Cytokinetics Presents New Data Related to the Safety and Long-Term Use of Aficamten at the European Society of Cardiology Congress 2024

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Data from Integrated Safety Analysis Across Three Clinical Trials
Reinforces Robust Safety Profile of Aficamten

Analysis from FOREST-HCM Demonstrates Successful
Withdrawal of Standard of Care Medications
in Patients with Obstructive HCM Treated with Aficamten

Company to Host Conference Call and Webcast
Tuesday, September 3rd at 8:00 AM Eastern Time

SOUTH SAN FRANCISCO, Calif., Sept. 01, 2024 (GLOBE NEWSWIRE) -- Cytokinetics, Incorporated (Nasdaq: CYTK) today announced that new data related to the safety and long-term use of *aficamten* were presented in a Late Breaking Clinical Trial presentation and oral presentation at the European Society of Cardiology Congress 2024 in London, UK. The presentations included an integrated safety analysis from three clinical studies of *aficamten* and an analysis of the withdrawal of standard of care medications in patients treated 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 study of *aficamten* in patients with hypertrophic cardiomyopathy (HCM).

"The emerging safety profile of *aficamten* observed across three clinical trials representing 206 patient years of exposure to *aficamten* provides a rationale for how *aficamten* may translate to real-world use as a cardiac myosin inhibitor of choice," said Stephen Heitner, M.D., Vice President, Head of Clinical Research. "We're encouraged by the promising safety and tolerability profile for *aficamten* as well as the observation that patients successfully withdrew background standard of care medications, with many able to simplify their treatment regimen to disease-specific monotherapy with *aficamten*. These findings were in an open-label setting, at the discretion of the patient and physician, and did not impact the safety or efficacy of *aficamten*. We look forward to results of MAPLE-HCM, the Phase 3 clinical trial assessing the potential superiority of *aficamten* as monotherapy compared to *metoprolol,* which we expect to disclose in the first half of next year."

Integrated Safety Analysis from Three Clinical Trials of *Aficamten* Reinforces Robust Safety Profile

Ahmad Masri, M.D., M.S., Director of the Hypertrophic Cardiomyopathy Center at Oregon Health and Science University presented data from an integrated safety analysis of *aficamten* across the Phase 2 clinical trial, REDWOOD-HCM (**R**andomized **E**valuation of **D**osing **W**ith CK-274 in **O**bstructive **O**utflow **D**isease in **HCM**), the Phase 3 clinical trial, SEQUOIA-HCM (**S**afety, **E**fficacy, and **Q**uantitative **U**nderstanding of **O**bstruction **I**mpact of ***A**ficamten* in **HCM**), and FOREST-HCM, the open-label extension clinical study of *aficamten*. Patients with obstructive HCM who received at least one dose of *aficamten* or placebo were included in this analysis. A total of 283 patients received at least one dose of *aficamten* and 153 patients received at least one dose of placebo. Overall, treatment with *aficamten* was well-tolerated with an adverse event profile similar to placebo. Across all three clinical studies, 11 patients (3.9%) experienced incidents of left ventricular ejection fraction (LVEF) <50%, but none were associated with clinical heart failure, and all were successfully managed by dose down-titration. Additionally, of the 1,588 total echocardiograms performed on patients treated with *aficamten* during the maintenance phases of each clinical study, only 0.7% of echocardiograms that were performed impacted the clinical management of patients and led to a reduction in dose. There were no dose interruptions and no treatment discontinuations in these three clinical studies of *aficamten* due to decreased LVEF.

Additionally, among patients treated with *aficamten* and compared to placebo, there was a low incidence of new onset atrial fibrillation and myocardial infarction. The rate of syncope events was also similar between groups (Table 1). This integrated safety analysis reinforces the safety profile of *aficamten* as relates to the potential management of HCM in a real-world setting.

Table 1. Integrated Safety Analysis

	Cumulative[a] *aficamten*-treated pool	**Placebo-controlled pool[b]**	
	Aficamten	***Aficamten***	**Placebo**
Number of participants	283	170	153
LVEF <50%[c], n (%)	11 (3.9)	9 (5.3)	1 (0.7)
LVEF <50% with clinical heart failure	0	0	1 (0.7)
Atrial fibrillation	12 (4.2)	4 (2.4)	5 (3.3)
New onset	5 (1.8)	1 (0.6)	3 (2.0)
Recurrent	7 (2.5)	3 (1.8)	2 (1.3)
Stroke	3 (1.1)	1 (0.6)	1 (0.7)
Myocardial infarction	1 (0.4)	0	1 (0.7)
Syncope	4 (1.4)	3 (1.8)	5 (3.3)
Death	0	0	0

[a] Parent and extension studies. [b] Placebo-controlled pool of REDWOOD-HCM and SEQUOIA-HCM. [c] Site read.

Withdrawal of SoC Medications Does Not Negatively Impact Efficacy or Safety of *Aficamten* in Patients with Obstructive HCM

Dr. Masri also presented data from an analysis related to the withdrawal of standard of care (SoC) medications in patients with obstructive HCM in FOREST-HCM. Of the 145 patients with obstructive HCM who completed at least 24 weeks of treatment with *aficamten* at the time of this analysis, 136 (93.8%) were receiving SoC medications including beta blockers, calcium channel blockers and disopyramide. Withdrawal of SoC medications was attempted at the discretion of the investigator in 64 (47%) patients, while a comparator group of 72 (53%) patients did not undergo SoC withdrawal. Successful withdrawal was defined as at least a 50% dose-reduction in one medication relative to baseline. Among patients who attempted withdrawal of SoC medications, 59 (92%) were successful, including 38 (64%) patients who discontinued at least one SoC medication and 27 (71%) patients who achieved and maintained monotherapy with *aficamten*. Following successful withdrawal of SoC medications, 23 (39%) patients underwent dose up-titration with *aficamten*.

Among those who attempted withdrawal of SoC medications, there were no statistically significant differences in the treatment effect of *aficamten* post-withdrawal compared to pre-withdrawal on resting left ventricular outflow tract gradient (LVOT-G), Valsalva LVOT-G, change in LVEF, New York Heart Association (NYHA) Functional Class, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS), high-sensitivity cardiac troponin I (hs-cTnI) and NT-proBNP. There were no differences in the efficacy of *aficamten* between the group of patients who attempted SoC withdrawal and the control group of patients who did not attempt SoC withdrawal. Further, no differences in safety profile emerged, with similar rates of adverse events, instances of LVEF <50% and new onset atrial fibrillation between groups. These data suggest that *aficamten* may be tolerated and effective as monotherapy in patients with obstructive HCM and warrants further evaluation.

Conference Call and Webcast

Cytokinetics will host a conference call on September 3, 2024 at 8:00 AM Eastern Time that will be simultaneously webcast and can be accessed from the Investors & Media section of Cytokinetics' website at www.cytokinetics.com. The live audio of the conference call can also be accessed by telephone by registering in advance at the following link: **Cytokinetics ESC Investor Conference Call**. Upon registration, participants will receive a dial-in number and a unique passcode to access the call. An archived replay of the webcast will be available via Cytokinetics' website for six months.

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.

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* was evaluated in SEQUOIA-HCM (**S**afety, **E**fficacy, and **Q**uantitative **U**nderstanding of **O**bstruction **I**mpact of **A**ficamten in **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) as well as the National Medical Products Administration (NMPA) in China. Cytokinetics expects to submit a New Drug Application (NDA) to the FDA in Q3 2024 and a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) in Q4 2024.

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.

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.[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 muscle biology-directed drug candidates 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 which were published in the *New England Journal of Medicine*. *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.

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, the labeling or post-marketing conditions that FDA or another regulatory body may require in connection with the approval of *aficamten*, and our ability release the data from MAPLE-HCM in the first half of 2025. 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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