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

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Author Contributions

Drs. Masri, Saberi, and Wei had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis

Concept and design: Drs. Masri and Saberi

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: Dr. Masri

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: Dr. Wei

Obtained funding: Cytokinetics, Incorporated

Data Availability Statement

Qualified researchers may submit a request containing the research objectives, endpoints/outcomes of interest, statistical analysis plan, data requirements, publication plan, and qualifications of the researcher(s). In general, Cytokinetics Inc. 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 arbitrated 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 analysis specifications. Requests may be submitted to medicalaffairs@cytokinetics.com.

Nonobstructive hypertrophic cardiomyopathy (nHCM) affects a significant proportion of patients with HCM and is without proven therapies. Cardiac myosin inhibitors (CMIs) target the

hypercontractility and impaired myocardial relaxation that underlie the pathophysiology in HCM. CMIs have been shown to be effective in treating patients with obstructive HCM (oHCM) and, owing to the shared underlying pathophysiology, have been proposed to treat nHCM.[1] Mavacamten, the first-in-class CMI, recently reported failure to improve patient-reported symptoms and peak oxygen consumption (pVO_2) for patients with symptomatic nHCM in a placebo-controlled trial (ODYSSEY-HCM, NCT05582395) and demonstrated a limited efficacy signal in the preceding phase 2 trial MAVERICK-HCM (NCT03442764). Moreover, of those patients opting to participate in the MAVA-LTE study (NCT03723655), the long-term extension study for patients originating in MAVERICK-HCM, one-third of patients developed left ventricular ejection fraction (LVEF) ≤50% despite a dosing strategy targeting 2 prespecified plasma mavacamten concentrations.[2]

Aficamten is a next-in-class CMI with a distinct pharmacologic profile.[3] The phase 2 study REDWOOD-HCM Cohort 4 (NCT04219826), 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)[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 non-participation included one screen fail due to arrythmia and the remaining 5 did not enroll due to site closure (1), personal reasons (2), or PI decision (2). None of these were related to heart failure, reduced LVEF, or AEs 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 dose by 5 mg if LVEF ≥55%; maintain if LVEF 50%–54%; decrease dose by 5 mg if LVEF 40% to <50%; and interrupt if LVEF <40%. Outcome measures included New York Heart Association (NYHA) 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 ± standard deviation (SD) or median (interquartile range [IQR]) as appropriate.

All 34 patients enrolled in FOREST-HCM (age 57.2 ± 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 daily[5] 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 daily). At 96 weeks, NYHA improved by at least one class in 27 patients (79.4%), of whom 20 (58.8%) became asymptomatic, with reduction in severely symptomatic patients (NYHA class III) from 41.2% at baseline to 11.8% at Week 96 (**Figure**). KCCQ-CSS mean ± SD improved by 11.2 ± 14.3

points (*P*<0.0001 relative to baseline), with 22 patients (64.7%) reporting improvements ≥5 points. Similar symptomatic changes were seen at 36 weeks of treatment, thus demonstrating continued durability of these effects.[5] NT-proBNP rapidly declined by Week 12[5] and remained low through 96 weeks (median [IQR]: −753.0 pg/mL [−1034.7, −471.3], *P*<0.0001; proportional decrease - geometric mean [95% CI]: 0.3 [0.2-0.4], *P*=0.0002). While there the reduction from baseline in hs-cTnI by Week 36[5] was not significant, by Week 96 this was now significant (median [IQR]: −7.3 ng/L [−11.7, −2.9]; *P*<0.005). There was a modest reduction in LVEF from baseline hyperdynamic state (70% ± 6%) to normal range at Week 12 (LVEF: 63% ± 8%, change from baseline: −6.2% ± 7.9%; *P*<0.0001) following titration, which remained stable within normal range up to Week 96 (LVEF: 64% ± 6%, change from baseline: −5.3% ± 6.7%; *P*<0.0001). Over the entire treatment period LVEF <50% was observed in four patients (range: 35%–49%; exposure-adjusted event rate: 5.4/100 patient-years), of whom two were previously reported.[5] The new cases occurred during the ensuing 60-weeks, both being asymptomatic. All episodes of LVEF <50% demonstrated reversibility after downtitration or short duration interruption (one subject had two non-sequential interruptions of a maximum of 23 days but has safely restarted and remained on aficamten; reduction in 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 ~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 on NYHA class and KCCQ-CSS likely exceeds that observed in placebo groups previously[6], and

this is mirrored by favourable and significant improvements in quantitative measures of important cardiac biomarkers.[1, 7] Importantly, the exposure-adjusted event rate for LVEF <50%, the primary on-target potential toxicity for CMIs, was modest, and only two instances occurred without potential confounders (atrial fibrillation and pulmonary vein isolation were temporally related in two 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), which employs similar eligibility criteria and dosing strategies to those evaluated in FOREST-HCM. As primary endpoints, 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 oHCM demonstrate the magnitude of early reduction in NT-proBNP and hs-cTnI along with improvement in symptoms (NYHA, KCCQ) 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 oHCM 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 favourable pharmacologic 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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Figure Legend

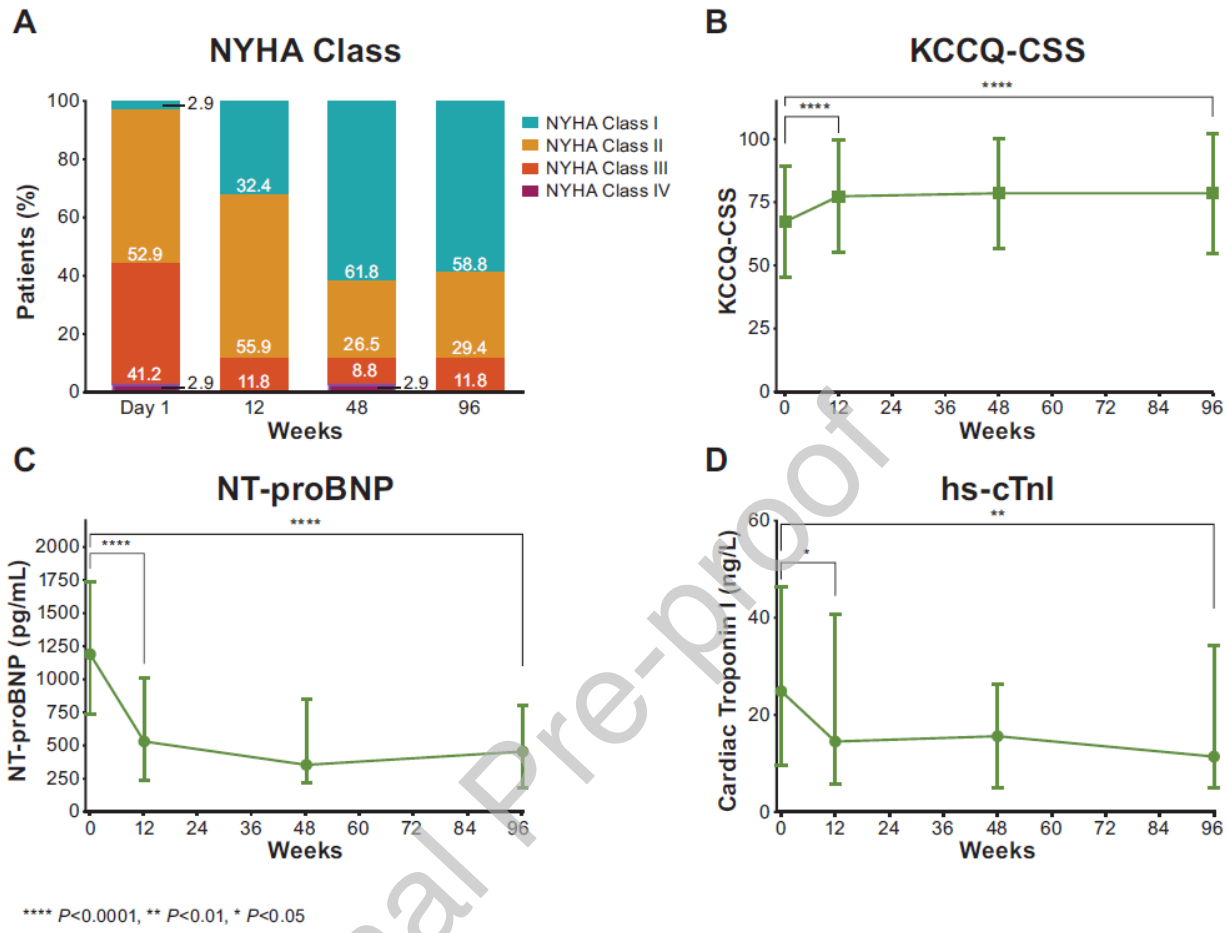

Figure. Efficacy endpoints in the nonobstructive HCM cohort of the FOREST-HCM trial. (A) NYHA functional class, (B) KCCQ-CSS, (C) NT-proBNP, and (D) hs-cTnI.

KCCQ-CSS are mean ± SD; NT-proBNP and hs-cTnI are median ± 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.