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ORIGINAL INVESTIGATIONS

Evaluation of Mavacamten in Symptomatic Patients With Nonobstructive Hypertrophic Cardiomyopathy

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ABSTRACT

BACKGROUND Patients with nonobstructive hypertrophic cardiomyopathy (nHCM) often experience a high burden of symptoms; however, there are no proven pharmacological therapies. By altering the contractile mechanics of the cardiomyocyte, myosin inhibitors have the potential to modify pathophysiology and improve symptoms associated with HCM.

OBJECTIVES MAVERICK-HCM (Mavacamten in Adults With Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy) explored the safety and efficacy of mavacamten, a first-in-class reversible inhibitor of cardiac-specific myosin, in nHCM.

METHODS The MAVERICK-HCM trial was a multicenter, double-blind, placebo-controlled, dose-ranging phase II study in adults with symptomatic nHCM (New York Heart Association functional class II/III), left ventricular ejection fraction (LVEF) ≥55%, and N-terminal pro–B-type natriuretic peptide (NT-proBNP) ≥300 pg/ml. Participants were randomized 1:1:1 to mavacamten at a pharmacokinetic-adjusted dose (targeting plasma levels of 200 or 500 ng/ml), or placebo for 16 weeks, followed by an 8-week washout. Initial dose was 5 mg daily with 1 dose titration at week 6.

RESULTS Fifty-nine participants were randomized (19, 21, 19 patients to 200 ng/ml, 500 ng/ml, placebo, respectively). Their mean age was 54 years, and 58% were women. Serious adverse events occurred in 10% of participants on mavacamten and in 21% participants on placebo. Five participants on mavacamten had reversible reduction in LVEF ≤45%. NT-proBNP geometric mean decreased by 53% in the pooled mavacamten group versus 1% in the placebo group, with geometric mean differences of −435 and −6 pg/ml, respectively ($p = 0.0005$). Cardiac troponin I (cTnI) geometric mean decreased by 34% in the pooled mavacamten group versus a 4% increase in the placebo group, with geometric mean differences of −0.008 and 0.001 ng/ml, respectively ($p = 0.009$).

CONCLUSIONS Mavacamten, a novel myosin inhibitor, was well tolerated in most subjects with symptomatic nHCM. Furthermore, treatment was associated with a significant reduction in NT-proBNP and cTnI, suggesting improvement in myocardial wall stress. These results set the stage for future studies of mavacamten in this patient population using clinical parameters, including LVEF, to guide dosing. (A Phase 2 Study of Mavacamten in Adults With Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy [MAVERICK-HCM]; NCT03442764) (J Am Coll Cardiol 2020;75:2649–60)

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ABBREVIATIONS AND ACRONYMS

cTnI = cardiac troponin I

HCM = hypertrophic cardiomyopathy

LV = left ventricular

LVEF = left ventricular ejection fraction

nHCM = nonobstructive hypertrophic cardiomyopathy

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

NYHA = New York Heart Association

oHCM = obstructive hypertrophic cardiomyopathy

PK = pharmacokinetic

pVO_2 = peak oxygen consumption

SAE = serious adverse event

ITT = intention to treat

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder that is often caused by sarcomeric gene variants and is characterized by unexplained left ventricular (LV) hypertrophy. HCM is typically divided into 2 broad categories (1,2): obstructive hypertrophic cardiomyopathy (oHCM; also known as HOCM), which is characterized by dynamic LV outflow tract obstruction; or nonobstructive hypertrophic cardiomyopathy (nHCM), which has no significant LV outflow tract obstruction (<30 mm Hg) at rest or with provocation (3). Regardless of the hemodynamic features,

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fundamental research has provided growing evidence of a shared underlying biomechanical abnormality. Sarcomeric gene variants that cause HCM can destabilize the low-energy, super-relaxed state of cardiac myosin and promote excessive cross-bridging with actin (4,5), culminating in the hypercontractility and impaired relaxation that are hallmarks of this disease (6).

Clinical management of HCM focuses on relieving symptoms. For patients with oHCM, lowering intracavitary gradients is a major therapeutic target to achieve symptom relief. Treatment strategies are much more limited for patients with nHCM. Current strategies focus on managing arrhythmias, particularly atrial fibrillation, and attempting to improve LV filling or congestion with beta-blockers, verapamil, and diuretics (2). Cardiac transplantation may be the only option for patients with severe refractory symptoms. Furthermore, recent studies have revealed more cumulative morbidity with nHCM than previously suspected, with a similar incidence of clinical events as patients with severe oHCM (7,8). Previous trials in nHCM targeting sodium transit, calcium trafficking, fibrosis, and cellular energetics with existing pharmacotherapies (ranolazine [9], eleclazine [10], spironolactone [11], losartan [12,13], perhexiline, and trimetazidine [14]) have been unsuccessful.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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Collectively, these issues highlight the inherent challenges and the pressing need to develop effective therapy for nHCM.

Mavacamten is a novel, first-in-class, small molecule, allosteric inhibitor of cardiac-specific myosin adenosine triphosphatase. It specifically reduces excessive cross-bridging with actin, which is believed to be an important contributor to the pathological hypercontractility associated with HCM (15–17). Mavacamten was well tolerated and effective in patients with oHCM in the phase II PIONEER-HCM (A Phase 2 Open-label Pilot Study Evaluating MYK-461 in Subjects With Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction; NCT02842242) study (18) and is currently being evaluated in patients with oHCM in the phase III EXPLORER-HCM (Clinical Study to Evaluate Mavacamten [MYK-461] in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy; NCT03470545) study. Moreover, in addition to relieving obstructive physiology by decreasing contractility, there is mechanistic evidence that mavacamten may also improve the abnormal relaxation and impaired myocardial energetics associated with HCM and that presumably drive symptoms in nHCM (16,19,20). Treatment with mavacamten stabilized the super-relaxed state of myosin, improving diastolic function and energetics in in vitro and in vivo animal models of HCM (21). Thus, we hypothesized that mavacamten could be beneficial for nHCM.

The primary objective of this phase II study was to assess the safety and tolerability of mavacamten in patients with symptomatic nHCM. Key exploratory objectives assessed the impact on symptoms, functional capacity, echocardiographic measures of diastolic and systolic function, and serum biomarkers.

METHODS

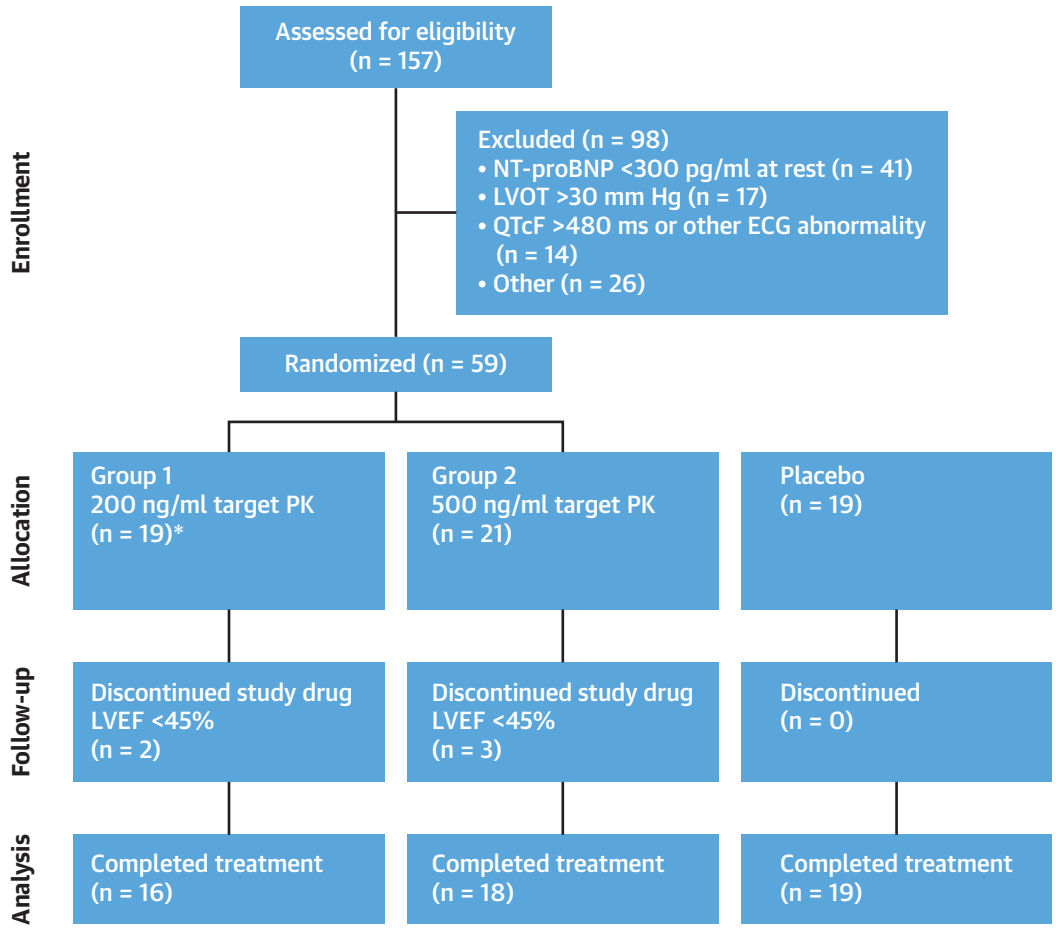
STUDY DESIGN. MAVERICK-HCM (Mavacamten in Adults With Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy [MAVERICK-HCM]; NCT03442764) was a phase II multicenter, exploratory, dose-ranging, double-blind, randomized, placebo-controlled study to assess the safety and tolerability of mavacamten in patients with symptomatic nHCM. Study participants received mavacamten for 16 weeks, with doses titrated at week 6 to target 1 of 2 serum drug concentrations (group 1: approximately 200 ng/ml; group 2: approximately 500 ng/ml) or placebo, followed by an 8-week post-treatment washout period. Participants who received beta-blockers or calcium-channel blockers at baseline were allowed to continue if the dose remained stable for at least 2 weeks before screening and was anticipated to remain unchanged throughout the treatment period.

Blinded dose adjustments were based on pharmacokinetic (PK) parameters and not clinical response or left ventricular ejection fraction (LVEF). Participants who completed the entire 16-week treatment course and full study were offered participation in an extension study in which all patients receive mavacamten (A Long-Term Safety Extension Study of Mavacamten in Adults Who Have Completed MAVERICK-HCM or EXPLORER-HCM; NCT03723655). The clinical research protocol was approved by the participating sites' institutional review boards. An independent Data Monitoring Committee regularly assessed interim safety data and advised on important emerging study conduct issues. The study conformed to the current revision of the Declaration of Helsinki and with the International Conference for Harmonization Good Clinical Practice regulations and guidelines.

STUDY POPULATION. Adults 18 years or older with body weight ≥45 kg were screened for eligibility (Supplemental Table 1). Participants with a diagnosis of nHCM consistent with current American and European guidelines, symptomatic (defined as being New York Heart Association [NYHA] functional class II/III), an elevated N-terminal pro–B-type natriuretic peptide (NT-proBNP) level >300 pg/ml (upper limit of normal was 125 pg/ml), LVEF ≥55%, and LV wall thickness ≥15 or ≥13 mm with a family history of HCM were included. Participants with resting or provocable (by Valsalva maneuver and/or exercise) LV outflow tract or an intracavitary gradient >30 mm Hg were excluded. Participants were expected to understand and comply with the study procedures, including the risks involved in the study, and provide written informed consent. Participants had to have normal safety laboratory parameters at baseline and follow strict measures to avoid pregnancy.

RANDOMIZATION. Participants were randomized 1:1:1 to group 1, group 2, or placebo, and stratified according to current treatment with beta-blocker and cardiopulmonary exercise testing ergometer type. Participants started on placebo or mavacamten at 5 mg/day. PKs were measured at week 4, and dose was adjusted at week 6 to 1 of 4 dose strengths (2.5, 5, 10, or 15 mg) based on group assignment. Blinded dosing adjustments were made only to target prespecified plasma drug levels and not based on changes in symptoms (NYHA functional class) or clinical parameters (e.g., NT-proBNP, troponin, LVEF). Protocol-defined treatment stop criteria were handled in the blinded environment via integration

FIGURE 1 CONSORT Diagram



CONSORT (Consolidated Standards of Reporting Trials) diagram. *One participant was randomized but not treated due to an AE. AE = adverse event; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PK = pharmacokinetic; QTcF = QT corrected using Fridericia's method.

of data from core laboratories into the interactive response system. Stop criteria included LVEF ≤45%, plasma drug concentration ≥1,000 ng/ml, or Fridericia-corrected QT interval of ≥500 ms.

STUDY ENDPOINTS. The primary objective was to evaluate the safety and tolerability of a 16-week course of mavacamten. Safety and exploratory efficacy analyses are described in detail in the following text and in the Supplemental Methods section. An exploratory composite functional endpoint that assessed study drug impact on peak oxygen consumption (pVO_2) and NYHA functional class was also evaluated. Specifically, the composite functional endpoint was defined as achieving the following at week 16 compared with baseline: 1) an improvement of at least 1.5 ml/kg/min in pVO_2 and a reduction of ≥1 NYHA functional class (type I); or 2) an improvement of ≥3.0 ml/kg/min in pVO_2 with no worsening in NYHA functional class (type II). This endpoint was included because it is serving as the primary endpoint for the EXPLORER-HCM trial in obstructive HCM.

STUDY ASSESSMENTS. Study assessments were performed per protocol with details provided in the Supplemental Methods section.

HCM GENOTYPING. HCM genetic testing was offered as an optional test to all participants, using the Hypertrophic Cardiomyopathy Panel from Invitae (Invitae, San Francisco, California). Details are provided in the Supplemental Methods section.

STATISTICAL ANALYSIS. A total of 60 participants were planned for the study, with equal allocation to

TABLE 1 Demographics and Baseline Characteristics

	Group 1 Mavacamten ~200 ng/ml (n = 19)	Group 2 Mavacamten ~500 ng/ml (n = 21)	Pooled Mavacamten (n = 40)	Placebo (n = 19)
Age, yrs	58.3 ± 13.7	50.0 ± 14.7	54.0 ± 14.6	53.8 ± 18.2
Female	9 (47.4)	12 (57.1)	21 (52.5)	13 (68.4)
Race				
Asian	1 (5.3)	0 (0.0)	1 (2.5)	0 (0.0)
Black or African American	1 (5.3)	1 (4.8)	2 (5.0)	0 (0.0)
White	17 (89.5)	18 (85.7)	35 (87.5)	17 (89.5)
Unknown	0 (0.0)	2 (9.5)	2 (5.0)	2 (10.5)
BMI, kg/m^2	28.8 ± 4.1	29.8 ± 6.1	29.3 ± 5.2	31.0 ± 4.9
Consented to optional HCM genotyping	14 (73.7)	14 (66.7)	28 (70.0)	12 (63.2)
Pathogenic or likely pathogenic HCM gene mutation of 40 with genetic testing	7 (50.0)	7 (50.0)	14 (50.0)	8 (66.7)
NT-proBNP (pg/ml) geometric mean	889 (747–1,575)	763 (606–1,261)	821 (790–1,293)	914 (770–1,558)
cTnI (ng/ml) geometric mean	0.024 (0–0.503)	0.023 (0.016–0.080)	0.023 (0–0.253)	0.020 (0.013–0.119)
cTnI >0.03 ng/ml*	6 (31.6)	7 (33.3)	13 (32.5)	6 (31.6)
NYHA functional class				
II	15 (78.9)	18 (85.7)	33 (82.5)	13 (68.4)
III	4 (21.1)	3 (14.3)	7 (17.5)	6 (31.6)
Peak VO_2, ml/kg/min	19.5 ± 5.2	21.0 ± 6.6	20.4 ± 6.0	17.9 ± 5.1
Maximal LV wall thickness, mm	20.9 ± 3.0	20.4 ± 4.8	20.6 ± 4.0	18.8 ± 3.5
LVEF, %	68.0 ± 5.2	69.4 ± 5.8	68.7 ± 5.5	66.4 ± 7.7
Lateral e′, cm/s	8.5 ± 3.8	7.7 ± 2.6	8.1 ± 3.2	7.8 ± 3.6
Septal e′, cm/s	5.3 ± 2.0	4.5 ± 1.6	4.9 ± 1.8	4.4 ± 1.7
E/e′ average	13.9 ± 5.4	14.2 ± 7.7	14.1 ± 6.6	18.5 ± 9.9
LVEDV, ml	59.5 ± 14.5	58.5 ± 18.6	58.9 ± 16.6	60.5 ± 21.6
LA volume index, ml/m^2	40.3 ± 16.1	34.5 ± 8.9	37.3 ± 13.0	40.8 ± 15.2
Peak gradient, mm Hg	8.1 ± 3.3	9.4 ± 3.6	8.8 ± 3.5	7.8 ± 2.5
Background HCM therapy				
Beta-blocker	12 (63.2)	13 (61.9)	25 (62.5)	12 (63.2)
Calcium-channel blocker	5 (26.3)	5 (23.8)	10 (25.0)	3 (15.8)
Neither	3 (15.8)	3 (14.3)	6 (15.0)	4 (21.1)

Values are mean ± SD, n (%), or mean (95% confidence interval). *99th percentile.

BMI = body mass index; CI = confidence interval; cTnI = cardiac troponin I; HCM = hypertrophic cardiomyopathy; LA = left atrial; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; NT-proBNP = N-terminal pro–B-type natriuretic peptide.

each treatment arm. Due to the exploratory nature of the study, no formal power calculations were conducted. Safety analyses were performed on all randomized participants who received at least 1 dose of study drug according to the treatment actually received, whereas efficacy analyses were performed on the intent-to-treat (ITT) population. In addition, change in key efficacy measures were also evaluated for subgroups of participants with elevated cardiac troponin I (cTnI) at baseline (pre-specified) and elevated E/e′ averaged from the septal and lateral walls (post hoc). cTnI results below the limit of detection (0.01 ng/ml) were imputed as one-half the limit (e.g., 0.005 ng/ml) for analysis. Post hoc analyses of high-sensitivity cTnI were performed on banked serum samples from baseline and week 16 using the ADVIA Centaur XPT immunoassay system (Siemens Healthineers, Berkeley, California).

For exploratory efficacy analyses, the difference between each active group versus placebo, as well as pooled active versus placebo was evaluated using the nonparametric Wilcoxon-Mann-Whitney *U* test, both with and without adjusting for stratification factors. Similarly, for categorical analyses, both the stratified Cochran-Mantel-Haenszel test and unstratified chi-square test were used. The study was not adequately powered to detect statistically significant treatment differences, and all p values presented here are descriptive in nature. For analyses focused on the elevated cTnI subset, results from the 2 mavacamten groups were pooled because of the size of this subset. Post hoc Pearson's correlation analyses and simple linear regression were performed to explore the strength of linear relationships on the difference of the log-transformed (whenever appropriate) data for specific parameters of interest. SAS version 9.4 (SAS

TABLE 2 TEAEs During Treatment and Washout (to 24 Weeks)

	Group 1 Mavacamten ~200 ng/ml (n = 18)	Group 2 Mavacamten ~500 ng/ml (n = 21)	Pooled Mavacamten (n = 39)	Placebo (n = 19)
Total no. of TEAEs	66	73	139	41
Participants with ≥1 TEAE	16 (88.9)	19 (90.5)	35 (89.7)	13 (68.4)
Occurred in ≥10.0% of participants in any group				
Dizziness	3 (16.7)	4 (19.0)	7 (17.9)	1 (5.3)
Palpitations	1 (5.6)	5 (23.8)	6 (15.4)	3 (15.8)
Fatigue	2 (11.1)	3 (14.3)	5 (12.8)	3 (15.8)
Dyspnea	1 (5.6)	3 (14.3)	4 (10.3)	3 (15.8)
Nasopharyngitis	2 (11.1)	2 (9.5)	4 (10.3)	2 (10.5)
Upper respiratory tract infection	1 (5.6)	3 (14.3)	4 (10.3)	0 (0.0)
Constipation	2 (11.1)	2 (9.5)	4 (10.3)	0 (0.0)
Nausea	2 (11.1)	2 (9.5)	4 (10.3)	2 (10.5)
Atrial fibrillation	0 (0.0)	3 (14.3)	3 (7.7)	1 (5.3)
Abdominal distension	2 (11.1)	0 (0.0)	2 (5.1)	0 (0.0)
Tooth abscess	2 (11.1)	0 (0.0)	2 (5.1)	0 (0.0)
Sinusitis	1 (5.6)	0 (0.0)	1 (2.6)	2 (10.5)
Total no. of SAEs	3	3	6	4
Participants with ≥1 SAE	2 (11.1)	2 (9.5)	4 (10.3)	4 (21.1)
Atrial fibrillation	0 (0.0)	2 (9.5)	2 (5.1)	1 (5.3)
Systolic dysfunction	0 (0.0)	1 (4.8)	1 (2.6)	0 (0.0)
Angina pectoris	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Atrial flutter	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Coronary artery disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Arthritis	1 (5.6)	0 (0.0)	1 (2.6)	0 (0.0)
Mental status changes	1 (5.6)	0 (0.0)	1 (2.6)	0 (0.0)
Renal failure	1 (5.6)	0 (0.0)	1 (2.6)	0 (0.0)

Values are n or n (%).
SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Institute, Cary, North Carolina) was used for statistical analyses, tabulations, and graphic presentations.

RESULTS

PARTICIPANT DISPOSITION AND CHARACTERISTICS. In total, 157 participants were assessed for eligibility and 59 were enrolled (19 in group 1, 21 in group 2, and 19 in the placebo group) from 35 sites in the United States (Figure 1). One participant randomized to group 1 withdrew from the study due to an adverse event that occurred before receiving treatment. Five participants discontinued treatment during the study due to meeting a protocol-defined stop criterion (LVEF ≤45%) but completed subsequent study visits through week 24.

Baseline characteristics are described in Table 1. Of the 59 symptomatic participants with nHCM (58% women), the mean age was 54 years (range: 18 to 90 years), and 78% of participants were in NYHA functional class II. The mean resting LVEFs at baseline for the pooled mavacamten population and the placebo group were 68.7 ± 5.5% and 66.4% ± 7.7%, respectively; 63% of participants were taking beta-blockers at baseline. Compared with the pooled mavacamten group, the placebo group had a higher proportion of women (mavacamten: 52.5% vs. placebo: 68.4%), more NYHA functional class III participants (mavacamten: 17.5% vs. placebo: 31.6%), and a modestly lower mean pVO_2 (mavacamten: 20.4 ± 6.0 ml/kg/min vs. placebo: 17.9 ± 5.1 ml/kg/min). Of the enrolled population, 40 elected to undergo genetic testing, of whom 22 were found to have a pathogenic or likely pathogenic sarcomeric gene mutation, and an additional 7 participants had a sarcomeric gene variant of unknown significance.

Analysis of baseline serum biomarkers (Table 1) revealed a geometric mean NT-proBNP of 821 pg/ml for the pooled mavacamten group and 914 pg/ml for the placebo group. For cTnI, the baseline geometric mean was 0.023 ng/ml for the pooled mavacamten group and 0.020 ng/ml for the placebo group. Forty participants had a detectable cTnI level, and among those, 19 (32%) had an elevated cTnI (>0.03 ng/ml or >99th percentile; 13 participants on mavacamten and 6 participants on placebo). For those with detectable cTnI, baseline geometric mean cTnI level was 0.03 ng/ml in the pooled mavacamten group and 0.05 ng/ml in the placebo group. Baseline $E/e'_{average}$ was elevated (>14) in 25 of 59 (42.4%) participants.

MAVACAMTEN DOSING. Exploratory analyses in this concentration-targeted, PK-based, and dose-ranging study aimed to identify potential optimal dosing strategies and measures of clinical response for symptomatic nHCM. For participants treated with mavacamten, target mean drug concentration of approximately 200 ng/ml (group 1) was achieved after approximately 4 weeks of dosing with mavacamten, whereas target mean drug concentration of approximately 500 ng/ml (group 2) was achieved after approximately 8 weeks of dosing (after dose titration at week 6) (Supplemental Figure 1).

PRIMARY ANALYSIS: SAFETY AND TOLERABILITY. In this exploratory, dose-ranging study (without a protocol-allowed mechanism for down-titration for exaggerated on-target pharmacology), mavacamten was well tolerated with the exception of 5 participants who discontinued treatment due to meeting pre-specified stopping criteria for a decrease in LVEF to <45%. A treatment-emergent adverse event was experienced by 90% of mavacamten-treated participants and 68% of placebo-treated participants (Table 2). The most common treatment-emergent

adverse events reported by participants in the mavacamten group were palpitations, dizziness, and fatigue; most were described as mild (76%) or moderate (21%), and self-limiting.

As listed in **Table 2**, a total of 8 participants (4 on mavacamten and 4 on placebo) experienced treatment emergent serious adverse events (SAEs). Most SAEs were cardiovascular in nature, and all participants recovered without long-term sequelae. Four (10.3%) participants in the pooled mavacamten group experienced 6 SAEs (atrial fibrillation, systolic dysfunction, arthritis, mental status changes, and renal failure) and 4 (21.1%) participants in the placebo group experienced 4 SAEs (atrial fibrillation, angina pectoris, atrial flutter, and coronary artery disease). The most common SAE in the study was atrial fibrillation and/or atrial flutter, which occurred in both the pooled mavacamten (n = 2; 5.1%) and placebo (n = 2; 10.5%) groups; all in participants with a history of atrial fibrillation.

Following dose adjustment at week 6, in group 1, there was 1 participant on 2.5 mg mavacamten, 15 on 5 mg, and 2 on 10 mg. In group 2, there were 4 participants on 5 mg mavacamten, 9 on 10 mg, and 8 on 15 mg. The overall change in LVEF was modest (mean absolute change in LVEF): group 1 −2.3 ± 5.3%; group 2 −5.6 ± 9.7%; pooled mavacamten −4.1 ± 8.0%; and placebo −2.3 ± 4.9%. However, planned echocardiographic assessment at weeks 11 to 12 identified 5 participants (12.5%; 2 participants in group 1, 3 in group 2) with a decrease in LVEF to ≤45% (range: 38% to 45%), which led to discontinuation of study drug per pre-specified stopping rules. Details regarding these 5 participants are provided in Supplemental Table 2. Four of the 5 participants (3 in group 2 and 1 in group 1) underwent the protocol-defined, concentration-targeted dose up-titration from 5 to 10 mg at week 6. The fifth participant (participant 5, group 1) remained on 5 mg. Per protocol, dose adjustments were based only on the PK-guided study design, and not guided by changes in clinical symptoms or monitoring parameters.

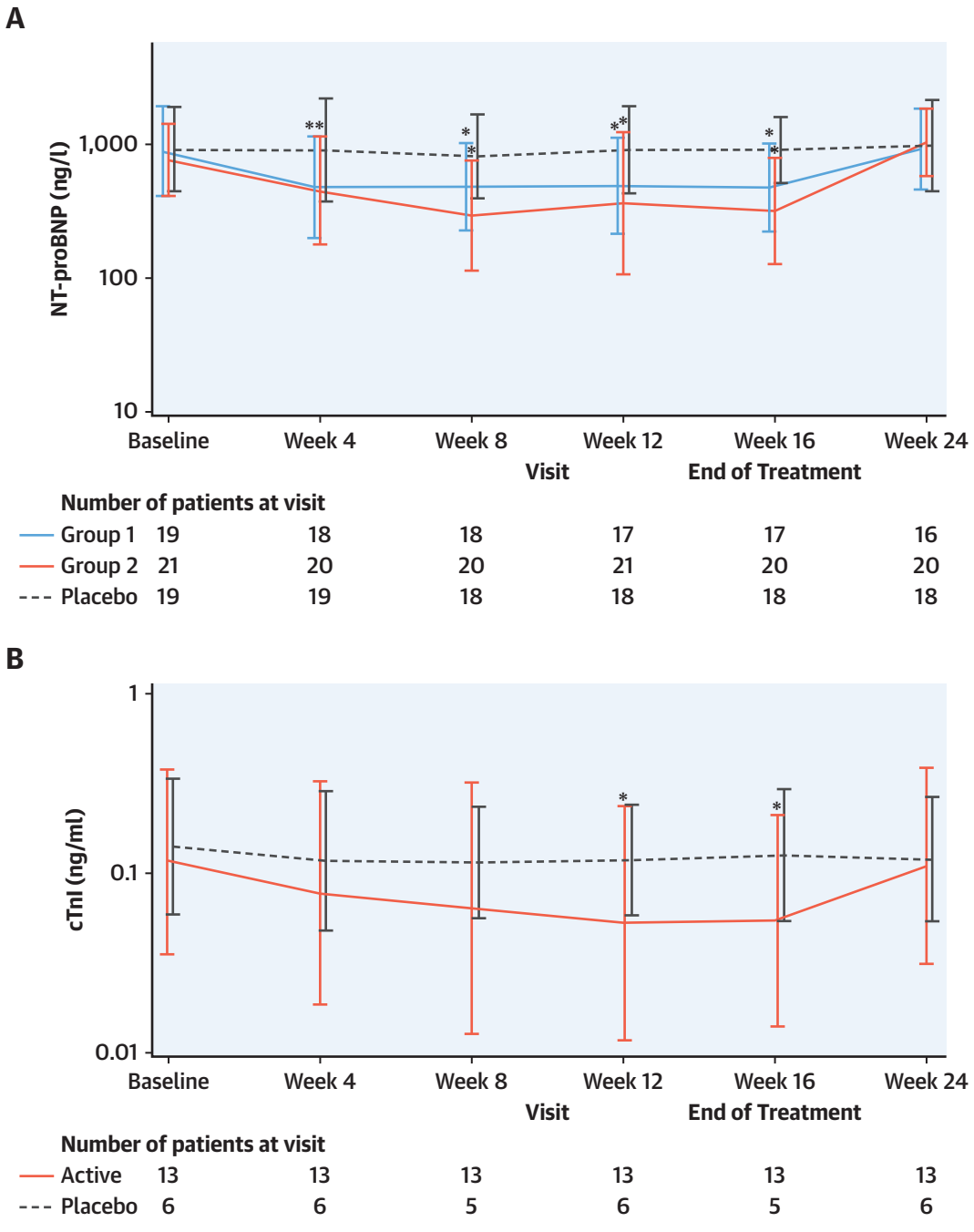
Recovery of LVEF was documented by serial transthoracic echocardiography, with 4 of the 5 participants returning to or toward baseline after approximately 4 weeks; the fifth subject (participant 1) showed recovery after approximately 12 weeks. In 4 participants, an increase in NT-proBNP was observed before or coincident with the transient reductions in LVEF (Supplemental Table 2). cTnI levels remained less than the 99th percentile in all 5 participants. Participant 2 had a history of atrial fibrillation and was admitted to the hospital with uncontrolled atrial fibrillation and systolic dysfunction. Diuresis and treatment with carvedilol resolved symptoms; however, LVEF returned to baseline after atrial fibrillation ablation. No significant QTc prolongation was observed in any participant.

EXPLORATORY ANALYSES: SERUM BIOMARKERS. The geometric mean for NT-proBNP decreased by 47% in group 1, by 58% in group 2, and by 53% (absolute change from baseline: −435 pg/ml) in the pooled mavacamten groups versus a decrease of 1% in the placebo group (absolute change from baseline: −6 pg/ml) at week 16 ($p = 0.0005$ for the difference between the pooled mavacamten and placebo groups) (**Figure 2A**). NT-proBNP in the pooled mavacamten group was lower than placebo at all time points from week 4 to week 16 ($p < 0.05$ at all time points using the Wilcoxon test). An initial decline in NT-proBNP was noted at week 4 on 5-mg daily dosing, provided to both groups. Group 2 participants showed a further decrease in NT-proBNP at week 8 (after week 6 titration), consistent with a dose-dependent effect. These lower NT-proBNP levels were maintained through week 16 and increased to baseline values at week 24 after the drug was discontinued.

There was a 34% decrease in the geometric mean of cTnI levels at week 16 in the pooled mavacamten group (absolute change from baseline: −0.008 ng/ml) in contrast to a 4% increase in the placebo group (absolute change from baseline: 0.001 ng/ml; $p = 0.009$) (Supplemental Table 3). Analyzing participants with elevated baseline cTnI, after study drug was stopped at week 16, cTnI levels increased to baseline by week 24 (**Figure 2B**). Following initial analyses of troponin results, high-sensitivity cTnI assays were performed on banked biomarker samples from baseline and week 16. The results from these assays confirmed the reduction in cTnI with mavacamten treatment (Supplemental Figure 2). In the pooled mavacamten group, there was a statistically significant correlation between the change in NT-proBNP at week 4 and the change in cTnI at week 16 ($r = 0.45$; $p = 0.006$). No significant correlation was seen in the placebo group ($r = -0.31$; $p = 0.212$).

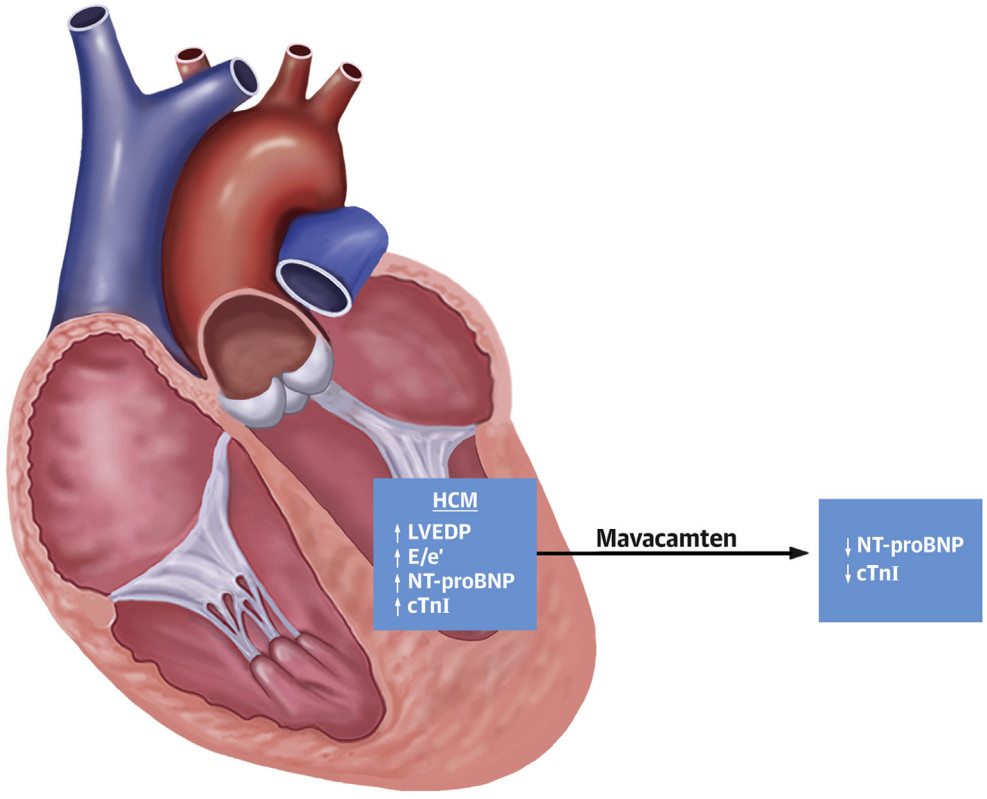
EXPLORATORY ANALYSES: ECHOCARDIOGRAPHIC PARAMETERS, SYMPTOMS, AND EXERCISE. Exploratory analyses were performed to assess the impact of 16 weeks of mavacamten treatment on echo parameters of diastolic function (E/e′, e′ velocity) and the composite functional endpoint, which was defined as achieving: 1) an improvement of at least 1.5 ml/kg/min in pVO_2 and a reduction of ≥1 NYHA functional class; or 2) an improvement of ≥3.0 ml/kg/min in pVO_2 with no worsening of NYHA functional class. In the ITT population, no

FIGURE 2 Biomarker Panel



(A) Geometric mean of N-terminal pro-B-type natriuretic peptide (NT-proBNP) over time through week 24 in groups 1 and 2 versus the placebo group (intention-to-treat population). The geometric mean over time by treatment group is shown. Bars indicate the geometric SD. *$p < 0.05$ comparing the percent change in NT-proBNP from baseline for the active group versus the placebo group using the nonparametric Wilcoxon test. **(B)** Geometric mean of cardiac troponin I (cTnI) over time in the subpopulation with baseline elevated cTnI. The geometric mean over time by treatment group is shown. Bars indicate the geometric SD. Elevated cTnI is defined as values >0.03 ng/ml. *$p < 0.05$ comparing the percent change in cTnI from baseline for the active group versus the placebo group using the non-parametric Wilcoxon test. Abbreviations as in Figure 1.

CENTRAL ILLUSTRATION **Improvement in Biomarkers of Cardiac Stress and Injury With Mavacamten Treatment**



Ho, C.Y. et al. J Am Coll Cardiol. 2020;75(21):2649–60.

In this phase II, dose-ranging, randomized, double-blind clinical trial, decreases from baseline in diastolic function and myocardial injury (E/e', N-terminal pro-B-type natriuretic peptide [NT-proBNP], and cardiac troponin I [cTnI]) were observed with 16 weeks of mavacamten treatment. LVEDP = left ventricular end-diastolic pressure.

significant changes were identified in E/e′ or e′ velocity across treatment groups. There was also no significant improvement in symptoms as assessed by the Kansas City Cardiomyopathy Questionnaire (mean change in overall score: group 1: 0.4 ± 8.7; group 2: 6.2 ± 10.7; placebo: 6.0 ± 17.6) (Supplemental Table 3).

There was no clear difference observed in the proportion of participants who achieved the composite functional endpoint in the ITT group (group 1: 16%; group 2: 29%; placebo: 22%) ($p > 0.05$) (**Table 3**). However, when analyzing a subgroup of participants with elevated cTnI (>99th percentile) or $E/e'_{average}$ (>14) at baseline (21 participants on mavacamten and 12 participants on placebo), 33% of mavacamten-treated participants met the composite functional endpoint, whereas none of the placebo-treated participants achieved this ($p = 0.03$) (Supplemental Table 4).

DISCUSSION

The phase II MAVERICK-HCM study tested a first-in-class cardiac myosin inhibitor in patients with symptomatic nHCM. The primary objective of this study was to assess the safety and tolerability of mavacamten in this population. Treatment with mavacamten was well tolerated in most participants. Although this exploratory, dose-ranging study was underpowered to detect clinical benefit, as reflected by pVO_2 or NYHA functional class, mavacamten was associated with a significant dose-dependent reduction in NT-proBNP, suggesting physiological benefit (**Central Illustration**). Despite reports of patients with nHCM having lower morbidity than patients with oHCM (22,23), at least 10% of these patients will progress to advanced heart failure, highlighting the great unmet need for effective therapy (23,24).

TABLE 3 Functional Individual and Composite Functional Endpoints

ITT Population	Group 1 Mavacamten ~200 ng/ml (n = 19)	Group 2 Mavacamten ~500 ng/ml (n = 21)	Pooled Mavacamten (n = 40)	Placebo (n = 19)
≥1 NYHA functional class improvement from baseline to week 16	10 (52.6)	7 (33.3)	17 (42.5)	7 (36.8)
95% CI	28.9 to 75.6	14.6 to 57.0	27.0 to 59.1	16.3 to 61.6
p value	0.32	0.85	0.68	—
Change in pVO_2 from baseline to week 16	0.36 (3.12)	0.12 (3.76)	0.22 (3.44)	0.58 (2.39)
95% CI	−1.44 to 2.16	−1.75 to 1.99	−1.02 to 1.46	−0.60 to 1.77
p value	0.87	0.67	0.93	—
Met composite functional endpoint, either type	3 (15.8)	6 (28.6)	9 (22.5)	4 (21.1)
95% CI	3.4 to 39.6	11.3 to 52.2	10.8 to 38.5	6.1 to 45.6
p value	0.75	0.58	0.92	—

Values are n (%), change in pVO_2 is mean (SD), unless otherwise indicated. Composite functional endpoint is defined as either improvement from baseline to week 16 of at least 1.5 ml/kg/min in peak oxygen consumption (pVO_2) and reduction of ≥1 in NYHA functional class, or improvement of at least 3.0 ml/kg/min in pVO_2 and no worsening in NYHA functional class. Three additional participants on mavacamten met the composite functional endpoint based on pVO_2 measurements recorded outside the intention-to-treat (ITT) visit window. These participants were classified as nonresponders in the ITT analysis. In an on-treatment analysis, 12 of 34 (35%) patients achieved the functional composite endpoint versus 21% placebo.

Other abbreviations as in Table 1.

Treatment-emergent adverse events were predominantly mild or moderate and self-limited. Consistent with its mechanism of action, mavacamten use was associated with a reversible decrease in LVEF in 5 participants, which resulted in protocol-directed drug discontinuation. Because this was a dose-ranging study with no opportunity for down-titration based on clinical parameters, these events were anticipated. In all instances, LVEF recovered, and although associated with transient increases in NT-proBNP, there was no evidence of cardiac injury. In future studies of patients with symptomatic nHCM, clinical parameters including symptoms, LVEF, and NT-proBNP may be used to guide effective and safe dosing.

MAVERICK-HCM was the first study to demonstrate that medical therapy in nHCM was associated with a significant dose-dependent reduction in NT-proBNP (**Central Illustration**). On average, mavacamten resulted in NT-proBNP reductions within 4 weeks of treatment. There was also a suggestion that mavacamten use was associated with a decline in cTnI in participants with elevated levels at baseline.

These results are notable because serum natriuretic peptide and cardiac troponin levels are markers of myocardial wall stress and injury. They have been used as biomarkers to predict adverse events and prognosis in patients with heart failure as well as HCM (25–27). BNP levels have been shown to be an independent predictor of morbidity and mortality in HCM (28). Elevated BNP levels have been associated with increased mortality and increased need for septal reduction therapy. Elevated troponin levels have been linked with cardiac magnetic resonance imaging evidence of myocardial fibrosis (29–32), a well-defined prognostic factor in HCM (31,33–39). In addition, in HCM, elevated high-sensitivity troponin T has been shown to predict heart failure (hazard ratio: 4.3 for NYHA functional class II and hazard ratio: 22.8 for NYHA functional class III), atrial fibrillation, and death in patients with HCM (25). Conversely, normal baseline high-sensitivity troponin I had a 98% negative predictive value for adverse outcomes.

There was no significant impact of mavacamten on symptoms or functional capacity in the ITT analysis. However, in an exploratory analysis of a subset of participants with more severe disease expression (reflected by baseline elevated E/e′ or cTnI), mavacamten therapy was associated with improved pVO_2 and NYHA functional class, similar to what was observed in the phase II PIONEER-HCM study in symptomatic oHCM (18).

STUDY LIMITATIONS. Limitations of the study included its exploratory and dose-finding nature, as well as its sample size, including limited participation from racial minorities. The treatment period might not have been sufficiently long to detect clinically meaningful differences in symptoms, quality of life or functional outcomes, despite reductions in levels of biomarkers of cardiac stress and injury. Finally, although this was an exploratory study, the risks of type I error were inflated due to multiple testing of subgroups and exploratory endpoints. Further studies are required to confirm and expand upon the findings of this phase II trial.

CONCLUSIONS

MAVERICK-HCM provided valuable insights regarding the use of a novel cardiac myosin inhibitor, mavacamten, in symptomatic patients with nHCM (**Central Illustration**). First, mavacamten was well-tolerated in most subjects. Second, mavacamten treatment was associated with a dose-dependent reduction in serum levels of NT-proBNP. Third, exploratory analyses suggested that patients with more advanced disease expression (elevated cTnI or E/e′) might be most responsive to therapy. The MAVERICK-HCM study suggests mavacamten has the potential to benefit patients with nHCM with dosing guided by clinical parameters, including LVEF. This study sets the groundwork for a future larger scale study in this important and underserved patient population.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with nHCM, the myosin inhibitor mavacamten was generally well tolerated and associated with reduction in NT-proBNP and cTnI plasma levels.

TRANSLATIONAL OUTLOOK: Clinical trials in larger groups of patients with nHCM are needed to assess the safety and efficacy of mavacamten to improve symptoms and clinical outcomes, and to identify subgroups most likely to benefit.

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KEY WORDS cardiac troponin I (cTnI), clinical study, hypertrophic cardiomyopathy, mavacamten, N-terminal pro-B-type natriuretic peptide (NT-proBNP)

APPENDIX For supplemental figures, tables, and Methods, please see the online version of this paper.