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METHODOLOGY AND MECHANISMS CORNER

Exercise Capacity in Patients With Obstructive Hypertrophic Cardiomyopathy

SEQUOIA-HCM Baseline Characteristics and Study Design

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HIGHLIGHTS

- oHCM has low hospitalization and mortality necessitating alternate measures of clinical benefit.
- Cardiopulmonary exercise testing objectively measures functional capacity and is a prognosticator for adverse clinical outcomes.
- SEQUOIA-HCM is a randomized, double-blind, placebo-controlled trial of aficamten in oHCM evaluating peak oxygen uptake.
- Positive aficamten effect on exercise capacity, functional class, and symptoms would be meaningful to patients.

ABSTRACT

Patients with obstructive hypertrophic cardiomyopathy (oHCM) have increased risk of arrhythmia, stroke, heart failure, and sudden death. Contemporary management of oHCM has decreased annual hospitalization and mortality rates, yet patients have worsening health-related quality of life due to impaired exercise capacity and persistent residual symptoms. Here we consider the design of clinical trials evaluating potential oHCM therapies in the context of SEQUOIA-HCM (Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM). This large, phase 3 trial is now fully enrolled (N = 282). Baseline characteristics reflect an ethnically diverse population with characteristics typical of patients encountered clinically with substantial functional and symptom burden. The study will assess the effect of aficamten vs placebo, in addition to standard-of-care medications, on functional capacity and symptoms over 24 weeks. Future clinical trials could model the approach in SEQUOIA-HCM to evaluate the effect of potential therapies on the burden of oHCM. (Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM [SEQUOIA-HCM]; NCT05186818). (J Am Coll Cardiol HF 2024;12:199–215) © 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 license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

CMI = cardiac myosin inhibitor

CMR = cardiac magnetic resonance

CPET = cardiopulmonary exercise testing

HCM = hypertrophic cardiomyopathy

KCCQ = Kansas City Cardiomyopathy Questionnaire

LVOT-G = left ventricular outflow tract gradient

oHCM = obstructive hypertrophic cardiomyopathy

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

pVO_2 = peak oxygen uptake

SAM = systolic anterior motion

SRT = septal reduction therapy

Hypertrophic cardiomyopathy (HCM) is a disease of the cardiac sarcomere that usually has an identified genetic basis.[1-3] A fundamental pathophysiologic abnormality in most cases of HCM is myocardial hypercontractility.[4] Cardiac hypertrophy occurs in the absence of increased loading conditions and is associated with reduced ventricular compliance. Histological features include myocyte hypertrophy, myocyte disarray, microvascular dysfunction, and myocardial fibrosis.[5] Patients with obstructive hypertrophic cardiomyopathy (oHCM), the most common form of the disease, have a resting or provocable left ventricular outflow tract gradient (LVOT-G), generated by direct contact between the mitral valve leaflets and a thickened interventricular septum during systole, often with associated mitral regurgitation.

Patients with oHCM have increased risk of arrhythmia, stroke, heart failure, and sudden death. However, decreased hospitalization and mortality rates with contemporary management have resulted in generally low annual event rates, and the disease has a low population prevalence (<1:500).[6-8] It is therefore not possible to perform randomized controlled clinical trials using hard endpoints such as mortality or hospitalizations caused by heart failure within a reasonable timeframe. Furthermore, the evaluation of functional and symptomatic endpoints is recommended to promote patient-centered clinical trial efficiency in heart failure.[9] In patients with oHCM, LVOT-G is a strong, independent determinant of adverse outcomes, including atrial fibrillation, stroke, heart failure, and sudden cardiac death.[10,11] LVOT-G is also the primary driver of exertional dyspnea, chest pain, fatigue, and exercise intolerance, which are heart failure symptoms that severely impact functional capacity. Peak oxygen uptake (pVO_2), measured by cardiopulmonary exercise testing (CPET), can be used to quantify functional capacity. Studies have demonstrated that pVO_2 in HCM has important prognostic implications and is able to independently predict heart failure death and total mortality (**Table 1**).[12-18] Here we consider the current treatments for oHCM and the available tools for quantifying clinically meaningful changes in symptom burden and patient outcomes. We describe the use of these tools, with a particular focus on pVO_2, to assess the safety and efficacy of aficamten in patients with symptomatic oHCM enrolled in SEQUOIA-HCM (Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM; NCT05186818), the phase 3 pivotal trial of this drug candidate.

TREATMENT APPROACHES FOR oHCM

As LVOT-G is the main driver of symptoms in oHCM, as well as a strong, independent predictor of progression to severe heart failure and death,[11] reducing LVOT-G has long been the primary goal in oHCM treatment. Pharmacologic therapy with non-vasodilating beta-blockers or nondihydropyridine calcium-channel blockers (verapamil, diltiazem), with or without the addition of disopyramide, forms the basis of the current medical treatment paradigm.[5,19-21] Patients with severe symptoms (NYHA functional class III/IV) and LVOT-G ≥50 mm Hg despite maximally tolerated medical therapy are

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

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TABLE 1 Studies Reporting Correlation Between CPET Variables and Prognosis in Patients With HCM

First Author	N	Follow-Up, y	Number of Events	Findings	Design	Demographics	Interventions
Coats et al[12]	1,898	Median 5.6	178	pVO_2 predicted all-cause mortality or heart transplant (death/transplant), adjusted HR: 0.82 (95% CI: 0.77-0.88); pVO_2 in combination with submaximal CPET parameters such as VE/VCO_2 and VAT predicted death from HF	Consecutive patients with HCM who underwent CPET between 1998 and 2010, single-center observational cohort study, University College London, United Kingdom	Mean age 46 y 67% male Mean BMI 27 kg/m^2 8% NYHA functional class III/IV 31% LVOT-G ≥30 mm Hg 51% CCB or BB 2% septal myectomy at baseline 1% alcohol septal ablation at baseline 3% defibrillator at baseline 4% AF	10% septal myectomy during follow-up 2% alcohol septal ablation during follow-up 18% defibrillator during follow-up
Masri et al[13]	1,005	Mean 5.5	94	% age-gender predicted pVO_2 associated with composite endpoint of death, appropriate ICD discharges, resuscitated sudden death, stroke, and HF admission, HR: 0.96 (95% CI: 0.93-0.98)	Consecutive adult patients with HCM who underwent CPET and echocardiography between 1997 and 2012, retrospective observational study, Cleveland Clinic, Ohio, USA	Mean age 50 y 64% male Mean BMI 30 kg/m^2 19% AF 11% ICD 77% BB 29% CCB 5% disopyramide 83% LVOT-G ≥30 mm Hg Mean echo LVEF 62% Mean maximal LVOT-G 92 mm Hg Mean pVO_2 21 mL/kg/min 32% NYHA functional class I 46% NYHA functional class II 22% NYHA functional class III 23% abnormal HRR at first minute	51% surgical relief of LVOTO 6% alcohol septal ablation
Cui et al[14]	752	Median 9.0	—[a]	Greater adjusted pVO_2 preoperatively (per 1% increase) associated with better long-term survival after myectomy, HR: 0.98 (95% CI: 0.96-1.00)	Patients with oHCM who had CPET within 6 mo before septal myectomy between 2005 and 2016, Mayo Clinic, Minnesota, USA	Median age 55.5 y 59% male Median BMI 30.6 kg/m^2 18% AF Median resting LVOT-G 52 mm Hg Median echo LVEF 71% Median pVO_2 18 mL/kg/min Median adjusted pVO_2 60% predicted	100% myectomy
Magri et al[15]	623	Median 3.7	25	VE/VCO_2 ≥31 independently associated with composite endpoint of SCD, aborted SCD, and appropriate ICD interventions	Consecutive outpatients with HCM prospectively followed between 2007 and 2015, multicenter (5 tertiary HCM centers), Italy	Mean age 49 y 69% male 6% NYHA functional class III/IV 5% AF 32% LVOTO 6% previous myectomy 12% ICD Median max LVOT-G 12 mm Hg Mean echo LVEF 63% Mean pVO_2 21 mL/kg/min Mean pVO_2 71% predicted 67% BB 9% verapamil 4% disopyramide	10% ICD during follow-up 7% surgical myectomy during follow-up

Continued on the next page

candidates for invasive septal reduction therapy (SRT) by either surgical myectomy or percutaneous alcohol septal ablation.[5] SRT is usually successful at relieving left ventricular outflow tract (LVOT) obstruction and it can lead to a marked improvement in symptoms, but it also has associated risks—the mortality rate is 1% to 2% even when performed by the most expert hands at the highest-volume centers.[22-25] In addition, although a successful SRT procedure will often address LVOT obstruction, this direct anatomic modification therapy does not address the underlying pathophysiology, and patient symptoms may reappear as the disease progresses.

First identified as a disease of the sarcomere based on the discovery of the R403Q sequence variant in beta-cardiac myosin,[26] knowledge of the genetic basis of oHCM and the role of sarcomeric gene mutations has grown. A more refined understanding of their

TABLE 1 Continued

First Author	N	Follow-Up, y	Number of Events	Findings	Design	Demographics	Interventions
Magri et al[16]	620	Median 3.8	84	Peak circulatory power (pVO_2 × peak SBP) and VE/VCO_2 slope independently associated with HF endpoints (HF death, CTX, progression to NYHA functional class III/IV, severe functional deterioration leading to SRT, hospitalization for HF worsening)	Consecutive outpatients with HCM, prospectively followed between 2007 and 2015, multicenter (5 HCM centers), Italy	Mean age 49 y 69% male 6% NYHA functional class III 32% LVOTO 6% myectomy 12% ICD Mean LVOT-G 26 mm Hg Mean echo LVEF 62% Mean pVO_2 21.1 mL/kg/min Mean pVO_2 71% predicted 67% BB 8% verapamil 4% disopyramide	4% myectomy during follow-up 10% ICD during follow-up
Smith et al[17]	295	Median 11.25	43	Post-myectomy pVO_2 nonresponder vs responder all-cause death, adjusted HR: 1.77 (95% CI: 1.06-3.34)	Consecutive patients with oHCM who underwent surgical myectomy between 1995 and 2016, single center, retrospective, Mayo Clinic, Minnesota, USA	Mean age 50 y 56% men Mean BMI 30.2 kg/m^2 Mean pVO_2 18.8 mL/kg/min Mean pVO_2 68% predicted Mean NYHA functional class 2.9 5% AF 76% BB 33% CCB	100% surgical myectomy
Finocchiaro et al[18]	156	Mean 2.25	21	pVO_2 <80% (HR: 4.11 [95% CI: 1.46-11.59]) and VE/VCO_2 >34 (HR: 3.14 [95% CI: 1.26-7.87]) associated with composite outcome of death, CTX, functional deterioration leading to SRT	Consecutive patients with HCM referred to single center with CPET, impedance cardiography and echo, Stanford University, USA, 2007 to 2012	Mean age 51 y 62% male 14% NYHA functional class III Mean pVO_2 26 mL/kg/min Mean echo LVEF 67% 27% LVOT-G >30 mm Hg at rest 35% LVOT-G >50 mm Hg at stress 53% BB 24% CCB	12 patients had clinical deterioration leading to SRT

Studies are shown in descending order of sample size. [a]In Cui, estimated 5- and 10-year survivals were 97% and 91%, respectively.

AF = atrial fibrillation; BB = beta-blocker; BMI = body mass index; CCB = calcium-channel blocker; CPET = cardiopulmonary exercise testing; CTX = cardiac transplantation; Echo = echocardiogram; HCM = hypertrophic cardiomyopathy; HF = heart failure; HRR = heart rate reserve; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; LVOT-G = left ventricular outflow tract gradient; LVOTO = left ventricular outflow tract obstruction; max = maximum; oHCM = obstructive hypertrophic cardiomyopathy; pVO_2 = peak oxygen uptake; SBP = systolic blood pressure; SCD = sudden cardiac death; SRT = septal reduction therapy; VAT = ventilatory anerobic threshold; VCO_2 = carbon dioxide uptake; VE = ventilatory efficiency.

contribution to the disease process has emerged, and this has led to the development of new, built-for-purpose treatments that target the fundamental molecular basis of oHCM. Cardiac myosin inhibitors (CMIs) are a novel class of drugs that selectively and reversibly inhibit cardiac myosin ATPase activity, thereby reducing the number of myosin molecules available to bind actin, and, consequently, blunting pathological hypercontractility.[27] In addition, by reducing contractility, systolic anterior motion (SAM) of the mitral valve with septal contact and associated mitral regurgitation may be addressed, further improving hemodynamics.[28]

The use of CMI therapy for treatment of symptomatic oHCM has been the subject of recent phase 3 clinical trials,[29,30] leading to regulatory approval and, subsequently, label expansion of mavacamten, a first-in-class CMI. Recent European guidelines recommend mavacamten as second-line medical therapy[21] and, while clinical guidelines in the United States have yet to be updated, there is broad consensus that mavacamten will fall into the medical treatment paradigm for symptomatic oHCM.

Aficamten is a next-in-class CMI that binds to a unique allosteric binding site on cardiac myosin, and has distinct physiochemical properties.[31,32] Aficamten was specifically engineered to have a half-life that allows once-daily dosing and attainment of steady-state plasma concentrations by 14 days, enabling echocardiographic-based dose titration as early as every 2 weeks, and reversibility following dose reduction or discontinuation of dosing; a shallow dose-response relationship with a resultant wide therapeutic window; and a lack of potential for drug-drug interactions. The pharmacokinetics and shallow nature of the exposure-response relationship are important properties, with the pharmacokinetics relating to the time to onset/offset of effect, and the exposure-response relationship relating to the onset of effect as the dose increases. The physiochemical properties of aficamten may yield benefits to patients in terms of efficacy, safety, and ease of use.[33]

pVO_2 AS A CLINICALLY MEANINGFUL ENDPOINT IN oHCM CLINICAL TRIALS

Measuring pVO_2 during CPET is the gold standard for determining oxygen uptake during maximal exercise, a direct correlate of cardiac output, and has minimal placebo effect.[9] In addition to objectively quantifying functional capacity more effectively than subjective measures such as NYHA functional class, pVO_2 has been repeatedly shown to independently predict clinically relevant outcomes in both oHCM and nonobstructive HCM (**Table 1**). The largest of the studies (>1,800 patients) reported that the risk of death or transplantation in HCM was reduced by 21% for each 1 mL/kg/min increase in pVO_2.[12]

Measurements of pVO_2 enable comprehensive assessment of the multiple mechanisms that contribute to exercise limitation in HCM. It is important to note that only SRT and CMIs have been shown to both reduce LVOT obstruction and improve pVO_2 (**Figure 1**),[12,13,17,29,34-42] and although beta-blocker therapy may be effective at treating the degree of obstruction, beta-blockers have yet to demonstrate improvements in pVO_2 or clinical event rates.[34,43] We therefore hypothesize that improvements in pVO_2 are very likely to translate into a reduction in future clinical events.

Because pVO_2 is uniquely positioned both as an objective measure of functional capacity and as a prognosticator of adverse clinical events in oHCM, it represents the sole primary endpoint for SEQUOIA-HCM. The inclusion and exclusion criteria (**Table 2**) were designed to target patients with cardiac-specific physiologic limitation (pVO_2 ≤90% predicted for age and sex, and with a respiratory exchange ratio ≥1.05 at baseline).[44] These criteria were also designed to avoid confounding factors that may independently impact exertional capacity (eg, chronic deconditioning, significant underlying lung disease, morbid obesity, orthopedic limitations).

QUANTIFICATION OF SYMPTOMS AS AN ENDPOINT IN oHCM CLINICAL TRIALS

Despite improvements in mortality and hospitalization rates, patients with oHCM receiving contemporary management have worsening health-related quality of life caused by impaired exercise capacity and persistent residual symptoms. NYHA functional classification carries substantial prognostic value in HCM[45] and is used in consensus documents in Europe and the United States[5,19,21] to guide health care professionals on when and how to implement therapies. Health care providers assign NYHA functional classes to their patients; as a consequence, they do not necessarily reflect the patients' self-assessment of their symptoms. A placebo response has been observed with NYHA functional class: in 2 recent trials, approximately one-third of patients with HCM assigned to placebo were reported as having experienced an improvement of ≥1 NYHA functional class.[46]

In contrast to the NYHA functional classification, the Kansas City Cardiomyopathy Questionnaire (KCCQ) specifically enables patient self-assessment of heart failure symptoms. The KCCQ evaluates multiple domains of health status through 23 questions, includes a temporal factor (recall of 2 weeks), and is not a categorical tool like the NYHA functional classification. Although the KCCQ was initially designed for health status quantification in patients who had heart failure with reduced ejection fraction, it is now also a validated instrument for oHCM.[47] The KCCQ is also subject to the placebo effect, although to a lesser degree than the NYHA functional classification.[46] Both tools have been included as key secondary endpoints in SEQUOIA-HCM.

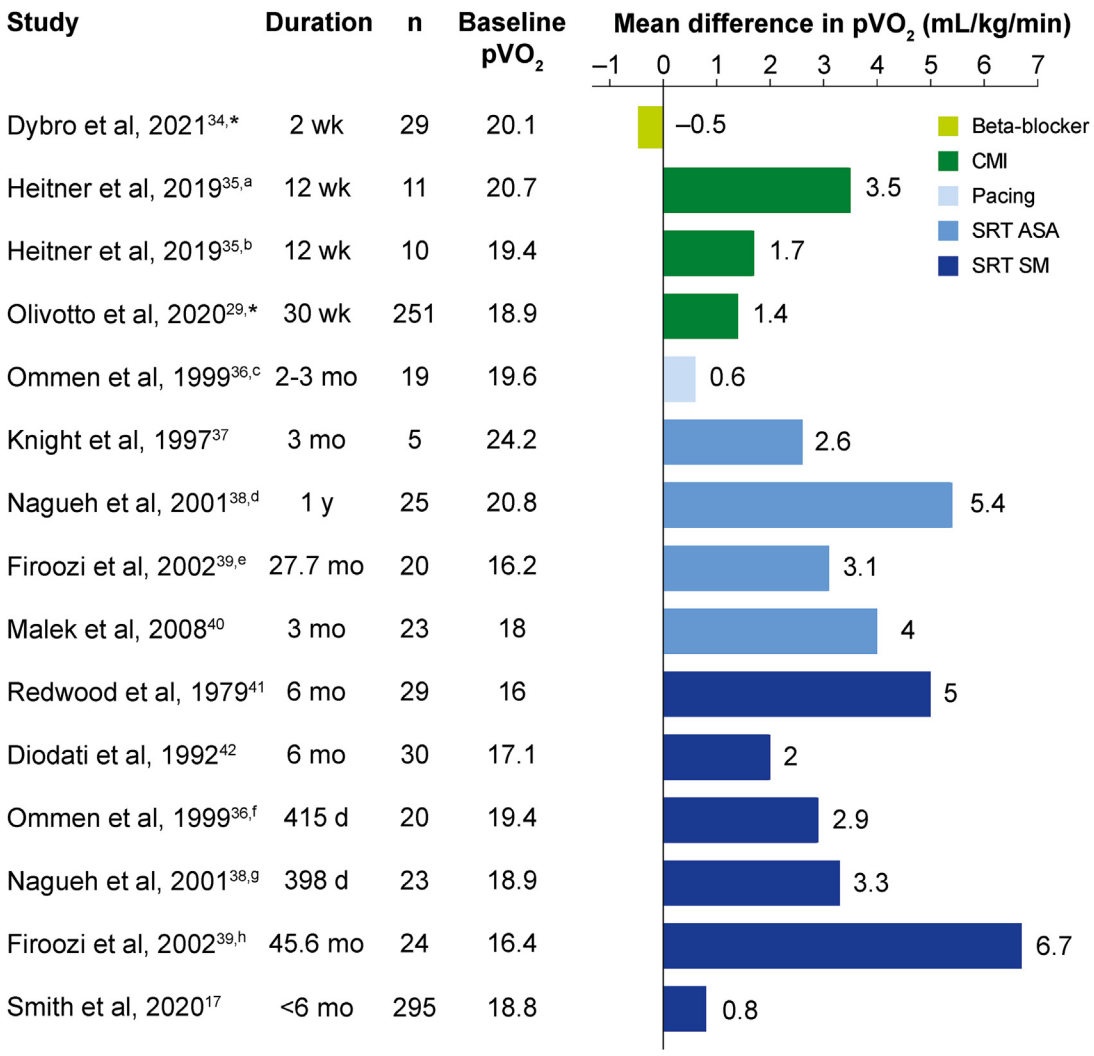
CARDIAC BIOMARKERS IN oHCM

The cardiac biomarkers high-sensitivity cardiac troponin-I (hs-cTnI) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are typically elevated in patients with oHCM; the degree of elevation is associated with heart failure symptoms as well as functional and structural anatomic abnormalities.[48-50] Although there are limited data regarding the clinical impact of biomarker dynamics in oHCM specifically, CMIs are effective at reducing both hs-cTnI and NT-proBNP.[29,46] In other forms of heart failure, substantial reductions in cardiac biomarkers have been strongly linked with important improvements in clinical outcomes, and further study of HCM populations is needed. The change from baseline in cardiac biomarkers is an exploratory endpoint in SEQUOIA-HCM.

STUDY RATIONALE

Aficamten is a next-in-class selective CMI that acts by binding directly to cardiac myosin at a distinct allosteric binding site. In a phase 1 study of healthy participants, aficamten reduced myocardial contractility in a dose-dependent manner, was well tolerated, and was associated with favorable pharmacologic features.[33] In a phase 2, dose-finding study (REDWOOD-HCM: Randomized Evaluation of Dosing With CK-274 in Obstructive Outflow Disease in HCM), aficamten treatment was explored at variable doses in 3

FIGURE 1 Change in pVO_2 With Pharmacologic and Invasive Therapies in oHCM



Bars show the mean point estimate of the difference in pVO_2 compared with baseline in response to pharmacologic and invasive therapies in oHCM. Baseline pVO_2 shows the mean values in the intervention group. The asterisk indicates randomized, double-blind, placebo-controlled trials. [a]Cohort A of PIONEER-HCM (A Phase 2 Open-label Pilot Study evaluating MYK-461 in Subjects With Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction) trial.[35] [b]Cohort B of PIONEER-HCM trial.[35] [c]Patients receiving a pacemaker in Ommen et al, 1999.[36] [d]Patients receiving SRT ASA in Nagueh et al, 2001.[38] [e]Patients receiving SRT ASA in Firoozi et al, 2002.[39] [f]Patients receiving SRT SM in Ommen et al, 1999.[36] [g]Patients receiving SRT SM in Nagueh et al, 2001.[38] [h]Patients receiving SRT SM in Firoozi et al, 2002.[39] ASA = alcohol septal ablation; CMI = cardiac myosin inhibitor; oHCM = obstructive hypertrophic cardiomyopathy; pVO_2 = peak oxygen uptake; SM = septal myectomy; SRT = septal reduction therapy.

separate cohorts of patients with oHCM.[46] In 2 placebo-controlled cohorts of patients with symptomatic oHCM, treatment with aficamten reduced LVOT-G at rest (mean difference: −40 ± 27 mm Hg and −43 ± 37 mm Hg in cohorts 1 and 2, respectively; $P = 0.0003$ and $P = 0.0004$ vs placebo) and LVOT-G with Valsalva (mean difference: −36 ± 27 mm Hg and −53 ± 44 mm Hg in cohorts 1 and 2, respectively; $P = 0.001$ and $P < 0.0001$ vs placebo).[46] Symptomatic improvement of ≥1 NYHA functional class was observed in 31% of patients on placebo, and in 43% and 64% of patients on aficamten in cohorts 1 and 2, respectively. These changes were seen in the setting of an acceptable safety profile with no treatment

TABLE 2 Key Eligibility Criteria for SEQUOIA-HCM

Inclusion criteria	Men and women aged between 18 and 85 years, inclusive, at screening
	BMI <35 kg/m^2
	Diagnosed with HCM per the following criteria: a. Has LV hypertrophy and nondilated LV chamber in the absence of other cardiac disease and b. Has an end-diastolic LV wall thickness as measured by the echocardiography core laboratory of • ≥15 mm in ≥1 myocardial segment OR • ≥13 mm in ≥1 wall segment *and* a known-disease-causing gene mutation or positive family history of HCM
	Has resting LVOT-G ≥30 mm Hg and post-Valsalva LVOT-G ≥50 mm Hg during screening as determined by the echocardiography core laboratory
	LVEF ≥60% at screening as determined by the echocardiography core laboratory
	NYHA functional class II or III at screening
	Hemoglobin ≥10 g/dL at screening
	RER ≥1.05 and pVO_2 ≤90% predicted on the screening CPET per the core laboratory
	Patients on beta-blockers, verapamil, diltiazem, or disopyramide should have been on a stable regimen for >6 wks prior to randomization and anticipate remaining on the same medication regimen during the trial. Patients treated with disopyramide must also be concomitantly treated with a beta-blocker and/or calcium-channel blocker
Exclusion criteria	Significant valvular heart disease (per investigator judgment) a. Moderate-severe valvular aortic stenosis and/or regurgitation b. Moderate-severe mitral regurgitation not caused by systolic anterior motion of the mitral valve
	Known or suspected infiltrative, genetic, or storage disorder causing cardiac hypertrophy that mimics oHCM (eg, Noonan syndrome, Fabry disease, amyloidosis)
	History of LV systolic dysfunction (LVEF <45%) or stress cardiomyopathy at any time during the clinical course of the disease
	Documented paroxysmal atrial fibrillation during the screening period
	Paroxysmal or permanent atrial fibrillation requiring rhythm restoring treatment (eg, direct-current cardioversion, atrial fibrillation ablation procedure, or antiarrhythmic therapy) ≤6 mo before screening. (This exclusion does not apply if atrial fibrillation has been treated with anticoagulation and adequately rate-controlled for >6 mo)
	History of syncope or sustained ventricular tachyarrhythmia with exercise within 6 mo before screening
	Has been treated with septal reduction therapy (surgical myectomy or percutaneous alcohol septal ablation) or has plans for either treatment during the trial period
	Inability to exercise on a treadmill or bicycle (eg, orthopedic limitations)
	Has received prior treatment with aficamten or mavacamten

LV = left ventricle; RER = respiratory exchange ratio; SEQUOIA-HCM = Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM; other abbreviations as in Table 1.

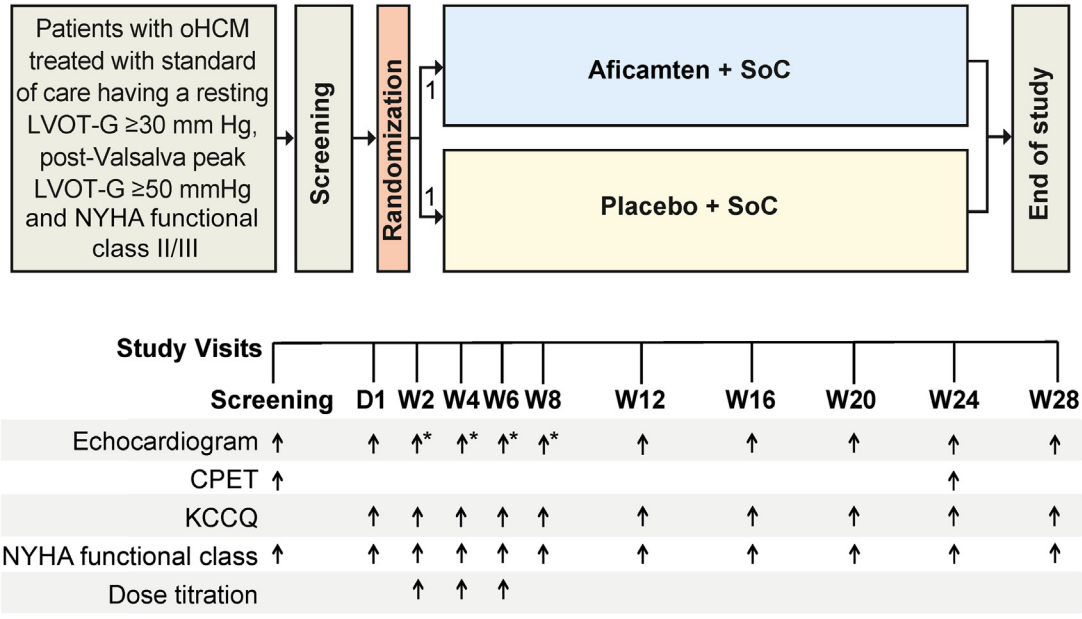
interruptions, and adverse events were similar between treatment arms.[46] A third cohort comprised the most medically refractory of patients with oHCM (ie, those receiving therapy that included disopyramide).[51] Treatment with aficamten was well tolerated and reductions in LVOT-G coupled with improvements in NYHA functional class and biomarkers were observed; an acceptable safety profile was also demonstrated.[51] Patients completing REDWOOD-HCM could participate in FOREST-HCM (Follow-up, Open-Label, Research Evaluation of Sustained Treatment with Aficamten in HCM; NCT04848506), an ongoing, open-label extension study designed to collect long-term safety and tolerability data on aficamten. FOREST-HCM has so far shown that the treatment effect of aficamten is durable for ≥1 year, maintaining LVOT-G values below thresholds at which SRT would be considered.[52,53] This supports the duration chosen for the conduct of SEQUOIA-HCM, as well as inclusion of the clinically important endpoint of duration of time meeting guideline eligibility for SRT (hemodynamic and symptom severity).

METHODS OF THE ONGOING SEQUOIA-HCM STUDY

STUDY DESIGN. SEQUOIA-HCM is a global, multicenter, randomized, placebo-controlled, double-blind, phase 3 trial in patients with symptomatic oHCM. Eligible patients have been randomized in a 1:1 ratio to receive aficamten or placebo for 24 weeks. Randomization was stratified by use of beta-blockers (yes or no) and CPET exercise modality (treadmill or bicycle). To ensure a representative and balanced patient population, the study protocol capped enrollment of patients with specific characteristics: patients taking beta-blockers were restricted to ∼70% of the total population; patients taking disopyramide to ∼10%; patients with persistent atrial fibrillation at screening to ∼15%; and patients using the bicycle CPET exercise modality to ∼50%.

Site-specific institutional review board/independent ethics committee approval was obtained before commencement of site participation. The trial is being conducted according to the Declaration of Helsinki and Good Clinical Practice.

FIGURE 2 Overview of the SEQUOIA-HCM Study



The asterisk indicates focused echocardiogram. The up-pointing arrows indicate that the procedures listed at the beginning of that row occur on the study visit timeline to which the arrow is pointing. CPET = cardiopulmonary exercise testing; D = Day; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVOT-G = left ventricular outflow tract gradient; SEQUOIA-HCM = Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM; SoC = standard of care; W = Week.

The patient inclusion criteria (Table 2, Supplemental Table 1) were selected to recruit patients with symptomatic oHCM on stable background HCM medical therapy, inclusive of disopyramide, when exercise capacity is primarily impaired by their oHCM. Each study site required prequalification by the core laboratories for CPET (Massachusetts General Hospital CPET Core Laboratory, Boston, Massachusetts, USA) and echocardiography (the Brigham and Women's Hospital Echocardiography Core Laboratory, Boston, Massachusetts, USA). The screening echocardiograms will be read and analyzed by the core laboratory to determine eligibility for trial participation. Postrandomization echocardiograms will be initially read by a qualified, unmasked, site-based echocardiographer who is not otherwise involved in the conduct of the trial and has been instructed to maintain confidentiality of echocardiographic results, unless doing so would compromise patient safety. Postrandomization echocardiograms will be also subsequently read in a blinded fashion at the echocardiography core laboratory.

STUDY DRUG DOSAGE AND ADMINISTRATION. The study design and aficamten dose titration schedule are shown in Figure 2. Aficamten or matching placebo will be started on day 1. The starting dose of aficamten will be 5 mg, administered once daily with or without food, with 3 subsequent opportunities (at weeks 2, 4, and 6) to undergo dose increase in 5-mg increments to a maximum dose of 20 mg according to site-read echocardiography measurements. At each visit, the unmasked site echocardiographer will input the left ventricular ejection fraction (LVEF) and resting and Valsalva LVOT-G values into the Interactive Web Response System, and uptitration will occur only if the peak Valsalva LVOT-G is ≥30 mm Hg and the biplane LVEF is ≥55%. If LVEF is <50%, the study drug will be downtitrated and no further dose escalation will be permitted. If LVEF <50% occurs in a patient receiving 5 mg of aficamten, the patient will receive placebo for the remainder of the treatment period. If LVEF is <40%, the drug will be temporarily interrupted and may restart after 7 days if LVEF has recovered and after discussion with the medical monitor.

TABLE 3 Endpoints of the SEQUOIA-HCM Trial

Endpoint	Description
Primary	Change in pVO_2 by CPET from baseline to wk 24
Secondary	Change in KCCQ-CSS from baseline to wk 12 and wk 24
	Proportion of patients with ≥1 class improvement in NYHA functional class from baseline to wk 12 and wk 24
	Change in post-Valsalva LVOT-G from baseline to wk 12 and wk 24
	Proportion of patients with post-Valsalva LVOT-G <30 mm Hg at wk 12 and wk 24
	Duration of guideline eligibility for SRT during the 24-wk treatment period for patients who were eligible for SRT at baseline
	Change in total workload during CPET from baseline to wk 24
Safety	Incidence of reported major adverse cardiac events (CV death, cardiac arrest, nonfatal stroke, nonfatal myocardial infarction, CV hospitalization)
	Incidence of new-onset persistent atrial fibrillation
	Incidence of appropriate ICD discharges and aborted sudden cardiac death
	Incidence of LVEF <50%
	Incidence of treatment-emergent adverse events
Exploratory	Compared with baseline, number of patients at wk 24 achieving either • Change from baseline of ≥1.5 mL/kg/min in pVO_2 *and* ≥1 class improvement in NYHA functional class OR • Change from baseline of ≥3.0 mL/kg/min in pVO_2 *and* no worsening of NYHA functional class
	Proportion of patients with improvement in KCCQ-CSS of ≥5 points at wk 12 and wk 24
	Proportion of patients with resting LVOT-G <30 mm Hg, post-Valsalva LVOT-G <50 mm Hg, and NYHA functional class I at wk 12 and wk 24
	Proportion of patients with resting LVOT-G <30 mm Hg, post-Valsalva LVOT-G <50 mm Hg, and ≥1 class improvement in NYHA functional class at wk 12 and wk 24
	Change from baseline to wk 24 in: • Ventilatory efficiency (VE/VCO_2 slope) • Circulatory power (VO_2 × systolic blood pressure) • VAT
	Change from baseline to wk 24 in individual responses to the EQ-5D-5L
	Change from baseline to wk 24 in summary and domain scores for the SAQ-7
	Change from baseline to wk 24 in echocardiographic measurements of cardiac structure and of systolic function including • LVEF • LVESV and LVEDV • Left atrial volume
	Change from baseline values in NT-proBNP, hs-cTnI, and other biomarkers through wk 24
	Change from baseline to wk 24 in CMR measurements of • LV mass index • LVEF • Septal, free wall, and maximal wall thickness • Left atrial volume index • LVESV • LVEDV
	Pharmacokinetic parameters through wk 24
	Proportion of patients who are eligible for SRT at wk 24, among patients who were eligible for SRT at baseline

CMR = cardiovascular magnetic resonance; CV = cardiovascular; EQ-5D-5L = EuroQol 5-dimension 5-level instrument; hs-cTnI = high-sensitivity cardiac troponin-I; ICD = implantable cardioverter-defibrillator; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SAQ-7 = Seattle Angina Questionnaire-7; VO_2 = oxygen uptake; other abbreviations as in Tables 1 and 2.

STUDY DURATION FOR PARTICIPANTS. After providing written informed consent, patients will undergo screening assessments and those eligible for the trial will be randomized within a 6-week window. The double-blind treatment period will last 24 weeks, with the week 24 visit representing the time point when the final efficacy measure will be collected. There will be a 4-week washout period for safety purposes. All enrolled patients will be followed according to the Schedule of Activities (Supplemental Table 2) from randomization to the date of their final visit, irrespective of whether or not they continue to receive the study drug; if a patient discontinues from the trial prematurely or withdraws consent, an early discontinuation visit will be performed where possible. Patients completing SEQUOIA-HCM will be offered the opportunity to participate in the aforementioned open-label, long-term extension study, FOREST-HCM.

STUDY ENDPOINTS. The study endpoints are listed in Table 3. The primary endpoint is change from baseline to week 24 in pVO_2, as measured by CPET; it will be considered met if the placebo-corrected change from baseline to week 24 in pVO_2 is significantly improved ($P < 0.05$). Secondary endpoints are designed to capture patient-reported outcomes

(KCCQ), functional capacity (NYHA functional classification), hemodynamic response (LVOT-G), and total exercise workload during CPET as defined by total watts. The duration spent meeting guideline eligibility for SRT during the 24-week treatment period also will be evaluated as a secondary endpoint. For the purpose of this evaluation, SRT guideline eligibility will be defined as severe symptoms (NYHA functional class III/IV) accompanied by severe obstruction (LVOT-G ≥50 mm Hg at rest or with provocation).

CARDIAC MAGNETIC RESONANCE SUBSTUDY. A cardiac magnetic resonance (CMR) substudy will assess the effects of aficamten on cardiac structure, function, and myocardial tissue characterization in up to the first 100 eligible patients with oHCM. Patients with an implantable cardioverter-defibrillator or pacemaker will be excluded, as will those unable to tolerate CMR, or those who do not consent to participate in the CMR substudy. A CMR will be performed during the screening period and again between the week 20 and week 24 visits. Various exploratory endpoints are planned for the CMR substudy, as shown in Table 3.

GENETICS SUBSTUDY. Patients who consent will have DNA analyzed using whole-genome sequencing, whole-exome sequencing, next-generation sequencing, and/or other methods to identify genetic variants.

STATISTICAL CONSIDERATIONS AND SAMPLE SIZE CALCULATION. Sample size was calculated based on an assumption of a difference in change from baseline in pVO_2 of 1.5 mL/kg/min for aficamten compared with placebo, an SD of 3.5 mL/kg/min, and ~10% missing data for the primary endpoint. A sample size of 270 patients at a randomization ratio of 1:1 (~135 randomized to aficamten and ~135 to placebo) will provide >90% power to detect the assumed difference in pVO_2 change from baseline to week 24 with a 2-sided type I error of 0.05.[54,55] Unless otherwise specified, efficacy analyses will be performed for all randomized patients. The primary analysis will test the null hypothesis that there is no treatment difference in the primary endpoint between patients randomized to placebo and those randomized to aficamten. Change from baseline in pVO_2 will be analyzed using an analysis of covariance (ANCOVA) model, with treatment group, randomization stratification factors, baseline pVO_2, and baseline weight as covariates. Missing pVO_2 at week 24 regardless of type of intercurrent events will be imputed using multiple imputation methodology under the "missing at random" assumption for the primary analysis of the primary estimate, because the proportion of patients with week 24 CPET missing is expected to be very low. Duration of SRT eligibility criteria will be analyzed using an ANCOVA model that includes treatment and the randomization stratification factor of use/nonuse of beta-blockers as fixed effects, and prespecified baseline characteristics as covariates only in the subgroup that is SRT eligible at baseline. Safety analyses will be performed on all patients who receive ≥1 dose of study drug.

Multiplicity will be addressed. The null hypothesis for the primary and secondary efficacy endpoints will be tested in a prespecified order. The testing hierarchy will be using a closed testing procedure to allow the testing of secondary endpoints at weeks 12 and 24, both using a 2-sided alpha level of 0.05 and only when the primary endpoint reaches statistical significance.

BASELINE CHARACTERISTICS. SEQUOIA-HCM is now fully enrolled. Of 511 patients who were screened, 257 (45%) failed screening and 282 were randomized (Table 4). The mean age of patients is 59.1 years (SD 12.9), 40% are female, and 22% are non-White. Medical treatment includes beta-blockers in 172 (61%), calcium-channel blockers in 75 (27%), and disopyramide in 36 (13%) patients. Baseline NYHA functional classification is class II for 214 patients (76%), class III for 67 patients (24%), and class IV for 1 patient (0.4%). One-quarter of patients (n = 68) were guideline-eligible for SRT based on peak LVOT-G ≥50 mm Hg and NYHA functional class ≥III. The mean (SD) baseline pVO_2 was 18.5 ± 4.5 mL/kg/min or 56.9% ± 11.8% of age- and sex-predicted pVO_2, and the mean KCCQ Clinical Summary Score was 74.7 ± 18.0 (Table 4). Key metrics that remain blinded and cannot be included at this time include LVEF, resting and Valsalva LVOT-G, and NT-proBNP.

DISCUSSION

SEQUOIA-HCM has been designed to test the hypothesis that the CMI aficamten can improve pVO_2 in patients with symptomatic oHCM (Central Illustration). Use of pVO_2 as the primary endpoint minimizes the effect of placebo, provides an objective metric of functional capacity, and is a clinically important prognosticator of risk for clinical events. To achieve a power of >90% for the primary endpoint, the design required that ~270 patients be enrolled, meaning that SEQUOIA-HCM is the largest interventional clinical trial in oHCM to date. Leveraging knowledge of the relationship between pVO_2, clinical events, and symptoms, SEQUOIA-HCM is the first trial of a CMI to use pVO_2 as the sole

TABLE 4 Patient Characteristics at Baseline (N = 282)

Age, y	59.1 (12.9)
Female	114 (40.4)
Race/ethnicity[a]	
White	222 (78.7)
Black	3 (1.1)
Asian	53 (18.8)
Hispanic	9 (3.2)
Other	4 (1.4)
Region	
United States	94 (33.3)
China	46 (16.3)
Europe and Israel	142 (50.4)
Vital signs	
Weight, kg	81.6 (15.71)
Body mass index, kg/m^2	28.1 (3.7)
Systolic blood pressure, mm Hg	125.3 (16.10)
Diastolic blood pressure, mm Hg	74.4 (10.63)
Heart rate, beats/min	65.6 (11.25)
HCM history	
History of known HCM-causing gene mutation	48 (17.0)
Positive family history of HCM	71 (25.2)
Time since initial HCM diagnosis (median), y	4.31 (1.7-8.5)
HCM medical therapies	
Beta-blocker	172 (61.0)
Nondihydropyridine calcium-channel blocker	75 (26.6)
Disopyramide	36 (12.8)
HCM symptoms	
KCCQ-CSS	74.7 (18.0)
NYHA functional class[b]	
II	214 (75.9)
III	67 (23.8)
IV	1 (0.4)
SRT guideline-eligible[b]	68 (24.1)
Comorbidities	
Hypertension[c]	136 (48.2)
Diabetes[d]	24 (8.5)
Permanent atrial fibrillation	1 (0.4)
Paroxysmal atrial fibrillation	40 (14.2)
Echocardiography	
LVEF	Blinded
Resting LVOT-G	Blinded
Valsalva LVOT-G	Blinded
CPET metrics	
Treadmill	155 (55)
Peak VO_2, mL/kg/min	18.5 (4.5)
Peak VO_2 percent of age- and sex-predicted[e]	56.9 (11.8)
Total workload, W	122.4 (41.3)
Biomarker	
hs-cTnI, ng/L	12.1 (7.7-27.3)
NT-proBNP, pg/dL	Blinded

Values are n (%), mean ± SD, or median (Q1-Q3), unless otherwise indicated. [a]>100% total caused by overlap in ethnicity and race. [b]NYHA functional class III and any LVOTO ≥50 mm Hg. [c]Combines "hypertension" and "essential hypertension." [d]Combines "type 2 diabetes mellitus," "type 1 diabetes mellitus," and "diabetes mellitus." [e]Fletcher et al.[44]

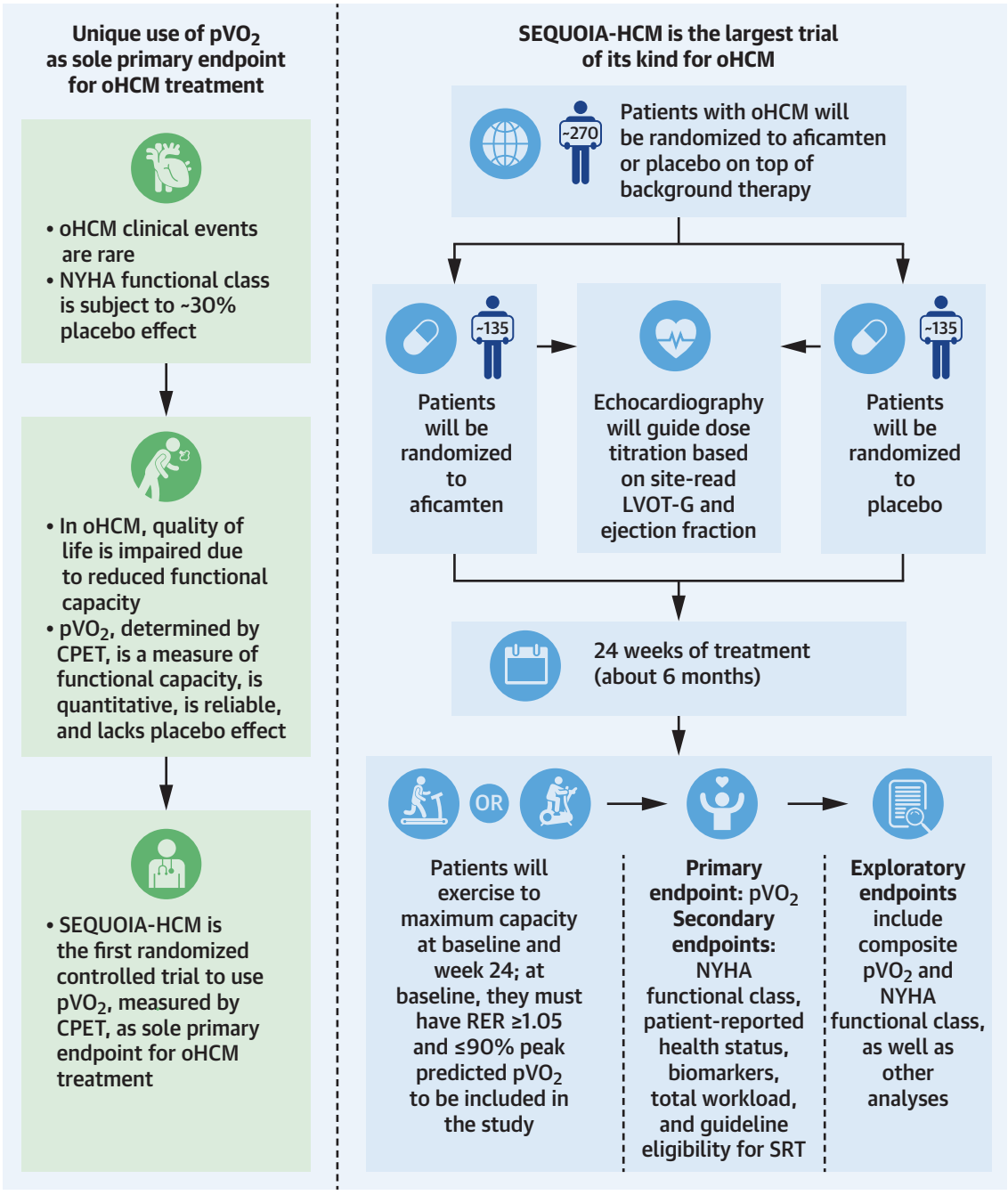
Abbreviations as in Tables 1 to 3.

primary endpoint. SEQUOIA-HCM is also the largest study to enroll patients with symptomatic oHCM without restrictions on background therapy, even including those who are refractory to all guideline-recommended medical therapies (such as disopyramide). SEQUOIA-HCM aims to add to the existing evidence from preclinical and clinical studies that aficamten can effectively and safely reduce LVOT-G while improving function and symptoms in patients with oHCM.[31,33,46] Leveraging the unique physiochemical properties of aficamten, the trial mimics potential real-world clinical implementation by solely using site-read echocardiograms to drive dose adjustments and inform the incidence of low LVEF safety events. The baseline characteristics of patients enrolled in SEQUOIA-HCM are overall quite similar to those in EXPLORER-HCM (Clinical Study to Evaluate Mavacamten [MYK-461] in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy);[29] however, there are some notable differences. SEQUOIA-HCM enrolled a greater proportion of non-White patients compared with EXPLORER-HCM (22% vs 3%, respectively), included those also receiving disopyramide as part of their medical regimen, and intentionally selected patients with lower pVO_2. Through enrollment of an ethnically diverse and typical symptomatic population of patients with oHCM, the results of SEQUOIA-HCM are anticipated to be applicable to current clinical practice.

IMPLICATIONS OF UNIQUE PHYSIOCHEMICAL CHARACTERISTICS OF AFICAMTEN. The unique physiochemical characteristics of aficamten support the sole use of echocardiography in dose titration and the enrollment of severely symptomatic patients. The half-life of aficamten (~3.4 days) accommodates a relatively fast uptitration period in SEQUOIA-HCM. In addition, the readily reversible pharmacodynamic effect may abrogate the need for dose interruption for intermediate LVEF values (in the range of 40%-49%), supporting the use of dose downtitration and enabling therapeutic consistency for patients with symptomatic oHCM.

KEY DRIVERS OF DECREASED EXERCISE CAPACITY AND SYMPTOMS IN oHCM. An adequate heart rate response is vital to increase cardiac output during exercise and chronotropic incompetence is associated with lower survival in HCM.[55,56] Both invasive and noninvasive physiological studies consistently demonstrate that reduced cardiac output and failure to augment stroke volume caused by LVOT

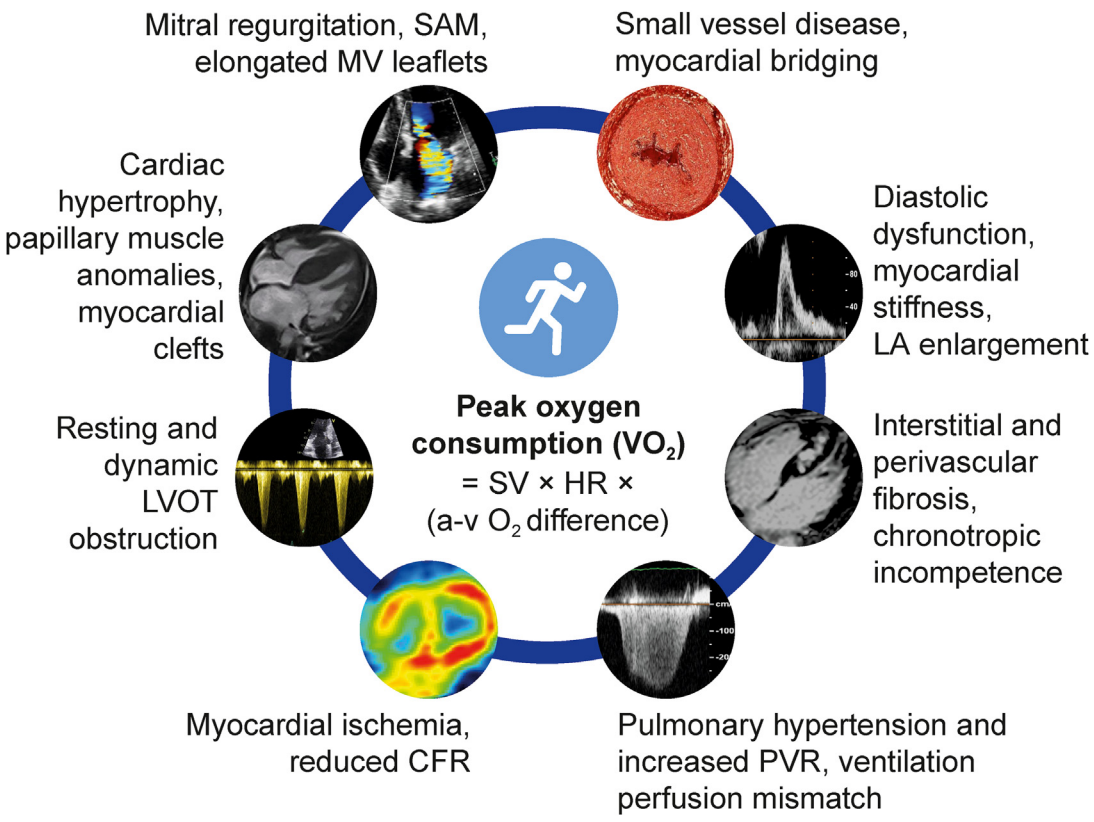
CENTRAL ILLUSTRATION Rationale and Design of SEQUOIA-HCM



Coats CJ, et al. J Am Coll Cardiol HF. 2024;12(1):199–215.

SEQUOIA-HCM will evaluate the treatment effect of aficamten on exercise capacity, as expressed by the change from baseline in PVO_2 in patients with oHCM and objective exercise incapacity deemed to result primarily from severe LVOT obstruction. CPET = cardiopulmonary exercise testing; LVOT = left ventricular outflow tract; LVOT-G = left ventricular outflow tract gradient; oHCM = obstructive hypertrophic cardiomyopathy; pVO_2 = peak oxygen uptake; RER = respiratory exchange ratio; SEQUOIA-HCM = Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM; SRT = septal reduction therapy.

FIGURE 3 Mechanisms of Exercise Limitation in oHCM



Peak oxygen consumption enables comprehensive assessment of the multiple mechanisms that contribute to exercise limitation in HCM. a-v = arterial-venous; CFR = coronary flow reserve; HR = heart rate; LA = left atrium; LVOT = left ventricular outflow tract; MV = mitral valve; oHCM = obstructive hypertrophic cardiomyopathy; PVR = pulmonary vascular resistance; SAM = systolic anterior motion; SV = stroke volume.

obstruction are the primary drivers of exercise limitation in oHCM, but the mechanisms are complex and dynamic (Figure 3).[43,57,58] The presence of SAM of the mitral valve and interventricular septal thickening causing hemodynamically meaningful LVOT obstruction (LVOT-G ≥30 mm Hg at rest or ≥50 mm Hg post-Valsalva) contributes not only to increased myocardial work and ischemia, but also to prolonged systolic ejection time. This, in turn, exacerbates underlying diastolic dysfunction, increasing left atrial pressure and resultant pulmonary hypertension. Finally, early and severe SAM is frequently associated with significant mitral regurgitation, which, coupled with the aforementioned mechanisms, contributes further to elevated left atrial and pulmonary pressures, and is strongly associated with heart failure symptoms.[12,13,39,59] The mechanism of action of aficamten is expected to address these key drivers of exercise intolerance and heart failure symptoms by substantially reducing LVOT-G. Assessment through CPET, focusing on pVO_2, accounts for the composite quantification of all myocardial pathophysiologic processes. In contrast, common noncardiac drivers of reduced exercise performance (eg, physical deconditioning, obesity, anemia, lung disease) may contribute to overall exercise intolerance but are not directly affected by improvement of hemodynamics in oHCM. Therefore, eligibility criteria implemented in SEQUOIA-HCM were designed to limit these potential confounders. By restricting enrollment to <70% patients on background beta-blockers, the study will more effectively explore the added treatment effect of aficamten across the spectrum of all currently recommended medical therapies—inclusive of nondihydropyridine calcium-channel blockers and disopyramide. We aim to produce evidence to support a more generalizable use-case for aficamten in patients in the clinical

setting. It is also important to note that in the EXPLORER-HCM trial, there was significant improvement in exercise capacity in the overall cohort of patients; however, the treatment effect of mavacamten appeared to be blunted in patients also receiving background beta-blockers.[60] This finding was further supported by the TEMPO (The Effect of Metoprolol in Patients with Hypertrophic Obstructive Cardiomyopathy) study, in which treatment with metoprolol effectively reduced LVOT-G but did not improve pVO_2.[34]

Treatment options for symptomatic oHCM necessarily cover a wide spectrum of disease severity, from mild symptoms readily addressed with medical therapy, to severe, drug-refractory symptoms that may require SRT. The consequent overlap in treatment strategies for varied patient symptom profiles suggests there may be a role for aficamten in treating patients who are eligible for SRT according to current treatment guidelines. Therefore, SEQUOIA-HCM includes a prespecified secondary endpoint that will evaluate the impact of aficamten vs placebo on the time spent guideline-eligible for SRT, in patients meeting those criteria at baseline, over the 24 weeks of therapy. The baseline characteristics of patients in SEQUOIA-HCM reflect a similar age demographic to those undergoing SRT in the United States.[61] A treatment duration of 24 weeks, compared with 16 weeks in VALOR-HCM (A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy), will increase knowledge about the practical application of CMI in the treatment pathway of oHCM.[5,32]

Patients completing SEQUOIA-HCM will have the opportunity to enroll in FOREST-HCM (open-label, long-term extension study), to gather longer term safety and efficacy data for aficamten. Interim data from patients who have now received >1 year of treatment in FOREST-HCM support the longer term safety and efficacy of the titration and dosing strategy for aficamten used in SEQUOIA-HCM. Sustained improvements in LVOT-G and NYHA functional class have been observed for at least a 48-week period, with 64% of patients reporting clinically important (≥5 points) improvement in KCCQ Clinical Summary Score by week 24.[52,53]

CONCLUSIONS

Mechanistically targeted and physiochemically optimized drug therapy for symptomatic oHCM requires thoughtful approaches to clinical trial design. The complex physiology of symptomatic oHCM and unique characteristics of aficamten co-inform the use of pVO_2 as the sole primary endpoint for SEQUOIA-HCM, with aficamten poised to potentially improve several of these individual myocardial pathophysiologies simultaneously. Improvement in pVO_2 may result in global improvement of myocardial efficiency, rather than representing a singular approach or simply eliminating LVOT obstruction. Clinically relevant secondary endpoints, including patient-centric symptom evaluation, NYHA functional class, reduction in LVOT-G, exercise workload, and time free from guideline eligibility for SRT while on treatment, reflect a disease-specific, patient-relevant study design. Specific pharmacologic features of aficamten, including ~3.4-day half-life, shallow dose-response curve, and lack of substantial currently identified drug-drug interactions, enable real-world titration strategies and the absence of limitations in background therapy in patients with symptomatic oHCM. That current guideline-recommended medical therapies are of limited efficacy and can be associated with unpleasant or unsafe side-effects, which supports the ongoing unmet need for these patients. The design of SEQUOIA-HCM leverages the importance of quantitative exercise capacity as a measure of symptoms and clinical risk, and of the unique features of aficamten; and it may be seen as a blueprint for future oHCM studies. The baseline characteristics of the patients enrolled in SEQUOIA-HCM demonstrate that we have successfully recruited a population representative of patient populations encountered in clinical practice, as well as patients in whom the treatment effect is most likely to be observed (ie, severe obstruction, objective exercise incapacity, substantial symptom burden, and representative utilization of all 3 classes of HCM-directed medical therapies). Through the thoughtful design of this trial and enrollment of the desired patient population, we believe that SEQUOIA-HCM is positioned to provide the data necessary to help transform this potential therapy into a medicine available for the treatment of patients with oHCM.

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