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METHODOLOGY AND MECHANISMS CORNER

Mavacamten in Symptomatic Nonobstructive Hypertrophic Cardiomyopathy

Design, Rationale, and Baseline Characteristics of ODYSSEY-HCM

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HIGHLIGHTS

- ODYSSEY-HCM is a phase 3 trial, RCT evaluating mavacamten in 580 symptomatic nHCM patients worldwide.
- It assesses improvements at Week 48 in "feel and function" using KCCQ-CSS and pVO_2.
- It utilizes blinded core-lab echoes to guide drug titration and discontinuation.
- The baseline characteristics are like other phase 3 HCM trials, but without latent LVOT obstruction.
- It aims to establish mavacamten as a standard treatment across the full HCM spectrum.

ABSTRACT

There are no approved therapies for patients with symptomatic nonobstructive hypertrophic cardiomyopathy (nHCM). The authors describe the baseline characteristics of ODYSSEY-HCM (A Study of Mavacamten in Non-Obstructive Hypertrophic Cardiomyopathy), a phase 3, randomized, double-blind, placebo-controlled trial conducted worldwide at 201 sites evaluating mavacamten in symptomatic adult patients with nHCM. The 2 primary endpoints are the changes from baseline to week 48 in: 1) Kansas City Cardiomyopathy Questionnaire 23-item Clinical Summary Score; and 2) peak oxygen consumption (pVO_2) on cardiopulmonary exercise testing. Dose titrations are made on blinded core laboratory assessments. Of 1,088 patients screened, 580 are randomized (mean age 56 $\pm$ 15 years, 46% women, 43% with family histories). All patients are nonobstructive and symptomatic (70% in NYHA functional class II and 30% class III), with a mean Kansas City Cardiomyopathy Questionnaire 23-item Clinical Summary Score of 58 $\pm$ 20, and 77% are on beta-blockers. The mean left ventricular ejection fraction and pVO_2 are 66% $\pm$ 4% and 18 $\pm$ 6 mL/kg/min, respectively. ODYSSEY-HCM will report if mavacamten improves patient-reported health status and exercise capacity in patients with symptomatic nHCM. (A Study of Mavacamten in Non-Obstructive Hypertrophic Cardiomyopathy (ODYSSEY-HCM); NCT05582395) (JACC Heart Fail. 2025;13:358–370) © 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-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Hypertrophic cardiomyopathy (HCM) is a complex inherited myocardial disease with an estimated prevalence of 1 in 500 individuals, with a varied clinical presentation in which individual phenotypic characteristics differ across various demographics. The most common phenotype is obstructive HCM, with its characteristic finding of dynamic left ventricular outflow tract (LVOT) obstruction, which has been reported to be present in about 50% to 70% of patients at reference centers.[1-3] A significant number of patients do not have evidence of LVOT obstruction and are considered to have nonobstructive hypertrophic cardiomyopathy (nHCM), often demonstrating significant mid and apical left ventricular (LV) hypertrophy. Without dynamic LVOT obstruction, a significant proportion of nHCM symptomatology arises from various factors, such as small hypercontractile LV cavity, midcavitary obstruction, low stroke volume, diastolic dysfunction, abnormal lusitropy, microvascular angina, pulmonary hypertension, arrhythmias, and chronotropic incompetence (**Central Illustration**).

At present, no approved medical therapy has been tested specifically for patients with symptomatic nHCM. Commonly used pharmacotherapies for nHCM include diuretic agents, beta-blockers, verapamil, and diltiazem. These treatments provide variable therapeutic benefits and overall have been shown to have both limited efficacy and tolerability due to their impact on blood pressure, inotropy, chronotropy, and conduction.[4,5] Recent trials have yielded mixed results using agents such as ranolazine (ion channel modulator), perhexiline, angiotensin receptor blockers, spironolactone (an aldosterone antagonist), and trimetazidine (myocardial energetics modulator).[6-10] Accordingly, safer and more effective treatments to reduce symptoms, improve quality of life, and increase functional capacity for patients with nHCM represent unmet medical needs described in guidelines from the American College of Cardiology/American Heart Association and the European Society of Cardiology.[1,3]

The search for a targeted therapy for HCM led to the identification of mavacamten, a selective, allosteric, and reversible inhibitor of beta-cardiac myosin that reversibly inhibits its binding to actin, directly inhibiting sarcomere force output to reduce contractility and improve ventricular compliance.[11] In previous studies of patients with symptomatic obstructive HCM, mavacamten reduced LVOT obstruction, improved quality of life, decreased symptom burden, improved exercise capacity, reduced eligibility for septal reduction therapy, and was associated with short- and long-term favorable cardiac remodeling.[12-24] As a result, mavacamten is now approved for commercial use in multiple countries around world, and in the most recent iteration of both U.S. and European guidelines, there are Class I and IIa recommendations, respectively, for the use of mavacamten for symptomatic patients with obstructive HCM.[1,3] On the basis of the recognition that the benefits of mavacamten (by targeting the core molecular defect) might extend beyond relief of LVOT obstruction, it is now being developed for patients with nHCM. In a small phase 2, placebo-controlled study, treatment with mavacamten was significantly associated with improvements (ie, decreases from baseline to week 16) observed in N-terminal pro-B-type natriuretic peptide (NT-proBNP) and troponin I.[25] These results support further development of mavacamten in nHCM to alleviate symptoms and improve functional capacity in a definitive phase 3 trial. In this paper, we describe the rationale, study design, and baseline characteristics of the ODYSSEY-HCM (A Study of Mavacamten in Non-Obstructive Hypertrophic Cardiomyopathy; NCT05582395) trial, which is evaluating mavacamten in adults with symptomatic nHCM.

ABBREVIATIONS AND ACRONYMS

CPET = cardiopulmonary exercise testing

HCM = hypertrophic cardiomyopathy

HFpEF = heart failure with preserved ejection fraction

iDMC = independent data monitoring committee

LVEF = left ventricular ejection fraction

LVOT = left ventricular outflow tract

nHCM = nonobstructive hypertrophic cardiomyopathy

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

PRO = patient-reported outcome

pVO_2 = peak oxygen consumption

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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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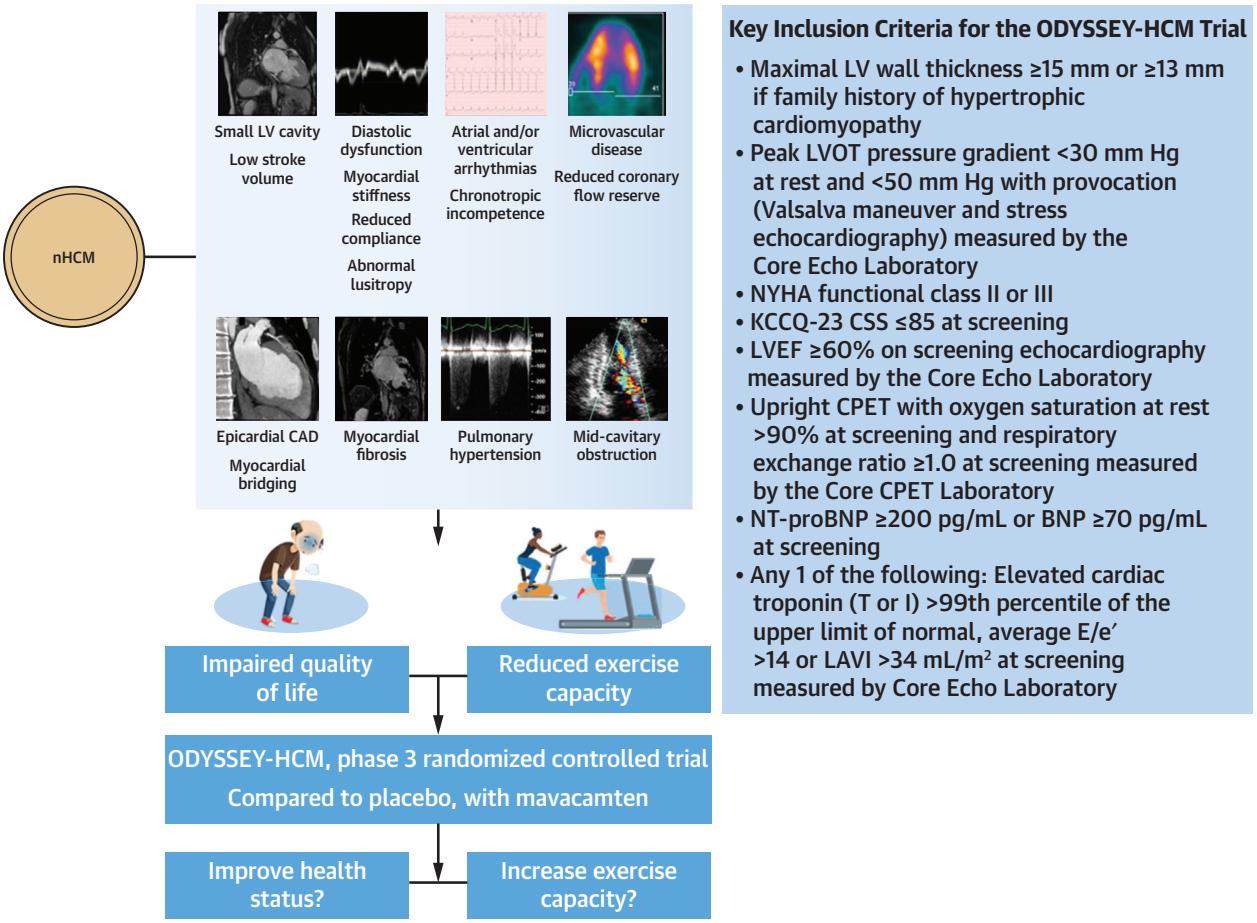
CENTRAL ILLUSTRATION nHCM



Key Inclusion Criteria for the ODYSSEY-HCM Trial

- Maximal LV wall thickness ≥15 mm or ≥13 mm if family history of hypertrophic cardiomyopathy
- Peak LVOT pressure gradient <30 mm Hg at rest and <50 mm Hg with provocation (Valsalva maneuver and stress echocardiography) measured by the Core Echo Laboratory
- NYHA functional class II or III
- KCCQ-23 CSS ≤85 at screening
- LVEF ≥60% on screening echocardiography measured by the Core Echo Laboratory
- Upright CPET with oxygen saturation at rest >90% at screening and respiratory exchange ratio ≥1.0 at screening measured by the Core CPET Laboratory
- NT-proBNP ≥200 pg/mL or BNP ≥70 pg/mL at screening
- Any 1 of the following: Elevated cardiac troponin (T or I) >99th percentile of the upper limit of normal, average E/e′ >14 or LAVI >34 mL/m^2 at screening measured by Core Echo Laboratory

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Various potential mechanisms that contribute to symptoms and impaired quality of life in patients with nonobstructive hypertrophic cardiomyopathy (nHCM) and key inclusion criteria for ODYSSEY-HCM (A Study of Mavacamten in Non-Obstructive Hypertrophic Cardiomyopathy). BNP = brain natriuretic peptide; CAD = coronary artery disease; CPET = cardiopulmonary exercise testing; KCCQ-23 CSS = Kansas City Cardiomyopathy Questionnaire 23-item Clinical Summary Score; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

METHODS

STUDY ORGANIZATION. ODYSSEY-HCM is a phase 3, randomized, double-blind, placebo-controlled, multicenter, international, parallel-group clinical trial that is being conducted at 201 experienced HCM sites across the world (Supplemental Material). ODYSSEY-HCM is approved by the Institutional Review Boards of the participating centers. Written informed consent was obtained from each participant prior to any study-related procedures. This trial is supervised by an executive committee and an independent data monitoring committee (iDMC). The trial is sponsored by Bristol Myers Squibb with Pharmaceutical Product Development (a wholly owned subsidiary of Thermo Fisher Scientific) serving as the contract research organization to provide monitoring, data, and site management. Cleveland Clinic Coordinating Center for Clinical Research (C5Research) is providing academic oversight, including coordination of the executive committee and national leadership as well as the imaging core laboratory. The Cardiovascular and Metabolic Disease Research Institute is serving as the core laboratory for cardiopulmonary exercise testing (CPET) analysis. C5Research is responsible for the independent conduct of the trial under charter, including maintaining requisite firewalls between the iDMC, the imaging core laboratory, and study

investigators employed by the Cleveland Clinic (M.Y.D. and S.E.N.). The executive committee, composed of experts in cardiovascular disease (specifically HCM), with relevant clinical and trial methodological expertise, provides scientific guidance and advice related to conduct, results analysis, and publication strategy for the trial. Additionally, a steering committee and national leaders from participating countries, other experts, and sponsor representatives aid in the scientific aspects of the study. All study personnel remain blinded to treatment assignments and results of imaging and key data until database lock. Statistical analysis of the final trial data will be performed by the statistical team at C5Research and independently validated by the Bristol Myers Squibb statistical team. The authors are primarily responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents. The iDMC is tasked with safeguarding the interests of study participants, assessing interim unblinded safety and efficacy data, and advising the sponsor and executive committee on important emerging study conduct issues. The iDMC may formulate recommendations in relation to the evaluation procedures and methodologies being used to survey and detect potential safety signals. Meeting frequency, membership, and conduct are described in the respective executive committee and iDMC charters.

STUDY POPULATION. The ODYSSEY-HCM has enrolled symptomatic patients who meet established American College of Cardiology/American Heart Association and European Society of Cardiology nHCM diagnostic criteria.[1,26] Full inclusion and exclusion criteria are summarized in **Table 1**. Key inclusion criteria include symptomatic adult patients with nHCM (≥18 years of age, peak LVOT gradient <30 mm Hg at rest and <50 mm Hg with provocation) NYHA functional class II or III, Kansas City Cardiomyopathy Questionnaire 23-item Clinical Summary Score (KCCQ-23 CSS) ≤85, left ventricular ejection fraction (LVEF) ≥60% on transthoracic echocardiography, respiratory exchange ratio ≥1.0 on CPET, and abnormal biomarkers as shown in **Table 1**. Key exclusion criteria include known infiltrative or storage disorder causing cardiac hypertrophy that mimics nHCM, history of unexplained syncope or sustained ventricular arrhythmias within 6 months prior to screening, nonpermanent atrial fibrillation detected at the time of screening, internal cardioverter-defibrillator placement or pulse generator change within 2 months prior to screening, acute heart failure from 4 weeks prior to screening up to randomization, coronary artery disease requiring intervention, coronary artery bypass graft surgery, other major cardiovascular surgery, stroke or transient ischemic attack 90 days prior to screening, any severe obstructive or regurgitant valvular heart disease expected to lead to surgery during the trial period, heart transplantation or listed for heart transplantation, currently implanted LV assist device, any medical condition that precludes upright exercise stress testing, clinically documented LV aneurysm ≥2 cm, and concomitant use of strong inhibitors of cytochrome P450 2C19. Patients with intraventricular LV obstruction could be enrolled in the absence of LVOT obstruction.

STUDY SCHEMA. Mavacamten is being studied as an add-on therapy to appropriate background HCM treatments, which could be continued for the duration of the study. Participants were clinically stable, and cardiac medications were not initiated, discontinued, or dose-adjusted within 2 weeks prior to screening and up to the day of randomization.

The overall study design is shown in **Figure 1**. The study includes a screening period of 5 weeks, with follow-up divided into 3 parts as follows.

Part A is a placebo-controlled, double-blind, randomized treatment period (day 1 to week 48). On day 1, eligible patients begin placebo-controlled dosing with mavacamten or placebo once daily for 48 weeks. Randomization occurred using an interactive voice or web response system in a 1:1 ratio to receive mavacamten or matching placebo. Randomization was stratified by: 1) NYHA functional class (II or III); 2) type of exercise (treadmill or exercise bicycle); and 3) beta-blocker use at baseline (yes or no). The starting dose of mavacamten is 5 mg. Patients could have mavacamten dose down-titrated at weeks 5 and 9 or uptitrated at weeks 12, 24 and 36, on the basis of LVEF read in a blinded manner by the core laboratory. Doses could include 1 mg, 2.5 mg, 5 mg, 10 mg, and 15 mg.

Part B is a placebo-crossover period in the long-term extension (weeks 48-96). All patients will receive mavacamten once daily until week 96. Patients who receive mavacamten during the initial 48 weeks will continue receiving the mavacamten dose they were taking at week 48 (no washout), while patients who received placebo during the first 48 weeks will begin mavacamten 5 mg at week 48 plus 1 day. Patients who were taking placebo during part A may have their mavacamten doses down-titrated at weeks 53 and 57 and uptitrated at weeks 60, 72, and 84, on the basis of LVEF read in a blinded manner by the core laboratory.

TABLE 1 Inclusion and Exclusion Criteria for the ODYSSEY-HCM Trial

Inclusion criteria

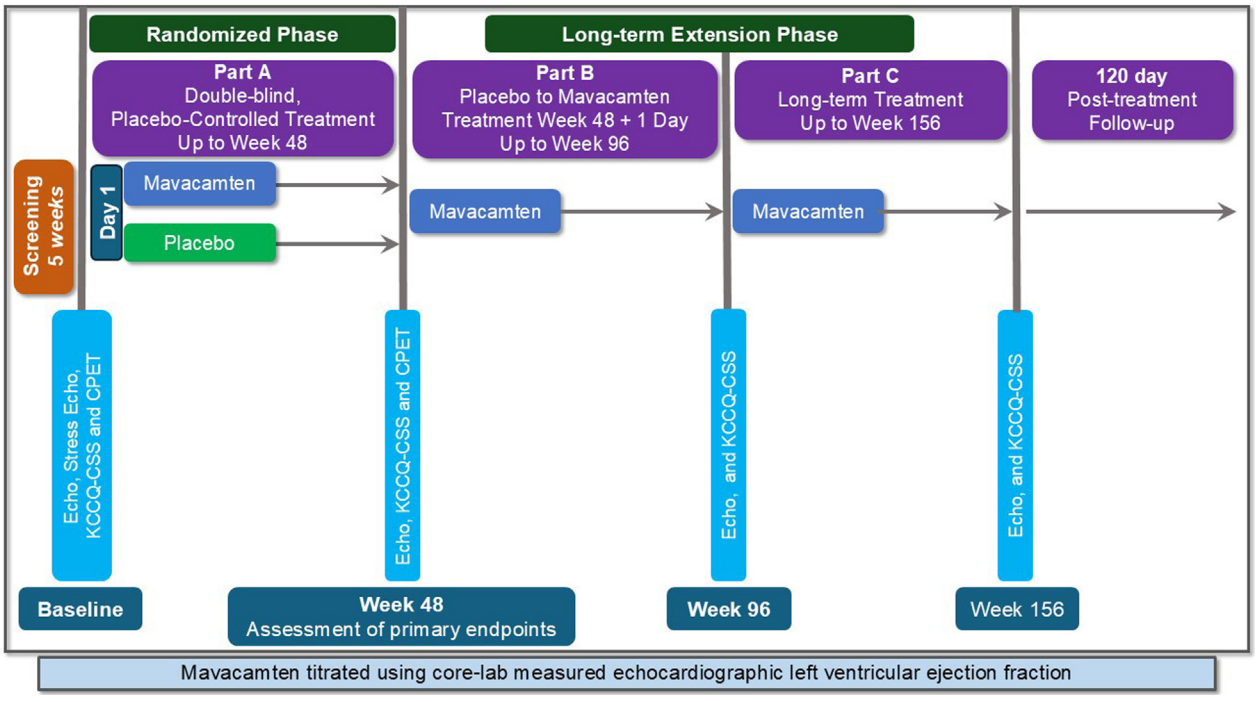
1. Signed written informed consent
2. Age ≥18 y
3. Type of participant and target disease characteristics
   a. Diagnosis of HCM consistent with current ACC Foundation/AHA and ESC guidelines as determined by core laboratory interpretation
   b. Peak LVOT pressure gradient <30 mm Hg at rest and <50 mm Hg with provocation (Valsalva maneuver and stress echocardiography)
   c. NYHA functional class II or III
   d. KCCQ-23 CSS ≤85 at screening
   e. LVEF ≥60% on screening echocardiography measured by core echocardiography laboratory
   f. CPET: documented oxygen saturation at rest >90% at screening, ability to perform upright CPET with a respiratory exchange ratio ≥1.0 at screening per central reading
   g. NT-proBNP or BNP ≥200 pg/mL or BNP ≥70 pg/mL at initial screening measurement if not in AF or atrial flutter at screening or NT-proBNP ≥500 pg/mL or BNP ≥150 pg/mL if in AF or atrial flutter at the time of screening; if the screened participant is either of African descent or has a body mass index ≥30.0 kg/m^2, screening NT-proBNP ≥160 pg/mL or BNP ≥55 pg/mL if not in AF or atrial flutter or NT-proBNP ≥400 pg/mL or BNP ≥135 pg/mL if in AF or atrial flutter
   h. Any of the following: i) evidence of myocardial damage, defined as elevated cardiac troponin (T or I) >99th percentile of the upper limit of normal of the assay used by the analyzing laboratory; or ii) evidence of LV diastolic dysfunction (average E/e′ ratio >14 on screening echocardiography measured by core echocardiography laboratory or LAVI >34 mL/m^2 on screening echocardiography measured by core echocardiography laboratory
4. Negative pregnancy test in women of child-bearing potential at screening and randomization

Exclusion criteria

1. Medical conditions
   a. Known infiltrative or storage disorder causing cardiac hypertrophy that mimics nHCM such as amyloidosis, Fabry disease, or Noonan syndrome with LV hypertrophy
   b. History of unexplained syncope within 6 mo prior to screening
   c. History of sustained ventricular tachyarrhythmia (>30 s) within 6 mo prior to screening
   d. Paroxysmal or persistent (nonpermanent) AF detected at the time of screening; permanent AF is allowed if the participant is anticoagulated and the investigator considers the heart rate adequately controlled
   e. ICD placement or pulse generator change within 2 mo prior to screening or planned new ICD placement during the study
   f. CV diseases or treatments that in the opinion of the investigator increase the unpredictability of or change the participants' clinical course
   g. Acute heart failure from 4 wks prior to screening up to randomization
   h. Coronary artery disease requiring intervention, including myocardial infarction (increase in cardiac enzymes in combination with symptoms of ischemia or new ischemic ECG changes), coronary artery bypass graft surgery, or other major CV surgery, stroke, or transient ischemic attack in the past 90 d
   i. Any severe obstructive or regurgitant valvular heart disease expected to lead to surgery during the trial period
   j. Heart transplant recipient or listed for heart transplantation
   k. Currently implanted LV assist device
   l. Clinically significant pulmonary disease associated with exertional dyspnea
   m. Major surgery, according to the investigator's assessment, performed within 90 d prior to screening or major scheduled elective surgery within 90 d after screening
   n. Gastrointestinal surgery or gastrointestinal disorder that could interfere with absorption of study intervention
   o. Any documented active or suspected malignancy or history of malignancy within 2 y prior to screening, except appropriately treated basal cell carcinoma of the skin, in situ carcinoma of uterine cervix, or low-risk prostate cancer (participants with pretreatment prostate-specific antigen <10 ng/mL, biopsy Gleason score ≤6, and clinical stage T1c or T2a)
   p. Any disease other than heart failure or HCM that the investigator considers to confer a reduced life expectancy
   q. Any condition that might jeopardize participant safety, limit the participants' participation in the trial, or undermine the interpretation of trial data
   r. Any medical condition that precludes upright exercise stress testing
   s. Patients with midcavity obstruction or apical HCM or post SRT are not excluded
   t. Clinically documented LV aneurysm ≥2 cm
2. Reproductive status: women who are breastfeeding or pregnant
3. Prior/concomitant therapy
   a. Inability to comply with restrictions and prohibited treatments
   b. Any adjustments of beta-blockers, verapamil, or diltiazem within 2 wks prior to screening and up to the day of randomization
   c. Concomitant use of strong inhibitors of cytochrome P450 2C19
4. Physical and laboratory test findings
   a. Severe (Child-Pugh class C) hepatic impairment
   b. Alanine aminotransferase or aspartate aminotransferase ≥3 times the upper limit of the laboratory reference range or total bilirubin ≥2 times the upper limit of the laboratory reference range
   c. Estimated glomerular filtration rate <15 mL/min/1.73 m^2 or on dialysis
   d. Body weight <45 kg
   e. Acoustic windows do not allow obtaining interpretable images by TTE
5. History of allergy to mavacamten
6. Other exclusion criteria
   a. Prisoners or participants who are involuntarily incarcerated
   b. Any other serious condition that in the opinion of the investigator could prevent participation in the study and follow-up, including active COVID-19 from 4 wks prior to screening up to randomization
   c. Completed a study with: 1) an investigational device <30 d prior to screening; or 2) an investigational drug <5 half-lives prior to screening
   d. Participants who have completed a study with mavacamten or aficamten
   e. Enrolled in another study and receiving any investigational treatment (device or drug) other than the study intervention given in this study

ACC = American College of Cardiology; AF = atrial fibrillation; AHA = American Heart Association; BNP = brain natriuretic peptide; CPET = cardiopulmonary exercise testing; CV = cardiovascular; ECG = electrocardiographic; ESC = European Society of Cardiology; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; KCCQ-23 CSS = Kansas City Cardiomyopathy Questionnaire 23-item Clinical Summary Score; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; nHCM = nonobstructive hypertrophic cardiomyopathy; NT-proBNP = N-terminal pro-B-type natriuretic peptide; ODYSSEY-HCM = A Study of Mavacamten in Non-Obstructive Hypertrophic Cardiomyopathy; SRT = septal reduction therapy; TTE = transthoracic echocardiography.

FIGURE 1 Study Design



Schema of the ODYSSEY-HCM trial. CPET = cardiopulmonary exercise testing; KCCQ-23 CSS = Kansas City Cardiomyopathy Questionnaire 23-item Clinical Summary Score.

Investigators will remain blinded to the dose of mavacamten. The doses will also include 1 mg, 2.5 mg, 5 mg, 10 mg, and 15 mg.

Part C is a long-term follow-up period (up to week 156). All patients will receive mavacamten once daily up to 156 weeks. The doses will include 1 mg, 2.5 mg, 5 mg, 10 mg, and 15 mg and could be titrated on the basis of site-read LVEF on echocardiography, after approval by the sponsor's medical monitor. Dose will remain blinded unless a decision is made to unblind once the primary analysis is complete. Whenever possible, background therapy for HCM will be maintained at the same dose from screening through week 48. Investigators are allowed to adjust background therapy if clinically indicated.

An individualized dose titration scheme was developed to optimize the balance between efficacy and safety. The scheme is based on extensive pharmacokinetic and pharmacodynamic modeling and simulation that uses core laboratory–measured values for LVEF obtained approximately monthly to determine dosing. A variety of general, echocardiographic, cardiopulmonary, laboratory, biomarker, patient-reported outcome (PRO), and symptom assessments will be performed at screening, on day 1, and at all subsequent study visits.

DRUG INTERRUPTION AND DISCONTINUATION. Drug discontinuation can occur at any time on the basis of the following criteria: 1) if LVEF ≤30% is identified either at the site or at the core laboratory, the investigator is instructed to stop the study intervention immediately and permanently; 2) if LVEF is <50%, the study drug is interrupted for at least 4 weeks, and if LVEF increases to ≥50% after at least 4 weeks, the study drug is resumed at the next lower dose (for participants on the 1-mg dose, the same dose will be resumed); and 3) if the study intervention is interrupted twice on the basis of LVEF <50% on a 1-mg dose, or matching placebo, the study drug is permanently discontinued. In addition to these criteria for permanent drug (and study) discontinuation, participants are planned to discontinue study treatment for the following reasons: 1) participant's request to stop study treatment; 2) any clinical adverse event, laboratory abnormality, or intercurrent illness that, in the opinion of the investigator, indicates that continued

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treatment with the study treatment is not in the best interest of the participant; 3) termination of the study by the sponsor; 4) pregnancy; 5) inability to freely provide consent because of imprisonment or involuntary incarceration; and 6) significant noncompliance with the protocol. Participants who request to discontinue study intervention will be offered to remain in the study and could continue to be followed for protocol-specified follow-up procedures, unless they specifically withdraw consent. Participants who permanently discontinue the study drug prior to week 48 would not be able to participate in the long-term extension (parts B and C).

STUDY PROCEDURES. All patients will undergo comprehensive echocardiographic and CPET assessments. Echocardiographic data will be used for dose titration and assessment of safety and efficacy. Echocardiographic examinations are performed by study-certified sonographers, following a study-specific protocol, and are analyzed at the C5Research imaging laboratory during the blinded treatment period. Because of its importance in the primary endpoint analysis, CPET is performed by study-certified CPET technicians, and results are analyzed at the Cardiovascular and Metabolic Disease Research Institute. PROs are used to assess quality of life and symptoms at home or during the visits, as defined in the protocol. All laboratory test results and electrocardiograms are analyzed at core laboratories.

STUDY ENDPOINTS. The 2 primary endpoints are defined as change from baseline to week 48 in KCCQ-23 CSS and peak oxygen consumption (pVO_2). The secondary and exploratory endpoints are defined as change from baseline in minute ventilation/carbon dioxide production slope to week 48, the proportion of participants with at least 1 class of NYHA functional class improvement from baseline to week 48, change from baseline in NT-proBNP to week 48, change from baseline in cardiac troponin T to week 48, change from baseline in Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness of Breath domain to week 48, and time to first major cardiovascular adverse event (MACE-Plus), defined as any cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, hospitalization for arrhythmias, or appropriate implantable cardioverter-defibrillator therapy.

SAFETY ENDPOINTS. Safety will be assessed throughout the study. Time to first MACE-Plus will be adjudicated by an outside independent adjudication committee.

GENETIC SUBSTUDY. Patients who consent will undergo genetic testing using various clinically approved methods (whole-genome sequencing, next-generation sequencing, or others) to identify genetic variants associated with HCM.

CARDIAC MAGNETIC RESONANCE SUBSTUDY. A cardiac magnetic resonance substudy will assess the effects of mavacamten on cardiac structure, function, and myocardial tissue characterization in participants who consent and do not exhibit any standard contraindications to cardiac magnetic resonance. Cardiac magnetic resonance will be performed during the screening period and the week 48 and week 96 visits. Exploratory endpoints (including cardiac structural and functional indexes and pregadolinium and postgadolinium tissue characterization) will be measured.

STATISTICAL CONSIDERATIONS. Continuous data will be presented as mean ± SD or median (IQR), as appropriate. The sample size for this study was estimated on the basis of the primary endpoints of changes from baseline to week 48 in KCCQ-23 CSS and pVO_2. The sample size calculation used the following assumptions on the basis of the MAVERICK-HCM (A Phase 2 Study of Mavacamten in Adults With Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy) study[25]: 1) increase of 5 points in mean KCCQ-23 CSS from baseline to week 48 between mavacamten and placebo, assuming a common SD of 14; and 2) increase of 1.3 mL/kg/min in mean pVO_2 from baseline to week 48 between mavacamten and placebo, assuming a common SD of 3.1. A sample size of 420 participants was expected to provide at least 95% power to reject the primary null hypothesis of KCCQ-23 CSS, at least 98% power to reject the primary null hypothesis of pVO_2, and at least 99% power to reject at least 1 primary null hypothesis adjusted for multiplicity. No interim analysis is planned for this study. The study will be considered positive if at least 1 primary endpoint is statistically significant. All efficacy analyses will be performed on the intention-to-treat population. A graphical testing strategy will be used to strongly control the overall type I error rate at 0.05 (2-sided). Details of the graphical testing strategy and analytical methods for each endpoint will be described in the statistical analysis plan.

RESULTS

ODYSSEY-HCM started enrollment in December 2022 and completed randomization in March 2024, with patients randomized on 5 continents. Among 1,088 patients screened, 508 (46.6%) failed screening, and

TABLE 2 Baseline Characteristics of the Study Population (N = 580)

Demographics	
Age, y	56 ± 15
<50	168 (29.0)
50-64	234 (40.3)
65-74	132 (22.8)
≥75	46 (7.9)
Female	266 (45.9)
Race	
White	186 (32.1)
Black	14 (2.4)
Asian	86 (14.8)
Other[a]	294 (50.8)
Ethnicity	
Hispanic or Latino	27 (4.7)
Not Hispanic or Latino	263 (45.3)
Other[a]	290 (50.0)
Region	
North America	119 (20.5)
South America	58 (10.0)
Europe	290 (50.0)
Asia (including India and Israel)	103 (17.8)
Australia	10 (1.7)
Vital signs	
Weight, kg	80.3 ± 17.7
Body mass index, kg/m^2	28.2 ± 5.0
Diastolic blood pressure, mm Hg	74.5 ± 11.5
Systolic blood pressure, mm Hg	124.3 ± 16.9
Heart rate, beats/min	64.6 ± 10.0
HCM history	
Time since initial diagnosis, y	10.3 ± 9.3
Family history of HCM	251 (43.3)
Family history of sudden cardiac death	84 (14.5)
History of internal cardioverter defibrillator	233 (40.2)
History of permanent pacemaker	25 (4.3)
History of prior septal reduction therapy	47 (8.1)
Comorbidities	
Hypertension	256 (44.1)
Coronary artery disease	40 (6.9)
Dyslipidemia	271 (46.7)
Diabetes mellitus	69 (11.9)
AF	176 (30.3)
Atrial flutter	25 (4.3)
Background HCM therapies	
Beta-blockers	449 (77.4)
Nondihydropyridine calcium-channel blockers	67 (11.6)
Disopyramide or cibenzoline	23 (4.0)
Symptoms and physical functioning	
NYHA functional class	
II	405 (69.8)
III	175 (30.2)
KCCQ-23 CSS	57.8 ± 20.0
Echocardiography (blinded reads by core laboratory)	
LVEF, %	65.7 ± 3.9
LV end-diastolic volume index, mL/m^2	42.5 ± 10.8
LV end-systolic volume index, mL/m^2	14.6 ± 4.3
LV mass index, g/m^2	122.6 ± 31.2
Maximum LV wall thickness, cm	2.1 ± 0.4
Resting LVOT gradient, mm Hg	9.4 ± 5.2
Post-Valsalva LVOT gradient, mm Hg	10.7 ± 6.7
Post-exercise LVOT gradient, mm Hg	14.9 ± 9.1
LAVI, mL/m^2	43.4 ± 15.5
Average E/e′ ratio	13.3 ± 5.6
Cardiopulmonary exercise testing	
Type of exercise testing	
Treadmill	267 (46)
Bicycle	313 (54)
pVO_2, mL/kg/min	18.2 ± 5.7
Percentage predicted pVO_2, %	67.8 ± 21.7
VE/VCO_2 slope	36.9 ± 8.6
Biomarkers	
NT-proBNP, ng/L	1,407.8 ± 1,587.7
Median (IQR)	922 (463-1,725)
High-sensitivity troponin T, ng/L	24.9 ± 29.0
Median (IQR)	18.4 (12.3-27.0)

Values are mean ± SD or n (%), unless otherwise indicated. [a]Race and ethnicity data are reported as currently available. These results will be updated in future publications once additional data is available.

pVO_2 = peak oxygen consumption; VCO_2 = carbon dioxide production; VE = minute ventilation; other abbreviations as in Table 1.

Continued in the next column

580 were randomized. Baseline characteristics of the study population are shown in Table 2. The mean age is 56 ± 15 years, and 46% are women, with a mean body mass index of 28.2 ± 5 kg/m^2. Average time from initial HCM diagnosis to randomization was 10.3 ± 9.3 years, 251 patients (43.3%) had family histories of HCM, and 47 (8.1%) had histories of prior septal reduction therapy. All patients are symptomatic, with 405 (69.8%) in NYHA functional class II and the rest in NYHA functional class III. The mean KCCQ-CSS is 57.8 ± 20.0, and 445 patients (76.7%) are on beta-blockers.

On core laboratory-confirmed echocardiographic measurements, all patients had preserved LVEF (mean 65.7% ± 3.9%) and were nonobstructive (mean resting gradient <30 mm Hg, both Valsalva and postexercise LVOT gradients <50 mm Hg), with increased LV mass index (122.6 ± 31.2 kg/m^2), left atrial volume index (43.4 ± 15.6 mL/m^2), and E/e′ ratio (13.3 ± 5.6). During CPET, 313 patients (54%) underwent bicycle ergometry, while the rest underwent treadmill testing, and the mean pVO_2 was 18.2 ± 5.7 mL/kg/min (67.8% ± 21.7% of predicted). The baseline biomarkers were elevated, with a median NT-proBNP of 922 ng/L (IQR: 463-1,725 ng/L) and a median high-sensitivity troponin T of 18.4 ng/L (IQR: 12.3-26.9 ng/L).

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DISCUSSION

ODYSSEY-HCM is a phase 3, randomized, double-blind, placebo-controlled, multicenter, international, parallel-group clinical trial conducted at 201 experienced HCM centers across the world. The mean age of the study population was similar to that of previous phase 3 trials in HCM patients, and 46% randomized patients were women.[12-14,27] This is a global trial, with representation from 5 continents. Body habitus, including body mass index, was also similar to that in other phase 3 trials in HCM.[12-14,28] Patients were symptomatic (about 70% in NYHA functional class II), with a significant impact on their health status, as manifested by a KCCQ-23 CSS of 57.8. Similar to prior phase 3 trials of mavacamten in obstructive HCM, all patients were receiving appropriate background HCM therapy, including 77% on beta-blockers.[12-14] Per study protocol, all patients had preserved LVEF and no LVOT obstruction, as documented on core laboratory echocardiographic measurements. Given the advanced disease burden, all patients had evidence of diastolic dysfunction, manifested as increased left atrial volume index and E/e′ ratio. Patients had elevated biomarkers and substantially impaired exercise capacity: the mean value of pVO_2 on CPET was 18.2 ± 5.7 mL/kg/min, and percentage predicted pVO_2 was 67.8% ± 21.7%.

Unlike studies in patients with obstructive HCM, in which an obvious key target of therapeutic intervention is to relieve LVOT obstruction and to reduce the need for septal reduction therapy, any clinical trial in nHCM must rely on demonstrating improvements in PROs, NYHA functional class, and exercise capacity, in addition to cardiac biomarkers. The KCCQ-23 has emerged as a key PRO instrument that has recently been validated in obstructive HCM.[29] As the practice of medicine focuses on enhancing the patient voice in treatment benefit assessment and engaging patients in selecting treatment through shared decision making, describing the health status outcomes patients might expect on the basis of PRO data is increasingly recommended in medical professional society guidelines and major health authorities (the U.S. Food and Drug Administration and European Medicine Agency), including the management of HCM.[1,3,30] Although favorable changes in various KCCQ-23 domains have been demonstrated in obstructive HCM patients following pharmacologic therapy, there is a paucity of evidence describing benefits of pharmacologic treatments for nHCM using PRO measures.[20,22,27] In fact, the magnitude of benefit observed with mavacamten on the KCCQ-23 in obstructive HCM patients is larger than those of most pharmacologic treatments for heart failure and closer to that of percutaneous valvular interventions.[14,20,22] However, changes occurring in the absence of an obstructive physiology are likely to be more subtle, and relying solely on PROs and physician-assessed NYHA functional class may be subjective and prone to bias and a placebo effect to some extent.[22,31]

As a result, for the ODYSSEY-HCM trial, to assess improvements in “feel and function,” 2 primary endpoints were chosen: change from baseline to week 48 in KCCQ-23 CSS and in change in pVO_2. Measurements of pVO_2 enable comprehensive assessment of the multiple mechanisms that contribute to exercise limitation in HCM. Indeed, measuring pVO_2 during CPET is the most precise technique for determining oxygen uptake during maximal exercise, a direct correlate of cardiac output, and has minimal placebo effect.[32] In addition to objectively quantifying functional capacity more effectively than subjective measures such as NYHA functional class, pVO_2 independently predicts clinically relevant outcomes in obstructive HCM.[13,27] It is also associated with long-term outcomes in patients with obstructive HCM and those with nHCM.[33,34] Additionally, we will measure minute ventilation/carbon dioxide production slope as a key secondary endpoint.

Another important consideration with regard to ODYSSEY-HCM trial design revolves around the stringent requirement of a core laboratory transthoracic echocardiographic assessment of LVEF to guide study participation eligibility and all dose-titrating and drug discontinuation decisions. This was done to minimize bias of investigator and site-read LVEF readings to guide dose titrations and drug discontinuations during the blinded portion of the study. As dynamic LVOT obstruction is often latent in many patients with HCM and missed on resting transthoracic echocardiography, a stringent protocol of provocative maneuvers on resting and stress echocardiography was used to identify patients with true nHCM.[35-37] In addition, every randomized patient met the stringent entry criteria for the diagnosis of nHCM per current guideline recommendations.[1-3] However, despite these rigorous standards in place, potential challenges of distinguishing nHCM from heart failure with preserved ejection fraction (HFpEF) or other diseases that also show increased wall thickness, such as cardiac amyloidosis, remain.[38] Indeed, typical patients with HFpEF tend to be more obese and have a higher proportion of

standard cardiovascular comorbidities such as hypertension, diabetes mellitus, and coronary artery disease. But as shown in **Table 2**, the present study population had very similar characteristics as those reported in other HCM trials, including body mass index and other cardiovascular comorbidities.[12-14,27] Additionally, the average maximal wall thickness of 2.1 ± 0.4 cm suggests against a considerable proportion of HFpEF patients who very rarely exceed 1.5 cm in LV wall thickness. Although no formal systematic mandatory exclusion of amyloidosis was required in the study, echocardiographic techniques such as LV global longitudinal strain and diastolic function assessment were carefully used by the core laboratory to limit the potential inclusion of mimickers. In case echocardiographic findings at baseline were suggestive of amyloid, investigators were contacted by the core laboratory so it could be excluded. Additionally, conditions that mimic HCM, such as amyloidosis, were ruled out using advanced echocardiographic techniques such as LV global longitudinal strain and diastolic function assessment.

Given the current estimated overall prevalence of HCM in the general population of 1 in 500 and the fact that patients with nHCM constitute about 30% to 50% of the HCM referral population, the number of such patients in the world is large, with a heterogeneous presentation, including those with significant mid and apical LV cavity hypertrophy.[1,2,26] Defining features of HCM are reduced LV compliance, reduced LV chamber size, and higher than normal LVEF. In the past, it was perceived that nHCM (especially the apical variant) constituted a more benign variant of HCM.[39] However, recent studies have shown mortality rates of 0.5% to 4.8% per year, like those in typical HCM.[40,41] Without the dynamic LVOT obstruction, a significant proportion of nHCM symptomatology arises from various factors, such as a small hypercontractile LV cavity, midcavitary obstruction, low stroke volume, diastolic dysfunction, abnormal lusitropy, microvascular angina, pulmonary hypertension, arrhythmias, and chronotropic incompetence (**Central Illustration**). In previous studies of patients with symptomatic obstructive HCM, mavacamten improved LVOT gradient and quality of life, reduced symptom burden, improved physical functioning, and reduced eligibility for septal reduction therapy. In addition, it also demonstrated a favorable biomarker profile and cardiac remodeling.[12,13,16-18,20,21,23,24] Given the lack of approved medical therapy for patients with symptomatic nHCM (without demonstrable dynamic LVOT obstruction) and currently available pharmacotherapies for nHCM (beta-blockers, verapamil, and diltiazem) demonstrating variable therapeutic effects and tolerability,[11] there is an unmet need for novel therapies. MAVERICK-HCM, a phase 2, placebo-controlled study, demonstrated significant improvements in NT-proBNP and troponin I, with a post hoc analysis identifying a subset of patients who responded better to mavacamten compared with placebo for the efficacy endpoints of changes from baseline in KCCQ-23 CSS and pVO_2.[25] Mavacamten was well tolerated in this nHCM study population, with only mild to moderate adverse events, no fatalities, and no differences in atrial tachyarrhythmias between mavacamten and placebo. These results provide the rationale for conducting the much larger phase 3 ODYSSEY-HCM trial. Dosing for the present trial was developed to optimize the balance between efficacy and safety independent of baseline metabolizer rate. This was based on extensive pharmacokinetic and pharmacodynamic modeling that uses core laboratory-read values for LVEF obtained approximately monthly to determine dosing. Indeed, cardiac myosin inhibitors such as mavacamten may improve diastole by countering multiple mechanisms, such as: 1) excess availability of on state(s) myosin heads, with elevations in residual cross-bridges hindering compliance and filling; 2) biochemical events prolonging cross-bridge detachment; 3) alterations in Ca^{2+} handling resulting in elevated diastolic levels; and 4) structural remodeling.[42]

There is at least 1 ongoing phase 3 trial (ACACIA-HCM [Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic nHCM]; NCT06081894) studying aficamten, a second cardiac myosin inhibitor, evaluating its efficacy in patients with nHCM using a primary endpoint of KCCQ-23 CSS. This study follows the favorable results of the open-label, phase 2 REDWOOD-HCM (Dose-Finding Study to Evaluate the Safety, Tolerability, PK, and PD of CK-3773274 in Adults With HCM) substudy in nHCM, which demonstrated improvements in NYHA functional class, KCCQ-23 CSS, and biomarkers.[43] Another therapy, ninerafaxstat, a novel cardiac mitotrope designed to restore myocardial energy homeostasis, has recently been shown in a phase 2 trial to improve ventilatory efficiency (minute ventilation/carbon dioxide production slope), but not pVO_2 or KCCQ-23 CSS, compared with placebo, with no major safety concerns.[44] As a result, it will be entering phase 3 trials soon. Whether the sodium-glucose cotransporter class of drugs, with its positive signal in HFpEF,[45] and emerging gene therapies will demonstrate efficacy in nHCM remains to be studied.

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CONCLUSIONS

The current report describes the study design and baseline characteristics of ODYSSEY-HCM, a phase 3, randomized, double-blind, placebo-controlled, multicenter, international, parallel-group clinical trial at 201 experienced HCM sites across the world. The aim of the trial is to establish mavacamten as a standard treatment across the full spectrum of symptomatic patients with HCM. It has completed enrollment, and results are expected in 2025.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Mavacamten is approved for treatment in symptomatic obstructive HCM. However, there is no approved therapy for patients with symptomatic nHCM. We describe the baseline characteristics of ODYSSEY-HCM (NCT05582395), a phase 3, randomized, double-blind, placebo-controlled trial conducted at 201 sites across the world. This trial is evaluating mavacamten in 580 adults with nHCM who are symptomatic despite background medical therapy.

TRANSLATIONAL OUTLOOK: ODYSSEY-HCM is the largest trial in patients with HCM, evaluating if mavacamten can improve patient-reported health status and exercise capacity in patients with symptomatic nHCM. The aim is to establish mavacamten as a standard treatment across the full spectrum of symptomatic patients with HCM.

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KEY WORDS characteristics, design, mavacamten, nonobstructive HCM

APPENDIX For ODYSSEY-HCM trial leadership and site investigators, please see the online version of this paper.