ORIGINAL ARTICLE

Mavacamten in Adolescents with Obstructive Hypertrophic Cardiomyopathy

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ABSTRACT

BACKGROUND

Approved pharmacologic therapies for pediatric hypertrophic cardiomyopathy are lacking, and surgical intervention may be indicated in patients with left ventricular outflow tract obstruction. The efficacy and safety of mavacamten, a cardiac myosin inhibitor that is available for adults, warrant evaluation in adolescents.

METHODS

We conducted a phase 3, double-blind, randomized, placebo-controlled trial involving symptomatic adolescents (12 to <18 years of age) with New York Heart Association class II or III obstructive hypertrophic cardiomyopathy. The patients were randomly assigned in a 1:1 ratio to receive mavacamten or placebo. The primary end point was the change from baseline to week 28 in left ventricular outflow tract pressure gradient provoked by the Valsalva maneuver.

RESULTS

A total of 44 patients underwent randomization; 23 patients (8 [35%] of whom were female) were assigned to mavacamten group, and 21 (5 [24%] of whom were female) were assigned to the placebo group. The mean (±SD) age of the patients was 14.7±1.7 years in the mavacamten group and 14.6±1.7 years in the placebo group, and the mean Valsalva left ventricular outflow tract gradient at baseline was similar in the two groups (78.4±34.1 mm Hg and 80.8±47.4 mm Hg, respectively). At week 28, the least-squares mean change in the Valsalva left ventricular outflow tract gradient was −48.5 mm Hg in the mavacamten group and −0.5 mm Hg in the placebo group (difference, −48.0 mm Hg; 95% confidence interval, −67.7 to −28.3; P<0.001). The incidence of adverse events was similar in the two groups. Two patients in each group had serious adverse events; in the mavacamten group, 1 patient had two episodes of syncope, and another had an inappropriate shock delivered by an implantable cardioverter–defibrillator; in the placebo group, 1 patient had chest pain, and another had depression with suicidal ideation. No patient had a reduction in the left ventricular ejection fraction to less than 50%. No deaths occurred during the trial.

CONCLUSIONS

Among adolescent patients with obstructive hypertrophic cardiomyopathy, the reduction in left ventricular outflow tract obstruction was significantly greater with mavacamten than with placebo over a 28-week period. (Funded by Bristol Myers Squibb; SCOUT-HCM ClinicalTrials.gov number, NCT06253221.)

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Hypertrophic cardiomyopathy is the most common inherited cardiovascular disease and is predominantly characterized by left ventricular hypertrophy in the absence of another cardiac, systemic, or metabolic disease.[1] Left ventricular outflow tract obstruction, characterized by a resting or provoked left ventricular outflow tract gradient of 30 mm Hg or greater, is common among patients with hypertrophic cardiomyopathy and can lead to severe symptoms, including heart failure.[1-5] Other pathophysiological features include diastolic dysfunction, mitral regurgitation, and autonomic dysfunction, which may be exacerbated by left ventricular outflow tract obstruction.[1]

Pediatric hypertrophic cardiomyopathy is a rare disease, with an estimated prevalence of 3 to 9 per 100,000 children.[6,7] Pediatric hypertrophic cardiomyopathy is associated with a worse prognosis than adult-onset hypertrophic cardiomyopathy, with a greater risk of life-threatening arrhythmias and approximately twice the risk of heart transplantation or sudden cardiac death.[8-13] No pharmacologic therapies have been approved by the Food and Drug Administration or the European Medicines Agency for pediatric hypertrophic cardiomyopathy, and current pharmacologic recommendations are extrapolated from evidence obtained in studies involving adults. Such recommendations include the use of beta-blockers, nondihydropyridine calcium-channel blockers, and disopyramide.[1,2,4,14] However, these treatments provide symptomatic relief only.[1,4,15] Approximately 7 to 23% of pediatric patients undergo surgical myectomy to relieve left ventricular outflow tract obstruction.[5,16] Thus, there remains a need for targeted pharmacologic therapy that can effectively reduce left ventricular outflow tract obstruction and mitigate symptoms in pediatric patients with obstructive hypertrophic cardiomyopathy.

Mavacamten is a selective, cardiac-specific myosin inhibitor approved for the treatment of adults with symptomatic New York Heart Association (NYHA) class II or III obstructive hypertrophic cardiomyopathy.[17] The efficacy and favorable safety profile of mavacamten in adults were shown in five phase 3 clinical trials, sustained in subsequent long-term extension studies, and confirmed in observational studies.[18-27] Although mavacamten was shown to be efficacious in genotypically diverse induced pluripotent stem-cell–derived cardiomyocytes from pediatric patients,[28] it was not clinically assessed in a pediatric cohort. Here, we report the results for the primary and secondary efficacy and safety end points in a phase 3 trial conducted to evaluate the efficacy and safety of mavacamten, as compared with placebo, in symptomatic adolescent patients (12 to <18 years of age) with obstructive hypertrophic cardiomyopathy.

Methods

Trial Organization and Oversight

SCOUT-HCM (Study of Mavacamten in Adolescents with Symptomatic Obstructive Hypertrophic Cardiomyopathy) is an ongoing phase 3, double-blind, randomized, placebo-controlled trial with active-treatment and long-term extension periods. Patients were enrolled at 28 sites in nine countries worldwide from April 2024 through April 2025.[29] The trial protocol, available with the full text of this article at NEJM.org, was approved by the relevant institutional review board or independent ethics committee at each site. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. Written assent was obtained from all the patients, and written informed consent was obtained from their representatives before trial initiation. The trial was designed by the sponsor (Bristol Myers Squibb), with input from the steering committee. Data were collected by the investigators and analyzed by the sponsor. The first author wrote the initial draft of the manuscript, with medical writing support that was funded by the sponsor, and vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol and statistical analysis plan (available with the protocol). All the authors provided input on the initial and subsequent drafts and provided final approval to submit the manuscript for publication.

An independent data monitoring committee reviewed safety and efficacy data throughout the trial. The date of the data lock for the current analysis (performed after all the patients completed the assessments at week 28) was November 25, 2025.

Trial Population

Adolescent patients (12 to <18 years of age) were eligible for inclusion if they had received a diag-

nosis of hypertrophic cardiomyopathy (defined as a maximal left ventricular wall thickness of ≥15 mm [or ≥13 mm with a family history of hypertrophic cardiomyopathy or the presence of a pathogenic or likely pathogenic genetic variant] or echocardiographic evidence of hypertrophy ≥2 standard deviations above the standardized mean for body size), had a left ventricular outflow tract pressure gradient during the Valsalva maneuver (a provocation maneuver involving forceful expiration against a closed glottis) of 30 mm Hg or greater, had a maximal left ventricular outflow tract gradient (at rest, during a Valsalva maneuver, or after exercise) of 50 mm Hg or greater, had a left ventricular ejection fraction (LVEF) of 60% or greater, and had NYHA functional class II or III symptoms. Patients with hypertrophic cardiomyopathy phenocopies (e.g., Noonan syndrome and Fabry disease) were excluded. The complete list of inclusion and exclusion criteria was previously published[29] and is also provided in Table S1 in the Supplementary Appendix, available at NEJM.org.

PROCEDURES

Eligibility was confirmed during a 5-week screening window. After enrollment, patients underwent randomization in a 1:1 ratio to receive mavacamten or placebo during the double-blind, placebo-controlled period (from baseline to week 28). Randomization was performed with the use of interactive response technology (YPrime) and was stratified according to age (12 to <15 years or 15 to <18 years) and beta-blocker use (yes or no).

Mavacamten therapy was initiated at a once-daily dose of 5 mg in patients with a body weight of 45 kg or greater at baseline or at a once-daily dose of 2.5 mg in patients with a body weight of 35 kg to less than 45 kg. The dose of mavacamten could be adjusted down (at weeks 5 and 9) or up (at weeks 12 and 24) by one dose level on the basis of echocardiographic assessment of the Valsalva left ventricular outflow tract gradient and LVEF (Table S2).[29] The possible mavacamten doses were 1 mg, 2.5 mg, 5 mg, 10 mg, and 15 mg. Concomitant treatment with background therapies for hypertrophic cardiomyopathy (i.e., beta-blockers, calcium-channel blockers, and disopyramide) was allowed, provided that the patient was receiving a stable dose for at least 14 days before screening. Additional details about the trial procedures are provided in the Supplementary Appendix.

END POINTS AND SAFETY

The primary end point was the change in left ventricular outflow tract pressure gradient provoked by the Valsalva maneuver from baseline to week 28. Secondary efficacy end points included the change from baseline to week 28 in resting and postexercise left ventricular outflow tract gradients, the maximal left ventricular wall thickness, the ratio of early mitral inflow velocity to mitral annular early diastolic velocity (E/e′ ratio), and the patient-reported Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) Shortness-of-Breath domain score (scores range from 0 to 18, with higher scores indicating a greater symptom burden). Additional secondary efficacy end points included any increase in peak oxygen uptake, a reduction in maximal left ventricular outflow tract gradient (resting or during the Valsalva maneuver) to less than 30 mm Hg, an improvement of at least one class in NYHA functional class, and an improvement of at least one grade in mitral regurgitation from baseline to week 28. Exploratory end points included the change in N-terminal pro–B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin I, and high-sensitivity cardiac troponin T from baseline to week 28.

Safety end points were the incidence of adverse events and of serious adverse events, a decrease in LVEF to less than 50% and to 30% or less, and the change in the QT interval (calculated with Fridericia's formula) from baseline to week 28. Reported are events that occurred after the first dose of mavacamten or placebo up to 8 weeks after the last dose, as well as those that had an onset date before the first dose of mavacamten or placebo but increased in severity or became serious after the first dose of mavacamten or placebo up to 8 weeks after the last dose.

STATISTICAL ANALYSIS

The statistical power for the analysis of the primary end point was calculated with the assumption that the mean (±SD) between-group difference in the change in Valsalva left ventricular outflow tract gradient from baseline to week 28 would be −36±40 mm Hg. A sample of 40 patients, randomly assigned in a 1:1 ratio, was estimated to provide approximately 80% power to detect a between-group difference at a two-sided significance level of 0.05. A treatment policy estimand consistent with the intention-to-treat principle was used in the primary analysis.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Variable	Mavacamten (N=23)	Placebo (N=21)
Demographic characteristics		
Age — yr	14.7±1.7	14.6±1.7
Female sex at birth — no. (%)	8 (35)	5 (24)
Race or ethnic group — no. (%)†		
White	15 (65)	15 (71)
Black or African American	3 (13)	0
Asian	0	2 (10)
Unknown	1 (4)	1 (5)
Not reported	4 (17)	3 (14)
Geographic region — no. (%)		
United States	15 (65)	14 (67)
Australia, Canada, or Europe	8 (35)	7 (33)
Clinical characteristics		
Body weight — kg	71.1±19.1	67.4±18.6
Hypertrophic cardiomyopathy genotype — no. (%)		
Pathogenic or likely pathogenic mutation	12 (52)	12 (57)
Variant of uncertain significance	5 (22)	6 (29)
Negative	5 (22)	2 (10)
Missing	1 (4)	1 (5)
Background therapy for hypertrophic cardiomyopathy — no. (%)‡		
Beta-blocker	19 (83)	18 (86)
Calcium-channel blocker	3 (13)	2 (10)
Disopyramide	4 (17)	5 (24)
NYHA functional class — no. (%)		
II	19 (83)	18 (86)
III	4 (17)	3 (14)
Median NT-proBNP (IQR) — pg/ml§	1776 (1226–2816)	1294 (670–2702)
Median high-sensitivity cardiac troponin I (IQR) — pg/ml¶	36.1 (13.2–168.0)	22.7 (14.5–59.6)
Echocardiographic measures		
LVOT gradient — mm Hg		
Resting	64.8±30.9	65.2±38.1
During a Valsalva maneuver	78.4±34.1	80.8±47.4
After exercise‖	89.5±42.8	104.7±51.7
LVEF — %	69.0±3.9	67.4±4.1
Maximal left ventricular wall thickness — mm	28.3±6.0	24.7 ±7.1
E/e′ ratio		
Lateral	14.3±8.6	12.5±6.9
Septal**	18.8±7.1	14.9±4.6
Average**	16.7±7.1	13.6±5.3

Table 1. (Continued.)

Variable	Mavacamten (N=23)	Placebo (N=21)
Presence of mitral regurgitation — no. (%)		
None	1 (4)	1 (5)
Mild	13 (57)	13 (62)
Moderate	8 (35)	5 (24)
Moderate to severe	1 (4)	2 (10)
Peak oxygen uptake — ml/kg/min††	26.1±7.1	26.1±7.6

* Plus–minus values are means ±SD. Baseline characteristics are shown for the randomized analysis population, which included all the patients who underwent randomization. Baseline was defined as the last available value on the day of or before administration of the first dose of mavacamten or placebo. E/e′ is the ratio of early mitral inflow velocity to mitral annular early diastolic velocity. IQR denotes interquartile range, LVEF left ventricular ejection fraction, LVOT left ventricular outflow tract, NT-proBNP N-terminal pro–B-type natriuretic peptide, and NYHA New York Heart Association.
† Race and ethnic group were reported by the patient.
‡ Concomitant treatment with a combination of background hypertrophic cardiomyopathy therapies was permitted.
§ Data were missing for two patients in the mavacamten group and for one patient in the placebo group.
¶ Data were missing for one patient in the placebo group.
‖ Data were missing for six patients in the mavacamten group and for four patients in the placebo group.
** Data were missing for one patient in the mavacamten group.
†† Data were missing for six patients in the mavacamten group and for two patients in the placebo group.

Efficacy analyses were performed in the intention-to-treat population (hereafter referred to as the randomized analysis population), except for the analysis of the change in postexercise left ventricular outflow tract gradient from baseline to week 28 (which was based on data from the subgroup of patients who underwent postexercise transthoracic echocardiography) and the analysis of the percentage of patients who had any increase in peak oxygen uptake from baseline to week 28 (which was based on data from the subgroup of patients who underwent cardiopulmonary exercise testing) (Table S3).

The analysis of the primary end point was performed with the use of a mixed-effect model for repeated measures, which included randomization stratification factors, Valsalva left ventricular outflow tract gradient at baseline, trial-group assignment, visit, and trial-group assignment–by–visit interaction as covariates or factors and patient as a random effect. Least-squares means from the model are presented with corresponding 95% confidence intervals. Data from patients who discontinued mavacamten or placebo because of death from noncardiovascular causes, as well as from those who had missing data, were imputed through a placebo-based multiple-imputation approach with a regression model that was based on data from the patients who received placebo and included stratification factors and Valsalva left ventricular outflow tract gradient values at baseline as covariates (Table S4).

The results for secondary and exploratory efficacy end points were summarized descriptively with estimates of between-group differences and 95% confidence intervals. The widths of the confidence intervals were not adjusted for multiplicity; therefore, these confidence intervals should not be interpreted as formal hypothesis testing. The statistical analyses that were performed for the secondary efficacy end points are described in the Supplementary Appendix. Missing data were not imputed for continuous secondary and exploratory end points. Safety end points were summarized descriptively. All statistical analyses were conducted with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS AND BASELINE CHARACTERISTICS

Of the 65 patients who had undergone screening for eligibility, 44 were randomly assigned to the mavacamten group (23 patients) or the placebo

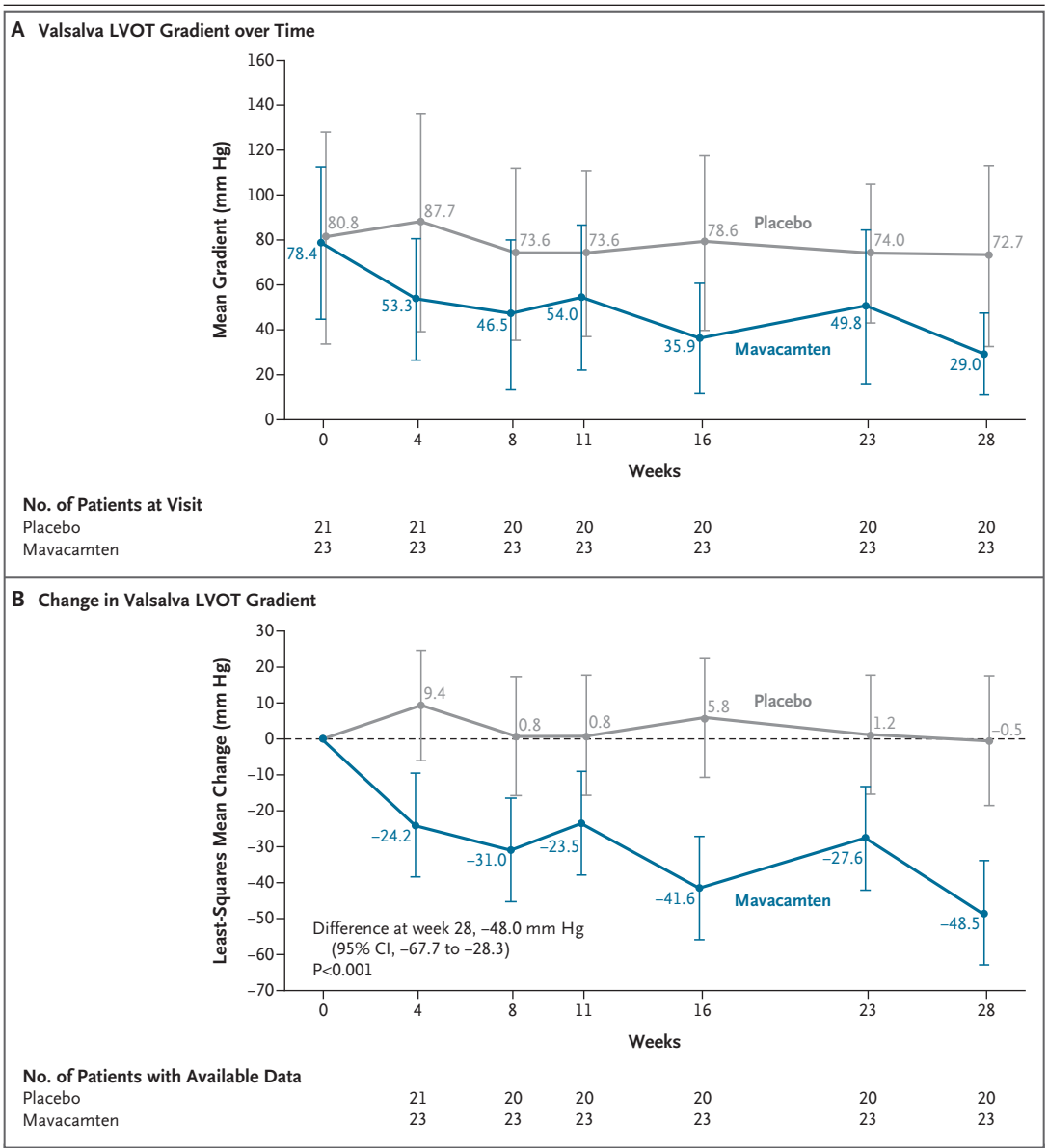


Figure 1. Valsalva Left Ventricular Outflow Tract Gradient over Time and Change from Baseline.

Panel A shows the left ventricular outflow tract pressure gradient during a Valsalva maneuver (Valsalva LVOT gradient) over time. I bars represent the standard deviation. Panel B shows the least-squares mean change from baseline in the Valsalva LVOT gradient. I bars represent the 95% confidence interval.

group (21 patients) (Fig. S1). One patient in the placebo group had persistent symptoms and was referred for myectomy. That patient requested unblinding of the trial-group assignment, which led to a per-protocol withdrawal from the trial; all the remaining patients (98%) completed the double-blind, placebo-controlled period. At baseline, the characteristics of the mavacamten group and the placebo group were generally well balanced, except for slight imbalances in the mean (±SD) body-mass index (the weight in kilograms divided by the square of the height in meters; 25.7±6.1 vs. 23.7±5.2), the median NT-proBNP level (1776 pg per milliliter [interquartile range, 1226 to 2816] vs. 1294 pg per milliliter [interquartile range, 670 to 2702]), and the median high-sensitivity cardiac troponin I level (36.1 pg per milliliter [interquartile range, 13.2 to 168.0] vs.

Table 2. Primary and Secondary End Points.*

End Point	Mavacamten (N=23)		Placebo (N=21)		Difference vs. Placebo (95% CI)
	No. of Patients Evaluated	Least-Squares Mean Change (95% CI)	No. of Patients Evaluated	Least-Squares Mean Change (95% CI)	
Primary end point					
Change from baseline to week 28 in Valsalva LVOT gradient — mm Hg	23	−48.5 (−63.0 to −34.0)	20	−0.5 (−18.7 to 17.6)	−48.0 (−67.7 to −28.3)†
Secondary efficacy end points					
Change from baseline to week 28 in resting LVOT gradient — mm Hg	23	−39.0 (−50.9 to −27.0)	20	8.1 (−5.0 to 21.2)	−47.0 (−62.7 to −31.4)
Change from baseline to week 28 in postexercise LVOT gradient — mm Hg	16	−31.2 (−46.3 to −16.1)	16	10.5 (−5.5 to 26.6)	−41.7 (−59.7 to −23.7)
Change from baseline to week 28 in maximal LV wall thickness — mm	23	−2.5 (−3.7 to −1.3)	20	−0.7 (−2.1 to 0.7)	−1.8 (−3.4 to −0.2)
Change from baseline to week 28 in E/e′ ratio					
Lateral	23	−3.8 (−5.4 to −2.3)	19	−0.6 (−2.3 to 1.1)	−3.2 (−5.2 to −1.3)
Septal	22	−3.5 (−5.1 to −1.8)	20	−0.7 (−2.6 to 1.2)	−2.8 (−5.0 to −0.5)
Average	22	−3.7 (−5.0 to −2.4)	19	−0.4 (−1.8 to 1.1)	−3.4 (−5.1 to −1.6)
Change from baseline to week 28 in HCMSQ SoB domain score — points‡	19	−1.1 (−2.4 to 0.2)	16	−0.8 (−2.3 to 0.6)	−0.3 (−2.0 to 1.5)

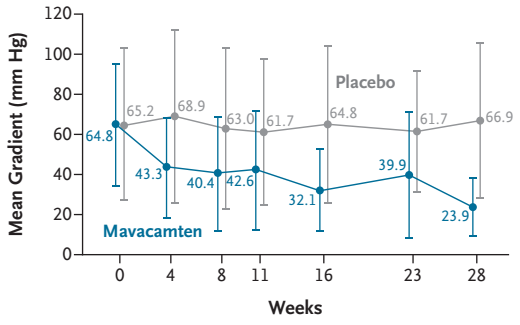
* Efficacy analyses were performed in the randomized analysis population, which included all the patients who underwent randomization. LV denotes left ventricular.
† P<0.001.
‡ Patient-reported Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath (HCMSQ SoB) domain scores range from 0 to 18, with higher scores indicating a greater symptom burden.

22.7 pg per milliliter [interquartile range, 14.5 to 59.6]) (Table 1 and Table S5). Overall, 91% of the patients in the mavacamten group started mavacamten at 5 mg (Table S6). All 23 patients who received mavacamten had a dose adherence of 80% or greater (percentage calculated from the actual cumulative dose divided by the expected cumulative dose).

EFFICACY

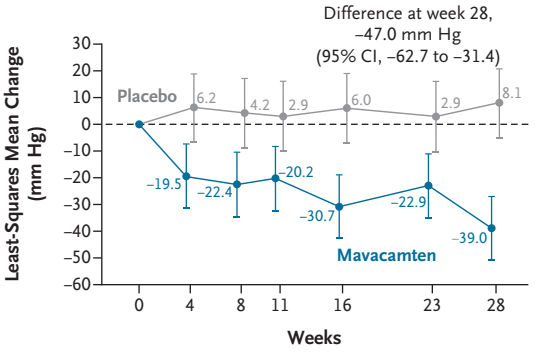
In the analysis of the primary efficacy end point, the mean Valsalva left ventricular outflow tract gradient decreased from 78.4±34.1 mm Hg at baseline to 29.0±18.3 mm Hg at week 28 in the mavacamten group (least-squares mean change, −48.5 mm Hg; 95% confidence interval [CI], −63.0 to −34.0), as compared with a decrease from 80.8±47.4 mm Hg to 72.7±40.1 mm Hg in the placebo group (least-squares mean change, −0.5 mm Hg; 95% CI, −18.7 to 17.6), which corresponds to a significant difference of −48.0 mm Hg (95% CI, −67.7 to −28.3) (P<0.001) (Fig. 1 and Table 2). The secondary efficacy endpoint analyses of the change from baseline to week 28 in resting left ventricular outflow tract gradient, postexercise left ventricular outflow tract gradient, maximal left ventricular wall thickness, and E/e′ ratio (lateral, septal, and average) were supportive of the primary analysis (Fig. 2 and Table 2). Additional secondary efficacy endpoint analyses were also supportive of the primary analysis; these analyses included the percentage of patients who, from baseline to week 28, had a reduction in the maximal left ventricular outflow tract gradient (resting or during the Valsalva maneuver) to less than 30 mm Hg (the threshold for guideline-based diagnosis of obstructive hypertrophic cardiomyopathy), an improve-

A Resting LVOT Gradient over Time



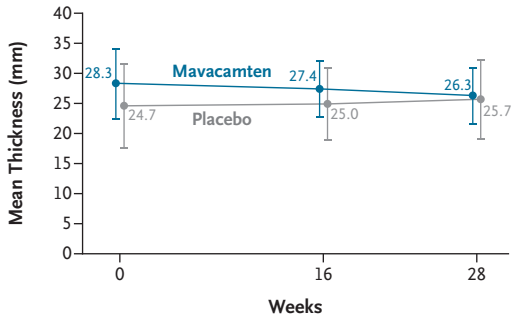
No. of Patients at Visit							
Placebo	21	21	20	20	20	20	20
Mavacamten	23	23	23	23	23	23	23

B Change in Resting LVOT Gradient



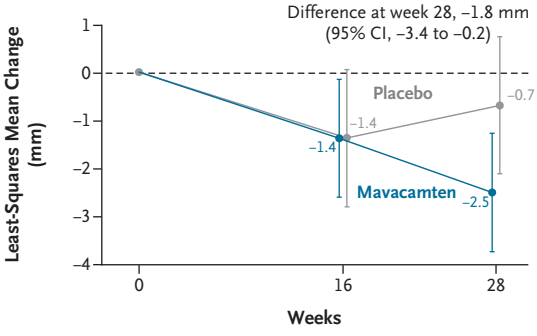
No. of Patients with Available Data							
Placebo	21	20	20	20	20	20
Mavacamten	23	23	23	23	23	23

C Maximal LV Wall Thickness over Time



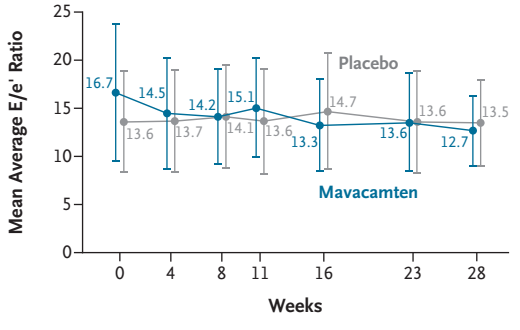
No. of Patients at Visit			
Placebo	21	20	20
Mavacamten	23	23	23

D Change in Maximal LV Wall Thickness



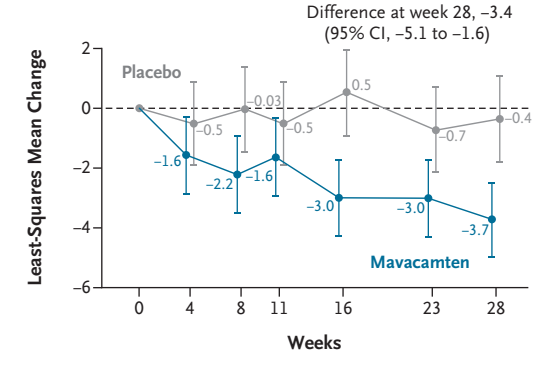
No. of Patients with Available Data			
Placebo	20	20
Mavacamten	23	23

E Average E/e' Ratio over Time



No. of Patients at Visit							
Placebo	21	21	20	20	20	19	19
Mavacamten	22	22	20	21	23	21	23

F Change in Average E/e' Ratio



No. of Patients with Available Data							
Placebo	21	20	20	20	19	19
Mavacamten	21	20	20	22	21	22

Figure 2 (facing page). Key Secondary Efficacy End Points over Time and Change from Baseline.

Panel A shows the mean resting LVOT gradient over time, and Panel B shows the least-squares mean change from baseline. Panel C shows the mean maximal left ventricular (LV) wall thickness over time, and Panel D shows the least-squares mean change from baseline. Panel E shows the mean average ratio of early mitral inflow velocity to mitral annular early diastolic velocity (E/e′) over time, and Panel F shows the least-squares mean change from baseline. I bars represent the standard deviation in Panels A, C, and E and the 95% confidence interval in Panels B, D, and F.

ment of at least one class in NYHA functional class, and an improvement of at least one grade in mitral regurgitation (Table S7).

The least-squares mean change in the patient-reported HCMSQ Shortness-of-Breath domain score was –1.1 points (95% CI, –2.4 to 0.2) in the mavacamten group and –0.8 points (95% CI, –2.3 to 0.6) in the placebo group, which corresponds to a difference of –0.3 points (95% CI, –2.0 to 1.5). In total, 73% of the patients in the mavacamten group and 44% of those in the placebo group had an increase from baseline in peak oxygen uptake, which represents a risk difference of 29.6 percentage points (95% CI, –5.7 to 58.3). In the analyses of the exploratory end points, the proportion of the geometric mean ratio at week 28 (relative to baseline) between the mavacamten group and the placebo group was 0.23 (95% CI, 0.14 to 0.37) for NT-proBNP level, 0.37 (95% CI, 0.23 to 0.60) for high-sensitivity cardiac troponin I level, and 0.55 (95% CI, 0.38 to 0.79) for high-sensitivity cardiac troponin T level.

SAFETY

Adverse events occurred in 18 patients (78%) in the mavacamten group and in 17 patients (81%) in the placebo group (Table 3). In the mavacamten group, 2 patients had serious adverse events — 1 patient had two episodes of syncope, and another had an inappropriate shock delivered by an implantable cardioverter–defibrillator. The syncope episodes, which occurred in a patient with a history of presyncope, were deemed by the site investigator to be related to mavacamten; the patient continued the assigned regimen throughout hospitalization and had no further episodes. The inappropriate shock delivery was considered by the site investigator to be unrelated to mavacamten, but the event resulted in temporary treatment interruption during the patient's hospitalization. In the placebo group, 2 patients had serious adverse events — 1 patient had chest pain, and another had depression with suicidal ideation.

The mean (±SE) change from baseline to week 28 in QT interval (calculated with Fridericia's formula) was –12.9±5.6 ms in the mavacamten group and 9.3±5.5 ms in the placebo group (Fig. S2). No patient in either trial group died or had an LVEF of less than 50% (Table 3).

DISCUSSION

In our trial involving adolescents with obstructive hypertrophic cardiomyopathy, mavacamten led to a significantly greater reduction in Valsalva left ventricular outflow tract gradient from baseline to week 28 (the primary end point) than placebo. The results of multiple secondary and exploratory efficacy end-point analyses supported the results for the primary end point, which potentially suggests that treatment with mavacamten, as compared with placebo, over a 28-week period leads to improvements in markers of obstruction (resting and postexercise left ventricular outflow tract gradients), diastolic function (lateral, septal, and average E/e′ ratio), cardiac hypertrophy (maximal left ventricular wall thickness), symptoms (NYHA class), mitral-valve dysfunction (mitral regurgitation grade), and biomarkers of cardiac stress (NT-proBNP) and myocardial injury (high-sensitivity cardiac troponin I level). Pharmacologic therapy that targets the source of hypercontractility in adolescents with hypertrophic cardiomyopathy is needed. This trial showed that mavacamten improved the Valsalva left ventricular outflow tract gradient in adolescent patients with obstructive hypertrophic cardiomyopathy, a finding suggesting that this treatment directly addresses the cause of the disease.

All the patients were symptomatic at baseline, despite the fact that a majority were receiving guideline-recommended beta-blocker therapy. The overall findings from this trial are consistent with those observed in five phase 3 clinical trials

Table 3. Summary of Safety Events.*

Adverse Event	Mavacamten (N=23)	Placebo (N=21)
	no. of patients (%)	
Any adverse event	18 (78)	17 (81)
Any treatment-related adverse event	2 (9)	3 (14)
Any serious adverse event	2 (9)	2 (10)
Any treatment-related serious adverse event	1 (4)	0
Any adverse event leading to an interruption in the trial regimen	1 (4)†	1 (5)
Any adverse event leading to discontinuation of the trial regimen	0	0
Any adverse event that resulted in death	0	0
Decrease in LVEF to <50%	0	0
Decrease in LVEF to ≤30%	0	0

* Safety analyses were performed in the safety analysis population, which included all the patients who underwent randomization and received at least one dose of mavacamten or placebo; the patients in the safety analysis population were the same as those in the randomized analysis population. Shown are adverse events that occurred after the first dose of mavacamten or placebo up to 8 weeks after the last dose, as well as those that had an onset date before the first dose of mavacamten or placebo but increased in severity or became serious after the first dose of mavacamten or placebo up to 8 weeks after the last dose. The relatedness of adverse events to mavacamten or placebo was determined by the site investigator.

† In one patient, an inappropriate shock was delivered by an implantable cardioverter–defibrillator that led to an interruption in treatment during the patient's hospitalization.

involving adults with symptomatic obstructive hypertrophic cardiomyopathy.[18-24] The patients in SCOUT-HCM had higher left ventricular outflow tract gradients, maximal left ventricular wall thickness, and cardiac biomarker levels at baseline than the adult patients in the EXPLORER-HCM trial,[18] all of which indicate a patient population with more severe disease. Also, in a finding consistent with those in previous studies comparing pediatric hypertrophic cardiomyopathy with adult-onset hypertrophic cardiomyopathy,[13,30] a greater percentage of patients were genotype-positive in our trial than in the EXPLORER-HCM trial, although this may have been influenced by a higher percentage of patients undergoing genetic testing. Overall, the trial sample was broadly representative of pediatric patients with hypertrophic cardiomyopathy (Table S8).

Our analysis suggested an association with improvement in NYHA class with mavacamten as compared with placebo. However, this was not reflected in an apparent improvement in the patient-reported HCMSQ Shortness-of-Breath domain score. The validity of the HCMSQ Shortness-of-Breath instrument in adolescent patients is not known; therefore, the results of our trial should be considered exploratory and to indicate a need for validated patient-reported outcome instruments for this population.

Changes in left ventricular wall thickness and measures of diastolic function with mavacamten as compared with placebo were in line with the improvement in the primary end point. We speculate that this may reflect a beneficial effect on cardiac structure, a finding consistent with those observed in previous trials of mavacamten.[31,32] In addition, our analysis indicated a possible association between mavacamten and reduced levels of NT-proBNP and high-sensitivity cardiac troponin I, two markers of disease severity that are associated with serious adverse outcomes, including progression of heart failure and death.[33-36] Adolescents with hypertrophic cardiomyopathy can have a cumulative lifetime burden of adverse outcomes, which may contribute to a poor long-term prognosis.[37] It is possible that intervention before adulthood may result in improved clinical outcomes later in life, given the relatively aggressive phenotype as compared with adult-onset hypertrophic cardiomyopathy, but further data are needed.[8,38,39] Data from the ongoing active-treatment and long-term extension periods (approximately 3 years in total) of the current trial may establish whether this reversal in hypercontractility is sustained over longer exposure.

No evidence of a difference in safety profile between mavacamten and placebo was noted. No patient in either trial group had an LVEF of less than 50%, and no patient died. Adolescent patients generally have a shorter duration of disease and fewer coexisting conditions than adult patients, despite having a more severe phenotype at presentation.[8,38,39] Overall, these findings show that the safety profile of mavacamten in symptomatic adolescents with obstructive hypertrophic cardiomyopathy was similar to the safety profile reported in adults, and no new safety signals were identified.

This trial has limitations. Owing to the lower prevalence of hypertrophic cardiomyopathy among children and adolescents than among adults, the trial sample was relatively small, which precluded in-depth analysis of the secondary and exploratory end points and did not allow for stratification according to sex or other subgroup analyses.

The patient population, although more ethnically diverse than the population in the EXPLORER-HCM trial,[18] was nevertheless predominantly White. Finally, the trial did not evaluate patients with obstructive hypertrophic cardiomyopathy younger than 12 years of age. Future studies that assess the efficacy and safety of mavacamten in a wider pediatric population (including children <12 years of age) and for a longer period are warranted.

In this phase 3 randomized trial of a cardiac myosin inhibitor in adolescent patients (12 to <18 years of age) with obstructive hypertrophic cardiomyopathy, mavacamten was more effective than placebo in reducing the Valsalva left ventricular outflow tract gradient over a 28-week treatment period.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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REFERENCES

1. Ommen SR, Ho CY, Asif IM, et al. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR guideline for the management of hypertrophic cardiomyopathy: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation 2024;149(23):e1239-e1311.
2. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC guidelines for the management of cardiomyopathies. Eur Heart J 2023;44:3503-626.
3. Maron MS, Olivotto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 2003;348:295-303.
4. Crean AM, Adler A, Arbour L, et al. Canadian Cardiovascular Society clinical practice update on contemporary management of the patient with hypertrophic cardiomyopathy. Can J Cardiol 2024;40:1503-23.
5. Norrish G, Cleary A, Field E, et al. Clinical features and natural history of preadolescent nonsyndromic hypertrophic cardiomyopathy. J Am Coll Cardiol 2022;79:1986-97.
6. Arola A, Jokinen E, Ruuskanen O, et al. Epidemiology of idiopathic cardiomyopathies in children and adolescents: a nationwide study in Finland. Am J Epidemiol 1997;146:385-93.
7. Nandi D, Hayes EA, Wang Y, Jerrell JM. Epidemiology of pediatric hypertrophic cardiomyopathy in a 10-year Medicaid cohort. Pediatr Cardiol 2021;42:210-4.
8. Abdelfattah OM, Martinez M, Sayed A, et al. Temporal and global trends of the incidence of sudden cardiac death in hypertrophic cardiomyopathy. JACC Clin Electrophysiol 2022;8:1417-27.
9. Alashi A, Svensson L, Klein J, et al. Characteristics and longer-term outcomes of contemporary patients <18 years of age with hypertrophic cardiomyopathy. Am J Cardiol 2021;140:110-7.
10. Miron A, Lafreniere-Roula M, Steve Fan C-P, et al. A validated model for sudden cardiac death risk prediction in pediatric hypertrophic cardiomyopathy. Circulation 2020;142:217-29.
11. Lynch A, Tatangelo M, Ahuja S, et al. Risk of sudden death in patients with RASopathy hypertrophic cardiomyopathy. J Am Coll Cardiol 2023;81:1035-45.
12. Conway J, Min S, Villa C, et al. The prevalence and association of exercise test abnormalities with sudden cardiac death and transplant-free survival in childhood hypertrophic cardiomyopathy. Circulation 2023;147:718-27.
13. Marston NA, Han L, Olivotto I, et al. Clinical characteristics and outcomes in childhood-onset hypertrophic cardiomyopathy. Eur Heart J 2021;42:1988-96.
14. Bogle C, Colan SD, Miyamoto SD, et al. Treatment strategies for cardiomyopathy in children: a scientific statement from the American Heart Association. Circulation 2023;148:174-95.
15. Ammirati E, Contri R, Coppini R, Cecchi F, Frigerio M, Olivotto I. Pharmacological treatment of hypertrophic cardiomyopathy: current practice and novel perspectives. Eur J Heart Fail 2016;18:1106-18.
16. Alexander PMA, Nugent AW, Daubeney PEF, et al. Long-term outcomes of hypertrophic cardiomyopathy diagnosed during childhood: results from a national population-based study. Circulation 2018;138:29-36.
17. Bristol Myers Squibb. Camzyos (mavacamten): highlights of prescribing information, April 2025 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/214998s010lbl.pdf).
18. Olivotto I, Oreziak A, Barriales-Villa R, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2020;396:759-69.
19. Rader F, Oręziak A, Choudhury L, et al. Mavacamten treatment for symptomatic obstructive hypertrophic cardiomyopathy: interim results from the MAVA-LTE study, EXPLORER-LTE cohort. JACC Heart Fail 2024;12:164-77.
20. Kitaoka H, Ieda M, Ebato M, et al. Phase 3 open-label study evaluating the efficacy and safety of mavacamten in Japanese adults with obstructive hypertrophic cardiomyopathy: the HORIZON-HCM study. Circ J 2024;89:130-8.
21. Garcia-Pavia P, Oręziak A, Masri A, et al. Long-term effect of mavacamten in obstructive hypertrophic cardiomyopathy. Eur Heart J 2024;45:5071-83.
22. Desai MY, Owens A, Geske JB, et al.

Myosin inhibition in patients with obstructive hypertrophic cardiomyopathy referred for septal reduction therapy. J Am Coll Cardiol 2022;80:95-108.
23. Desai MY, Wolski K, Owens A, et al. Mavacamten in patients with hypertrophic cardiomyopathy referred for septal reduction: week 128 results from VALOR-HCM. Circulation 2025;151:1378-90.
24. Tian Z, Li L, Li X, et al. Effect of mavacamten on Chinese patients with symptomatic obstructive hypertrophic cardiomyopathy: the EXPLORER-CN randomized clinical trial. JAMA Cardiol 2023;8:957-65.
25. Bilen O, Adler A, Bastiaenen R, et al. Mavacamten monotherapy in real-world patients with obstructive hypertrophic cardiomyopathy: evidence from COLLIGO-HCM. Circ Genom Precis Med 2026;19(1):e005502.
26. Desai MY, Seto D, Cheung M, et al. Mavacamten: real-world experience from 22 months of the risk evaluation and mitigation strategy (REMS) program. Circ Heart Fail 2025;18(1):e012441.
27. Reza N, Dubey A, Mahmud N, et al. Long-term real-world outcomes of mavacamten in symptomatic obstructive hypertrophic cardiomyopathy up to 108 weeks. J Clin Med 2025;14:8181.
28. Kinnear C, Said A, Meng G, et al. Myosin inhibitor reverses hypertrophic cardiomyopathy in genotypically diverse pediatric iPSC-cardiomyocytes to mirror variant correction. Cell Rep Med 2024;5:101520.
29. Rossano J, Canter C, Wolf C, et al. Mavacamten in symptomatic adolescent patients with obstructive hypertrophic cardiomyopathy: design of the phase 3 SCOUT-HCM trial. Am Heart J 2026;292:107283.
30. Akinrinade O, Lesurf R, Lougheed J, et al. Age and sex differences in the genetics of cardiomyopathy. J Cardiovasc Transl Res 2023;16:1287-302.
31. Cremer PC, Geske JB, Owens A, et al. Myosin inhibition and left ventricular diastolic function in patients with obstructive hypertrophic cardiomyopathy referred for septal reduction therapy: insights from the VALOR-HCM study. Circ Cardiovasc Imaging 2022;15(12):e014986.
32. Hegde SM, Lester SJ, Solomon SD, et al. Effect of mavacamten on echocardiographic features in symptomatic patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2021;78:2518-32.
33. Coats CJ, Gallagher MJ, Foley M, et al. Relation between serum N-terminal pro-brain natriuretic peptide and prognosis in patients with hypertrophic cardiomyopathy. Eur Heart J 2013;34:2529-37.
34. D'Amato R, Tomberli B, Castelli G, et al. Prognostic value of N-terminal pro-brain natriuretic peptide in outpatients with hypertrophic cardiomyopathy. Am J Cardiol 2013;112:1190-6.
35. Wu G, Liu J, Wang S, et al. N-terminal pro-brain natriuretic peptide and sudden cardiac death in hypertrophic cardiomyopathy. Heart 2021;107:1576-83.
36. Zhang Y, Liu M, Zhang C, Zou Y, Kang L, Song L. Role of biomarkers of myocardial injury to predict adverse outcomes in hypertrophic cardiomyopathy. Circ Cardiovasc Qual Outcomes 2024;17(2):e010243.
37. Ho CY, Day SM, Ashley EA, et al. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the sarcomeric human cardiomyopathy registry (SHaRe). Circulation 2018;138:1387-98.
38. Balaji S, DiLorenzo MP, Fish FA, et al. Risk factors for lethal arrhythmic events in children and adolescents with hypertrophic cardiomyopathy and an implantable defibrillator: an international multicenter study. Heart Rhythm 2019;16:1462-7.
39. Lafreniere-Roula M, Bolkier Y, Zahavich L, et al. Family screening for hypertrophic cardiomyopathy: is it time to change practice guidelines? Eur Heart J 2019;40:3672-81.