* with Priority Review.

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.

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, however, there are an estimated 400,000-800,000 additional patients who remain undiagnosed in the U.S.[2,3,4] 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.[5] 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.[6] 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 leading muscle biology specialty biopharmaceutical company focused on discovering, developing and commercializing muscle biology-directed drug candidates as potential treatments for debilitating diseases in which muscle performance is compromised. As a pioneer in muscle and the mechanics of muscle performance, Cytokinetics is intent on meaningfully improving the lives of patients through global access to innovative medicines. Cytokinetics is readying for potential regulatory approvals and commercialization of *aficamten,* a potential next-in-class cardiac myosin inhibitor, following positive results from SEQUOIA-HCM, the pivotal Phase 3 clinical trial in patients with obstructive hypertrophic cardiomyopathy (HCM). *Aficamten* is also being evaluated in additional clinical trials enrolling patients with obstructive and non-obstructive HCM. Cytokinetics is also developing *omecamtiv mecarbil*, a cardiac myosin 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 with potential therapeutic application to a specific type of muscular dystrophy and other conditions of impaired skeletal muscle function.

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, treatment effect or potential benefits of *aficamten* or any of our other drug candidates or 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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