Annals of Internal Medicine ORIGINAL RESEARCH

Mavacamten Treatment for Obstructive Hypertrophic Cardiomyopathy

A Clinical Trial

Stephen B. Heitner, MD; Daniel Jacoby, MD; Steven J. Lester, MD; Anjali Owens, MD; Andrew Wang, MD; David Zhang, PhD, MBA; Joseph Lambing, PhD; June Lee, MD; Marc Semigran, MD; and Amy J. Sehnert, MD

Background: Mavacamten, an orally administered, small-molecule modulator of cardiac myosin, targets underlying biomechanical abnormalities in obstructive hypertrophic cardiomyopathy (oHCM).

Objective: To characterize the effect of mavacamten on left ventricular outflow tract (LVOT) gradient.

Design: Open-label, nonrandomized, phase 2 trial. (Clinical Trials.gov: NCT02842242)

Setting: 5 academic centers.

Participants: 21 symptomatic patients with oHCM.

Intervention: Patients in cohort A received mavacamten, 10 to 20 mg/d, without background medications. Those in cohort B received mavacamten, 2 to 5 mg/d, with β-blockers allowed.

Measurements: The primary end point was change in postexercise LVOT gradient at 12 weeks. Secondary end points included changes in peak oxygen consumption (pVO_2), resting and Valsalva LVOT gradients, left ventricular ejection fraction (LVEF), and numerical rating scale dyspnea score.

Results: In cohort A, mavacamten reduced mean postexercise LVOT gradient from 103 mm Hg (SD, 50) at baseline to 19 mm Hg (SD, 13) at 12 weeks (mean change, −89.5 mm Hg [95% CI, −138.3 to −40.7 mm Hg]; $P = 0.008$). Resting LVEF was also reduced (mean change, −15% [CI, −23% to −6%]). Peak VO_2 increased by a mean of 3.5 mL/kg/min (CI, 1.2 to 5.9 mL/kg/min). In cohort B, the mean postexercise LVOT gradient decreased from 86 mm Hg (SD, 43) to 64 mm Hg (SD, 26) (mean change, −25.0 mm Hg [CI, −47.1 to −3.0 mm Hg]; $P = 0.020$), and mean change in resting LVEF was −6% (CI, −10% to −1%). Peak VO_2 increased by a mean of 1.7 mL/kg/min (SD, 2.3) (CI, 0.03 to 3.3 mL/kg/min). Dyspnea scores improved in both cohorts. Mavacamten was well tolerated, with mostly mild (80%), moderate (19%), and unrelated (79%) adverse events. The most common adverse events definitely or possibly related to mavacamten were decreased LVEF at higher plasma concentrations and atrial fibrillation.

Limitation: Small size; open-label design.

Conclusion: Mavacamten can reduce LVOT obstruction and improve exercise capacity and symptoms in patients with oHCM.

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For author affiliations, see end of text.

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Hypertrophic cardiomyopathy (HCM) is a genetic heart muscle disease that is caused by mutations in genes encoding sarcomere proteins (1, 2) and has an autosomal dominant pattern of inheritance. Obstructive HCM (oHCM), defined as a resting or provoked peak instantaneous left ventricular (LV) outflow gradient of at least 30 mm Hg, occurs in approximately 70% of patients with HCM. The phenotype of oHCM is characterized by LV hypercontractility, hypertrophy, reduced compliance, and LV outflow tract (LVOT) obstruction, which may result in exertional dyspnea, fatigue, chest pain, and limited exercise capacity (3). Despite management with β-blockers or nondihydropyridine calcium-channel blockers, symptoms and disease burden persist for many patients with oHCM, and therapeutic options are limited (2, 4). For those with refractory symptomatic disease, septal reduction therapies (such as surgical myectomy or percutaneous alcohol septal ablation) can be effective, but these invasive procedures carry risk and are not widely accessible, and their success depends on operator experience (5).

Mutations in cardiac myosin heavy chain and other sarcomere proteins seem to increase net power generation by the sarcomere, consistent with the hypercontractile state and, secondarily, impaired myocardial compliance that is clinically observed (6–8). Mavacamten is a first-in-class, cardiac-specific, small-molecule allosteric modulator of β-cardiac myosin that reversibly inhibits its binding to actin (9, 10). It is intended to reduce resting and dynamic LVOT obstruction in patients with oHCM by normalizing the function of myosin protein in hypercontractile hearts (11), regardless of the presence of a sarcomeric gene mutation. In a feline model of oHCM, treatment with mavacamten reduced contractility and relieved obstruction in an exposure-dependent manner (12). Three phase 1 clinical studies in 86 healthy volunteers and 15 patients with HCM documented the pharmacokinetic profile to inform phase 2 dose selection, and a favorable safety profile was observed across a meaningful dose range (Sehnert AJ. Personal communication). The totality of the pharmacokinetic, pharmacodynamic, and tolerability data from these studies led to the design of the phase 2, open-label PIONEER-HCM study.

The primary objective of the PIONEER-HCM study was to characterize the effect of 12 weeks of mavacamten treatment on reducing postexercise peak LVOT gradient in patients with symptomatic oHCM.

See also:

Web-Only
Supplement

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Cohort A (*n* = 11)	Cohort B (*n* = 10)
Mean age (range), *y*	56 (22–70)	58 (26–67)
Sex, *n (%)*		
Male	7 (64)	5 (50)
Female	4 (36)	5 (50)
Mean body mass index (SD), *kg/m²*	29.7 (4.1)	32.3 (5.4)
Mean heart rate (SD), *beats/min*	76 (10)	62 (8)
Mean blood pressure (SD), *mm Hg*		
Systolic	136 (13)	132 (14)
Diastolic	75 (8)	77 (15)
NYHA functional class, %		
II	64	50
III	36	50
Background HCM therapy, *n (%)**		
β-Blocker	9 (82)	9 (90)
Calcium-channel blocker	1 (9)	0 (0)
Disopyramide	5 (45)	0 (0)
Echocardiography parameters		
Mean interventricular septum thickness (SD), *cm*	1.7 (0.2)	1.5 (0.2)
Systolic anterior motion of mitral valve, *n (%)*	11 (100)	9 (90)
Mean left atrial volume index (SD), *mL/m²*	30 (10)	41 (20)
Mitral regurgitation present, *n (%)*	11 (100)	10 (100)

HCM = hypertrophic cardiomyopathy; NYHA = New York Heart Association.
* Patients in cohort A discontinued background HCM therapy ≥14 d before starting use of mavacamten.

METHODS

Trial Design and Oversight

PIONEER-HCM was a prospective, phase 2, multicenter, open-label study conducted at 5 U.S. academic centers between 7 October 2016 and 17 November 2017. Its goals were to characterize pharmacokinetics and pharmacodynamics, evaluate safety and tolerability, and demonstrate proof of concept for mavacamten in treating patients with symptomatic oHCM. The study protocol was approved by the site-specific institutional review boards and funded by MyoKardia. The employees of MyoKardia as well as the academic investigators participated in data analysis and vouch for the accuracy and completeness of the data and the fidelity of the trial to the final protocol. Statistical analysis was performed by clinical research organizations (Pharmaceutical Product Development [PPD] and Advance Research Associates [ARA]) on behalf of the sponsor, and data tables were provided to the investigators who were involved in interpretation of the data. An independent data monitoring committee (IDMC) regularly reviewed the study data to help identify emerging safety or conduct issues. All patients provided informed consent, and the study was done in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

The study was conducted in 2 sequential cohorts (A and B), each comprising a 12-week treatment phase with once-daily oral mavacamten followed by a 4-week posttreatment phase (**Appendix Figure 1**, available at Annals.org). Cohort A was designed to demonstrate proof of concept for mavacamten-induced reduction in contractility (targeted relative reduction in LV ejection fraction [LVEF] of 15% to 20%) and to characterize the pharmacokinetic and pharmacodynamic relationship with a starting dose of 10 mg/d for patients weighing 60 kg or less and 15 mg/d for those weighing more than 60 kg. In cohort A, use of calcium-channel blockers, β-blockers, and disopyramide was discontinued at least 14 days before the first dose of mavacamten. Patients underwent weekly evaluations, including echocardiography, with change in LVEF at week 4 used to titrate the dose (**Appendix Figure 1**). Dose adjustment or interruption was also permitted after consultation between the investigator and the medical monitor. Cohort B was designed to further characterize dose response at lower concentrations of mavacamten, and patients previously receiving β-blockers were permitted to continue treatment at the same dose throughout the study. The starting dose of mavacamten in cohort B was 2 mg/d for all patients, with an increase to 5 mg/d at the end of week 4 if there was a relative decrease in resting LVOT gradient less than 50% from baseline (**Appendix Figure 1**).

Patients

Patients were eligible for inclusion if they had a diagnosis of HCM based on the presence of LV hypertrophy (LV wall thickness ≥15 mm [≥13 mm in those with a family history of HCM]), LVOT obstruction (resting LVOT gradient ≥30 mm Hg and postexercise LVOT gradient ≥50 mm Hg), and symptoms (New York Heart Association [NYHA] functional class II or III). Those with exertional syncope in the previous 6 months, sustained ventricular tachycardia, LV systolic dysfunction (LVEF <45%), persistent atrial fibrillation (AF) or AF at screening, history of paroxysmal AF with documented resting heart rate above 100 beats/min within 1 year of screening, or history of obstructive coronary artery disease were excluded. The full eligibility criteria and description of echocardiography assessments are included in the study protocol (**Supplement**, available at Annals.org).

Procedures

The schedule of procedures and assessments was identical for both cohorts (**Appendix Figure 1**). Details of procedures are included in the protocol. Patients were assessed at weekly visits for 8 weeks, followed by an end-of-treatment visit at week 12, a 4-week posttreatment period, and an end-of-study visit at week 16. The clinical status of patients was recorded serially throughout the study (physical examination, vital signs, NYHA functional class, numerical rating scale [NRS] dyspnea score, and Kansas City Cardiomyopathy Questionnaire Overall Summary Score [KCCQ OSS]). Comprehensive laboratory testing; plasma drug concentration measurement (pharmacokinetics); HCM genotyping; pharmacogenetic testing (CYP2C19 polymorphisms); electrocardiography; and rest, Valsalva, and postexercise echocardiography were performed as well as continuous cardiac rhythm monitoring. In addition, cardiopulmonary exercise testing was performed on day 1 and at week 12 for evaluation of peak oxygen consumption (pVO_2), ven-

tilatory efficiency (volume expired/carbon dioxide production slope [VE/VCO_2]), and other variables.

Outcomes

The primary end point was change in postexercise LVOT gradient at 12 weeks compared with baseline. Secondary end points included the proportion of patients achieving a postexercise LVOT gradient less than 30 mm Hg, change in NRS dyspnea score, change in pVO_2 and VE/VCO_2, effect on resting and Valsalva LVOT gradients, change in resting LVEF, and reversibility after 4 weeks of washout. Exploratory end points included change in symptoms measured by the NYHA functional classification and the KCCQ OSS and change in serum *N*-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration. The primary, secondary, and exploratory end points we report were designated a priori. Several secondary and exploratory end points (some echocardiographic parameters, derivatives from cardiopulmonary exercise testing, arterial pulse wave morphology assessment, and subgroups of patients achieving negligible gradients) are not reported here but will be reported elsewhere (**Supplement**).

Statistical Analysis

The sample size was based on practical considerations and was consistent with this early phase 2 study. Ten patients receiving mavacamten would provide 80% power to detect a 30–mm Hg decrease from baseline in postexercise peak LVOT gradient and more than 99% power to detect a 50–mm Hg decrease. This was under the assumption of a 1-sided α level of 0.05 and a common SD of 35 mm Hg.

Changes from baseline to week 12 in the primary outcome of postexercise LVOT gradient were compared with zero (no change) using the Wilcoxon signed-rank test. A similar analysis was conducted for secondary echocardiographic end points (resting and Valsalva LVOT gradients). Other secondary and exploratory end points were presented descriptively as means, SDs, and 95% CIs. A *P* value less than 0.05 was considered statistically significant for the primary end point. All observed data were included in data summaries and analyses. Patients with a missing baseline or week 12 value were not included in summaries of changes between these 2 time points. No imputation was performed for missing data. All statistical analyses were performed using SAS, version 9.2 or higher (SAS Institute).

Role of the Funding Source

Funding for the PIONEER-HCM study was provided by MyoKardia, which played a central role in the design, conduct, and analysis of the study. This was a phase 2 study that followed the completion of 3 phase 1 studies by MyoKardia to determine dosing for the phase 2 study. The study was designed and the protocol was written with input from experts in the HCM field, including the participating study site investigators. MyoKardia funded and had primary oversight of the clinical research organization used for conduct of the study (PPD). MyoKardia also funded and had final approval over the work of the biostatistical teams at PPD and ARA who developed and executed the statistical analysis plans. The biostatistics and clinical science

Table 2. Primary, Secondary, and Exploratory End Points

End Point	Cohort A (*n* = 11)		Cohort B (*n* = 10)	
	Mean Baseline Value (SD)	Change at Week 12 (95% CI)	Mean Baseline Value (SD)	Change at Week 12 (95% CI)
Primary end point				
Postexercise LVOT gradient, *mm Hg**	103 (50) (*n* = 9)	−89.5 (−138.3 to −40.7) (*n* = 8)	86 (43) (*n* = 9)	−25.0 (−47.1 to −3.0) (*n* = 9)
Secondary end points				
Resting LVOT gradient, *mm Hg*	60 (28) (*n* = 11)	−47.8 (−72.2 to −23.4) (*n* = 10)	86 (63) (*n* = 10)	−48.5 (−82.8 to −14.1) (*n* = 10)
Valsalva LVOT gradient, *mm Hg*	97 (32) (*n* = 11)	−84.7 (−113.8 to −55.7) (*n* = 10)	100 (65) (*n* = 10)	−47.1 (−82.1 to −12.1) (*n* = 10)
Resting LVEF, *%*	70 (7) (*n* = 11)	−14.6 (−23.1 to −6.2) (*n* = 10)	75 (5) (*n* = 10)	−5.5 (−9.8 to −1.2) (*n* = 10)
pVO_2, *mL/kg/min*	20.7 (7.4) (*n* = 11)	3.5 (1.2 to 5.9) (*n* = 10)	19.4 (4.6) (*n* = 10)	1.7 (0.03 to 3.3) (*n* = 10)
VE/VCO_2	32.2 (5.4) (*n* = 11)	−2.2 (−6.1 to 1.7) (*n* = 10)	32.3 (4.4) (*n* = 10)	−2.5 (−4.3 to −0.7) (*n* = 10)
NRS dyspnea score†	4.9 (1.6) (*n* = 11)	−3.1 (−4.1 to −2.1) (*n* = 10)	4.0 (2.6) (*n* = 10)	−3.0 (−5.0 to −1.0) (*n* = 10)
Exploratory end points				
NYHA functional class	2.4 (0.5) (*n* = 11)	−0.9 (−1.4 to −0.4) (*n* = 10)	2.5 (0.5) (*n* = 10)	−1.0 (−1.3 to −0.7) (*n* = 10)
KCCQ OSS‡	65 (16) (*n* = 11)	14.4 (7.3 to 21.5) (*n* = 10)	61 (26) (*n* = 10)	16.0 (0.3 to 31.6) (*n* = 10)
Median change in NT-proBNP level (IQR), *pg/mL*	930 (647) (*n* = 11)	−425 (−748 to −68) (*n* = 10)	1834 (3209) (*n* = 9)	−81 (−637 to −16) (*n* = 9)
Systolic blood pressure, *mm Hg*	136 (13) (*n* = 11)	−6.5 (−16.8 to 3.8) (*n* = 10)	132 (14) (*n* = 10)	−9.2 (−19.7 to 1.3) (*n* = 10)
Diastolic blood pressure, *mm Hg*	75 (8) (*n* = 11)	8.8 (−0.1 to 17.7) (*n* = 10)	77 (15) (*n* = 10)	1.2 (−7.5 to 9.9) (*n* = 10)

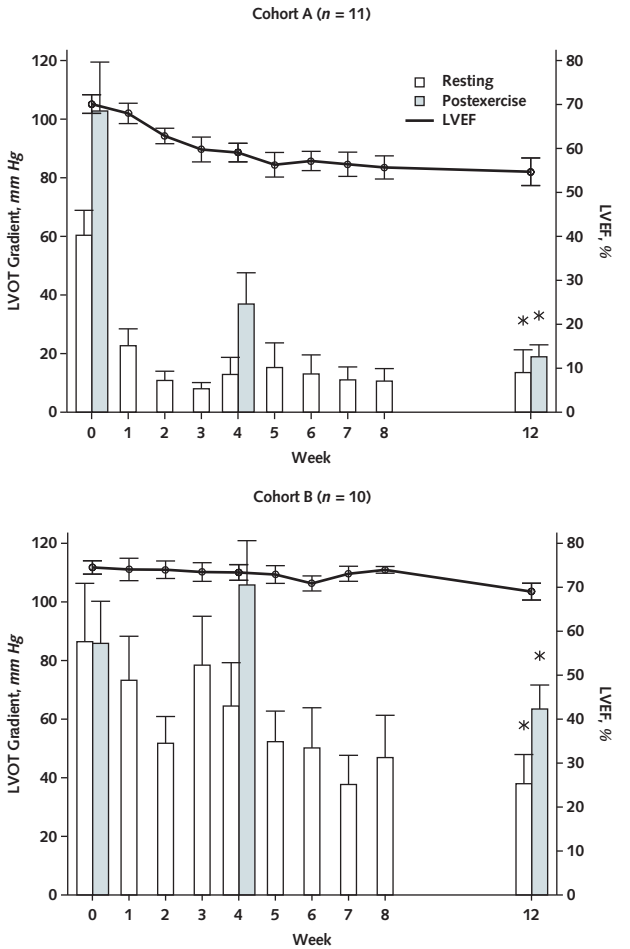
IQR = interquartile range; KCCQ OSS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NRS = numerical rating scale; NT-proBNP = *N*-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; pVO_2 = peak oxygen consumption; VE/VCO_2 = volume expired/carbon dioxide production slope.

* In cohort A, 2 patients did not have postexercise measures (1 was unable to exercise at baseline and 1 had an image that was technically difficult to interpret), and 1 who discontinued because of an adverse event did not have a 12-wk measurement. In cohort B, 1 patient did not have postexercise measures because of technical issues related to imaging.

† Indicates perception of severity. Scores range from 1 to 10, with 10 being the most severe. A clinically significant change is defined as ≥1.

‡ Measures perception of overall health. Scores range from 0 to 100, with higher scores reflecting better health status. A clinically significant change is defined as ≥6.

Figure 1. Effect of mavacamten on LVOT obstruction and LVEF.



Patients in cohort A (*top*) showed a protocol-directed decrease in mean LVEF from 70% to a normal level of 55%. A reduction in resting LVOT obstruction occurred by week 2 of therapy and was maintained throughout the treatment phase. There was a similar but less rapid resolution of postexercise LVOT gradient, and by week 12, the mean postexercise peak LVOT gradient was below the threshold for surgical consideration. Patients in cohort B (*bottom*) experienced a more gradual and less marked, albeit significant, reduction in mean LVEF (from 75% to 69%) and resting and postexercise LVOT gradients. LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract.
* $P < 0.05$.

teams at MyoKardia interpreted the results of analyses along with the study investigators. The decision to submit the manuscript was made jointly by MyoKardia and the academic authors.

RESULTS

Twenty-five patients were assessed for eligibility; 2 in each cohort did not meet inclusion criteria and were excluded. Twenty of 21 patients completed the study; 1 patient terminated participation before week 4 because of a serious adverse event (**Appendix Figure 2**, available at Annals.org). All patients entering the study were included for analysis of the primary and secondary outcomes. Two patients in cohort A and 1 in cohort B had uninterpretable postexercise LVOT gradients (1 patient was unable to exercise at baseline because of mental fatigue, and Doppler signals for 2 patients were technically unsuitable for analysis).

Patient Characteristics

Baseline characteristics of all patients are shown in **Table 1**. Nine of the patients were women, ages ranged from 22 to 70 years, 57% had NYHA class II disease, and 43% had NYHA class III disease. Twenty of the 21 patients completed 12 weeks of therapy (**Appendix Figure 2**). Almost all were receiving at least 1 form of standard medical therapy when they presented for screening, and there was a high degree of resting and provoked LVOT obstruction. The mean LVEF at baseline was 70% (SD, 7%) in cohort A and 75% (SD, 5%) in cohort B. In cohort A, 4 patients started and continued use of mavacamten at 15 mg/d, and 1 patient started and continued use of 10 mg/d throughout the study. There were 6 dose titrations in 5 patients (3 increases and 3 decreases). The 11th patient discontinued use of mavacamten by week 4 (see the Safety section). In cohort B, all patients started use of mavacamten at a dose of 2 mg/d, and all had an increase to 5 mg/d at week 4.

Effect of Mavacamten on LVOT Obstruction

The median mavacamten dose at 12 weeks in cohort A was 15 mg/d (range, 10 to 20 mg/d). The mean postexercise LVOT gradient was 103 mm Hg (SD, 50) at baseline and 19 mm Hg (SD, 13) at 12 weeks (mean change, −89.5 mm Hg [95% CI, −138.3 to −40.7 mm Hg]; $P = 0.008$) (**Table 2** and **Figure 1** [*top*]). Eight of the 11 participants in cohort A achieved a postexercise LVOT gradient less than 30 mm Hg. Improvements were also seen in resting LVOT gradient (mean change, −48 mm Hg [CI, −72 to −23 mm Hg]; $P = 0.006$) and Valsalva LVOT gradient (mean change, −85 mm Hg [CI, −114 to −56 mm Hg]; $P = 0.002$). In cohort B, all 10 patients received 5 mg/d at week 12, and they had smaller reductions in postexercise LVOT gradient (mean change, −25.0 mm Hg [CI, −47.1 to −3.0 mm Hg]; $P = 0.020$), resting LVOT gradient (mean change, −49 mm Hg [CI, −83 to −14 mm Hg]; $P = 0.004$), and Valsalva LVOT gradient (mean change, −47 mm Hg [CI, −82 to −12 mm Hg]; $P = 0.002$) (**Table 2** and **Figure 1** [*bottom*]). None of the patients in cohort B achieved a postexercise LVOT gradient less than 30 mm Hg.

Secondary and Exploratory End Points

The mean change in NYHA functional class was −0.9 in cohort A, with 2 patients improving by 2 classes, 5 improving by 1 class, 3 remaining unchanged, and 1 withdrawing from the study early. In cohort B, the mean change in NYHA functional class was −1.0, with 1 patient improving by 2 classes, 8 improving by 1 class, and 1 remaining unchanged. Transitions in NYHA functional class are shown in **Appendix Figure 3** (available at Annals.org). The NRS dyspnea score and KCCQ OSS also improved (**Table 2**).

Patients in cohort A had a greater mean increase in pVO_2 (3.5 mL/kg/min [SD, 3.3]) than those in cohort B (1.7 mL/kg/min [SD, 2.3]). The difference in VE/VCO_2 after 12 weeks of treatment was similar in both cohorts.

Serum NT-proBNP concentrations were reduced in both cohorts, with median changes of −425 pg/dL (interquartile range, −748 to −68 pg/dL) in cohort A and −81 pg/dL (interquartile range, −637 to −16 pg/dL) in cohort B (**Table 2**). Systolic anterior motion of the mitral valve was noted in 20 of the 21 patients at enrollment; by week 12, this had resolved in 9 of 11 patients in cohort A but none in cohort B.

Resting LVEF changed by −15% (CI, −23% to −6%) in cohort A and −6% (CI, −10% to −1%) in cohort B. The LVEF returned to baseline levels 4 weeks after treatment. There was also a return toward baseline measures of LVOT obstruction and NT-proBNP concentration and a return of symptoms at week 16 (**Appendix Table**, available at Annals.org).

Of the 21 patients who consented to DNA sequencing, 10 were found to have genetic variants, and 5 of these had known pathogenic variants in sarcomere protein genes (2 in *MYH7* and 3 in *MYBPC3*) (**Figure 2**). Although the pharmacodynamic response to mavacamten seen in persons with known variants seems to be similar to that in patients without identified mutations, the small number of patients studied precluded subgroup analysis.

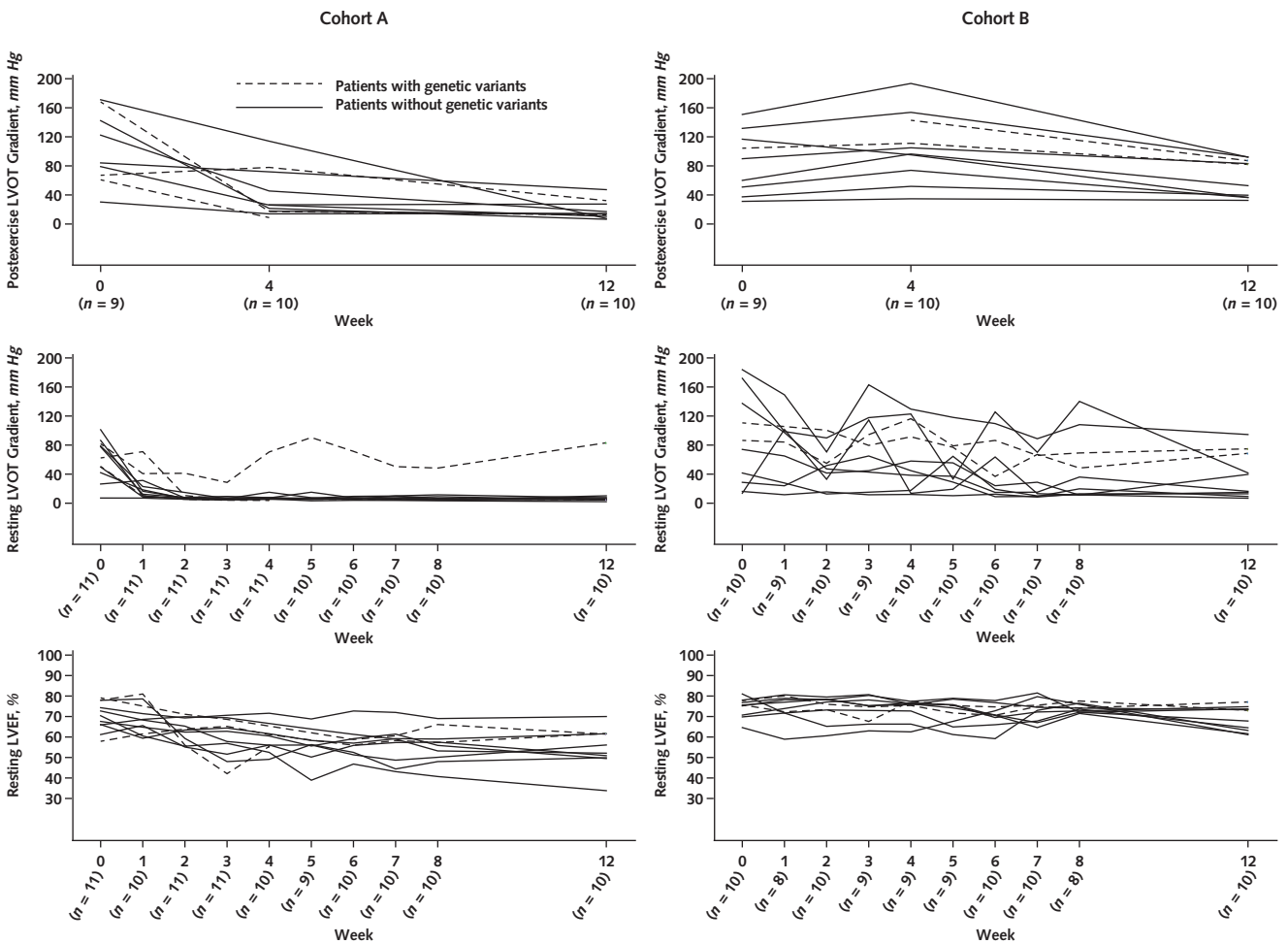
Pharmacodynamics

Mavacamten decreased LVEF in a concentration-dependent manner, with substantial reductions in LVOT obstruction occurring at plasma concentrations between 350 and 695 ng/mL (**Figure 3**). In this range, all patients maintained an LVEF of 50% or greater. Plasma concentrations above 1000 ng/mL were associated with an exaggerated decrement in LVEF beyond what is necessary to obliterate the LVOT gradient (34% to 49% at plasma concentrations of 695 to 1500 ng/mL) in 4 patients. Of note, we observed a return of LVEF toward baseline values 4 weeks after treatment (**Appendix Table**).

Safety

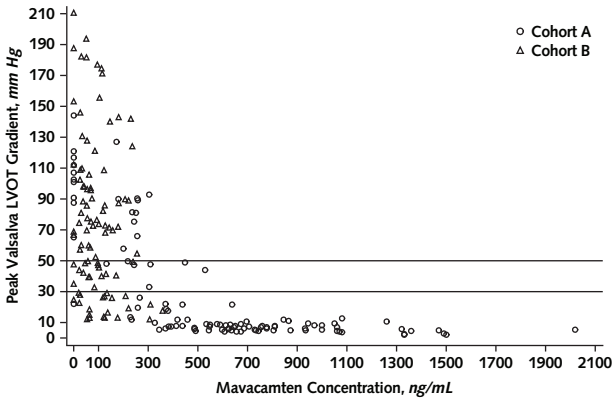
Mavacamten was generally well tolerated, with most adverse events described as mild (80%) to mod-

Figure 2. Spaghetti plots of patients in cohort A (*left*) and cohort B (*right*).



Solid lines indicate patients without a sarcomeric gene mutation (gene-negative), and dashed lines indicate patients with either a known disease-causing variant or a variant of unknown significance (gene-positive). Of note, 1 gene-positive patient in cohort A who had a blunted pharmacodynamic response was taking only 10 mg/d throughout the study and had low pharmacokinetics (201 to 305 ng/mL). LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract.

Figure 3. Valsalva LVOT gradient versus plasma concentration of mavacamten.



The figure shows a threshold (350 ng/mL) above which no patients are considered to have severe LVOT obstruction according to current clinical guidelines. Patients in cohort A showed a high frequency of attaining therapeutic drug concentrations. Patients in cohort B, a dose-finding cohort, showed that at plasma concentrations <300 ng/mL, actionable peak LVOT gradients persisted, albeit lower than when compared with baseline. All available data up to week 12 (5 to 11 visits per patient) are included in the plot. Each point represents 1 patient visit. LVOT = left ventricular outflow tract.

erate (19%) and considered by the treating physicians to be unrelated to the drug (79%) (Table 3). No safety concerns were highlighted by the IDMC. The most common adverse events related to mavacamten were decrease in LVEF (3 events definitely related) and AF (5 events possibly related). Two of the 5 AF events are described here, and the other 3 were intermittent and resolved in 2 patients. No sustained arrhythmias were observed by cardiac rhythm monitoring, and there was no evidence of QT prolongation, even at higher concentrations. One serious adverse event that was possibly related to mavacamten occurred in a patient in cohort A with a history of paroxysmal AF who discontinued use of metoprolol and disopyramide 16 days before initiating use of mavacamten per protocol. The patient underwent electrical cardioversion for persistent AF after approximately 2 weeks of study; AF recurred, leading to hospitalization and treatment with amiodarone. The patient elected to stop use of the study drug between weeks 3 and 4.

Patients were invited to participate in an open-label extension of the study, and 13 elected to do so. Ongoing safety monitoring in 10 patients through at least 12 weeks (as of 30 October 2018) revealed no additional safety concerns (Table 3).

DISCUSSION

In this small proof-of-concept and open-label study, treatment of patients with oHCM with 12 weeks of mavacamten, a reversible allosteric modulator of β-cardiac myosin, resulted in rapid and marked reduction in postexercise LVOT gradient (82% mean reduction in cohort A and 29% mean reduction with lower doses in cohort B). Patients with plasma mavacamten concentrations of 350 ng/mL or higher frequently achieved an LVOT gradient less than 30 mm Hg (the threshold for obstruction in HCM) and less than 50 mm Hg (the threshold for consideration of septal reduction therapy) (13, 14) (Figure 2). This was matched by a clinically important improvement in symptoms (15, 16) and exertional capacity. Improvements were also seen in participants with and without background β-blocker therapy, with and without sarcomeric genetic variants, and over a wide age range, although small sample sizes precluded firm conclusions. Of note, we identified a drug concentration threshold at which LVOT obstruction was eliminated without exaggerated negative inotropy. Overall, mavacamten was well tolerated by most patients at exposures that effectively reduced LVOT obstruction, and reductions in LVEF beyond those necessary to alleviate LVOT obstruction were found to be reversible.

The phenotypic hallmarks of oHCM are myocardial hypercontractility, LVOT obstruction due to anterior mitral leaflet-septal contact, mitral regurgitation, and reduced LV compliance. Mutations in cardiac myosin have been found to increase sarcomeric contractility (6, 7), which manifests clinically as supranormal LVEF. Mavacamten has been shown to attenuate hypercontractility, LV hypertrophy, myofibrillar disarray, and fibrosis in animal models (12, 17). Septal reduction therapy (18, 19), the current gold standard for symptomatic oHCM that is refractory to maximally tolerated medical therapy, is recommended in the European and American guidelines (13, 14). Although septal reduction therapy is often effective, it is highly invasive and does not address the molecular underpinnings of oHCM. Furthermore, experts believe that it should be done only by experienced operators in the context of a comprehensive HCM center (13, 14), which limits access for many patients with oHCM worldwide. The concept of normalizing hypercontractility is well accepted (20–22), but available medical therapies are often only partially effective or poorly tolerated.

In both cohorts, patients experienced, to a variable extent, improvement in symptoms, pVO_2, and LV wall stress (defined by a numerical reduction in NT-proBNP level) (23). Although this study had an open-label design and the influence of placebo cannot be estimated, it is interesting that in cohort B, several patients experienced improvements (for example, in pVO_2 or NT-proBNP level) that seemed out of proportion to gradient reduction. This suggests that there are additional mechanisms for symptoms or that the efficacy of mavacamten may extend beyond reducing hypercontractility. Experimental data may provide a partial explanation and represent a potentially important area for ongoing investigation (24).

Mavacamten seems to be well tolerated. In this study, plasma concentrations between 350 and 695 ng/mL were associated with relief of LVOT obstruction while maintaining LVEF within normal limits. There was a single serious adverse event that resulted in discontinuation of the study drug in a patient with persistent AF, and the IDMC found the overall safety profile to be satisfactory. Atrial fibrillation may have been related to mavacamten in 3 other patients. Ongoing observa-

Table 3. Adverse Events During Treatment

Adverse Events	Cohort A (*n* = 11)*	Cohort B (*n* = 10)*	Extension Study (*n* = 12)†
Total, *n*	62	59	17
Mild, *n (%)*	47 (76)	50 (85)	15 (88)
Moderate, *n (%)*	14 (23)	9 (15)	2 (12)
Serious, *n (%)*	1 (2)	0	0
Led to treatment discontinuation, *n (%)*	1 (2)	0	0

	Assessed as Being Related to Study Drug, *n*	Patients With Event, *n*		
		Cohort A (*n* = 11)*	Cohort B (*n* = 10)*	Extension Study (*n* = 12)†
Occurred in ≥15% of patients in either cohort				
Ventricular tachycardia‡	0	1	4	0
Atrial fibrillation§	5	3	1	0
Angina pectoris	0	0	2	0
Headache	1	3	2	0
Dizziness	0	1	3	3
Nausea	1	2	0	0
Fatigue	1	2	2	3
Rash at application site	0	1	2	0
Exertional dyspnea	1	2	0	0
Upper respiratory tract infection	0	2	2	2
Urinary tract infection	0	2	0	0
Decreased ejection fraction	3	3	0	0
Rash	0	2	0	0

* Includes time receiving study medication and 4-wk posttreatment period.
† Through 30 October 2018. Includes 5 patients from cohort A and 7 from cohort B who were redosed in an open-label extension.
‡ All events were nonsustained.
§ Five events in 3 patients were considered possibly related to mavacamten. Two of the 5 events occurred in the patient who discontinued use of the study drug.

tional and trial data will provide additional safety information.

Our study has important limitations. As mentioned, this was an open-label phase 2 study, and the effect of placebo could not be assessed, particularly on the subjective metrics. In addition, the study was small, excluded patients with NYHA functional class IV, and involved only 5 sites in the United States. On the basis of the results of this study, we have undertaken 2 larger studies: the phase 3 trial EXPLORER-HCM (Clinical Study to Evaluate Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy) (ClinicalTrials.gov: NCT03470545), a randomized, placebo-controlled, prospective, international study (*n* = 220), and MAVERICK-HCM (A Phase 2 Study of Mavacamten in Adults with Symptomatic Nonobstructive Hypertrophic Cardiomyopathy) (ClinicalTrials.gov: NCT03442764), a randomized, placebo-controlled study (*n* = 60). In addition, 13 of the original 21 PIONEER-HCM patients have been redosed in an open-label extension study of mavacamten (ClinicalTrials.gov: NCT03496168), and 10 of 13 had received at least 12 weeks of treatment by 30 October 2018.

In conclusion, in this proof-of-concept study, mavacamten treatment was clinically beneficial in patients with oHCM, with reduction in the degree of LVOT obstruction and improvements in exertional capacity and symptoms, particularly among patients achieving plasma drug concentrations above 350 ng/mL. If confirmed in larger studies, these data suggest a potential role for mavacamten in the treatment of oHCM.

From Oregon Health & Science University, Portland, Oregon (S.B.H.); Yale New Haven Hospital, New Haven, Connecticut (D.J.); Mayo Clinic Arizona, Scottsdale, Arizona (S.J.L.); Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania (A.O.); Duke University Medical Center, Durham, North Carolina (A.W.); and MyoKardia, South San Francisco, California (D.Z., J.L., J.L., M.S., A.J.S.).

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and a pending patent for treatment of hypertrophic cardiomyopathy with pyrimidinedione. Dr. Lee reports employment with MyoKardia. Dr. Semigran reports employment with MyoKardia. Dr. Sehnert reports employment with MyoKardia. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M18-3016.

Data Sharing Statement: The complete deidentified patient data set, the analytic and statistical code, and the informed consent form will be made available to researchers whose proposed use of the data has been approved by a publications committee for study of specific questions related to oHCM (e-mail, asehnert@myokardia.com).

Corresponding Author: Stephen B. Heitner, MD, Knight Cardiovascular Institute, Oregon Health & Science University, UHN62, 3181 SW Sam Jackson Park Road, Portland, OR 97239; e-mail, heitner@ohsu.edu.

Current author addresses and author contributions are available at Annals.org.

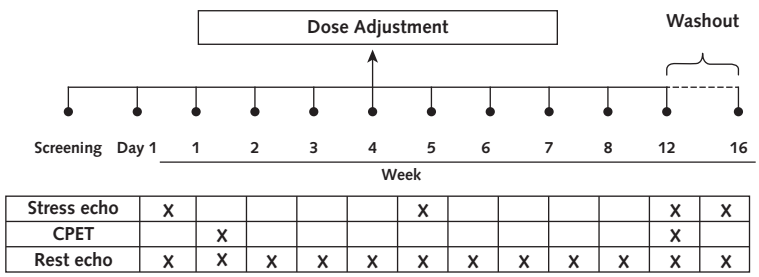
References

1. **Marian AJ, Braunwald E.** Hypertrophic cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. Circ Res. 2017;121:749-70. [PMID: 28912181] doi:10.1161/CIRCRESAHA.117.311059
2. **Maron BJ.** Clinical course and management of hypertrophic cardiomyopathy. N Engl J Med. 2018;379:655-68. [PMID: 30110588] doi:10.1056/NEJMra1710575
3. **Maron BJ, Rowin EJ, Udelson JE, Maron MS.** Clinical spectrum and management of heart failure in hypertrophic cardiomyopathy. JACC Heart Fail. 2018;6:353-63. [PMID: 29655822] doi:10.1016/j.jchf.2017.09.011
4. **Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, et al.** Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). Circulation. 2018;138:1387-98. [PMID: 30297972] doi:10.1161/CIRCULATIONAHA.117.033200
5. **Kim LK, Swaminathan RV, Looser P, Minutello RM, Wong SC, Bergman G, 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;1:324-32. [PMID: 27438114] doi:10.1001/jamacardio.2016.0252
6. **Chuan P, Sivaramakrishnan S, Ashley EA, Spudich JA.** Cell-intrinsic functional effects of the α-cardiac myosin Arg-403-Gln mutation in familial hypertrophic cardiomyopathy. Biophys J. 2012;102:2782-90. [PMID: 22735528] doi:10.1016/j.bpj.2012.04.049
7. **Sommese RF, Sung J, Nag S, Sutton S, Deacon JC, Choe E, et al.** Molecular consequences of the R453C hypertrophic cardiomyopathy mutation on human ß-cardiac myosin motor function. Proc Natl Acad Sci U S A. 2013;110:12607-12. [PMID: 23798412] doi:10.1073/pnas.1309493110
8. **Spudich JA, Aksel T, Bartholomew SR, Nag S, Kawana M, Yu EC, et al.** Effects of hypertrophic and dilated cardiomyopathy mutations on power output by human ß-cardiac myosin. J Exp Biol. 2016;219:161-7. [PMID: 26792326] doi:10.1242/jeb.125930
9. **Grillo MP, Erve JCL, Dick R, Driscoll JP, Haste N, Markova S, et al.** In vitro and in vivo pharmacokinetic characterization of mavacamten, a first-in-class small molecule allosteric modulator of beta cardiac myosin. Xenobiotica. 2018:1-16. [PMID: 30044681] doi:10.1080/00498254.2018.1495856
10. **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;292:16571-7. [PMID: 28808052] doi:10.1074/jbc.M117.776815
11. **Anderson RL, Trivedi DV, Sarkar SS, Henze M, Ma W, Gong H, et al.** Deciphering the super relaxed state of human ß-cardiac myosin and the mode of action of mavacamten from myosin molecules to muscle fibers. Proc Natl Acad Sci U S A. 2018;115:E8143-E8152. [PMID: 30104387] doi:10.1073/pnas.1809540115
12. **Stern JA, Markova S, Ueda Y, Kim JB, Pascoe PJ, Evanchik MJ, et al.** A small molecule inhibitor of sarcomere contractility acutely relieves left ventricular outflow tract obstruction in feline hypertrophic cardiomyopathy. PLoS One. 2016;11:e0168407. [PMID: 27973580] doi:10.1371/journal.pone.0168407
13. **Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al; Authors/Task Force members.** 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;35:2733-79. [PMID: 25173338] doi:10.1093/eurheartj/ehu284
14. **Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al.** 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2011;58:2703-38. [PMID: 22075468] doi:10.1016/j.jacc.2011.10.825
15. **Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, Jones P, et al; Cardiovascular Outcomes Research Consortium.** Monitoring clinical changes in patients with heart failure: a comparison of methods. Am Heart J. 2005;150:707-15. [PMID: 16209970]
16. **Oxberry SG, Bland JM, Clark AL, Cleland JG, Johnson MJ.** Minimally clinically important difference in chronic breathlessness: every little helps. Am Heart J. 2012;164:229-35. [PMID: 22877809] doi:10.1016/j.ahj.2012.05.003
17. **Green EM, Wakimoto H, Anderson RL, Evanchik MJ, Gorham JM, Harrison BC, et al.** A small-molecule inhibitor of sarcomere contractility suppresses hypertrophic cardiomyopathy in mice. Science. 2016;351:617-21. [PMID: 26912705] doi:10.1126/science.aad3456
18. **Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, et al.** Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med. 2003;348:295-303. [PMID: 12540642]
19. **Sorajja P, Valeti U, Nishimura RA, Ommen SR, Rihal CS, Gersh BJ, et al.** Outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation. 2008;118:131-9. [PMID: 18591440] doi:10.1161/CIRCULATIONAHA.107.738740
20. **Pollick C.** Muscular subaortic stenosis: hemodynamic and clinical improvement after disopyramide. N Engl J Med. 1982;307:997-9. [PMID: 7202121]
21. **Flamm MD, Harrison DC, Hancock EW.** Muscular subaortic stenosis. Prevention of outflow obstruction with propranolol. Circulation. 1968;38:846-58. [PMID: 4177137]
22. **Bonow RO, Dilsizian V, Rosing DR, Maron BJ, Bacharach SL, Green MV.** Verapamil-induced improvement in left ventricular diastolic filling and increased exercise tolerance in patients with hypertrophic cardiomyopathy: short- and long-term effects. Circulation. 1985;72:853-64. [PMID: 4040821]
23. **Forfia PR, Watkins SP, Rame JE, Stewart KJ, Shapiro EP.** Relationship between B-type natriuretic peptides and pulmonary capillary wedge pressure in the intensive care unit. J Am Coll Cardiol. 2005;45:1667-71. [PMID: 15893185]
24. **del Rio CL, Ueyama Y, Baker DC, Dalton SR, Lucats L, Janiak P, et al.** In vivo cardiac effects of mavacamten (MYK-461): evidence for negative inotropy and improved compliance [abstract]. Circulation. 2018;136:A20593.

Current Author Addresses: Dr. Heitner: Knight Cardiovascular Institute, Oregon Health & Science University, UHN62, 3181 SW Sam Jackson Park Road, Portland, OR 97239.
Dr. Jacoby: Section of Cardiovascular Medicine, Yale University School of Medicine, 15 York Street, New Haven, CT 06510.
Dr. Lester: Mayo Clinic Arizona, 13400 East Shea Boulevard, Scottsdale, AZ 85259.
Dr. Owens: Perelman Center for Advanced Medicine, University of Pennsylvania, East Pavilion, 2nd Floor, 3400 Civic Center Boulevard, Philadelphia, PA 19104.
Dr. Wang: Duke University Medical Center, DUMC 3428, Durham, NC 27710.
Drs. Zhang, Lambing, Lee, Semigran, and Sehnert: MyoKardia, 333 Allerton Avenue, South San Francisco, CA 94080.

Author Contributions: Conception and design: S.B. Heitner, S.J. Lester, A. Owens, J. Lambing, J. Lee, M. Semigran.
Analysis and interpretation of the data: S.B. Heitner, D. Jacoby, S.J. Lester, A. Owens, A. Wang, D. Zhang, J. Lambing, J. Lee, M. Semigran, A.J. Sehnert.
Drafting of the article: S.B. Heitner, D. Jacoby, S.J. Lester, A. Wang, D. Zhang, J. Lambing, J. Lee, A.J. Sehnert.
Critical revision of the article for important intellectual content: S.B. Heitner, D. Jacoby, S.J. Lester, A. Owens, A. Wang, J. Lee, M. Semigran, A.J. Sehnert.
Final approval of the article: S.B. Heitner, D. Jacoby, S.J. Lester, A. Owens, A. Wang, D. Zhang, J. Lambing, J. Lee, M. Semigran, A.J. Sehnert.
Provision of study materials or patients: S.B. Heitner, D. Jacoby, S.J. Lester, A. Owens, A. Wang.
Statistical expertise: D. Zhang.
Obtaining of funding: S.B. Heitner, M. Semigran.
Administrative, technical, or logistic support: S.B. Heitner, J. Lambing, M. Semigran, A.J. Sehnert.
Collection and assembly of data: S.B. Heitner, S.J. Lester, A. Wang, J. Lee, M. Semigran.

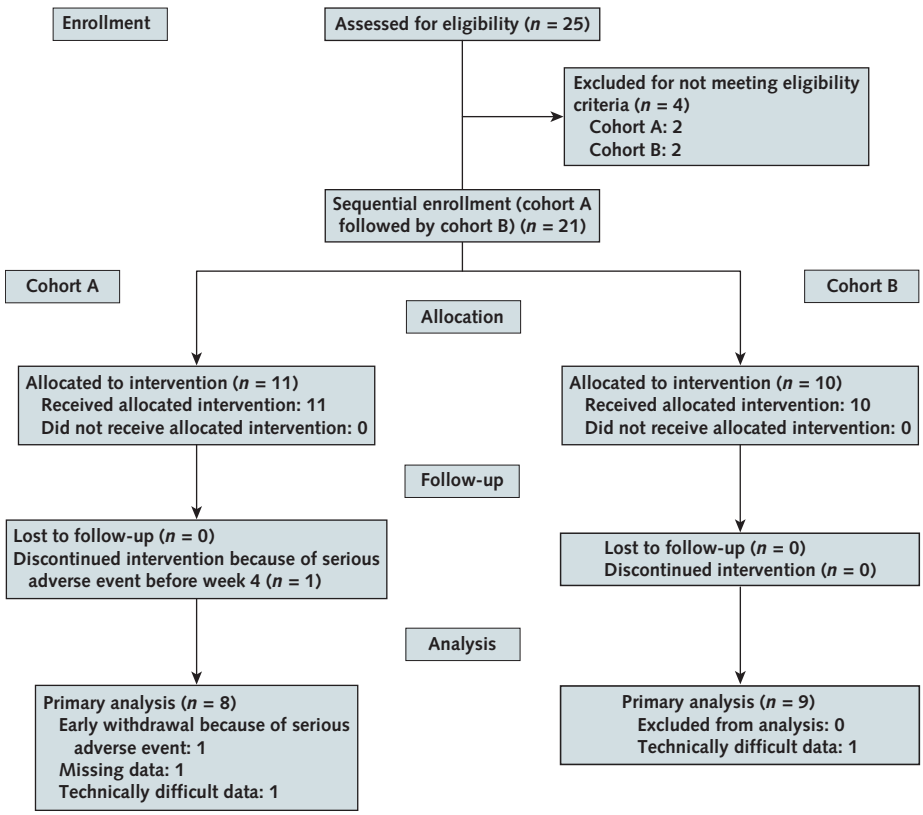
Appendix Figure 1. PIONEER-HCM study design.



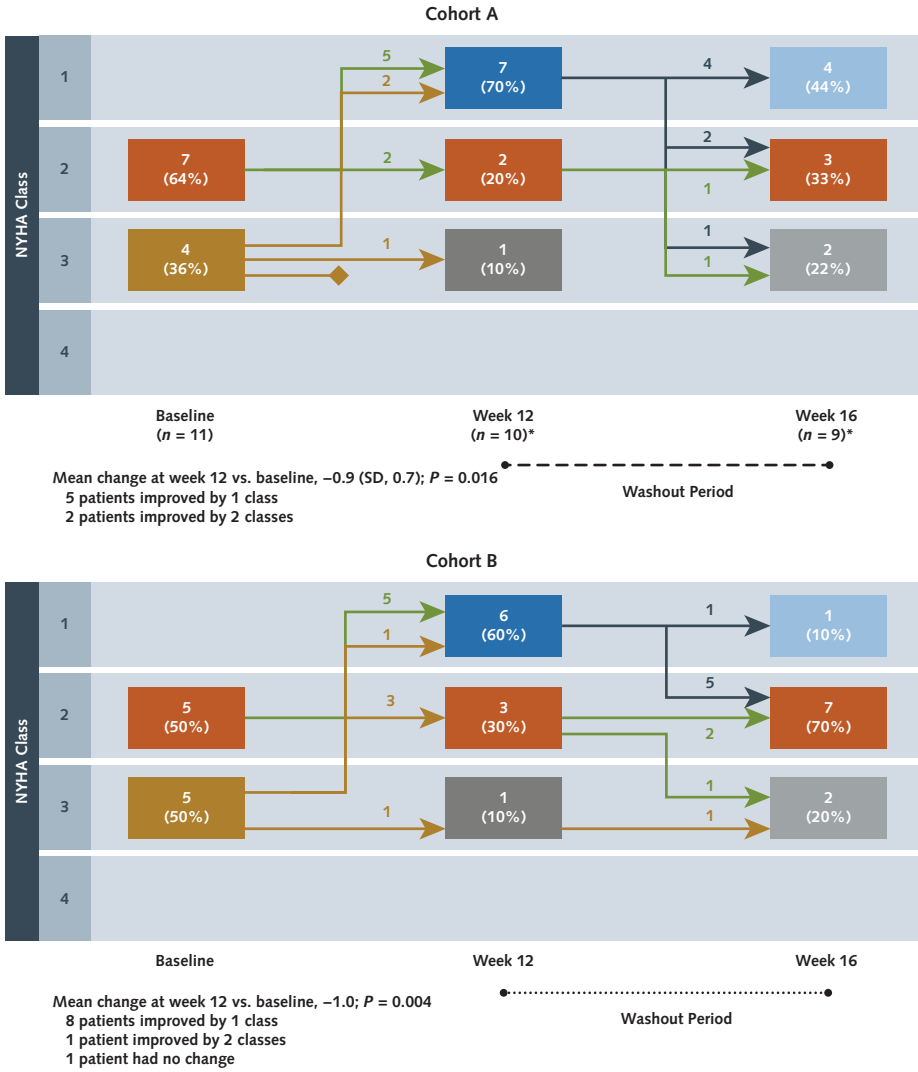
	Starting Dose	Dose Adjustment Algorithm	Doses in Study
Cohort A (*n* = 11)	10 mg (weight ≤60 kg) 15 mg (weight >60 kg)	Based on percentage decrease in LVEF from baseline	10 mg, 15 mg, 20 mg
Cohort B (*n* = 10)	2 mg	Based on percentage decrease in resting LVOT peak gradient from baseline	2 mg, 5 mg

Patients in cohort A started use of mavacamten at 10 to 20 mg/d, with a dose titration at week 4 based on a targeted relative reduction in resting LVEF of 15% to 20% compared with baseline. Patients in cohort B started use of mavacamten at 2 to 5 mg/d, with the potential to increase to 5 mg/d at week 4 if the resting LVOT gradient had not decreased by >50% compared with baseline. Of note, all participants in cohort B increased the dose from 2 to 5 mg/d at week 4. CPET = cardiopulmonary exercise test; echo = echocardiogram; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; PIONEER-HCM = Reduction in Left Ventricular Outflow Tract Gradient with Mavacamten (MYK-461) in Symptomatic Obstructive Cardiomyopathy Patients.

Appendix Figure 2. Study flow diagram.



Appendix Figure 3. NYHA functional class transitions.



NYHA = New York Heart Association.
* Some patients terminated participation early or had missing data.

Appendix Table. Results at Baseline and 16 Weeks

End Point	Cohort A		Cohort B	
	Mean Baseline Value (SD)	Mean Change at 16 Weeks (95% CI)	Mean Baseline Value (SD)	Mean Change at 16 Weeks (95% CI)
Postexercise peak LVOT gradient, *mm Hg**	103 (50) (*n* = 9)	−45.1 (−91.2 to 1.0) (*n* = 8)	86 (43) (*n* = 9)	−3.5 (−27.5 to 20.5) (*n* = 9)
Resting LVOT gradient, *mm Hg*	60 (28) (*n* = 11)	−29.5 (−63.1 to 4.2) (*n* = 10)	86 (63) (*n* = 10)	−9.1 (−30.0 to 11.7) (*n* = 10)
Valsalva LVOT gradient, *mm Hg*	97 (32) (*n* = 11)	−60.6 (−91.8 to −29.4) (*n* = 10)	100 (65) (*n* = 10)	−9.5 (−38.5 to 19.6) (*n* = 10)
Resting LVEF, %	70 (7) (*n* = 11)	−6.2 (−12.2 to −0.2) (*n* = 10)	75 (5) (*n* = 10)	−2.8 (−7.5 to 2.0) (*n* = 10)
NYHA functional class	2.4 (0.5) (*n* = 11)	−0.4 (−1.0 to 0.2) (*n* = 10)	2.5 (0.5) (*n* = 10)	−0.4 (−0.8 to −0.03) (*n* = 10)
KCCQ OSS	65 (16) (*n* = 11)	10.5 (−3.6 to 24.6) (*n* = 10)	61 (26) (*n* = 10)	6.1 (−4.3 to 16.4) (*n* = 10)
NRS dyspnea score	4.9 (1.6) (*n* = 11)	−2.2 (−4.6 to 0.2) (*n* = 10)	4.0 (2.6) (*n* = 10)	−0.8 (−2.3 to 0.7) (*n* = 10)
Median change in NT-proBNP level (IQR), *pg/mL*	930 (647) (*n* = 11)	−629.5 (−804 to 158) (*n* = 10)	1834 (3209) (*n* = 9)	240 (4 to 311) (*n* = 10)
Systolic blood pressure, *mm Hg*	136 (13) (*n* = 11)	−5.2 (−13.0 to 2.6) (*n* = 10)	132 (14) (*n* = 10)	−1.4 (−16.5 to 13.7) (*n* = 10)
Diastolic blood pressure, *mm Hg*	75 (8) (*n* = 11)	3.4 (−6.0 to 12.8) (*n* = 10)	77 (15) (*n* = 10)	−2.3 (−11.9 to 7.3) (*n* = 10)

IQR = interquartile range; KCCQ OSS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NRS = numerical rating scale; NT-proBNP = *N*-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.
* In cohort A, 2 patients did not have postexercise measures (1 was unable to exercise at baseline and 1 had an image that was technically difficult to interpret) and 1 patient who discontinued because of an adverse event did not have a 12-wk measurement. In cohort B, 1 patient did not have postexercise measures because of technical issues related to imaging.