



Brief Report

Safety and Efficacy of Aficamten in Patients With Nonobstructive Hypertrophic Cardiomyopathy: A 96-Week Analysis From FOREST-HCM

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Non-obstructive hypertrophic cardiomyopathy (nHCM) affects a significant proportion of patients with HCM and is without proven therapies. Cardiac myosin inhibitors (CMLs) target the hypercontractility and impaired myocardial relaxation that underlie the pathophysiology of HCM. CMLs have been shown to be effective in treating patients with obstructive HCM and, owing to the shared underlying pathophysiology, have been proposed to treat nHCM.¹ Mavacamten, the first-in-class CML, recently reported failure to improve patient-reported symptoms and peak oxygen consumption for patients with symptomatic nHCM in a placebo-controlled trial (ODYSSEY-HCM [A Study of Mavacamten in Non-Obstructive Hypertrophic Cardiomyopathy], NCT05582395) and demonstrated a

limited efficacy signal in the preceding phase 2 trial MAVERICK-HCM (NCT03442764 [A Phase 2 Study of Mavacamten in Adults With Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy]). Moreover, of those patients opting to participate in MAVA-LTE (NCT03723655 [A Long-Term Safety Extension Study of Mavacamten in Adults Who Have Completed MAVERICK-HCM or EXPLORER-HCM]), the long-term extension study for patients originating in MAVERICK-HCM, one-third of patients developed a left ventricular ejection fraction of (LVEF) $\leq 50\%$ despite a dosing strategy targeting 2 pre-specified plasma mavacamten concentrations.²

Aficamten is a next-in-class CML with a distinct pharmacological profile.³ The phase 2 study REDWOOD-HCM

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Cohort 4 (NCT04219826 [Dose-finding Study to Evaluate the Safety, Tolerability, PK, and PD of CK-3773274 in Adults With HCM]), which enrolled 41 patients with nHCM, found aficamten was well-tolerated over 10 weeks, with improvement in symptoms and biomarkers as well as infrequent LVEF <50% events.⁴ These findings were similarly observed over 36 weeks of aficamten treatment in the long-term, open-label FOREST-HCM study (NCT04848506 [Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of Aficamten in Adults With HCM]).⁵ If aficamten is found to be effective, safe, and achieves regulatory approval, the intended use would be chronic; therefore, long-term safety and efficacy data are critical in this patient population. As such, here we report the 96-week experience with aficamten in nHCM patients enrolled in FOREST-HCM.

The detailed study design has been previously published.⁵ Of the original 41 patients enrolled in REDWOOD-HCM Cohort 4 (1 subject in the safety analysis was excluded from efficacy analysis due to site Good Clinical Practice violations), 7 patients did not participate in FOREST-HCM. One patient died during REDWOOD-HCM (previously reported). Reasons for nonparticipation included 1 screen failure due to arrhythmia, and the remaining 5 did not enroll due to site closure (1), personal reasons (2), or principal investigator decision (2). None of these were related to heart failure, reduced LVEF, or adverse events related to aficamten. Patients were initiated on 5 mg of aficamten and could dose escalate in 5-mg increments to a maximum of 20 mg at ≥ 2 -week intervals. Decisions to dose escalate were based on echocardiographically determined LVEF and were at the investigator's discretion after integrating clinical assessments. The following criteria were used: increase the dose by 5 mg if the LVEF was $\geq 55\%$; maintain if the LVEF was 50%–54%; decrease dose by 5 mg if the LVEF was 40% to <50%; and interrupt if the LVEF was <40%. Outcome measures included New York Heart Association (NYHA) functional class, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS), LVEF, cardiac biomarkers N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin I (hs-cTnI), and safety parameters. Data are presented as mean \pm standard deviation or median (interquartile range) as appropriate.

All 34 patients enrolled in FOREST-HCM (age 57.2 \pm 15.3 years, 62% were women) were followed for 96 weeks. Baseline characteristics have previously been published,⁵ and patients were highly symptomatic with abnormal markers of myocardial wall stress. At the end of titration, most patients were on 20 mg/d⁵ and generally remained at stable doses over the 96 weeks (11.8%, 11.8%, 17.6%, and 58.8% respectively for 5, 10, 15, and 20 mg/d). At 96 weeks, NYHA functional class improved by at least one class in 27 patients (79.4%), of whom 20 (58.8%) became asymptomatic, with a decrease in severely symptomatic

patients (NYHA functional class III) from 41.2% at baseline to 11.8% at week 96 (Figure 1A). The mean KCCQ-CSS improved by 11.2 \pm 14.3 points ($P < 0.0001$ relative to baseline), with 22 patients (64.7%) reporting improvements of ≥ 5 points. Similar symptomatic changes were seen at 36 weeks of treatment, thus demonstrating the continued durability of these effects.⁵ NT-proBNP rapidly decreased by week 12⁵ and remained low through 96 weeks (median -753.0 pg/mL, interquartile range -1034.7 to -471.3 pg/mL, $P < 0.0001$; proportional decrease, geometric mean 0.3, 95% confidence interval 0.2–0.4, $P = 0.0002$). Although there was a decrease from baseline in hs-cTnI by week 36,⁵ it was not significant; however, by week 96 this difference became significant (median -7.3 ng/L, interquartile range -11.7 to -2.9 ng/L, $P < 0.005$). There was a modest decrease in LVEF from baseline hyperdynamic state ($70 \pm 6\%$) to normal range at week 12 (LVEF $63 \pm 8\%$, change from baseline $-6.2 \pm 7.9\%$, $P < 0.0001$) after titration, which remained stable within the normal range up to week 96 (LVEF $64 \pm 6\%$, change from baseline $-5.3 \pm 6.7\%$, $P < 0.0001$). Over the entire treatment period, an LVEF of <50% was observed in 4 patients (range 35%–49%, exposure-adjusted event rate 5.4/100 patient-years), of whom 2 were previously reported.⁵ The new cases occurred during the ensuing 60 weeks, and both were asymptomatic. All episodes of LVEF <50% demonstrated reversibility after downtitration or short duration interruption (1 patient had two nonsequential interruptions of a maximum of 23 days but safely restarted and remained on aficamten; the decrease in the LVEF occurred in the setting of a recent acute illness and recurrent persistent atrial fibrillation).

These long-term data from FOREST-HCM demonstrate that, for approximately 2 years, aficamten was well-tolerated in these nHCM patients, with most achieving the highest available dose and demonstrating sustained improvements in heart failure symptoms and marked improvements in cardiac biomarkers. Although this is an open-label trial, the magnitude of benefit observed for NYHA functional class and KCCQ-CSS likely exceeds that observed in placebo groups previously,⁶ and this finding is mirrored by favorable and significant improvements in quantitative measures of important cardiac biomarkers.^{1,7} Importantly, the exposure-adjusted event rate for an LVEF of <50%, the primary on-target potential toxicity for CMLs, was modest, and only 2 instances occurred without potential confounders (atrial fibrillation and pulmonary vein isolation were temporally related in 2 others). These patients were managed largely by simple dose reduction without the need to discontinue therapy.

These findings are supportive of the ongoing phase 3 pivotal trial ACACIA-HCM (NCT06081894 [Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic nHCM]),

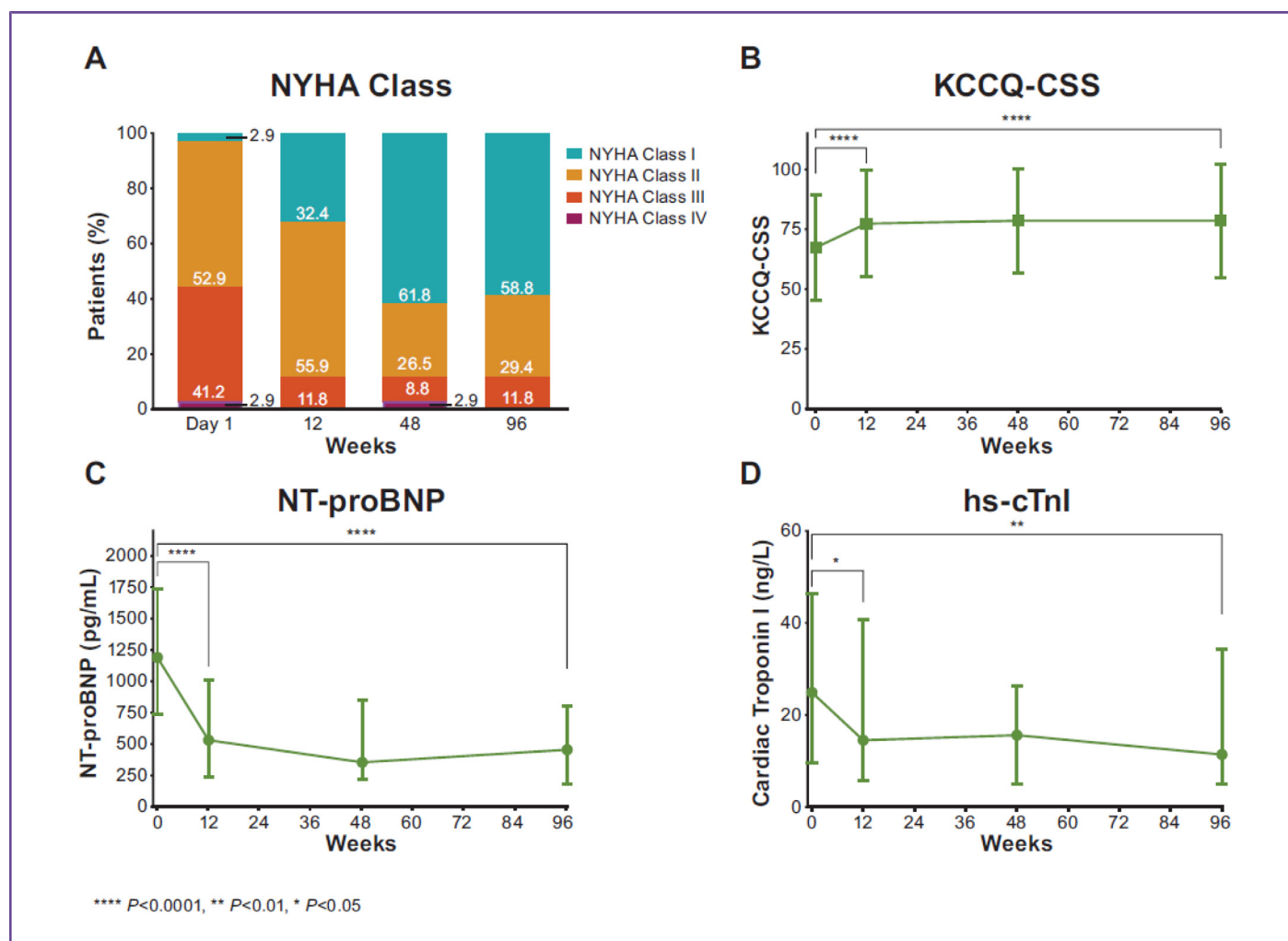


Figure 1. Efficacy end points in the nonobstructive HCM cohort of the FOREST-HCM trial. (A) NYHA functional class, (B) KCCQ-CSS, (C) NT-proBNP, and (D) hs-cTnI. KCCQ-CSS are mean \pm SD; NT-proBNP and hs-cTnI are median \pm interquartile range. hs-cTnI, high-sensitivity cardiac troponin I; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

which uses similar eligibility criteria and dosing strategies as those evaluated in FOREST-HCM. As primary end points, ACACIA-HCM evaluates exercise capacity as assessed with cardiopulmonary exercise testing and symptom improvement; exercise capacity was not evaluated in FOREST-HCM. Findings from the SEQUOIA-HCM trial in patients with obstructive HCM demonstrate that the magnitude of early reduction in NT-proBNP and hs-cTnI along with improvement in symptoms (NYHA functional class, KCCQ scores) may be predictors of improvement in peak oxygen uptake,⁸ all of which are seen in this nHCM population in FOREST-HCM. However, it is unknown if these correlations from an obstructive HCM population will translate to a nHCM population, a question that may be answered in ACACIA-HCM. Finally, it is important to note the current results reflect an optimized dosing strategy, enabled by the favorable pharmacological properties of aficamten, which aimed at maximizing dose without compromising safety. Taken together, this 96-week overview of aficamten treatment for patients with

symptomatic nHCM in FOREST-HCM provides support for the ongoing, pivotal randomized controlled trial ACACIA-HCM.



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Data Availability Statement

Qualified researchers may submit a request containing the research objectives, end points/outcomes of interest, statistical analysis plan, data requirements, publication plan,

and qualifications of the researcher(s). In general, Cytokinetics does not grant external requests for individual patient data for the purpose of reevaluating safety and efficacy issues already addressed in the product labeling. Requests are reviewed by a committee of internal advisors, and if not approved, may be further reviewed by a Data Sharing Independent Review Panel. Upon approval, information necessary to address the research question will be provided under the terms of a data sharing agreement. This may include anonymized individual patient data and/or available supporting documents, containing fragments of analysis code where provided in the analysis specifications. Requests may be submitted to medicalaffairs@cytokinetics.com.

Conflicts of Interest

Dr Masri has received consultant/advisor fees from Tenaya, Attralus, Cytokinetics Incorporated, Bristol Myers Squibb, Eidos, Pfizer, Lexicon, Alnylam, Haya, Intellia, and Ionis and has received research grants from Ionis, Akcea, Pfizer, Cytokinetics Incorporated, Ultromics, and the Wheeler Foundation. Dr Sherrid has received consultant fees/honoraria from Pfizer and has served as a consultant for Cytokinetics Incorporated, without payment. Dr Choudhury has received advisor fees from Cytokinetics Incorporated. Pablo Garcia-Pavia has received speakers' bureau fees from Bristol Myers Squibb, Pfizer, BridgeBio, Ionis, AstraZeneca, Novo Nordisk, Intellia, and Alnylam; has received consulting fees from Bristol Myers Squibb, Cytokinetics Incorporated, Rocket Pharma, Lexeo Therapeutics, Pfizer, Bayer, BridgeBio, Daiichi-Sankyo, Neurimmune, Alnylam, AstraZeneca, Novo Nordisk, Attralus, Intellia, Idoven, General Electric, and Alexion; and has received research/educational support to their institution from Pfizer, BridgeBio, Novo Nordisk, AstraZeneca, Intellia, and Alnylam. Dr Kramer has received research grants from Bristol Myers Squibb and Eli Lilly and has served as a consultant for Eli Lilly. Dr Barriaes-Villa has received consultant/advisor fees from MyoKardia/Bristol Myers Squibb, Pfizer, Sanofi, Alnylam, and Cytokinetics Incorporated. Dr Cooper has received consulting fees from Bristol Myers Squibb, Bayer, Pfizer, and Alnylam. Dr Elliott has received consulting fees from Bristol Myers Squibb, Pfizer, and Cytokinetics Incorporated; has received speaker fees from Pfizer; and has an unrestricted grant from Sarepta. Dr Hegde's institution has received fees for core lab services from Cytokinetics Incorporated and Bristol Myers Squibb and has received advisor fees from Cytokinetics Incorporated. Dr Maron has received consultant/advisor fees from Imbria, Edgewise, and BioMarin; and has received steering committee fees for SEQUOIA-HCM from Cytokinetics Incorporated. Dr Nassif has received research and grant support to their institution from Cytokinetics Incorporated and Bristol Myers Squibb. Dr Oreziak has received investigator fees from Cytokinetics Incorporated and

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