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METHODOLOGY AND MECHANISMS CORNER

Aficamten vs Metoprolol for Obstructive Hypertrophic Cardiomyopathy

MAPLE-HCM Rationale, Study Design, and Baseline Characteristics

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HIGHLIGHTS

- Beta-blockers remain first-line therapy for symptomatic oHCM despite limited evidence.
- MAPLE-HCM: phase 3 trial comparing aficamten vs metoprolol for symptomatic oHCM.
- MAPLE-HCM will provide data on aficamten as first-line or monotherapy for oHCM.

ABSTRACT

Beta-blockers and nondihydropyridine calcium-channel blockers have been standard-of-care (SOC) medications for patients with symptomatic obstructive hypertrophic cardiomyopathy (oHCM), even though these agents do not directly affect the underlying pathophysiology of the disease. Cardiac myosin inhibitors act by decreasing the number of myosin heads binding to actin, reducing the pathologic hypercontractility of HCM, and have been shown to improve exercise capacity and alleviate symptoms in oHCM when added to SOC medications. Cardiac myosin inhibitors are currently considered as second-line therapy in the absence of head-to-head comparison studies vs SOC medications. The aim of the ongoing phase 3 study MAPLE-HCM (Metoprolol vs Aficamten in Patients With LVOT Obstruction on Exercise Capacity in HCM) is to fill this evidence gap by evaluating aficamten as both first-line therapy for newly diagnosed oHCM and as a monotherapy alternative for patients currently on SOC drugs. The authors describe the rationale, design, and baseline characteristics of patients in this study. (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Metoprolol Succinate in Adults With Symptomatic oHCM [MAPLE-HCM]; NCT05767346) (JACC Heart Fail. 2025;13:346–357) © 2025 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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Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disorder characterized by left ventricular hypertrophy that cannot be explained by another condition. Clinical manifestations of HCM include heart failure symptoms, angina pectoris, dizziness and syncope, arrhythmias, and, rarely, sudden death. The underlying pathophysiologic basis of HCM is hypercontractility at the cardiac sarcomere level, resulting in hyperdynamic systolic function, impaired relaxation, and myocardial hypertrophy and fibrosis. Approximately two-thirds of patients with HCM have obstructive HCM (oHCM), a phenotype of the disease characterized by hypertrophy of the basal septum, systolic anterior motion of the anterior leaflet of the mitral valve with septal contact, and obstruction of left ventricular outflow, resulting in a pressure gradient and associated mitral regurgitation. In patients with oHCM, left ventricular outflow tract (LVOT) obstruction is thought to be the primary driver of the development of symptoms.[1,2]

TRADITIONAL PHARMACOLOGIC MANAGEMENT OF oHCM

As activation of cardiac beta-adrenergic receptors increases myocardial contractility and LVOT obstruction,[3,4] beta-adrenergic receptor blockade (beta-blockers) was the first pharmacologic strategy introduced for the management of oHCM. Several small, nonrandomized studies with propranolol conducted in the 1960s supported this approach.[4,5] Despite their frequent side effects, which include fatigue, depression, and erectile dysfunction, beta-blockers continue to be first-line therapy for symptomatic oHCM.[1,2] The use of other drugs with negative inotropic effects, such as non-dihydropyridine calcium-channel blockers and disopyramide, is also supported by observational studies.[6-9] Expert consensus guidelines recommend the substitution of beta-blockers with verapamil or diltiazem and/or the addition of disopyramide should symptoms persist or beta-blocker treatment not be tolerated.[1,2]

The effects of beta-blockers in patients with symptomatic oHCM were examined recently in a randomized, double-blind, placebo-controlled crossover study.[10] After withdrawal of standard-of-care (SOC) medication for oHCM, 29 patients received either metoprolol or placebo in random order for 2 weeks, each drug separated by a 1-week washout period. Metoprolol was titrated to a maximum tolerated dose (up to 150 mg/d), with efficacy assessments made at the transition points within the study. Metoprolol significantly reduced LVOT gradients at rest, during exercise, and after exercise compared with placebo. Metoprolol also improved NYHA functional classification, Canadian Cardiovascular Society angina grade, and Kansas City Cardiomyopathy Questionnaire-Overall Summary Score. However, metoprolol did not improve peak oxygen consumption (pVO_2) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) level. The study supported using metoprolol for symptomatic relief in patients with oHCM.

CARDIAC MYOSIN INHIBITORS IN oHCM

Cardiac myosin inhibitors (CMIs) constitute a new drug class that directly targets the underlying pathophysiology of HCM (ie, hypercontractility at the level of the sarcomere). CMIs are small molecules that reduce the number of actin-myosin cross-bridges within the cardiac sarcomere, thereby decreasing contractility. By targeting the underlying pathophysiology of HCM, CMIs have already been demonstrated to alleviate symptoms and improve functional capacity. In the short and medium term, CMIs have shown promising results for some structural parameters, such as left atrial volume and left ventricular mass, that are considered to be closely related to complications in oHCM. However, the potential for CMIs to mitigate downstream clinical outcomes would require additional studies with longer follow-up.

ABBREVIATIONS AND ACRONYMS

CMI = cardiac myosin inhibitor

CPET = cardiopulmonary exercise testing

HCM = hypertrophic cardiomyopathy

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

LVEF = left ventricular ejection fraction

LVOT = left ventricular outflow tract

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

oHCM = obstructive hypertrophic cardiomyopathy

pVO_2 = peak oxygen consumption

SOC = standard of care

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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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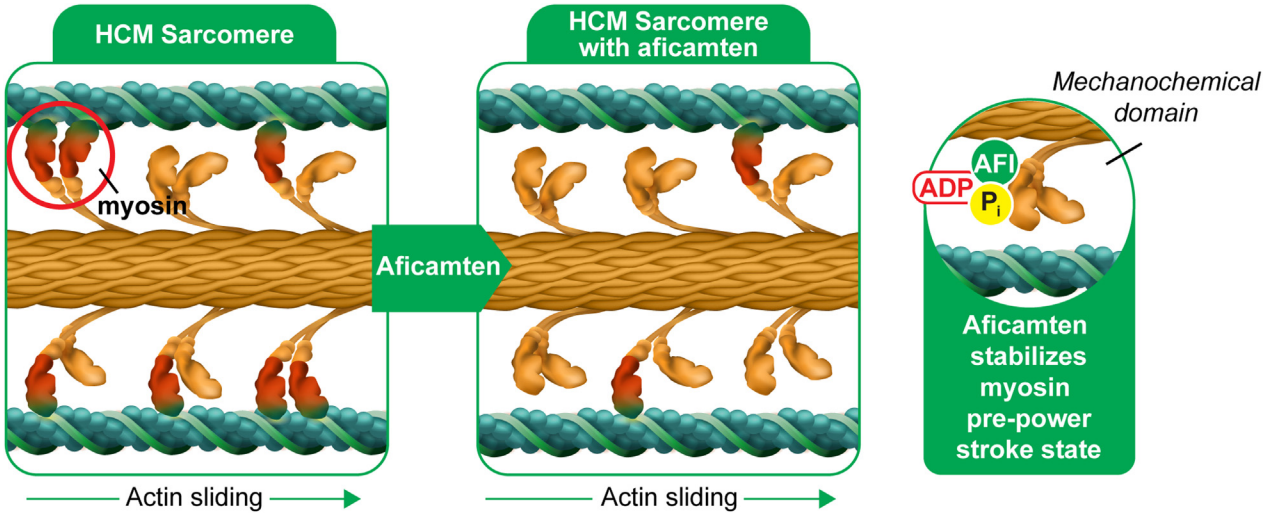
FIGURE 1 Aficamten Mechanism of Action



AFI decreases myocardial hypercontractility by reversibly binding to cardiac myosin, stabilizing the myosin pre–power stroke state, and reducing excessive myosin-actin cross-bridges. ADP = adenosine diphosphate; AFI = aficamten; HCM = hypertrophic cardiomyopathy; Pi = inorganic phosphate.

To date, CMIs have been studied in 3 completed phase 3 studies, all of which evaluated their impact as add-on therapy.[11-13]

Mavacamten, the first-in-class CMI, received approval from the U.S. Food and Drug Administration and the European Medicines Agency after completion of the phase 3 clinical trial EXPLORER-HCM (Evaluation of Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy; NCT03470545). Mavacamten, when added to SOC medication, was found to improve LVOT gradient, NYHA functional class, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS), and pVO_2.[11] Prespecified subgroup analysis of EXPLORER-HCM demonstrated heterogeneity in the treatment effect of background beta-blocker use on pVO_2, wherein patients taking beta-blockers failed to achieve a significant change in pVO_2 on mavacamten. A post hoc analysis of EXPLORER-HCM concluded that chronotropic incompetence in patients receiving beta-blockers was responsible for the absence of an increase in pVO_2 with the addition of mavacamten.[14]

Aficamten is a next-in-class CMI that was specifically designed to optimize specific pharmacologic characteristics to maximize benefit/risk and ease patient management. These features include a half-life of about 3.4 days, low pharmacokinetic variability, metabolism by multiple cytochrome P450 enzyme pathways and thus a low likelihood of clinically relevant drug-drug interactions, lack of teratogenicity, and a shallow dose-response relationship that results in a wide therapeutic window (**Figure 1**).[15]

To date, aficamten has been studied in phase 2 (REDWOOD-HCM [Dose-Finding Study to Evaluate the Safety, Tolerability, PK, and PD of CK-3773274 in Adults With HCM]; NCT04219826)[16-18] and phase 3 (SEQUOIA-HCM [Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM]; NCT05186818) clinical trials, both of which demonstrated consistent efficacy and favorable safety profiles.[13] Patients with oHCM who received aficamten for 24 weeks in addition to SOC medications in SEQUOIA-HCM showed substantial improvements in exercise capacity (least squares mean increase in pVO_2 of 1.74 mL/kg/min; $P = 0.000002$), health status, LVOT gradient, and NT-proBNP concentration as well as reduction in symptoms.[13] Overall, aficamten was well tolerated, with few instances of left ventricular ejection fraction (LVEF) <50%, none of which was associated with clinical heart failure and none of which required treatment interruption.[13] Importantly, and in contrast to EXPLORER-HCM,[11] prespecified subgroup analysis in SEQUOIA-HCM did not demonstrate heterogeneity of treatment effect on the basis of background beta-blocker use, as patients on beta-

blockers demonstrated significant improvements in peak exercise capacity.[13]

CMIs AS MONOTHERAPY

Current American and European guidelines consider mavacamten as second-line medical therapy, which may be added to a beta-blocker (or non-dihydropyridine calcium-channel blocker) in patients with persistent symptoms.[1,2] In that CMIs have demonstrated efficacy when added to SOC therapy, there exists a clear evidence gap assessing whether CMIs would be more effective as monotherapy and, potentially, first-line treatment. In contrast to current SOC medications, CMIs are specifically designed to address the molecular underpinnings of HCM.[19] In addition to the already demonstrated improvements in symptoms and functional capacity, they have the potential to allow the avoidance of off-target side effects of current SOC therapies.

Preliminary support for the efficacy and safety of CMIs as monotherapy for symptomatic oHCM arises from FOREST-HCM (Open-Label Extension Study to Evaluate the Long-Term Safety and Tolerability of Aficamten in Adults With HCM; NCT04848506), the long-term, open-label extension study of aficamten in patients who completed a prior aficamten study. Patients participating in the ongoing FOREST-HCM study are eligible for background therapy reduction or withdrawal at the discretion of the site investigator. Successful SOC withdrawal was defined as at least a 50% dose reduction in ≥1 medication. Among the 145 patients with oHCM followed for at least 24 weeks, 64 (47%) had attempted background therapy reduction or withdrawal. Of these 64 patients, 59 (92%) achieved successful background therapy reduction or withdrawal, 38 (64%) discontinued at least 1 background medication, and 27 (46%) withdrew from all background medications, thus achieving aficamten monotherapy. Overall, NYHA functional class, LVOT gradient, and biomarkers were similar between those who underwent background therapy reduction or withdrawal and the remainder of patients in FOREST-HCM.[20]

Similarly, it was recently reported in a cumulative interim analysis of the mavacamten long-term open-label extension study (MAVA-LTE [A Long-Term Safety Extension Study of Mavacamten in Adults Who Have Completed MAVERICK-HCM or EXPLORER-HCM]; NCT03723655) that 30 of 231 patients on mavacamten (13% of the total cohort) were either not taking (n = 17) or had been discontinued from (n = 13) background therapy.[21,22] These patients maintained the therapeutic benefits of mavacamten in the absence of SOC therapy.

Although these data provide the rationale for monotherapy from a safety perspective, the overall number of patients on CMI monotherapy to date is limited, the experience is observational, and most patients received CMI monotherapy only after initial exposure to combination treatment, without specific focus on newly diagnosed patients. Indeed, the European Society of Cardiology guidelines specifically indicate that CMIs would not be considered first-line therapy or monotherapy in the absence of a head-to-head comparison with current SOC therapy.[1] MAPLE-HCM (Metoprolol vs Aficamten in Patients With LVOT Obstruction on Exercise Capacity in HCM; NCT05767346), the first randomized active comparator trial of a CMI and a beta-blocker, is designed to provide this comparison.

MAPLE-HCM STUDY METHODS

DESIGN. MAPLE-HCM is an ongoing head-to-head, phase 3 clinical trial in patients with symptomatic oHCM conducted at approximately 80 sites in North America, South America, Europe, Israel, and China (NCT05767346). Eligible patients were randomized in a 1:1 ratio in double-blind, double-dummy fashion to receive aficamten plus placebo (for metoprolol) or metoprolol plus placebo (for aficamten) for 24 weeks. Randomization was stratified by cardiopulmonary exercise testing (CPET) exercise modality (treadmill or bicycle) and by duration of oHCM diagnosis and previous pharmacologic therapy. To understand whether current or recent use of SOC therapy and/or duration of oHCM diagnosis affects the effect of aficamten treatment, patients were divided into 2 groups upon study entry. Group 1 includes patients who are treatment naive or currently untreated (no medical therapy within 12 months), irrespective of the duration of oHCM diagnosis, and those with histories of oHCM ≤12 months with or without medical therapy. Group 2 consists of patients with >12-month histories of oHCM treated with SOC agents within the past 12 months. To ensure a representative and balanced patient population, the study protocol capped enrollment of patients with specific characteristics (Supplemental Table 1): patients with previous exposure to mavacamten and/or septal reduction therapy >6 months before enrollment were each limited to about 10% of the total patients, whereas patients using the bicycle CPET exercise modality

TABLE 1 Key Entry Criteria

Key Inclusion Criteria	Key Exclusion Criteria
NYHA functional class II or III at screening	Medical indication for either beta-blocker or calcium channel blockers prohibiting drug discontinuation
Diagnosed with oHCM per the following criteria: a. Has LV hypertrophy with 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: • ≥15 mm in ≥1 myocardial segments OR • ≥13 mm in ≥1 wall segments and a known disease-causing gene mutation or family history of HCM	Contraindication to beta-blocker therapy
Screening echocardiography with: • Resting LVOT-G ≥30 mm Hg AND/OR • Post-Valsalva LVOT-G ≥50 mm Hg AND • LVEF ≥60%	Resting systolic BP >160 mm Hg Resting heart rate >100 beats/min
RER ≥1.05 and pVO_2 <100% predicted	History of paroxysmal or persistent atrial fibrillation or atrial flutter; atrial flutter treated with radiofrequency ablation without recurrence within the past 6 mo prior to screening is allowed
KCCQ-CSS ≤90 at screening visit 2	Septal reduction therapy within 6 mo of screening
Participants previously exposed to mavacamten are allowed to participate but must be off mavacamten for ≥8 wks prior to signing informed consent form; medical monitor approval needed	Has received prior treatment with aficamten or previously intolerant (reduced LVEF requiring permanent drug discontinuation) to mavacamten

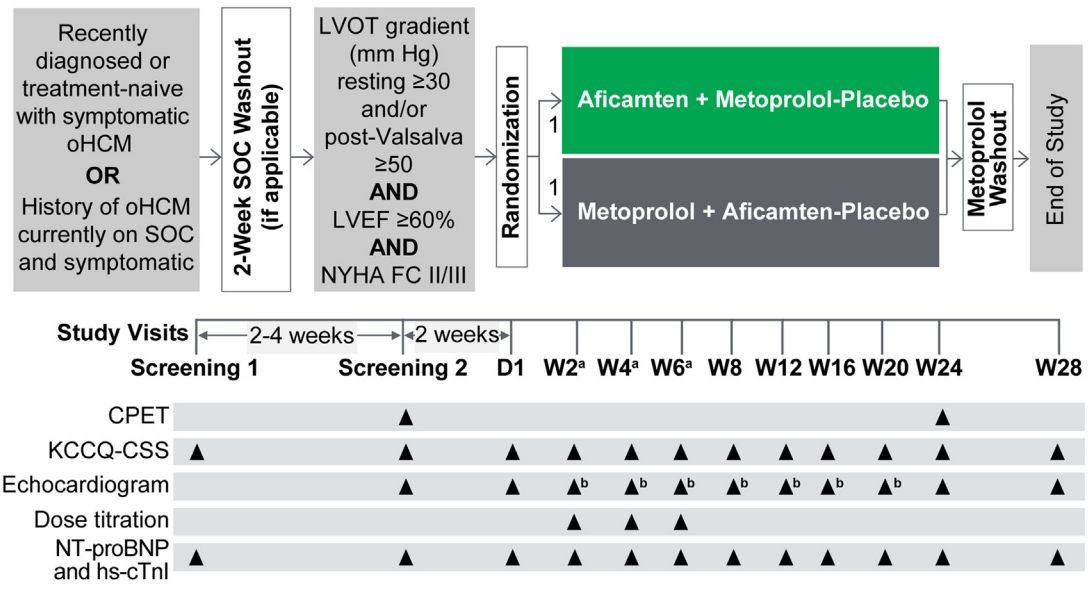
BP = blood pressure; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire clinical summary score; LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT-G = left ventricular outflow tract gradient; oHCM = obstructive hypertrophic cardiomyopathy; pVO_2 = peak oxygen uptake; RER = respiratory exchange ratio.

were limited to about 50% of the total study population.

The trial is conducted in accordance with the principles of the Declaration of Helsinki and International Council for Harmonization Guideline for Good Clinical Practice. Site-specific Institutional Review Board or independent ethics committee approval was obtained before commencement of site participation. A study steering committee composed of academic leaders, investigators, the sponsor, and a patient representative provides oversight. The patient inclusion and exclusion criteria (Table 1) were selected to recruit patients whose exercise capacity is impaired primarily by oHCM. Eligibility requirements include left ventricular hypertrophy ≥15 mm (or ≥13 mm in the presence of a disease-causing genetic variant or family history of HCM) by core laboratory echocardiography, LVEF ≥ 60%, and resting LVOT gradient ≥ 30 mm Hg and/or post-Valsalva LVOT gradient ≥ 50 mm Hg. Patients were also required to demonstrate subjective and quantitative evidence of symptoms, as evidenced by NYHA functional class II or III, KCCQ-CSS ≤ 90, and age- and sex-predicted pVO_2 < 100% (per exercise core laboratory). Each study site has been certified by the core laboratories for CPET (Massachusetts General Hospital CPET Core Laboratory) and echocardiography (Brigham and Women's Hospital Echocardiography Core Laboratory). Screening echocardiograms were analyzed by the core laboratory to determine eligibility for trial participation. Postrandomization echocardiograms are read in a blinded manner by qualified, site-based echocardiographers who are not otherwise involved in study conduct. As previously described, the site study staff and sponsor remain masked to all echocardiographic results throughout the study conduct, unless patient safety is a concern.[23] Echocardiograms are subsequently analyzed, blinded to treatment assignment, by the core laboratory, the data from which are used for statistical analyses. Additional assessments that remain similarly masked include NT-proBNP and titration vital signs.

STUDY DRUG DOSAGE AND ADMINISTRATION. The study design and dose titration schedule are shown in Figure 2 and Table 2, respectively. After providing written informed consent, patients underwent screening; eligible patients were randomized

FIGURE 2 Study Schema



[a]Titration visit. [b]Focused echocardiogram. CPET = cardiopulmonary exercise testing; D = day; hs-cTnI = high-sensitivity cardiac troponin-I; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA FC = New York Heart Association functional class; oHCM = obstructive hypertrophic cardiomyopathy; SOC = standard of care; W = week.

within 6 weeks. Patients on SOC therapy (ie, beta-blockers and/or nondihydropyridine calcium-channel blockers) began washout of these drugs at screening visit 1. Patients were excluded if they were on current or recent (within 4 weeks of screening) therapy with disopyramide. At the discretion of the site principal investigator, patients were instructed to reduce the dose of SOC medications every 2 days until these medications were discontinued. Patients received no SOC medication for ≥7 days prior to screening visit 2, at which time the screening assessments were completed.

Patients were randomized in a 1:1 manner to either aficamten or metoprolol. At each visit (weeks 2, 4, and 6), the site echocardiographer inputs heart rate, blood pressure, post-Valsalva LVOT gradient, and LVEF into the interactive web response system, and the pre-programmed algorithm subsequently provides dose adjustment instructions. Patients assigned to receive aficamten started at a dose of 5 mg once daily and escalate to doses of 10, 15, and 20 mg once daily if they meet the 2 echocardiographic escalation criteria (LVEF ≥55% and post-Valsalva LVOT gradient ≥30 mm Hg) or remain at their current doses if escalation criteria are not met. Patients assigned to metoprolol start at a dose of 50 mg once daily and escalate to doses of 100, 150, and 200 mg once daily if they meet the 2 echocardiographic (LVEF ≥55% and post-Valsalva LVOT gradient ≥30 mm Hg) and 2 vital sign criteria (systolic blood pressure

TABLE 2 Titration Algorithm

Dose Adjustment Metric	Aficamten	Metoprolol
Systolic BP	NA	≥90 mm Hg: can increase dose <90 mm Hg: reduce dose (any visit)
Heart rate	NA	≥55 beats/min: can increase dose 50-54 beats/min: no dose change <50 beats/min: reduce dose (any visit)
LVEF	≥55%: can increase dose 50%-54%: no dose change 40%-49%: reduce dose (any visit) <40%: temporary discontinuation (any visit)	
Post-Valsalva LVOT gradient	≥30 mm Hg: can increase dose <30 mm Hg: no dose change	

For dose escalation, all criteria must be met. For down-titration or investigational product discontinuation, only 1 criterion must be met. LVOT = left ventricular outflow tract; NA = not applicable; other abbreviations as in Table 1.

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TABLE 3 Trial Endpoints

Objectives	Endpoints
Primary	
Evaluate effect of aficamten vs metoprolol on exercise capacity in participants with symptomatic oHCM	• Change in pVO_2 by CPET from baseline to week 24
Secondary	
Evaluate effect of aficamten vs metoprolol on NYHA functional class	• Proportion of participants with ≥1 class improvement in NYHA functional class from baseline to week 24
Evaluate effect of aficamten vs metoprolol on participant health status	• Change in KCCQ-CSS from baseline to week 24
Evaluate effect of aficamten vs metoprolol on structural remodeling	• Change in LVMI from baseline to week 24 • Change in LAVI from baseline to week 24
Evaluate effect of aficamten vs metoprolol on NT-proBNP level	• Change in NT-proBNP from baseline to week 24
Evaluate the effect of aficamten vs metoprolol on post-Valsalva LVOT gradient	• Change in post-Valsalva LVOT gradient from baseline to week 24
Safety	
Evaluate safety and tolerability profile of aficamten vs metoprolol in participants with oHCM	• Patient incidence of reported major adverse cardiac events (CV death, cardiac arrest, nonfatal stroke, nonfatal myocardial infarction, CV hospitalization) • Participant incidence of AEs • Participant incidence of LVEF <50%

AE = adverse event; CPET = cardiopulmonary exercise testing; CV = cardiovascular; LAVI = left atrial volume index; LVMI = left ventricular mass index; NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviations as in Tables 1 and 2.

≥90 mm Hg and heart rate ≥55 beats/min) or remain at their current doses if any of the escalation criteria are not met.

Study medications cannot be up-titrated after week 6 but are down-titrated to the next lowest dose at any visit throughout trial if any of the following criteria are met: 1) LVEF <50% (all patients); 2) heart rate <50 beats/min (only patients assigned to metoprolol); or 3) systolic blood pressure <90 mm Hg (only patients assigned to metoprolol). If at any time during the trial a patient experiences an adverse event that, in the investigator's judgment, is drug related and compels the patient to request study drug dose adjustment, the dose may be reduced to the previous dose level; for patients receiving the initial dose, study medication is discontinued. If LVEF is <40% at any time in either arm, study medication is discontinued for at least 7 days; if LVEF is subsequently ≥55%, study medication may be restarted at the next lower dose per site investigator judgment after discussion with the medical monitor.

The double-blind treatment period lasts 24 weeks; final efficacy measures are collected at the week 24 visit. This visit is followed by a 4-week washout period, during which metoprolol or placebo for metoprolol is down-titrated for up to about 2 weeks. All patients are followed according to the schedule of activities from randomization to their final visit, irrespective of whether they continue to receive the study drug; if a patient withdraws from the trial, an early discontinuation visit is performed when possible. All patients completing MAPLE-HCM are offered the opportunity to participate in FOREST-HCM, the long-term open-label extension study in which they receive open-label aficamten.

STUDY ENDPOINTS. The primary endpoint is the change in exercise capacity (pVO_2) from baseline to week 24. Secondary efficacy endpoints include changes in NYHA functional class, KCCQ-CSS, left ventricular mass index, left atrial volume index, NT-proBNP, and post-Valsalva LVOT gradient. Safety endpoints include major adverse cardiac events and incidence of LVEF <50% (Table 3).

OPTIONAL GENETICS SUBSTUDY. Patients who consent undergo whole-genome sequencing, next-generation sequencing, and/or other methods to identify HCM-related genetic variants. The influence of genetic variants on the efficacy and safety of aficamten will be explored in subsequent analyses.

OPTIONAL HCM PATIENT EXPERIENCE SUBSTUDY. To better understand the patient experience with oHCM, an optional substudy is being conducted at participating centers in the United States. Patients who consent undergo 2 (entry and exit) semi-structured, qualitative interviews conducted remotely by trained personnel from an independent vendor and complete surveys that assess the impact of the different treatment approaches on patients' lives, goals, and overall experiences.

STATISTICAL ANALYSIS. Efficacy analyses will be performed on the full analysis set, which includes 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 metoprolol and those randomized to aficamten in the full analysis set. Assuming a difference in change from baseline in pVO_2 of 2 mL/kg/min for aficamten compared with metoprolol, an SD of 3 mL/kg/min, and 10% of patients missing change from baseline data of the primary endpoint, a sample size of 170 patients (randomized in a 1:1 ratio to aficamten and metoprolol) provides >90% power to detect a difference in pVO_2 change from baseline to week 24 with a 2-sided type I error of 0.05. Change from baseline in pVO_2 will be analyzed using an analysis-of-covariance method with treatment group, randomization stratification factors (CPET exercise modality and recently diagnosed vs chronic oHCM), baseline pVO_2, and 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, as the proportion of patients with week 24 CPET missing is expected to be very low. The proportion of responders in NYHA functional class will be analyzed using the Cochran-Mantel-Haenszel test stratified by randomization stratification factors. Other changes from baseline endpoints will be analyzed using the mixed model for repeated measures method. The primary and secondary endpoints will be analyzed by subgroup (group 1 vs group 2), with the treatment effect and treatment interaction included in the statistical model. To preserve the overall type I error rate at 0.05 for the primary and secondary endpoints, a multiple-testing procedure will be implemented. Safety analyses will be performed on the safety analysis set, which includes all patients who received at least 1 dose of aficamten or metoprolol.

BASELINE CHARACTERISTICS OF THE STUDY POPULATION. Of 281 patients screened, 175 were randomized (Table 4). The mean age at randomization was 57.7 ± 13.2 years, 41.7% are women, and 16% are non-White. Seventy-six percent of patients required washout of SOC medications (beta-blocker, nondihydropyridine calcium-channel blocker, or both) prior to randomization. Baseline NYHA functional class was II for 122 patients (69.7%) and III for 53 patients (30.3%). The mean baseline pVO_2 was 19.9 ± 5.1 mL/kg/min, or 60.6% ± 13.6% of age- and sex-predicted pVO_2. The mean baseline KCCQ-CSS was 65.7 ± 16.5. For those patients requiring washout of SOC medications, the mean KCCQ-CSS decreased from 68.9 ± 18.3 to 64.7 ± 15.3 during screening, prior to randomization. In addition, the proportion of participants who withdrew SOC medications with NYHA functional classification III increased from 14% to 29% after screening SOC washout. Three patients were excluded because of inability to tolerate SOC washout. Randomization was stratified according to CPET modality (58.9% treadmill, 41.1% bicycle) and duration of oHCM diagnosis or ongoing treatment: 34.3% had been diagnosed ≤12 months previously or were treatment naive (group 1), and 65.7% were diagnosed >12 months ago and were taking SOC medications (group 2). The baseline characteristics were similar between groups 1 and 2. Key metrics that remain masked and cannot be reported at this time include LVEF, resting and post-Valsalva LVOT gradient, and NT-proBNP.

DISCUSSION

MAPLE-HCM is the first trial to evaluate CMIs as monotherapy for patients with symptomatic oHCM (Central Illustration). By directly comparing the safety and efficacy of aficamten and the beta-blocker metoprolol, one of the most frequently used SOC medications, in randomized, double-blind fashion, this study will provide insights into the placement of aficamten in the treatment paradigm for symptomatic oHCM. Furthermore, it is noteworthy that, despite more than 50 years of the use of beta-blockers as first-line therapy for the treatment of patients with oHCM, there has been only 1 placebo-controlled, randomized study that evaluated the efficacy of beta-blockers (TEMPO [The Effect of Metoprolol in Patients With Hypertrophic Obstructive Cardiomyopathy]), which was conducted over a very short treatment period and included only 29 patients.[10] Although MAPLE-HCM is designed to compare aficamten and metoprolol, the study will also deliver the most comprehensive prospective evaluation of the performance of metoprolol in patients with oHCM and thus further inform the management of symptomatic oHCM.

Historically, pharmacologic treatment options for symptomatic oHCM have been limited to beta-blockers, nondihydropyridine calcium-channel blockers, and disopyramide,[6] all of which act through negative inotropic effects but do not directly address the underlying pathophysiology of the disease. The recent approval of mavacamten, a first-in-class CMI, has expanded the therapeutic landscape for oHCM. However, because of the design of the pivotal EXPLORER-HCM study, which tested mavacamten vs placebo when added to SOC, current guidelines position mavacamten as a second-line

TABLE 4 Baseline Characteristics

	Group 1[a] (n = 60)	Group 2[a] (n = 115)	All Participants (N = 175)
Age, y	58.4 ± 13.02	57.4 ± 13.35	57.7 ± 13.2
Female	25 (41.7)	48 (41.7)	73 (41.7)
Race, ethnicity			
White	47 (78.3)	94 (81.7)	141 (80.6)
Black or African American	0	1 (0.9)	1 (0.6)
Asian	10 (16.7)	15 (13.0)	25 (14.3)
Other/unknown/not reported	3 (4.1)	5 (4.4)	8 (2,435)
Hispanic/Latino	6 (10.0)	16 (13.9)	22 (12.6)
BMI, kg/m^2	28.7 ± 3.2	28.1 ± 3.7	28.3 ± 3.5
History of SRT[b]	2 (3.3)	2 (1.7)	4 (2.3)
History of mavacamten use[c]	1 (1.7)	6 (5.2)	7 (4.0)
Comorbidities			
Hypertension	20 (33.3)	41 (35.7)	61 (34.9)
Diabetes mellitus	5 (8.3)	2 (1.7)	7 (4.0)
Chronic kidney disease	1 (1.7)	4 (3.5)	5 (2.9)
Systolic blood pressure at screening, mm Hg[d]	124.0 ± 13.8	126.3 ± 14.3	125.5 ± 14.1
NYHA functional class			
II	43 (71.7)	79 (68.7)	122 (69.7)
III	17 (28.3)	36 (31.3)	53 (30.3)
KCCQ-CSS	69.7 ± 15.3	63.6 ± 16.7	65.7 ± 16.5
hs-cTnI, ng/L	11.6 (6.8-31.7)	13.5 (7.2-28.6)	12.9 (7.2-29.9)
SOC washout prerandomization	34 (56.7)	99 (86.1)	133 (76.0)
SOC medications prior to washout			
Beta-blocker	33 (55.0)	90 (78.3)	123 (70.3)
Nondihydropyridine calcium-channel blocker	5 (8.3)	17 (14.8)	22 (12.6)
CPET			
pVO_2, mL/kg/min	20.4 ± 5.0	19.6 ± 5.1	19.9 ± 5.1
% predicted	62.7 ± 13.6	59.5 ± 13.6	60.6 ± 13.6
Peak RER	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1
Total workload, W	120.0 ± 41.9	117.1 ± 42.7	118.0 ± 42.3
Modality			
Treadmill	35 (58.3)	68 (59.1)	103 (58.9)
Bicycle	25 (41.7)	47 (40.9)	72 (41.1)

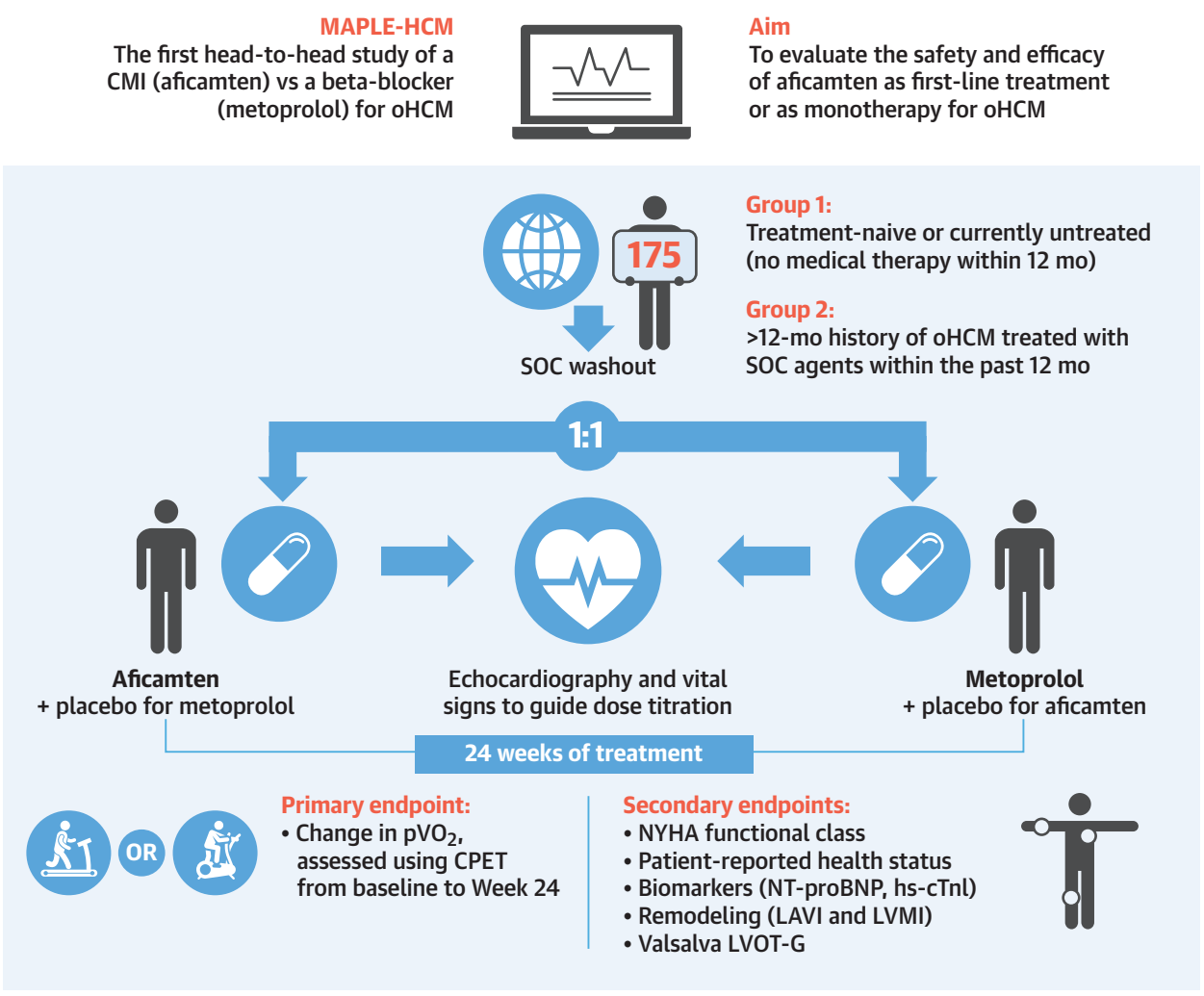
Values are mean ± SD, n (%), or median (Q1-Q3). [a]Recently diagnosed (group 1) includes patients who are treatment naive or currently untreated (no medical therapy within 12 months), irrespective of the duration of oHCM diagnosis, and those with histories of oHCM ≤12 months with or without medical therapy. Chronic oHCM (group 2) consists of patients with >12-month histories of oHCM treated with SOC agents within the past 12 months. [b]Patients who remain symptomatic after SRT >6 months prior to screening. Of the 4 with histories of SRT, 1 had a history of alcohol septal ablation. [c]Patients previously exposed to mavacamten are allowed to participate if they have been off mavacamten at least 8 weeks prior to screening and had no safety issues. [d]Systolic blood pressure at screening visit 2 was assessed for eligibility.

BMI = body mass index; hs-cTnI = high-sensitivity cardiac troponin-I; SOC = standard of care; SRT = septal reduction therapy; other abbreviations as in Tables 1 to 3.

agent for patients with persistent symptoms despite SOC therapy. SEQUOIA-HCM, the phase 3 trial comparing aficamten with placebo in addition to background SOC therapy, was similarly conducted. It is therefore expected, on the basis of the recent results from SEQUOIA-HCM, that aficamten would also likely be considered a second-line agent. Although there are observational data available for both mavacamten and aficamten as monotherapy, the number of patients who have received CMI as monotherapy is very limited. Thus, the efficacy and safety profiles of CMI used in isolation are unknown. MAPLE-HCM aims to fill this evidence gap by evaluating aficamten, the next-in-class CMI with favorable pharmacokinetic and pharmacodynamic properties, as potentially both first-line therapy for newly diagnosed oHCM and a monotherapy for patients currently on SOC drugs.

Patients enrolled in MAPLE-HCM are representative of patients with HCM encountered in clinical practice, including a relevant percentage (34%) of newly diagnosed or treatment-naive patients. Mean age, gender distribution, and NYHA functional classification are similar to those in SEQUOIA-HCM. In contrast, mean baseline KCCQ-CSS is lower in MAPLE-HCM than it was in SEQUOIA-HCM, possibly in part because of withdrawal of SOC medication prior to determination of the score. Interestingly, the modest decline in KCCQ-CSS in response to SOC withdrawal during screening is similar to the mean increase

CENTRAL ILLUSTRATION **MAPLE-HCM Study Design**



Garcia-Pavia P, et al. JACC Heart Fail. 2025;13(2):346-357.

CMI = cardiac myosin inhibitor; CPET = cardiopulmonary exercise testing; hs-cTnI = high-sensitivity cardiac troponin-I; LAVI = left atrial volume index; LVMI = left ventricular mass index; LVOT-G = left ventricular outflow tract gradient; MAPLE-HCM = Metoprolol vs Aficamten in Patients With LVOT Obstruction on Exercise Capacity in HCM; NT-proBNP = N-terminal pro-B-type natriuretic peptide; oHCM = obstructive hypertrophic cardiomyopathy; pVO_2 = peak oxygen uptake; SOC = standard of care.

detected in response to metoprolol treatment in the TEMPO trial,[10] with both demonstrating changes below the threshold considered to be clinically meaningful.[24] Despite this observed deterioration in symptoms, only 3 patients had limiting symptoms after SOC washout that precluded randomization in the study.

The primary endpoint, change in pVO_2, provides an objective metric of functional capacity and is also an important prognostic parameter of clinical events in oHCM. Change in pVO_2 was also the primary endpoint in the SEQUOIA-HCM trial, in which the use of aficamten on top of SOC demonstrated significant improvements in exercise capacity and hemodynamic status, reduction in symptoms, and reduction in eligibility for septal reduction therapy, coupled with a reassuring safety profile. A cross-sectional retrospective analysis of CPET data in 1,898 patients with HCM supports the concept that pVO_2 differences have prognostic value, wherein a 1.0 mL/kg/min decrease was associated with an 18% increase in death or transplantation.[25]

Although beta-blockers are the recommended first-line therapy for symptomatic oHCM, their use in other cardiomyopathies has been associated with a decrease in exercise capacity (pVO_2) as a result of chronotropic incompetence. Importantly, the only available controlled study in patients with oHCM did not demonstrate this,[10] and a subgroup analysis conducted in SEQUOIA-HCM did not show a differential treatment effect of aficamten by background beta-blocker use. Consequently, it is not yet known what the overall impact of the complex interaction between the expected reduction in LVOT gradients, decreased myocardial ischemia, and an associated reduction in heart rate as a result of beta-blocker use will be; this is a question we hope to answer in MAPLE-HCM.

MAPLE-HCM is further designed to address treatment-related questions specifically from a patient perspective. As demonstrated in SEQUOIA-HCM, the side effect profile of aficamten is similar to that of placebo, and therefore, treatment with aficamten as monotherapy may obviate the unwanted side effects of beta-blockers, calcium-channel blockers, and disopyramide. Compared with patients with many other cardiovascular diseases, patients with oHCM are, on average, younger; side effects associated with beta-blockers, such as fatigue, erectile dysfunction, and hair loss, may have a greater impact on their quality of life. The patient experience substudy of MAPLE-HCM is structured to assess, in the most protean way possible, the impact of the different treatment approaches on patients' lives, goals, and overall experiences. This substudy is likely to shed light on key, but often overlooked, patient-centric impacts of both aficamten and metoprolol.

The study design of MAPLE-HCM has several strengths. The inclusion of both treatment-naive patients and those on existing SOC therapy will allow evaluation of the efficacy of aficamten in newly diagnosed patients and also as an alternative for patients previously receiving first-line agents. The use of metoprolol as an active comparator sets a high bar for demonstrating the efficacy of aficamten and is specifically aimed at providing detailed information about the response to beta-blockers in oHCM, a critical gap in the field despite several decades of beta-blocker use as first-line therapy. The stratified randomization design ensures balance between treatment arms with respect to key prognostic factors such as exercise modality and duration of oHCM diagnosis and previous therapy received.

STUDY LIMITATIONS. Limitations of the study include its 24-week treatment period duration. Although sufficient to detect changes in exercise capacity and symptoms, the full comparative effect of targeted HCM therapy vs beta-blockade regarding clinical events, remodeling, and disease progression may require more extended follow-up. Also, the 24-week treatment period may not be sufficient to capture fully the impact of not being exposed to the side effects associated with beta-blocker treatment. Assessment of the long-term safety of aficamten is being undertaken in FOREST-HCM, in which a large proportion of patients enrolled in MAPLE-HCM are anticipated to continue, providing the potential for longer term follow-up of this treatment approach.

CONCLUSIONS

MAPLE-HCM will deliver critical evidence to contemporary cardiology practice. This clinical trial will evaluate aficamten as a potential therapy that may redefine the current therapeutic scheme for symptomatic oHCM. By providing a direct comparison between aficamten and metoprolol, this study will inform clinical decision making and guideline recommendations.

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KEY WORDS aficamten, beta-blocker, gradient, hypertrophic cardiomyopathy, obstructive

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