

Phase 2 Study of Aficamten in Patients With Obstructive Hypertrophic Cardiomyopathy



Martin S. Maron, MD,^a Ahmad Masri, MD,^b Lubna Choudhury, MD,^c Iacopo Olivetto, MD,^d Sara Saberi, MD,^e Andrew Wang, MD,^f Pablo Garcia-Pavia, MD, PhD,^{g,h} Neal K. Lakdawala, MD,ⁱ Sherif F. Nagueh, MD,^j Florian Rader, MD,^k Albree Tower-Rader, MD,^l Aslan T. Turer, MD,^m Caroline Coats, MD, PhD,ⁿ Michael A. Fifer, MD,¹ Anjali Owens, MD,^o Scott D. Solomon, MD,ⁱ Hugh Watkins, MD, PhD,^p Roberto Barriaes-Villa, MD,^q Christopher M. Kramer, MD,^r Timothy C. Wong, MD,^s Sharon L. Paige, MD, PhD,^t Stephen B. Heitner, MD,^t Stuart Kupfer, MD,^t Fady I. Malik, MD, PhD,^t Lisa Meng, PhD,^t Amy Wohltman, ME,^t Theodore Abraham, MD,^u on behalf of the REDWOOD-HCM Steering Committee and Investigators

ABSTRACT

BACKGROUND Left ventricular outflow tract (LVOT) obstruction is a major determinant of heart failure symptoms in obstructive hypertrophic cardiomyopathy (oHCM). Aficamten, a next-in-class cardiac myosin inhibitor, may lower gradients and improve symptoms in these patients.

OBJECTIVES This study aims to evaluate the safety and efficacy of aficamten in patients with oHCM.

METHODS Patients with oHCM and LVOT gradients ≥ 30 mm Hg at rest or ≥ 50 mm Hg with Valsalva were randomized 2:1 to receive aficamten ($n = 28$) or placebo ($n = 13$) in 2 dose-finding cohorts. Doses were titrated based on gradients and ejection fraction (EF). Safety and changes in gradient, EF, New York Heart Association functional class, and cardiac biomarkers were assessed over a 10-week treatment period and after a 2-week washout.

RESULTS From baseline to 10 weeks, aficamten reduced gradients at rest (mean difference: -40 ± 27 mm Hg, and -43 ± 37 mm Hg in Cohorts 1 and 2, $P = 0.0003$ and $P = 0.0004$ vs placebo, respectively) and with Valsalva (-36 ± 27 mm Hg and -53 ± 44 mm Hg, $P = 0.001$ and <0.0001 vs placebo, respectively). There were modest reductions in EF ($-6\% \pm 7.5\%$ and $-12\% \pm 5.9\%$, $P = 0.007$ and $P < 0.0001$ vs placebo, respectively). Symptomatic improvement in ≥ 1 New York Heart Association functional class was observed in 31% on placebo, and 43% and 64% on aficamten in Cohorts 1 and 2, respectively (nonsignificant). With aficamten, N-terminal pro-B-type natriuretic peptide was reduced (62% relative to placebo, $P = 0.0002$). There were no treatment interruptions and adverse events were similar between treatment arms.

CONCLUSIONS Aficamten resulted in substantial reductions in LVOT gradients with most patients experiencing improvement in biomarkers and symptoms. These results highlight the potential of sarcomere-targeted therapy for treatment of oHCM. (J Am Coll Cardiol 2023;81:34–45) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



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From the ^aLahey Hospital and Medical Center, Burlington, Massachusetts, USA; ^bOregon Health & Science University, Portland, Oregon, USA; ^cNorthwestern University, Chicago, Illinois, USA; ^dAzienda Ospedaliera Universitaria Careggi, Florence, Italy; ^eUniversity of Michigan Medical Center, Ann Arbor, Michigan, USA; ^fDuke University Hospital, Durham, North Carolina, USA; ^gHospital Universitario Puerta de Hierro de Majadahonda, IDIPHISA, CIBERCV, Madrid, Spain; ^hCentro Nacional de Investigaciones Cardiovasculares, Madrid, Spain; ⁱBrigham and Women's Hospital, Boston, Massachusetts, USA; ^jMethodist DeBakey Heart and Vascular Center, Houston, Texas, USA; ^kCedars Sinai Medical Center, Los Angeles, California, USA; ^lMassachusetts General Hospital, Boston, Massachusetts, USA; ^mUT Southwestern Medical Center, Dallas, Texas, USA; ⁿUniversity of Glasgow, Glasgow, United Kingdom; ^oUniversity of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA; ^pUniversity of Oxford, Oxford, United Kingdom; ^qComplejo Hospitalario Universitario de A Coruña, A Coruña, Spain; ^rUniversity of Virginia Health System, Charlottesville, Virginia, USA; ^sUniversity of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA; ^tCytokinetics Incorporated, South San Francisco, California, USA; and the ^uUniversity of California, San Francisco, San Francisco, California, USA.

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The strongest determinant of progressive heart failure symptoms in patients with hypertrophic cardiomyopathy (HCM) is left ventricular outflow tract (LVOT) obstruction.^{1–4} Hypercontractility of the left ventricle (LV) is a major contributor to the mechanism of outflow obstruction by promoting mitral valve-ventricular septal contact and the resultant pressure gradient between the LV cavity and systemic circulation.^{1,5} Current pharmacologic therapy provides incomplete relief of heart failure symptoms in many patients with obstructive HCM (oHCM), often due to suboptimal gradient reduction and/or off-target adverse drug effects, underscoring an important unmet treatment need for this disease.^{2–6}

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Recently, cardiac myosin inhibitors have shown the potential to reduce cardiac contractility and lower LVOT gradients, representing a potentially novel medical therapy to improve heart failure symptoms and functional capacity in patients with oHCM.^{7–10} This clinical benefit was shown by the first-in-class oral myosin inhibitor mavacamten as reported in the phase 3 clinical trial EXPLORER-HCM (Clinical Study to Evaluate Mavacamten [MYK-461] in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy).⁸

Aficamten (formerly CK-3773274) is a next-in-class selective inhibitor of cardiac myosin that acts by binding directly to cardiac myosin at a distinct allosteric binding site.¹¹ As a result, it reduces the number of actin-myosin cross-bridges,¹¹ which are responsible for the myocardial hypercontractility present in HCM (Central Illustration). In a phase I study of healthy participants, aficamten reduced myocardial contractility in a dose-dependent manner and was well tolerated and associated with a number of key and potentially favorable pharmacologic features, including a half-life enabling dose-titration every 2 weeks, a shallow exposure-response relationship, reversibility of drug effect within 24 hours of discontinuing of dosing, and a lack of significant drug-drug interactions.^{11,12}

In this phase II trial (REDWOOD-HCM; Randomized Evaluation of Dosing With CK-3773274 in Obstructive Outflow Disease in HCM; NCT04219826), the safety and tolerability of aficamten were

studied in patients with symptomatic oHCM across a range of doses. Additionally, the effect on several clinically relevant disease variables was assessed.

METHODS

STUDY DESIGN. REDWOOD-HCM was a phase II, multicenter, randomized, placebo-controlled, double-blind, dose-finding study in patients with symptomatic oHCM performed between January 31, 2020, and May 25, 2021, at 30 academic centers in North America and Europe. The protocol was approved by site-specific Institutional Review Boards and funded by Cytokinetics. Employees of Cytokinetics as well as the academic investigators participated in data analysis and vouch for the accuracy of the data. An independent data-monitoring committee regularly reviewed the unblinded study data to ensure patient safety. All patients provided informed consent, and the study was performed in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

Two sequential cohorts with overlapping doses were enrolled. After a 4-week screening period, eligible patients were randomized 2:1 to once-daily aficamten vs placebo. Patients started at the lowest dose and would escalate up to each of 2 higher doses of aficamten adjusted based on echocardiographic criteria during the initial 4 weeks of the study, and treatment continued for an additional 6 weeks (total 10 weeks of treatment). Throughout the 10-week treatment period, and 2 weeks after the last dose, patients underwent echocardiographic, laboratory (including serum drug concentration), and clinical evaluations. An additional clinical follow-up was conducted at end-of-study, 4 weeks after the last dose (Supplemental Table 1). Both cohorts were designed to evaluate the safety and tolerability of aficamten, and to characterize the pharmacodynamically active dose that might be used in a future phase III trial in oHCM.

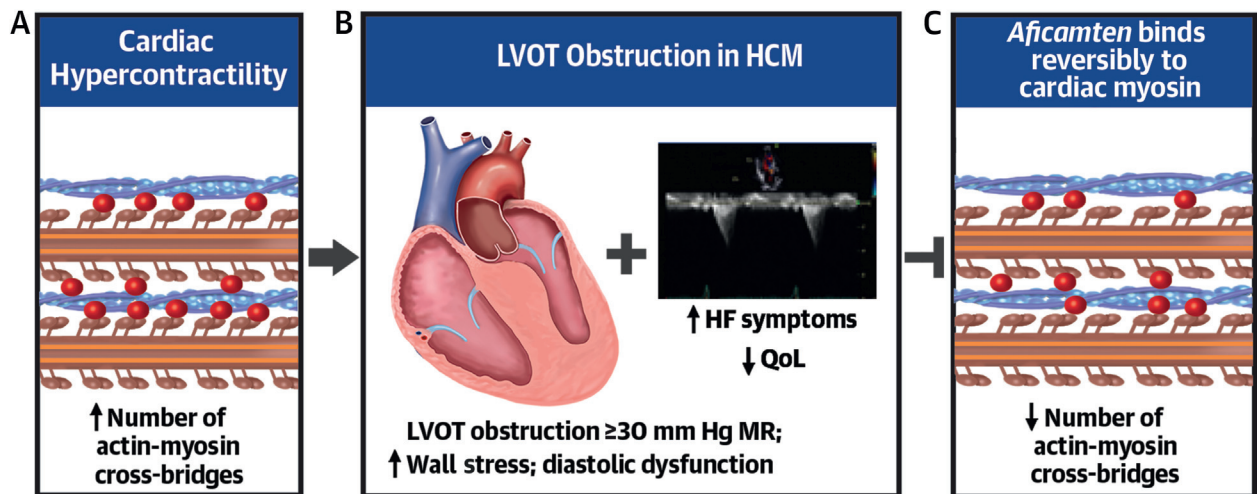
STUDY POPULATION. Briefly, eligible patients included adult males and females 18 to 85 years of age with a clinical diagnosis of symptomatic oHCM (New York Heart Association [NYHA] functional class II or III)

ABBREVIATIONS AND ACRONYMS

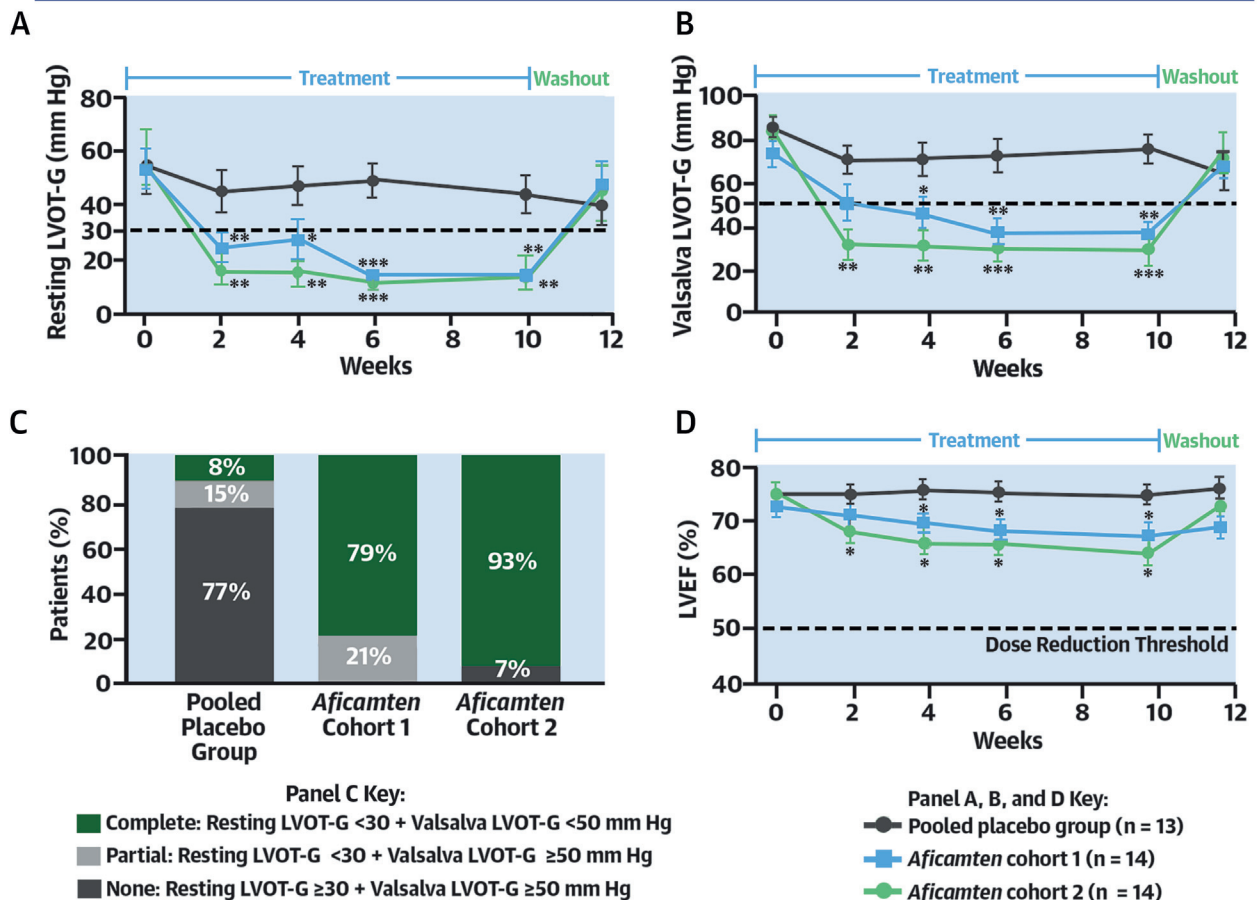
EF = ejection fraction
HCM = hypertrophic cardiomyopathy
LV = left ventricular
LVOT = left ventricular outflow tract
NYHA = New York Heart Association
SAE = serious adverse event

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

CENTRAL ILLUSTRATION Aficamten in Obstructive Hypertrophic Cardiomyopathy



REDWOOD-HCM Cohort 1 and 2: Phase II, Randomized (2:1), Placebo-Controlled Study of Aficamten in Symptomatic oHCM



based on a maximal LV wall thickness of ≥ 15 mm (or ≥ 13 mm with a positive family history of HCM or with a known disease-causing gene mutation) and echocardiographic evidence severe LVOT obstruction (resting LVOT gradient ≥ 50 mm Hg or resting LVOT gradient ≥ 30 mm Hg and < 50 mm Hg but with Valsalva LVOT gradient ≥ 50 mm Hg). Patients were required to have a left ventricular ejection fraction (LVEF) $\geq 60\%$ at baseline. Patients on background therapy (beta-blockers, calcium-channel blockers, or ranolazine) were required to be on stable doses for > 4 weeks before enrollment.

Key exclusion criteria included: history of prior septal reduction therapy or a plan for this during the study period, aortic stenosis or fixed subaortic obstruction, known phenocopy for HCM (eg, Noonan syndrome, Fabry disease, and amyloidosis), a history of LVEF $< 45\%$, paroxysmal or permanent atrial fibrillation requiring rhythm-restoring treatment ≤ 6 months before screening, paroxysmal atrial fibrillation during the screening period, obstructive coronary artery disease, documented history of myocardial infarction, and prior treatment with cardiotoxic agents. Treatment with disopyramide within 4 weeks of screening was not allowed. A full list of the inclusion and exclusion criteria is provided in [Supplemental Table 2](#).

INTERVENTION. In Cohort 1, aficamten was started at 5 mg, and doses were titrated at Weeks 2 and 4, if echocardiographic criteria were met, to 10 mg and then 15 mg; patients in Cohort 2 were started on 10 mg of aficamten, and doses were adjusted at the same time points to 20 mg and then 30 mg if echocardiographic criteria were met.

At Weeks 2 and 4, an echocardiogram was performed 2 hours after study drug administration. If the echocardiogram showed an LVEF $\geq 50\%$ and either a resting LVOT gradient ≥ 30 mm Hg or a Valsalva gradient ≥ 50 mm Hg, patients were uptitrated to the next higher dose, respectively ([Supplemental Table 3](#)). If at Weeks 2 or 4 these echocardiographic parameters were not met, patients remained on the

same dose. If LVEF was $< 50\%$ at any time, patients underwent dose reduction, or were placed on placebo if on the starting dose. If the LVEF was $< 40\%$, the study drug was permanently discontinued. An unblinded sonographer at the study site performed the echocardiograms and an unblinded cardiologist who was not the study investigator interpreted the echocardiogram images, measured the LVOT gradient and LVEF, and entered the results into an interactive web response system which dispensed the proper dose based on the echocardiographic criteria. The site investigator was blinded to the echocardiograms and results. Because LVEF and LVOT gradients were determinants of study eligibility per investigator interpretation, the baseline values reported in [Table 1](#) are those obtained from the site. All other echocardiographic data were determined by a central core laboratory blinded to treatment assignment.

Representatives of Cytokinetics and the steering committee conducted interim reviews of the blinded safety, echocardiographic, and deidentified pharmacokinetic data available from Cohort 1 to recommend the dose levels of aficamten to be administered in Cohort 2. The unblinded data-monitoring committee reviewed the recommendation along with the available safety, pharmacokinetic, and echocardiographic data, and ratified the recommendation for the doses explored in Cohort 2.

ENDPOINTS. The primary objective was to determine the safety and tolerability of different doses of aficamten in patients with symptomatic oHCM in terms of patients' incidence of reported adverse events, serious adverse events (SAEs), and LVEF $< 50\%$. Key secondary and exploratory endpoints included the change from baseline in resting and Valsalva LVOT gradients over 10 weeks of treatment, the proportion of patients with complete hemodynamic response (defined as resting and Valsalva LVOT gradients < 30 mm Hg and < 50 mm Hg, respectively), and the change from baseline in LVEF, N-terminal pro-B-type natriuretic peptide (NT-proBNP), hs-troponin, and NYHA functional class.

CENTRAL ILLUSTRATION Continued

(A) Cardiac sarcomere in hypertrophic cardiomyopathy (HCM) with increased number of actin-myosin cross-bridges resulting in myocardial hypercontractility. (B) Increased cardiac contractility contributes to the mechanism of left ventricular outflow tract (LVOT) obstruction, a major determinant of heart failure symptoms and decreased quality of life in patients with HCM. (C) Aficamten binds selectively and reversibly to myosin, reducing actin-myosin cross-bridge interactions and decreasing contractility. (Bottom Panel) Impact of aficamten on LVOT gradients and ejection fraction. Changes over time in aficamten-treated Cohorts 1 and 2 and pooled placebo groups in LVOT gradients at rest (A) and following Valsalva maneuver (B). Mean over time is shown, error bars indicate the standard error. (C) Bar graph showing proportion of patients with HCM according to hemodynamic response at completion of the 10-week treatment period. (D) Changes in LVEF over time. Error bars are SDs. LVEF = left ventricular ejection fraction; LVOT-G = left ventricular outflow tract gradient; QoL = quality of life. Asterisks indicate comparison of mean change in each aficamten cohort with the placebo group. * $P < 0.05$. ** $P < 0.01$. *** $P < 0.0001$.

TABLE 1 Baseline Demographic and Clinical Characteristics

	Pooled Placebo (n = 13)	Aficamten Cohort 1 (n = 14)	Aficamten Cohort 2 (n = 14)	Pooled Aficamten (n = 28)
Age, y	59 (53-64)	59 (39-67)	57 (53-72)	57 (26-33)
Female	8 (62)	4 (29)	11 (79)	15 (54)
White	12 (92)	14 (100)	14 (100)	28 (100)
BMI, kg/m ²	26 (25-32)	30 (26-34)	28 (26-32)	39 (26-33)
NYHA functional class				
II	11 (85)	10 (71)	7 (50)	17 (61)
III	2 (15)	4 (29)	7 (50)	11 (39)
NT-proBNP, pg/mL	532 (129-958)	206 (123-755)	549 (297-1,438)	388 (202-1,261)
High-sensitivity cardiac troponin I, ng/mL	8 (3-38)	16 (7-83)	8 (5-19)	12 (5-29)
Basal interventricular septal wall thickness, mm	16 (13-18)	18 (15-20)	16 (14-18)	17 (14-19)
Posterior wall thickness, mm	11 (11-12)	13 (12-14)	11 (11-12)	12 (11-14)
LAVI, mL/m ²	30 (28-37)	32 (25-37)	34 (27-38)	33 (27-38)
LVEDD, mm	40 (37-42)	39 (35-44)	39 (35-42)	39 (35-42)
LVEF, % ^a	75 (69-75)	70 (65-78)	70 (65-80)	70 (65-79)
LVOT-G at rest, mm Hg ^a	71 (44-94)	45 (37-67)	66 (50-81)	53 (42-70)
LVOT-G with Valsalva, mm Hg ^a	89 (80-105)	83 (68-90)	91 (69-100)	84 (69-100)
Medications				
Beta-blocker	11 (85)	10 (71)	11 (79)	21 (75)
Calcium-channel blocker	2 (15)	5 (36)	2 (14)	7 (25)

Values are median (IQR) or n (%). ^aSite-reported echocardiographic values.
 BMI = body mass index; LAVI = left atrial volume index; LVEDD = left ventricular end diastolic dimension;
 LVEF = left ventricular ejection fraction; LVOT-G = left ventricular outflow tract gradient;
 NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

STATISTICAL ANALYSIS. This was the first study of aficamten in patients with oHCM; the analyses of dose, pharmacodynamics, and their relationships are descriptive and hypothesis-generating in nature. The sample size was not chosen based on statistical considerations from an efficacy standpoint; however, approximately 18 participants per cohort is considered adequate for the initial evaluation of safety and tolerability. The analyses evaluated the treatment effect on secondary and exploratory endpoints related to the change from baseline to Week 10 in patients receiving placebo or those receiving aficamten in patients who received ≥ 1 dose of study drug and had a baseline and ≥ 1 postbaseline core-laboratory echocardiography assessment. Analyses were conducted by cohort with placebo pooled across both cohorts.

Treatment differences for echocardiographic data at Week 10 by cohort were estimated using an analysis of covariance model that included change from baseline as the dependent variable and the baseline value as a covariate. The terms for treatment (aficamten or pooled placebo), visit, and treatment-by-visit interaction were included as fixed effects with

the unstructured variance-covariance structure. Least-squares (LS) means in each treatment arm as well as the difference of the LS means were provided along with the 90% CI given the exploratory nature of the study. Logistic regressions were used to estimate the proportion difference in NYHA functional class improvement at Week 10 in terms of odds ratio between aficamten from Cohorts 1 and 2 combined vs pooled placebo and the corresponding 90% Wald CIs. For cardiac biomarkers, the analysis of covariance model was used to include natural log transformed proportional change from baseline as the dependent variable, and natural log transformed baseline value as a covariate with treatment as a fixed effect. The treatment effect estimates were back-transformed exponentially and presented. Geometrics LS means estimates for proportional change from baseline at Week 10 were provided for each treatment arm along with the corresponding 90% CIs. The treatment difference was described by the geometrics LS means estimate of proportional change from baseline ratio and the corresponding 90% CIs. There were no adjustments for multiplicity. Statistical analysis was performed by Cytokinetics using SAS 9.4.

RESULTS

STUDY PATIENTS. Baseline characteristics of the study patients are shown in **Table 1**. There was no significant difference in Clinical and imaging variables between patients treated with aficamten in Cohort 1 (n = 14) and Cohort 2 (n = 14) and those treated with placebo (n = 13) (**Table 1**). The median age of patients in the aficamten cohorts was 57 years (range: 33 to 78 years), and 54% were female. The median maximal LV wall thickness was 17 mm (range: 13 to 24 mm). All patients were receiving either beta-blocker or calcium-channel blocker therapy. A positive family history of HCM was reported in 18% of patients on aficamten and in 31% of patients on placebo.

In Cohort 1, in which patients were initiated on aficamten 5 mg, the final dose was 5 mg in 4 patients, 10 mg in 5 patients, and 15 mg in 5 patients (average final dose: 10 mg). In Cohort 2, in which patients were initiated on aficamten 10 mg, the final dose was 10 mg in 9 patients, 20 mg in 4 patients, and 30 mg in 1 patient (average final dose: 14 mg) (**Supplemental Figure 1**). All patients completed the study, and all data points were available for analysis except 1 patient randomized to placebo, who terminated participation at Week 10. For this patient, all data points were available except the Week 10 LVOT gradient value.

LVOT GRADIENTS. After 10 weeks of treatment, resting LVOT gradients decreased in patients receiving aficamten in Cohort 1 from 54 ± 25 mm Hg to 13 ± 4 mm Hg (LS mean difference $\pm$ SE: -29 ± 7.2 mm Hg, 90% CI: -41 mm Hg to -16 mm Hg; $P = 0.0003$ vs placebo) and in Cohort 2 from 58 ± 36 mm Hg to 15 ± 22 mm Hg (-28 ± 7.2 mm Hg, 90% CI: -40 mm Hg to -16 mm Hg; $P = 0.0004$ vs placebo), whereas the LVOT gradient for the pooled placebo group was 52 ± 27 mm Hg at baseline and 44 ± 25 mm Hg at Week 10 (-13 ± 5.2 mm Hg, 90% CI: -22 mm Hg to -4 mm Hg) (**Central Illustration**) (**Table 2**). At Week 12, following a 2-week post-treatment washout period, resting LVOT gradients for aficamten-treated patients in both cohorts returned to baseline levels (47 ± 32 mm Hg and 45 ± 35 mm Hg, respectively, for Cohorts 1 and 2) (**Central Illustration**).

After 10 weeks of treatment, Valsalva LVOT gradients decreased in patients receiving aficamten in Cohort 1 from 74 ± 25 mm Hg to 38 ± 14 mm Hg (LS mean difference $\pm$ SE, -33 ± 9.2 mm Hg, 90% CI: -48 mm Hg to -17 mm Hg; $P = 0.001$ vs placebo) and in aficamten Cohort 2 from 82 ± 37 mm Hg to 30 ± 30 mm Hg (-43 ± 9.1 mm Hg, 90% CI: -59 mm Hg to -28 mm Hg; $P < 0.0001$ vs placebo), and in the pooled placebo group from 85 ± 21 mm Hg to 76 ± 23 mm Hg (-8 ± 6.7 mm Hg 90% CI: -19 mm Hg to 3.2 mm Hg) (**Central Illustration**). After a 2-week washout period, Valsalva LVOT gradients in aficamten Cohorts 1 and 2 had returned to baseline levels (68 ± 22 mm Hg and 74 ± 40 , respectively, for Cohorts 1 and 2) (**Central Illustration**).

After 2 weeks of therapy on the starting dose of aficamten, 25 patients (89%) in the combined treatment arms had resting LVOT gradients <30 mm Hg, and 18 patients (64%) had Valsalva LVOT gradients <50 mm Hg. At Week 6, when patients were on their final dose of aficamten, 27 patients (96%) had resting LVOT gradients <30 mm Hg, and 20 patients (71%) had Valsalva LVOT gradients <50 mm Hg (**Central Illustration**).

A complete hemodynamic response (resting LVOT gradient <30 mm Hg and Valsalva gradient <50 mm Hg at Week 10) occurred in 11 of 14 patients (79%) in aficamten Cohort 1 and 13 of 14 patients (93%) in aficamten Cohort 2, compared with only 1 of 12 (8%) in the pooled placebo group (**Central Illustration**). Of the 4 patients treated with aficamten who did not achieve a complete hemodynamic response, 3 patients had a partial response with resting LVOT gradient <30 mm Hg but a Valsalva gradient ≥ 50 mm Hg, and 1 patient had no significant

TABLE 2 Peak Left Ventricular Outflow Tract Gradients Over Time (mm/Hg)

	Baseline	Week 2	Week 4	Week 6	Week 10	Week 12
Resting LVOT gradient						
Placebo (n = 13)	52.1	45	47.1	49	44	39.6
Cohort 1 (n = 14)	53.8	24.3	27.3	13.9	13.4	47.3
P value vs placebo	—	0.007	0.025	<0.0001	0.0003	—
Cohort 2 (n = 14)	58.2	15.5	16.1	10.9	15.1	44.9
P value vs placebo	—	0.0002	0.0006	<0.0001	0.0004	—
Valsalva LVOT gradient						
Placebo (n = 13)	84.6	71.3	71.3	73.4	76	64.9
Cohort 1 (n = 14)	74.4	51.3	46.1	37.1	38.1	68
P value vs placebo	—	0.097	0.038	0.0003	0.001	—
Cohort 2 (n = 14)	82.3	32.3	31.5	30.3	29.8	73.9
P value vs placebo	—	0.0005	0.0005	<0.0001	<0.0001	—

Peak left ventricular outflow tract gradients over time are displayed for both resting and Valsalva. Mean gradients are presented. P values reflect least squares mean difference between pooled placebo and individual treatment group for both rest and Valsalva.

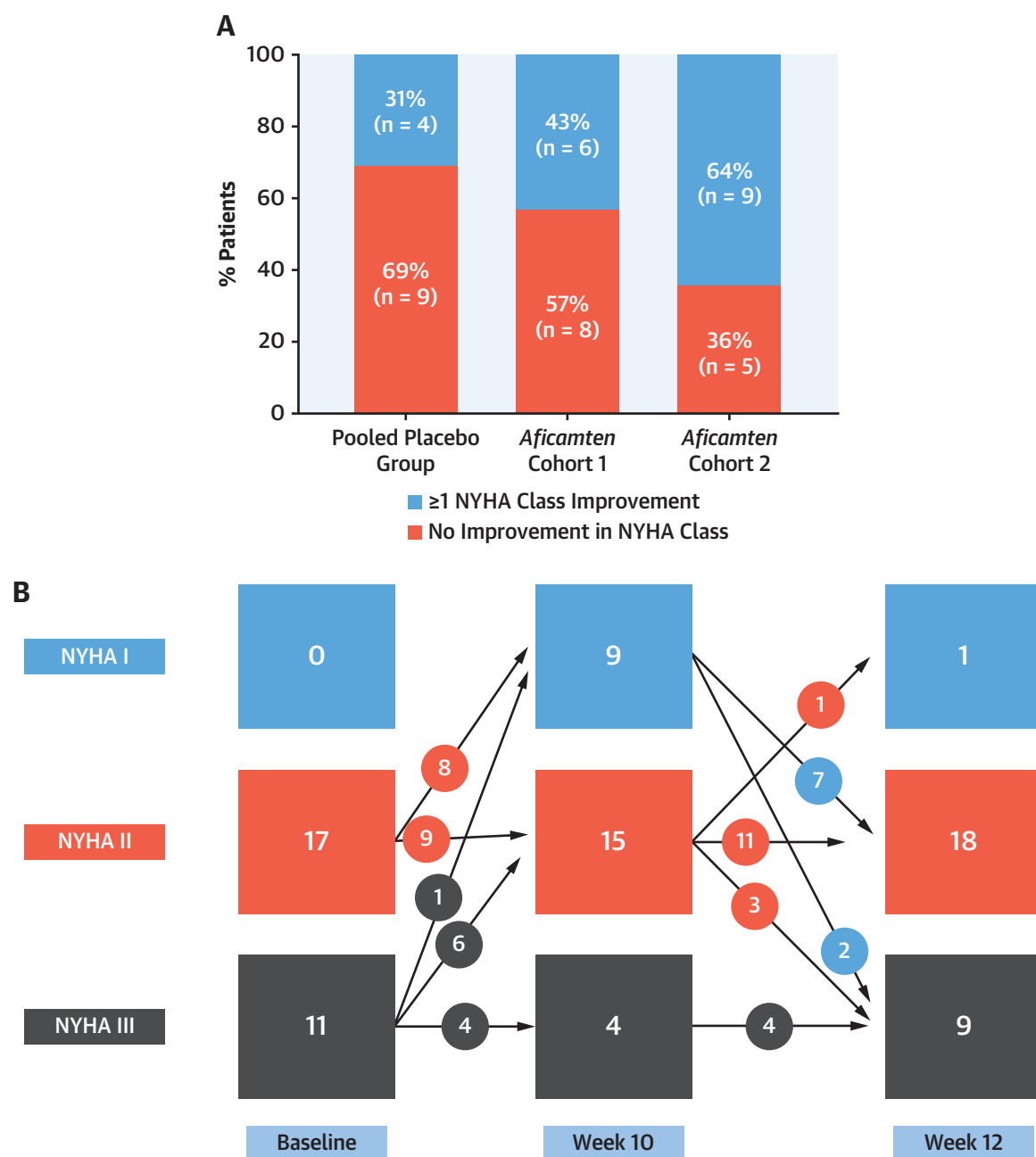
LVOT = left ventricular outflow tract.

hemodynamic response with either resting or Valsalva LVOT gradients (**Central Illustration**).

CHANGES IN LVEF. Over the treatment period, LVEF decreased in patients receiving aficamten in Cohort 1 from $73\% \pm 6\%$ to $67\% \pm 9\%$ (LS mean difference vs placebo $\pm$ SE, -7.2 ± 2.5 , $P = 0.007$) and in Cohort 2 from $75\% \pm 6\%$ to $64\% \pm 8\%$ (LS mean difference vs placebo $\pm$ SE, -11.7 ± 2.5 , $P < 0.0001$), with no change in the placebo group ($75\% \pm 6\%$ to $75\% \pm 4\%$; $P = 0.50$) (**Central Illustration**). Analysis of the relationship between aficamten dose and LVEF revealed a dose-dependent decrease with a mean reduction in LVEF of -0.6% (SE: 0.084) per mg of aficamten. An additional analysis of the relationship of plasma drug concentration to LVEF is shown in **Supplemental Figure 2**.

Two patients receiving aficamten in Cohort 2 developed LVEF $<50\%$, including 1 patient with an LVEF of 43% at Week 4 who underwent per protocol dose reduction (20 mg to 10 mg) with a resultant increase in LVEF to 57% at Week 6. The second patient had an LVEF of 49% while receiving 20 mg at Week 10, which was the last day of dosing and so study drug was discontinued per protocol. In both patients, their LVEF returned to baseline, 57% and 71% respectively, at the next echocardiogram 2 weeks later, and neither patient experienced an adverse event. There were no treatment interruptions, and no patients met the stopping criteria of LVEF $<40\%$.

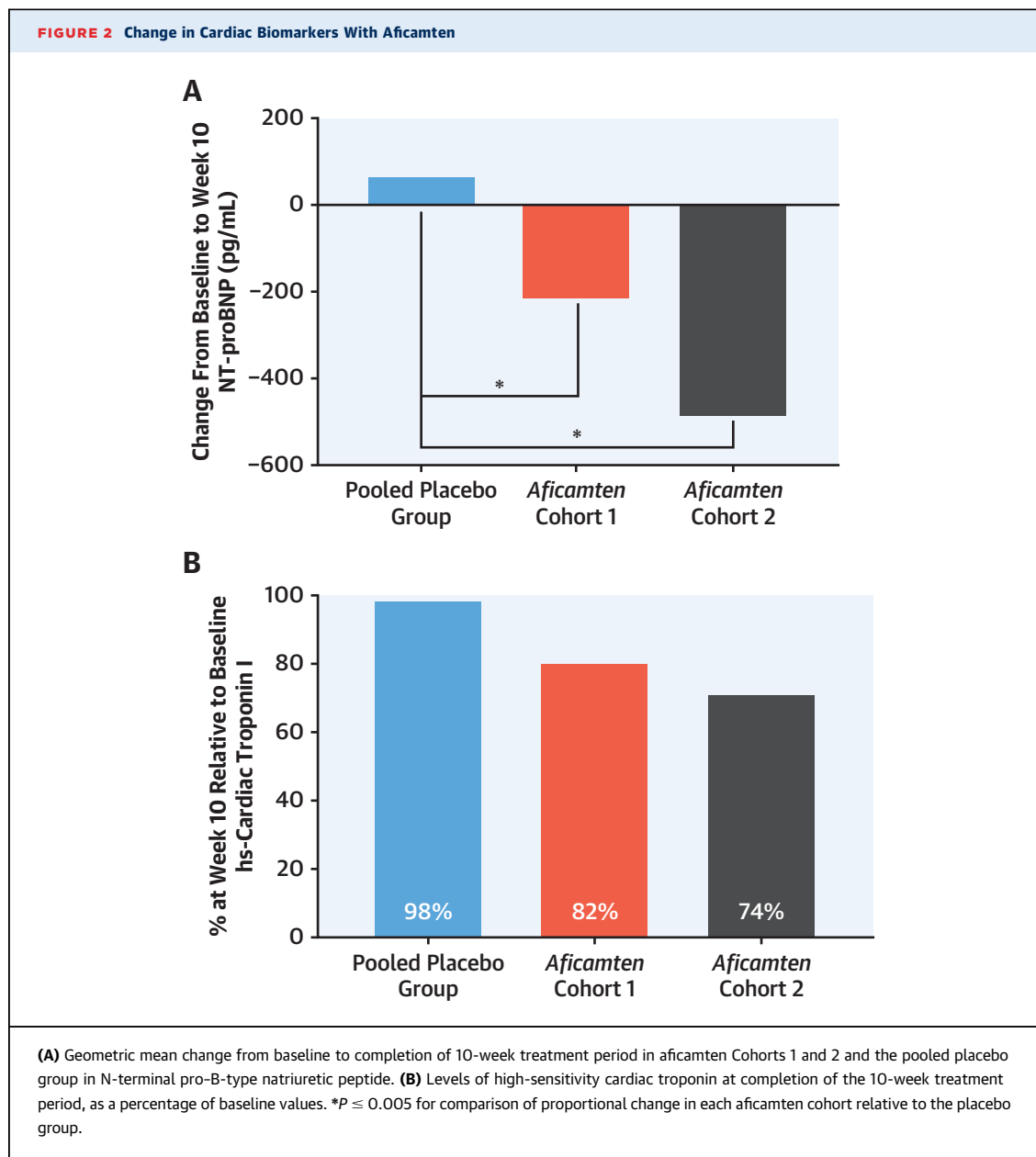
NYHA FUNCTIONAL CLASS. Across Cohorts 1 and 2 in patients treated with aficamten, 15 of 28 (54%) patients experienced a change of ≥ 1 NYHA functional class, 43% in Cohort 1 and 64% in Cohort 2 (**Figure 1A**),

FIGURE 1 Change in Heart Failure Symptoms With Aficamten

(A) Bar graph showing the proportion of patients with hypertrophic Cardiomyopathy in aficamten-treated Cohorts 1 and 2 and pooled placebo groups with improvement of ≥ 1 New York Heart Association (NYHA) functional class at completion of the 10-week treatment period. (B) Transition in NYHA functional class from baseline to completion of 10-week treatment period and after washout at Week 12 for each patient in aficamten Cohorts 1 and 2.

including 6 patients who improved from class III to II, 8 from class II to I, and one from class III to I (Figure 1B). Among the 15 patients with symptomatic improvement, 13 (87%) also had a complete hemodynamic response, whereas the remaining 2 patients

had partial responses with Valsalva LVOT gradients remaining >50 mm Hg. Of the 13 patients who did not experience improvement in NYHA functional class, 11 (85%) also achieved a complete hemodynamic response, and the remaining 2 patients had partial



responses with Valsalva LVOT gradients remaining >50 mm Hg. NYHA functional class responders were not different from nonresponders with respect to several other relevant baseline characteristics, including age, sex, body mass index, comorbidities, maximal LV wall thickness, LVEF, or final doses of aficamten. In the pooled placebo group, 4 of 13 (31%) patients experienced a change of ≥ 1 NYHA functional class, including 3 patients who improved from class III to II, 1 from class II to I, and 1 from class III to I. No patients in either the aficamten or placebo arms experienced a worsening of NYHA functional class at Week 10.

CARDIAC BIOMARKERS. Across Cohorts 1 and 2 in patients treated with aficamten, NT-proBNP decreased from a geometric mean of 490 pg/mL (%CV 192) to 165 pg/mL (%CV 145), whereas the pooled placebo group increased from 395 pg/mL (%CV 227) to 460 pg/mL (%CV 179) (Figure 2A). Aficamten treatment was associated with a 62% proportional reduction in NT-proBNP levels at Week 10 compared with placebo ($P < 0.001$). Importantly, 25 of 27 patients on aficamten (93%) experienced at least some reduction in NT-proBNP levels compared with only 6 of 12 placebo-treated patients (50%). At the end of treatment, a modest correlation was noted

TABLE 3 Adverse Events During Treatment

	Cohort 1 (n = 14)	Cohort 2 (n = 14)	Placebo (n = 13)
Treatment-emergent adverse event			
Total	33	26	40
Leading to early termination	0	0	0
Related	1	0	6
Moderate or severe	5	5	8
Severe	0	0	4
Treatment-emergent serious adverse event	1	1	5
Fatal adverse event	0	0	0

Values are number of patients having at least one event in that category.

between the proportional improvement in resting and Valsalva LVOT gradients and reduction in NT-proBNP levels ($r = 0.3$ and $r = 0.45$, respectively).

Median baseline levels of hs-troponin were 12 ng/L (IQR: 5-29 ng/L) for the pooled aficamten group and 8 ng/L (IQR: 3-38 ng/L) for pooled placebo. At Week 10, relative to baseline hs-troponin levels, patients receiving placebo had no change (2% relative reduction from baseline) whereas aficamten treated patients in Cohorts 1 and 2 experienced 18% relative reduction ($P = 0.29$ compared with placebo) and 26% relative reduction ($P = 0.097$ compared with placebo), respectively (Figure 2B).

SAFETY. Aficamten was well tolerated. There were no SAEs that resulted in early termination of drug, no treatment-related SAEs, and no treatment interruptions or discontinuations due to adverse events. Most adverse events were reported to be mild or moderate (96%) (Table 3).

There were 3 patients who experienced an SAE in the study, 2 in Cohort 1, and 1 in Cohort 2. One patient (Cohort 1 randomized to placebo) experienced cardiogenic shock due to stress cardiomyopathy after discontinuation of study drug at Week 10. A second patient (Cohort 1 randomized to aficamten) developed an exacerbation of pre-existing back pain that resulted in an emergency-room visit. The third patient (Cohort 2 randomized to aficamten) was a 72-year-old male with multiple cardiovascular risk factors diagnosed with a non-ST-segment elevation myocardial infarction who underwent elective percutaneous angioplasty after completing the study. None of these events were considered by the investigators to be related to study drug.

Overall, the number of patients experiencing ≥ 1 treatment-emergent adverse event was balanced for the groups receiving aficamten (75%) vs placebo (88%). There were no adverse events of atrial fibrillation, ventricular arrhythmias, or evidence of QT

prolongation reported in the aficamten group, and 1 patient on placebo experienced an episode of paroxysmal atrial fibrillation during the reported episode of stress cardiomyopathy. Aficamten treatment did not impact blood pressure, heart rate, or other laboratory measures.

DISCUSSION

HCM has evolved to a highly treatable genetic heart disease.^{2,13} However, important unmet treatment needs remain, including the priority for additional medication options to improve symptom burden in patients with oHCM.^{5,6} Aficamten is a next-in-class myosin inhibitor that targets the myofilament apparatus to decrease the number of actin-myosin cross-bridges, resulting in a dose-dependent reduction in contractility.^{11,12} In principle, interventions that decrease contractility will lower outflow gradients, which can then be expected to improve symptoms and functional capacity in patients with obstructive HCM (Central Illustration).^{7-9,14,15} This rationale provides the basis for advancing myosin inhibitor therapy to this population of HCM.

In this proof-of-concept, placebo-controlled, dose-finding phase II clinical trial in patients with oHCM, aficamten was well tolerated and provided significantly greater improvement compared with placebo in all clinically relevant secondary and exploratory endpoints. Indeed, the capability of aficamten to markedly reduce LVOT gradients was shown over a relatively short treatment period of 10 weeks, with complete hemodynamic response in nearly all patients, including 93% of patients in Cohort 2. Furthermore, across the entire spectrum of doses, aficamten resulted in a rapid decrease in outflow tract gradients as early as 2 weeks after initiation (resting LVOT gradient <30 mm Hg in 89% of patients), providing patients the potential for prompt normalization of LV systolic pressures (Central Illustration).

This robust hemodynamic response is particularly notable because aficamten converted the majority of patients with oHCM to gradient levels that are below the current threshold for consideration of septal reduction therapies, such as myectomy or alcohol septal ablation.^{2,3,16,17} Therefore, these data support the further study of aficamten as a potential additional medical therapy for symptomatic oHCM patients in whom optimal hemodynamic and symptom control is not achieved despite the use of beta-blockers or calcium-channel blockers. Aficamten was also associated with marked reductions in NT-proBNP and hs-troponin (in Cohort 2), suggesting that

aficamten treatment may result in other potential downstream pathophysiologic benefits including decreases in LV wall stress and reduction in myocardial injury. Whether the mechanism of biomarker improvement is primarily related to normalization of LV systolic pressure, improved microvascular blood flow, or through other downstream effects of direct myosin modulation requires further study.

The early and sustained hemodynamic effect of aficamten was accompanied by marked clinical benefit in heart failure symptoms in most patients. Symptom improvement of ≥ 1 NYHA functional class occurred in more than one-half of patients treated with aficamten, including 64% in Cohort 2 with most of that improvement resulting in patients transitioning from class II to becoming entirely asymptomatic (class I). This presents an opportunity to improve quality of life, possibly to normal, through treatment with aficamten in patients who continue to be frustrated by limiting symptoms despite conventional therapy. In addition, aficamten converted 7 patients from advanced heart failure symptoms (class III) to a less symptomatic status (class II or I). This is a particularly relevant point because septal reduction therapy is often undertaken to convert patients with advanced limiting symptoms (class III) to asymptomatic or mildly symptomatic status, raising the possibility this could also be achieved in select patients with drug therapy.^{16,17}

We also identified a subset of patients with oHCM who did not experience improvement in symptom burden as assessed by NYHA functional class over the relatively short study duration despite normalization of LVOT gradients and improvement in cardiac biomarkers after aficamten therapy. The reasons for the persistent symptoms remains uncertain, although it is well established that reporting of symptoms in oHCM can often be associated with marked fluctuations due to the inherently dynamic nature of the disease.^{4,6} Additionally, this short study may not have allowed for sufficient recovery time from the global deconditioning associated with sedentary lifestyle in some patients living with oHCM over long periods. On the other hand, we also cannot exclude the possibility that, in some of these patients, symptom limitation may have been a result of residual latent LVOT obstruction occurring with routine daily activities that were not detected using Valsalva maneuver as a provocative test, as opposed to post-exercise gradients.¹⁸

The opportunity to develop strategies to optimize aficamten dosing in the future to provide additional gradient suppression (or elimination) may provide such patients with clinical benefit beyond what was

observed in this early investigation. When comparing patients with or without symptom improvement, we were not able to identify any differences in a number of relevant clinical or morphologic variables (including age, medical comorbidities, maximal LV wall thickness, and LVEF). In this regard, larger studies are being conducted that aim to provide important insights on the relationship between the magnitude of obstruction relief, heart failure symptoms, and LVEF. These data will best inform aficamten dosing strategies in patients with oHCM.

The robust LVOT gradient reduction with aficamten was achieved by mitigating hypercontractility (one of the most important disease characteristics contributing to the development of LVOT obstruction) with only modest change in systolic function for most patients. In previous studies with myosin inhibitors, an LVEF cutoff of $<50\%$ was considered to represent a relevant safety threshold, although the precise risks in HCM associated with pharmacotherapy-induced decreases in LVEF are not well defined.^{8,9} In fact, the 2 patients who developed an LVEF of $<50\%$ in our study reported improvement in heart failure symptoms and reductions in NT-proBNP despite mildly reduced LVEF, and both patients returned to their baseline systolic function at the end of the study.

The generally favorable balance between LVOT gradient reduction and myocardial contractility observed in this early-stage investigation may be a function of several key features related to the distinct pharmacologic profile of aficamten. Specifically, the shallow exposure-response relationship allows for smaller changes in LVEF over a range of doses, representative of a relatively wide therapeutic window.¹² This may also allow for a tailored approach to dosing in individuals, translating to potential for greater lowering of LVOT gradients with less risk of exceeding the safety threshold for LVEF reduction. Additionally, as shown in this study, dose adjustments every 2 weeks allowed for frequent dose adjustments and prompt gradient reduction. Importantly, in the 2 cases where the LVEF decreased to $<50\%$, reversibility of the pharmacodynamic effect was observed at the next time point 2 weeks later, enabling down-titration without potentially the need for treatment interruption. Future investigations will provide greater clarity to determine if these aspects of the pharmacologic profile of aficamten can be leveraged to maximize clinical efficacy while maintaining safety, as well as provide a more comprehensive understanding of how aficamten relates to currently approved first-generation myosin inhibitor therapy.⁸

Aficamten was well tolerated with no treatment-related SAEs, and no patient discontinued use of the drug during the study period. The occurrence of treatment-emergent adverse events in patients on aficamten compared with placebo was similar. Patients completing this study were offered the opportunity to enroll in an open-label extension study with aficamten; this trial as well as future clinical trials will further inform the drug's safety profile.

STUDY LIMITATIONS. The relatively short treatment duration limits the determination of potential effects of aficamten on cardiac structure and disease modification, including left atrial size and LV wall thickness, as well as clarifying the durability of gradient reduction over longer periods.¹⁹ The ongoing open-label extension study of aficamten, FOREST-HCM (NCT04848506), is intended to provide greater insight into these questions with up to 5 years of treatment planned. There was no prospective assessment of genetic variants within the trial and only historical genotyping was available from the clinical records, limiting the reliability of ascertaining HCM-specific mutation status.

In addition, we did not include objective measures of functional capacity with cardiopulmonary exercise testing and as such could not assess the impact of drug therapy on measures of cardiopulmonary reserve measured by peak VO_2 or exercise-induced LVOT obstruction. However, it is notable that in the EXPLORER-HCM trial, mavacamten was associated with improvements in functional capacity (peak VO_2) in patients with oHCM who achieved LVOT gradient reductions similar to those we observed with aficamten, and this metric will be evaluated in the pivotal phase 3 study with aficamten.⁸

CONCLUSIONS

Treatment with aficamten across a range of doses was associated with rapid, sustained, and substantial reductions in LVOT gradients in most patients with oHCM. This was paralleled by improvements in heart failure symptoms and clinically relevant biomarkers. Aficamten was well tolerated with no serious drug-related adverse events. On the basis of these data, the clinical efficacy and safety of aficamten will be evaluated in a phase 3 clinical trial of patients with symptomatic obstructive HCM (Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM [SEQUOIA-HCM]; NCT05186818).

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ADDRESS FOR CORRESPONDENCE: Dr Martin S. Maron, HCM Center at Lahey Hospital, 67 South Bedford St, Suite 302W, Burlington, Massachusetts 01805, USA. E-mail: martin.maron@lahey.org. Twitter: [@MartinMaronMD](https://twitter.com/MartinMaronMD).

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND

PROCEDURAL SKILLS: In patients with symptomatic oHCM, the cardiac myosin inhibitor aficamten was well tolerated and reduced myocardial contractility resulting in substantial decreases in LVOT gradients, paralleled by improvement in heart failure symptoms and NT-proBNP.

TRANSLATIONAL OUTLOOK: A larger pivotal study will assess clinically relevant outcomes including changes in exercise capacity, quality of life biomarkers, and outflow tract gradient during treatment with aficamten.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.