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RESEARCH ARTICLE

Long-term impact of aficamten on patient-reported outcome measures in obstructive hypertrophic cardiomyopathy: results from FOREST-HCM

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Abstract

Aims

Treatment with aficamten in patients with obstructive hypertrophic cardiomyopathy (oHCM) led to significant improvements in patient-reported outcomes (PROs) in the pivotal SEQUOIA-HCM trial over 24 weeks, but its longer-term impact has not been described. The aim of this study was to describe the long-term effects of aficamten across multiple PROs in FOREST-HCM, an open-label extension study.

Methods and Results

Participants with oHCM completing an aficamten trial were offered enrolment in FOREST-HCM. The Kansas City Cardiomyopathy Questionnaire (KCCQ), Seattle Angina Questionnaire 7-item, EuroQol Five-Dimensional Questionnaire index, and visual analogue scale were administered at baseline and at weeks 12, 24, 36, and 48. Associations among PROs and clinical markers of oHCM severity were assessed with Spearman correlation coefficients. A total of 172 participants (mean age 60.4 [SD ± 13.1] years; 45.3% female) completed ≥48 weeks of follow-up as of 31 August 2024, and were included. Significant improvements in all PROs were observed by week 12 and sustained through

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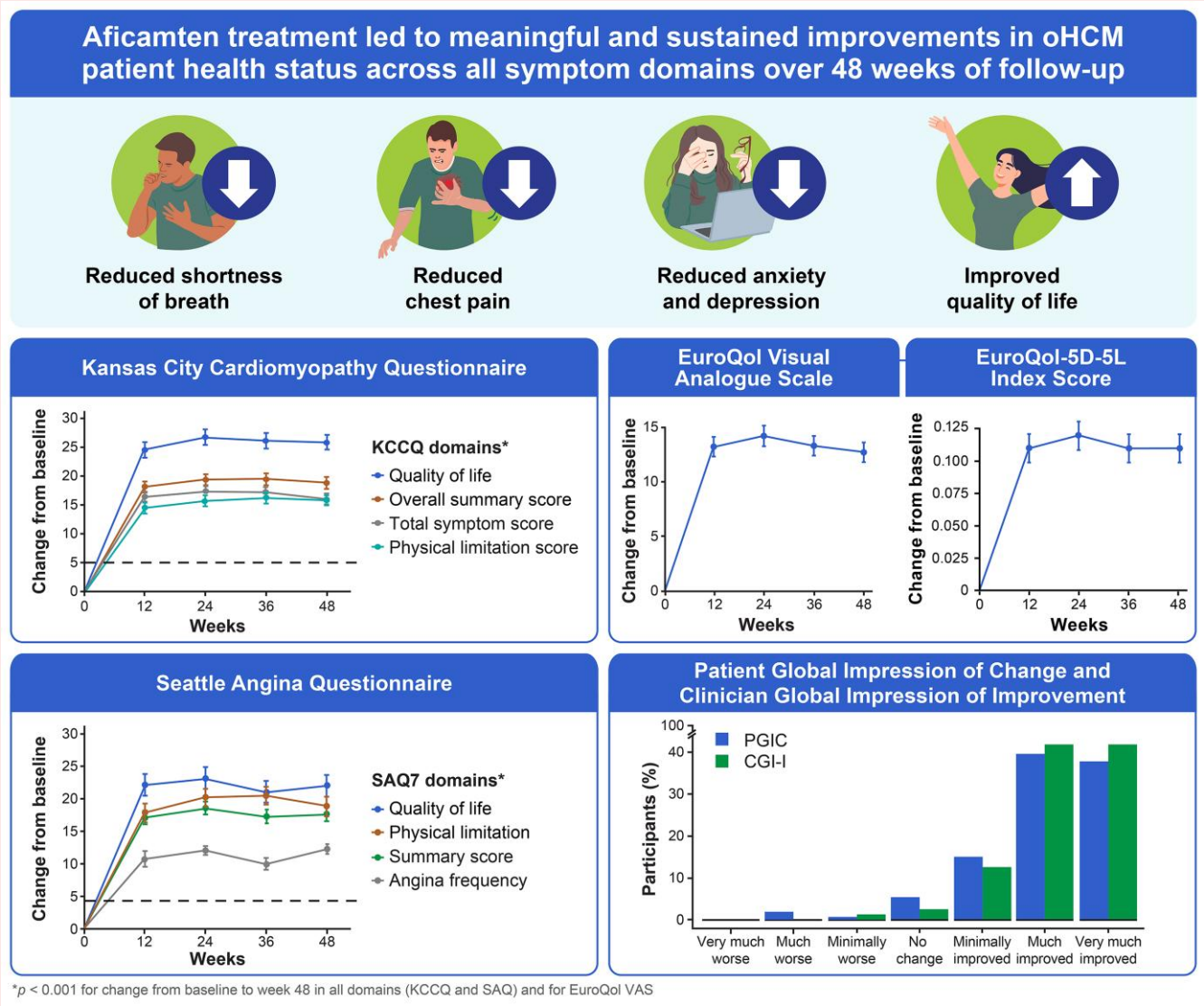
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week 48. At 48 weeks, mean Kansas City Cardiomyopathy Questionnaire–Overall Summary Score improved by 18.8 (16.9–20.6) points, ($P < .001$), with the largest gains in the KCCQ Quality of Life domain (25.8 points [23.2–28.5; $P < .001$]). Seattle Angina Questionnaire 7-item -Summary Scores increased by 17.2 (15.1–19.4; $P < .001$), and EuroQol Five-Dimensional Questionnaire index and visual analogue scale scores improved by 0.11 and 12.7 points, respectively ($P < .001$). Improvements in PROs were significantly correlated with important clinical measures of oHCM.

Conclusions Aficamten resulted in sustained improvements across multiple health status dimensions, which also correlated with clinical markers of oHCM severity.

Clinical trials registration NCT04848506

Graphical abstract



Keywords Hypertrophic cardiomyopathy • Quality of life • Patient-centred care

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Introduction

Hypertrophic cardiomyopathy (HCM) is a common inherited cardiac disorder driven by excessive actin–myosin interactions, resulting in myocardial hypercontractility and subsequent left ventricular (LV) hypertrophy, diastolic dysfunction, and left ventricular outflow tract (LVOT) obstruction.[1–3] Patients with obstructive HCM (oHCM) can experience significant functional impairment from a wide range of symptoms, including fatigue, dyspnoea, light-headedness, chest pain, palpitations, and exercise intolerance.[4,5]

Symptom improvement is one of the primary treatment objectives in managing patients with oHCM.[6] For many years, pharmacologic treatment strategies focused on nondisease specific therapies that reduced myocardial contractility.[7,8] Cardiac myosin inhibitors (CMIs), including mavacamten and aficamten, represent a novel class of disease-specific agents that directly target the pathologic actin-myosin interactions underlying HCM, leading to improved cardiac energetics and reduced hypercontractility.[9–12] In the pivotal SEQUOIA-HCM (Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM; NCT05186818) trial, 24 weeks of treatment with aficamten led to substantial improvements in participants' self-reported health status as measured by the Kansas City Cardiomyopathy Questionnaire–Overall Summary Score (KCCQ-OSS) and the Seattle Angina Questionnaire 7-Item–Summary Score (SAQ7-SS).[10,13]

The long-term impact of aficamten treatment on patient-reported health status has not been previously described. To address this gap in knowledge, the effects of aficamten on a broad range of patient-reported outcomes (PROs) in patients with oHCM were assessed in the open-label extension trial FOREST-HCM (A Follow-Up, Open-Label, Research Evaluation of Sustained Treatment with Aficamten in Hypertrophic Cardiomyopathy; NCT04848506). Establishing the long-term health status benefits of aficamten may better inform patients and clinicians when considering CMI therapy.

Methods

Study design

FOREST-HCM is an ongoing, open-label extension study for eligible patients with obstructive and nonobstructive HCM who participated in clinical trials of aficamten (REDWOOD-HCM [Randomized Evaluation of Dosing With CK-3773274 in Obstructive Outflow Disease in HCM; NCT04219826], SEQUOIA-HCM, MAPLE-HCM [Metoprolol vs Aficamten in Patients with LVOT Obstruction on Exercise Capacity in HCM; NCT05767346], and ACACIA-HCM [Assessment Comparing Aficamten to Placebo on Cardiac Endpoints in Adults with Non-Obstructive HCM; NCT06081894]). The study designs of REDWOOD-HCM, SEQUOIA-HCM, and MAPLE-HCM have been previously published.[10,14,15] Participants received an initial aficamten dose of 5 mg daily, adjusted in 5 mg increments up to 20 mg at ≥2-week intervals according to site-read echocardiographic criteria. Participants enrolled in FOREST-HCM were required to have successfully completed a previous aficamten trial and have a LV ejection fraction (LVEF) ≥55%. Echocardiographic assessments were centrally adjudicated at a core laboratory. The study protocol was approved by local site institutional review boards. All participants with oHCM completing ≥48 weeks of FOREST-HCM follow-up as of 31 August 2024, were included.

Patient-reported outcomes

Kansas City Cardiomyopathy Questionnaire

The KCCQ is a 23-item PRO originally designed to measure health status in patients with heart failure that has been subsequently validated in patients with oHCM.[16–18] It includes seven domains: symptom frequency, symptom burden, symptom stability, physical limitations, social limitations, quality of life, and self-efficacy. The symptom frequency and symptom burden domains are merged into the Total Symptom Score (TSS). The CSS combines the Physical Limitation Score (PLS) and TSS to mirror the key concepts of the New York Heart Association (NYHA) functional class. The OSS combines the CSS with the Social Limitation Score (SLS) and Quality of Life Score (QLS) to provide a more holistic summary of patients' health status. Scores for each domain range from 0 to 100, with summary scores 0–24 representing very poor to poor health status, 25–49 poor to fair, 50–74 fair to good, and 75–100 good to excellent health status.[17] Prior studies have shown that changes in the KCCQ-OSS and CSS of 5, 10, 15, and 20 points represent clinically important small, moderate, large, and very large changes, respectively.[17] The KCCQ has a 2-week recall period and was administered at baseline and at weeks 12, 24, 36, and 48.

Seattle Angina Questionnaire

The SAQ7 was developed to assess the frequency and impact of chest pain in patients with coronary artery disease and was previously included in the SEQUOIA-HCM trial analyses to assess this symptom and its impact on patients' health in oHCM.[13,19] The SAQ7 includes domains that assess the frequency of chest pain and its impact on patients' physical limitations and quality of life. These domains are combined into the SAQ7-SS, which ranges from 0 to 100, with higher scores indicating better health status. Similar to the KCCQ, prior studies have shown that changes in the SAQ7 of 5, 10, 15, and 20 points represent clinically important small, moderate, large, and very large changes, respectively. The SAQ7-Angina Frequency Score (SAQ7-AF) is also on a scale from 0 to 100, with scores 0–30 indicating daily chest pain, 31–60 weekly chest pain, 61–99 monthly chest pain, and a score of 100 indicating no chest pain over the prior 4-week recall period of the SAQ. The SAQ7 was included in the study protocol after initiation; therefore, baseline data were unavailable for some participants. For study participants who were enrolled after the protocol amendment, the SAQ7 was administered at baseline and weeks 12, 24, 36, and 48.

EuroQol Five-Dimensional Questionnaire

The EuroQol Five-Dimensional Questionnaire (EQ-5D) is a widely used generic instrument for the measurement of health-related quality of life.[20,21] It consists of two parts: the EQ-5D index and the visual analogue scale (VAS). The index includes five questions with a 5-point Likert scale (EQ-5D-5L): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. By using country-specific weights assigned to each response, a societal-based utility can be assigned for economic analyses, where 1 represents best possible health and 0 represents death, and this can be used to calculate quality-adjusted life years. The minimal clinically important difference for the EQ-5D-5L index score has not been well established in cardiovascular disease, but general population-based estimates range from 0.037 to 0.10.[22] The VAS enables patients to quantify their current overall health state along a range of 0 (death) to 100 (best imaginable health state). For heart failure patients, the EQ-VAS threshold of ≥5 points has commonly been used to define clinically meaningful change, with ≥10 points representing considerable improvement or worsening.[23] The EQ-5D-5L and VAS were included in the study protocol after initiation; therefore, baseline data were unavailable for some participants. For study participants who were enrolled after the protocol amendment, the EQ-5D-5L and VAS were administered at baseline and weeks 12, 24, 36, and 48.

Patient global impression of change

The Patient Global Impression of Change (PGIC) survey was administered at weeks 12, 24, 36, and 48. The PGIC is a single-item survey that asks patients 'Since the start of the study, my overall status is:' with responses being limited to a 7-point scale from 'Very Much Worse' to 'Very Much Improved' and provides a simple metric of a patient's perception of their condition in response to treatment.[24]

Clinician global impression of improvement

The Clinician Global Impression of Improvement (CGI-I) survey was administered to the treating clinicians at weeks 12, 24, 36, and 48. As the CGI-I uses the same 7-point scale as the PGIC, it was included to assess concordance between clinician and patient perspectives on symptom improvement.[24]

Statistical analysis

Baseline characteristics were summarized using mean ± standard deviation (SD) or median and interquartile ranges for continuous variables, as well as counts and percentages for categorical variables. In addition to summary

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scores, item- and domain-level responses from the KCCQ, SAQ7, and EQ-5D-5L were summarized descriptively at baseline and follow-up. Endpoints of change from baseline through week 48 were summarized using descriptive statistics. Changes in mean KCCQ summary scores, SAQ7 summary scores, and EQ-5D-5L index and VAS scores from baseline through 48 weeks were tested using mixed models for repeated measures that included model terms of baseline value, visit week, and baseline value by visit interaction and reported as least-squares mean differences. The mixed models for repeated measures used an unstructured covariance matrix. Models were fit using restricted maximum likelihood.

Analyses of the SAQ7, EQ-5D-5L, and VAS were limited to participants with available baseline and follow-up data, as these measures were added after trial initiation. Imputation was not performed given that data were missing owing to the study design (i.e. missing completely at random) rather than due to loss to follow-up.

Subgroup analyses were conducted based on baseline beta blocker use, gender, age group (<65 or ≥65 years), baseline KCCQ-OSS (≤50 or >50), and baseline NYHA class (II vs III). Exploratory descriptive analyses were also performed to evaluate PROs according to subsequent development of new-onset atrial fibrillation or reduction in LVEF to <50% during aficamten treatment.

The relationship between PRO scores was summarized using Spearman correlations. The relationships among PRO scores and between PROs and clinical measures of HCM severity, including troponin, N-terminal pro-B-type natriuretic peptide (NT-proBNP), LVOT gradient at rest and with Valsalva, and NYHA class, were summarized using Spearman correlations. Analyses were performed using SAS Enterprise Software Version 8.3.

Results

As of August 2024, 172 participants with oHCM had reached 48 weeks of follow-up and were included. Reasons for participant exclusion are documented in Supplementary Table S1 and included early discontinuation in the parent study, screen failure, and failure to reach the required follow-up duration at data cutoff. The mean age ±SD was 60.4 ± 13.1 years and 78 (45.3%) were female (*Table 1*). At baseline, participants had marked LVOT obstruction (Valsalva LVOT gradient of 93 ± 40 mmHg), and the majority (103/172, 59.9%) had NYHA class II symptoms. At baseline, 140 participants (81.4%) were taking beta-blockers, 25 (14.5%) calcium channel blockers, and 33 (19.2%) disopyramide.

Baseline PROs were consistent with moderately impaired health status, with mean (±SD) KCCQ-OSS of 65.9 ± 20.3, SAQ7-SS of 69.7 ± 21.7, EQ-5D-5L index of 0.8 ± 0.22, and VAS of 68.3 ± 18.1. With regards to missing data, 40 participants (23.3%) did not have baseline SAQ7, EQ-5D-5L index, or VAS scores collected because they were enrolled prior to inclusion of these PROs in the study protocol, though no meaningful differences were observed between participants with and without these baseline assessments (Supplementary Table S2).

Table 1 Baseline characteristics

	Overall (*n* = 172)
Demographics	
Age, y	60.4 ± 13.1
Female (%)	78 (45.3)
White (%)	164 (95.3)
Asian (%)	3 (1.7)
Black (%)	4 (2.3)
Other (%)	1 (0.6)
Medical history	
Hypertension (%)	95 (55.2)
Family history of HCM (%)	50 (29.1)
Known pathogenic sarcomere variant (%)	39 (22.7)
Atrial fibrillation (%)	37 (21.5)
Coronary artery disease (%)	24 (14.5)
Diabetes mellitus (%)	32 (18.6)
BMI at baseline, kg/m^2	28.9 ± 4.4
Baseline HCM therapy	
Beta-blocker only (%)	107 (62.2)
Calcium-channel blocker only (%)	18 (10.5)
Beta-blocker + calcium-channel blocker (%)	3 (1.7)
Beta-blocker + disopyramide (%)	29 (16.9)
Calcium-channel blocker + disopyramide (%)	3 (1.7)
Beta-blocker + calcium-channel blocker + disopyramide (%)	1 (0.6)
Implantable cardioverter-defibrillator (%)	34 (19.8)
Baseline measures of HCM severity	
NYHA functional class (%)	
I	1 (0.6)
II	103 (59.9)
III	68 (39.5)
IV	0
NT-proBNP, pg/mL (median[IQR])	843 (357–1758)
hs-cardiac-TnI, ng/L (median[IQR])	12 (6, 23)
Site-read peak LVOT gradient at rest, mmHg	58 ± 38
Site-read peak LVOT gradient with Valsalva, mmHg	93 ± 40
Site-read LVEF, %	68 ± 6
Baseline PRO	
KCCQ	
OSS (*n* = 172)	65.9 ± 20.3
CSS (*n* = 172)	71.5 ± 19.1
TSS (*n* = 172)	71.5 ± 19.3
PLS (*n* = 172)	71.5 ± 21.4
QLS (*n* = 172)	52.1 ± 23.9
SES (*n* = 172)	80.1 ± 22.7
SLS (*n* = 171)	68.5 ± 25.8
SAQ7	
SS (*n* = 132)	69.7 ± 21.7
AF (*n* = 131)	81.5 ± 17.7
PL (*n* = 125)	66.5 ± 26.4
QLS (*n* = 132)	59.8 ± 29.6
EQ-5D-5L	
Index (*n* = 132)	0.77 ± 0.22
VAS (*n* = 132)	68.3 ± 18.1

AF, angina frequency; BMI, body mass index; CSS, Clinical Summary Score; EQ-5D-5L, 5-level EuroQol Five-Dimensional Questionnaire; HCM, hypertrophic cardiomyopathy; hs-cardiac-TnI, high sensitivity cardiac troponin I; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OSS, Overall Summary Score; PL, physical limitation; PLS, physical limitation score; PRO, patient-reported outcome; QLS, quality of life score; SAQ7, Seattle Angina Questionnaire 7-item; SES, self efficacy score; SLS, social limitation score; SS, summary score; TSS, total symptom score; VAS, visual analogue scale

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Significant improvements in all PROs were observed by week 12 and sustained through week 48 (*Tables 2–4*).

KCCQ

Improvements were seen across all domains, including symptom frequency and severity, physical limitation, social limitation, and quality of life. Least-squares mean differences (95% CI) between the KCCQ-CSS and OSS from baseline to 48 weeks were 15.6 (14.0–17.3; $P < .001$) and 18.8 (16.9–20.6; $P < .001$), respectively (*Figure 1*). The largest gains were seen in the QLS, which had the lowest baseline mean ± SD score of 52.1 ± 23.9, but improved by 25.8 points (95% CI: 23.2–28.5; $P < .001$). Item-level analyses of the KCCQ revealed substantial improvement in response to the question 'How

Table 2 Least-squares mean differences in Kansas City Cardiomyopathy Questionnaire scores from baseline to 48 weeks

KCCQ	Visit											
	Week 12			Week 24			Week 36			Week 48		
Summary score	*n*	LSMD[a]	*P* value	*n*	LSMD[a]	*P* value	*n*	LSMD[a]	*P* value	*n*	LSMD[a]	*P* value
OSS	171	18.1 (16.2–20.0)	<.001	168	19.3 (17.4–21.2)	<.001	171	19.4 (17.6–21.3)	<.001	171	18.8 (16.9–20.6)	<.001
CSS	171	15.1 (13.5–16.8)	<.001	168	16.2 (14.6–17.9)	<.001	171	16.6 (14.9–18.2)	<.001	171	15.6 (14.0–17.3)	<.001
TSS	171	15.8 (14.0–17.6)	<.001	168	16.8 (15.0–18.6)	<.001	171	16.7 (14.9–18.5)	<.001	171	15.5 (13.7–17.3)	<.001
PLS	171	14.4 (12.7–16.2)	<.001	168	15.6 (13.8–17.4)	<.001	169	16.2 (14.4–18.0)	<.001	168	15.7 (13.9–17.5)	<.001
QLS	170	24.6 (21.9–27.2)	<.001	168	26.6 (24.0–29.3)	<.001	171	26.1 (23.4–28.7)	<.001	171	25.8 (23.2–28.5)	<.001
SES	170	4.2 (2.3–6.1)	<.001	168	5.3 (3.4–7.2)	<.001	171	6.4 (4.5–8.3)	<.001	170	5.1 (3.1–7.0)	<.001
SLS	166	17.3 (15.0–19.7)	<.001	162	18.1 (15.7–20.4)	<.001	165	18.6 (16.2–20.9)	<.001	162	17.7 (15.3–20.1)	<.001

[a]Least-squares mean difference (95% CI).
CSS, Clinical Summary Score; KCCQ, Kansas City Cardiomyopathy Questionnaire; LSMD, least-squares mean difference; OSS, Overall Summary Score; PLS, physical limitation score; QLS, quality of life score; SES, self efficacy score; SLS, social limitation score; TSS, total symptom score

Table 3 Least-squares mean differences in Seattle Angina Questionnaire 7-item scores from baseline to 48 weeks

SAQ7	Visit											
	Week 12			Week 24			Week 36			Week 48		
Summary score	*n*	LSMD[a]	*P* value	*n*	LSMD[a]	*P* value	*n*	LSMD[a]	*P* value	*n*	LSMD[a]	*P* value
SS	131	16.6 (14.2–18.9)	<.001	128	18.1 (16.2–20.0)	<.001	131	16.8 (14.6–18.9)	<.001	131	17.2 (15.1–19.4)	<.001
AF	130	10.8 (8.4–13.1)	<.001	127	12.1 (10.6–13.5)	<.001	130	9.9 (8.1–11.7)	<.001	130	12.3 (10.7–13.8)	<.001
PL	120	17.9 (15.0–20.7)	<.001	119	20.2 (17.6–22.8)	<.001	120	20.4 (17.7–23.1)	<.001	118	18.8 (15.9–21.8)	<.001
QLS	131	22.2 (18.9–25.5)	<.001	128	23.1 (19.9–26.4)	<.001	130	21.0 (17.7–24.4)	<.001	131	22.0 (18.7–25.4)	<.001

[a]Least-squares mean difference (95% CI).
AF, angina frequency; LSMD, least-squares mean difference; PL, physical limitation; QLS, quality of life score; SAQ7, Seattle Angina Questionnaire 7-item; SS, summary score

Table 4 Least-squares mean differences in 5-level EuroQol Five-Dimensional Questionnaire scores from baseline to 48 weeks

EQ-5D-5L	Visit											
	Week 12			Week 24			Week 36			Week 48		
Summary score	*n*	LSMD[a]	*P* value	*n*	LSMD[a]	*P* value	*n*	LSMD[a]	*P* value	*n*	LSMD[a]	*P* value
Index	132	0.11 (0.09–0.13)	<.001	128	0.12 (0.10–0.14)	<.001	131	0.11 (0.09–0.14)	<.001	130	0.11 (0.09–0.13)	<.001
VAS	132	13.2 (11.4–15.0)	<.001	128	14.2 (12.4–16.0)	<.001	131	13.3 (11.5–15.1)	<.001	130	12.7 (10.9–14.5)	<.001

[a]Least-squares mean difference (95% CI).
EQ-5D-5L, 5-level EuroQol Five-Dimensional Questionnaire; LSMD, least-squares mean difference; VAS, visual analogue scale

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much has HCM limited your enjoyment of life?' At baseline, only 16.9% of participants (29/172) reported no limitations in enjoyment of life, whereas at 48 weeks this proportion increased to 54.7% (93/170) (Supplementary Table S3). When examining clinically important thresholds of change in KCCQ-OSS at 48 weeks of follow-up, the majority of participants (134/171; 78.4%) improved by ≥5 points, with the largest proportion (72/171; 42.1%) achieving a very large (≥20-point) improvement (*Figure 2*).

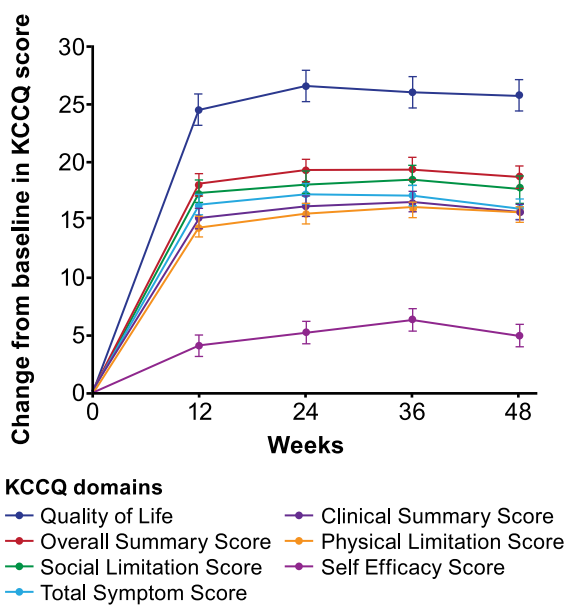


Figure 1 Mean change ±SE in KCCQ scores from baseline to week 48. KCCQ, Kansas City Cardiomyopathy Questionnaire

SAQ7

The SAQ7-SS increased by 17.2 points (95% CI: 15.1–19.4; $P < .001$) at 48 weeks. The most substantial improvement was seen in the SAQ7-QLS, which like the KCCQ-QLS, had the lowest mean (±SD) baseline score (59.8 ± 29.6) and increased by 22.0 points (95% CI: 18.7–25.4; $P < .001$) at 48 weeks (*Figure 3*). Correspondingly, item-level analyses demonstrated an increase in the proportion of participants reporting no limitations in enjoyment of life at 48 weeks compared with baseline (73.8% [124/168] vs 45.8% [60/131]) (Supplementary Table S4). Additionally, while at baseline 50% (65/130) of participants experienced chest pain at least 1–2 times per week, this proportion decreased to 16% (27/168) at 48 weeks (Supplementary Table S4). The majority of participants experienced clinically meaningful improvement in symptoms, based on ≥5-point increase from baseline in the SAQ7-SS (87/131, 66.4%), with the largest subgroup (50/131; 38.2%) demonstrating a very large improvement (≥20-point increase) at 48 weeks (*Figure 4*).

EQ-5d-5l index and VAS

The EQ-5D-5L index improved by 0.11 (95% CI: 0.09–0.13; $P < .001$), and the VAS increased by 12.7 points (95% CI: 10.9–14.5; $P < .001$) (*Figure 5*). Domain-level analyses of the index score demonstrated improvements in symptoms of anxiety and depression. At baseline, 47.7% of participants reported no anxiety/depression, whereas at 48 weeks this increased to 64.1% of participants. Improvements were also observed across all other EQ-5D-5L dimensions, including mobility, self-care, usual activities, and pain/discomfort (Supplementary Table S5).

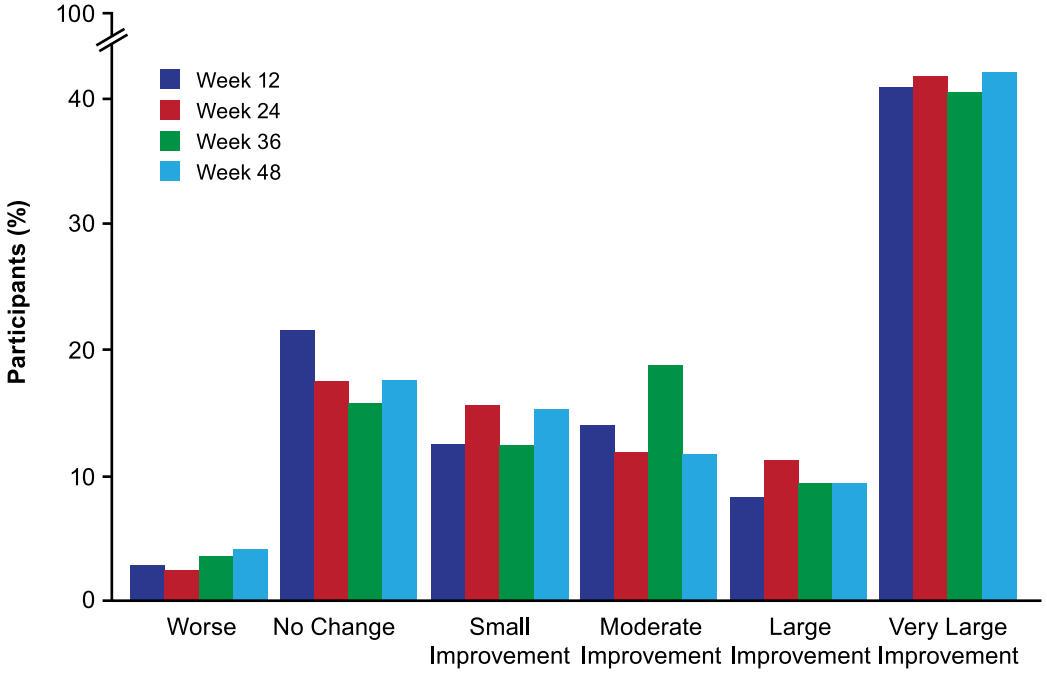


Figure 2 Distribution of participants with clinically important changes in KCCQ-OSS thresholds at weeks 12, 24, 36, and 48. KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire–Overall Summary Score

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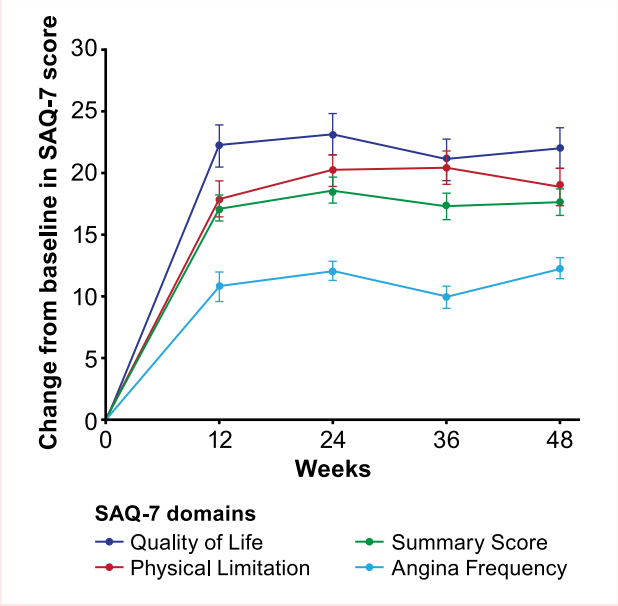


Figure 3 Mean change ±SE in SAQ7 scores from baseline to week 48. SAQ7, Seattle Angina Questionnaire 7-item

PGIC

At 12 weeks, 76.7% of participants (102/133) reported feeling 'Much Improved' or 'Very Much Improved' on the PGIC, and 91.7% (122/133) reported feeling at least 'Minimally Improved'. A similar proportion (129/167; 77.2%) of participants reported feeling 'Much Improved' or 'Very Much Improved' by 48 weeks, and 92.2% of participants (154/167) reported feeling at least 'Minimally Improved'. The ratio of participants feeling improved to unchanged or worse was 11.8.

CGI-I

At 48 weeks, the majority of clinicians (140/167, 83.8%) reported their patients were either 'Much Improved' or 'Very Much Improved', and 96.4% (161/167) of physicians reported their patients were at least 'Minimally Improved'. The distribution of improvement according to the clinician perspective was similar to that of the patient perspective, based on the PGIC, although clinician perception tended to be more favourable than the patients' own perceptions of their conditions (*Figure 6*).

Subgroup analysis

No significant differences in treatment benefit were observed according to beta-blocker use (Supplementary Table S6). There were also no significant differences observed based on gender, age group (<65 or ≥65 years), baseline KCCQ-OSS (≤50 or >50), or baseline NYHA class (II vs III) (Supplementary Figure S1).

Exploratory descriptive analysis

Six participants (2.3 per 100 pt-yr) experienced a transient reduction in LVEF to <50% during the study period, requiring dose reduction per protocol, and no participants experienced reduction in LVEF to <40% (Supplementary Table S7). Among the individuals who experienced transient reduction in LVEF, health status improvements were still observed, with least-squares mean increase of 30.2 points (95% CI: 11.8–48.7, $P < .001$) in the KCCQ-OSS and 18.5 points (4.08–32.8, $P = .01$) in the SAQ7-SS at 48 weeks. Four (1.5 per 100 pt-yr) participants developed new-onset atrial fibrillation after starting aficamten. Improvements in health status were also noted in this subgroup, with an increase of 19.1 (6.3–31.9, $P = .004$) in the KCCQ-OSS and 17.2 (4.6–29.7, $P = .008$) in the SAQ7-SS at 48 weeks of follow-up.

Correlation analysis

Changes in PROs from baseline to week 48 were significantly correlated with each other (*Table 5*). Improvements in PROs demonstrated modest but consistent correlations with key clinical and biochemical measures of oHCM severity, including troponin, NT-proBNP, LVOT gradient at rest and with Valsalva, and ≥1 NYHA class improvement (*Table 6*). Spearman coefficients ranged from approximately 0.15 to 0.30 in magnitude (Supplementary Figure S2). Improvements in KCCQ and EQ-5D scores were associated with reductions in NT-proBNP and LVOT gradients ($r \approx -0.16$ to -0.30) and with improvements in NYHA functional class ($r \approx 0.21$–0.26).

Discussion

One of the primary goals of treatment in HCM is to improve patient symptoms, functional capacity, and quality of life. PROs offer the ability to understand the impact of treatments on health status from patients' perspectives. In this long-term open-label extension study, treatment with aficamten in patients with oHCM was associated with significant and sustained improvements in multiple PROs over 48 weeks, particularly in quality of life. Notably, improvements in health status were evident as early as week 12 and were subsequently maintained through week 48, underscoring both the rapid onset and durability of patient-perceived benefit. These findings extend the results of the SEQUOIA-HCM trial by demonstrating meaningful and durable health status improvement beyond six months, with evidence of benefit across multiple dimensions of the patient experience. Moreover, the correlations among PROs and between PROs and clinical markers of disease severity reinforce the clinical relevance and construct validity of these instruments in assessing the patient experience of oHCM.

Despite the importance of assessing patient-reported health status in HCM, a recent review of registered clinical trials found that PROs were included as an outcome in only 19% of oHCM studies.[25,26] Encouragingly, their use has increased in recent years, with both mavacamten and aficamten development programmes incorporating the KCCQ-OSS as an alpha-controlled secondary endpoint.[9,10,13,27] Although the KCCQ is the most commonly used PRO in HCM trials, patients have identified several important symptoms not specifically captured by the KCCQ, including chest pain, palpitations, dizziness, and the mental toll of living with oHCM.[18] In both SEQUOIA-HCM and the present study, significant improvements in SAQ7 emphasize the value of including instruments that assess chest pain more directly.[13] In this study, treatment with aficamten was also associated with improvements across all dimensions of the EQ-5D-5L, particularly anxiety/depression, reflecting both the direct effects of symptom relief and the secondary benefits of improved functional status and reduced disease burden on emotional well-being, which are often underrecognized aspects of the patient experience. These findings underscore the importance of integrating multidimensional PROs to fully characterize the therapeutic effects of new treatments in oHCM.

When placed in context, the magnitude of benefit with aficamten far exceeds that observed with traditional pharmacologic therapies. A prior study assessing the effect of metoprolol in oHCM demonstrated a mean improvement in KCCQ-OSS of 2.3 points over placebo.[28] In MAPLE-HCM, the mean change in KCCQ-CSS was 15.8 points in the aficamten group compared with 8.7 points in the metoprolol group at 24 weeks.[15] The mean improvement in KCCQ-OSS of 18.8 points seen in this open label study is more akin to the gains in health status

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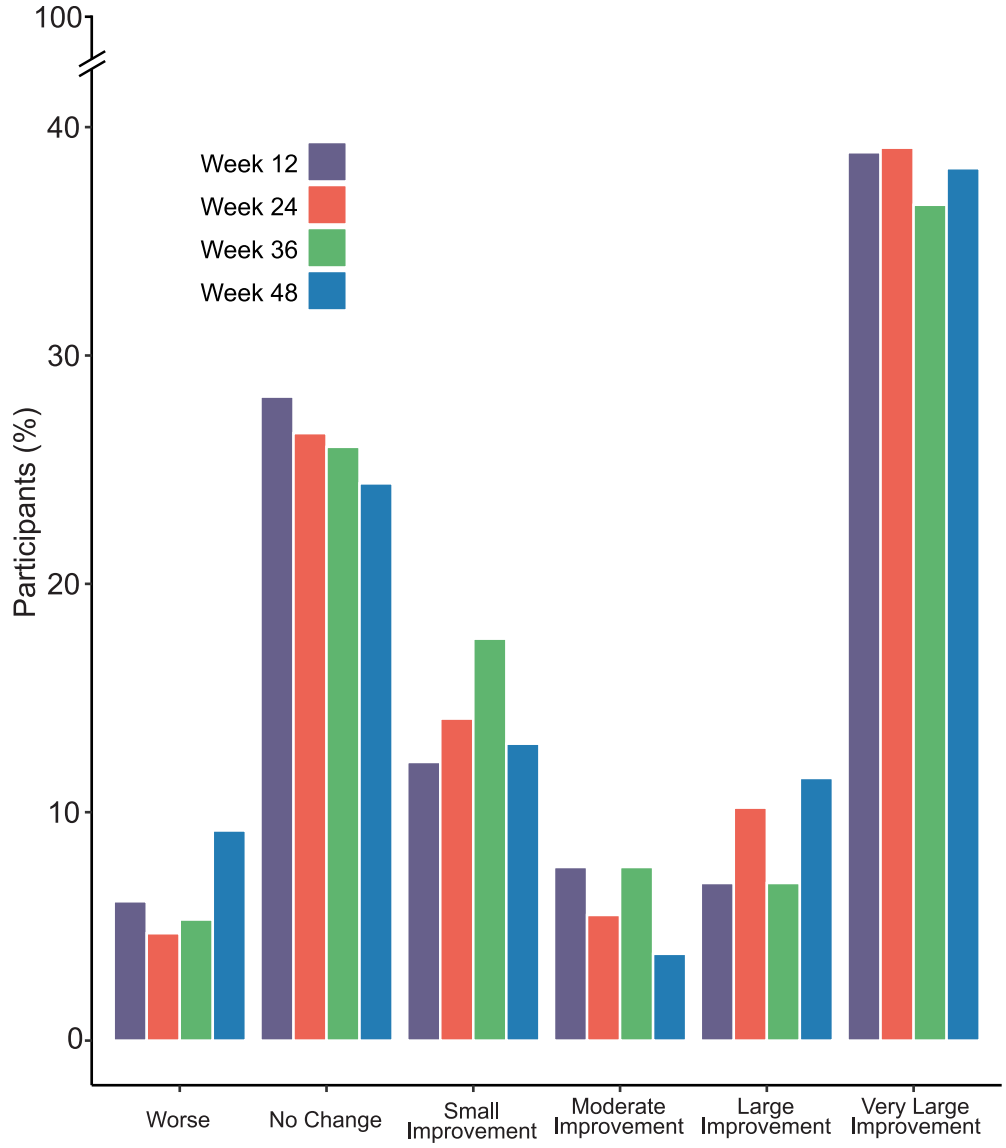


Figure 4 Distribution of participants with clinically important changes in Seattle Angina Questionnaire 7-Item–Summary Score thresholds at weeks 12, 24, 36, and 48

achieved after transcatheter valve interventions.[29,30] Assessment of intraindividual changes in the KCCQ demonstrated that 78% of participants had at least a 5-point clinically meaningful improvement in KCCQ-OSS, with the largest group of participants experiencing ≥20-point gains, corresponding to very large improvements in health status. Similarly, 77% of participants reported feeling either 'Much Improved' or 'Very Much Improved' on the PGIC. Importantly, these improvements were sustained through almost 1 year of follow-up, providing insight into the long-term patient experience with aficamten. Aficamten also led to substantial improvements in generic health status, as measured by a mean increase of 0.11 points in the EQ-5D-5L index and 12.7 points in the VAS. By comparison, dapagliflozin treatment in patients with heart failure yielded mean increases of 0.02 points in the index score and 2.9 points in the VAS after eight months of follow-up.[31,32] Taken together, the extent of improvement across both disease-specific and generic PRO instruments reinforces the efficacy of aficamten in meaningfully enhancing overall health status in patients with oHCM.

While longer-term data are available on the impact of mavacamten on PROs, the MAVA-LTE extension study collected only the HCMSQ Shortness-of-Breath domain and the EQ-5D-5L index, providing a narrower view of patient-perceived health status.[33] In MAVA-LTE, treatment with mavacamten led to an early improvement in the EQ-5D-5L index (mean increase of .08 points at 12 weeks), which was maintained through week 180. These findings parallel our observations of sustained health-status benefits with long-term aficamten therapy. However, while mavacamten and aficamten share a mechanism of action as CMIs, they differ substantially in binding sites, pharmacokinetics, half-life, and dose titration characteristics. These differences may influence both safety and efficacy measures over time. Direct long-term evaluation of aficamten remains essential, and the present study provides the first comprehensive multidimensional assessment of PROs

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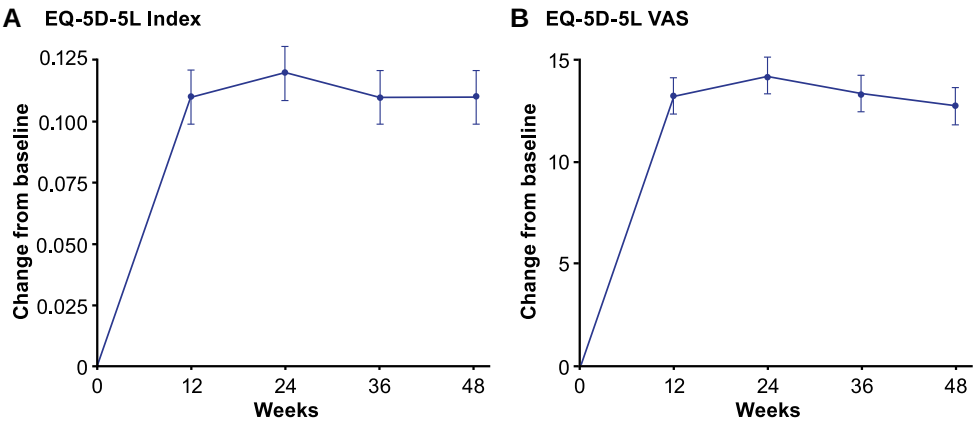


Figure 5 Mean change ±SE in (A) EQ-5d-5l index and (B) VAS scores from baseline to week 48. EQ-5D-5L, 5-level EuroQol Five-Dimensional Questionnaire; VAS, visual analogue scale

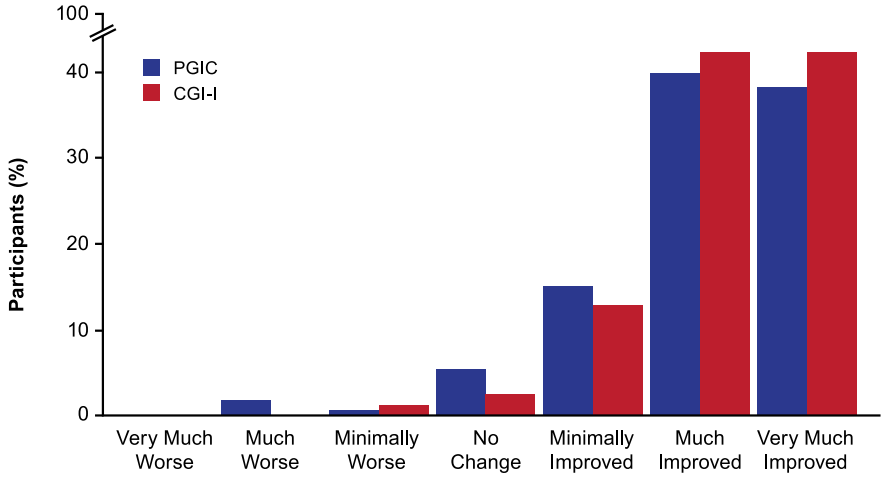


Figure 6 Summary of PGIC and CGI-I at week 48. CGI-I, Clinician Global Impression of Improvement; PGIC, Patient Global Impression of Change

Table 5 Correlation between change from baseline to week 48 in patient-reported outcome measures*

PRO[a]	SAQ7-SS	SAQ7-AF	SAQ7-PL	SAQ7-QLS	EQ-5D-5L index
KCCQ-CSS	0.58 (0.45–0.68)	0.49 (0.34–0.61)	0.67 (0.56–0.76)	0.53 (0.39–0.64)	0.60 (0.47, 0.70)
KCCQ-OSS	0.63 (0.51–0.72)	0.52 (0.38–0.64)	0.70 (0.59–0.78)	0.57 (0.44–0.68)	0.60 (0.48–0.70)
KCCQ-TSS	0.58 (0.45–0.68)	0.52 (0.38–0.63)	0.64 (0.51–0.73)	0.53 (0.40–0.65)	0.51 (0.37–0.63)
KCCQ-PLS	0.52 (0.39–0.64)	0.41 (0.26–0.55)	0.64 (0.52–0.73)	0.45 (0.3–0.58)	0.58 (0.45–0.68)
KCCQ-QLS	0.62 (0.50–0.71)	0.53 (0.39–0.64)	0.62 (0.49–0.72)	0.59 (0.46–0.69)	0.55 (0.42–0.66)
KCCQ-SES	0.20 (0.03–0.36)	0.21 (0.04–0.37)	0.19 (0.003–0.35)	0.19 (0.02–0.35)	0.18 (0.01–0.34)
KCCQ-SLS	0.54 (0.40–0.65)	0.42 (0.29–0.55)	0.64 (0.52–0.74)	0.47 (0.32–0.60)	0.53 (0.38–0.64)
EQ-5D-5L index	0.54 (0.41–0.65)	0.46 (0.32–0.59)	0.52 (0.37–0.64)	0.43 (0.28–0.56)	—

*$P < .05$ for all correlations.
[a]Spearman correlation coefficient (95% confidence interval).
AF, angina frequency; CSS, Clinical Summary Score; EQ-5D-5L, 5-level EuroQol Five-Dimensional Questionnaire; KCCQ, Kansas City Cardiomyopathy Questionnaire; OSS, Overall Summary Score; PL, physical limitation; PLS, physical limitation score; PRO, patient-reported outcome; QLS, quality of life score; SAQ7, Seattle Angina Questionnaire 7-item; SES, self efficacy score; SLS, social limitation score; SS, summary score; TSS, total symptom score

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Table 6 Relation between change from baseline to week 48 in patient-reported outcomes and clinical measures of hypertrophic cardiomyopathy severity

Outcome measure	Spearman correlation	95% CI	P value
KCCQ-CSS			
Troponin	−0.16	−0.31, −0.01	.04
NT-proBNP	−0.18	−0.32, −0.03	.02
LVOT Valsalva	−0.18	−0.32, −0.03	.02
LVOT resting gradient	−0.21	−0.34, −0.06	.01
NYHA ≥1 class improvement	0.25	0.10, 0.39	<.001
KCCQ-OSS			
Troponin	−0.16	−0.31, −0.01	.03
NT-proBNP	−0.17	−0.31, −0.02	.03
LVOT Valsalva	−0.19	−0.33, −0.04	.01
LVOT resting gradient	−0.21	−0.35, −0.06	.01
NYHA ≥1 class improvement	0.26	0.11, 0.39	<.001
SAQ7-SS			
Troponin	−0.15	−0.32, 0.02	.09
NT-proBNP	−0.14	−0.31, 0.03	.11
LVOT Valsalva	−0.14	−0.31, 0.03	.1
LVOT resting gradient	−0.21	−0.37, −0.04	.01
NYHA ≥1 class improvement	0.16	−0.01, 0.32	.07
EQ-5D-5L index			
Troponin	−0.27	−0.42, −0.10	.002
NT-proBNP	−0.16	−0.33, 0.01	.06
LVOT Valsalva	−0.12	−0.29, 0.05	.17
LVOT resting gradient	−0.3	−0.45, −0.13	<.001
NYHA ≥1 class improvement	0.21	0.04, 0.37	.02
EQ-5D VAS			
Troponin	−0.23	−0.39, −0.06	<.01
NT-proBNP	−0.08	−0.25, 0.10	.38
LVOT Valsalva	−0.08	−0.25, 0.09	.37
LVOT resting gradient	−0.22	−0.38, −0.05	.01
NYHA ≥1 class improvement	0.22	0.05, 0.38	.01

CSS, Clinical Summary Score; EQ-5D-5L, 5-level EuroQol Five-Dimension 5-Level Questionnaire; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OSS, Overall Summary Score; SAQ7-SS, Seattle Angina Questionnaire 7-item Summary Score

during extended treatment. Ongoing and future studies will be important to further clarify how long-term effects compare across agents within this drug class.

The principal safety concern with CMIs pertains to their impact on LV function. Six participants (2.3 per 100 pt-yr) in this study had a transient reduction in LVEF to <50%; however, these participants still experienced significant health status improvements. There is also emerging evidence that mavacamten use may be associated with incident or recurrent atrial fibrillation.[34–37] In the current study, only four participants (1.5 per 100 pt-yr) developed new-onset atrial fibrillation after starting aficamten but similarly demonstrated improvements in health status, although interpretation is limited by the small number of events. These findings highlight the need for further longitudinal evaluation in larger real, world cohorts.

Collectively, this study builds upon the results of the SEQUOIA-HCM trial by demonstrating that long-term treatment with aficamten yields durable and clinically meaningful improvements in health status across multiple PROs. By capturing diverse dimensions of health status, these findings highlight the ability of aficamten to significantly improve the lived experience of patients with oHCM. As the therapeutic landscape for HCM continues to evolve, ensuring that patient experience remains central will be essential to evaluating the true impact of emerging therapies.

Study limitations

This study has several limitations. First, participants were required to have completed a prior aficamten trial and to meet eligibility criteria, including LVEF ≥55%. As such, the study population may represent a selected cohort enriched for those who tolerated and responded to therapy, which may limit the generalizability of these findings to broader populations of patients with oHCM. Second, the open-label design and lack of a control group may introduce bias in the assessment of treatment effects, particularly for subjective endpoints such as PROs, and the potential contribution of placebo and expectation effects cannot be excluded. Third, although multiple PRO instruments were used, not all domains of patient experience may have been fully captured, and certain symptoms, such as dizziness and palpitations, were not specifically addressed, although are highly correlated with other symptoms that were assessed, such as shortness of breath and fatigue.[18] Fourth, because the SAQ7 and EQ-5D-5L index and VAS were included in the study protocol after initiation, baseline data were missing for some participants. Finally, this study did not address differences in PROs on the basis of patient sex, race, or geographic origin, which may be important for understanding heterogeneity in treatment response and tailoring patient-centred care.

Conclusions

In this long-term extension study, treatment with aficamten was associated with meaningful and sustained improvements in health status. This improvement was seen across all symptom domains and correlated with important clinical measures of disease severity. These findings build on prior evidence from SEQUOIA-HCM and support the use of aficamten to improve symptoms, functional status, and quality of life in patients with oHCM. Findings also underscore the value of incorporating multidimensional, patient-centred endpoints in future HCM trials to better capture the full therapeutic impact of novel treatments.

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Supplementary data

Supplementary data are available at *European Journal of Heart Failure* online.

Declarations

Disclosure of Interest

S.D.W. has received consulting fees from Cytokinetics and Bristol Myers Squibb. L.W.L. has no disclosures to report. A.M. has received

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Data Availability

Qualified researchers may submit a request containing the research objectives, endpoints/outcomes of interest, statistical analysis plan, data requirements, publication plan, and qualifications of the researcher(s). In general, Cytokinetics, Incorporated, does not grant external requests for individual patient data for the purpose of re-evaluating safety and efficacy issues already addressed in the product labelling. Requests are reviewed by a committee of internal advisors, and if not approved, may be further arbitrated by a Data Sharing Independent Review Panel. On approval, the information necessary to address the research question will be provided under the terms of a data sharing agreement. This may include anonymized individual patient data and/or available supporting documents, containing fragments of analysis code where provided in analysis specifications. Requests may be submitted to medicalaffairs@cytokinetics.com

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Ethical Approval

Ethical Approval was not required.

Pre-registered Clinical Trial Number

None supplied.

References

1. Marian AJ, Braunwald E. Hypertrophic cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. *Circ Res* 2017;**121**:749–70. https://doi.org/10.1161/CIRCRESAHA.117.311059
2. Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. *J Am Coll Cardiol* 2012;**60**:705–15. https://doi.org/10.1016/j.jacc.2012.02.068
3. Frey N, Luedde M, Katus HA. Mechanisms of disease: hypertrophic cardiomyopathy. *Nat Rev Cardiol* 2011;**9**:91–100. https://doi.org/10.1038/nrcardio.2011.159
4. Maron BJ, Desai MY, Nishimura RA, Spirito P, Rakowski H, Towbin JA, *et al.* Management of hypertrophic cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol* 2022;**79**:390–414. https://doi.org/10.1016/j.jacc.2021.11.021
5. Sherrid MV, Shetty A, Winson G, Kim B, Musat D, Alviar CL, *et al.* Treatment of obstructive hypertrophic cardiomyopathy symptoms and gradient resistant to first-line therapy with β-blockade or verapamil. *Circ Heart Fail* 2013;**6**:694–702. https://doi.org/10.1161/CIRCHEARTFAILURE.112.000122
6. Ommen SR, Ho CY, Asif IM, Balaji S, Burke MA, Day SM, *et al.* 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR guideline for the management of hypertrophic cardiomyopathy: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation* 2024;**149**:e1239–311. https://doi.org/10.1161/CIR.0000000000001250
7. Liang LW, Lumish HS, Sewanan LR, Shimada YJ, Maurer MS, Weiner SD, *et al.* Evolving strategies for the management of obstructive hypertrophic cardiomyopathy. *J Cardiac Fail* 2024;**30**:1136–53. https://doi.org/10.1016/j.cardfail.2024.04.024
8. Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. *N Engl J Med* 2018;**379**:655–68. https://doi.org/10.1056/NEJMra1710575
9. Olivotto I, Oreziak A, Barriales-Villa R, Abraham TP, Masri A, Garcia-Pavia P, *et al.* Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2020;**396**:759–69. https://doi.org/10.1016/S0140-6736(20)31792-X
10. Maron MS, Masri A, Nassif ME, Barriales-Villa R, Arad M, Cardim N, *et al.* Aficamten for symptomatic obstructive hypertrophic cardiomyopathy. *N Engl J Med* 2024;**390**:1849–61. https://doi.org/10.1056/NEJMoa2401424
11. Anderson RL, Trivedi DV, Sarkar SS, Henze M, Ma W, Gong H, *et al.* Deciphering the super relaxed state of human β-cardiac myosin and the mode of action of mavacamten from myosin molecules to muscle fibers. *Proc Natl Acad Sci U S A* 2018;**115**:E8143–52. https://doi.org/10.1073/pnas.1809540115
12. Chuang C, Collibee S, Ashcraft L, Wang W, Vander Wal M, Wang X, *et al.* Discovery of aficamten (CK-274), a next-generation cardiac myosin inhibitor for the treatment of hypertrophic cardiomyopathy. *J Med Chem* 2021;**64**:14142–52. https://doi.org/10.1021/acs.jmedchem.1c01290
13. Sherrod CF, Saberi S, Nassif ME, Claggett BL, Coats CJ, Garcia-Pavia P, *et al.* Effect of aficamten on health status outcomes in obstructive hypertrophic cardiomyopathy: results from SEQUOIA-HCM. *J Am Coll Cardiol* 2024;**84**:1773–85. https://doi.org/10.1016/j.jacc.2024.08.014
14. Maron MS, Masri A, Choudhury L, Olivotto I, Saberi S, Wang A, *et al.* Phase 2 study of aficamten in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2023;**81**:34–45. https://doi.org/10.1016/j.jacc.2022.10.020
15. Garcia-Pavia P, Maron MS, Masri A, Merkely B, Nassif ME, Peña-Peña ML, *et al.* Aficamten or metoprolol monotherapy for obstructive hypertrophic cardiomyopathy. *N Engl J Med* 2025;**393**:949–60. https://doi.org/10.1056/NEJMoa2504654
16. 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**:1245–55. https://doi.org/10.1016/S0735-1097(00)00531-3
17. 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**:2379–90. https://doi.org/10.1016/j.jacc.2020.09.542
18. Nassif M, Fine JT, Dolan C, Reaney M, Addepalli P, Allen VD, *et al.* Validation of the Kansas City Cardiomyopathy Questionnaire in symptomatic obstructive hypertrophic cardiomyopathy. *JACC Heart Fail* 2022;**10**:531–9. https://doi.org/10.1016/j.jchf.2022.03.002
19. Chan PS, Jones PG, Arnold SA, Spertus JA. Development and validation of a short version of the Seattle Angina Questionnaire. *Circ Cardiovasc Qual Outcomes* 2014;**7**:640–7. https://doi.org/10.1161/CIRCOUTCOMES.114.000967

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20. Herdman M, Gudex C, Lloyd A, Janssen Mf, Kind P, Parkin D, *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;**20**:1727–36. https://doi.org/10.1007/s11136-011-9903-x
21. Batóg P, Rencz F, Péntek M, Gulácsi L, Filipiak KJ, Prevolnik Rupel V, *et al.* EQ-5D studies in cardiovascular diseases in eight Central and Eastern European countries: a systematic review of the literature. *Kardiol Pol* 2018;**76**:860–70. https://doi.org/10.5603/KP.a2018.0033
22. McClure NS, Sayah FA, Xie F, Luo N, Johnson JA. Instrument-defined estimates of the minimally important difference for EQ-5D-5L index scores. *Value Health* 2017;**20**:644–50. https://doi.org/10.1016/j.jval.2016.11.015
23. Lawson CA, Benson L, Squire I, Zaccardi F, Ali M, Hand S, *et al.* Changing health related quality of life and outcomes in heart failure by age, sex and subtype. *EClinicalMedicine* 2023;**64**:102217. https://doi.org/10.1016/j.eclinm.2023.102217
24. Guy W. *ECDEU Assessment Manual for Psychopharmacology Revised, 1976*. Rockville, MD: National Institutes of Health, 1976.
25. Reza N, Day SM, Owens AT. Patient-reported outcomes in clinical studies of patients with hypertrophic cardiomyopathy. *Prog Cardiovasc Dis* 2023;**80**:60–5. https://doi.org/10.1016/j.pcad.2023.08.007
26. Khan MS, Jawad MA, Ikemura N, Sherrod CF, O'Keefe EL, Chan PS, *et al.* The rise of patient-reported outcome measures: trends in heart failure clinical trials. *J Card Fail* 2025;**31**:730–4. https://doi.org/10.1016/j.cardfail.2024.09.019
27. Spertus JA, Fine JT, Elliott P, Ho CY, Olivotto I, Saberi S, *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**:2467–75. https://doi.org/10.1016/S0140-6736(21)00763-7
28. 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**:2505–17. https://doi.org/10.1016/j.jacc.2021.07.065
29. Arnold SV, Li Z, Vemulapalli S, Baron SJ, Mack MJ, Kosinski AS, *et al.* Association of transcatheter mitral valve repair with quality of life outcomes at 30 days and 1 year: analysis of the Transcatheter Valve Therapy Registry. *JAMA Cardiol* 2018;**3**:1151–9. https://doi.org/10.1001/jamacardio.2018.3359
30. Arnold SV, Spertus JA, Lei Y, Allen KB, Chhatriwalla AK, Leon MB, *et al.* Use of the Kansas City Cardiomyopathy Questionnaire for monitoring health status in patients with aortic stenosis. *Circ Heart Fail* 2013;**6**:61–7. https://doi.org/10.1161/CIRCHEARTFAILURE.112.970053
31. Yang M, Kondo T, Talebi A, Jhund PS, Docherty KF, Claggett BL, *et al.* Dapagliflozin and quality of life measured using the EuroQol 5-dimension questionnaire in patients with heart failure with reduced and mildly reduced/preserved ejection fraction. *Eur J Heart Fail* 2024;**26**:1524–38. https://doi.org/10.1002/ejhf.3263
32. Hanna M, Damy T, Grogan M, Stewart M, Gundapaneni B, Patterson TA, *et al.* Impact of tafamidis on health-related quality of life in patients with transthyretin amyloid cardiomyopathy (from the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial). *Am J Cardiol* 2021;**141**:98–105. https://doi.org/10.1016/j.amjcard.2020.10.066
33. Garcia-Pavia P, Oręziak A, Masri A, Barriales-Villa R, Abraham TP, Owens AT, *et al.* Long-term effect of mavacamten in obstructive hypertrophic cardiomyopathy. *Eur Heart J* 2024;**45**:5071–83. https://doi.org/10.1093/eurheartj/ehae579
34. Nguyen O, Wiedrick J, Massera D, Adlestein E, Frejat S, Castrichini M, *et al.* Incidence and outcomes of atrial fibrillation and systolic dysfunction in patients receiving Mavacamten for obstructive hypertrophic cardiomyopathy: a multicenter study. medRxiv. https://doi.org/10.1101/2025.09.15.25335783, 19 September 2025, preprint: not peer reviewed.
35. Liang LW, Lumish HS, Shimada YJ, Weiner SD. Incidence and recurrence of atrial fibrillation among patients with obstructive hypertrophic cardiomyopathy treated with mavacamten: a single-center experience. *Clin Res Cardiol* 2024;**115**:887–91. https://doi.org/10.1007/s00392-024-02496-1
36. Castrichini M, Alsidawi S, Geske JB, Newman DB, Arruda-Olson AM, Bos JM, *et al.* Incidence of newly recognized atrial fibrillation in patients with obstructive hypertrophic cardiomyopathy treated with mavacamten. *Heart Rhythm* 2024;**21**:2065–7. https://doi.org/10.1016/j.hrthm.2024.04.055
37. Boyle TA, Reza N, Hyman M, Supple G, See VY, Marzolf A, *et al.* Atrial fibrillation in patients receiving mavacamten for obstructive hypertrophic cardiomyopathy: real-world incidence, management, and outcomes. *JACC Clin Electrophys* 2025;**11**:411–3. https://doi.org/10.1016/j.jacep.2024.10.014

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