Mavacamten in Symptomatic Obstructive Hypertrophic Cardiomyopathy

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Background: Mavacamten, a first-in-class cardiac myosin inhibitor, targets fundamental biomechanical abnormalities of hypertrophic cardiomyopathy (HCM), a condition lacking disease-specific medical therapy. We assessed the efficacy and tolerability of mavacamten in symptomatic obstructive HCM (oHCM) compared to placebo.

Methods: EXPLORER-HCM was a phase 3, randomized, double-blind trial in symptomatic oHCM. Patients with gradient ≥50 mmHg and New York Heart Association (NYHA) class II-III received mavacamten (N=123; 5-mg then two-step titration) or placebo (N=128) for 30 weeks. The primary endpoint was either: 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 worsening of NYHA class. Secondary endpoints assessed outflow gradient, pVO_2, NYHA class, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS), and HCM Symptom Questionnaire Shortness-of-Breath subscore (HCMSQ-SoB).

Results: After 30 weeks, 36.6% patients on mavacamten achieved the primary endpoint versus 17.2% on placebo (+19.4%; 95% confidence interval [CI] 8.7 to 30.1; P<0.001). Significant benefit was seen across secondary endpoints (P<0.001 for all). Compared to placebo, mavacamten demonstrated greater reduction in post-exercise outflow gradient by 35.5 mmHg (95% CI, –43.1 to –27.9), greater increase in pVO2 by 1.4 ml/kg/min (95% CI, 0.6 to 2.1), 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] . A greater proportion of patients on mavacamten improved ≥1 NYHA class (+33.8% vs. placebo; 95% CI, 22.1 to 45.4; P<0.001). Safety and tolerability were comparable to placebo.

Conclusions: In patients with symptomatic oHCM, mavacamten was safe and effective in improving symptoms, exercise capacity, outflow obstruction and quality-of-life. Mavacamten is

the first disease-specific molecule showing clinical benefit in oHCM (Funded by MyoKardia; EXPLORER-HCM ClinicalTrials.gov number, NCT03470545.)

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a myocardial disorder characterized by primary left ventricular (LV) hypertrophy,[1,2] and commonly caused by pathogenic variants in cardiac sarcomeric protein genes. Core pathophysiologic features include LV hypercontractility, reduced compliance, and, in many patients, resting or provokable dynamic left ventricular outflow tract (LVOT) obstruction (obstructive hypertrophic cardiomyopathy, oHCM).[2-4] Patients with oHCM are often symptomatic and experience increased lifelong burden of disease, including atrial fibrillation, heart failure, and malignant ventricular arrhythmias.[2,5] Current treatment for oHCM focuses on symptomatic relief and relies on beta-blockers, non-dihydropyridine calcium channel blockers and disopyramide.[6-9] However, these non-specific agents are often inadequate in controlling symptoms, may be poorly tolerated,[10] and fail to address the underlying molecular mechanisms of HCM. Invasive septal reduction therapy (SRT) with either surgical septal myectomy or alcohol septal ablation[7,11] can effectively help patients with drug-refractory symptoms, but carry the risks inherent to invasive procedures and require expertise that is not universally available.[12-14] 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[15,16] to target the underlying pathophysiology of oHCM by reducing actin-myosin cross-bridge formation, countering excess contractility and improving myocardial energetics.[17] Mavacamten successfully relieved LVOT gradients and improved diastolic dysfunction in preclinical and clinical studies.[16,18-21] In the phase 2 open-label PIONEER-HCM study (NCT02842242), mavacamten treatment was well tolerated and

significantly reduced post-exercise LVOT gradients.[20]Treatment was also associated with improvements in exercise capacity and New York Heart Association (NYHA) functional class. Based on these results, the EXPLORER-HCM trial (NCT03470545) was designed to assess the efficacy and safety of mavacamten in improving symptoms and functional capacity in oHCM.

METHODS

Trial Design and Oversight

EXPLORER-HCM was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. Details of the trial design have been published previously.[22] The protocol was approved by site institutional review boards and the trial was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. Enrollment occurred at 68 sites in 13 countries. 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 independently replicated by the Duke Clinical Research Institute. Data tables 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

Eligible patients were aged ≥18 years with a diagnosis of oHCM (unexplained LV hypertrophy with maximal LV wall thickness of ≥15 mm [or ≥13 mm if family history of HCM]), peak LVOT gradient ≥50 mm Hg at screening, measured at rest or with provocation, LV ejection

fraction (LVEF) of ≥55%, and NYHA Functional Class II or III symptoms. Patients who underwent SRT >6 months prior to screening were enrolled if otherwise eligible.[22] With the exception of disopyramide, patients were allowed to continue standard medical therapy (eg, beta-blocker, verapamil, or diltiazem), if dosing remained stable for ≥2 weeks prior to screening and was anticipated to remain unchanged throughout the study.

Procedures

At the start of the 30-week, double-blind treatment period, patients were randomized 1:1 to receive once-daily treatment with mavacamten (starting dose 5 mg) or placebo. Randomization was stratified based on NYHA Functional Class (II or III), current treatment with a beta-blocker (yes or no), ergometer type (treadmill or bicycle), and consent for a cardiovascular magnetic resonance (CMR) imaging sub-study (yes or 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 administered to achieve reduction in LVOT gradient and a mavacamten plasma concentration between 350-700 ng/mL. All dose titrations were blinded and based on core laboratory evaluation of LVEF, Valsalva LVOT gradient, pharmacokinetics (PK), and QT interval with Fridericia correction (QTcF).[22] Prespecified criteria for temporary discontinuation of study drug, including decrease in LVEF below 50%, are described in the Supplementary Appendix.

Patients were evaluated every 2 or 4 weeks for the 30-week treatment period, followed by an end-of-study visit at week 38 for safety. Cardiopulmonary exercise (CPET) testing was performed at screening and week 30. Transthoracic echocardiography (TTE) and twelve-lead electrocardiograms (ECGs) were performed at rest serially throughout the study and TTE was also performed following exercise testing at baseline and week 30. Continuous 48-hour cardiac rhythm monitoring was obtained at screening, week 12, and week 26. Laboratory testing and pharmacokinetics (PK) plasma drug concentration were regularly performed for safety. Genetic

testing for pharmacogenetics (CYP2C19 genotype) and HCM gene panel testing (optional) was also performed. Results from these procedures were determined by central core laboratories. [22]

Outcomes

The primary endpoint was a composite to assess clinical response at week 30 compared to baseline, defined as 1) ≥1.5 mL/kg/min improvement in pVO_2 and ≥1 NYHA Functional Class reduction **OR** 2) ≥3.0 mL/kg/min improvement in pVO_2 and no worsening of NYHA Functional Class.

Secondary endpoints included change from baseline to week 30 in the following: post-exercise LVOT gradient, pVO_2, proportion of patients with ≥1 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.[22] These were tested in hierarchical order, upon achieving significance in the primary endpoint and thereafter in the preceding secondary endpoint (with two-tailed $P<0.05$ required to proceed). Additional prespecified exploratory endpoints included change from baseline to week 30 in resting and Valsalva 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 endpoints included frequency and severity of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs).

Statistical Analysis

The study was designed to randomize a minimum of 220 patients. Sample size was estimated to provide 96% power to detect a 25% difference between treatment arms, at a two-sided $P<0.05$.[22]

All randomized patients received ≥1 dose of study drug and were included in the efficacy and safety analysis populations. Efficacy analyses were performed using the intention-to-treat

principle. Safety data were analyzed using descriptive statistics without formal statistical testing. The primary efficacy endpoint was analyzed using the Cochran–Mantel–Haenszel test for stratified categorical data. For secondary efficacy endpoints, continuous variables were analyzed using analysis of variance (ANOVA) comparing between group means. Categorical endpoints were analyzed using the Cochran–Mantel–Haenszel test adjusting for stratification factors. PROs were assessed using a mixed model for repeated measurements. Efficacy was also assessed in prespecified subgroup analyses based on baseline demographic and disease characteristics. SAS version 9.4 was used for statistical analyses. Details are provided in the Supplementary Appendix and Statistical Analysis Plan.

RESULTS

Patient Characteristics

From May 2018 to August 2019, 429 adults with oHCM were screened for eligibility and 251 (59%) were randomized to mavacamten (123 patients) or placebo (128 patients) (Fig. S1 in the Supplementary Appendix). Baseline characteristics were generally well balanced between the groups, except for a greater proportion of females and higher baseline NT-proBNP level in the mavacamten treatment arm (Table 1). Most patients (73%; 183/251) had NYHA class II symptoms at baseline and 92% were on background beta-blocker or calcium channel blocker therapy. Nineteen patients had prior SRT.

Overall, 244 (97.2%) patients completed the treatment period. Five patients discontinued treatment prior to week 30 (Fig. S1 in the Supplementary Appendix); three were 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). Additionally, two patients (one on mavacamten [scheduling reasons], one on placebo [COVID19 reasons]) did not complete Week 30 visits within window. No patients were lost to follow up.

Efficacy

Primary Endpoint

At the end of treatment (week 30), 36.6% (45/123) of patients on mavacamten achieved the primary endpoint, compared to 17.2% (22/128) on placebo, representing a 19.4% increased response rate with active treatment (95% confidence interval [CI] 8.7 to 30.1]; P<0.001) (Table 2). Furthermore, mavacamten led to an improvement of both the primary endpoint components (pVO_2 ≥3.0 and ≥1 NYHA Class) in 20.3% of mavacamten-patients versus 7.8% of placebo-treated patients (+12.5% [95% CI, 4.0 to 21.0]).

Secondary endpoints

Mavacamten was associated with significant improvement in all secondary endpoints compared with placebo (Table 2), showing reduced LVOT gradient, increased pVO_2, and improved symptoms as assessed by physicians (NYHA Class) or patients (PROs). Peak post-exercise LVOT gradient in patients on mavacamten decreased from 85.7 mmHg (95% CI, 79.5 to 91.8) to 38.1 mmHg (95% CI, 32.3 to 44.0), while there was no meaningful change in gradient in patients on placebo (84.7 [95% CI, 78.4 to 91.0] to 73.4 [95% CI 67.2 to 79.6] mmHg; Figure 1A). Thus, compared to placebo, mavacamten demonstrated greater reduction in mean post-exercise LVOT gradient by 36 mmHg (95% CI, –43.1 to –27.9; P<0.001) (Table 2 and Figure 1A). Similar improvements, sustained over time, occurred in Valsalva and resting LVOT gradients (Fig. 1B-C). In parallel, mavacamten showed an increase in pVO_2 of 1.4 mL/kg/min when compared to placebo (95% CI, 0.58 to 2.12; P<0.001), and 34% more patients had ≥1 NYHA Class improvement (95% CI, 22.1 to 45.4; P<0.001) with mavacamten. The proportion of patients who achieved NYHA Class I status was 49.6% (61/123) with mavacamten and 21.1% (27/128) with placebo (Fig. S2 of the Supplementary Appendix).

Mavacamten treatment was consistently associated with improved PROs at week 30. Both KCCQ-CCS (positive change better) and HCMSQ-SoB scores (negative change better)

improved more in the mavacamten arm than in the placebo arm (+9.1 [95% CI, 5.5 to 12.7] and -1.8 [95% CI, −2.4 to −1.2; P<0.001 for both comparisons).The benefit of mavacamten for the primary endpoint was consistent across most prespecified subgroups, including patients with and without a pathogenic or likely pathogenic sarcomere gene mutation. However, a greater magnitude of effect was observed in patients without concomitant beta-blockade (mavacamten n=29, placebo n=33) (difference 52.6% [95% CI, 32.9 to 72.2]) versus those on beta-blockers (mavacamten n=94, placebo n=95) (difference, 8.7% [95% CI, ─3.6 to 21.1]). All secondary endpoints, including decrease in LVOT gradient, consistently showed a benefit for mavacamten across pre-specified sub-groups and irrespective of beta-blocker use (Figure 2).

Exploratory Endpoints

Mavacamten eliminated LVOT obstruction (post-exercise gradient <30 mmHg) in 56.6% of patients, versus 7.1% on placebo (difference 49.6%; 95% CI 39.3 to 59.8, P<0.001), and reduced it below the standard threshold for invasive SRT (post-exercise gradient 50 mmHg) in 74.3%, versus 20.8% on placebo (difference 53.5%; 95% CI 42.0 to 65.0, P<0.001) (Table S1, Supplementary Appendix). Optimal response, defined as elimination of gradient (<30 mm Hg at rest, Valsalva and post-exercise) and symptoms (NYHA Class I) was achieved by 27.4% (32 of 117) of patients on mavacamten versus 0.8% (1 of 126) on placebo (difference 26.6%; 95% CI, 18.3 to 34.8) (Table S1, Supplementary Appendix). Mavacamten improved serum biomarkers of wall stress and myocardial injury. Relative to placebo, mavacamten reduced NT-proBNP by 80% (geometric mean ratio, 0.202 [95% CI, 0.169 to 0.241], P<0.001) and hs-cTnI by 41% (geometric mean ratio, 0.589 [95% CI, 0.500 to 0.693], P<0.001) at week 30. Changes in baseline systolic function associated with mavacamten were small: the mean reduction in LVEF was -3.9%, versus -0.01% with placebo (a –4.0% difference; 95% CI, –5.5 to –2.5) (Figure 2D).

Safety

Treatment-emergent adverse events were largely mild and not related to treatment (Table 3 and Table S2 in Supplementary Appendix). Twelve SAEs were reported by 8.1% of patients on mavacamten versus 20 events reported by 8.6% on placebo (Table 3). Serious cardiac adverse events occurred in four patients in the mavacamten group (two atrial fibrillation, two stress cardiomyopathy) and four in the placebo group (three atrial fibrillation, one atrial fibrillation and congestive heart failure). One patient in the placebo group experienced sudden death. Protocol-driven temporary treatment discontinuation for transient LVEF (<50%) occurred in five patients (three on mavacamten, two on placebo) and for QT_CF changes in six patients (three on mavacamten, three on placebo). All patients had their LVEF and QTcF returned to normal, resumed treatment and completed the study showing measures of efficacy (Table S3 in supplementary appendix). Four additional patients had LVEF <50% (48% [n=1] and 49% (n=3)] at week 30, which recovered to baseline values at week 38 in in all patients (one patient not evaluated by a study visit echo due to COVID19). There were no temporary discontinuations for PK >1000 ng/mL.

DISCUSSION

In this randomized, placebo-controlled, phase 3 trial, treatment with mavacamten, a first-in-class cardiac myosin inhibitor, was effective and well tolerated in alleviating symptoms, improving exercise performance and reducing LVOT gradients in patients with oHCM. Using a primary endpoint comprised of both objective (pVO_2) and subjective (NYHA Class) measures of functional capacity, clinical response was nearly 20% greater with mavacamten treatment versus placebo, including 34% more patients improving more than one functional class and 12% more achieving both pVO_2 ≥3.0 and ≥1 NYHA Class improvement. Treatment benefit was consistent across most pre-specified subgroup analyses, irrespective of age, gender, genetic status, body mass index and baseline NYHA class. Notably, while mavacamten was developed to specifically target biophysical abnormalities identified to result from beta-myosin heavy chain

mutations in pre-clinical models, clinical benefit in our study extended to both sarcomeric and non-sarcomeric HCM.

Secondary and exploratory endpoints interrogating different aspects of disease suggest a broad benefit from mavacamten. Mavacamten was consistently superior to placebo across all secondary efficacy endpoints, including reducing post-exercise LVOT gradient, increasing pVO_2, improving NYHA Class, and improving PROs. Optimal response to treatment, defined as elimination of obstruction (resting and provocable gradients <30 mmHg) and symptoms (NYHA class I) was achieved in over one-quarter of patients in mavacamten (27%), compared to <1% in the placebo group. This is analogous to best-case results from invasive SRT.[12,13] Patient-reported quality of life, assessed using KCCQ-CSS and HCMSQ, a novel instrument designed to assess symptoms specifically in HCM patients, confirmed a highly favorable impact of mavacamten on subjective well-being.

Targeted inhibition of cardiac myosin by mavacamten resulted in dramatic reduction in post-exercise gradients from an average of 86 to 38 mmHg; resting gradients decreased from 52 to 14 mmHg. Moreover, mavacamten use led to marked reduction in serum NT-proBNP (by 80% versus placebo) and hs-cTnI levels (by 41% versus placebo), suggesting potential long-term benefit.[24] This substantial hemodynamic effect was achieved with only modest reduction in global LV systolic function, with a mean reduction in LVEF <4%. Two patients on placebo and 3 patients on mavacamten experienced transient reductions in LVEF <50% during the treatment period and underwent protocol-defined temporary dose interruption in the blinded environment. All 5 resumed treatment and completed the study with recovery of LVEF. In addition, 4 patients had LVEF measured at 48 or 49% at week 30 (end of treatment) with LVEF returning to baseline levels at week 38.

Sub-group analysis found that a positive clinical response to mavacamten clinical response was achieved in a smaller percentage of patients receiving concomitant beta-blockers compared with those not receiving beta-blockers, despite similar reductions in LVOT gradient

and improvements in quality of life. This likely relates to the detrimental impact of beta-blockers on peak cardio-respiratory performance, predominantly due to blunting of peak heart rate.[23] Notably, the change in VE/VCO_2 slope, a heart-rate independent CPET parameter associated with cardiac output,[25] showed similar improvements with mavacamten versus placebo regardless of beta blocker use.

Overall, this study introduces a new era in the treatment of HCM, with disease-specific therapies that target fundamental molecular and biophysical abnormalities. Furthermore, the pleiotropic effects of mavacamten may benefit pathophysiological abnormalities across the HCM spectrum, including diastolic and energetic abnormalities present in both obstructive and nonobstructive disease.[18,19,21] For patients with oHCM, mavacamten may offer a noninvasive option capable of improving symptoms and functional capacity and eliminating LVOT gradients with substantially greater ease and availability than invasive SRTs. As shown, mavacamten may be safely added to standard of care drugs (beta-blockers or calcium channel blockers) and in patients with prior, unsuccessful SRT.

Limitations of this study include low representation of non-Caucasian patients and exclusion of patients with severe (NYHA Class IV) symptoms or concomitant disopyramide treatment (this will be examined in the forthcoming VALOR-HCM study; NCT04349072). Furthermore, although genetic testing was offered to all study participants, patients were not uniformly genotyped, and inclusion was not limited to carriers of specific gene mutations. Further study is needed to assess the impact of genetic background on drug response. Additionally, studies are ongoing to assess the long-term effects and safety of mavacamten (MAVA-LTE; NCT03723655).

In conclusion, mavacamten improved exercise capacity, symptoms, LVOT gradient, and quality of life in patients with oHCM. The results of this pivotal trial provide evidence to support the first disease-specific treatment for patients with oHCM.

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FIGURE LEGENDS

Figure 1. LVOT gradients and LVEF over Time.

Mean (95%CI) over time is shown for post-exercise LVOT gradient (panel A), Valsalva LVOT gradient (panel B), resting LVOT gradient (panel C), and LVEF (panel D). Geometric mean (95% CI) over time is shown for NT-proBNP (panel E) and cTnI (panel F). The dashed lines represent the threshold for guideline-based invasive intervention (LVOT gradient >50 mmHg) or protocol threshold for temporary discontinuation (LVEF<50%). LVEF denotes left ventricular ejection fraction, LVOT, left ventricular outflow tract

Figure 2: Forest Plot of Treatment Effect on Change in Post-exercise LVOT Gradient Across Subgroups.

The first secondary endpoint was the difference in change from baseline to week 30 in post-exercise LVOT gradient between treatment groups — solid vertical line represents this difference in the overall study cohort (−36 mmHg) — which was consistent across sub-groups. The x-axis shows the difference in LVOT reduction between mavacamten and placebo groups (larger negative values represent greater effect of mavacamten). The dashed vertical line indicates no change between treatment groups from baseline to week 30.

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
Male sex — no. (%)	66 (53.7)	83 (64.8)
White race — no. (%)	115 (93.5)	114 (89.1)
Region, n (%)		
United States	53 (43.1)	55 (43.0)
Non-United States	70 (56.9)	73 (57.0)
HCM genetic testing performed	90 (73.2)	100 (78.1)
Pathogenic/likely pathogenic sarcomere gene variant	21 (23.3)	21 (21.0)
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)
Background HCM therapy — no. (%)		
Beta-blocker	94 (76)	95 (74)
Calcium channel blocker	25 (20)	17 (13)
ICD — no. (%)	27 (22.0)	29 (22.7)
BMI — kg/m^2	29.7±4.9	29.2±5.6
Heart rate — beats/min	63±10	62±11
Blood pressure — mm Hg		
Systolic	128±16	128±15
Diastolic	75±11	76±10
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

Median NT-proBNP (Q1, Q3) — pg/mL†	784 (373, 1759)	648 (354, 1360)
Median hs-cTnI (Q1, Q3) — ng/mL	10.6 (5.0, 23.6)	10.0 (5.0, 22.0)
Echocardiographic parameters		
LVEF — %	74±6	74±6
Maximum LV wall thickness — mm	20±4	20±3
LVOT gradient at rest — mm Hg	52±29	51±32
LVOT gradient Valsalva — mm Hg	72±32	74±32
LVOT gradient post-exercise — mm Hg‡	86±34	85±36
LA volume index — mL/m^2 §	40±12	41±14

*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.

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 two patients in the placebo group.

§Data on LA volume index was missing in one patient in the mavacamten group.

||Data on interventricular septal thickness were missing in two patients in the mavacamten group and one patient in the placebo group.

BMI denotes body mass index, 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, hs-cTnI, high sensitivity cardiac troponin I, pVO_2 peak oxygen consumption.

Table 2. Primary and Secondary Endpoints*

	Mavacamten (N = 123)	**Placebo (N = 128)**	**Difference (95% CI) P value**
Primary endpoint			
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, 30.1) <0.001
≥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, 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, 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, 21.0)
Secondary endpoints			
Mean change from baseline to Week 30 in post-exercise LVOT gradient— mmHg	–47.2±40.3	–10.7±29.6	–35.5 (–43.1, –27.9) <0.001
Mean change from baseline to Week 30 in pVO_2 — mL/kg/min	1.4±3.1	–0.05±3.0	1.35 (0.58, 2.12) <0.001
Patients with ≥1 NYHA Class improvement from baseline to Week 30 — no. (%)	80 (65.0)	40 (31.3)	33.8 (22.2, 45.4) <0.001
Mean change from baseline to Week 30 in KCCQ-CSS	13.6±14.4	4.2±13.7	9.1 (5.5, 12.7) <0.001
Mean change from baseline to Week 30 in HCMSQ-SoB	–2.8 (2.7)	–0.9 (2.4)	–1.8 (–2.4, –1.2) <0.001

*Plus–minus values are means±SD.

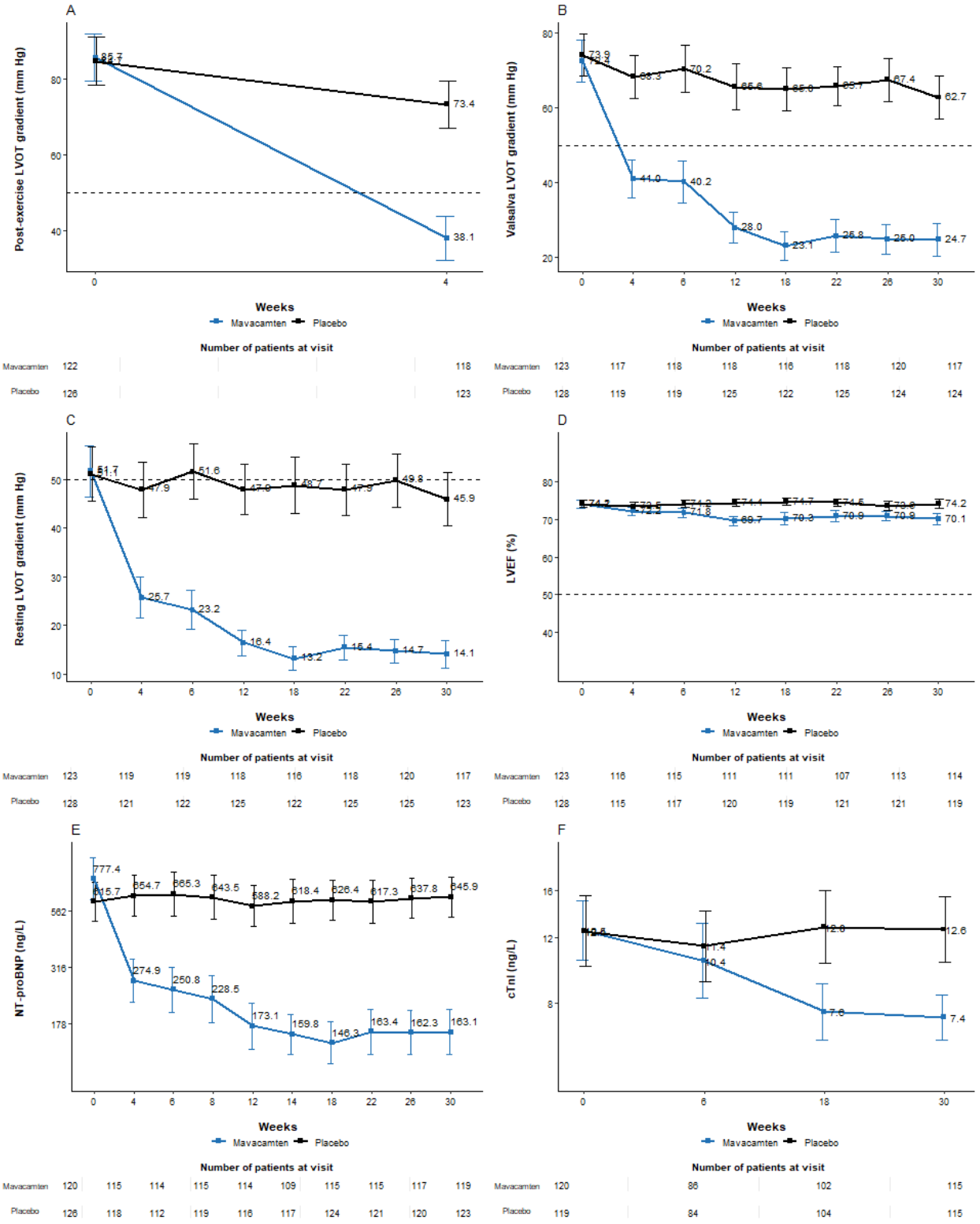
HCMSQ-SoB denotes Hypertrophic Cardiomyopathy Symptom Questionnaire-Shortness of Breath Score, KCCQ-CSS Kansas City Cardiomyopathy Questionnaire-Clinical Symptom Score, LVOT left ventricular outflow tract, NYHA New York Heart Association, and pVO_2 peak oxygen consumption.

Table 3: Summary of Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

Adverse Events Preferred Term	Mavacamten N=123 n (%)	Placebo N=128 n (%)
Number of patients with ≥1 TEAE, n (%)	108 (87.8)	101 (78.9)
Total number of SAEs, n	12	20
Number of patients with ≥1 SAE, n (%)	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)

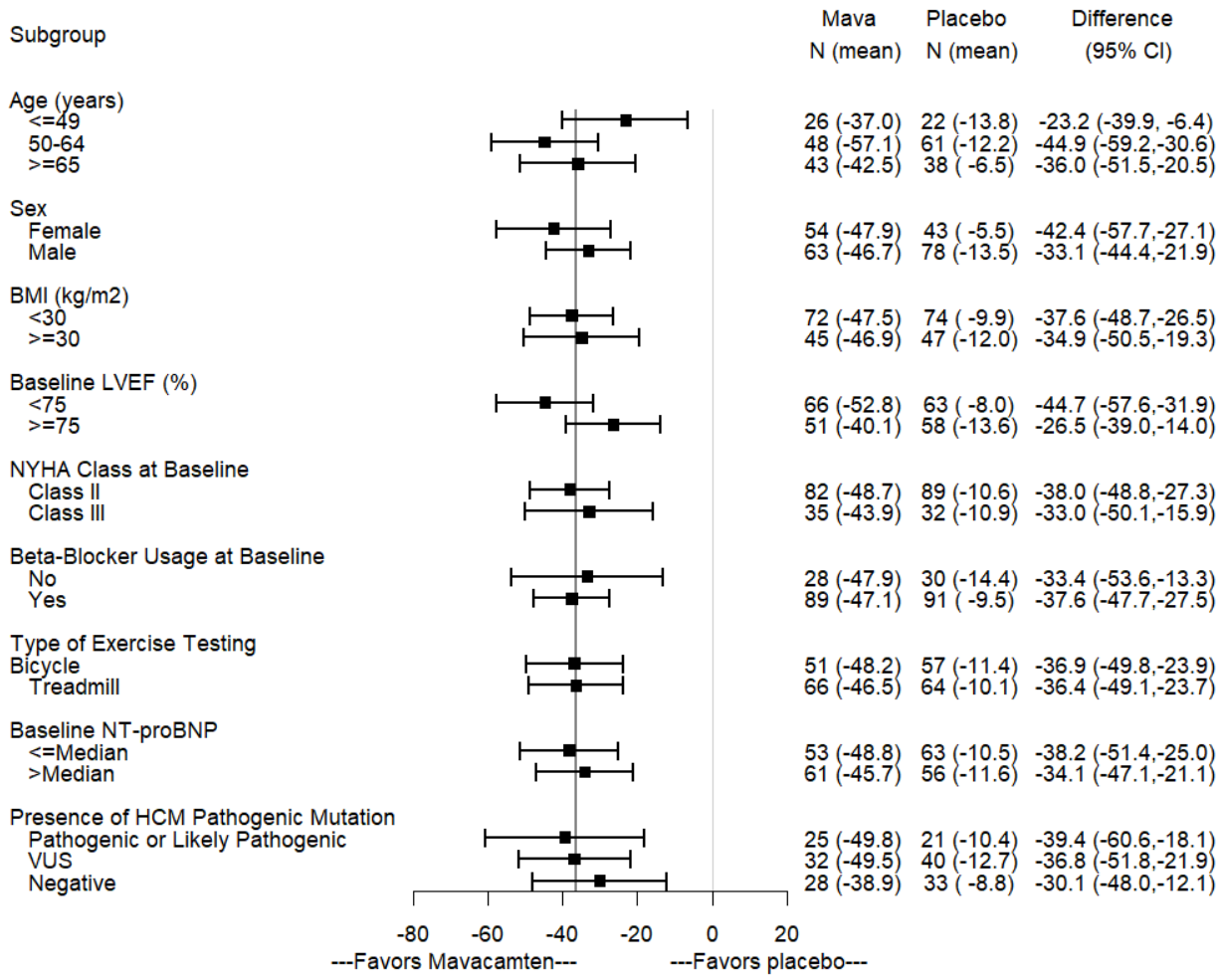
FIGURES

Figure 1. Changes in LVOT gradient, Biomarkers and LVEF over Time.



LVEF denotes left ventricular ejection fraction and LVOT, left ventricular outflow tract. . NT-proBNP, N-terminal pro B-type natriuretic peptide, and hs-cTnI, high sensitivity cardiac troponin I.

Figure 2: Forest Plot of Treatment Effect on Change in Post-exercise LVOT Gradient Across Subgroups.



BMI denotes body mass index, LVEF, left ventricular ejection fraction, LVOT, left ventricular outflow tract, NYHA, New York Heart Association, NT-proBNP, N-terminal pro B-type natriuretic peptide, and VUS, variant of uncertain significance.

SUPPLEMENTARY APPENDIX

Contents

Study Investigators

<<Please provide full list of study investigators. MyoK will fill in>>

Belgium—; Czech Republic—; Denmark—; France—; Germany—; Israel—; Italy—;

Netherlands—; Poland—; Portugal—; Spain—; United Kingdom—; United States—

Supplementary Methods

Temporary treatment discontinuation

Dosing was temporarily discontinued based on prespecified safety criteria of left ventricular ejection fraction (LVEF) <50%, plasma drug concentration >1000 ng/mL, and excessive QT interval corrected using Fridericia's formula (QTcF) prolongation. Criteria for excessive QTcF prolongation depended on QRS width as determined by the electrocardiogram (ECG) core laboratory:

- If QRS was narrow (<120 ms), then temporary discontinuation criteria were the smaller of a 15% increase from baseline QTcF OR QTcF ≥520 ms
- If QRS was wide (≥120 ms), then temporary discontinuation criteria were the smaller of a 15% increase from baseline QTcF OR QTcF ≥550 ms

If one or more criteria was met, the study drug was discontinued and patients returned for reassessment 2-4 weeks later. If the parameter(s) returned to an acceptable range, the study drug was restarted at a reduced dose 2-4 weeks after the reassessment visit (total time 4-6 weeks). Sham discontinuation alerts were also programmed in the interactive response system (IXRS) to maintain blinding.

Statistical analyses

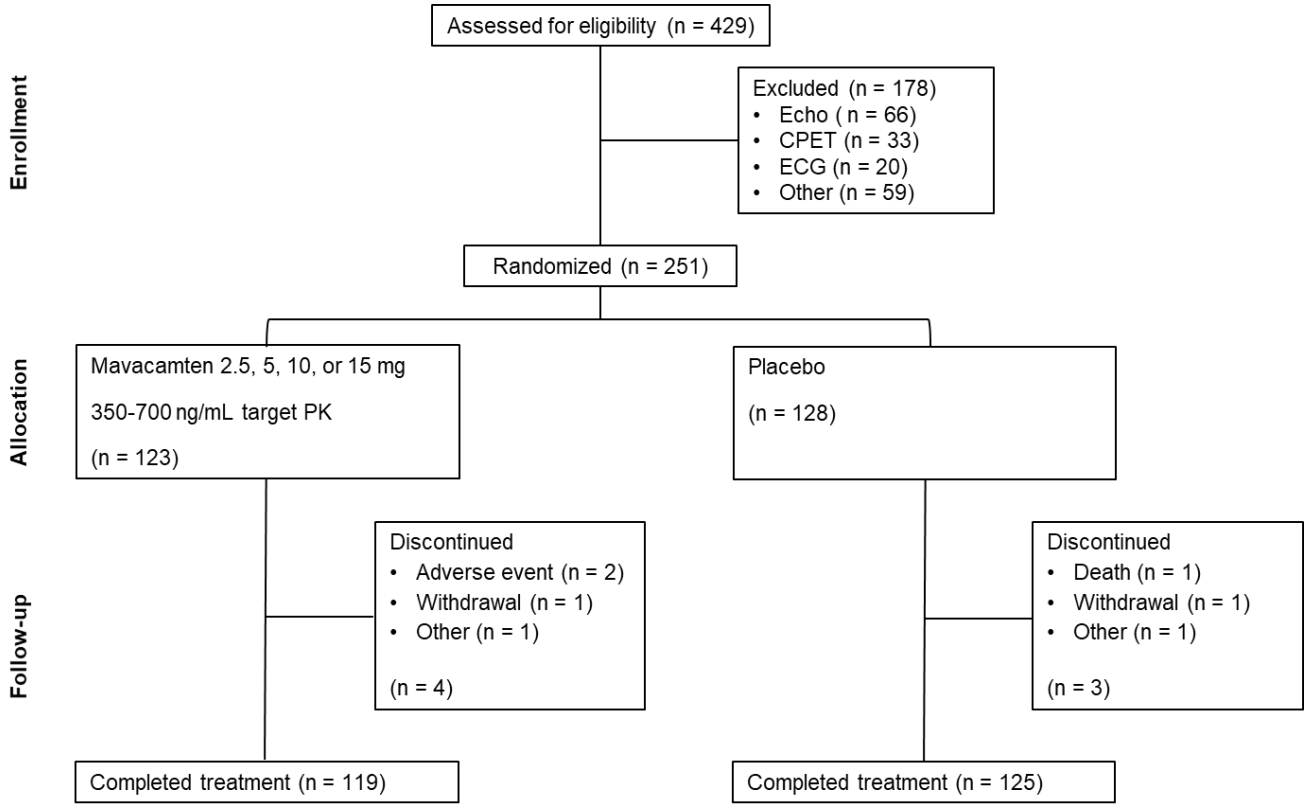
The primary composite endpoint was analyzed using the Cochran–Mantel–Haenszel test stratified by baseline New York Heart Association (NYHA) Class, beta-blocker use, and ergometer type (based on the IXRS). The P value and 95% confidence interval (CI) were derived using an exact method. If week 30 pVO_2 was missing, no imputation was performed, and the patient was considered a non-responder. If pVO_2 was available but NYHA Class was missing at week 30, NYHA Class was imputed with data from week 26, if available. Patients whose response status was missing at week 30 were classified as non-responders.

Continuous secondary endpoints (left ventricular outflow tract [LVOT] gradient and peak oxygen consumption [pVO_2]) and were analyzed using an analysis of variance (ANOVA) model with treatment group (mavacamten vs placebo), corresponding baseline value, and stratification factors (beta-blocker use, NYHA Class, and ergometer type) as fixed effects. The categorical secondary endpoint (proportion of patients with ≥1 NYHA Class improvement) was analyzed using the Cochran–Mantel–Haenszel test stratified on NYHA Class, beta-blocker use, and ergometer type (based on IXRS). The P value and 95% CI were derived using an exact method. If the NYHA Class was missing at week 30, it was imputed with the NYHA class at week 26, if available. PROs were assessed using a mixed model for repeated measurements (MMRM) controlling for baseline value, treatment group, time points, the interaction between treatment and timepoint, and stratification factors (beta-blocker use, NYHA Class, and ergometer type) as fixed effects and subject as random effect. All post-baseline data up to week 30 were included in the model.

The exploratory endpoints of resting and Valsalva LVOT gradient were analyzed using an ANOVA model with treatment group (mavacamten vs placebo), corresponding baseline value, and stratification factors (beta-blocker use, NYHA Class, and ergometer type) as fixed effects. ***<<please confirm>>*** LVEF was analyzed using MMRM controlling for baseline value, treatment group, time points, the interaction between treatment and timepoint, and stratification factors (beta-blocker use, NYHA Class, and ergometer type) as fixed effects and subject as random effect. For the exploratory biomarker endpoints, the geometric mean ratio, 95% Cis, and P values were estimated using MMRM with data up to Week 30 using the log transformed variables by controlling for baseline value, treatment group, time point, interaction between treatment and time, and stratification factors (beta-blocker use, NYHA Class, and ergometer type).

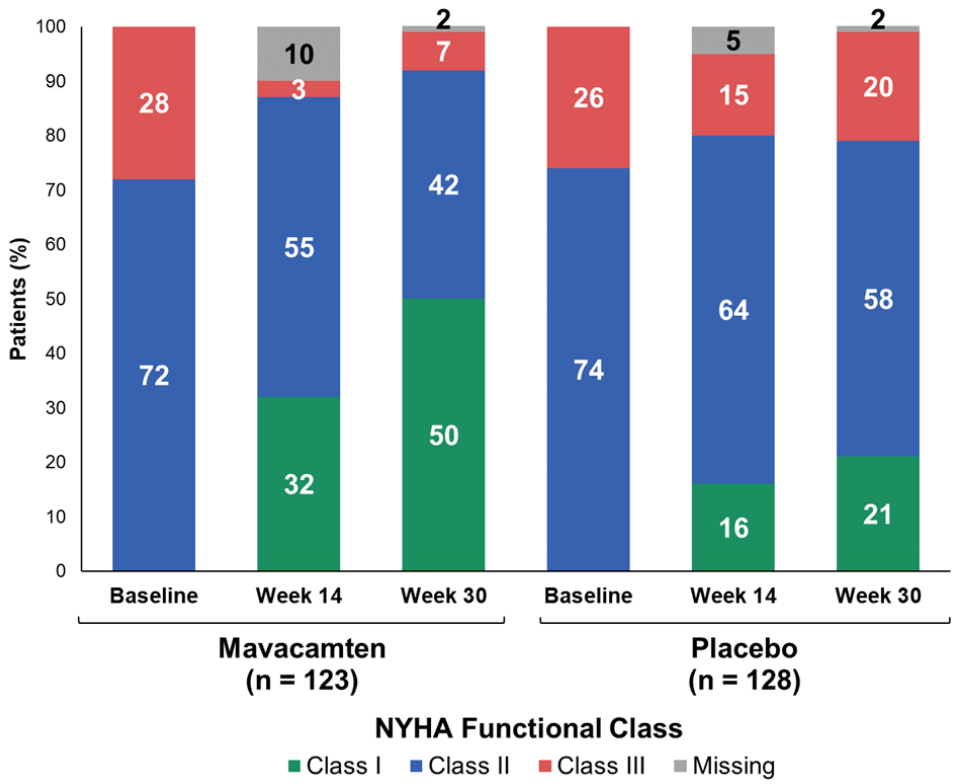
Selected efficacy endpoints were analyzed by pre-specified subgroups at baseline per the Statistical Analysis Plan. A forest plot summarizing the 95% CIs of the treatment effect on change from baseline to week 30 in post-exercise LVOT gradient across subgroups was generated.

Figure S1. Screening, Enrollment, and Follow-up.



All randomized patients were included in the efficacy analysis. All randomized patients received ≥1 dose of study drug and were included in the efficacy and safety analyses. CPET denotes cardiopulmonary exercise testing, Echo, echocardiography, ECG, electrocardiogram, and PK, pharmacokinetic.

Figure S2. Change in NYHA Functional Class over Time.



NYHA denotes New York Heart Association.

Table S1. Key Exploratory Efficacy Endpoints

	Mavacamten	Placebo	Difference (95% CI)
Post-exercise LVOT peak gradient <50 mm Hg,* n/N (%)	75/101 (74.3)	22/106 (20.8)	53.5 (42.0. 65.0)
Post-exercise LVOT peak gradient <30 mm Hg,† n/N (%)	64/113 (56.6)	8/113 (7.1)	49.6 (39.3, 59.8)
Optimal response,‡ n/N (%)	32/117 (27.4)	1/126 (0.8)	26.6 (18.3, 34.8)

*****Threshold for guideline-based invasive intervention.

†Threshold for guideline-based diagnosis of obstruction.

‡Defined as NYHA Class I and all LVOT peak gradients <30 mm Hg (post-exercise, resting, and Valsalva).

LVOT denotes left ventricular outflow tract and NYHA, New York Heart Association.

Table S2. Summary of Treatment-Emergent Adverse Events (TEAEs)

Adverse Events Preferred Term	Mavacamten N=123 Any Grade n (%)	Placebo N=128 Any Grade n (%)	Mavacamten N=123 Grade 3 or higher n (%)	Placebo N=128 Grade 3 or higher n (%)
Total number of TEAEs, Grade 3 or higher			10 (2.4)	21 (5.0)
Number of patients with ≥1 TEAE	108 (87.8)	101 (78.9)	8 (6.5)	13 (10.2)
Cardiovascular TEAEs occurring in ≥1% of patients in any group				
Atrial fibrillation	8 (6.5)	9 (7.0)	2 (1.6)	3 (2.3)
Palpitations	8 (6.5)	9 (7.0)	0	0
Cardiac failure	2 (1.6)	5 (3.9)	0	0
Ventricular tachycardia	2 (1.6)	2 (1.6)	0	0
Stress cardiomyopathy	2 (1.6)	0	1 (0.8)	0
Angina pectoris	1 (0.8)	5 (3.9)	0	0

Grade 3 = severe, life-threatening or fatal

Table S3. Summary of Patients with LVEF <50%

Patient	Treatment Group	Visit Sequence*	LVEF (%)	NYHA	NT-proBNP (ng/mL)	W30 Efficacy Assessments	SAE/AEs on or near time of Low LVEF
1	Mavacamten	D1 W4 **W6** W30	92 74 **35** 83	II II II I	D1 - 220 W4 - 109 W6 - 86 W30 - 59	No increase in pVO2 LVOT gradient <30 KCCQ +7.3	66 yo F with SAE stress cardiomyopathy at W6 with BNP rise to 1132. Recovered and resumed dosing after 8 week interruption.
2	Mavacamten	D1 W12 **W18** W30	70 53 **45** 65	II I I I	D1 - 416 W12 - 115 W18 - 152 W30 - 203	Improve pVO2 +6.6 LVOT gradient <30 KCCQ +21.9	60 yo M with AE dyspnea from W19-21.
3	Mavacamten	D1 W12 **W18** W30	84 69 **43** 73	III II II II	D1 - 1342 W12 - 96 W18 - 70 W30 - 166	Improve pVO2 +2.3 LVOT gradient >50 KCCQ -3.7	55 yo M with no preceding AEs.
4	Placebo	D1 **W4** W30	54 **49** 60	III III II	D1 - 434 W4 - 572 W30 - 681	No increase in pVO2 LVOT gradient >50	56 yo M with AE palpitations from W4-12 in patient with history of AF.

5	Placebo	D1 W6 **W12** W30	64 64 **42** 57	II II III II	D1 – 4858 W6 - 5311 W12 - 4345 W30 - 5252	No increase in pVO2 LVOT gradient >50 KCCQ +21.3	70 yo M with no reported AEs.
6	Mavacamten	D1 W26 **W30**	70 64 **48**	II II II	D1 - 434 W26 - 16 W30 - 11	No increase in pVO2 LVOT gradient <30 KCCQ -2.1	49 yo M with AE arthralgia W19-30.
7	Mavacamten	D1 W26 **W30**	74 61 **49**	II I II	D1 - 864 W26 - 174 W30 - 121	No increase in pVO2 LVOT gradient <30 KCCQ +21.4	62 yo M with AE nasopharyngitis W26-28.
8	Mavacamten	D1 W26 **W30**	66 61 **49**	II II II	D1 - 634 W26 - 343 W30 - 1164	No increase in pVO2 LVOT gradient <30 KCCQ – no W30	50 yo M with new onset AF from W26 through EOT. SAE infection W27-29.
9	Mavacamten	D1 W26 **W30**	80 55 **49**	III II II	D1 - 136 W26 - 319 W30 - 1494	No increase in pVO2 LVOT gradient <30 KCCQ +34.9	35 yo M with history of ongoing AF. AE at W30 dyspnea, fatigue followed by SAE in post-treatment period, including AF with RVR, ablation.

LVOT denotes left ventricular outflow tract, NT-proBNP,N-terminal pro B-type natriuretic peptide, NYHA, New York Heart Association, KCCQ, Kansas City Cardiomyopathy Questionnaire