Circulation: Heart Failure

METHODS PAPER

Study Design and Rationale of EXPLORER-HCM

Evaluation of Mavacamten in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy

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BACKGROUND: Obstructive hypertrophic cardiomyopathy (oHCM) is characterized by unexplained left ventricular (LV) hypertrophy associated with dynamic LV outflow tract obstruction. Current medical therapies are nonspecific and have limited efficacy in relieving symptoms. Mavacamten is a first-in-class targeted inhibitor of cardiac myosin, which has been shown to reduce LV outflow tract obstruction, improve exercise capacity, and relieve symptoms of oHCM in the PIONEER-HCM phase 2 study.

METHODS: EXPLORER-HCM is a multicenter, phase 3, randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of mavacamten in treating symptomatic oHCM. Eligible adults with oHCM and New York Heart Association Functional Class II or III are randomized 1:1 to receive once-daily, oral mavacamten, or matching placebo for 30 weeks. The primary composite functional end point is clinical response at week 30 compared to baseline defined as either (1) an increase in peak oxygen consumption ≥1.5 mL/kg/min and reduction of at least one New York Heart Association class; or (2) an improvement of ≥3.0 mL/kg/min in peak oxygen consumption with no worsening of New York Heart Association class. Secondary end points include change in postexercise LV outflow tract gradient, New York Heart Association class, peak oxygen consumption, and patient-reported outcomes assessed by the Kansas City Cardiomyopathy Questionnaire and a novel HCM-specific instrument. Exploratory end points aim to characterize the effect of mavacamten on multiple aspects of oHCM pathophysiology.

CONCLUSIONS: EXPLORER-HCM is a phase 3 trial in oHCM testing a first-in-class, targeted strategy of myosin inhibition to improve symptom burden and exercise capacity through reducing LV outflow tract obstruction. Results of this trial will provide evidence to support the first disease-specific treatment for HCM.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03470545.

Key Words: cardiomyopathy ■ exercise ■ hypertrophy ■ oxygen consumption

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease often caused by pathogenic variation in genes encoding the cardiac sarcomere.[1,2] HCM is clinically characterized by unexplained left ventricular (LV) hypertrophy, decreased compliance, and myocardial fibrosis.[2–4] Dynamic LV outflow tract (LVOT) obstruction due to systolic anterior motion of the mitral valve is a common manifestation. Obstructive HCM (oHCM), defined by the presence of either a resting or provoked peak LVOT gradient ≥30 mm Hg, is frequently associated with dyspnea, effort intolerance, angina, palpitations, and syncope.[3,4] Symptomatic patients often experience atrial fibrillation, heart failure (HF), and reduced quality of life.[4,5]

Current first-line medical therapy for patients with symptomatic oHCM include β-blockers (of which only

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Nonstandard Abbreviations and Acronyms

CPET	cardiopulmonary exercise testing
HCM	hypertrophic cardiomyopathy
HCMSQ	Hypertrophic Cardiomyopathy Symptom Questionnaire
HF	heart failure
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
oHCM	obstructive hypertrophic cardiomyopathy
pVO_2	peak oxygen consumption

propranolol carries a Food and Drug Administration indication based on an uncontrolled series of 13 patients) or nondihydropyridine calcium channel blockers.[3,4] Disopyramide, a class 1a antiarrhythmic agent with negative inotropic effects, is typically considered for patients refractory to first-line therapy. These nonspecific agents often have either modest efficacy or substantial side effects, limiting symptomatic benefit. Guidelines from the American College of Cardiology Foundation/American Heart Association and European Society of Cardiology[3,4] recommend that patients with drug-refractory symptoms and LVOT gradient >50 mm Hg consider invasive septal reduction therapy with either surgical septal myectomy or alcohol septal ablation.

Symptoms of oHCM can be effectively improved with septal reduction therapy, but these invasive procedures expose patients to the inherent risks of cardiac surgery or coronary instrumentation, require appropriate anatomic features, and depend on operators with adequate skill and expertise. Furthermore, a small but significant proportion of patients (≈4%) may continue to experience limiting symptoms following septal reduction therapy and will require additional intervention.[6,7] This highlights that the pathophysiology of oHCM is complex and multifactorial, extending beyond obstruction to encompass abnormalities in diastolic function, coronary microvascular flow, and myocardial energetics.

STUDY RATIONALE

Available pharmacological strategies fail to address the underlying molecular mechanisms of oHCM and have not demonstrated disease-modifying effect.[3,4] This gap in our therapeutic armamentarium is well recognized. In recent years, several drugs with potentially promising therapeutic targets have been investigated in obstructive and nonobstructive HCM but have failed to demonstrate efficacy. These include attempts to modulate myocardial energetics (perhexiline and trimetazidine),[8] to inhibit the late-sodium channel (ranolazine and eleclazine),[9,10] and to decrease fibrosis (spironolactone, valsartan, and losartan).[11–13]

Fundamental research has demonstrated that HCM-causing sarcomeric gene variants can destabilize the low-energy super-relaxed state of cardiac myosin and promote excessive cross-bridging with actin.[14] This results in higher myocardial energy utilization, disordered relaxation, and hypercontractility. Independent of genotype, this hypercontractile state seems to represent a final common pathway of the oHCM phenotype resulting in a complex cascade of downstream functional and energetic abnormalities.[2] Given that these pathological changes ultimately contribute to myocardial fibrosis and dysfunction, a targeted agent to restore more physiological actin-myosin interaction has the potential to improve both molecular abnormalities and symptoms in patients with HCM.

Mavacamten (previously known as MYK-461) is a novel small molecule, selective allosteric inhibitor of cardiac myosin ATPase designed to target fundamental abnormalities associated with HCM (Figure [A]). It was developed to be selective for cardiac rather than skeletal muscle function. Preclinical and phase 1 (https://www.clinicaltrials.gov; Unique identifier: NCT02356289) studies have supported cardioselectivity and no detected impact on skeletal muscle function.[15,16] In vitro data from human cardiac myocytes demonstrated that mavacamten was capable of restoring the proportion of myosin in the super-relaxed state, thereby reducing the excess cross-bridges and normalizing ATP consumption.[17] Preclinical data from a mouse model of HCM showed that administration of mavacamten reduced contractility, eliminated systolic anterior motion, and relieved LVOT pressure gradients. If given early in life, mavacamten appeared to attenuate the development of ventricular hypertrophy, cardiomyocyte disarray, and myocardial fibrosis.[15]

Phase 1 studies with mavacamten investigated the safety and tolerability and helped inform the dosing strategy for the open-label phase 2 clinical trial, PIONEER-HCM (https://www.clinicaltrials.gov; Unique identifier: NCT02842242).[18] Individualized daily dosing in PIONEER-HCM identified a target therapeutic range (350 to 700 ng/mL plasma concentration) in which participants showed the desired pharmacodynamic effects by the end of the 12-week treatment period, including marked reduction of postexercise LVOT gradient and improvement in exercise capacity and symptoms. Similar dose-effect relationships were present in participants with and without sarcomere mutations and in participants with and without background medical therapy for oHCM. Overall, mavacamten was well tolerated, with the majority

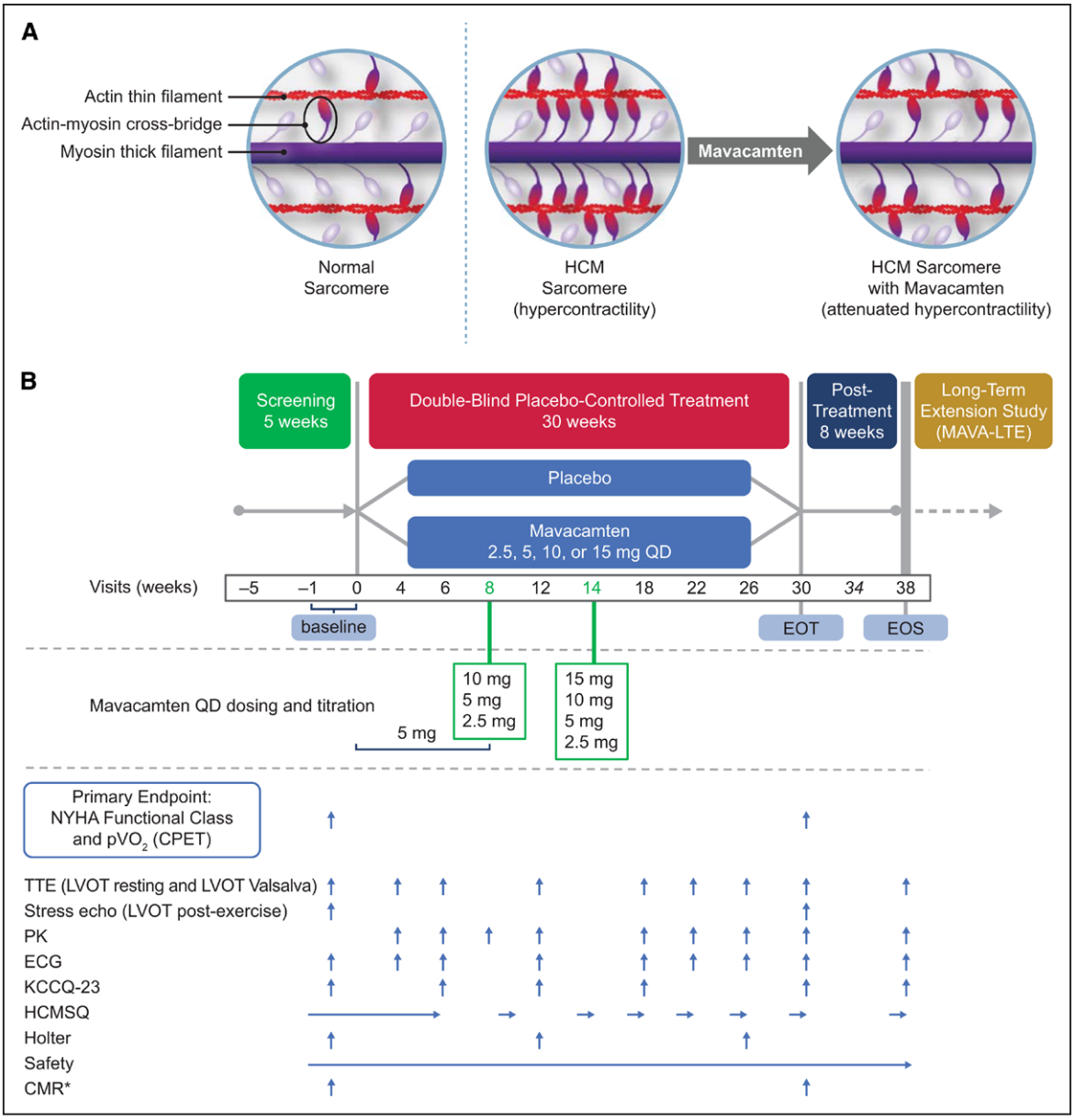

Figure. Mavacamten mechanism of action and study design.
A, Mechanism of action: Hypertrophic cardiomyopathy (HCM)–associated sarcomere mutations may result in an excessive number of actin-myosin cross-bridges, leading to cardiac hypercontractility and hypertrophy. These pathophysiologic changes are effectively countered by mavacamten, a small molecule inhibitor specific to cardiac myosin that reduces excessive myosin-actin cross-bridging. **B**, Study design: Explorer-HCM comprises 3 periods: screening (day −35 to day −1), double-blind treatment period (day 1 [randomization] to week 30/end-of-treatment [EOT]), and post-treatment follow-up period (week 30/EOT to week 38/end-of-study [EOS]). The study includes 12 visits (a phone call at week 34) that include clinical and physical evaluations, adverse event (AE)/serious AE assessments, documentation of concomitant medications, and pharmacokinetics (PK). At all visits, except weeks 8 and 14, ECGs, resting transthoracic echocardiographies (TTEs), and laboratory assessments are conducted and evaluated at core laboratories. Cardiopulmonary exercise testing (CPET) is performed at screening and week 30 and evaluated at a core laboratory. New York Heart Association (NYHA) functional class and overall clinical and physical status are evaluated at the clinical study site and by the same assessor at baseline and week 30. Participants complete the daily HCM Symptom Questionnaire (HCMSQ) on a hand-held electronic device for the first 6 weeks of treatment and for 7 consecutive days before visits at week 10 (at home), 14, 18, 22, 26, 30/EOT, and 38/EOS; and they complete the Kansas City Cardiomyopathy Questionnaire (23-item version; KCCQ-23) at day 1 and weeks 6, 12, 18, 30/EOT, and 38/EOS. Holter monitor (48 h) is performed at screening and weeks 12 and 26, and accelerometer is also performed at screening and week 26. During the 8-week post-treatment period, study drug is discontinued. After assessments at week 38/EOS, participants may consent to continue into mavacamten long-term extension study (MAVA-LTE), where all participants receive mavacamten while remaining blinded to dose and original treatment assignment. CMR indicates cardiac magnetic resonance; LVOT, left ventricular outflow tract; and pVO_2, peak oxygen consumption.
*CMR, cardiac magnetic resonance, in a substudy.

of adverse events being mild (80%) or moderate (19%), self-limited, and assessed by investigators as unrelated (79%) to the study drug. The most common adverse events in PIONEER-HCM related to mavacamten were dose-related reversible decrease in LV ejection fraction (LVEF) below 50% (range, 34% to 49%) at higher

plasma concentrations of 695 to 1500 ng/mL (n=3), and recurrent atrial fibrillation (n=3).[18] Thirteen of 21 participants who participated in PIONEER-HCM opted to participate in the ongoing open-label extension (OLE) study (PIONEER-OLE; https://www.clinicaltrials.gov; Unique identifier: NCT03496168). This experience provided the rationale and informed the design and dosing strategy for the phase 3 EXPLORER-HCM trial.

METHODS

The appropriately redacted clinical protocol Statistical Analysis Plan will be made available to researchers whose proposed use of the data has been approved by the study's publications committee (email: asehnert@myokardia.com).

Study Organization

EXPLORER-HCM is a multicenter, phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mavacamten in adults with symptomatic oHCM at 68 sites in 13 countries (Figure). The Steering Committee is composed of academic cardiologists with relevant clinical and methodological expertise, and an HCM patient, who provide key perspectives on trial design, execution, and patient-reported outcomes (PROs). Additional study oversight is provided by an Independent Data Monitoring Committee to assess safety and a Clinical Event Adjudication Committee to adjudicate prespecified safety end points. The Independent Data Monitoring Committee also makes recommendations for continuing, modifying, or stopping the study based upon the totality of evidence provided by ongoing reviews of safety, efficacy, and study conduct data.

This trial is sponsored by MyoKardia with Pharmaceutical Product Development (Morrisville, North Carolina), serving as the clinical research organization. Duke Clinical Research Institute (Durham, North Carolina) performs data coordination for the Independent Data Monitoring Committee, Steering Committee management, and statistical services, as described below. EXPLORER-HCM fully adheres to the ethical principles of the Declaration of Helsinki and the specifications of the International Conference on Harmonization and Good Clinical Practice. Written informed consent will be obtained from each participant before participation in any study-related procedures.

Study Population

The EXPLORER-HCM study population consists of adults with symptomatic oHCM. Full inclusion/exclusion criteria are summarized in Table I in the Data Supplement. Key inclusion criteria are age ≥18 years; diagnosis with oHCM consistent with current American College of Cardiology Foundation/American Heart Association and European Society of Cardiology guidelines (unexplained LV hypertrophy with maximal LV wall thickness of ≥15 mm [or ≥13 mm with family history of HCM]); and at least one peak LVOT gradient ≥50 mm Hg (at rest or with provocation [Valsalva maneuver or post exercise]); in addition, Valsalva LVOT gradient ≥30 mm Hg at baseline was required for subsequent dose titration; LVEF ≥55%; New York Heart Association (NYHA) functional class II or III; and able to perform an upright cardiopulmonary exercise testing (CPET) with a respiratory exchange ratio of ≥1.0 at screening. Key exclusion criteria include history of syncope or sustained ventricular tachyarrhythmia with exercise within 6 months before screening, atrial fibrillation present at screening, and treatment or planned treatment with disopyramide, ranolazine, or a combination of β-blockers and calcium channel blockers.

Study Treatment

Planned study duration is ≈43 weeks and comprised of 3 periods: (1) screening: up to 5 weeks (day −35 to day −1); (2) double-blind treatment: 30 weeks (day 1 [randomization] to week 30/end-of-treatment); (3) post-treatment follow-up: 8 weeks (week 30/end-of-treatment to week 38/end-of-study; Figure). Mavacamten doses being evaluated in the study include 2.5, 5, 10, and 15 mg. β-blockers or calcium channel blockers can be continued if started before trial participation, but concomitant disopyramide use is not allowed.

At the start of the 30-week treatment period (day 1), participants are randomized 1:1 via an interactive response system (IXRS) to receive double-blind oral, once-daily treatment with mavacamten (5 mg) or matching placebo, followed by subsequent scheduled dose adjustments, performed as described below. Randomization is stratified based upon NYHA functional class (II or III), current treatment with β-blocker, ergometer type (treadmill or bicycle), and consent for the cardiovascular magnetic resonance (CMR) imaging substudy.

During the 8-week post-treatment period, study drug is discontinued. Participants return for key assessments at week 38, after which they may elect to consent and continue into the mavacamten long-term extension study (MAVA-LTE) (https://www.clinicaltrials.gov; Unique identifier: NCT03723655), where all participants receive mavacamten while remaining blinded to dose and original treatment assignment. Participants in MAVA-LTE begin on 5 or 2.5 mg mavacamten per day as determined by IXRS programmed protocol criteria and undergo dose titration based on LVEF and Valsalva LVOT gradient measures from site-read echocardiograms at weeks 4, 8, and 12. Data from MAVA-LTE will complement results from the EXPLORER titration and dose adjustment algorithm described below to ultimately arrive at a clinically feasible and safe dosing strategy.

Titration and Dose Adjustment

The double-blind treatment period includes a 2-step, blinded dose titration scheme with opportunities to increase dose at week 8 and week 14. This strategy is designed to achieve a safe and effective dose for each individual. Participants are started on 5 mg of oral, once-daily mavacamten, or matching placebo on day 1. All dose titrations are blinded and programmed via the IXRS system to remain unchanged, be reduced, or be increased, as guided by core laboratory determination of LVEF, Valsalva LVOT gradient, pharmacokinetics, and QT interval with Fridericia correction (Table II in the Data Supplement).

The dosing scheme for EXPLORER-HCM was designed to avoid plasma drug concentration levels exceeding 1000 ng/mL and to maintain levels within the 350 to 700 ng/mL range. The pharmacokinetics modeling simulations performed for the study, which assumed 15 mg/day as the highest dose, projected that ≈85% of participants would achieve the target concentration range (350–700 ng/mL), with 15% falling below this range.

Prespecified criteria for temporary discontinuation of study drugs are based on safety parameters of LVEF (<50%), pharmacokinetics (>1000 ng/mL), and QT interval with Fridericia correction (>15% increase from baseline). If ≥1 criteria are met and study drug is discontinued, participants return to the site in 2 to 4 weeks for a reassessment visit. If the parameter(s) return to acceptable range, the study drug is restarted at a reduced dose 2 to 4 weeks after the reassessment visit (total time 4–6 weeks). Sham discontinuation alerts are also programmed in the IXRS system to maintain blinding. Each of the parameters described above (eg, LVEF, QT interval with Fridericia correction, and pharmacokinetics) are analyzed and reported by core laboratories, with the results integrated into IXRS to manage dose adjustments in the double-blind environment as specified in the study protocol.

Study Objectives and Efficacy End Points

Primary End Point

The primary end point of EXPLORER-HCM is a composite functional end point at week 30 of treatment with mavacamten versus placebo, defined as achieving: (1) an improvement of at least 1.5 mL/kg/min in peak oxygen consumption (pVO_2) as determined by CPET and a reduction of ≥1 NYHA functional class; or (2) an improvement of at least 3.0 mL/kg/min in pVO_2 with no worsening in NYHA functional class (Table). Data from baseline and week 30 will be used for analysis.

Rationale for the Primary End Point

Obstructive HCM is a dynamic condition associated with substantial symptomatic burden.[5] Reduced functional capacity with exercise limitation is common, reflecting the consequences of dynamic obstruction, diastolic abnormalities, and impaired myocardial energetics.[1–4] Because the rates of mortality, stroke, transplantation, and hospitalization are low, it is not feasible to power randomized trials in HCM to identify benefit for such clinical end points. Thus, the primary goal of EXPLORER-HCM is to test whether mavacamten can improve symptom burden and functional capacity— issues of great importance to patients and providers. As described above, this will be assessed with 2 independent indicators: NYHA functional class and pVO_2. By doing so, we leverage the established objectivity and prognostic relevance of pVO_2 while also including a standard measure of symptom burden that is meaningful to patients. We anticipate that the combined interrogation of these 2 parameters will provide complementary assessments of the impact of treatment on exercise capacity, symptoms, and functional status. In addition, this design is also intended to attenuate a potential placebo response rate if assessing NYHA class alone (up to ≈30%).[19]

NYHA functional class has been widely used in clinical trials as an outcome measure to assess how HF impacts physical activities. pVO_2, measured by CPET, is a direct, objective, and reproducible measure of exercise capacity,[20] which has been shown to correlate with NYHA functional class, PROs, and quality of life in HCM.[20] Data from the large, multicenter Sarcomeric Human Cardiomyopathy Registry indicated that pVO_2 is an independent predictor of clinically significant cardiac events and death in patients with HCM.[21]

Published studies in HF and HCM established minimally important change thresholds for pVO_2. The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study showed that even modest increases in pVO_2 (≈1 mL/[kg·min]) were associated with better clinical outcomes in patients with chronic HF, comparable to values >1 mL/kg/min.[22] Likewise, an increase of 1 mL/kg/min was shown to represent a clinically relevant threshold of improvement in HCM, associated with reduced risk of all-cause mortality or cardiac transplantation.[23,24] Furthermore, based on previous studies assessing invasive septal reduction therapy, an increase of 3 mL/kg/min in pVO_2 was considered to have clinical relevance in oHCM.[25]

In the phase 2 PIONEER-HCM trial, treatment with mavacamten led to a mean increase in pVO_2 of 3.5 mL/kg/min in participants who discontinued β-blockers and received 15 to 20 mg per day of mavacamten, and a mean increase of 1.7 mL/kg/min in participants who continued using β-blockers and received a maximum of 5 mg mavacamten per day.[18] Importantly, increases in pVO_2 were accompanied by improvements in NYHA functional class, Numerical Rating Scale dyspnea score, LVOT gradients, ventilatory efficiency, and serum NT-proBNP (N-terminal pro B-type natriuretic peptide) concentration.

Secondary and Exploratory End Points

Secondary end points include analyses of change from baseline to week 30 for mavacamten versus placebo in the following parameters: postexercise LVOT gradient, pVO_2, NYHA class, and 2 PROs: health-related quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire, and HCM core symptoms (shortness of breath subscore) as assessed by a newly developed instrument, the Hypertrophic Cardiomyopathy Symptom Questionnaire (Table and Methods in the Data Supplement). The final hierarchical order of secondary end points is dictated by the Statistical Analysis Plan.

Exploratory end points aim to characterize the change from baseline to week 30 in multiple parameters assessing cardiac function, hemodynamics, myocardial structure, and cardiac rhythm for mavacamten versus placebo (Table).

Safety End Points

Safety is assessed throughout the study, and safety end points are listed in the Table. The following safety end points are adjudicated by the Clinical Event Adjudication Committee: death, stroke, acute myocardial infarction, all hospitalizations (cardiovascular and noncardiovascular), HF events (includes HF hospitalizations and emergency room/urgent outpatient visits for HF), atrial fibrillation/flutter (new from screening), implantable cardioverter-defibrillator therapy, resuscitated cardiac arrest, ventricular tachyarrhythmias (includes ventricular tachycardia and ventricular fibrillation). The Independent Data Monitoring Committee meets regularly for safety reviews and may be unblinded to treatment allocation and all safety and efficacy data. Safety is monitored by medical history, physical examination, ECG, observed and participant-reported adverse events, pregnancy testing, and safety laboratory results. Any abnormal findings judged by the investigator to be clinically important are recorded as an adverse event or serious adverse event.

Study Procedures

The study includes 12 visits with serial assessment of cardiac structure, function, and symptoms using echocardiography, 12-lead ECG, NYHA functional class, and laboratory testing,

Table. Study End Points

Primary composite functional end point	Clinical response defined as achieving: (1) an improvement of 1.5 mL/kg/min or more in pVO_2 as determined by CPET, and a reduction of one or more class in NYHA functional class, at the end of wk 30 dosing period; OR (2) an improvement of 3.0 mL/kg/min or more in pVO_2 with no worsening in NYHA functional class
Secondary efficacy end points	Change from baseline to week 30 in:
	Postexercise LVOT peak gradient
	pVO_2 as determined by CPET
	Proportion of patients with at least 1 class improvement in NYHA functional class from baseline to week 30
	Change from baseline to week 30 in:
	Patient-reported health-related quality of life as assessed by the KCCQ score
	Patient-reported severity of HCM symptoms as assessed by the HCMSQ shortness of breath subscore
Exploratory efficacy end points	Proportion of patients achieving:
	Postexercise LVOT peak gradient <50 mm Hg or <30 mm Hg at week 30
	Changes from baseline to week 30 in:
	Echocardiographic indices of cardiac structure (LV wall thickness) as well as systolic and diastolic function
	Cardiac biomarkers (NT-proBNP, hs-cardiac-troponin-I)
	Cardiac rhythm patterns
	Daily step count and other accelerometer parameters
	HCM risk prediction model
Safety	Incidence of:
	Major adverse cardiac events (death, stroke, acute myocardial infarction)
	Hospitalizations (both CV and non-CV) and HF events
	AF/flutter (new since screening)
	ICD therapy and resuscitated cardiac arrest
	Ventricular tachyarrhythmias (includes VT, VF, and torsades de pointes)
	Syncope and seizures
	Frequency and severity of treatment-emergent adverse events and serious adverse events, and laboratory abnormalities (including trends in NT-proBNP)
CMR substudy end points	Primary end point
	Change from baseline to week 30 in LV mass index
	Secondary end points
	Change from baseline to week 30 in myocardial fibrosis as measured by late gadolinium enhancement
	Changes from baseline to week 30 in cellular hypertrophy, left atrial volume and function, and LV function

AF indicates atrial fibrillation; CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise testing; CV, cardiovascular; HCM, hypertrophic cardiomyopathy; HCMSQ, HCM Symptom Questionnaire; HF, heart failure; ICD, implantable cardioverter-defibrillator; KCCQ, the Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; pVO_2, peak oxygen consumption; VF, ventricular fibrillation; and VT, ventricular tachycardia.

including biomarkers (eg, NT-proBNP; Figure [B] and Table III in the Data Supplement). CPET and recording of daily physical activity using a wrist-worn accelerometer are performed at baseline and end of treatment. Cardiac rhythm monitoring with 48-hour Holter is performed at the beginning, middle, and end of treatment. PROs are administered to interrogate quality of life and symptom burden at home and during clinic visits per-protocol (Methods in the Data Supplement). Participants with implantable cardioverter-defibrillator will also have their implantable cardioverter-defibrillator interrogated at baseline, weeks 12 and 30.

Because echocardiographic data are essential for dose titration and assessment of safety and efficacy, all echocardiographic studies are performed by study-certified sonographers at clinical sites, following a study-specific protocol, and analyzed at the Cardiovascular Imaging Core Laboratory (CICL, Boston, MA). Due to its importance in the primary end point assessment, CPET is also performed by study-certified technicians, following a study-specific protocol and analyzed at the Cardiovascular Metabolic Research Institute core laboratory, Palo Alto, CA. ECG and Holter data are also read by a dedicated core laboratory (eResearch Technology, Inc, ERT, Philadelphia, PA).

Additional subgroup analyses will evaluate associations between pharmacogenomic markers of metabolism and pathogenic/likely pathogenic sarcomere gene variation on clinical response, using results from prior clinical HCM genetic testing or a 58-gene cardiomyopathy panel (Invitae, San Francisco, CA) for participants who consent to this option.

CMR Substudy

The goal of the CMR substudy is to evaluate the effect of mavacamten on myocardial mass, structure, and function (Table). For substudy participants, the CMR examination is performed on day 1 (up to 5 days prior) and week 30 (up to 5 days

prior) and submitted to the CMR core laboratory at Brigham and Women's Hospital. The primary end point of the CMR substudy is change from baseline to week 30 in the LV mass index. Change in the degree of myocardial fibrosis as measured by late gadolinium enhancement and change in cardiac chamber volume and function will also be explored.

Statistical Considerations

The study was designed to randomize a minimum of 220 participants, with 110 in each of the 2 treatment groups. Randomization was stratified by NYHA functional class (II or III), current treatment with β-blocker (yes or no), type of ergometer (treadmill or exercise bicycle), and consent for the CMR substudy (yes or no). This sample size is estimated to provide adequate power to determine the superiority of mavacamten in improving pVO_2 and NYHA functional class relative to placebo. The power calculation is derived, assuming a clinically meaningful difference of 25% between mavacamten and placebo participants in achieving the primary composite functional end point. In the phase 2 PIONEER-HCM study, ≈50% of the participants treated with mavacamten achieved the EXPLORER-HCM composite functional end point by the end of the 12-week treatment period. Assuming that a similar percentage of EXPLORER-HCM participants in the active treatment arm and 25% in placebo arm will achieve the primary end point at the end of 30-week dosing period, the sample size of 110 participants per arm will provide 96% power at 2-sided 5% statistical significance level.

The primary analysis will be conducted through the 30-week treatment period based on the intention-to-treat population, including all randomized participants, regardless of whether they receive study drug, with analyses conducted according to the randomized treatment assignment. To minimize false discovery among the secondary end points, appropriate methods will be employed to control the familywise Type 1 error in multiple testing. Once all participants have completed their week 38/end-of-study visit, all data will be cleaned and locked. Analysis of these data will be used to inform study objectives relating to follow-up safety and reversibility of drug effect. SAS Version 9.4 or higher will be used for statistical analyses.

No imputation of missing data will be done in the study. For mixed model repeated measure analyses, missing data are handled by the model implicitly. For responder analyses, if the participant's responder status cannot be determined due to missing data, the participant will be treated as nonresponder. For other analyses, missing data will not be included in the analyses.

Statistical analyses will be performed per a prespecified Statistical Analysis Plan by the sponsor, with an independent analysis of primary and secondary end points by Duke Clinical Research Institute biostatistics.

Trial Status

As of August 14, 2019, study enrollment was completed with 251 participants randomized, including 38 participants in the CMR imaging substudy. Screening was stopped when it was estimated, based on the screen fail rate, that target enrollment of 220 participants would be achieved ±15%.

SUMMARY

Advances in our understanding of the molecular mechanisms of HCM have led to the development of mavacamten—a novel myosin inhibitor that directly targets the underlying pathophysiology of HCM. EXPLORER-HCM is a pivotal, first-in-class clinical trial investigating the efficacy of mavacamten in improving symptoms and functional capacity in oHCM. It is also the most comprehensive, most geographically diverse, and adequately powered randomized clinical trial conducted to date in HCM.

The comprehensive clinical and safety data collected in this trial will provide the opportunity to not only assess mavacamten efficacy but also to advance understanding of symptoms and hemodynamic abnormalities associated with oHCM. oHCM is a highly dynamic condition, often with day-to-day variability in symptoms.[1,2] This, compounded by the relatively low event rates seen in HCM, has resulted in challenges with the traditional single end point approach used in clinical trials. Published data in HF and HCM,[22–24] analyses of the Sarcomeric Human Cardiomyopathy Registry (SHaRe) cohort,[21] and insights from the phase 2 PIONEER-HCM trial[18] informed the selection of the primary end point for EXPLORER-HCM as a responder analysis, comprised of changes of pVO_2 and NYHA functional class. This approach leverages the established objectivity and prognostic relevance of pVO_2[20] while also assessing subjective limitation and quality of life. Improving symptom burden and functional capacity are critical objectives and a major unmet need in a disease characterized by relatively low mortality but substantial impact on daily activities and well-being.

An array of secondary and exploratory end points will further dissect out the finer details regarding the effect of mavacamten on oHCM, including symptoms, functional capacity, LVOT gradient, serum biomarkers of myocardial injury and hemodynamic stress, and cardiac structure. Multiple participant-generated data elements will provide a multidimensional insight into symptom burden and participant experience, including wrist-worn accelerometry to measure activity, and a novel HCM-specific PRO tool (Hypertrophic Cardiomyopathy Symptom Questionnaire). By involving a patient representative in our Steering Committee to specifically advise on the patient perspective, we hope to have incorporated aspects of study design that clinicians and scientists cannot achieve in isolation.

Mavacamten causes a dose-dependent reduction in LVEF, and developing a safe dosing strategy was of paramount importance. Pharmacokinetics- and pharmacodynamic-guided dose titration in EXPLORER-HCM was designed to identify the lowest effective dose to reduce LVOT gradient (at rest and with provocation) while maintaining normal LVEF. We are also testing a clinical echocardiography-guided dose titration protocol in the long-term extension study, MAVA-LTE, to develop a well tolerated,

effective strategy that can be implemented in the outpatient setting (in contrast to the echocardiographic core laboratory-guided dose titration during the study period). Lastly, the safety data from EXPLORER-HCM will be aggregated with the ongoing PIONEER-OLE and MAVA-LTE extension studies to gain the maximal possible experience regarding the safety of mavacamten.

In summary, we anticipate that EXPLORER-HCM will provide evidence for the first potential disease-specific treatment for oHCM and launch a new era of targeted drug development for patients with cardiovascular diseases.

ARTICLE INFORMATION

Affiliations

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Disclosures

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