

ORIGINAL RESEARCH

Effect of Aficamten on Health Status Outcomes in Obstructive Hypertrophic Cardiomyopathy

Results From SEQUOIA-HCM



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ABSTRACT

BACKGROUND A primary goal in treating obstructive hypertrophic cardiomyopathy (oHCM) is to improve patients' health status: their symptoms, function, and quality of life. The health status benefits of aficamten, a novel cardiac myosin inhibitor, have not been comprehensively described.

OBJECTIVES This study sought to determine the effect of aficamten on patient-reported health status, including symptoms of fatigue, shortness of breath, chest pain, physical and social limitations, and quality of life.

METHODS SEQUOIA-HCM (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic oHCM) randomized symptomatic adults with oHCM to 24 weeks of aficamten (n = 142) or placebo (n = 140), followed by a 4-week washout. The Kansas City Cardiomyopathy Questionnaire (KCCQ) and Seattle Angina Questionnaire 7-item (SAQ7) were serially administered. Changes in mean KCCQ—Overall Summary Score (KCCQ-OSS) and SAQ7—Summary Score (SAQ7-SS) from baseline to 24 weeks and following treatment withdrawal were compared using linear regression adjusted for baseline scores and randomization strata. Proportions of patients with clinically important changes were compared.

RESULTS Among 282 participants, the mean age was 59 ± 13 years, 115 (41%) were female, and 223 (79%) were White. Baseline KCCQ-OSS (69.3 ± 20.1 vs 67.3 ± 18.8) and SAQ7-SS (72.0 ± 21.0 vs 72.4 ± 18.3) were similar between aficamten and placebo groups. Treatment with aficamten, compared with placebo, improved both the mean KCCQ-OSS (13.3 ± 16.3 vs 6.1 ± 12.6; mean difference: 7.9; 95% CI: 4.8–11.0; *P* < 0.001) and SAQ7-SS (11.6 ± 17.4 vs 3.8 ± 14.4; mean difference: 7.8; 95% CI: 4.7–11.0; *P* < 0.001) at 24 weeks, with benefits emerging within 4 weeks. No heterogeneity in treatment effect was found across subgroups. A much larger proportion of participants experienced a very large health status improvement (≥20 points) with aficamten vs placebo (KCCQ-OSS: 29.7% vs 12.4%, number needed to treat: 5.8; SAQ7-SS: 31.2% vs 13.9%, number needed to treat: 5.8). Participants' health status worsened significantly more after withdrawal from aficamten than placebo (KCCQ-OSS: −16.2 ± 19.0 vs −3.0 ± 9.6; *P* < 0.001; SAQ7-SS: −17.4 ± 21.4 vs −2.5 ± 13.3), further confirming a causal effect of aficamten.

CONCLUSIONS In patients with symptomatic oHCM, treatment with aficamten resulted in markedly improved health status, including significant improvement in chest pain-related health status, than placebo. (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic oHCM [SEQUOIA-HCM]; [NCT05186818](https://clinicaltrials.gov/ct2/show/study/NCT05186818)) (JACC. 2024;84:1773–1785) © 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 AND ACRONYMS

KCCQ = Kansas City
Cardiomyopathy Questionnaire

LV = left ventricular

LVEF = left ventricular ejection
fraction

LVOT = left ventricular outflow
tract

LVOT-G = left ventricular
outflow tract gradient

NNT = number needed to treat

oHCM = obstructive
hypertrophic cardiomyopathy

OSS = Overall Summary Score

SAQ7 = Seattle Angina
Questionnaire 7-item

SS = Summary Score

Obstructive hypertrophic cardiomyopathy (oHCM) is a condition characterized by excessive actin-myosin cross-bridges, resulting in left ventricular (LV) hypercontractility, LV hypertrophy, myocardial fibrosis, and obstruction of the left ventricular outflow tract (LVOT).¹ Abnormal myocardial structure and function also affect coronary blood flow through distal vessel compression and impaired microcirculation.^{2,3} Accordingly, those living with oHCM frequently experience shortness of breath, palpitations, fatigue, and chest pain that can affect their function and quality of life.⁴ A primary goal in managing oHCM is to improve patients' health status. However, medical therapies, aside from mavacamten,⁵ the first-in-class

cardiac myosin inhibitor, have limited data and uncertain clinically meaningful effects on health status.

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Aficamten, a next-in-class small-molecule cardiac myosin inhibitor, reduces actin-myosin cross-bridging and relieves myocardial hypercontractility.⁶ In early phase studies, aficamten demonstrated important reductions in left ventricular outflow tract gradients (LVOT-Gs) and markedly improved patients' symptoms.⁷⁻⁹ More recently, the SEQUOIA-HCM (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic oHCM; [NCT05186818](#)) study demonstrated that aficamten significantly improved measures of exercise capacity (peak VO₂), as measured by cardiopulmonary exercise testing.¹⁰ The 23-item Kansas City Cardiomyopathy Questionnaire (KCCQ)—Overall Summary Score (OSS) and the 7-item Seattle Angina Questionnaire (SAQ7)—Summary Score

(SS) were collected to better understand the impact of treatment from patients' perspectives. While the KCCQ-OSS has been validated in oHCM and quantifies the severity and frequency of fatigue, shortness of breath, and swelling, along with their impact on physical and social function and patients' disease-specific quality of life, it does not capture frequency and impact of chest pain, which were assessed by the SAQ7-SS. This prespecified report provides the first in-depth analyses of the health status outcomes of aficamten, along with patient-centered descriptions of the clinical magnitude of these effects, so that patients and providers can have a better understanding of treatment benefit from patients' perspectives.

METHODS

SEQUOIA-HCM was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial that enrolled adult participants with symptomatic oHCM. Details of the study design have previously been published.¹¹ Participants were randomized 1:1 to either aficamten or placebo with the KCCQ, SAQ7, and other measures of disease burden collected at each study visit. Doses of aficamten (range 5-20 mg) or matching placebo were adjusted during the first 6 weeks of the study according to site-interpreted echocardiographic criteria with goal of reducing LVOT-Gs while maintaining left ventricular ejection fraction (LVEF) at $\geq 50\%$. Key inclusion criteria were LV septal hypertrophy ≥ 15 mm, or ≥ 13 if genetic testing or family history were indicative of oHCM, an LVOT-G ≥ 30 mm Hg at rest and ≥ 50 mm Hg with Valsalva physiology, and an LVEF $\geq 60\%$. Participants were excluded if they had significant valvular heart disease other than mitral regurgitation caused by systolic anterior motion, ventricular hypertrophy

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from infiltrative diseases, uncontrolled atrial or ventricular arrhythmias, prior or planned septal reduction therapies, inability to complete cardiopulmonary exercise testing, or prior cardiac myosin inhibitors treatment. Ethical approval of the study was approved institutionally by the Internal Review Board at each participating site and each participant signed informed consent prior to randomization.

PATIENT-REPORTED OUTCOMES. The KCCQ is a 23-item patient-reported outcome, originally developed for patients with heart failure to quantify symptoms, function, and quality of life¹² and has recently been validated in the oHCM population.¹³ Individual KCCQ domains measure symptoms, physical and social limitations, and quality of life and are combined into a Clinical Summary Score (the average of the total symptom and physical limitation domains) and an OSS (including all 4 domains) to provide a more complete description of patients' health status.¹⁴ The KCCQ has a 2-week recall period and was collected at baseline and 2, 4, 6, 8, 12, 16, 20, 24, and 28 weeks.

Although the KCCQ captures many of the key symptoms experienced by those with oHCM, it does not quantify chest pain (angina).⁴ The SAQ7 is a 7-item patient-reported outcome that was collected to capture the frequency and impact of chest pain on participants' health status.¹⁵ Like the KCCQ, the SAQ7 includes the frequency of chest pain, the physical limitations associated with chest pain, and its impact on patients' quality of life. Domains are combined into the SS (SAQ7-SS) that most comprehensively quantifies the impact of chest pain on patients' health status.¹⁶ Although not yet validated in oHCM, it was included to provide a more comprehensive assessment of aficamten on clinical outcomes important to patients with oHCM, given the prevalence and relevance of chest pain on patients' quality of life.⁴ The SAQ7 has a 4-week recall period and was collected at baseline and 4, 8, 12, 16, 20, 24, and 28 weeks.

Both the KCCQ and SAQ7 range from 0 to 100, with higher scores indicating better health status. Scores from 0 to 24 represent very poor to poor health status, from 25 to 49 are poor to fair, from 50 to 74 are fair to good, and from 75 to 100 are good to excellent.^{12,16} For the SAQ7-Angina Frequency Score, scores from 0 to 30 reflect daily chest pain, 31 to 60 indicate weekly symptoms, 61 to 99 monthly chest pain, and a score of 100 indicates no chest pain over the prior month.¹⁶

When assessing the magnitude of treatment benefit for an individual participant, decreases in

scores ≤ -5 points indicate clinically important deterioration; scores between -5 and <5 represent clinical stability; 5 and <10 reflect small but important improvements; and 10 and <15 suggest a moderately large improvement; changes in scores of 15 to <20 are a large improvement; and improvements by ≥ 20 are very large changes from both patients' and clinicians' perspectives.¹⁷ These thresholds were selected because they have been validated for the KCCQ in oHCM,¹³ but thresholds for interpreting the SAQ7 are extrapolated from its use in chronic epicardial coronary disease. Because the majority of chest pain in oHCM is due to increased wall stress and microvascular dysfunction, data relating SAQ7 scores to myocardial blood flow reserve and those with microvascular disease support its application to the oHCM population.^{18,19} Culturally and linguistically appropriate versions of each questionnaire were used in each country.²⁰

STATISTICAL ANALYSIS. Participants were included in this prespecified analysis if they had baseline and follow-up patient-reported outcome data. Whereas the KCCQ-Clinical Summary Score was a prespecified secondary endpoint in SEQUOIA-HCM given its qualification by the U.S. Food and Drug Administration, the OSS includes the Social Limitation Score and Quality of Life score to more completely quantify the impact of treatment on patients' symptoms, function, and quality of life. Accordingly, for this analysis, the primary endpoints were the change in KCCQ-OSS and SAQ7-SS from baseline to week 24. We additionally analyzed the impact of treatment withdrawal between weeks 24 and 28 on patients' health status.

Baseline characteristics by treatment group were summarized using mean $\pm$ SD or median (Q1-Q3) for continuous variables, as well as counts and percentages for categorical variables. To evaluate the treatment effect of aficamten, changes in KCCQ-OSS and SAQ7-SS were evaluated using linear regression models adjusted for the baseline and randomization stratification variables (beta-blocker use, cardiopulmonary exercise test modality). This method was chosen given the low prevalence of missing data. Heterogeneity of treatment benefit was explored among predefined patient characteristics (sex, age, body mass index, LVEF, N-terminal pro-B-type natriuretic peptide, peak VO_2 , cardiopulmonary exercise test modality, baseline oHCM treatment, and baseline health status) and tested with interaction terms as exploratory endpoints. Effect sizes are reported as point estimates with 95% CIs. A prespecified

TABLE 1 Baseline Characteristics By Treatment Group

	Placebo (n = 140)	Aficamten (n = 142)
Demographics		
Age, y	59.0 ± 13.3	59.2 ± 12.6
Female	59 (42.1)	56 (39.4)
White	115 (82.1)	108 (76.1)
Asian	25 (17.9)	29 (20.4)
Black	0 (0)	3 (2.1)
Other	0 (0)	2 (1.4)
North American	45 (32.1)	49 (34.5)
Chinese	22 (15.7)	24 (16.9)
European and/or Israeli	73 (52.1)	69 (48.6)
Medical history		
Hypertension	70 (50.0)	75 (52.8)
Known pathogenic sarcomere variant	25 (17.9)	24 (16.9)
Family history of HCM	34 (24.3)	41 (28.9)
Paroxysmal atrial fibrillation	20 (14.3)	21 (14.8)
Coronary artery disease	16 (11.4)	19 (13.4)
Diabetes mellitus	9 (6.4)	14 (9.9)
Permanent atrial fibrillation	1 (0.7)	2 (1.4)
BMI at baseline, kg/m ²	28.2 ± 3.7	28.0 ± 3.8
Baseline HCM therapy		
Beta-blocker	87 (62.1)	86 (60.6)
Calcium-channel blocker	36 (25.7)	45 (31.7)
Disopyramide	20 (14.3)	16 (11.3)
Implantable cardioverter-defibrillator	17 (12.1)	22 (15.5)
Baseline measures of HCM severity		
NYHA functional class		
II	106 (75.7)	108 (76.1)
III	33 (23.6)	34 (23.9)
IV	1 (0.7)	0 (0.0)
NT-proBNP, pg/mL	692 (335-1,795)	818 (377-1,630)
hs-cTnI, ng/L	12 (8, 25)	13 (8, 34)
Peak LVOT-G at rest, mm Hg	55 ± 32	55 ± 27
Peak LVOT-G with Valsalva, mm Hg	83.3 ± 32	82.9 ± 32
LVEF, %	75 ± 6	74.8 ± 5.5
LV maximal wall thickness, cm	2.1 ± 0.3	2.1 ± 0.3
Cardiopulmonary exercise testing		
CPET modality: cycle ergometer	63 (45.0)	64 (45.1)
CPET modality: treadmill	77 (55.0)	78 (54.9)
Total workload, W	125 ± 42	120 ± 39
Peak VO ₂ , mL/kg/min	18.6 ± 4.5	18.4 ± 4.4
Predicted oxygen uptake, %	57.6 ± 13.0	56.2 ± 10.6
Peak respiratory exchange ratio	1.18 ± 0.09	1.19 ± 0.11
Baseline health status		
KCCQ		
OSS	67.3 ± 18.8	69.3 ± 20.1
CSS	73.7 ± 17.6	75.6 ± 18.4
TSS	73.7 ± 19.6	76.6 ± 19.9
PLS	73.7 ± 18.2	74.6 ± 19.3
SLS	67.7 ± 24.1	68.6 ± 24.3
QOL	53.7 ± 22.6	56.8 ± 26.4

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experienced clinically important changes from baseline, as described.¹² The number needed to treat (NNT) was estimated by calculating the reciprocal of the absolute difference between the aficamten and placebo groups.

Because the missingness of the patient-reported outcomes was negligible (<3% across all time points), no imputations or sensitivity analyses were performed. Analyses were performed by an independent academic research group using STATA version 18 (StataCorp LLC). No statistical adjustments were made for the multiple comparisons, given the high correlation among the health status outcomes.²¹

RESULTS

TRIAL POPULATION. A total of 282 participants were randomized and subsequently included in the analyses, of whom 142 (50.3%) received aficamten. The mean age was 59.2 ± 12.6 years and 115 (40.8%) were women. The overall baseline characteristics were similar between treatment arms, including baseline KCCQ-OSS (69.3 ± 20.1 vs 67.3 ± 18.8) and SAQ7-SS (72.0 ± 21.0 vs 72.4 ± 18.3) and their domain scores (Table 1).

TREATMENT EFFECTS. The mean ± SD KCCQ-OSS and SAQ7-SS by study visit and treatment assignment are shown in Figure 1. The KCCQ-OSS (Figure 1A, Central Illustration) increased in both aficamten and placebo groups, but diverged in magnitude of improvement early during drug titration. Changes were sustained with statistically significant improvements until week 24, the end of the treatment period. The change in KCCQ-OSS from baseline to week 24 was 13.3 ± 16.3 in aficamten vs 6.1 ± 12.6 in placebo-treated participants (mean difference: 7.9; 95% CI: 4.8-11.0; *P* < 0.001). Similarly, the SAQ7-SS (Figure 1B, Central Illustration) improved more in those treated with aficamten (11.6 ± 17.4) than those treated with placebo (3.8 ± 14.4; mean difference: 7.8; 95% CI: 4.7-11.0; *P* < 0.001). The health status differences over time between aficamten and placebo for all domains of the KCCQ and SAQ7 are similar and are included in Supplemental Tables 1 to 8.

EFFECTS OF TREATMENT WITHDRAWAL. When treatment was withdrawn between weeks 24 and 28 (Figure 1), a decline in the health status of both treatment groups was observed, with much larger decrements in those who had been treated with aficamten. Compared with week 24, those in the aficamten arm experienced greater decreases in their KCCQ-OSS (−16.2 ± 19.0 vs 3.0 ± 9.6; *P* < 0.001) and SAQ7-SS (−17.4 ± 21.4 vs 2.5 ± 13.3; *P* < 0.001).

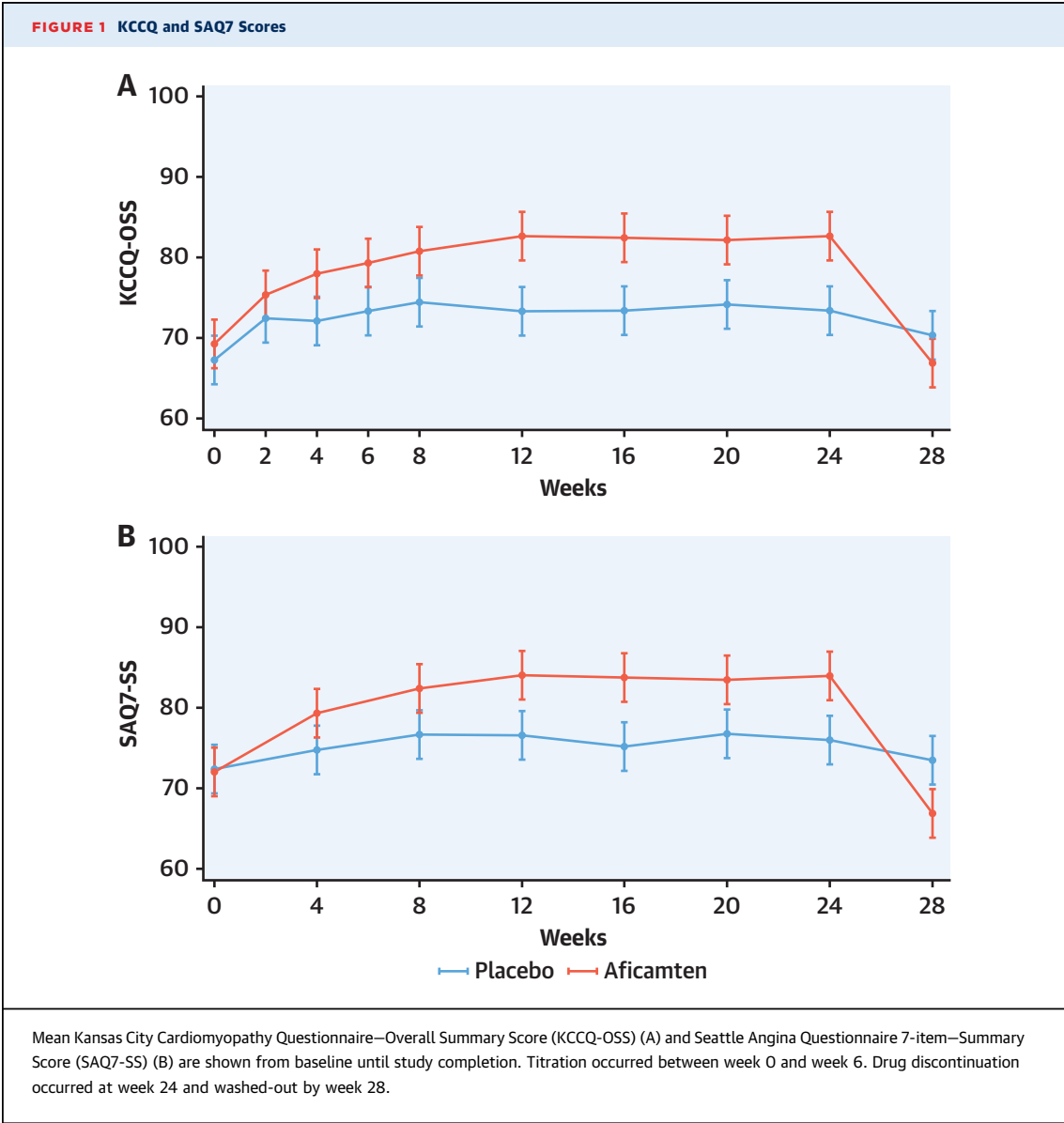
α of <0.05 was used to define statistical significance, without adjustment for multiple comparisons.

To quantify the patient-level impact of treatment, we also examined the proportions of patients who

RESPONDER ANALYSES OF PATIENT-LEVEL, CLINICALLY IMPORTANT HEALTH STATUS CHANGES. The proportions of the population experiencing different magnitudes of KCCQ-OSS and SAQ7-SS changes from baseline to week 24 are shown in [Figure 2](#) and the [Central Illustration](#). The largest differences in these distributions for the KCCQ-OSS were for those who experienced very large health status improvements (≥ 20 points). Of those treated with aficamten, 41 (29.7%) as compared with 17 (12.4%) of those treated with placebo experienced a ≥ 20 point improvement. This absolute difference of 17.3% equates to an estimated NNT of 5.8 (95% CI: 3.7-12.7) for 1 patient treated with aficamten to feel markedly better after 24 weeks, as compared with placebo

TABLE 1 Continued		
	Placebo (n = 140)	Aficamten (n = 142)
SAQ7		
SS	72.4 ± 18.3	72.0 ± 21.0
AF	83.5 ± 16.5	83.3 ± 15.7
PLS	71.4 ± 23.8	72.0 ± 24.9
QOL	61.5 ± 28.5	60.5 ± 29.8

Values are mean ± SD, n (%), or median (Q1-Q3).
AF = Angina Frequency Score; BMI = body mass index; CPET= cardiopulmonary exercise test; CSS= Clinical Summary Score; HCM = hypertrophic cardiomyopathy; hs-cTnI = high-sensitivity cardiac troponin I; KCCQ = Kansas City Cardiomyopathy Questionnaire; LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT-G = left ventricular outflow tract gradient; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OSS = Overall Summary Score; PLS = Physical Limitation Score; QOL = Quality of Life Score; SAQ7 = Seattle Angina Questionnaire 7-item; SLS = Social Limitation Score; SS = Summary Score; TSS = Total Symptom Score.



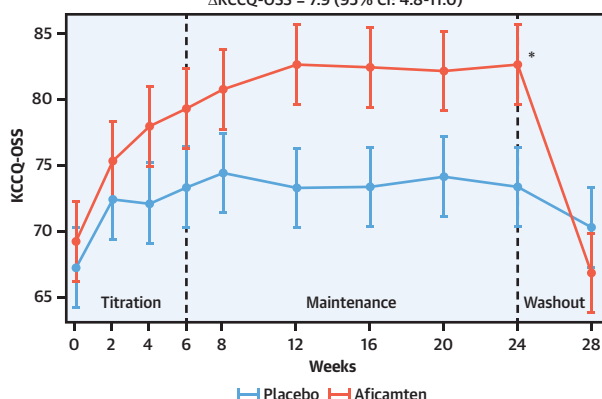
CENTRAL ILLUSTRATION Effect of Aficamten on Health Status Outcomes in Obstructive Hypertrophic Cardiomyopathy: Results From SEQUOIA-HCM

In the SEQUOIA-HCM trial, patients with obstructive hypertrophic cardiomyopathy on aficamten vs placebo for 24 weeks were more likely to have:



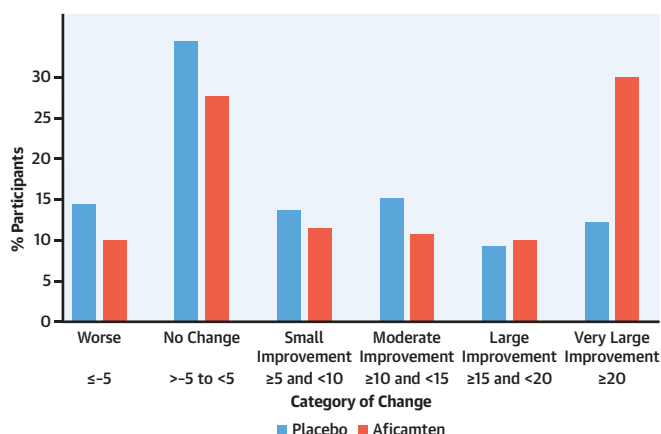
Mean Kansas City Cardiomyopathy Questionnaire Overall Summary Scores (KCCQ-OSS)

Δ KCCQ-OSS = 7.9 (95% CI: 4.8-11.0)



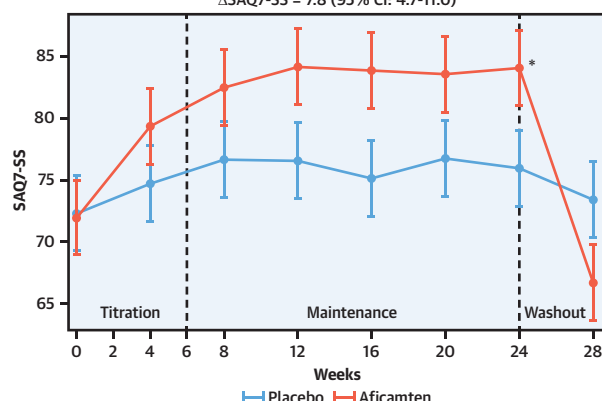
*P < 0.001 for between group difference in mean change from baseline to week 24

Distribution of Participants Changing by Clinically Important KCCQ-OSS Thresholds at 24 Weeks



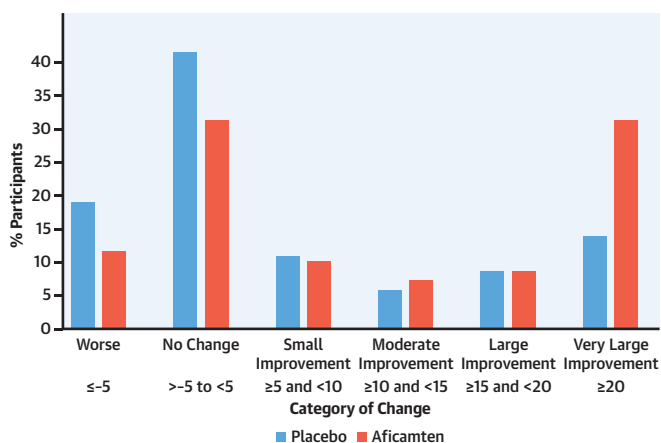
Mean Seattle Angina Questionnaire Summary Scores (SAQ7-SS)

Δ SAQ7-SS = 7.8 (95% CI: 4.7-11.0)



*P < 0.001 for between group difference in mean change from baseline to week 24

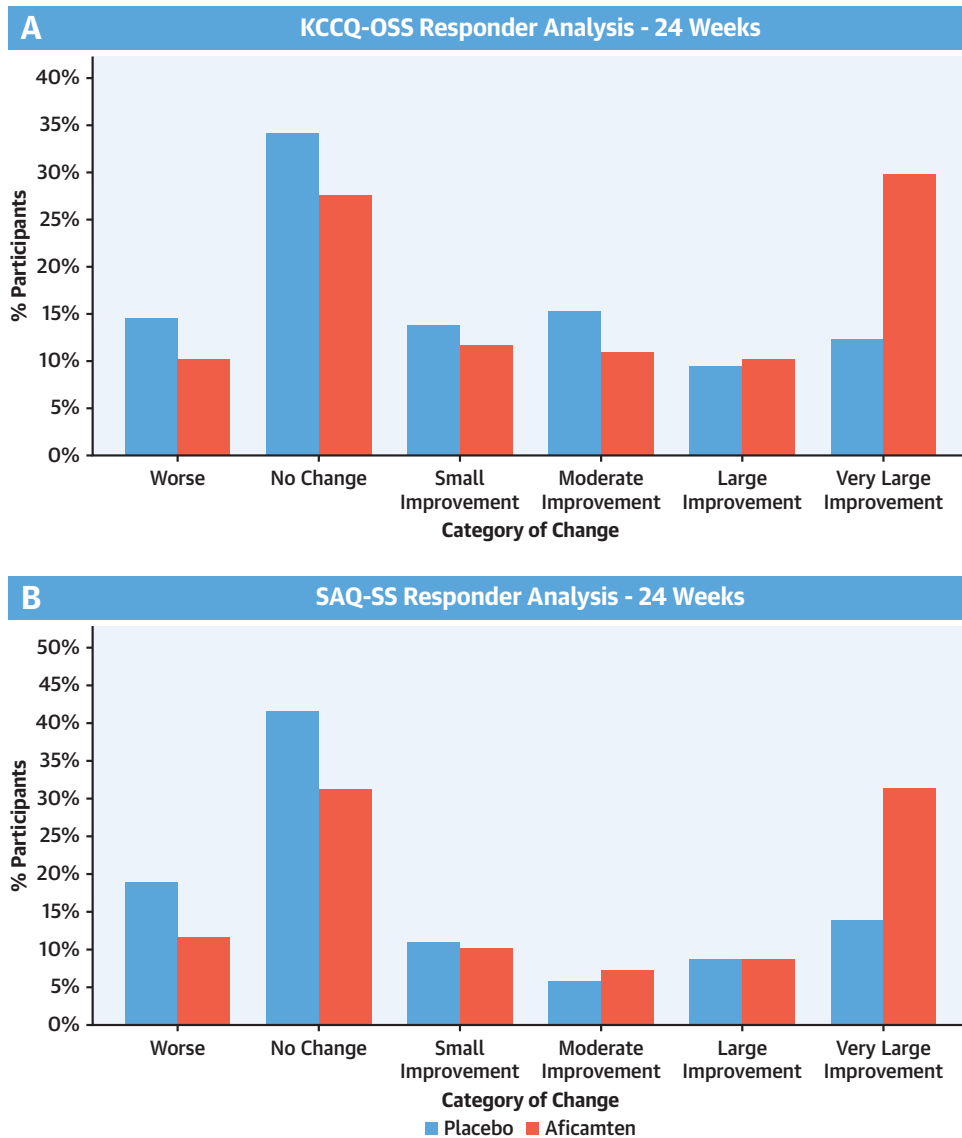
Distribution of Participants Changing by Clinically Important SAQ7-SS Thresholds at 24 Weeks



Sherrod IV CF, et al. JACC. 2024;84(19):1773-1785.

Mean KCCQ-OSS and SAQ7-SS scores over time and distributions of clinically important changes. KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire—Overall Summary Score; NNT = number needed to treat; SAQ7-SS = Seattle Angina Questionnaire 7-item—Summary Score; SEQUOIA-HCM = Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic oHCM.

FIGURE 2 KCCQ and SAQ Responder Analyses

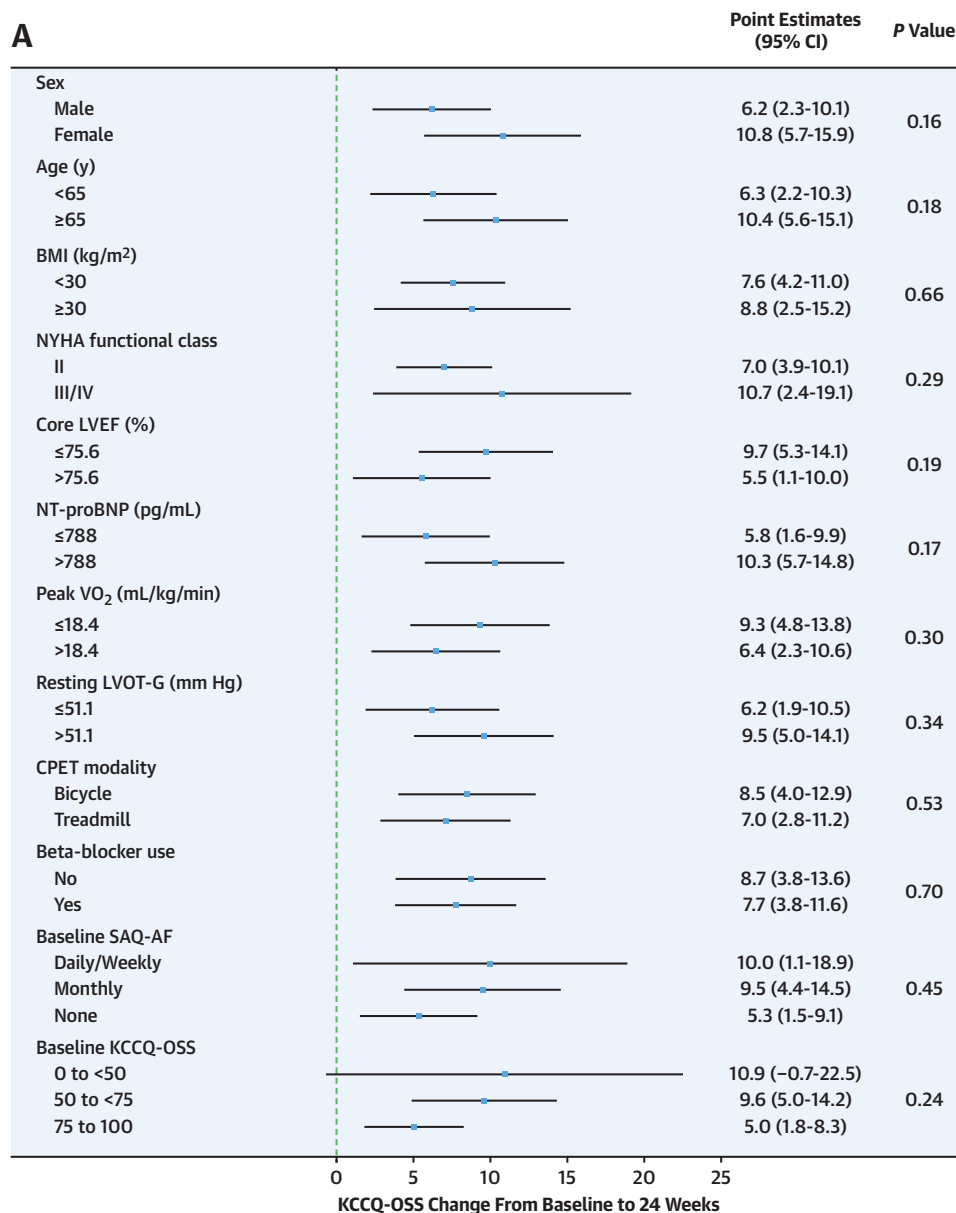


Proportions of clinically meaningful changes are described from baseline to week 24 for KCCQ-OSS (A) and SAQ7-SS (B). Changes in participants' health status were categorized as deteriorated (≤ -5), no clinically important change (> -5 to < 5), small to moderate improvement (≥ 5 and < 10), moderate to large improvement (≥ 10 and < 15), large improvement (≥ 15 to < 20), or very large improvement (≥ 20). Abbreviations as in [Figure 1](#).

treatment. These results were similar for the SAQ7-SS, with 43 (31.2%) of those assigned to aficamten experiencing a very large (≥ 20 point) improvement compared with 19 (13.9%) of those assigned to placebo. These differences also equate to an NNT of 5.8 (95% CI: 3.7-13.1) for 1 patient to have a very large improvement in SAQ7-SS with aficamten as compared with placebo.

SUBGROUP ANALYSES. [Figures 3A and 3B](#) demonstrates the treatment benefit of aficamten across subgroups for the KCCQ-OS and SAQ7-SS, respectively. No heterogeneity of treatment benefit was observed by participants' demographics (ie, sex, age, body mass index), echocardiographic characteristics (ie, LVEF and LVOT-G at rest), exercise capacity (ie, peak VO_2), N-terminal pro-B-type natriuretic

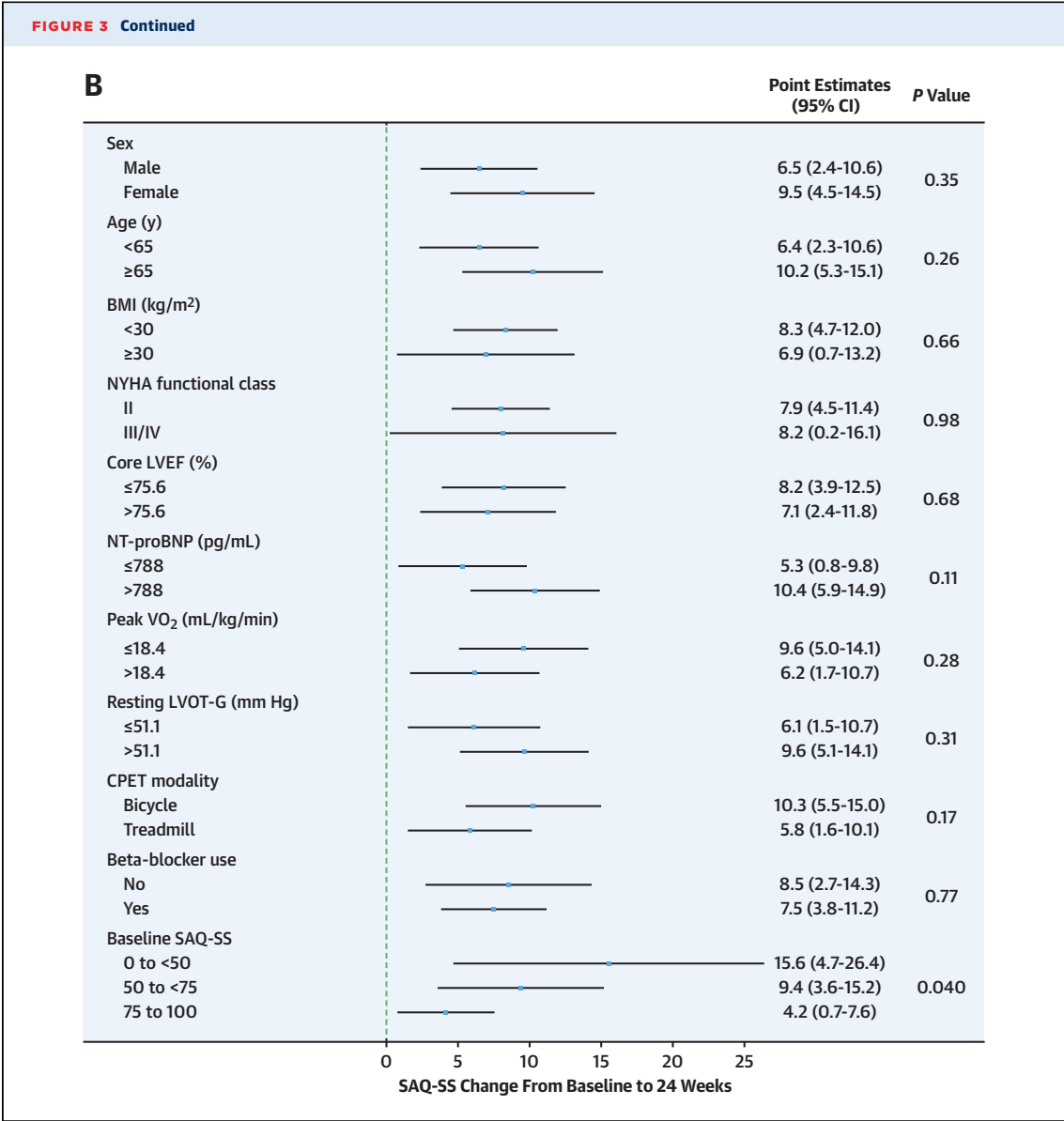
FIGURE 3 KCCQ and SAQ Subgroup Analyses



Interactions by participants' characteristics are depicted for the KCCQ-OSS (A) and SAQ7-SS (B). AF = Angina Frequency Score; BMI = body mass index; CPET= cardiopulmonary exercise test; LVEF = left ventricular ejection fraction; LVOT-G = left ventricular outflow tract gradient; NT-proBNP = N-terminal pro-B-type natriuretic peptide; Abbreviations as in [Figure 1](#).

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peptide levels, randomization strata (beta-blocker use at baseline, cardiopulmonary exercise test modality), or baseline KCCQ-OSS (all $P_{\text{interaction}} > 0.05$). Further, the baseline frequency of chest pain did not appear to affect KCCQ benefit. However, there was a signal that those with poor to fair overall angina-related health status (SAQ7-SS <50) attained greater benefit from aficamten (greater change with aficamten in SAQ7-SS = 15.6 points; 95% CI: 4.7-26.4) than those with good to excellent baseline angina-related health status (SAQ7-SS = 75-100; $P_{\text{interaction}} = 0.04$), although the latter still benefited from treatment (SAQ7-SS improvement with aficamten = 4.2; 95% CI: 0.7-7.6).



DISCUSSION

A primary goal of oHCM treatment is to improve patients’ health status. Therefore, understanding the impact of new treatments on symptoms, function, and quality of life from patients’ perspectives is essential. This prespecified analysis of the SEQUOIA-HCM trial provides the first comprehensive description of the health status benefits of aficamten, along with insights into the clinical magnitude of these improvements from patients’ perspectives, as measured by the KCCQ-OSS and SAQ7-SS. This occurred as early as week 2 with consistent and sustained benefit through 24 weeks of therapy.

These improvements were similar across clinical subgroups, with little evidence of heterogeneity in treatment effect. The observed population-level mean treatment effects were driven by a substantially greater proportion of aficamten-treated patients obtaining very large (≥20 points) clinical benefits from myosin inhibition after 24 weeks of therapy. The NNT for 1 patient to obtain this very large improvement in their health status (≥20 points) for both the KCCQ and SAQ7 was between 5 and 6. Further confirming the direct causal effect of aficamten, these health status benefits rapidly dissipated after treatment was stopped. Collectively, these data provide compelling support for aficamten

significantly improving the health status of patients with symptomatic oHCM.

These findings support and substantially extend the current published data for oHCM treatment. Although traditional oHCM studies have focused on physiological outcomes, such as exercise capacity and imaging parameters (eg, LVOT-G), these may not reflect patients' lived experiences because patients rarely exert themselves to the limit of their capacity and do not "feel" their anatomy or physiology. This highlights the importance of understanding disease severity from patients' perspectives using patient-reported outcomes. Historically, medical approaches to treating oHCM have been limited to negative inotropic drugs, including beta-blockers, calcium-channel blockers, or disopyramide, where symptoms have generally been quantified from clinicians' rather than patients' perspectives.^{22,23} Among these only metoprolol has described a mean greater improvement in the KCCQ-OSS by 2.4 points after 2 weeks of treatment.²⁴ While septal reduction therapy has been an effective treatment option at high-volume centers,^{25,26} only 1 uncontrolled, observational study evaluated its efficacy on the KCCQ.^{27,28} The introduction of mavacamten, a first-generation cardiac myosin inhibitor, demonstrated marked improvements in the KCCQ, similar to that observed with aficamten in SEQUOIA-HCM, but suffered from substantially more missing data than in the current study.²⁹ Moreover, SEQUOIA-HCM also assessed chest pain from patients' perspectives using the SAQ7, which has never been previously described, to our knowledge. Finally, this study extends the original report from SEQUOIA-HCM¹⁰ by providing a more complete assessment of participants' health status, along with the distributions of patient-level change.

The unique insights from the SEQUOIA-HCM trial on chest pain symptoms are important since prior studies have not assessed the effect of treatment on these symptoms. Chest pain is common in oHCM, and potential explanations for aficamten's efficacy in relieving chest pain may be due to improving blood flow in distal epicardial vessels and myocardial microcirculation through attenuation of hypercontractility, reduced wall stress, and oxygen demand due to relief of obstruction or direct aficamten effect on myosin adenosine triphosphatase activity.^{2,3} Regardless of the mechanism, because chest pain is an important symptom in those with oHCM,⁴ these data provide important insights into the health status benefits of aficamten.

Interpreting the clinical significance of new therapies can be challenging, particularly for anatomical or physiological measures of disease severity. In

contrast, patient-reported outcomes, such as the KCCQ and SAQ7, are direct measures of the impact of treatment from patients' perspectives. Nevertheless, focusing on mean treatment differences between groups requires interpreting those mean differences from patients' perspectives by examining the distribution of clinically important changes between groups.¹² The KCCQ categories of intraindividual changes used to reflect clinical significance have been well established in the scientific literature, including among patients with oHCM.^{13,17} In this trial, the mean treatment benefits with aficamten were primarily driven by a much greater proportion of patients having very large clinical changes in their health status. When compared with prior work in other cardiomyopathies, aficamten improves population-level scores more similarly to invasive valvular interventions than to traditional pharmacologic therapies.^{30,31} Very large improvements (≥ 20 points) have an NNT between 5 and 6 for 1 patient to benefit for mitral transcatheter repair and aficamten,³² whereas with sodium glucose co-transporter 2 inhibitors in the treatment of heart failure (independent of EF), the NNT for very large benefits is between 13 and 14.³³ When looked at collectively, the impact of aficamten on health status is among the most effective pharmacologic therapies across the spectrum of cardiomyopathies.

Several aspects of the SEQUOIA-HCM study design are worth highlighting to guide future implementation of aficamten when treating oHCM. First, this is the largest and most complete study evaluating the effect of cardiac myosin inhibitors on patient-reported health status with very high data completion, supporting the veracity and generalizability of the findings to patients meeting the inclusion and exclusion criteria of SEQUOIA-HCM. Second, although patients with refractory oHCM often needed referral to the few specialty centers that could offer septal reduction therapy, the availability of an effective medical option may enable broader access to treatment that can potentially reduce disparities in care, particularly among rural and socially disadvantaged populations with less access to specialized centers of excellence.³⁴⁻³⁶ Third, dosing adjustments were based on site-interpreted, rather than core lab-interpreted, echocardiograms; that is much more practical in routine clinical practice. Finally, not only do the data from this study provide important patient-centered insights to the benefits of treatment, they also highlight the rapidity of benefit and reversal with drug discontinuation, which could potentially enhance treatment adherence, particularly if patient-reported outcomes measures are used to help monitor

patients' response to treatment in routine clinical care.

STUDY LIMITATIONS. The SEQUOIA-HCM study extended the insights of aficamten's health status benefits by capturing the chest pain-associated health status impact of oHCM by using the SAQ7 to supplement the KCCQ. However, other patient symptoms, such as lightheadedness and palpitations, were not directly measured. However, prior validation work for the KCCQ suggests a strong association between its domains and these disease manifestations, suggesting that few patients solely have symptoms not captured by the KCCQ.¹³ Unlike the KCCQ, where prior work has clarified the clinical importance of individual patients' changes in scores, these data are not available for the SAQ7. Additional analyses are needed to validate the SAQ7 in oHCM and define clinically important thresholds of change. Further, it is unknown whether aficamten is as effective in pediatric patients or in adult patients without obstruction or those with only exercise-induced obstruction. Ongoing studies in these populations, including ACACIA-HCM (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic nHCM; [NCT06081894](#)) and CEDAR-HCM (Clinical Evaluation of Dosing with Aficamten to Reduce Obstruction in a Pediatric Population in HCM), will provide much needed additional data to guide treatment. Lastly, the duration of SEQUOIA-HCM was relatively short, and longer-term studies are needed to better understand whether these health status benefits are sustained, is currently being undertaken with the ongoing FOREST-HCM (Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of Aficamten in Adults; [NCT04848506](#)) study.

CONCLUSIONS

In the SEQUOIA-HCM trial, patients with symptomatic oHCM experienced substantial health status benefits, as compared with placebo, early after initiation of aficamten and throughout 24 weeks of therapy, which was consistent across numerous subgroups, including severity of LVOT-G and background oHCM therapy. These benefits, as quantified by KCCQ and SAQ7, were primarily driven by a substantially greater proportion of aficamten-treated patients experiencing very large improvements in their health status, including relief of limiting chest pain, with an estimated NNT of ~6. Further supporting the direct benefits of aficamten on

participant's health status, these benefits were reversed shortly after drug withdrawal. Collectively, these insights provide strong support that aficamten may be an effective treatment option in patients with oHCM to improve their symptoms, function, and quality of life.

ACKNOWLEDGMENTS The authors thank the investigators, study participants, and their families.

Qualified researchers may submit a request containing the research objectives, endpoints/outcomes of interest, a statistical analysis plan, data requirements, a publication plan, and qualifications of the researcher(s). Requests are reviewed by a committee of internal and external advisors. If approved, information necessary to address the research question will be provided under the terms of a data sharing agreement. Data sharing requests will be considered after applications for marketing authorization in the United States and Europe have been reviewed and final decisions rendered. There is no end date for eligibility to submit a data sharing request for this study. Requests may be submitted to medicalaffairs@cytokinetics.com.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The SEQUOIA-HCM study was funded by Cytokinetics, Incorporated. Study design and data analysis were supported by the funder and aided by coauthors. Manuscript drafting was completed independently but reviewed by the funder. Dr Sherrod has received support from the National Heart, Lung, and Blood Institute (award number T32HL110837). Dr Saberi has received consultant/advisor fees from Bristol Myers Squibb; and has received research grants from Bristol Myers Squibb, Cytokinetics, Novartis, and Actelion Pharmaceuticals. Dr Nassif has received research and grant support from AstraZeneca and Cytokinetics; and has received consulting/advisory fees from Vifor and Cytokinetics. Dr Coats has received speaker fees from Alnylam and Pfizer; and has received advisory fees from Cytokinetics and Roche Diagnostics. Dr Garcia-Pavia has received speaker fees from Pfizer, AstraZeneca, Novo Nordisk, Ionis, BridgeBio, Bristol Myers Squibb, Intellia, and Alnylam; has received consultant/advisor fees from Pfizer, Alnylam, MyoKardia/Bristol Myers Squibb, Cytokinetics, Neuroimmune, Intellia, Ionis, BridgeBio, Lexeo, Rocket, Attralus, and AstraZeneca; and has received research/educational grants to his institution from Pfizer, AstraZeneca, Novo Nordisk, BridgeBio, and Alnylam. Dr Januzzi has received funding from the Hutter Family Professorship; has served as a board member for Imbria Pharmaceuticals; has served as a Director at Jana Care; has received grant support from Abbott, Applied Therapeutics, HeartFlow, Innolife, and Roche Diagnostics; has received consulting income from Abbott, Beckman, Bristol Myers Squibb, Boehringer Ingelheim, Janssen, Novartis, Pfizer, Merck, Roche Diagnostics, and Siemens; and has participated in clinical endpoint committees/Data Safety Monitoring Boards for Abbott, AbbVie, CVRx, Intercept, and Takeda. Dr Lewis has received research funding from the National Institutes of Health (R01-HL 151841, R01-HL131029, and R01-HL159514), American Heart Association (15GPSGC-24800006), Amgen, Cytokinetics, Applied Therapeutics, AstraZeneca, and SoniVie; has received honoraria for Advisory Boards from Pfizer, Merck, Boehringer Ingelheim, Novartis, American Regent, Cycleron,

Cytokinetics, and Amgen; and has received royalties from UpToDate for scientific content authorship related to exercise physiology. Dr Maron has received consultant/advisor fees from Imbria, Edgewise, and BioMarin; and has received Steering Committee fees for SEQUOIA-HCM from Cytokinetics, Incorporated. Dr Olivotto has received Speakers Bureau fees from Bristol Myers Squibb, Amicus, and Genzyme; has received consultant/advisor fees from Bristol Myers Squibb, Cytokinetics, Sanofi Genzyme, Amicus, Bayer, Tenaya, Rocket Pharma, and Lexeo; and has received research grant funding from Bristol Myers Squibb, Cytokinetics, Sanofi Genzyme, Amicus, Bayer, Menarini International, Chiesi, and Boston Scientific. Drs Butzner, Jacoby, Heitner, Kupfer, Malik, and Meng, and Ms Wohltman are employees of Cytokinetics Incorporated; and hold stock in Cytokinetics Incorporated. Dr Spertus has provided consultative services on patient-reported outcomes and evidence evaluation to Alnylam, AstraZeneca, Bayer, Merck, Janssen, Bristol Myers Squibb, 4DT Medical, Terumo, Cytokinetics, Imbria, and United Healthcare; holds research grants from Bristol Myers Squibb, and Janssen; owns the copyrights to the Seattle Angina Questionnaire, Kansas City Cardiomyopathy Questionnaire, and Peripheral Artery Questionnaire; and has served on the Board of Directors for Blue Cross Blue Shield of Kansas City. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Aficamten, a next-in-class cardiac myosin inhibitor, has been shown to improve exercise capacity in oHCM. Given the centrality of patients' health status in the management of oHCM, comprehensively understanding the impact of aficamten on patient-reported health status is essential to support its use. In our analysis of the SEQUOIA-HCM trial, we identified clinically important improvements in patients' symptoms, function, and quality of life in those treated with aficamten, benefits that were lost shortly after drug discontinuation.

TRANSLATIONAL OUTLOOK: Because aficamten markedly improved patient-reported health status in oHCM, there is a need to understand how best to identify patients with symptomatic oHCM, where cardiac myosin inhibitors should be considered to improve their health status. These data can support shared decision-making when patients consider alternative treatment options.

REFERENCES

- Marian AJ, Roberts R. The molecular genetic basis for hypertrophic cardiomyopathy. *J Mol Cell Cardiol*. 2001;33(4):655-670. <https://doi.org/10.1006/jmcc.2001.1340>
- Pasternac A, Noble J, Streulens Y, Elie R, Henschke C, Bourassa MG. Pathophysiology of chest pain in patients with cardiomyopathies and normal coronary arteries. *Circulation*. 1982;65(4):778-789. <https://doi.org/10.1161/01.cir.65.4.778>
- Raphael CE, Cooper R, Parker KH, et al. Mechanisms of myocardial ischemia in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2016;68(15):1651-1660. <https://doi.org/10.1016/j.jacc.2016.07.751>
- Zaiser E, Sehnert AJ, Duenas A, Saberi S, Brookes E, Reaney M. Patient experiences with hypertrophic cardiomyopathy: a conceptual model of symptoms and impacts on quality of life. *J Patient-Rep Outcomes*. 2020;4(1):102. <https://doi.org/10.1186/s41687-020-00269-8>
- Spertus JA, Fine JT, Elliott P, et al. Mavacamten for Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy (EXPLORER-HCM): health status analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2021;397(10293):2467-2475. [https://doi.org/10.1016/S0140-6736\(21\)00763-7](https://doi.org/10.1016/S0140-6736(21)00763-7)
- Chuang C, Collibee S, Ashcraft L, et al. Discovery of aficamten (CK-274), a next-generation cardiac myosin inhibitor for the treatment of hypertrophic cardiomyopathy. *J Med Chem*. 2021;64(19):14142-14152. <https://doi.org/10.1021/acs.jmedchem.1c01290>
- Malik FI, Robertson LA, Armas DR, et al. A phase 1 dose-escalation study of the cardiac myosin inhibitor aficamten in healthy participants. *JACC Basic Transl Sci*. 2022;7(8):763-775. <https://doi.org/10.1016/j.jacbts.2022.04.008>
- Maron MS, Masri A, Choudhury L, et al. REDWOOD-HCM Steering Committee and Investigators. Phase 2 study of aficamten in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2023;81(1):34-45. <https://doi.org/10.1016/j.jacc.2022.10.020>
- Owens AT, Masri A, Abraham TP, et al. REDWOOD-HCM Investigators. Aficamten for drug-refractory severe obstructive hypertrophic cardiomyopathy in patients receiving disopyramide: REDWOOD-HCM Cohort 3. *J Card Fail*. 2023;29(11):1576-1582. <https://doi.org/10.1016/j.cardfail.2023.07.003>
- Maron MS, Masri A, Nassif ME, et al. SEQUOIA-HCM Investigators. Aficamten for symptomatic obstructive hypertrophic cardiomyopathy. *N Engl J Med*. 2024;390(20):1849-1861. <https://doi.org/10.1056/NEJMoa2401424>
- Coats CJ, Maron MS, Abraham TP, et al. SEQUOIA-HCM Investigators. Exercise capacity in patients with obstructive hypertrophic cardiomyopathy: SEQUOIA-HCM baseline characteristics and study design. *JACC Heart Fail*. 2024;12(1):199-215. <https://doi.org/10.1016/j.jchf.2023.10.004>
- Spertus JA, Jones PG, Sandhu AT, Arnold SV. Interpreting the Kansas City Cardiomyopathy Questionnaire in clinical trials and clinical care: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2020;76(20):2379-2390. <https://doi.org/10.1016/j.jacc.2020.09.542>
- Nassif M, Fine JT, Dolan C, et al. Validation of the Kansas City Cardiomyopathy Questionnaire in symptomatic obstructive hypertrophic cardiomyopathy. *JACC Heart Fail*. 2022;10(8):531-539. <https://doi.org/10.1016/j.jchf.2022.03.002>
- Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol*. 2000;35(5):1245-1255. [https://doi.org/10.1016/s0735-1097\(00\)00531-3](https://doi.org/10.1016/s0735-1097(00)00531-3)
- Chan PS, Jones PG, Arnold SV, Spertus JA. Development and validation of a short version of the Seattle Angina Questionnaire. *Circ Cardiovasc Qual Outcomes*. 2014;7(5):640-647.
- Thomas M, Jones PG, Arnold SV, Spertus JA. State of the Art Review: Interpreting the Seattle Angina Questionnaire as an outcome in clinical trials and in clinical care. *JAMA Cardiol*. 2021;6(5):593-599. <https://doi.org/10.1001/jamacardio.2020.7478>
- Spertus J, Peterson E, Conard MW, et al. Cardiovascular Outcomes Research Consortium. Monitoring clinical changes in patients with heart failure: a comparison of methods. *Am Heart J*. 2005;150(4):707-715. <https://doi.org/10.1016/j.ahj.2004.12.010>

18. Schumann CL, Mathew RC, Dean JHL, et al. Functional and economic impact of INOCA and influence of coronary microvascular dysfunction. *JACC Cardiovasc Imaging*. 2021;14(7):1369-1379. <https://doi.org/10.1016/j.jcmg.2021.01.041>
19. Suppogu N, Wei J, Quesada O, et al. Angina relates to coronary flow in women with ischemia and no obstructive coronary artery disease. *Int J Cardiol*. 2021;333:35-39. <https://doi.org/10.1016/j.ijcard.2021.02.064>
20. CV Outcomes, Inc. Instruments and Licenses. Accessed August 7, 2024. www.cvoutcomes.org/
21. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology*. 1990;1(1):43-46.
22. Sherrod MV, Pearle G, Gunsburg DZ. Mechanism of benefit of negative inotropes in obstructive hypertrophic cardiomyopathy. *Circulation*. 1998;97(1):41-47. <https://doi.org/10.1161/01.CIR.97.1.41>
23. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy. *Circulation*. 2020;142(25):e558-e631. <https://doi.org/10.1161/CIR.0000000000000937>
24. Dybro AM, Rasmussen TB, Nielsen RR, Andersen MJ, Jensen MK, Poulsen SH. Randomized trial of metoprolol in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2021;78(25):2505-2517. <https://doi.org/10.1016/j.jacc.2021.07.065>
25. Hadaya J, Verma A, Sanaiha Y, Shemin RJ, Benharash P. Volume-outcome relationship in septal myectomy for hypertrophic obstructive cardiomyopathy. *Surgery*. 2023;174(2):166-171. <https://doi.org/10.1016/j.surg.2023.04.028>
26. Altibi AM, Ghanem F, Zhao Y, et al. Hospital procedural volume and clinical outcomes following septal reduction therapy in obstructive hypertrophic cardiomyopathy. *J Am Heart Assoc*. 2023;12(10):e028693. <https://doi.org/10.1161/JAHA.122.028693>
27. Desai MY, Tower-Rader A, Szpakowski N, Mentias A, Popovic ZB, Smedira NG. Association of septal myectomy with quality of life in patients with left ventricular outflow tract obstruction from hypertrophic cardiomyopathy. *JAMA Netw Open*. 2022;5(4):e227293. <https://doi.org/10.1001/jamanetworkopen.2022.7293>
28. Tower-Rader A, Szpakowski N, Popovic ZB, et al. Patient reported outcomes in obstructive hypertrophic cardiomyopathy undergoing myectomy: results from SPIRIT-HCM study. *Prog Cardiovasc Dis*. 2023;80:66-73. <https://doi.org/10.1016/j.pcad.2023.06.001>
29. Olivetto I, Oreziak A, Barriaes-Villa R, et al, EXPLORER-HCM Investigators. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2020;396(10253):759-769. [https://doi.org/10.1016/S0140-6736\(20\)31792-X](https://doi.org/10.1016/S0140-6736(20)31792-X)
30. Garcia RA, Benton MC, Spertus JA. Patient-reported outcomes in patients with cardiomyopathy. *Curr Cardiol Rep*. 2021;23(7):91. <https://doi.org/10.1007/s11886-021-01511-5>
31. Arnold SV, Goates S, Sorajja P, et al, TRILUMINATE Pivotal Trial Investigators. Health status after transcatheter tricuspid-valve repair in patients with severe tricuspid regurgitation. *J Am Coll Cardiol*. 2024;83(1):1-13. <https://doi.org/10.1016/j.jacc.2023.10.008>
32. Arnold SV, Chinnakondepalili KM, Spertus JA, et al Investigators COAPT. Health status after transcatheter mitral-valve repair in heart failure and secondary mitral regurgitation: COAPT trial. *J Am Coll Cardiol*. 2019;73(17):2123-2132. <https://doi.org/10.1016/j.jacc.2019.02.010>
33. Nassif ME, Windsor SL, Gosch K, et al. Dapagliflozin improves heart failure symptoms and physical limitations across the full range of ejection fraction: pooled patient-level analysis from DEFINE-HF and PRESERVED-HF trials. *Circ Heart Fail*. 2023;16(7):e009837. <https://doi.org/10.1161/CIRCHEARTFAILURE.122.009837>
34. Fanaroff AC, Evans PT, Nathan AS. Rural-urban disparities in cardiovascular outcomes. *J Am Coll Cardiol*. 2022;79(3):280-282. <https://doi.org/10.1016/j.jacc.2021.11.016>
35. Rajagopalan N, Leung SW, Craft RS, Bailey AL. Improving cardiovascular health in rural United States. *JACC Adv*. 2024;3(7):100950. <https://doi.org/10.1016/j.jacadv.2024.100950>
36. Loccoch EC, Joynt MKE, Wang Y, Kazi DS, Yeh RW, Wadhera RK. Rural-urban disparities in outcomes of myocardial infarction, heart failure, and stroke in the United States. *J Am Coll Cardiol*. 2022;79(3):267-279. <https://doi.org/10.1016/j.jacc.2021.10.045>

KEY WORDS aficamten, hypertrophic cardiomyopathy, patient-reported outcomes

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