Mavacamten for Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy: a Double-blind, Randomized, Placebo-controlled Phase 3 Trial

Iacopo Olivotto, MD, Artur Oreziak, MD, Roberto Barriales-Villa, MD, Theodore P Abraham, MD, Ahmad Masri, MD, Pablo Garcia-Pavia, MD, Sara Saberi, MD, Neal K Lakdawala, MD, Matthew T Wheeler, MD, Anjali Owens, MD, Milos Kubanek, MD, Wojciech Wojakowski, MD, Morten K Jensen, MD, Juan Gimeno-Blanes, MD, Kia Afshar, MD, Jonathan Myers, PhD, Sheila M Hegde, MD, Scott D Solomon, MD, Amy J Sehnert, MD, David Zhang, PhD, Wanying Li, PhD, Mondira Bhattacharya, MD, Jay M Edelberg, MD, Cynthia Burstein Waldman, JD, Steven J Lester, MD, Andrew Wang, MD, Carolyn Y Ho, MD, and Daniel Jacoby, MD, on behalf of EXPLORER-HCM Study Investigators

Azienda Ospedaliera Universitaria Careggi and University of Florence, Florence, Italy (I Olivotto MD); 1st Department of Arrhythmia, National Institute of Cardiology, Warsaw, Poland (A Oreziak MD); Unidad de Cardiopatías Familiares, Instituto de Investigación Biomédica de A Coruña (INIBIC), Complexo Hospitalario Universitario de A Coruña, Servizo Galego de Saúde (SERGAS), Universidade da Coruña, A Coruña and Centro de Investigación Biomédica en Red (CIBERCV), Madrid — all in Spain (R Barriales-Villa MD); Division of Cardiology, University of California San Francisco, San Francisco, CA (Prof TP Abraham MD); Knight Cardiovascular Institute, Oregon Health & Science University, Portland, OR (A Masri MD); Department of Cardiology, Hospital Universitario Puerta de Hierro, Madrid, Centro de Investigación Biomédica en Red (CIBERCV), Madrid, and Universidad Francisco de Vitoria (UFV), Pozuelo de Alarcón — all in Spain (P Garcia-Pavia MD); Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI (S Saberi MD); Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA (NK Lakdawala MD, SM Hegde MD, Prof SD Solomon MD, CY Ho MD); Department of Medicine, Division of

Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA (MT Wheeler MD); University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA (A Owens MD); Department of Cardiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic (M Kubanek MD); Division of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland (Prof W Wojakowski MD); Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark (MK Jensen MD); Inherited Cardiac Disease Unit, University Hospital Virgen de la Arrixaca, Murcia, Spain (J Gimeno-Blanes MD); Intermountain Medical Center Heart Institute, Intermountain Medical Center, Murray, UT (K Afshar MD); Division of Cardiology, Veterans Affairs Palo Alto Healthcare System and Stanford University, Palo Alto, CA (Prof J Myers PhD); MyoKardia, Inc., Brisbane, CA (AJ Sehnert MD, D Zhang PhD, W Li PhD, M Bhattacharya MD, JM Edelberg MD); HCMBeat, Los Angeles, CA (CB Waldman JD); Department of Cardiovascular Diseases, Mayo Clinic Arizona, Phoenix, AZ (SJ Lester MD); Duke University School of Medicine, Durham, NC (Prof A Wang MD); and Department of Internal Medicine, Section of Cardiovascular Medicine, Yale University, New Haven, CT (D Jacoby MD).

Correspondence to:

Prof. Iacopo Olivotto

Cardiomyopathy Unit

Azienda Ospedaliera Universitaria Careggi

University of Florence

Largo Brambilla 1, 50134, Florence, Italy

+39-055-7945138

iacopo.olivotto@unifi.it

RESEARCH IN CONTEXT

Evidence before this study

The gaps in therapeutic options for hypertrophic cardiomyopathy (HCM) are well recognized. Several agents, such as perhexiline, trimetazidine, ranolazine, eleclazine, spironolactone, valsartan, and losartan, have demonstrated no or limited efficacy in prospective trials. In patients with obstructive HCM (oHCM; also known as HOCM) guideline-recommended pharmacological therapy is administered on an empirical basis, in the absence of randomized controlled trials, and includes beta-blockers or non-dihydropyridine calcium channel blockers. Disopyramide represents an additional agent in individuals refractory to first-line therapy. While beneficial for some patients, use of these drugs is limited by side effects, and often fails to provide optimal control of left ventricular outflow gradients and symptoms, leaving an unmet burden of disease in many patients with oHCM.

Mavacamten, a first-in-class targeted inhibitor of cardiac myosin, has reduced hypercontractility, eliminated systolic anterior motion (SAM) of the mitral valve, and relieved left ventricular outflow tract (LVOT) obstruction in a mouse model of HCM. Moreover, mavacamten treatment appeared to suppress the development of ventricular hypertrophy, cardiomyocyte disarray, and myocardial fibrosis in mice. In the phase 2 PIONEER-HCM study, treatment of patients with oHCM led to improvements in post-exercise LVOT gradients, exercise capacity, and symptoms, and was generally well tolerated, with the majority of adverse effects being mild or moderate, self-limiting, and unrelated to the study drug.

Added value of this study

This pivotal phase 3 EXPLORER-HCM trial is the largest placebo-controlled randomized clinical trial conducted to date in HCM. The majority of patients in the active treatment and placebo arms continued to receive currently available background HCM therapy except disopyramide

(i.e., monotherapy with beta-blockers or non-dihydropyridine calcium channel blockers). The primary composite functional end point as well as sequential secondary end points were designed and discussed with HCM experts, patients, and regulatory authorities to comprehensively assess treatment benefits for oHCM. The end points comprise measures of symptoms and functional capacity as well as LVOT obstruction and health status. After 30 weeks of treatment with mavacamten, there was a significant benefit across the composite primary end point, its components, and all secondary end points, as well as relevant improvements in patient-reported measures and reductions in biomarkers of cardiac wall stress and injury. Treatment with mavacamten was generally well tolerated and the safety profile was comparable to placebo. Seven patients on mavacamten (3 patients during the 30-week treatment and 4 patients at the end of treatment) and 2 on placebo experienced a transient decrease in LVEF to <50%. All completed the study.

Implications of all the available evidence

Results from this phase 3 trial demonstrate significant efficacy of the first targeted pharmacologic therapy designed specifically to address the primary underlying pathophysiologic basis of oHCM. Treatment with mavacamten led to clinically meaningful improvements in hemodynamic status, functional capacity, and subjective well-being. An ongoing, long-term extension of the study will provide further evidence for clinical benefit and safety of mavacamten in the treatment of oHCM over 5 years.

SUMMARY

Background: Cardiac muscle hypercontractility is a key pathophysiologic abnormality in hypertrophic cardiomyopathy (HCM), and a major determinant of dynamic left ventricular outflow tract (LVOT) obstruction. Available pharmacological options for HCM are limited and non-disease–specific. We assessed the efficacy and safety of mavacamten, a first-in-class cardiac myosin inhibitor, in symptomatic obstructive HCM (oHCM).

Methods: In this phase 3, randomized, double-blind trial, HCM patients with LVOT gradient ≥50 mm Hg and New York Heart Association (NYHA) class II-III symptoms received mavacamten (starting at 5 mg) or placebo for 30 weeks. The primary end point was 1) ≥1·5 ml/kg/min increase in peak oxygen consumption (pVO_2) and ≥1 NYHA class improvement ***OR*** 2) ≥3·0 ml/kg/min pVO_2 increase without NYHA class worsening. Secondary end points assessed changes in post-exercise LVOT gradient, pVO_2, NYHA class, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS), and HCM Symptom Questionnaire Shortness-of-Breath subscore (HCMSQ-SoB). This trial is registered with ClinicalTrials.gov, NCT03470545.

Findings: Forty-five of 123 (36·6%) patients on mavacamten versus 22 of 128 (17·2%) on placebo achieved the primary end point (difference, +19·4%; 95% confidence interval [CI], 8·7 to 30·1; p=0·0005). Patients on mavacamten achieved greater reduction versus placebo in post-exercise LVOT gradient (–36 mm Hg [95% CI, –43·2 to –28·1]; p<0·0001), greater increase in pVO_2 (+1·4 mL/kg/min [95% CI, 0·6 to 2·1]; p=0·0006), and improved symptom scores (KCCQ-CSS [+9·1; 95% CI, 5·5 to 12·7], HCMSQ-SoB [–1·8; 95% CI, –2·4 to –1·2]; p<0·0001). Thirty-four percent more mavacamten-treated patients improved ≥1 NYHA class (95% CI, 22·2 to 45·4; p<0·0001). Safety and tolerability were comparable to placebo.

Interpretation: Treatment with mavacamten improved exercise capacity, LVOT obstruction, symptoms, and health status in oHCM patients. The results of this pivotal trial support a role for disease-specific treatment in HCM.

Funding: MyoKardia

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a myocardial disorder characterized by primary left ventricular (LV) hypertrophy.[1,2] This complex disease can be broadly defined by pathologically enhanced cardiac myosin-actin interactions, with core pathophysiologic features that include hypercontractility, diastolic abnormalities, and dynamic left ventricular outflow tract (LVOT) obstruction.[2-4] Patients with obstructive HCM (oHCM; also known as HOCM) are often symptomatic and may experience atrial fibrillation, heart failure, and malignant ventricular arrhythmias.[2,5] Current treatment for oHCM focuses on symptomatic relief using beta-blockers, non-dihydropyridine calcium channel blockers, and disopyramide.[6-9] However, these nonspecific agents are often inadequate or poorly tolerated,[10] fail to address the underlying molecular mechanisms of HCM, and do not modify natural history. Invasive septal reduction therapy (SRT), including surgical septal myectomy and alcohol septal ablation, can effectively help patients with drug-refractory symptoms,[6,7] but carries risks inherent to invasive procedures and requires expertise that is not universally available.[11-13] Thus, developing effective pharmacological therapy for oHCM is an important unmet need.

Mavacamten is a first-in-class, small molecule, selective allosteric inhibitor of cardiac myosin-ATPase specifically developed to target the underlying pathophysiology of HCM by reducing actin-myosin cross-bridge formation, [14,15] thereby reducing contractility and improving myocardial energetics.[16] In preclinical and early clinical studies, treatment with mavacamten successfully relieved LVOT gradients and improved parameters of LV filling.[15,17-20] In the phase 2 open-label PIONEER-HCM study (NCT02842242), mavacamten was well tolerated and significantly reduced post-exercise LVOT gradients in oHCM.[19] Treatment was also associated with improvements in exercise capacity and New York Heart Association (NYHA) functional class. Based on these results, the pivotal EXPLORER-HCM trial (NCT03470545) was

conducted to assess the efficacy and safety of mavacamten for targeted medical treatment of oHCM.

METHODS

Trial Design and Oversight

EXPLORER-HCM was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. The trial design was published previously,[21] and the protocol was approved by site institutional review boards at 68 sites in 13 countries and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided informed consent. The trial was overseen by a Steering Committee, independent data monitoring committee, and a clinical event adjudication committee. Data were collected, managed, and analyzed by the sponsor according to a predefined statistical analysis plan, and results were independently validated by the Duke Clinical Research Institute. Analysis outputs were provided to the investigators/authors who were involved in data interpretation. Both the authors and sponsor employees participated in data analysis and vouch for the accuracy and completeness of the data and fidelity of the trial to the final protocol. The first draft of the manuscript was written by the first author and members of the Steering Committee. All authors critically reviewed and approved the manuscript.

Patients

The inclusion and exclusion criteria were primarily developed to prioritize safety and include a patient population adequately representative of a real-world symptomatic oHCM. Eligible patients were at least 18 years old with a diagnosis of oHCM (unexplained LV hypertrophy with maximal LV wall thickness of ≥15 mm [or ≥13 mm if familial HCM]); peak LVOT gradient at least 50 mm Hg at rest, after Valsalva maneuver, or post-exercise; LV ejection fraction (LVEF) at

least 55%; and NYHA class II or III symptoms. Patients must have been able to safely perform upright cardiopulmonary exercise testing (CPET). Key exclusion criteria included a history of syncope or sustained ventricular tachyarrhythmia with exercise ≤6 months prior to screening, QT interval corrected using Fridericia's formula (QTcF) >500 ms, paroxysmal or intermittent atrial fibrillation present on screening electrocardiogram, and persistent or permanent atrial fibrillation not on anticoagulation for ≥4 weeks and/or not adequately rate-controlled within 6 months prior to screening. Patients who underwent SRT more than 6 months prior to screening were enrolled if otherwise eligible.[21] Patients were allowed to continue standard HCM medical therapy except disopyramide (for safety reasons), including monotherapy with beta-blockers or calcium channel blockers, if dosing remained stable for at least 2 weeks prior to screening and no changes were anticipated during the study.

Procedures

Patients were randomized 1:1 to receive once-daily treatment with mavacamten (starting dose 5 mg) or placebo for 30 weeks (end of treatment). Randomization was stratified by NYHA class (II or III), current beta-blocker use (yes/no), ergometer type (treadmill or bicycle), and consent for cardiovascular magnetic resonance imaging substudy (yes/no). Mavacamten dose adjustments occurred per a blinded dose titration scheme at weeks 8 and 14. Individualized doses of 2·5, 5, 10, or 15 mg were ultimately administered to achieve target reduction in LVOT gradient less than 30 mm Hg and a mavacamten plasma concentration between 350 and 700 ng per mL.[21] Prespecified criteria for temporary discontinuation of study drug, including LVEF less than 50%, are described in the Supplementary Appendix.

Patients were evaluated every 2 or 4 weeks during the 30-week treatment period. CPET and post-exercise transthoracic echocardiography (TTE) were performed at screening and week 30. Resting TTE, electrocardiograms, safety laboratory testing, and determination of mavacamten

plasma concentration were performed serially throughout the study. Results were determined by central core laboratories blinded to treatment assignment.[21] Genetic testing for a 60-gene HCM genetic testing panel (if consent provided) was also performed.

End points

The primary end point was a composite to assess clinical response at week 30 compared with baseline, defined as achieving 1) at least 1·5 ml per kg per minute improvement in pVO_2 and at least one NYHA class reduction **OR** 2) at least 3·0 ml per kg per minute improvement in pVO_2 and no worsening of NYHA class.

Secondary end points included change from baseline to week 30 in post-exercise LVOT gradient, pVO_2, proportion of patients with at least one NYHA class improvement, and measures of patient-reported outcomes (PROs), including Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS) and HCM Symptom Questionnaire Shortness-of-Breath (HCMSQ-SoB) subscore.[21] These were tested and Type-I error controlled in hierarchical order (sequence as indicated above) upon achieving significance in the primary end point (with two-tailed $p<0·05$ required to proceed). Additional prespecified exploratory end points assessed complete response (all LVOT gradients less than 30 mm Hg and NYHA class I), proportion of patients with improvement in LVOT gradients, and serum concentrations of N-terminal pro B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin I (hs-cTnI). Prespecified safety end points included frequency and severity of treatment-emergent adverse events and serious adverse events.

Statistical Analysis

The study was designed to randomize a minimum of 220 patients. The sample size was estimated to provide 96% power to detect a 25% difference between treatment arms in the primary end point, at a two-sided $p<0.05$.[21]

All randomized patients received at least one dose of study drug. Efficacy and safety analyses were based on this population, and efficacy analyses followed intention-to-treat principle. Missing data were not imputed unless prespecified in the statistical analysis plan. The missing NYHA class at week 30 were imputed with week 26 value, if available, in the case of primary end point and NYHA response. Patients with non-evaluable primary end point and NYHA secondary end point were considered as nonresponders, whereas LVOT gradient and pVO_2 were analyzed with all available data without imputation performed, and PROs were analyzed with all available data using mixed-effects model repeated measures, which implicitly handles the missing data in the patients that have baseline and ≥1 post-baseline value in the analysis (additional details provided in Supplementary Appendix). The primary efficacy end point and improvement in NYHA class were analyzed using the Cochran–Mantel–Haenszel test for stratified categorical data. Continuous variables in secondary efficacy end points were compared between treatment groups by analysis of covariance (ANCOVA) or by mixed model for repeated measurements. Efficacy was also assessed in prespecified subgroups based on baseline demographic and disease characteristics. Safety data were analyzed using descriptive statistics without statistical inference. SAS version 9.4 was used for statistical analyses. Details are provided in the Supplementary Appendix and Statistical Analysis Plan.

This trial is registered with ClinicalTrials.gov, NCT03470545.

Role of funding source

The study was funded by MyoKardia. MyoKardia co-authors were involved in trial design, statistical analysis, data interpretation, and were involved in reviewing the manuscript, in

collaboration with academic co-authors. All authors had access to the study data and had final responsibility for the decision to submit for publication.

RESULTS

Patient Characteristics

From May 2018 to August 2019, 429 adults with oHCM were screened, of which 251 (59%) were enrolled and randomized to mavacamten (123 patients) or placebo (128 patients) (figure S1, Supplementary Appendix). Enrolled patients showed the expected features of oHCM cohorts in terms of mean LV wall thickness, rates of positive HCM family history, and rate of ICD implantation (table 1). Mean age was 58.5 years in both treatment arms, and the study included a broad age range, with 21% of patients aged <50 years, 45% aged 50-64 years, and 34% aged ≥65 years. Baseline characteristics were balanced between groups, except for a smaller proportion of males and patients with a history of atrial fibrillation, and higher baseline NT-proBNP level in the mavacamten arm (table 1). Most patients (73%) had NYHA class II symptoms at baseline, and almost all (92%) were on background beta-blocker or calcium channel blocker therapy – only 4 patients in the mavacamten group and 16 in the placebo group were not on background HCM therapy. Almost all patients were compliant and maintained their background HCM therapy unchanged throughout the study or required minor adjustments (16 patients in the mavacamten arm and 10 patients in the placebo arm adjusted dose of beta-blocker therapy). Nineteen patients had prior SRT.

Overall, 244 (97·2%) patients completed treatment. Five patients discontinued treatment prematurely (figure S1, Supplementary Appendix); three due to adverse events (two on mavacamten [atrial fibrillation and syncope], one on placebo [sudden death]); two patients withdrew (one on mavacamten, one on placebo). No patients were lost to follow-up.

Efficacy

Primary End Point

At end of treatment, 36·6% (45 of 123) of patients on mavacamten achieved the primary end point, compared with 17·2% (22 of 128) on placebo (+19·4%, 95% confidence interval [CI] 8·7 to 30·1; p=0·0005) (table 2). Furthermore, 20·3% of patients on mavacamten had both at least 3·0 ml per kg per minute increase in pVO_2 and at least one class improvement in NYHA class, versus 7·8% on placebo (difference, +12·5% [95% CI, 4·0 to 21·0]).

Secondary End Points

Mavacamten treatment was associated with significant improvement in all secondary end points compared with placebo (table 2), with patients showing reduced LVOT gradient, increased pVO_2, and improved symptoms as assessed by physicians (NYHA class) or by themselves (PROs). Peak post-exercise LVOT gradient decreased from 86 mm Hg (95% CI, 79·5 to 91·8) to 38 mm Hg (95% CI, 32·3 to 44·0) with mavacamten, while for placebo the change was from 84 mm Hg (95% CI, 78·4 to 91·0) to 73 mm Hg (95% CI, 67·2 to 79·6) (figure 1A), demonstrating a greater reduction by 36 mm Hg with mavacamten (95% CI, −43·2 to −28·1; p<0·0001) (table 2).

In parallel, patients on mavacamten showed a greater increase in pVO_2 by 1·4 ml per kilogram per minute on average compared with placebo (95% CI, 0·58 to 2·12; p=0·0006). Also, 65·0% (80 of 123) of mavacamten-treated patients had at least one NYHA class improvement versus 31·3% (40 of 128) on placebo (difference, 33·8% [95% CI, 22·2 to 45·4]; p<0·0001). The proportion of patients who achieved NYHA class I status was 50% (61 of 123) with mavacamten and 21% (27 of 128) with placebo (figure 2). Mavacamten treatment was also associated with improved PROs. Both KCCQ-CCS (positive change better) and HCMSQ-SoB (negative change

better) scores improved more with mavacamten than with placebo (+9·1 [95% CI, 5·5 to 12·7], −1·8 [95% CI, −2·4 to −1·2], respectively; p<0·0001 for both comparisons).

Exploratory End Points

Patients treated with mavacamten showed rapid and sustained improvement in resting and Valsalva LVOT gradients compared with placebo (figure 1C-D). Complete response (defined as reduction in all LVOT gradients to less than 30 mm Hg and NYHA class I) was achieved by 27·4% (32 of 117) of patients on mavacamten versus 0·8% (1 of 126) on placebo (+26·6%; 95% CI, 18·3 to 34·8) (table 3). Mavacamten treatment relieved LVOT obstruction (post-exercise gradient less than 30 mm Hg) in 50% more patients (64 of 113 [57%] vs 8 of 114 [7%]; 95% CI, 39·3 to 59·9), and reduced it below the standard threshold for invasive SRT (<50 mm Hg) in 54% more patients (75 of 101 [74%] vs 22 of 106 [21%]; 95% CI, 42·0 to 65·0) compared with placebo (table 3). In contrast to the sharp decline in LVOT gradients, changes in baseline systolic function associated with mavacamten were small: mean reduction in LVEF was –3·9%, versus–0·01% with placebo (difference, –4·0%; 95% CI, –5·5 to –2·5) (figure 1B). Decreases in cardiac biomarkers were similarly rapid and sustained, parallel to the hemodynamic changes observed (figure 1E-F). At week 30 compared with baseline, the reduction in NT-proBNP after mavacamten treatment was 80% greater than for placebo (proportion of geometric mean ratio between the two arms, 0·202 [95% CI, 0·169 to 0·241]); reduction in hs-cTnI was 41% greater (0·589 [95% CI, 0·500 to 0·693]).

Subgroup Analyses

Patients treated with mavacamten showed consistent benefit for the primary end point across prespecified subgroups. We further examined the subgroups of patients receiving versus not receiving background beta-blockade therapy. Importantly, the majority of patients not using beta-blockers were prescribed non-dihydropyridine calcium channel blockers, with very few

patients in each treatment arm taking neither (4 of 123 in the mavacamten group and 16 of 128 in the placebo were not on any background HCM therapy). In patients without concomitant beta-blockade, the effect was greater (29 on mavacamten, 33 on placebo; difference 52·6% [95% CI, 32·9 to 72·2]) versus those on beta-blockers (94 on mavacamten, 95 on placebo; difference 8·7% [95% CI, −3·6 to 21·1]), and this observation remained in a multivariable model after adjusting for baseline covariates (figure 3A). As expected, the mean peak heart rate with exercise tended to be lower for the subgroup of patients using beta-blockers compared with those not using beta-blockers (119 bpm vs 138 bpm, respectively at baseline). Similarly, mean pVO_2, a component of the primary end point, was lower for the beta-blocker subgroup at baseline, and the mean (SD) change at week 30 in pVO_2 was also observed to be lower (1·1 [3·1] ml/kg/min) for patients using beta-blockers compared with (2·2 [3·0] mL/kg/min) for those who were not using beta-blockers. Heart rate independent parameters of CPET, including VE/VCO_2 slope, showed improvements with mavacamten treatment compared to placebo irrespective of beta-blocker use. The VE/VCO_2 slope change from baseline at week 30 was −2·5 (95% CI, −3·7 to −1·4) in the beta-blocker subgroup, −2·5 (95% CI −4·8 to −0·2) in the non-beta-blocker subgroup, and −2·6 (95% CI, −3·6 to −1·5) in the overall cohort. Rates of improvement by at least one NYHA class with mavacamten treatment were also similar among patients receiving beta-blockers or not (65%). Furthermore, all secondary end points, including change in LVOT gradient (figure 3B), showed consistent benefit for mavacamten across prespecified subgroups, irrespective of beta-blocker use.

Safety

Treatment-emergent adverse events were largely mild (table 4 and table S1, Supplementary Appendix). Eleven serious adverse events were reported by 8·1% of patients on mavacamten versus 20 events reported by 8·6% on placebo (table 4). Serious cardiac adverse events occurred in four patients in the mavacamten group (two atrial fibrillation, two stress

cardiomyopathy; one of these presented at time of a study visit and simultaneously triggered a temporary discontinuation for LVEF less than 50% (table S2, Supplementary Appendix) and four in the placebo group (three with atrial fibrillation, one with atrial fibrillation and congestive heart failure). One patient in the placebo group experienced sudden death. Overall, nine patients (seven on mavacamten and two on placebo) had a transient decrease in LVEF to less than 50%. Five patients (three on mavacamten, two on placebo) had protocol-driven temporary treatment discontinuation for LVEF less than 50% during the 30-week treatment (median LVEF 48%, range 35 to 49%; table S2, Supplementary Appendix). LVEF normalized in all patients, and they resumed treatment and completed the study. Four additional patients on mavacamten had LVEF less than 50% (range 48 to 49%) at week 30 (end-of-treatment visit). LVEF was confirmed to recover to baseline after the 8-week washout period in three patients. The fourth patient experienced a procedural complication and severe LVEF drop following atrial fibrillation ablation during the washout period, followed by partial recovery (to LVEF 50%). Six patients (three on mavacamten, three on placebo) met predefined criteria for changes in QT interval corrected using Fridericia's formula and underwent temporary discontinuation followed by resumption and completion of treatment. There were no temporary discontinuations for mavacamten plasma concentration greater than 1000 ng per ml.

There were no treatment differences noted on laboratory values, ECGs, or vital signs at rest, including no significant changes in heart rate and blood pressure from baseline to week 30 with mavacamten. Continuous cardiac monitoring with 48-hour Holter was conducted at baseline, week 12, and week 26. There were no significant differences during treatment between groups in the number (%) of patients with any atrial fibrillation detected (eg, in each group there were 2 [2%] at week 12 and 4 [3.5%] at week 26). There were similar numbers of patients with episodes of non-sustained ventricular tachycardia (NSVT) detected in each group and at each timepoint (eg, n [%] at baseline: 35 [31%] in the mavacamten group and 35 [30%] in the placebo

group; week 12: 26 [26%] with mavacamten vs 33 [34%] with placebo, and week 26: 24 [21%] with mavacamten vs 23 [20%] with placebo). The summary of episodes per subject at each time point showed 1.5-2 times more episodes in patients on placebo compared to those on mavacamten.

DISCUSSION

In this phase 3 trial in symptomatic oHCM, treatment with mavacamten, a first-in-class cardiac myosin inhibitor, was well tolerated and superior to placebo across the primary and all secondary end points. Mavacamten treatment was effective in reducing LVOT gradients and improving symptoms, exercise performance, and health status in a representative population of patients with oHCM. Significantly more patients treated with mavacamten achieved the primary end point that leveraged both objective (pVO_2) and subjective (NYHA class) assessments of functional capacity and symptoms. Specifically, the proportion improving at least one NYHA class or achieving both primary end point components (at least 3·0 ml per kg per minute pVO_2 increase and at least one NYHA class improvement) was 34% and 13% greater, respectively, than placebo. Findings were consistent across all secondary efficacy end points. Furthermore, complete response, defined as reduction in all LVOT gradients below 30 mm Hg and reaching NYHA class I, was achieved in 27% of patients treated with mavacamten and <1% of patients on placebo, demonstrating that mavacamten may be capable of achieving marked relief of symptoms and LVOT obstruction. Assessing severely symptomatic oHCM patients eligible for SRT, the VALOR-HCM study (NCT04349072) will investigate the ability of mavacamten to provide a non-invasive treatment option reducing the need for surgical or percutaneous procedures.

PRO assessments, using KCCQ-CSS and the novel HCMSQ-SoB specifically designed to evaluate symptomatic burden in HCM patients, showed a favorable impact of mavacamten on subjective well-being. Notably, the improvement seen in KCCQ-CSS scores is several-fold higher than that observed in recent heart failure drug trials and is nearly half of that achieved with placement of a left ventricular assist device for end-stage heart failure.[22,23] Clinical benefit was sustained, achieved in addition to treatment with beta-blockers or calcium antagonists and accompanied by a reduction in serum NT-proBNP and hs-cTnI levels, two predictors of long-term outcome in HCM.[24-26] Similar decreases in cardiac biomarkers were recently reported in the MAVERICK-HCM study in nonobstructive patients, suggesting that gradient reduction may only partially explain the benefit observed in EXPLORER-HCM.[20] These effects require further investigation in a translational setting.[16,18]

Benefit from mavacamten extended across most prespecified subgroups. Not unexpectedly, patients receiving concomitant beta-blockers showed an attenuated effect on the composite primary end point, which includes pVO_2, compared with those not on beta-blockers. We do not believe that the use of beta-blockers attenuates the primary mechanism by which mavacamten works, as is evident by the extent of gradient reduction and other improvements observed. Rather, the observed effect on the primary end point is related to the well-established heart rate limitations on CPET performance.[27,28] Indeed, the mean peak heart rate with exercise tended to be lower for the subgroup of patients using beta-blockers compared with those not using beta-blockers. Improvements in mean pVO_2, were smaller for patients receiving versus not receiving background beta-blockers. However, the change in VE/VCO_2 slope, a heart-rate independent CPET parameter associated with cardiac output,[29] showed similar improvements with mavacamten versus placebo regardless of beta-blocker use, and where the starting mean VE/VCO_2 slope for each was at levels associated with elevated risk for mortality in patients with chronic heart failure (e.g., 33 to 35). In terms of hemodynamic status, symptoms and general

well-being as well as reductions in biomarkers of cardiac wall stress and injury (outcomes and assessments not captured by CPET performance), patients on background beta-blockers benefitted the same as those not on beta-blockers. Further detailed analyses of this finding will be pursued in a future study.

Mavacamten was generally well tolerated, whether used with beta-blockers or calcium channel blockers, and/or in those with prior, unsuccessful SRT or as monotherapy in a small number of patients. Only modest reductions in mean global LV systolic function were observed, with seven patients on mavacamten (four patients at the end of treatment) developing LVEF less than 50%, which normalized after temporary interruption of therapy in all patients and did not impact study completion. Otherwise, the safety profile of mavacamten was comparable to that of placebo. Studies are ongoing to assess the long-term efficacy and safety of mavacamten over 5 years (MAVA-LTE; NCT03723655).

Study limitations include the exclusion of patients on disopyramide and patients with severe (NYHA class IV) symptoms. Both populations will be examined in the VALOR-HCM study. Furthermore, younger patients and non-Caucasians had low representation in this study.

In conclusion, in this first positive randomized phase 3 trial in patients with oHCM, mavacamten treatment improved functional capacity, LVOT gradient, symptoms, and key aspects of health status. The results of this pivotal trial support a role for disease-specific treatment in HCM.

Contributors

IO, AJS, JME, CBW, SJL, AW, DZ, CYH, and DJ designed the trial and study protocol and contributed to data analysis. IO, DJ, and CYH drafted the manuscript. DZ and WL were responsible for statistical analysis. IO, A Oreziak, RB-V, TPA, AM, PG-P, SS, NKL, MTW, A Owens, MK, WW, MKJ, JG-B, KA, JM, SMH, SDS, SJL, AW, CYH, and DJ participated in data

collection. All authors contributed to data interpretation and the critical review and revision of the manuscript, had access to the study data, and had final responsibility for the decision to submit for publication.

Declaration of interests

IO has received grants from MyoKardia, Sanofi-Genzyme, Shire, and Bayer; personal fees from Sanofi-Genzyme, Shire, and Bayer; payments as a consultant from MyoKardia. AM has received grants from Pfizer and Akcea. SS, NKL, A Owens, and SMH report personal fees from MyoKardia, during the conduct of the study. SDS has received grants from MyoKardia, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol-Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis, Lone Star Heart, Mesoblast, National Institutes of Health/National Heart, Lung, and Blood Institute, Novartis, Sanofi Pasteur, Theracos; and personal fees from MyoKardia, Alnylam, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Cytokinetics, Gilead, GlaxoSmithKline, Novartis, Theracos, Akros, Arena, Cardior, Corvia, Daiichi-Sankyo, Ironwood, Merck, Roche, Takeda, Quantum Genetics Cardurion, AoBiome, Janssen, Tenaya, and Cardiac Dimensions. AJS, DZ, WL, MB, JME, and CBW are employees of MyoKardia and report stocks or stock options from MyoKardia. SJL has received payments as a consultant from MyoKardia. AW has received grants from MyoKardia; personal fees from Cytokinetics; and payments as a consultant from MyoKardia. CYH has received payments as a consultant from MyoKardia and Ambry Genetics Corp. DJ has received personal fees from MyoKardia. All other authors declare no competing interests.

Data sharing

Data request may be submitted to MyoKardia via medinfo@myokardia.com and must include a description of the research protocol.

Acknowledgments

The authors would like to thank study coordinators, cardiac sonographers, exercise physiologists, the MyoKardia study team, and especially the patients and their families. Medical writing and editorial support were provided by Kim Fuller, PhD, of SciFluent Communications and were financially supported by MyoKardia.

REFERENCES

1. Marian AJ, Braunwald E. Hypertrophic cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. Circ Res 2017; 121(7): 749-70.
2. Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. N Engl J Med 2018; 379(7): 655-68.
3. Seferovic PM, Polovina M, Bauersachs J, et al. Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2019; 21(5): 553-76.
4. Sequeira V, Bertero E, Maack C. Energetic drain driving hypertrophic cardiomyopathy. FEBS Lett 2019; 593(13): 1616-26.
5. Ho CY, Day SM, Ashley EA, et al. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the sarcomeric human cardiomyopathy registry (SHaRe). Circulation 2018; 138(14): 1387-98.
6. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011; 124(24): e783-831.
7. Authors/Task Force m, Elliott PM, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014; 35(39): 2733-79.
8. Kaltenbach M, Hopf R, Kober G, Bussmann W, Keller M, Petersen Y. Treatment of hypertrophic obstructive cardiomyopathy with verapamil. Heart 1979; 42(1): 35-42.
9. Cohen LS, Braunwald E. Amelioration of angina pectoris in idiopathic hypertrophic subaortic stenosis with beta-adrenergic blockade. Circulation 1967; 35(5): 847-51.

10. Ammirati E, Contri R, Coppini R, Cecchi F, Frigerio M, Olivotto I. Pharmacological treatment of hypertrophic cardiomyopathy: current practice and novel perspectives. Eur J Heart Fail 2016; 18(9): 1106-18.
11. Liebregts M, Vriesendorp PA, Mahmoodi BK, Schinkel AF, Michels M, ten Berg JM. A systematic review and meta-analysis of long-term outcomes after septal reduction therapy in patients with hypertrophic cardiomyopathy. JACC Heart Fail 2015; 3(11): 896-905.
12. Wells S, Rowin EJ, Boll G, et al. Clinical profile of nonresponders to surgical myectomy with obstructive hypertrophic cardiomyopathy. Am J Med 2018; 131(6): e235-e9.
13. Kim LK, Swaminathan RV, Looser P, et al. Hospital volume outcomes after septal myectomy and alcohol septal ablation for treatment of obstructive hypertrophic cardiomyopathy: US Nationwide Inpatient Database, 2003-2011. JAMA Cardiol 2016; 1(3): 324-32.
14. Grillo MP, Erve JCL, Dick R, et al. In vitro and in vivo pharmacokinetic characterization of mavacamten, a first-in-class small molecule allosteric modulator of beta cardiac myosin. Xenobiotica 2019; 49(6): 718-33.
15. Kawas RF, Anderson RL, Ingle SRB, Song Y, Sran AS, Rodriguez HM. A small-molecule modulator of cardiac myosin acts on multiple stages of the myosin chemomechanical cycle. J Biol Chem 2017; 292(40): 16571-7.
16. Anderson RL, Trivedi DV, Sarkar SS, et al. Deciphering the super relaxed state of human beta-cardiac myosin and the mode of action of mavacamten from myosin molecules to muscle fibers. Proc Natl Acad Sci U S A 2018; 115(35): E8143-E52.
17. del Rio CL, Ueyama Y, Baker DC, et al. In vivo cardiac effects of mavacamten (MYK-461): evidence for negative inotropy and improved compliance. Circulation 2018; 136(Suppl 1).
18. Green EM, Wakimoto H, Anderson RL, et al. A small-molecule inhibitor of sarcomere contractility suppresses hypertrophic cardiomyopathy in mice. Science 2016; 351(6273): 617-21.

19. Heitner SB, Jacoby D, Lester SJ, et al. Mavacamten treatment for obstructive hypertrophic cardiomyopathy: a clinical trial. Ann Intern Med 2019; 170(11): 741-8.
20. Ho CY, Mealiffe ME, Bach RG, et al. Evaluation of Mavacamten in Symptomatic Patients With Nonobstructive Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2020; 75(21): 2649-60.
21. Ho CY, Olivotto I, Jacoby D, et al. Study design and rationale of EXPLORER-HCM: evaluation of mavacamten in adults with symptomatic obstructive hypertrophic cardiomyopathy. Circ Heart Fail 2020; 13(6): e006853.
22. Lewis EF, Claggett BL, McMurray JJ, et al. Health-related quality of life outcomes in PARADIGM-HF. Circ Heart Fail 2017; 10(8): e003430.
23. Cowger JA, Naka Y, Aaronson KD, et al. Quality of life and functional capacity outcomes in the MOMENTUM 3 trial at 6 months: a call for new metrics for left ventricular assist device patients. J Heart Lung Transplant 2018; 37(1): 15-24.
24. Kubo T, Kitaoka H, Okawa M, et al. Combined measurements of cardiac troponin I and brain natriuretic peptide are useful for predicting adverse outcomes in hypertrophic cardiomyopathy. Circ J 2011; 75(4): 919-26.
25. Geske JB, McKie PM, Ommen SR, Sorajja P. B-type natriuretic peptide and survival in hypertrophic cardiomyopathy. J Am Coll Cardiol 2013; 61(24): 2456-60.
26. Seydelmann N, Liu D, Krämer J, et al. High-sensitivity troponin: a clinical blood biomarker for staging cardiomyopathy in Fabry disease. J Am Heart Assoc 2016; 5(6): e002839.
27. Nielen JT, de Vries F, van der Velde JH, et al. The association between β-blocker use and cardiorespiratory fitness: the maastricht study. J Cardiovasc Pharmacol Ther 2019; 24(1): 37-45.
28. Malhotra R, Bakken K, D'Elia E, Lewis GD. Cardiopulmonary exercise testing in heart failure. JACC Heart Fail 2016; 4(8): 607-16.

29. Myers J, Gujja P, Neelagaru S, Burkhoff D. Cardiac output and cardiopulmonary responses to exercise in heart failure: application of a new bio-reactance device. J Card Fail 2007;13(8):629-36.

FIGURE LEGENDS

Figure 1: **LVOT gradients, LVEF, and cardiac biomarkers over time**

Mean (95% CI) post-exercise LVOT gradient over time (panel A), LVEF (panel B), resting LVOT gradient (panel C), and Valsalva LVOT gradient (panel D). Geometric mean (95% CI) over time is shown for NT-proBNP (panel E) and hs-cTnI (panel F). The dashed lines represent the threshold for guideline-based invasive intervention (LVOT gradient >50 mm Hg) in panels A and D, the threshold for guideline-based diagnosis of obstruction (LVOT gradient <30 mm Hg) in panel C, and the protocol threshold for temporary discontinuation (LVEF<50%) in panel B. hs-cTnI=high-sensitivity cardiac troponin I. LVEF=left ventricular ejection fraction. LVOT=left ventricular outflow tract. NT-proBNP=N-terminal pro B-type natriuretic peptide.

Figure 2. **Change in NYHA Functional Class over Time.**

Percentage of patients who had NYHA class I, II, or III at baseline, after 14 and 30 weeks of treatment, reported for mavacamten and placebo groups. NYHA=New York Heart Association.

Figure 3: **Forest plot of treatment effect on primary end point and post-exercise LVOT gradient by subgroups**

Panel A shows the mean difference in patients meeting the primary end point. The dashed vertical line (overall effect) represents the between-treatment group difference in the overall study cohort (19·4), and the solid vertical line (no effect) indicates no difference between treatment groups. Panel B shows the mean difference in LVOT gradient reduction between mavacamten and placebo. The dashed vertical line (overall effect) represents the between-treatment group difference in the overall study cohort (−36 mm Hg). The solid vertical line indicates findings if there was no difference between treatment groups. Patients with non-evaluable primary end point were considered as nonresponders. BMI=body mass index. HCM=hypertrophic cardiomyopathy. LVEF=left ventricular ejection fraction. LVOT=left

574 ventricular outflow tract. NT-proBNP=N-terminal pro B-type natriuretic peptide. NYHA=New
575 York Heart Association. VUS=variant of uncertain significance.
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599

TABLES

Table 1: **Baseline demographics and patient characteristics***

Characteristic	Mavacamten (N = 123)	Placebo (N = 128)
Age — yr	58·5±12·2	58·5±11·8
Female sex — no. (%)	57 (46·3)	45 (35·2)
White race — no. (%)	115 (93·5)	114 (89·1)
Region — no. (%)		
United States	53 (43·1)	55 (43·0)
Non-United States	70 (56·9)	73 (57·0)
HCM genetic testing performed — no. (%)	90 (73·2)	100 (78·1)
Pathogenic/likely pathogenic HCM gene variant — no./ no. tested (%)	28/90 (31·1)	22/100 (22·0)
Family history of HCM — no. (%)	33 (26·8)	36 (28·1)
History of atrial fibrillation — no. (%)	12 (9·8)	23 (18·0)
History of septal reduction therapy — no. (%)	11 (8·9)	8 (6·3)
History of hypertension — no. (%)	57 (46·3)	53 (41·4)
History of hyperlipidaemia — no. (%)	27 (22·0)	39 (30·5)
History of coronary artery disease — no. (%)	12 (9·8)	6 (4·7)
History of obesity — no. (%)	15 (12·2)	14 (10·9)
History of type 2 diabetes mellitus — no. (%)	6 (4·9)	7 (5·5)
History of asthma — no. (%)	17 (13·8)	11 (8·6)
History of chronic obstructive pulmonary disease — no. (%)	2 (1·6)	3 (2·3)
Background HCM therapy — no. (%)		
Beta-blocker	94 (76·4)	95 (74·2)
Calcium channel blocker	25 (20·3)	17 (13·3)
ICD — no. (%)	27 (22·0)	29 (22·7)

Body-mass index — kg/m^2	29·7±4·9	29·2±5·6
Heart rate — beats/min	63±10·1	62±10·6
Blood pressure — mm Hg		
Systolic	128±16·2	128±14·6
Diastolic	75±10·8	76±9·9
NYHA functional class — no. (%)		
II	88 (71·5)	95 (74·2)
III	35 (28·5)	33 (25·8)
pVO_2 — ml/kg/min	18·9±4·9	19·9±4·9
NT-proBNP, geometric mean (CV%) — ng/L†	777 (136)	616 (108)
hs-cTnI, geometric mean (CV%) — ng/L‡	12·5 (208)	12·5 (373)
Echocardiographic parameters		
LVEF — %	74±6	74±6
Maximum LV wall thickness — mm	20±4	20±3
LVOT gradient, rest — mm Hg	52±29	51±32
LVOT gradient, Valsalva — mm Hg	72±32	74±32
LVOT gradient, post-exercise — mm Hg§	86±34	84±36
LA volume index — ml/m^2 ||	40±12	41±14
LA diameter — mm¶	42±5.3	42±6.0

*Plus–minus values are means ±SD, unless otherwise shown.

†Data on NT-proBNP were missing in three patients in the mavacamten group and two patients in the placebo group. The variation numbers (CV%) are coefficient of variation, which is defined as the ratio of the standard deviation to the mean.

‡Data on hs-cTnI were missing in three patients in the mavacamten group and nine patients in the placebo group.

§Data on post-exercise LVOT gradient were missing in one patient in the mavacamten group and one patient in the placebo group.

||Data on LA volume index were missing in one patient in the mavacamten group.

¶Data on LA diameter were missing in five patients each in the mavacamten and placebo groups.

HCM=hypertrophic cardiomyopathy. hs-cTnI=high sensitivity-cardiac troponin I. ICD=implantable cardioverter-defibrillator. LA=left atrial, LVEF=left ventricular ejection fraction. LVOT=left ventricular outflow tract. NYHA=New York Heart Association. NT-proBNP=N-terminal pro B-type natriuretic peptide. pVO_2=peak oxygen consumption.

Table 2: **Primary and secondary end points***

	Mavacamten (N = 123)	**Placebo (N = 128)**	**Difference† (95% CI) p value**
Primary End Point§			
EITHER ≥1·5 ml/kg/min increase in pVO_2 with ≥1 NYHA class improvement **OR** ≥3·0 ml/kg/min increase in pVO_2 with no worsening of NYHA class — no. (%)	45 (36·6)	22 (17·2)	19·4 (8·7 to 30·1) 0·0005
≥1·5 ml/kg/min increase in pVO_2 with ≥1 NYHA class improvement — no. (%)	41 (33·3)	18 (14·1)	19·3 (9·0 to 29·6)
≥3·0 ml/kg/min increase in pVO_2 with no worsening of NYHA class — no. (%)	29 (23·6)	14 (10·9)	12·6 (3·4 to 21·9)
BOTH ≥3·0 ml/kg/min increase in pVO_2 **AND** ≥1 NYHA class improvement — no. (%)	25 (20·3)	10 (7·8)	12·5 (4·0 to 21·0)
Secondary End Points‡			
Post-exercise LVOT gradient			
Change from baseline to week 30 — mm Hg	–47±40 (n = 117)	–10±30 (n = 122)	–36 (–43·2 to –28·1) <0·0001
pVO_2			
Change from baseline to week 30 — ml/kg/min	1·40±3·1 (n = 120)	–0·05±3·0 (n = 125)	1·35 (0·58 to 2·12) 0·0006
≥1 NYHA class improvement§			
Improvement from baseline to week 30 — no. (%)	80 (65·0) (n = 123)	40 (31·3) (n = 128)	34 (22·2 to 45·4) <0·0001
KCCQ-CSS‖			
Change from baseline to week 30 in KCCQ-CSS	13·6±14·4 (n = 92)	4·2±13·7 (n = 88)	9·1 (5·5 to 12·7) <0·0001
HCMSQ-SoB‖			

Change from baseline to week 30 in HCMSQ-SoB	–2·8±2·7 (n = 85)	–0·9±2·4 (n = 86)	–1·8 (–2·4 to –1·2) <0·0001

*Plus–minus values are means ±SD.

†Model estimated least-square mean differences were reported for continuous variables.

‡N = number analyzable for secondary end point based on availability of both baseline and week 30 values.

§Patients with non-evaluable primary end point and NYHA secondary end point were considered as nonresponders. The response rates were calculated with N value as the denominator.

||Due to the smaller numbers evaluable for PRO end points, additional post-hoc analyses comparing the reasons for missing data were performed. Baseline demographic and disease characteristics, and key efficacy and safety parameters for patients with or without missing data in KCCQ-CSS or HCMSQ-SoB revealed no consistent pattern of differences between those groups. Furthermore, worst case scenario analyses showed that, even after imputing the missing data with unfavorable results toward the mavacamten group, the estimated treatment effects on KCCQ-CSS or HCMSQ-SoB remained statistically significant ($p<0·05$). These analyses supported the notion that missingness-at-random assumption was not violated. Data in the Table reflect the pre-specified analyses.

HCMSQ-SoB=Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath Score. KCCQ-CSS=Kansas City Cardiomyopathy Questionnaire-Clinical Symptom Score. LVOT=left ventricular outflow tract. NYHA=New York Heart Association. pVO_2=peak oxygen consumption.

Table 3: **Key exploratory efficacy end points**

	Mavacamten	**Placebo**	**Difference (95% CI)**
Complete response — no./total no. (%)*	32/117 (27·4)	1/126 (0·8)	26·6 (18·3, 34·8)
Post-exercise LVOT peak gradient <50 mm Hg — no./total no. (%)†	75/101 (74·3)	22/106 (20·8)	53·5 (42·0· 65·0)
Post-exercise LVOT peak gradient <30 mm Hg — no./total no. (%)‡	64/113 (56·6)	8/114 (7·0)	49·6 (39·3, 59·9)

*Defined as New York Heart Association class I and all LVOT peak gradients less than 30 mm Hg (post-exercise, resting, and Valsalva).

†Threshold for guideline-based invasive intervention. Only patients with baseline post-exercise LVOT peak gradient at least 50 mm Hg were assessed.

‡Threshold for guideline-based diagnosis of obstruction. Only patients with baseline post-exercise LVOT peak gradient at least 30 mm Hg were assessed.

LVOT=left ventricular outflow tract.

Table 4: **Summary of treatment-emergent adverse events and serious adverse events**

Adverse Events Preferred Term	**Mavacamten N = 123**	**Placebo N = 128**
Patients with ≥1 treatment-emergent adverse event — no. (%)	108 (87·8)	101 (78·9)
Total number of serious adverse events	11	20
Patients with ≥1 serious adverse event — no. (%)	10 (8·1)	11 (8·6)
Atrial fibrillation	2 (1·6)	4 (3·1)
Syncope	2 (1·6)	1 (0·8)
Stress cardiomyopathy	2 (1·6)	0
Sudden death	0	1 (0·8)
Transient ischemic attack	0	1 (0·8)
Cardiac failure congestive	0	1 (0·8)
Diverticulitis	1 (0·8)	0
Viral gastroenteritis	0	1 (0·8)
Urinary tract infection	0	2 (1·6)
Infection	1 (0·8)	0
Rheumatoid arthritis	0	1 (0·8)
Contusion	1 (0·8)	0
Forearm fracture	1 (0·8)	0
Dehydration	0	1 (0·8)
Vocal cord polyp	0	1 (0·8)
Cholesteatoma	0	1 (0·8)
Prostate cancer	0	1 (0·8)

FIGURES

Figure 1: **Changes in LVOT gradient, LVEF, and cardiac biomarkers over time**

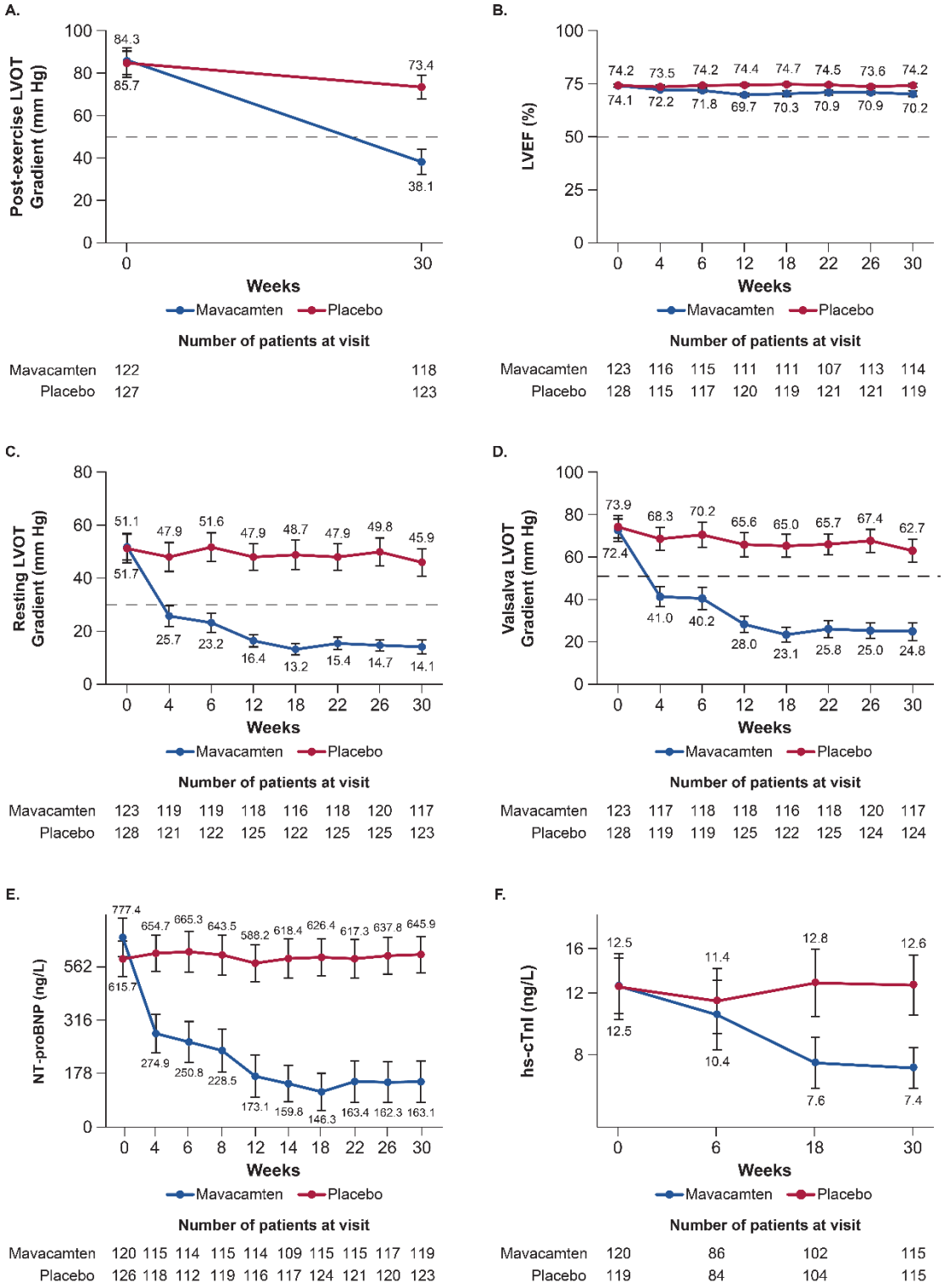
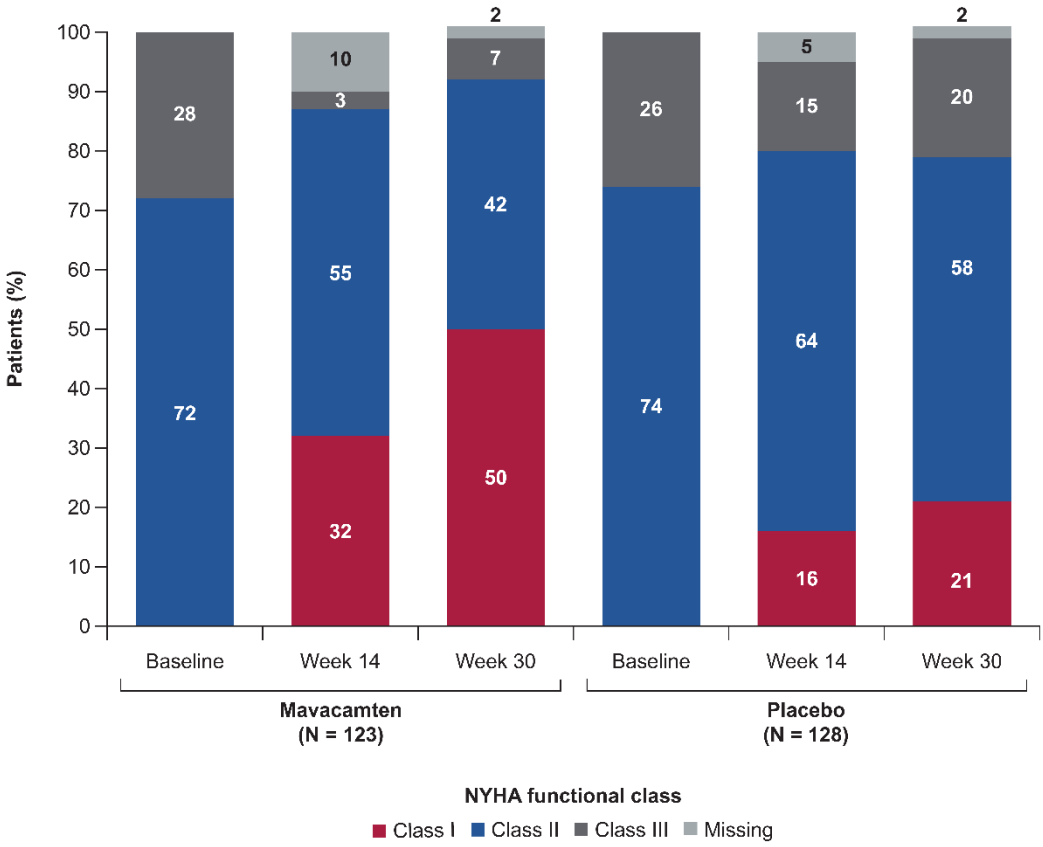


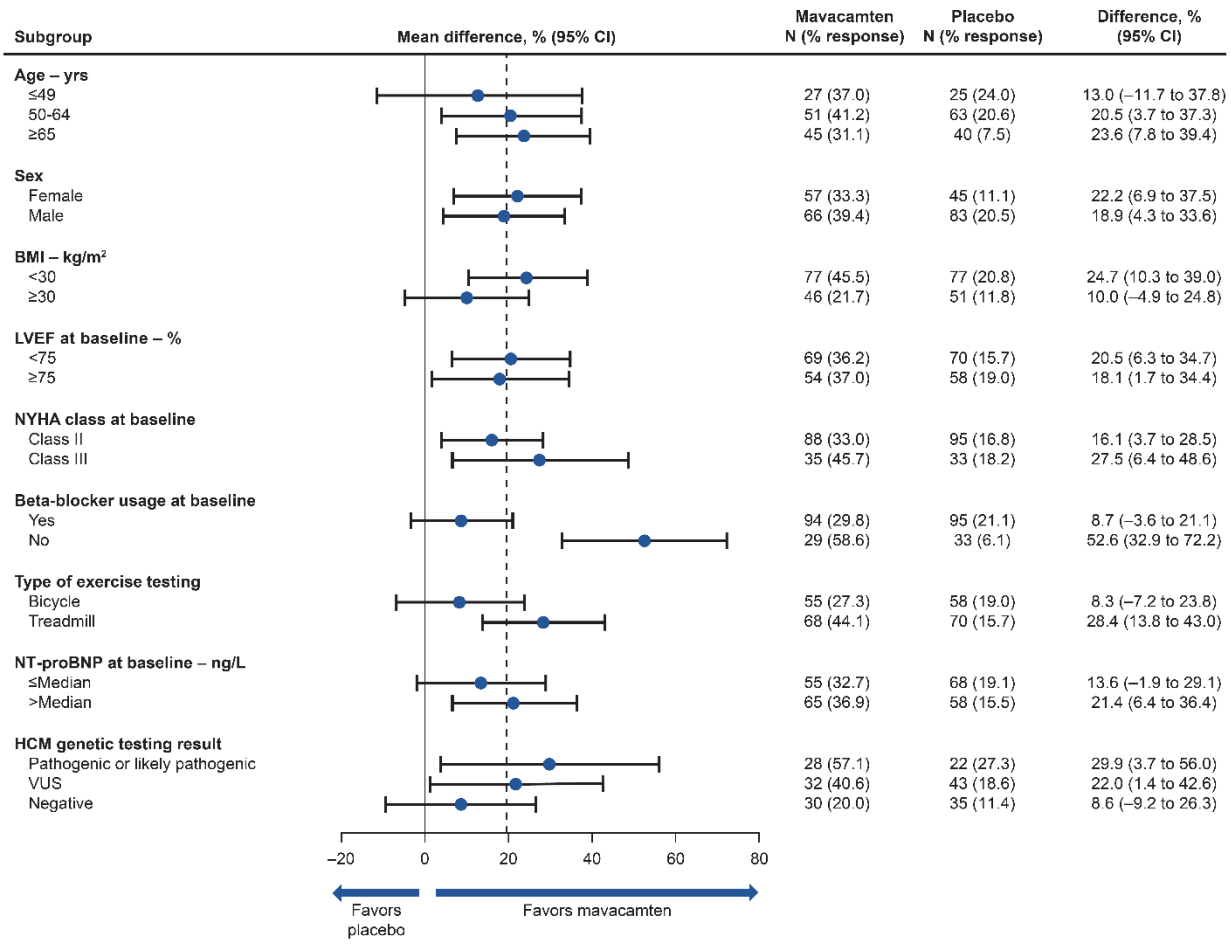
Figure 2: **Change in NYHA functional class over time.**



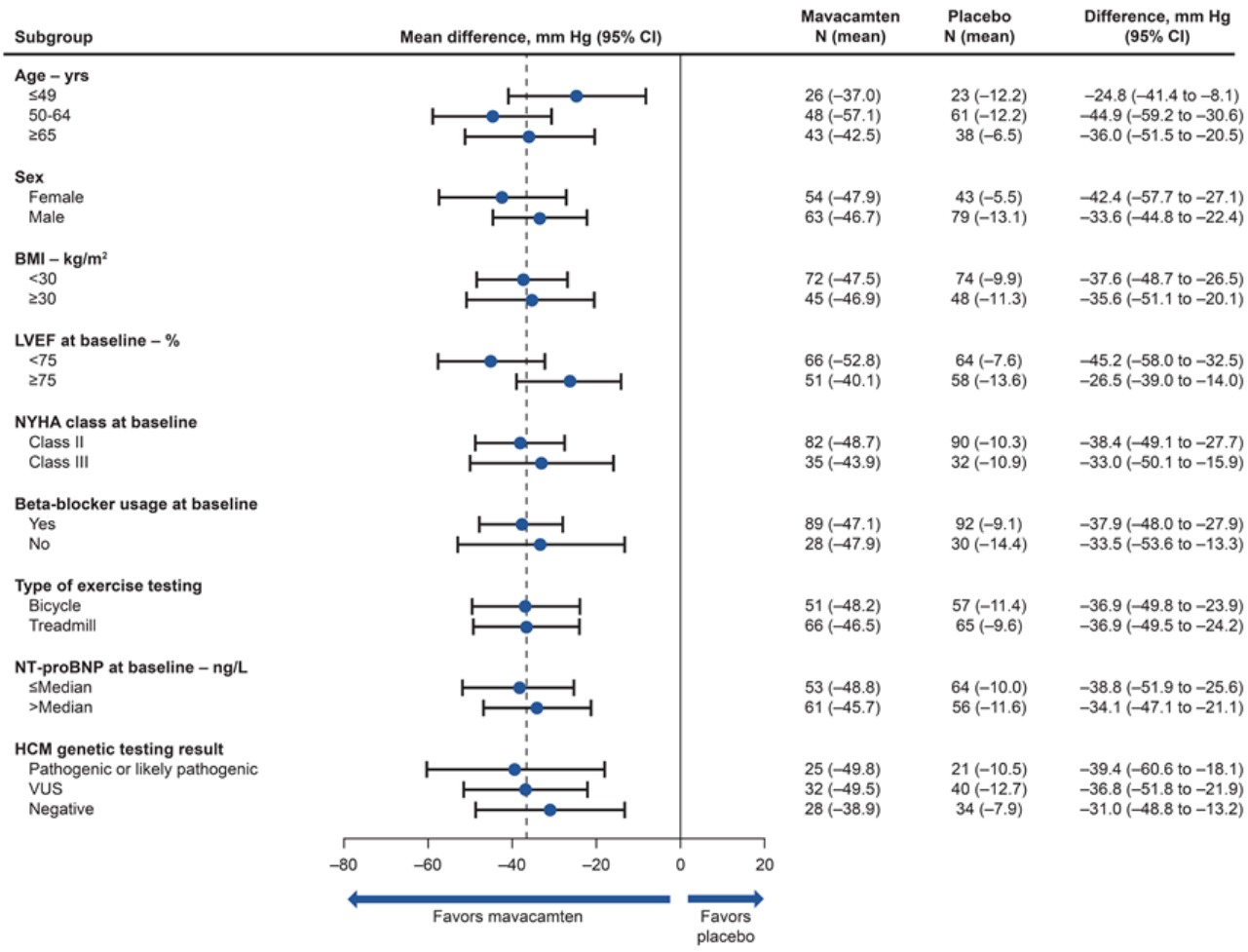
group

Figure 3: **Forest plot of treatment effect on primary end point and post-exercise LVOT gradient by subgroups**

A.



B.


Subgroup
Mean difference, mm Hg (95% CI)
Mavacamten N (mean)
Placebo N (mean)
Difference, mm Hg (95% CI)
Age – yrs
≤49 26 (–37.0) 23 (–12.2) –24.8 (–41.4 to –8.1)
50-64 48 (–57.1) 61 (–12.2) –44.9 (–59.2 to –30.6)
≥65 43 (–42.5) 38 (–6.5) –36.0 (–51.5 to –20.5)
Sex
Female 54 (–47.9) 43 (–5.5) –42.4 (–57.7 to –27.1)
Male 63 (–46.7) 79 (–13.1) –33.6 (–44.8 to –22.4)
BMI – kg/m²
<30 72 (–47.5) 74 (–9.9) –37.6 (–48.7 to –26.5)
≥30 45 (–46.9) 48 (–11.3) –35.6 (–51.1 to –20.1)
LVEF at baseline – %
<75 66 (–52.8) 64 (–7.6) –45.2 (–58.0 to –32.5)
≥75 51 (–40.1) 58 (–13.6) –26.5 (–39.0 to –14.0)
NYHA class at baseline
Class II 82 (–48.7) 90 (–10.3) –38.4 (–49.1 to –27.7)
Class III 35 (–43.9) 32 (–10.9) –33.0 (–50.1 to –15.9)
Beta-blocker usage at baseline
Yes 89 (–47.1) 92 (–9.1) –37.9 (–48.0 to –27.9)
No 28 (–47.9) 30 (–14.4) –33.5 (–53.6 to –13.3)
Type of exercise testing
Bicycle 51 (–48.2) 57 (–11.4) –36.9 (–49.8 to –23.9)
Treadmill 66 (–46.5) 65 (–9.6) –36.9 (–49.5 to –24.2)
NT-proBNP at baseline – ng/L
≤Median 53 (–48.8) 64 (–10.0) –38.8 (–51.9 to –25.6)
>Median 61 (–45.7) 56 (–11.6) –34.1 (–47.1 to –21.1)
HCM genetic testing result
Pathogenic or likely pathogenic 25 (–49.8) 21 (–10.5) –39.4 (–60.6 to –18.1)
VUS 32 (–49.5) 40 (–12.7) –36.8 (–51.8 to –21.9)
Negative 28 (–38.9) 34 (–7.9) –31.0 (–48.8 to –13.2)
–80
–60
–40
–20
0
20
Favors mavacamten
Favors placebo