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Efficacy and Safety of Aficamten in Symptomatic Nonobstructive Hypertrophic Cardiomyopathy: Results From the REDWOOD-HCM Trial, Cohort 4

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ABSTRACT

Background: This open-label phase 2 trial evaluated the safety and efficacy of aficamten in patients with nonobstructive hypertrophic cardiomyopathy (nHCM).

Methods: Patients with symptomatic nHCM (left ventricular outflow tract obstruction gradient $\leq$ 30 mmHg, left ventricular ejection fraction [LVEF] $\geq$ 60%, N-terminal pro-B-type natriuretic peptide [NT-proBNP] > 300 pg/mL) received aficamten 5–15 mg once daily (doses adjusted according to echocardiographic LVEF) for 10 weeks.

Results: We enrolled 41 patients (mean $\pm$ SD age 56 $\pm$ 16 years; 59% female). At Week 10, 22 (55%) patients experienced an improvement of $\geq$ 1 New York Heart Association class; 11 (29%) became asymptomatic. Clinically relevant improvements in Kansas City Cardiomyopathy Questionnaire Clinical Summary Scores occurred in 22 (55%) patients. Symptom relief was paralleled by reductions in NT-proBNP levels (56%; $P < 0.001$) and high-sensitivity cardiac troponin I (22%; $P < 0.005$). Modest reductions in LVEF (mean $\pm$ SD) of −5.4% $\pm$ 10 to 64.6% $\pm$ 9.1 were observed. Three (8%) patients had asymptomatic reduction in LVEF < 50% (range: 41%–48%), all returning to normal after 2 weeks of

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washout. One patient with prior history of aborted sudden cardiac death experienced a fatal arrhythmia during the study.

Conclusions: Aficamten administration for symptomatic nHCM was generally safe and was associated with improvements in heart failure symptoms and cardiac biomarkers.

Trial registration: ClinicalTrials.gov Identifier: NCT04219826 (*J Cardiac Fail 2024;00:1−10*)

Key Words: Hypertrophic cardiomyopathy, nHCM, aficamten, cardiac myosin inhibitor.

Treatment of hypertrophic cardiomyopathy (HCM) is generally focused on improving heart failure (HF) symptoms in patients with obstructive HCM (oHCM), with repurposed medicines, invasive septal reduction and, more recently, targeted drug therapy with cardiac myosin inhibitors.[1−4] However, among the one-third of patients with HCM who do not have left ventricular outflow tract (LVOT) obstruction, a substantial proportion develop symptoms that impact daily life and, in some cases, progress to end-stage HF requiring heart transplantation.[5−8] There are multiple pathological mechanisms of symptoms in nHCM, but most patients demonstrate impaired left ventricular (LV) filling and small LV diastolic volume, resulting in increased left-sided filling pressures and decreased stroke volume despite normal or high LV ejection fraction (LVEF).

In contrast to oHCM, no medical therapies have been proven to improve symptoms or natural history in nonobstructive HCM (nHCM), underscoring the important unmet medical need.[5−7] Current treatment options are limited to off-label use of HF and antihypertensive medications, management of medical comorbidities and arrhythmias, diuretics for congestion, mitigation of sudden cardiac death risk with implantable defibrillators in patients at high risk, and consideration for heart transplantation in patients with refractory HF.[9,10]

Aficamten is a next-in-class cardiac myosin inhibitor designed to target the underlying pathophysiology thought to result in HF symptoms, including hypercontractility and diastolic dysfunction in HCM. Aficamten has favorable pharmacological properties, including a half-life of 3.5 days, a shallow exposure/response of LVEF with a wide therapeutic window, and no known drug-drug interactions.[11,12]

In the oHCM cohorts in the REDWOOD-HCM (Randomized Evaluation of Dosing With CK-274 in Obstructive Outflow Disease in HCM) trial (NCT04219826), aficamten was found to be safe and effective in reducing LVOT gradients and improving HF symptoms, echocardiographic parameters of diastolic function and cardiac biomarkers.[13−15] The encouraging efficacy and promising pharmacological and safety profiles supported this dose-finding, proof-of-concept study of aficamten in nHCM (Cohort 4).

Methods

Study Design

Cohort 4 of REDWOOD-HCM was a phase 2, open-label study in patients with symptomatic nHCM. Recruitment for Cohort 4 occurred at 15 academic centers in North America and Europe between March 22 and November 23, 2022. The study protocol was approved by local ethics committees. An independent data-monitoring committee periodically reviewed the study's data. All patients provided informed consent, and the study was done in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

Throughout the 10-week treatment period and 2 weeks after the last dose (washout period), patients underwent echocardiographic, laboratory and clinical evaluations. An additional phone visit was conducted at Week 14 (end of study). Patients completing the study were offered participation in an open-label, long-term extension study (Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of Aficamten in Adults With HCM) (FOREST-HCM; NCT04848506).

For the exploratory responder analysis, response was defined as a $\geq$ 50% reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels from baseline to Week 10, which has been associated with reductions in HF clinical endpoints,[16−18] and symptom improvement ($\geq$ 1 New York Heart Association [NYHA] class or $\geq$ 5 Kansas City Cardiomyopathy Questionnaire Clinical Summary Score [KCCQ-CSS] points).

Study Population

Eligible patients (18−85 years) were symptomatic (NYHA class II or III) with phenotypic nHCM, NT-proBNP $>$ 300 pg/mL, and LVEF $\geq$ 60% at baseline. Patients receiving beta-blockers, calcium channel blockers or ranolazine were required to be on stable dosages for $>$ 4 weeks prior to randomization.

Key exclusion criteria included history of recent septal-reduction therapy ($<$ 1 year from screening), phenocopies for HCM, any history of LVEF $<$ 45%, and paroxysmal or permanent atrial fibrillation (AF) requiring rhythm-

restoring treatment ≤ 6 months before screening. Inclusion/exclusion criteria are summarized in Supplementary Table S1.

Intervention

Aficamten was started at 5 mg orally daily on Day 1, and doses were adjusted at 2-week intervals in 5-mg increments to a maximum of 15 mg daily by Week 4. Doses were increased if the site-read LVEF was ≥ 55% (Weeks 2 and 4 only), maintained at the current dosage level for LVEF 50%−54%, decreased to the next lower dosage strength (or placebo if on 5 mg) if LVEF was between 40% and 50%, and discontinued if LVEF was < 40%. At Week 6, if LVEF was < 50%, the dosage was reduced to the prior dosage level. LVEF was measured at the site by an unmasked echocardiologist, who was not part of other study-related activities, and entered into the interactive web response system for dosage-adjustment purposes at Weeks 2, 4 and 6. LVEF data were not shared with the site investigators unless deemed necessary from a safety perspective. Full analysis of echocardiograms was subsequently carried out by the core laboratory to ensure consistent measurement methodology for later analyses and was not shared with sites or incorporated into dosage titration or maintenance monitoring during the study.

Aficamten was self-administered orally, daily, at home, except on study visit days when the dose was taken on site for pharmacokinetic sampling per protocol. Compliance was assessed at each visit based on the number of returned study drugs, which was documented in the source documents.

Endpoints

The primary objective was to determine the safety and tolerability of aficamten and the incidence of LVEF < 50%. Secondary and exploratory endpoints included proportion of patients with ≥ 1 class improvement in NYHA class; change from baseline in KCCQ-CSS, Seattle Angina Questionnaire 7-item Angina Frequency (SAQ7-AF), LVEF, NT-proBNP, and high-sensitivity cardiac troponin T and I (hs-cTnI); and the exposure/response relationship for aficamten on LVEF.

Statistical Analysis

This is the first study of aficamten in patients with nHCM, and analyses of dosage, pharmacokinetics, pharmacodynamics, and their relationships were descriptive. Continuous variables were summarized using number of patients with observations (n), mean, standard deviation (SD), median, and quartiles. Geometric means (% coefficient variation) were presented for variables not normally distributed. Categorical variables were summarized using counts and percentages. Patients were considered to have symptomatic angina at baseline if their SAQ7-AF score was ≤ 80; change from baseline in SAQ7-AF was summarized in these patients only. Change from baseline endpoints was tested using a paired *t* test. The relationship of aficamten to the change in LVEF was evaluated using a linear mixed-effect model for repeated measures with LVEF changes from baseline as the dependent variable, baseline as the covariate, and maximum day match post-dose pharmacokinetic concentration as the explanatory variable. Random participant effect was specified. Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

Study's Patients

The baseline characteristics of participants are shown in Table 1 and are generally reflective of patients seen clinically. We enrolled 41 patients who received ≥ 1 dose of aficamten; 1 was excluded from the efficacy analysis because of a serious violation of Good Clinical Practice, and 39 of 40 participants completed the treatment phase (Supplementary Fig. S1). All patients were initiated on aficamten 5 mg orally daily; final dosages at Week 10 were 10 mg daily in 5 (13%) patients and 15 mg daily in 35 (88%) patients. One patient suffered a fatal cardiac arrest soon after Week 6; 1 completed all on-treatment visits but withdrew before Week 12.

Measures of Symptom Burden (NYHA Class and KCCQ)

At Week 10, 22 of 40 (55%) patients showed ≥ 1 class improvement in NYHA: 11 (28%) with class III−II, 3 (8%) with class III−I, and 8 (20%) with class II−I. Of the remaining 18 patients, functional class remained unchanged in 15 (38%) patients; 1 (3%) experienced worsening of functional class, and 2 did not have Week 10 assessments (1 death, 1 not evaluated). Functional class subsequently returned toward baseline after aficamten was withdrawn during the washout period (Weeks 10−12) in 24 (62%) patients (Fig. 1, A) (Supplementary Fig. S2).

With aficamten treatment, health status as assessed by KCCQ-CSS improved from a mean ± SD baseline of 67 ± 20 to 78 ± 22 points at Week 10 (change from baseline 11 ± 15). Categorical assessment of changes in KCCQ-CSS revealed that 22 (56.4%) patients improved by ≥ 5 points, representing a clinically meaningful improvement in health status. Of the patients, 5 (13%) reported a small (5−9 points) improvement in health status, 7 (18%) demonstrated moderate to large (10−19 points) improvement, and 10 (25.6%) experienced large to very large (≥ 20 points) improvement. KCCQ-CSS remained unchanged for 14 (36%) patients, with 3 (7.7%) reporting worsening of health status; 1 did not complete the Week 10 KCCQ. Of the 22 patients experiencing a clinically significant improvement in KCCQ-CSS, 15 (68%) also showed

Table 1 Baseline characteristics

Characteristic	n = 40
Age, mean±SD (range), y	55.9±16.0 (22–82)
Sex, female, n (%)	24 (60)
Race, n (%)	
White	26 (65)
Black or African American	8 (20)
Asian	2 (5)
Other	4 (10)
BMI, mean±SD, kg/m^2	30.0±7.2
NYHA class, n (%)	
II	21 (53)
III	19 (48)
Kansas City Cardiomyopathy Questionnaire Clinical Summary Score, mean±SD	67.1±20.3
Seattle Angina Questionnaire 7-item Angina Frequency, mean±SD	63.1±11.1
Atrial fibrillation/flutter, n (%)	4 (10)
Mid-cavitary obstruction, n (%)	7 (18)
Positive family history of HCM, n (%)	11 (28)
Prior septal reduction therapy n (%)	5 (12.5)
Background HCM therapy, n (%)	
Beta-blocker	29 (73)
Calcium channel blocker	4 (10)
NT-proBNP, median (IQR), pg/mL	1105.5 (756–2082)
High-sensitivity cardiac troponin I, median (IQR), ng/L	22.7 (9.1–74.6)
Echocardiography	
Left ventricular ejection fraction, %±SD	70±7.3
Maximal wall thickness, mean±SD, mm	19.2±4.8
Lateral e', mean±SD, m/s[1]	6.9±2.7
Septal e', mean±SD, cm/s[1]	4.3±1.3
E/e', mean±SD[1]	11.6±4.9
Left atrial volume index, mean±SD, mL/m^2	34.2±11.3
Left end-systolic volume index, mean±SD, mL/m^2	8.9±3.4
Left end-diastolic volume index, mean±SD, mL/m^2	29.8±8.3
Left ventricular mass index, mean±SD, g/m^2	128.8±30.9

[1]Data shown for patients not in atrial fibrillation (n=36).BMI, body mass index; CSS, Clinical Summary Score; e', lateral early diastolic myocardial velocity; HCM, hypertrophic cardiomyopathy; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

improvements in NYHA class at Week 10. The KCCQ-CSS (mean ± SD) showed a smaller, persistent increase from baseline to Week 12, after washout, of 8 ± 14 points, from 67 ± 20–75 ± 22 (Fig. 1, B, C).

Angina Burden

In 13 patients who reported symptomatic angina at baseline (SAQ7-AF score ≤ 80), aficamten was associated with a mean ± SD increase in SAQ7-AF of 13 ± 16 points from baseline to Week 10, including 9 who had a ≥ 10-point improvement. Angina frequency increased during the washout period (Fig. 1, D).

Cardiac Biomarkers

Aficamten treatment was associated with a significant improvement in NT-proBNP levels from a median (IQR) of 1105 (756–2082) pg/mL at baseline to 593 (316–1087) pg/mL by Week 10, representing a proportional reduction of 56% ($P < 0.0001$). There appeared to be a dose-dependent reduction in NT-proBNP levels from baseline to Week 6, without evidence of hysteresis beyond the dosage adjustment period (Fig. 2).

Aficamten treatment also resulted in significant reductions of hs-cTnI from a median (IQR) of 23 (9–75) ng/mL at baseline to 18 (7–95) ng/mL by Week 10, a proportional reduction of 22% ($P < 0.005$). Biomarker values returned to baseline after the 2-week washout period (Fig. 2).

Change in Systolic Function

There was a modest mean ± SD reduction in LVEF by 5% ± 10 by Week 10 ($P < 0.0001$), although it remained within normal limits (65% ± 9.1) (Fig. 3, A). The exposure/response relationship for aficamten on LVEF revealed a slope of -0.01% per ng/dL, similar to that of oHCM cohorts ($P = 0.4$) (Fig. 3, B) (Supplementary Fig. S4). The absolute mean ± SD global longitudinal strain at baseline and Week 10 were unchanged at 12.7% ± 3.6 and 12.5% ± 3.0, respectively.

Echocardiographic Markers of Diastolic Function

After excluding 4 patients with baseline AF, there was a statistically significant improvement in septal and lateral mitral annular early diastolic tissue velocity (e') (mean ± SD). From baseline to Week 10, lateral and septal e' improved from 7 ± 3 cm/s to 8 ± 3 cm/s (Δ = 1.1 ± 1.9, 95% CI 0.46–1.76; $P = 0.001$), and 4 ± 1 to 5 ± 2 cm/s (Δ = 1.1 ± 1.2; 95% CI 0.66–1.48; $P < 0.001$).

The mean ratio of mitral early-inflow velocity (E) to lateral e' (E/e'), an echocardiographic marker of filling pressures, was normal at baseline (11.6 ± 4.9). At Week 10, the mean lateral E/e' was 10.9 ± 4.0 (similar to changes in septal E/e'). The left atrial volume index, another measure of filling pressures, mildly increased both at baseline (32.9 ± 9.9 mL/m^2) and at Week 10 (34.8 ± 10.4 mL/m^2), with no significant difference (Δ = 1.9 ± 5.8 mL/m^2; $P = 0.06$) detected over the 10-week treatment period (Supplementary Fig. S3). Additionally, data available from all patients showed a small, but statistically significant, decrease in the maximal wall thickness (−0.8 mm, 95% CI 1.1–0.5) in the setting of similar LV mass index (−3.8 g/m^2, 95% CI 12.4–4.8).

Exploratory Responder Analysis

Subgroup analyses were performed to evaluate the impact of specific baseline characteristics on treatment heterogeneity, including familial HCM (either a known pathogenic gene variant or a positive family history), evidence of abnormal E/e' or elevated hs-cTnI, presence of midcavitary obstruction, or baseline obesity (body mass index ≥ 30 kg/m^2). At a significance level of $P < 0.05$,

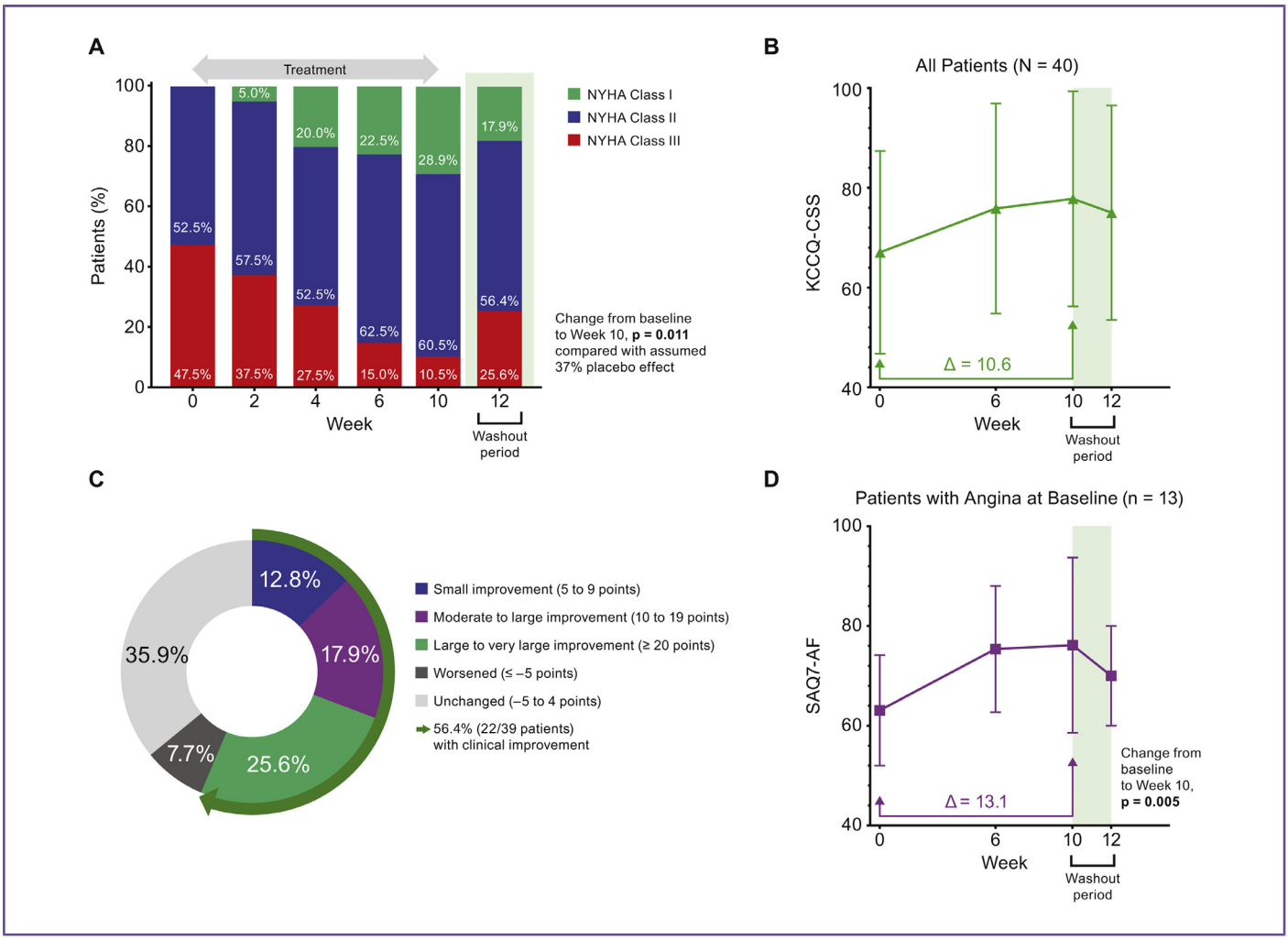


Fig. 1. Symptom burden and functional capacity over a 10-week aficamten treatment period and 2-week washout. A, Categorical change in NYHA class. B, [a]Mean change in KCCQ-CSS. C, Categorical change in KCCQ-CSS. D, [a]Change in SAQ7-AF score. [a]Data are presented as mean and SD. KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; NYHA, New York Heart Association; nHCM, nonobstructive hypertrophic cardiomyopathy; SAQ7-AF, Seattle Angina Questionnaire-Angina Frequency; SD, standard deviation.

there were no clear differentiators of response according to any of these baseline characteristics.

Safety

Aficamten was generally well tolerated; most adverse events were reported as being mild or moderate (61%) in severity (Table 2). One patient reported fatigue (nonserious AE) and requested a dosage reduction from 15 mg to 10 mg at Week 9. Four serious AEs (SAEs) occurred during the treatment period, none of which were deemed related to aficamten by investigators, and none of which resulted in early termination or drug discontinuation.

Three (8%) patients were had LVEF < 50% according to the core echocardiography laboratory at Week 10, all in the absence of signs or symptoms of HF. Of these patients, 2 had permanent AF/flutter, 1 of whom was experiencing rapid ventricular response rates prompting a change in therapy. The third patient remained in sinus rhythm throughout the study but had a history of paroxysmal AF and reported complete relief of symptoms (NYHA class I) at Week 10. All 3 had normal LVEFs after the 2-week washout period (Supplementary Table S2).

One patient suffered a fatal cardiac arrest shortly after the Week 6 study visit. This event occurred in a 43-year-old severely symptomatic (NYHA class III) female with a known pathogenic gene mutation, a history of long-QT syndrome with 2 prior aborted sudden-death episodes, and an implantable cardioverter defibrillator (ICD) in situ. The patient had undergone a per protocol Week 6 evaluation 2 days prior to her death and reported overall improvements in her symptoms and functional capacity (NYHA class II); there were also improvements in both NT-proBNP levels and hs-cTnI (1103−368 pg/mL and 5.8−< 3.5 ng/L, respectively). The Week 6 echocardiogram showed LVEF > 70%, her global longitudinal strain had

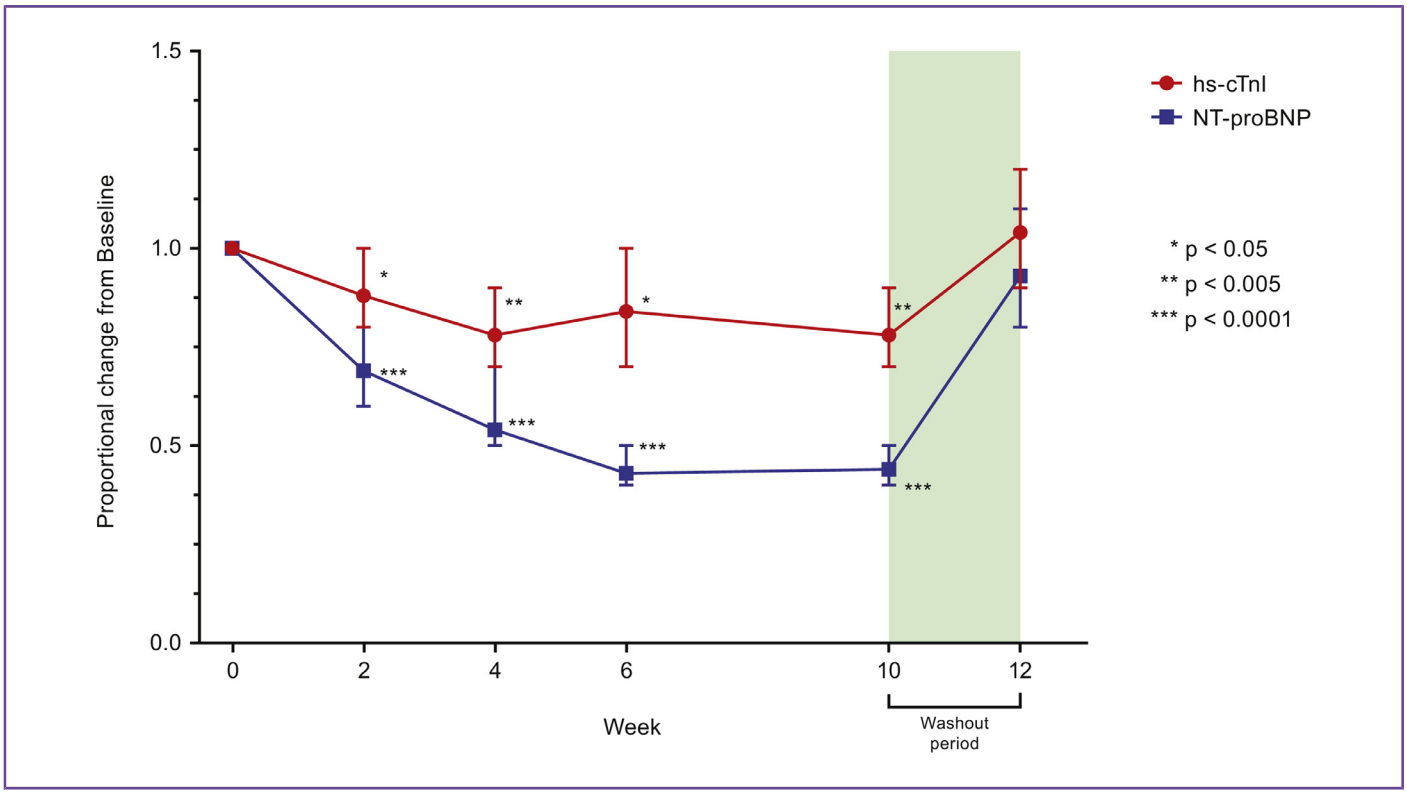


Fig. 2. Proportional change from baseline in cardiac biomarkers. Data are presented as mean proportional change and 95% CI. CI, confidence intervals; hs-cTnI, high-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

improved compared with baseline, her interval corrected using Fridericia's formula (QTcF) did not increase (463 ms on Day 1 and Week 6), and her plasma drug concentrations were all within the expected range. There were 2 witnessed ICD discharges during resuscitation, but the ICD was not studied, and no postmortem was performed, in accordance with the family's wishes. The investigator and data safety monitoring board agreed that the event was probably related to the underlying disease and not to the study's drug. No other patient in the study had sudden cardiac death or an appropriate ICD intervention during the study. Of the other patients, 3 experienced nonrelated

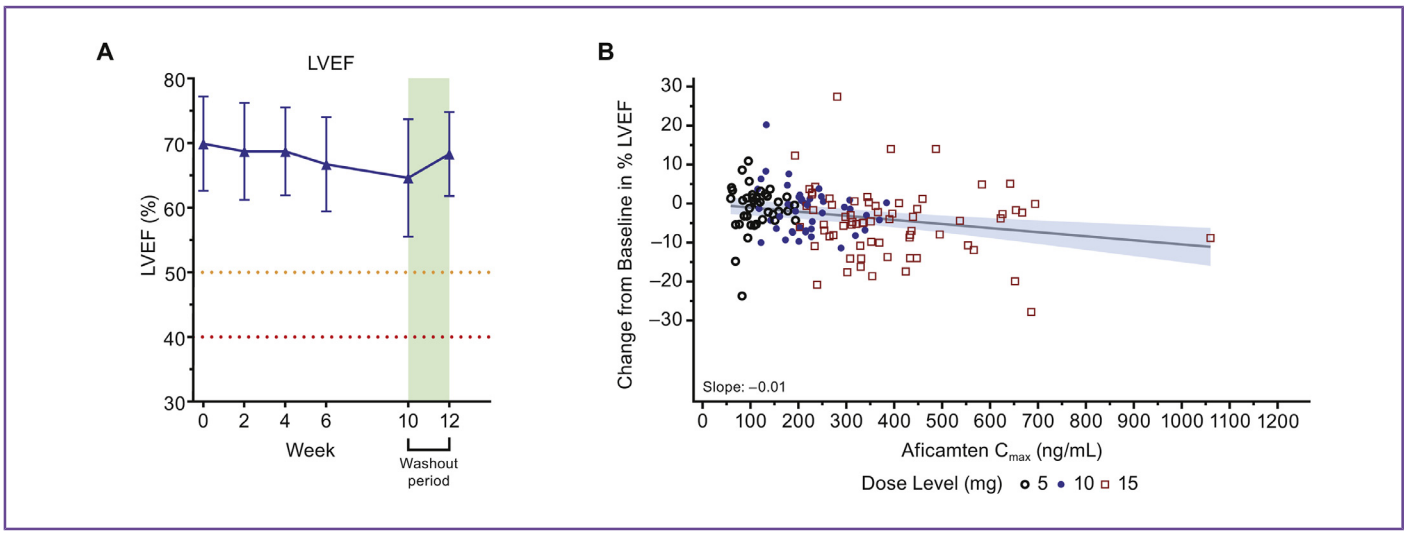


Fig. 3. Effect of aficamten on LVEF. LVEF measured by A, serial echocardiograms[a] and B, in relationship to aficamten plasma concentration. [a]Data are presented as mean and SD. Horizontal dotted lines represent the thresholds at which IP was down-titrated to the previous dosage (yellow) or was discontinued (red). C_{max}, maximum plasma concentration; aficamten, ; LVEF, left ventricular ejection fraction; SD, standard deviation.

Table 2 Treatment-emergent adverse events

n = 41	n (%)
Patients with ≥1 TEAE	28 (68.3)
Occurred in ≥10% of patients	
Fatigue	7 (17.1)
Dizziness	4 (9.8)
Patients with TESAEs	4 (9.8)
Myasthenia gravis	1 (2.4)
Atrial fibrillation	1 (2.4)
Cardiac arrest	1 (2.4)
Bronchitis	1 (2.4)
Patients with fatal TEAEs	1 (2.4)
Patients with TEAEs leading to drug discontinuation[1]	0
Patients with severe TEAEs	3 (7.3)
Patients with moderate TEAEs	16 (39.0)
Patients with related AEs per investigator	4 (9.8)

All patients enrolled in the study, including the patient excluded from the efficacy analysis, are included in the safety analysis.

[1]One patient self-interrupted the study drug for 2 days because of the AE of palpitations in the setting of upper respiratory infection. Patient restarted study drug upon instruction from site. Palpitations resolved. AE, adverse event; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

SAEs of bronchitis, myasthenia gravis and new-onset AF (none requiring hospitalization).

Discussion

In this proof-of-concept phase 2 study, aficamten therapy was well tolerated and significantly improved angina and HF symptoms in the majority of patients with nHCM. There were also substantial improvements in several clinically relevant exploratory endpoints (change from baseline to Week 10 in NYHA functional class and symptoms, cardiac biomarkers), and the relationship of LVEF to plasma drug concentration was further established. Notably, the changes in clinical and imaging variables occurred over a relatively short treatment period (10 weeks), with patients exposed to maximally tolerated dosages of aficamten after 4 weeks of the 10-week treatment period.

Symptom improvement of ≥ 1 NYHA functional class occurred in more than half of the patients treated with aficamten, including 28% who became asymptomatic. Additionally, 35% of patients improved from severe HF symptoms to being mildly symptomatic or asymptomatic. This is particularly relevant, because patients with nHCM represent 1 of the most challenging groups in the entire HCM spectrum, with no proven therapies other than heart transplantation, which is available to only a minority and is associated with all the complexities of organ transplantation.

It is also notable that more than half of the patients showed a clinically relevant improvement in health status (≥ 5 points) as assessed by the KCCQ, including 44% of patients who experienced a moderate to very large improvement in overall health status. This is important because the KCCQ, a recently validated instrument for quantification of patient-reported health status in HCM, provides a patient-centric, physician-independent assessment. In this regard, 7 of the 22 patients who reported clinically significant improvement in the KCCQ were not concurrently assessed as having improvement in NYHA class, highlighting the importance of patients' self-assessment.

The improvements in symptom burden and health status with aficamten were probably achieved through the effects of the drug on various aspects of the pathophysiology responsible for HF in nHCM. By reducing the proportion of actively engaged actin-myosin cross-bridges in the cardiac sarcomere, aficamten results in a modest overall reduction in contractility and appears to improve myocardial relaxation. This mechanism of benefit is supported both by the observed changes in noninvasive measures of diastolic function with echocardiography and by the substantial reductions in NT-proBNP levels. In addition, through the effects of aficamten in improving myocardial relaxation, LV wall stress is likely to be decreased. This may result in improved myocardial blood flow and, combined with decreased systolic work, may result in less ischemia, as supported by both a reduction in angina frequency and lowering of hs-cTnI. Aficamten is a cardiac myosin ATPase inhibitor, which, consequently, may also directly reduce ATP consumption and impart a favorable effect on overall myocardial energetics.[12]

An earlier phase 2 study testing the hypothesis that myosin inhibition may favorably impact patients with nHCM was the 16-week pharmacokinetic-guided, placebo-controlled trial with mavacamten, MAVERICK-HCM (Mavacamten in Adults With Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy).[19] That study did not demonstrate a difference in either NYHA class or KCCQ-CSS, but this could be explained by various important study differences. First, in MAVERICK-HCM, drug dosing was based on prespecified and arbitrary plasma drug-concentration targets, whereas REDWOOD-HCM Cohort 4 dosed aficamten to the maximum tolerated dosage available. There were also comparatively more patients with NYHA class III and higher levels of NT-proBNP in REDWOOD-HCM Cohort 4. Despite the higher degree of disease burden, the more rapid dosage escalation of aficamten was well tolerated, with only 3 patients experiencing reversible LVEF of < 50%, all of whom had histories of atrial dysrhythmias, and none of whom experienced HF symptoms. It is encouraging to note that no SAEs were attributed to aficamten, and no patients discontinued treatment owing to AEs during the study.

Achieving a balance between relieving symptoms and avoiding exaggerated pharmacodynamic effects on LVEF is the desired goal for the proposed treatment paradigm, and aficamten may be uniquely suited to achieve this. The shallow exposure/response relationship, allowing for gradual and predictable changes in LVEF over a wide range of dosages and a half-life that enables dosage adjustment as early as every 2 weeks, translates into the potential to achieve the

maximally tolerated dosage within a short time. Analyses of plasma drug concentrations vs change from baseline in LVEF in this cohort suggest that the slope of this relationship remained shallow, in accordance with the predictions from preclinical and healthy volunteer studies and similar to that of patients with oHCM (Supplementary Fig. S4).[11] Importantly, this analysis assumes linearity of the slope of LVEF change over drug concentrations, and the maximal dosage used in oHCM was 30 mg (Cohorts 1–3) vs 15 mg in nHCM (Cohort 4).

Limitations

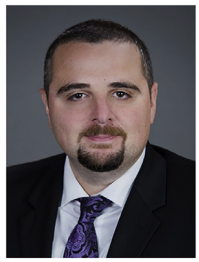
Our study has several limitations. First, this was a small open-label study, and there is a potential for bias on subjective endpoints (NYHA class, KCCQ and SAQ7-AF). However, we observed significant decreases in plasma cardiac biomarkers and echocardiographic measures, which reveal directionally similar improvements and strengthen clinical observations.[20–23] Second, this was a short dosage-finding study; therefore, the study was unable to address the safety of longer-term treatment. Finally, objective measures of exercise capacity with cardiopulmonary exercise testing were not assessed.

Conclusions

In this preliminary and exploratory study, treatment with aficamten, a next-in-class cardiac myosin inhibitor, was associated with improvements in a number of measures of clinical efficacy, including a reduction in both HF symptoms and angina in a substantial proportion of patients. This is underscored by concomitant improvements in noninvasive measures of diastolic function and wall stress, which elevates the potential of aficamten as an effective treatment for nHCM. This study will form the basis for the larger phase-3 placebo-controlled study (Assessment Comparing aficamten to Placebo on Cardiac Endpoints In Adults with Non-Obstructive HCM (ACACIA-HCM, NCT06081894), which will include both the clinically meaningful impact on health status as well as objective measures of exercise performance.

Lay Summary

Nonobstructive hypertrophic cardiomyopathy (nHCM) is a disease in which the heart muscle becomes abnormally thickened. There are no proven medical therapies. Aficamten is a new cardiac myosin inhibitor designed to target the underlying cause of HCM. REDWOOD-HCM Cohort 4 was the first study to explore the efficacy and safety of aficamten in people with symptoms of nHCM. Most patients reported improved health and functional status. There was also significant decrease in blood levels of biomarkers indicating excessive pressure within the heart and damage to heart muscle cells. These results support a larger placebo-controlled study of aficamten for people with nHCM (ACACIA-HCM).



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Proposed tweet

In the open-label phase 2 trial REDWOOD-HCM Cohort 4, doses of aficamten were assessed for symptomatic nonobstructive HCM. Treatment was well tolerated and resulted in improvements in KCCQ, NYHA, angina, and biomarkers, supporting a larger pivotal phase 3 trial, ACACIA-HCM.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2024.02.020.

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