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Impact of Aficamten on Disease and Symptom Burden in Obstructive Hypertrophic Cardiomyopathy

Results From SEQUOIA-HCM

Martin S. Maron, MD,[a] Ahmad Masri, MD, MS,[b] Michael E. Nassif, MD, MS,[c] Roberto Barriales-Villa, MD, PhD,[d] Theodore P. Abraham, MD,[e] Michael Arad, MD,[f] Nuno Cardim, MD, PhD,[g] Lubna Choudhury, MD, MRCPI,[h] Brian Claggett, PhD,[i] Caroline J. Coats, MD, PhD,[j] Hans-Dirk Düngen, MD, PhD,[k] Pablo Garcia-Pavia, MD, PhD,[l] Albert A. Hagège, MD,[m] James L. Januzzi, MD,[n,o] Ian Kulac, MS,[i] Matthew M.Y. Lee, PhD, MBChB,[j] Gregory D. Lewis, MD,[n] Chang-Sheng Ma, MD,[p] Michelle Michels, MD, PhD,[q] Artur Oreziak, MD, PhD,[r] Anjali T. Owens, MD,[s] John A. Spertus, MD, MPH,[c] Scott D. Solomon, MD,[i] Jacob Tfelt-Hansen, MD, PhD,[t] Marion van Sinttruije, MA,[u] Josef Veselka, MD, PhD,[v] Hugh C. Watkins, MD, PhD,[w] Daniel L. Jacoby, MD,[x] Stephen B. Heitner, MD,[x] Stuart Kupfer, MD,[x] Fady I. Malik, MD, PhD,[x] Lisa Meng, PhD,[x] Amy Wohltman, ME,[x] Iacopo Olivotto, MD,[y] the SEQUOIA-HCM Investigators

ABSTRACT

BACKGROUND Aficamten is a cardiac myosin inhibitor that mitigates left ventricular outflow gradients in obstructive hypertrophic cardiomyopathy (oHCM). The clinical efficacy of aficamten across multiple outcome domains in oHCM has not been fully defined.

OBJECTIVES This responder analysis from the SEQUOIA-HCM (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic oHCM) trial characterizes the clinical impact of aficamten.

METHODS Patients who were symptomatic of oHCM were randomized to aficamten (n = 142) or placebo (n = 140) daily for 24 weeks. Outcomes assessed included the proportion of patients with complete hemodynamic response (rest and Valsalva gradient <30 mm Hg and <50 mm Hg, respectively), relief in limiting symptoms (≥1 improvement in NYHA functional class and/or ≥10-point change in Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score), enhanced exercise capacity (≥1.5 mL/kg/min change in peak oxygen uptake), and ≥50% reduction in N-terminal pro-B-type natriuretic peptide. Eligibility for septal reduction therapy was also evaluated.

RESULTS At 24 weeks, patients treated with aficamten vs placebo showed significant improvement in limiting symptoms (71% vs 42%), were more likely to have complete hemodynamic response (68% vs 7%), demonstrated enhanced exercise capacity (47% vs 24%), and showed a decrease ≥50% in N-terminal pro-B-type natriuretic peptide (84% vs 8%) ($P \leq 0.002$ for all). An improvement in ≥1 of these outcome measures was achieved in 97% of patients treated with aficamten (vs 59% placebo), including 23% on aficamten who achieved all 4 outcomes compared with none in placebo. Among 32 patients receiving aficamten and 29 patients receiving placebo who were eligible for septal reduction therapy, 28 (88%) from the aficamten group were no longer eligible at 24 weeks compared with 15 (52%) from the placebo group ($P = 0.002$).

CONCLUSIONS Treatment with aficamten was associated with substantial improvements across a broad range of clinically relevant efficacy measures. These results underscore the wide-ranging potential of aficamten for treatment of patients with symptomatic oHCM (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults with oHCM [SEQUOIA-HCM]; NCT05186818) (JACC. 2024;84:1821-1831) © 2024 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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ABBREVIATIONS AS ACRONYMS

CPET = cardiopulmonary exercise testing

hs = high sensitivity

KCCQ-CCS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score

LV = left ventricular

NT-proBNP = N-terminal pro-B-type natriuretic peptide

oHCM = obstructive hypertrophic cardiomyopathy

pVO_2 = peak oxygen uptake

SRT = septal reduction therapy

Historically, the efficacy of therapeutic interventions in obstructive hypertrophic cardiomyopathy (oHCM) has been defined predominantly by reductions in left ventricular (LV) outflow tract gradients coupled with improvements in heart failure symptoms assessed by NYHA functional class.[1-8] However, these parameters fail to provide a comprehensive picture of the clinical benefit. Recently, patient-reported outcome measures, such as the Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS), have shown enhanced sensitivity in assessing clinically relevant changes in symptomatic burden and quality of life, reflecting what matters more to patients.[9-12] Other measures reflecting favorable impact of treatment in oHCM include enhanced exercise capacity[13-15] and improvement in cardiac biomarkers.[16,17] Ideally, a global evaluation of therapeutic interventions for oHCM should integrate all these metrics.

SEE PAGES 1832 AND 1835

Aficamten is a novel cardiac myosin inhibitor that modulates cardiac sarcomere function resulting in a number of effects particularly well suited to address the pathophysiology of oHCM to address treatment goals and unmet needs of patients.[18-22] One of the principal effects of aficamten is mitigating myocardial hypercontractility, which in the phase 2 REDWOOD-HCM (Dose-finding Study to Evaluate the Safety, Tolerability, PK, and PD of CK-3773274 in Adults With HCM) trial resulted in reduced LV outflow gradients in patients with oHCM.[21] These results supported advancement to the pivotal phase 3 study SEQUOIA-HCM (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults with oHCM; NCT05186818) in which aficamten was clearly superior to placebo with regard to the primary endpoint of exercise capacity as well as a number of secondary measures.[19] In this prespecified subanalysis of SEQUOIA-HCM, we sought to characterize the broad clinical impact of aficamten by integrating an array of measures addressing different aspects of the oHCM disease burden to enhance our understanding of the efficacy of this medical therapy and how it may potentially be best implemented in the management of patients with hypertrophic cardiomyopathy (HCM).

METHODS

STUDY DESIGN. SEQUOIA-HCM was an international phase 3 double-blind, randomized, placebo-controlled trial performed between February 1, 2022, and May 15, 2023, in which 282 patients with oHCM underwent randomization (n = 142 to aficamten, n = 140 to placebo) at 101 academic medical centers in North America, Europe, Israel, and China. The treatment duration was 24 weeks. The trial details have been previously described.[19,22] The protocol was

From the [a]Lahey Hospital and Medical Center, Burlington, Massachusetts, USA; [b]Oregon Health and Science University, Portland, Oregon, USA; [c]University of Missouri Kansas City Healthcare Institute for Innovations in Quality and Saint Luke's Mid America Heart Institute Kansas City, Kansas City, Missouri, USA; [d]Complexo Hospitalario Universitario A Coruña, INIBIC, CIBERCV-ISCIII, A Coruña, Spain; [e]University of California, San Francisco, San Francisco, California, USA; [f]Chaim Sheba Medical Center, Ramat-Gan and Tel Aviv University, Israel; [g]Hospital CUF Descobertas, Lisbon, Portugal; [h]Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; [i]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [j]School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, Scotland; [k]Charité Campus Virchow-Klinikum, Berlin, Germany; [l]Hospital Universitario Puerta de Hierro de Majadahonda, IDIPHISA, CIBERCV, and Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain; [m]Département de Cardiologie, Assistance Publique Hôpitaux de Paris, Hôpital Européen Georges-Pompidou, Paris, France; [n]Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA; [o]Heart Failure and Biomarker Trials, Baim Institute for Clinical Research, Boston, Massachusetts, USA; [p]Beijing Anzhen Hospital, Capital Medical University, Beijing, China; [q]Erasmus University Medical Center, Cardiovascular Institute, Thoraxcenter, Department of Cardiology Rotterdam, Rotterdam, the Netherlands; [r]National Institute of Cardiology, Warsaw, Poland; [s]University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA; [t]Section of Forensic Genetics, Department of Forensic Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, and Department of Cardiology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark; [u]Hypertrophic cardiomyopathy patient author, Zwolle, the Netherlands; [v]Department of Cardiology, Angiology and Intensive Care, Klinikum Chemnitz gGmbH, Medical Campus Chemnitz of the Technische Universität Dresden, Dresden, Germany; [w]Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom; [x]Cytokinetics, Incorporated, South San Francisco, California, USA; and the [y]Meyer Children's Hospital, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Florence, Italy.

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.

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approved by site-specific Institutional Review Boards and funded by Cytokinetics. Employees of Cytokinetics, in collaboration with academic investigators, conducted data analyses and vouch for its accuracy. An independent data-monitoring committee regularly reviewed the unblinded study data to ensure participant safety. All participants 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.

STUDY POPULATION. The SEQUOIA-HCM trial enrolled adults 18 to 85 years of age with a clinical diagnosis of symptomatic oHCM (NYHA functional class II or III). Eligibility criteria included LV wall thickness ≥15 mm (or ≥13 mm with a positive family history of HCM or a known disease-causing gene mutation), echocardiographic evidence of LV outflow tract gradient ≥30 mm Hg at rest and ≥50 mm Hg following Valsalva maneuver, and reduced exercise capacity (predicted peak oxygen uptake [pVO_2] ≤90%). Participants receiving background therapy (beta-blockers, non-dihydropyridine calcium channel blockers, and/or disopyramide) were expected to maintain stable doses throughout the study. Other key inclusion and exclusion criteria have been previously described.[19,22]

INTERVENTION. Participants were randomized in a 1:1 ratio to receive either aficamten or placebo via an interactive web response system. Randomization was stratified based on beta-blocker use (yes/no) and cardiopulmonary exercise testing (CPET) modality (treadmill/bicycle) and implemented in the interactive web response system. Aficamten was administered orally at an initial dose of 5 mg once daily, with potential echocardiographic-guided dose titrations in 5-mg increments (at weeks 2, 4, and 6), up to a maximum dose of 20 mg, based on site-read LV ejection fraction and Valsalva LV outflow tract gradients assessed by an echocardiographic cardiologist blinded to treatment assignment. To minimize potential bias, the site investigator and study team were blinded to echocardiogram images and results. Echocardiograms were later assessed by a central core laboratory, which was also blinded to treatment assignment. An independent data-monitoring committee formally reviewed accumulated data at intervals to assess participant risk during the trial.

Participants underwent evaluations every 2 (titration) or 4 (maintenance) weeks during the 24-week treatment period. CPETs were conducted at screening and at week 24 (end of treatment). Resting transthoracic echocardiography, electrocardiograms, safety laboratory testing, and clinical assessments occurred at each study visit. The data-monitoring committee formally reviewed accumulated data at intervals to assess risk during the trial.

ENDPOINTS. The primary objective of this analysis was to characterize the number of responses achieved in patients on aficamten compared with placebo with respect to 4 clinically relevant outcomes: 1) complete hemodynamic response (rest and Valsalva gradients <30 mm Hg and <50 mm Hg, respectively); 2) relief in limiting symptoms (≥1 improvement in NYHA functional class and/or ≥10 point increase in KCCQ-CCS); 3) enhanced exercise capacity (≥1.5 mL/kg/min change in pVO_2); and 4) cardiac biomarker response (≥50% decrease from baseline in N-terminal pro-B-type natriuretic peptide [NT-proBNP]). An analysis of study participants who achieved ≥1 of these outcomes was performed to characterize the extent of clinical response to aficamten. In addition, compared with baseline, the proportion of patients in the aficamten group with a 50% relative reduction in high-sensitivity (hs)-troponin concentrations at week 24 was compared to the placebo group.

Threshold values for the 4 outcome measures were considered to represent clinically meaningful changes. Specifically, reductions in LV outflow tract gradients <50 mm Hg have been associated with significant improvement in limiting symptoms of ≥1 NYHA functional class and excellent long-term survival.[3,8,23] Increases in KCCQ-CCS are associated with substantial reductions in adverse cardiovascular events across different heart failure populations, with a change ≥10 points considered to represent a moderate to large improvement in health status, whereas changes of <5 points reflect no significant change, and 5 to <10 points considered to be small.[9,11,12] Prior studies, which formed the basis for approval of new therapy in oHCM, considered a pVO_2 ≥1.5 mL/kg/min as a clinically relevant threshold for change in exercise capacity in HCM, whereas more modest improvements in pVO_2 have been associated with increased survival in heart failure populations.[24,25] Finally, a ≥50% decrease in serum levels of NT-proBNP has been associated with enhanced survival in populations with non-HCM heart failure.[16,26]

In addition, treatment effect was assessed with a prespecified analysis of patients who achieved improvement in limiting symptoms and exercise capacity defined by ≥1.5 mL/kg/min change in pVO_2 and ≥1 NYHA functional class improvement or pVO_2 ≥3.0 mL/kg/min^2 and no worsening in NYHA

TABLE 1 Demographic and Clinical Characteristics of Patients at Baseline

	Aficamten (n = 142)	Placebo (n = 140)
Mean age, y	59.2 ± 12.6	59.0 ± 13.3
Female	56 (39.4)	59 (42.1)
Medical history		
Hypertension	75 (52.8)	70 (50.0)
Family history or known gene mutation	47 (33.1)	44 (31.4)
Family history of HCM	41 (28.9)	34 (24.3)
Pathogenic sarcomere mutation	24 (16.9)	25 (17.9)
Paroxysmal atrial fibrillation	21 (14.8)	20 (14.3)
Coronary artery disease	19 (13.4)	16 (11.4)
Diabetes	14 (9.9)	9 (6.4)
Permanent atrial fibrillation	2 (1.4)	1 (0.7)
Background HCM therapy		
Beta-blocker	86 (60.6)	87 (62.1)
Calcium-channel blocker	45 (31.7)	36 (25.7)
Disopyramide	16 (11.3)	20 (14.3)
None	19 (13.4)	22 (15.7)
Implantable cardioverter-defibrillator	22 (15.5)	17 (12.1)
KCCQ-CSS, points	75.6 ± 18.4	73.7 ± 17.6
NYHA functional class		
II	108 (76.1)	106 (75.7)
III	34 (23.9)	33 (23.6)
IV	0 (0)	1 (0.7)
Median NT-proBNP, pg/mL	818 (377-1630)	692 (335-1795)
Geometric mean NT-proBNP	735 [604-894]	710 [587-859]
Median hs-cTnI, ng/L	12.9 (7.6-33.6)	11.5 (7.7-25.0)
Geometric mean hs-cTnI	17.1 [14.1-20.8]	16.5 [13.3-20.7]
Exercise modality		
Treadmill	78 (54.9)	77 (55.0)
Cycle	64 (45.1)	63 (45.0)
Cardiopulmonary exercise testing		
Total workload, W	120.4 ± 38.9	124.7 ± 42.5
Predicted pVO_2, %	56.2 ± 10.6	57.6 ± 13.0
pVO_2, mL/kg/min	18.4 ± 4.4	18.6 ± 4.5
Peak RER	1.2 ± 0.11	1.2 ± 0.09
RER <1.1, %	32 (2)	26 (18)
Echocardiographic parameters		
Valsalva outflow tract gradient, mm Hg	82.9 ± 32	83.3 ± 32.7
Resting LV outflow tract gradient, mm Hg	54.8 ± 27	55.3 ± 32.1
LV ejection fraction, %	74.8 ± 5.5	74.8 ± 6.3
Maximal LV wall thickness, mm	20.7 ± 3.0	21.0 ± 3.0

Values are mean ± SD, n (%), median (Q1-Q3), or mean [95% CI].

HCM = hypertrophic cardiomyopathy; hs-cTnI = high-sensitivity cardiac troponin I; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LV = left ventricular; NT-proBNP = N-terminal pro-B-type natriuretic peptide; pVO_2 = peak oxygen uptake; RER = respiratory exchange ratio.

functional class[24] and by determining guideline eligibility for septal reduction therapy at week 24 compared with those eligible at baseline (defined as NYHA functional class III or IV and LV outflow gradient at rest or with provocation ≥50 mm Hg in patients who had elected, along with their cardiology provider, not to pursue septal reduction therapy [SRT] at the time of inclusion into SEQUOIA-HCM).[6]

STATISTICAL ANALYSIS. The statistical analysis plan for this secondary analysis was prespecified in the supplemental statistical analysis plan (Supplemental Appendix). For each clinical efficacy outcome, week 24 data were applied when available. For patients with missing data, the last available observation (week 8 to week 20) was used. Patients with no available data on or after week 8 were classified as not meeting the efficacy criteria. Patients were then classified according to the number of efficacy outcome definitions that they met.

Baseline characteristics were summarized using mean ± SD or median (Q1-Q3) for continuous normal and skewed variables, as well as counts (%) for categorical variables. These characteristics were compared across groups using trend tests (linear regression, chi-square tests of trend, and Cuzick's nonparametric trend tests).

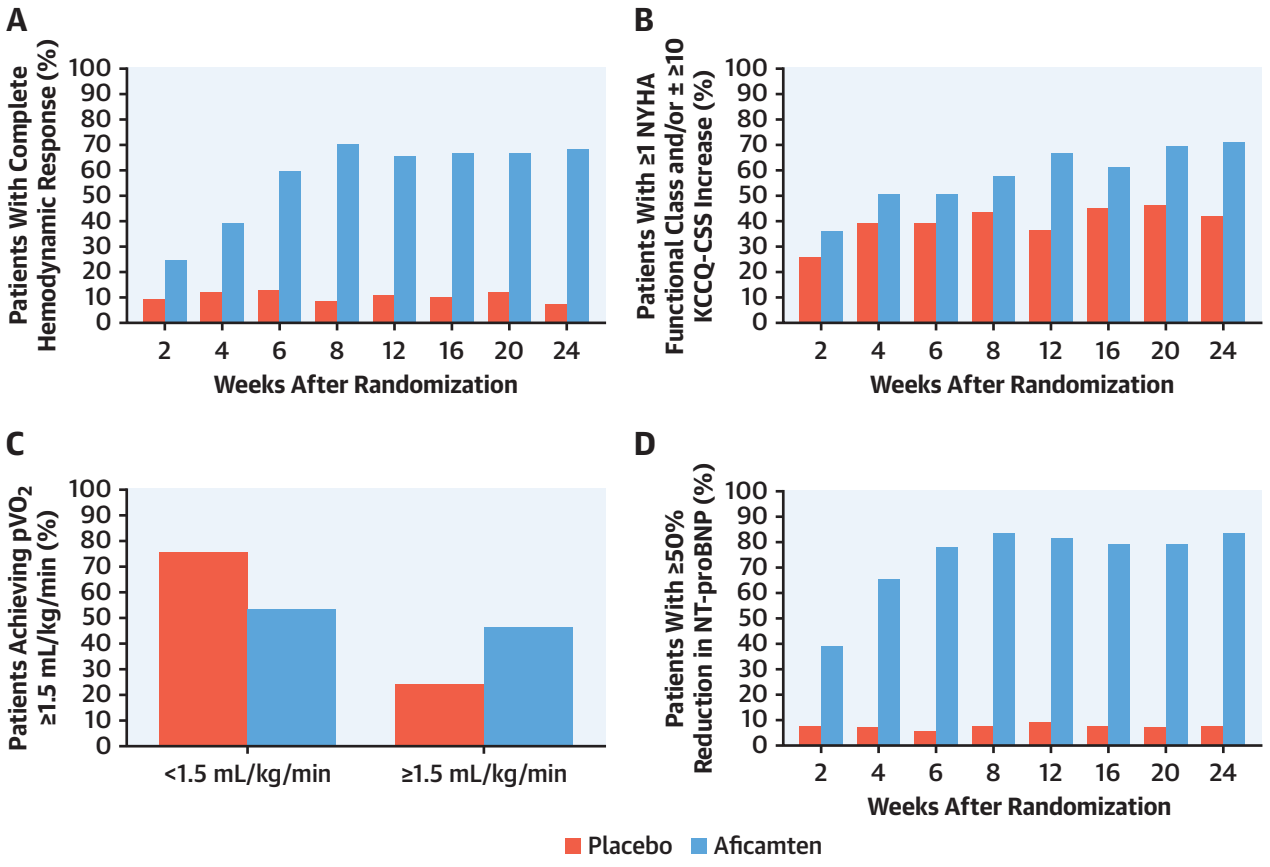
The proportion of patients meeting each efficacy outcome were compared between treatment groups using chi-square tests and linear regression was used to assess the treatment effect of aficamten vs placebo on change in efficacy outcomes while also adjusting for baseline value, CPET modality, and beta-blocker use. Placebo-corrected difference refers to the estimated treatment effect obtained by comparing outcomes in aficamten patients to those on placebo. Numbers needed to treat (NNTs), and associated confidence intervals were obtained by inverting the between-group risk. All analyses were conducted using STATA version 16 (StataCorp LLC). No adjustments were made for multiple comparisons. Two-sided P values <0.05 were considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS. The baseline characteristics for the study population were balanced between groups treated with aficamten and placebo (Table 1).

EFFICACY OUTCOMES. LV outflow tract gradients. At week 24, an outflow tract gradient <30 mm Hg at rest and <50 mm Hg with Valsalva was achieved in 97 (68%) patients treated with aficamten and 10 (7%) patients who received placebo ($P < 0.001$) (Figure 1A). As early as week 8, following completion of dose titration and achievement of steady-state dose, a complete hemodynamic response was achieved in 100 (70%) patients treated with aficamten and 12 (9%) who received placebo ($P < 0.001$). In

FIGURE 1 Clinical Response Measures in Patients With Obstructive Hypertrophic Cardiomyopathy From Baseline to Week 24



(A) Complete hemodynamic response (rest gradient <30 mm Hg and Valsalva <50 mm Hg). (B) Symptomatic response (≥1 improvement in NYHA functional class and/or ≥10 increase in Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS). (C) Exercise response (peak oxygen uptake [pVO_2] ≥1.5 mL/kg/min). (D) Proportion of patients with ≥50% reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) relative to baseline.

addition, the magnitude of rest and Valsalva gradient reductions was greater in those treated with aficamten compared to placebo, decreasing respectively from 55 ± 27 mm Hg to 20 ± 17 mm Hg at rest (placebo-corrected difference −40 mm Hg; 95% CI: −46 to −34 mm Hg; $P < 0.001$) and from 83 ± 32 mm Hg to 35 ± 25 mm Hg with Valsalva (placebo-corrected difference −50 mm Hg; 95% CI: −57 to −44 mm Hg; $P < 0.001$).

Heart failure symptoms (NYHA functional class and/or KCCQ-CSS). At week 24, a significantly greater proportion of patients with oHCM treated with aficamten vs placebo experienced ≥1 functional class improvement in NYHA and/or a ≥10-point increase in KCCQ-CSS (n = 101 [71%] vs n = 59 [42%]; $P < 0.001$) (Figure 1B). Of the 101 symptomatic responders on aficamten, 18 (18%) achieved a ≥10-point improvement in KCCQ-CSS score with no improvement in NYHA functional class, 31 (31%) had a <10-point improvement in KCCQ but ≥1 functional class improvement in NYHA, and the remaining 52 (51%) patients experienced an improvement in both NYHA functional class and KCCQ (vs 13 [9%] treated with placebo) ($P < 0.001$).

At end of treatment, 55 of 142 aficamten patients (39%) improved from NYHA functional class II to I, 15 (11%) from class III to I, 13 (9%) from class III to II, 54 (38%) with no change, and 3 (2%) worsened from class II to III. For KCCQ-CSS at end of treatment, 70 (49%) patients experienced a moderate to large improvement ≥10 points, 18 (13%) had a small change of ≥5 to <10 points, and 52 (37%) had no significant change or worsening (<+5 points) (2 patients withdrew early).

Exercise capacity. An improvement in exercise capacity with a pVO_2 ≥1.5 mL/kg/min occurred in 66

TABLE 2 Change With Aficamten in Exercise Capacity by pVO_2 and Limiting Symptoms With NYHA Functional Class

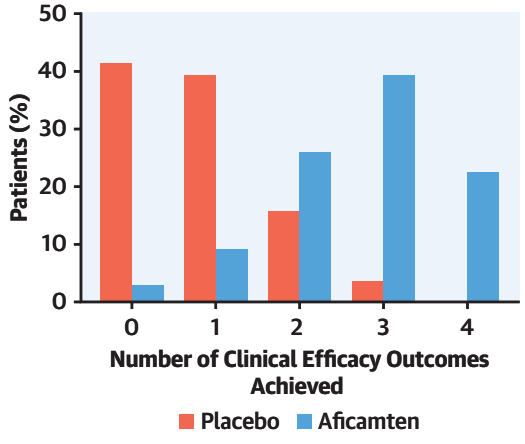
Change	Aficamten (n = 142)	Placebo (n = 140)
≥1.5 mL/kg/min increase in pVO_2 and ≥1 NYHA functional class improvement or ≥3.0 mL/kg/min increase in pVO_2 and no worsening of NYHA functional class	60 (42)	19 (14)
≥1.5 mL/kg/min increase in pVO_2 and ≥1 NYHA functional class improvement	44 (31)	9 (6)
≥3.0 mL/kg/min increase in pVO_2 and no worsening of NYHA functional class	37 (26)	13 (9)
≥3.0 mL/kg/min increase in pVO_2 and ≥1 NYHA functional class improvement	21 (15)	3 (2)
Common rate difference (vs placebo)	29	–
95% CI common rate difference	(19-39)	–
P value	<0.0001	–

Values are n (%) unless otherwise indicated.
Abbreviation as in Table 1.

(47%) patients receiving aficamten and in 34 (24%) receiving placebo ($P < 0.001$) (Figure 1C). The responder endpoint of pVO_2 ≥1.5 mL/kg/min and ≥1 improvement in NYHA functional class or pVO_2 ≥3.0 mL/kg/min^2 and no worsening in NYHA functional class was met by 42.3% of aficamten-treated and 13.6% of placebo-treated patients, for a placebo-corrected difference of 28.7% (95% CI: 18.8%-38.6%; $P < 0.001$) and an NNT of 3.0 (Table 2).

Cardiac biomarkers. Compared with baseline, the proportion of patients in the aficamten group with a 50% relative reduction in NT-proBNP and hs-troponin concentrations at week 24 was significantly greater than in the placebo group (84% vs 8% [Figure 1D] and 31% vs 4%, respectively; $P < 0.001$). Geometric mean values of NT-proBNP decreased from baseline vs week 24 from 735 ng/L (604 vs 894 ng/L) to 143 ng/L (120 vs 171 ng/L) in patients receiving aficamten and remained unchanged from 710 ng/L (587 vs 859 ng/L) to 717 ng/L (596 vs 863 ng/L) in placebo group, whereas hs-troponin decreased from 17.1 ng/L (14.1 vs 20.8 ng/L) to 9.5 ng/L (8.0 vs 11.3 ng/L) with aficamten and remained unchanged from 16.6 ng/L (13.3 vs 20.7 ng/L) to 16.5 ng/L (13.7 vs 19.9 ng/L) with placebo ($P < 0.001$ for both comparisons compared with placebo).

FIGURE 2 Number of Clinical Efficacy Outcomes Achieved at End of Treatment With Aficamten vs Placebo



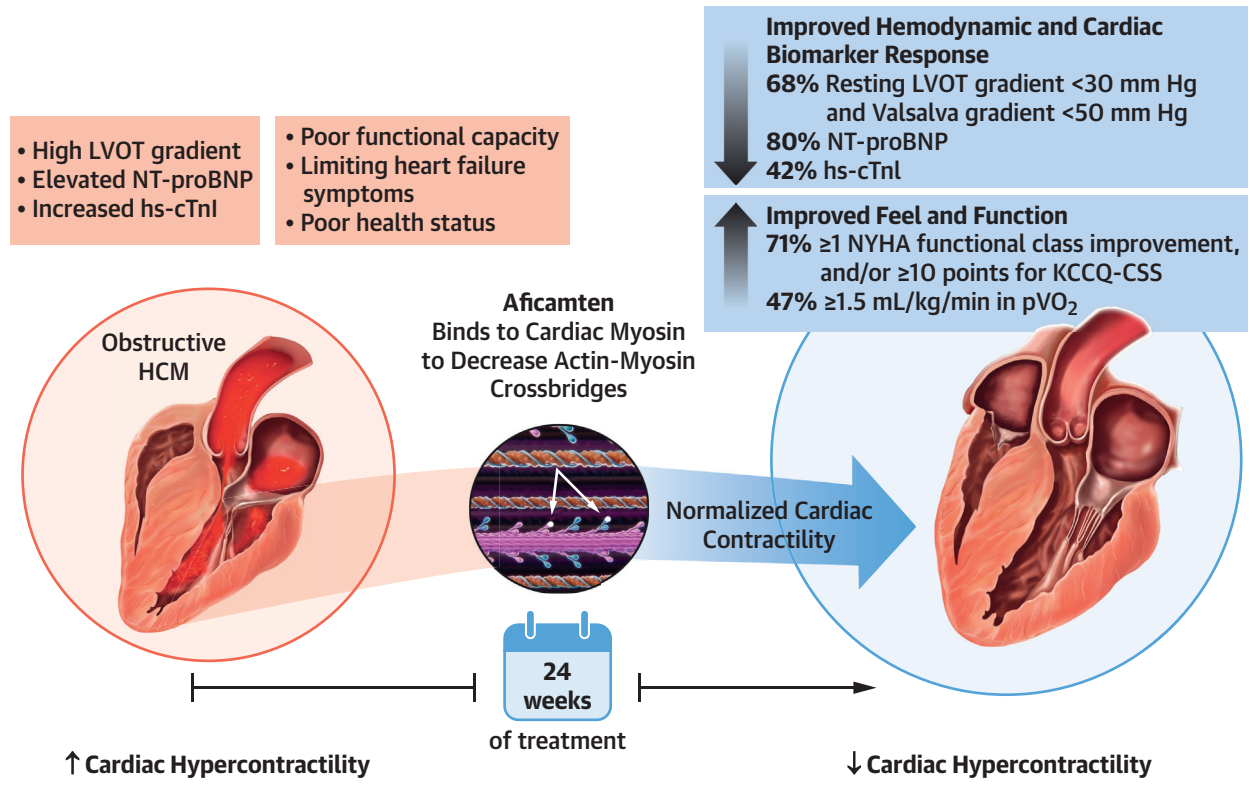
ELIGIBILITY FOR SRT. At study entry, 61 (22%) patients with oHCM were eligible for SRT based on guideline criteria (LV outflow gradient ≥50 mm Hg at rest or Valsalva and NYHA functional class III or IV), of which 32 (23%) were assigned to aficamten and 29 (20%) to placebo. At week 24, 28 (88%) patients treated with aficamten were no longer guideline-eligible for SRT vs 15 (52%) on placebo ($P < 0.002$).

Aficamten patients were no longer guideline-eligible for SRT at week 24 due to improvement in both symptoms and gradient in 18 patients, improvement to NYHA functional class II or I in 9 patients, or an outflow gradient <50 mm Hg in 1 patient. In contrast, 15 (52%) patients on placebo were not eligible for SRT at week 24 including: 10 patients who improved to class II or I, or an outflow gradient <50 mm Hg in 3 patients, or an improvement in both symptoms and gradient in 2 patients.

GLOBAL CLINICAL RESPONSE TO AFICAMTEN. At week 24 of treatment, 138 (97%) patients treated with aficamten achieved ≥1 of the prespecified clinical response measures vs 82 (59%) placebo patients ($P < 0.001$). Within the aficamten treatment arm, 32 (23%) improved in all 4 outcome measures, 56 (39%) improved in 3 measures, 37 (26%) improved in 2, and 13 (9%) patients achieved 1 measure. Correspondingly in the placebo arm, no patient achieved all 4 measures, 5 (4%) achieved 3 measures, 22 (16%) achieved 2, and 55 (39%) achieved 1 measure (Figure 2, Central Illustration). For each of the outcome measures, the number of patients needed to treat with aficamten to achieve benefit ranged from 1.3 to 4.5 (Table 3). Individual patient responses to these outcome measures for aficamten compared to placebo are shown in Supplemental Figure 1.

A categorical reduction ≤50% in NT-proBNP was the most common outcome measure achieved with aficamten treatment (84%), followed by improvement in limiting symptoms (71%) and hemodynamic response (68%). An improvement in limiting symptoms was the most common outcome measure achieved with placebo treatment (42%), followed by

CENTRAL ILLUSTRATION **Global Efficacy of Aficamten in Obstructive Hypertrophic Cardiomyopathy**



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HCM = hypertrophic cardiomyopathy; hs-cTnI = high-sensitivity cardiac troponin I; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro-B-type natriuretic peptide; pVO_2 = peak oxygen uptake; SRT = septal reduction therapy.

improvement in pVO_2 (24%) and categorical reduction ≤50% in serum levels of NT-proBNP (8%).

DISCUSSION

Clinical trials often focus on analyses of a single or composite outcome to describe efficacy of treatment.[2,24] However, understanding the totality of benefit is important to patients and physicians who consider initiating new treatments. In this analysis of the phase 3 SEQUOIA-HCM trial, patients with symptomatic oHCM treated with the novel cardiac myosin inhibitor aficamten had significant benefits across a multitude of outcome domains. Over the relatively short treatment period of 24 weeks, nearly all patients (97%) treated with aficamten experienced a clinically meaningful improvement in one or more measures, including decreases in LV outflow tract gradients, relief in the burden of limiting symptoms, enhanced exercise capacity as assessed by CPET, and substantial lowering of cardiac biomarkers. Notably, approximately 80% of those treated with aficamten experienced improvements in multiple efficacy outcomes, with more than one-fifth achieving improvement in all 4 domains, compared with zero patients in the placebo group.

The expansive clinical and hemodynamic benefits of aficamten can be attributed to its effect on LV outflow tract gradients, which is the HCM disease feature that represents the most powerful determinant of disease-related morbidity.[1,4,6,27,28] Aficamten mitigates outflow obstruction by targeting myocardial hypercontractility and consequently addressing the primary functional driver of obstruction (ie, mid-systolic contact of the mitral valve with the ventricular septum).[18,20,21,29] At the end of the treatment period, aficamten was associated with a complete hemodynamic response (rest and Valsalva gradient <30 mm Hg and <50 mm Hg, respectively) in two-thirds of patients.

TABLE 3 Impact of Treatment Effect Relative to Placebo

Outcome	Placebo	Aficamten	Risk Difference (95% CI), %	NNT (95% CI)
Complete hemodynamic response	10 (7.1)	97 (68.3)	+61.2 (+52.4 to +69.9)	1.6 (1.4-1.9)
Improvement in heart failure symptoms	59 (42.1)	101 (71.1)	+28.9 (+17.9 to +40.1)	3.5 (2.5-5.6)
Enhanced exercise capacity	34 (24.3)	66 (46.5)	+22.2 (+11.3 to +33.0)	4.5 (3.0-8.8)
Reduction in NT-proBNP	11 (7.9)	119 (83.8)	+75.9 (+68.4 to +83.5)	1.3 (1.2-1.5)

Values are n (%) unless otherwise indicated.
NNT = number needed to treat; other abbreviation as in Table 1.

Decreases in outflow tract gradients with aficamten occurred early in treatment, with the vast majority of treated patients achieving a complete hemodynamic response following the end of the dose-titration phase (week 6); this benefit remained throughout the maintenance phase (weeks 8 to 24). Such relatively prompt lowering of outflow gradients may fulfill an aspiration currently not completely addressed with other medical therapies for oHCM available today,[2,7,24] and reflects the benefits of a relatively short half-life of aficamten, which allows dose titration as frequently as every 2 weeks.[18]

Circulating concentrations of NT-proBNP were reduced to <50% of baseline in most patients treated with aficamten. Increased concentrations of this cardiac biomarker, along with troponins, have been associated with adverse outcome in HCM.[16] In addition, in non-HCM heart failure populations, decreases in NT-proBNP of this same magnitude have been associated with lower rates of cardiovascular death and hospitalization. Although it remains uncertain whether reducing levels of NT-proBNP may translate into similar clinical benefits in HCM, these support the beneficial pathophysiologic effects of aficamten on LV wall stress and cardiomyocyte damage.[17]

The relief of outflow tract gradients paralleled other particularly favorable changes with aficamten, including the 71% of patients who experienced a clinically meaningful improvement in limiting symptoms. Close to half of patients treated with aficamten resolved their symptoms completely (ie, improved to NYHA functional class I) by the end of the treatment period. In addition, when assessing response to treatment with respect to both how patients feel (ie, NYHA functional class) and function (exercise capacity), measures that represent the primary treatment goal in HCM,[1,2,4,6] benefit was achieved in 42% of those treated with aficamten over the 24-week study period (Table 2).

In the primary analysis, we elected to characterize the impact of aficamten on symptom burden by combining the traditional physician-derived NYHA functional classification and the validated patient-reported outcome instrument KCCQ-CSS. It is increasingly recognized that, in HCM, relevant discrepancies exist between patients' and physicians' interpretation of symptom burden.[9-12] In this regard, KCCQ-CSS has shown excellent sensitivity for detection of clinically meaningful changes in HCM heart failure symptoms and quality of life.[11] This principle was underscored by findings from this analysis that showed that nearly 1 in 5 patients with oHCM who reported a moderate to large improvement in health status (KCCQ-CSS ≥10 points) with aficamten were not deemed by their physician to have improved. Therefore, the clinical benefit of aficamten, with respect to the most relevant treatment priority of symptom relief and improved quality of life, may be less than appreciated if assessed using only the NYHA functional classification.

Similar to mavacamten in the EXPLORER-HCM (Clinical Study to Evaluate Mavacamten [MYK-461] in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy) trial, we also observed an important placebo effect in this trial. Although most notable with respect to symptoms, objective measures were also observed to change in placebo group, including improvements in exercise capacity, NT-proBNP, and outflow obstruction. The mechanisms responsible for changes in placebo are likely complex, including how an HCM patient perceives the impact of their chronic, lifelong, and often progressive disease on daily symptoms and quality of life. In addition, HCM pathophysiology itself is unique in that its expression is inherently variable and likely lends itself to otherwise unanticipated placebo effects. For example, the magnitude of outflow obstruction can be substantially influenced by alterations in loading conditions or myocardial contractility. For this reason, interventions that we may not easily appreciate, such as changes in lifestyle or behavior (because of the placebo effect) can affect magnitude of outflow gradients and in the process influence both subjective and objective outcome

measures. However, for each of the clinically relevant outcomes, aficamten was associated with a substantially more favorable NNT (1.3 to 4.5), which shows a large magnitude of treatment effect relative to placebo.

These data have important potential implications for the management of oHCM. In most patients with debilitating symptoms not well controlled with beta-blockers and/or calcium-channel blockers (with or without disopyramide), the addition of aficamten provides the opportunity to restore normal (or near normal) quality of life. This potential of aficamten is particularly relevant to those patients with oHCM who are guideline-eligible for SRT due to advanced symptoms and high outflow gradients. Over the short treatment period, aficamten treatment resulted to transiting to a less symptomatic NYHA functional status (class II or I) and/or reduced gradients to <50 mm Hg and therefore below the current guideline-based threshold for consideration of SRT in the majority of these patients.[6] In this regard, although SEQUOIA-HCM did not directly compare aficamten to surgical myectomy and alcohol septal ablation, these data demonstrate aficamten as a potential alternative medical option to SRT, similar to the experience with mavacamten in VALOR-HCM (A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who are Eligible for Septal Reduction Therapy).[30] This is particularly relevant for those patients who do not wish to pursue invasive therapies, are at increased operative risk, or do not have access to procedural expertise.

STUDY LIMITATIONS. The outcome measures were prespecified based on currently accepted threshold of efficacy in HCM; however, the dichotomous analysis may have resulted in the underestimation in some patients with HCM of a clinically meaningful response to aficamten. The relatively short treatment duration limits the opportunity to determine if, with longer exposure to aficamten, additional clinical efficacy outcomes may be achieved in patients who did not experience benefit after 24 weeks of therapy. FOREST-HCM (Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of Aficamten in Adults With HCM; NCT04848506), the ongoing open-label extension study of aficamten with up to 5 years of treatment planned, is intended to provide greater insight into these questions. In addition, the impact of aficamten on potentially beneficial changes on the structural phenotype, including changes in left atrial size, LV mass, or myocardial fibrosis will be comprehensively assessed in other follow-up investigations using multimodality cardiovascular imaging. These results are not necessarily translatable to the one-third of patients with nonobstructive HCM; however, the ongoing phase 3 randomized clinical trial ACACIA-HCM (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic nHCM; NCT06081894) is intended to assess the efficacy and safety of aficamten in this setting.

CONCLUSIONS

Treatment with aficamten, a novel cardiac myosin inhibitor, in patients with oHCM was associated with broad clinical efficacy, including rapid and sustained reductions in outflow gradients, significant relief in burden of limiting symptoms, enhanced exercise capacity, and improvement in cardiac biomarkers. The combined benefit of aficamten on hemodynamics and symptomatic status also resulted in converting patients with oHCM who were guideline-eligible for SRT at baseline to no longer meeting these criteria. These results underscore the wide-ranging potential of aficamten for treatment of patients with symptomatic obstructive HCM.

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ADDRESS FOR CORRESPONDENCE: Dr Martin S. Maron, HCM Center at Lahey Clinic, 41 Mall Road, Burlington, Massachusetts 01805, USA. E-mail: martin.maron@lahey.org. X handle: @MartinMaronMD.

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APPENDIX For supplemental material and a supplemental figure, please see the online version of this paper.

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