ORIGINAL ARTICLE

Aficamten for Symptomatic Obstructive Hypertrophic Cardiomyopathy

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ABSTRACT

BACKGROUND

One of the major determinants of exercise intolerance and limiting symptoms among patients with obstructive hypertrophic cardiomyopathy (HCM) is an elevated intracardiac pressure resulting from left ventricular outflow tract obstruction. Aficamten is an oral selective cardiac myosin inhibitor that reduces left ventricular outflow tract gradients by mitigating cardiac hypercontractility.

METHODS

In this phase 3, double-blind trial, we randomly assigned adults with symptomatic obstructive HCM to receive aficamten (starting dose, 5 mg; maximum dose, 20 mg) or placebo for 24 weeks, with dose adjustment based on echocardiography results. The primary end point was the change from baseline to week 24 in the peak oxygen uptake as assessed by cardiopulmonary exercise testing. The 10 prespecified secondary end points (tested hierarchically) were change in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS), improvement in the New York Heart Association (NYHA) functional class, change in the pressure gradient after the Valsalva maneuver, occurrence of a gradient of less than 30 mm Hg after the Valsalva maneuver, and duration of eligibility for septal reduction therapy (all assessed at week 24); change in the KCCQ-CSS, improvement in the NYHA functional class, change in the pressure gradient after the Valsalva maneuver, and occurrence of a gradient of less than 30 mm Hg after the Valsalva maneuver (all assessed at week 12); and change in the total workload as assessed by cardiopulmonary exercise testing at week 24.

RESULTS

A total of 282 patients underwent randomization: 142 to the aficamten group and 140 to the placebo group. The mean age was 59.1 years, 59.2% were men, the baseline mean resting left ventricular outflow tract gradient was 55.1 mm Hg, and the baseline mean left ventricular ejection fraction was 74.8%. At 24 weeks, the mean change in the peak oxygen uptake was 1.8 ml per kilogram per minute (95% confidence interval [CI], 1.2 to 2.3) in the aficamten group and 0.0 ml per kilogram per minute (95% CI, −0.5 to 0.5) in the placebo group (least-squares mean between-group difference, 1.7 ml per kilogram per minute; 95% CI, 1.0 to 2.4; P<0.001). The results for all 10 secondary end points were significantly improved with aficamten as compared with placebo. The incidence of adverse events appeared to be similar in the two groups.

CONCLUSIONS

Among patients with symptomatic obstructive HCM, treatment with aficamten resulted in a significantly greater improvement in peak oxygen uptake than placebo. (Funded by Cytokinetics; SEQUOIA-HCM ClinicalTrials.gov number, NCT05186818.)

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*A complete list of the SEQUOIA-HCM investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Hypertrophic cardiomyopathy (HCM) is one of the most common genetic heart diseases worldwide. It affects men and women equally and has been identified in persons of diverse ethnic backgrounds.[1-7] HCM is characterized by a thickened, nondilated left ventricle[1,3,6] and often causes exertional dyspnea and reduced exercise capacity, which can impair quality of life.[3,6,8,9] Left ventricular outflow tract obstruction, which results from contact of the mitral valve with the ventricular septum during systole, is one of the principal determinants of HCM-related complications and therefore is an important target for therapy.[10-12] Cardiac hypercontractility, which results from an excessive number of actin–myosin cross-bridges within the cardiac sarcomere, is an important mechanism that promotes outflow obstruction. Other factors include elongation of the mitral valve leaflets, apical displacement of the papillary muscles, and protrusion of the hypertrophied ventricular septum into the left ventricular outflow tract.[11,13] This impedance to blood flow generates a left ventricular outflow tract pressure gradient, which can be reliably quantified with the use of echocardiography.[1,3,6,10,12]

Invasive therapies for obstructive HCM, such as surgical myectomy and percutaneous alcohol septal ablation, are effective in relieving left ventricular outflow tract gradients and favorably affect the clinical course, including providing long-term relief of limiting symptoms.[14] However, these interventions are associated with risk, and surgical expertise is confined to select high-volume centers.[15] In addition, established pharmacologic therapies have limited efficacy, including suboptimal reduction of the outflow tract gradient and relief of symptoms. Moreover, these therapies have not been shown to increase objective measures of exercise capacity and have been associated with side effects that prevent their use in some patients.[1,6,16-19] Therefore, drugs that are safe and reliably improve how patients feel and function with minimal side effects remain an important unmet need in the treatment of this disease.[6,18] Mavacamten, a recently approved cardiac myosin inhibitor, has been shown to improve exercise capacity and reduce symptoms in patients with obstructive HCM.[20-22]

Aficamten is a reversible inhibitor of cardiac myosin that reduces left ventricular contractility by decreasing the number of active actin–myosin cross-bridges within the sarcomere. Aficamten was designed to have a shallow dose–response relationship (i.e., small reductions in left ventricular ejection fraction as the dose is increased, indicating a wide therapeutic window) and a plasma half-life that allows for personalized dose adjustments as often as every 2 weeks — features that differentiate it from mavacamten.[23-25] In a phase 2 trial, treatment with aficamten resulted in significant reductions in left ventricular outflow tract gradients in patients with obstructive HCM.[26] The SEQUOIA-HCM (Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM) trial was conducted to evaluate the efficacy and safety of aficamten in adult patients with symptomatic obstructive HCM.[27]

METHODS

TRIAL DESIGN AND OVERSIGHT

The SEQUOIA-HCM trial was a phase 3, international, double-blind, randomized, placebo-controlled trial in which patients with symptomatic obstructive HCM received aficamten or placebo in addition to standard drug therapy. The trial design has been described previously,[27] and the trial protocol is available with the full text of this article at NEJM.org.

In collaboration with Cytokinetics (the sponsor), a steering committee designed the trial, selected the trial centers, and oversaw the conduct and monitoring of the trial (which was performed by a contract research organization [ICON, Dublin, Ireland]). An institutional review board or independent ethics committee at each trial center approved the protocol. All the patients provided written informed consent, and the trial was conducted in accordance with the provisions of the Declaration of Helsinki and with the International Council for Harmonisation Good Clinical Practice guidelines. Only an independent data monitoring committee, which met quarterly, had access to and reviewed unblinded safety data during the conduct of the trial. This committee first met in December 2022 to review results that included safety data from 64 patients.

The database was locked on December 21, 2023, and the data were subsequently unblinded. The investigators (see the Supplementary Appendix, available at NEJM.org) and the sponsor performed the statistical analyses; the results were independently confirmed by an academic author

from the Cardiovascular Division at Brigham and Women's Hospital. The first author drafted the initial version of the manuscript, and all the authors participated in the interpretation of the data, the critical review of the manuscript, and the decision to submit the manuscript for publication. The authors who had access to the data vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PARTICIPANTS

Eligible patients were between the ages of 18 and 85 years and had a confirmed clinical diagnosis of HCM, which was defined by a left ventricular wall thickness of at least 15 mm in the absence of pressure overload or other discernible causes. Patients were required to have a left ventricular ejection fraction of at least 60% at screening and to have left ventricular outflow tract gradients of at least 30 mm Hg at rest and at least 50 mm Hg after the Valsalva maneuver. Patients also needed to have New York Heart Association (NYHA) functional class II or III heart failure, along with decreased exercise capacity, which was defined by a predicted peak oxygen uptake of 90% or less on the basis of age and sex.[28] A complete list of the inclusion and exclusion criteria is provided in Table S1 in the Supplementary Appendix. All the patients were allowed to continue background therapy, provided that the doses had been stable for more than 6 weeks before randomization.

PROCEDURES

Eligible patients were randomly assigned in a 1:1 ratio to receive aficamten or placebo. Randomization was performed with the use of an interactive Web-response system and stratified according to the use of beta-blockers (yes or no) and the method of cardiopulmonary exercise testing (treadmill or cycle ergometer). Enrollment of patients taking beta-blockers and disopyramide was capped at approximately 70% and 10% of the trial population, respectively, and enrollment of those with persistent atrial fibrillation at screening was capped at 15%. Enrollment of patients being tested with the use of a cycle ergometer was capped at 50%.

Oral aficamten or placebo (manufactured by Patheon) was administered once daily for 24 weeks; the tablets were identical in appearance. Patients received blister cards containing 5-mg aficamten tablets or matching placebo in daily rows of four, which were accessed by patients according to the appropriate dose. The starting dose of aficamten was 5 mg, with three subsequent opportunities (at weeks 2, 4, and 6) to increase the dose by 5-mg increments, to a maximum dose of 20 mg. At each visit, an echocardiographic cardiologist who was unaware of the trial-group assignments assessed the left ventricular outflow tract gradient at rest and after the Valsalva maneuver and the left ventricular ejection fraction. The findings from each assessment were then entered into an interactive Web-response system that determined the associated dose level of aficamten or placebo that would need to be administered on the basis of predetermined criteria, and trial-drug kits were subsequently dispensed from the site inventory (Table S2).

The site investigators and trial team members were unaware of the N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels and the echocardiography results. In accordance with the statistical analysis plan (provided with the trial protocol), echocardiographic and cardiopulmonary exercise testing data were derived at the core laboratory; laboratory personnel were also unaware of the trial-group assignments.

Patients were followed during the 24-week treatment period and during a 4-week washout period at the end of the trial. Assessments were performed according to the schedule of activities (Table S3).

END POINTS

The primary end point was the change from baseline to week 24 in the peak oxygen uptake as assessed during cardiopulmonary exercise testing by the core laboratory (Table S4). Before the unblinding of the trial-group assignments, cardiopulmonary exercise testing studies that were invalid owing to equipment failures, transient noncardiac issues, or major deviations from cardiopulmonary exercise testing procedures were excluded from the analysis.

The 10 prespecified secondary end points (which were tested hierarchically in the order that follows) were the change from baseline to week 24 in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations); an improvement from baseline of at least one NYHA functional class at week 24; the change from baseline to week 24 in the left ventricular

outflow tract gradient after the Valsalva maneuver; the occurrence of a left ventricular outflow tract gradient of less than 30 mm Hg after the Valsalva maneuver at week 24; the duration of eligibility for septal reduction therapy during the 24-week treatment period among patients who were eligible for such therapy at baseline (with eligibility defined by NYHA functional class III or IV disease and a left ventricular outflow tract gradient [at rest or after the Valsalva maneuver] of ≥50 mm Hg); the change from baseline to week 12 in the KCCQ-CSS; an improvement from baseline of at least one NYHA functional class at week 12; the change from baseline to week 12 in the left ventricular outflow tract gradient after the Valsalva maneuver; the occurrence of a left ventricular outflow tract gradient of less than 30 mm Hg after the Valsalva maneuver at week 12; and the change in the total workload as assessed by cardiopulmonary exercise testing at week 24. An exploratory end point was the geometric mean proportional change in the NT-proBNP level.

STATISTICAL ANALYSIS

The statistical power for the primary end point was calculated under the assumption that the difference between the aficamten and placebo groups in the change from baseline in the peak oxygen uptake at week 24 would be 1.5 ml per kilogram of body weight per minute, with a standard deviation of 3.5 ml per kilogram per minute, and that no more than 70% of the patients would be receiving beta-adrenergic blockers and no more than 50% of the patients would undergo cardiopulmonary exercise testing with the use of a cycle ergometer. With the assumption that 10% of the primary end-point data would be missing, it was estimated that a sample of 270 patients with a randomization ratio of 1:1 would provide the trial with at least 90% power to detect the between-group difference in the change from baseline in the peak oxygen uptake at week 24 at a two-sided type I error level of 0.05.

Unless otherwise specified, the efficacy analyses were performed in the full analysis set, which included all the patients who had undergone randomization. The primary analysis tested the null hypothesis that there would be no between-group difference with respect to the primary end point in the full analysis set. The change from baseline in the peak oxygen uptake was analyzed with the use of an analysis of covariance (ANCOVA) model, with trial group, randomization stratification factors, baseline peak oxygen uptake, and baseline weight as covariates. Missing peak oxygen uptake data at week 24 were imputed with the use of a multiple-imputation regression model under the assumption that the data were missing at random.

To preserve the overall type I error at a two-sided level of 0.05, the primary and secondary end points were tested with the use of a closed testing procedure. The primary end point was to be tested first at a two-sided level of 0.05. If the primary end point showed a significant treatment effect at a two-sided P value of less than 0.05, then the secondary end points would be tested sequentially at a two-sided level of 0.05.

Secondary end points that examined the proportion of patients in the full analysis set who had a response to aficamten were analyzed with the use of the Cochran–Mantel–Haenszel test stratified according to randomization stratification factors. The P values and 95% confidence intervals were calculated with the use of an exact method. Other end points that assessed changes from baseline were analyzed with the use of mixed models for repeated measures (MMRMs), with trial group, visit, randomization stratification factors, and interactions of trial group by visit and with the use of baseline value by visit as fixed effects and with baseline values as covariates. The duration of eligibility for septal reduction therapy was analyzed with the use of an ANCOVA model, with trial group and beta-blocker use as fixed effects and with adjustment for the baseline covariates that were selected according to the stepwise selection method. The proportional change in the NT-proBNP level, an exploratory end point, was calculated as the ratio of the value at week 24 to the baseline value and was not adjusted for multiplicity. The log-transformed proportional change was analyzed with the use of an MMRM, with the log baseline value as a covariate and with trial group, randomization stratification factors, visit, log baseline value by visit, and interactions of trial group by visit as fixed effects. Model-based geometric least-squares mean estimates were calculated by back-transforming (exponentiating) the estimate from the model. The statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENT CHARACTERISTICS

From February 1, 2022, to May 15, 2023, a total of 543 patients were screened for eligibility at 101 sites in 14 countries, of whom 282 underwent randomization and received aficamten or placebo. The most common reasons for exclusion from trial participation were an inadequately elevated left ventricular outflow tract gradient after the Valsalva maneuver or not meeting cardiopulmonary exercise testing criteria (Fig. S1). A total of 142 patients were randomly assigned to receive aficamten and 140 to receive placebo; 273 patients completed the trial, and 9 patients discontinued treatment. Of these 9 patients, 3 remained in the trial and underwent the cardiopulmonary exercise testing at week 24 and 6 withdrew before the end of the trial.

The demographic and clinical characteristics of the patients who had undergone randomization appeared to be similar in the two groups (Table 1 and Table S5) and to be representative of patients with symptomatic obstructive HCM in the general population (Table S6). Overall, the mean age was 59.1 years, 59.2% were men, the baseline mean resting left ventricular outflow tract gradient was 55.1 mm Hg, and the baseline mean left ventricular ejection fraction was 74.8%. In addition, 61.3% of the patients were receiving beta-blockers at screening and 12.8% were receiving disopyramide, 1.1% had persistent atrial fibrillation at screening, and 45.0% used a cycle ergometer for cardiopulmonary exercise testing. At the end of the dose-escalation phase (week 8), 3.6%, 12.9%, 35.0%, and 48.6% of the patients assigned to the aficamten group were receiving aficamten at a dose of 5 mg, 10 mg, 15 mg, and 20 mg, respectively.

EFFICACY

The mean change from baseline to week 24 in the peak oxygen uptake was 1.8 ml per kilogram per minute (95% confidence interval [CI], 1.2 to 2.3) among patients in the aficamten group and 0.0 ml per kilogram per minute (95% CI, −0.5 to 0.5) among those in the placebo group (Fig. 1A and Table 2). The placebo-corrected least-squares mean difference between the groups in the peak oxygen uptake was 1.7 ml per kilogram per minute (95% CI, 1.0 to 2.4; P<0.001) (Fig. 1B and Table 2); these results appeared to be consistent across all the prespecified subgroups (Fig. 2). Values for peak oxygen uptake were missing for 19 patients (9 in the aficamten group and 10 in the placebo group).

The results for each of the 10 secondary end points showed a significant benefit of aficamten over placebo (Table 2). At week 24, aficamten treatment led to a least-squares mean difference in the KCCQ-CSS of 7 points (95% CI, 5 to 10), an improvement from baseline of at least one NYHA class in 58.5% of the patients as compared with 24.3% of those in the placebo group, a least-squares mean difference in the left ventricular outflow tract gradient after the Valsalva maneuver of −50 mm Hg (95% CI, −57 to −44), and a left ventricular outflow tract gradient of less than 30 mm Hg after the Valsalva maneuver in 49.3% of the patients as compared with 3.6% of those in the placebo group. The effect of aficamten on the left ventricular outflow tract gradient after the Valsalva maneuver was relatively rapid, with a least-squares mean difference between the groups of −20 mm Hg (95% CI, −27.3 to −13.3) after 2 weeks. These changes in hemodynamics and symptoms were also reflected in the significantly less amount of time that patients in the aficamten group were eligible (according to professional guidelines) for septal reduction therapy, with a least-squares mean difference of 78 fewer days (95% CI, −100 to −56) in the aficamten group than in the placebo group (Table 2). The results of the secondary end points, including those assessed at week 12, are shown in Figure 3 and in Table 2.

In an exploratory analysis, the geometric mean proportional change from baseline to week 24 in the serum NT-proBNP level, a clinically used biomarker of heart failure severity, was 0.20 (95% CI, 0.17 to 0.22) in the aficamten group and 1.00 (95% CI, 0.91 to 1.07) in the placebo group (Table 2). At week 28, after a 4-week washout period, the left ventricular outflow tract gradients at rest and after the Valsalva maneuver, as well as the KCCQ-CSS, did not appear to differ substantially between the groups (Fig. 3).

SAFETY

Serious adverse events were reported in 8 patients (5.6%) in the aficamten group and in 13 patients (9.3%) in the placebo group (Table 2 and Table S7).

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

Characteristic	Aficamten (N = 142)	Placebo (N = 140)
Age — yr	59.2±12.6	59.0±13.3
Female sex — no. (%)	56 (39.4)	59 (42.1)
Race — no. (%)†		
White	108 (76.1)	115 (82.1)
Asian	29 (20.4)	25 (17.9)
Black	3 (2.1)	0
Other	2 (1.4)	0
Geographic region — no. (%)		
North America	49 (34.5)	45 (32.1)
China	24 (16.9)	22 (15.7)
Europe or Israel	69 (48.6)	73 (52.1)
Medical history — no. (%)		
Hypertension	75 (52.8)	70 (50.0)
Family history of HCM or presence of known genetic mutation for HCM	47 (33.1)	44 (31.4)
Family history of HCM	41 (28.9)	34 (24.3)
Pathogenic sarcomere variant	24 (16.9)	25 (17.9)
Paroxysmal atrial fibrillation	21 (14.8)	20 (14.3)
Coronary artery disease	19 (13.4)	16 (11.4)
Diabetes	14 (9.9)	9 (6.4)
Permanent atrial fibrillation	2 (1.4)	1 (0.7)
Background HCM therapy — no. (%)		
Beta-blocker	86 (60.6)	87 (62.1)
Calcium-channel blocker	45 (31.7)	36 (25.7)
Disopyramide	16 (11.3)	20 (14.3)
None	19 (13.4)	22 (15.7)
Implantable cardioverter–defibrillator — no. (%)	22 (15.5)	17 (12.1)
KCCQ-CSS‡	76±18	74±18
NYHA functional class — no. (%)§		
II	108 (76.1)	106 (75.7)
III	34 (23.9)	33 (23.6)
IV	0	1 (0.7)
Median NT-proBNP (IQR) — pg/ml	818 (377–1630)	692 (335–1795)
Median high-sensitivity cardiac troponin I (IQR) — ng/liter	12.9 (7.6–33.6)	11.5 (7.7–25.0)
Echocardiographic variables		
Left ventricular outflow tract gradient after Valsalva maneuver — mm Hg	82.9±32	83.3±32.7
Resting left ventricular outflow tract gradient — mm Hg	54.8±27	55.3±32.1
Left ventricular ejection fraction — %	74.8±5.5	74.8±6.3
Maximal left ventricular wall thickness — mm	20.7±3.0	21.0±3.0

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. HCM denotes hypertrophic cardiomyopathy, IQR interquartile range, and NT-proBNP N-terminal pro–B-type natriuretic peptide.
† Race was reported by the patient.
‡ The Kansas City Clinical Questionnaire clinical summary score (KCCQ-CSS) ranges from 0 to 100, with higher scores indicating fewer symptoms and physical limitations.
§ New York Heart Association (NYHA) functional classes range from I to IV, with higher values indicating greater disability.

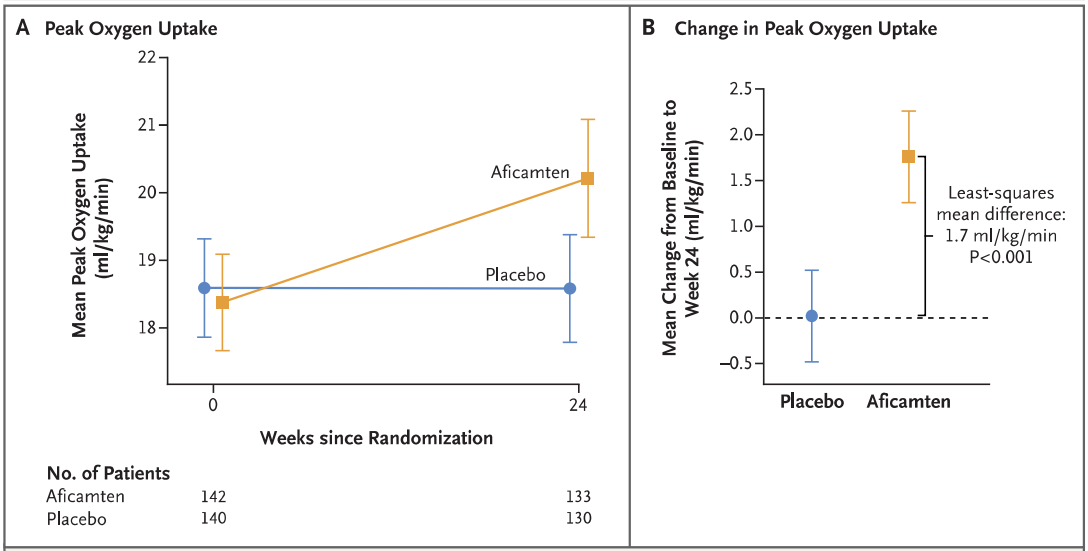

Figure 1. Changes in Exercise Capacity from Baseline to Week 24.

Panel A shows the mean peak oxygen uptake values at baseline and at week 24. Panel B shows the least-squares mean estimate of change in the peak oxygen uptake. I bars denote 95% confidence intervals.

One adverse event (paranoia) resulted in early discontinuation of aficamten, and two adverse events (syncope and acute lymphocytic leukemia) resulted in early discontinuation of placebo (Table S8). Three adverse events resulted in temporary interruptions of aficemten or placebo, including acute cholecystitis in 1 patient in the aficamten group and bronchopneumonia and verrucous carcinoma removal in 1 patient each in the placebo group. The number of patients who had at least one adverse event after the start of administration of aficamten or placebo was 105 (73.9%) in the aficamten group and 99 (70.7%) in the placebo group (Table 2); these events included atrial fibrillation (2.8% and 2.9%, respectively) and ventricular fibrillation (0% and 0.7%, respectively). Palpitations were more common in the aficamten group than in the placebo group (7.0% vs. 2.9%), as was hypertension (7.7% vs. 2.1%) (Table S8).

At week 24, the left ventricular ejection fraction in the aficamten group was modestly lower than that in the placebo group (least-squares mean difference, –4.8 percentage points; 95% CI, –6.3 to –3.2); after the 4-week washout period, there was no marked difference between the groups in the left ventricular ejection fraction (least-squares mean difference, –1 percentage points; 95% CI, –2 to 0). On the basis of the core laboratory assessment, a transient reduction of less than 50% in the left ventricular ejection fraction occurred in 5 patients (3.5%) in the aficamten group and in 1 patient (0.7%) in the placebo group; 7 patients (4.9%) in the aficamten group underwent a per-protocol dose reduction on the basis of the site echocardiographic evaluation. None of the patients in the aficamten group with a left ventricular ejection fraction of less than 50% had an interruption of treatment or an exacerbation of heart failure.

DISCUSSION

In this international, randomized, placebo-controlled trial involving patients with symptomatic obstructive HCM, aficamten improved exercise capacity (as assessed by cardiopulmonary exercise testing) over a 24-week treatment period. Aficamten treatment was also associated with significantly greater improvements than placebo in all the secondary end points. The efficacy of aficamten was evident by week 12, with significantly greater improvements in left ventricular outflow tract gradients, health status, and symptoms. The incidence of adverse events appeared to be similar in the aficamten and placebo groups.

The effect of aficamten on exercise capacity appeared to be similar across a variety of prespecified subgroups, including patients who had been severely symptomatic (NYHA class III or IV

Table 2. Primary, Secondary, and Exploratory End Points and Adverse Events.*

Variable	Aficamten (N=142)		Placebo (N=140)		Difference (95% CI)†	P Value
	Patients	Mean Change from Baseline (95% CI)	Patients	Mean Change from Baseline (95% CI)		
	no. (%)		*no. (%)*			
Primary end point: peak oxygen uptake by cardiopulmonary exercise testing at wk 24 — ml per kilogram per minute	133 (93.7)	1.8 (1.2 to 2.3)	130 (92.9)	0.0 (–0.5 to 0.5)	1.7 (1.0 to 2.4)	<0.001
Secondary end points						
KCCQ-CSS at wk 24	138 (97.2)	11 (9 to 14)	137 (97.9)	5 (3 to 7)	7 (5 to 10)	<0.001
Improvement of ≥1 NYHA functional class at wk 24	83 (58.5)	NA	34 (24.3)	NA	34.2 (23.4 to 45.0)	<0.001
Left ventricular outflow tract gradient after the Valsalva maneuver at wk 24 — mm Hg	137 (96.5)	–47.6 (–54 to –41)	134 (95.7)	1.8 (–4 to 8)	–50 (–57 to –44)	<0.001
Left ventricular outflow tract gradient of <30 mm Hg after the Valsalva maneuver at wk 24	70 (49.3)	NA	5 (3.6)	NA	45.7 (36.9 to 54.5)	<0.001
Total duration of septal reduction therapy eligibility during treatment period — days‡	32 (22.5)	36.5 (27.0 to 46.1)	29 (20.7)	114.2 (93.6 to 134.8)	–78 (–100 to –56)	<0.001
KCCQ-CSS at wk 12	140 (98.6)	11 (9 to 13)	136 (97.1)	5 (3 to 7)	7 (5 to 10)	<0.001
Improvement of ≥1 NYHA functional class at wk 12	69 (48.6)	NA	25 (17.9)	NA	30.8 (20.6 to 41.0)	<0.001
Left ventricular outflow tract gradient after the Valsalva maneuver at wk 12 — mm Hg	139 (97.9)	–44.8 (–51 to –39)	137 (97.9)	2.8 (–3 to 8)	–48 (–55 to –42)	<0.001
Left ventricular outflow tract gradient of <30 mm Hg after the Valsalva maneuver at wk 12	74 (52.1)	NA	8 (5.7)	NA	46.4 (37.3 to 55.5)	<0.001
Total workload during cardiopulmonary exercise testing at wk 24 — watts	134 (94.4)	14.1 (9.5 to 18.6)	129 (92.1)	1.4 (–2.3 to 5.1)	12.2 (6.4 to 18.0)	<0.001
Exploratory end point: geometric mean proportional change in NT-proBNP at wk 24§	133 (93.7)	0.20 (0.17 to 0.22)	133 (95.0)	1.00 (0.91 to 1.07)	0.20 (0.17 to 0.23)	—

Any serious adverse event	8 (5.6)	—	13 (9.3)	—	—	—
Any serious adverse event that led to discontinuation of aficamten or placebo	0	—	2 (1.4)	—	—	—
Any serious adverse event that led to interruption of aficamten or placebo	1 (0.7)	—	2 (1.4)	—	—	—
Any adverse event	105 (73.9)	—	99 (70.7)	—	—	—
Any adverse event that led to discontinuation of aficamten or placebo	1 (0.7)	—	2 (1.4)	—	—	—
Any adverse event that led to interruption of aficamten or placebo	2 (1.4)	—	2 (1.4)	—	—	—

* NA denotes not applicable. Because the statistical analysis plan did not include a provision for correcting for multiplicity for the exploratory end points, the results for the geometric mean proportional change in NT-proBNP are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals in this table have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.

† Differences are given as the least-squares mean difference between the groups in the mean change from baseline for the primary end point and all the secondary end points, except for two (improvement of ≥1 NYHA functional class and left ventricular outflow tract gradient of <30 mm Hg after the Valsalva maneuver). These two end points were measured as categorical variables and are given as the percentage-point difference between the groups in the percentage of patients who had an improvement of at least one NYHA functional class and in the percentage of those who had a left ventricular outflow tract gradient of less than 30 mm Hg after the Valsalva maneuver, respectively. The difference for the geometric mean proportional change in NT-proBNP is given as the geometric least-squares mean ratio.

‡ Septal reduction therapy eligibility is defined by NYHA functional class III or IV disease and a left ventricular outflow tract gradient (at rest or after the Valsalva maneuver) of at least 50 mm Hg. This analysis was performed only in patients who met these eligibility criteria at baseline.

§ The proportional change in NT-proBNP was defined as the ratio of the NT-proBNP level (in picograms per milliliter) at week 24 to the baseline NT-proBNP level (in picograms per milliliter).

Subgroup	Placebo	Aficamten	Least-Squares Mean Difference in Peak Oxygen Uptake (95% CI)
	no. of patients		*ml/kg/min*
Overall	140	142	1.7 (1.0–2.4)
Sex			
Male	81	86	1.8 (0.9–2.7)
Female	59	56	1.4 (0.4–2.5)
Age			
<65 yr	84	85	2.0 (1.1–2.8)
≥65 yr	56	57	1.4 (0.3–2.5)
Body-mass index			
<30	94	97	1.8 (1.0–2.7)
≥30	46	45	1.6 (0.3–2.8)
NYHA functional class			
II	106	108	1.7 (0.9–2.5)
III or IV	34	34	1.9 (0.5–3.3)
Left ventricular ejection fraction			
≤75.6%	68	73	1.8 (0.8–2.8)
>75.6%	72	69	1.6 (0.6–2.6)
NT-proBNP			
≤788 pg/ml	73	66	1.7 (0.7–2.7)
>788 pg/ml	65	73	2.0 (1.0–2.9)
Method of cardiopulmonary exercise testing			
Cycle ergometer	63	64	1.0 (0.0–2.1)
Treadmill	77	78	2.3 (1.4–3.2)
Peak oxygen uptake			
≤18.4 ml/kg/min	67	74	1.6 (0.6–2.5)
>18.4 ml/kg/min	73	68	1.9 (1.0–2.9)
Beta-blocker use			
Yes	87	86	1.6 (0.7–2.5)
No	53	56	1.9 (0.8–3.1)
Resting left ventricular outflow tract gradient			
≤51.1 mm Hg	69	72	1.3 (0.3–2.3)
>51.1 mm Hg	71	70	2.1 (1.2–3.1)
KCCQ-CSS			
≤78.1	75	67	1.8 (0.8–2.8)
>78.1	65	75	1.7 (0.7–2.6)
Genetic testing result			
Pathogenic or probably pathogenic	22	20	2.6 (0.9–4.2)
Variant of uncertain significance or negative	70	71	1.4 (0.5–2.3)

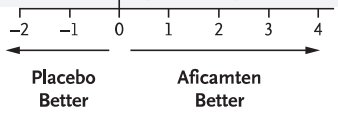

Figure 2. Subgroup Analysis of the Primary End Point.

The subgroups that are defined according to left ventricular ejection fraction, N-terminal pro–B-type natriuretic peptide (NT-proBNP), peak oxygen uptake, resting left ventricular outflow tract gradient, and Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) are categorized according to values less than or equal to the median baseline value and values greater than the median baseline value. The KCCQ-CSS ranges from 0 to 100, with higher scores indicating fewer symptoms and physical limitations. New York Heart Association (NYHA) functional classes range from I to IV, with higher values indicating greater disability. The body-mass index is the weight in kilograms divided by the square of the height in meters. Because the statistical analysis plan did not include a provision for correcting for multiplicity for the subgroup analysis, the results of this analysis are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.

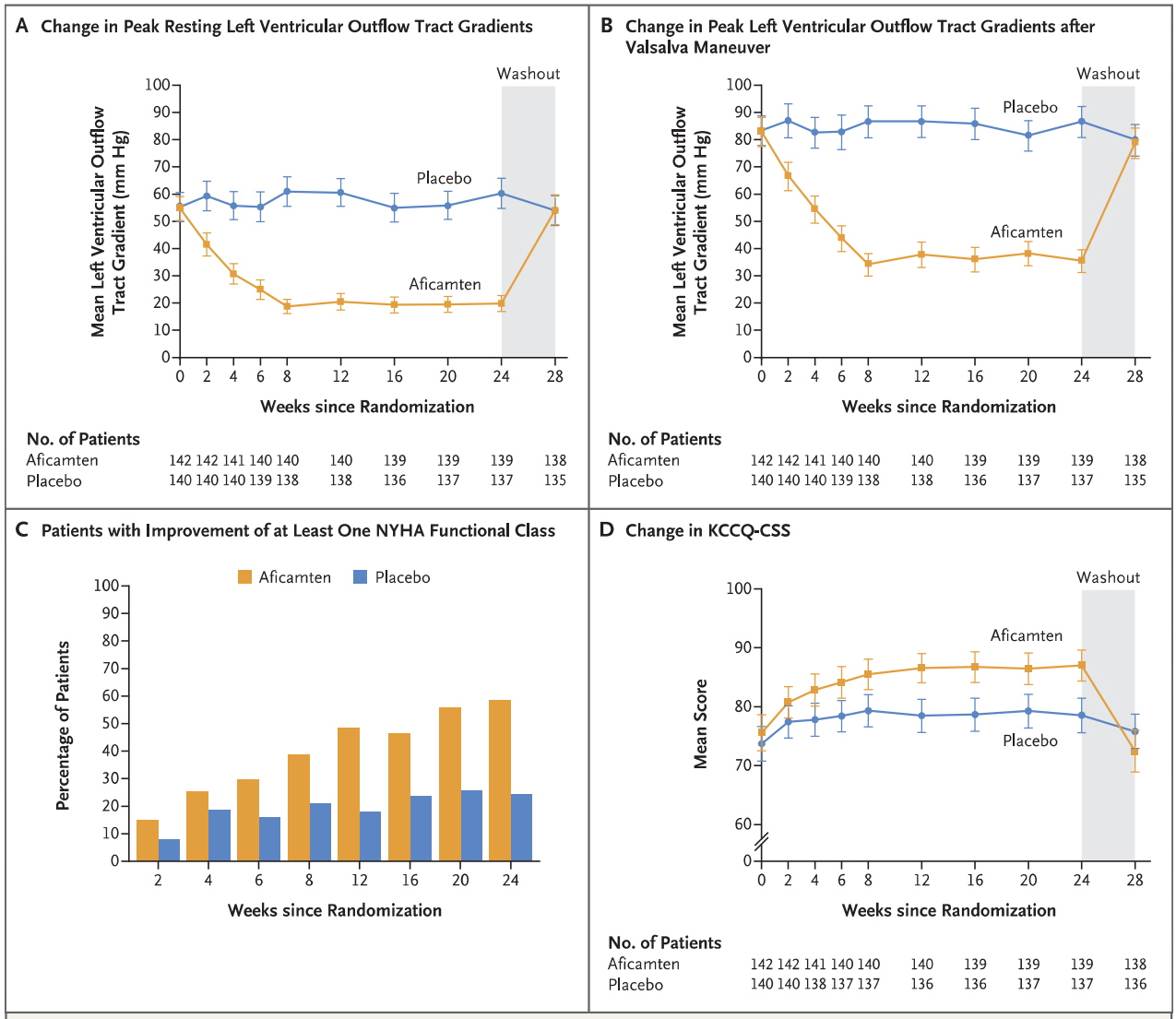

Figure 3. Key Secondary End Points and Other Outcomes.

Shown are the change from baseline in the mean peak resting left ventricular outflow tract gradient (Panel A), the change from baseline in the mean peak left ventricular outflow tract gradient after the Valsalva maneuver (Panel B), the percentage of patients with an improvement from baseline of at least one NYHA functional class (Panel C), and the change from baseline in the mean KCCQ-CSS (Panel D). The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.

heart failure) and functionally limited (peak oxygen uptake of ≤18 ml per kilogram per minute) at baseline. In contrast to the results that were observed with mavacamten in the EXPLORER-HCM trial, which suggested an attenuation of benefit among patients who were receiving beta-blockers,[22] the treatment effects of aficamten appeared to be similar with or without background beta-blocker use and independent of the presence of a pathogenic sarcomere gene variant.

The increase in exercise capacity most likely reflects the highly favorable effect of aficamten in providing a rapid and sustained reduction in left ventricular outflow tract gradients throughout the treatment period. Aficamten was associated with other favorable outcomes, including a significantly greater improvement in limiting symptoms and a substantially greater reduction in the serum NT-proBNP level than placebo.[29] In addition, a reduction in symptoms was associated

with a clinically meaningful enhancement of overall health status as evidenced by increases in the KCCQ-CSS.[30]

The opportunity to improve the way that patients with obstructive HCM feel and function, despite the use of conventional medical therapy, is consistent with patient-centric treatment goals[1,6] and therefore underscores the potential benefit of aficamten as drug therapy in this population of patients with HCM. Moreover, because HCM-related deaths are infrequent,[1-3] end points that are based on functional capacity and relief of symptoms have formed the basis for regulatory approval of new treatments. We also observed that some patients who received aficamten did not have an improvement in NYHA class. Further trials are needed to clarify the reasons for this finding and to determine whether those patients would have symptom relief with longer exposure to aficamten.

The outcomes observed in this trial with aficamten appear to be generalizable to the broad, global population of patients with obstructive HCM encountered in clinical practice. Women were well represented (40.8%) in this trial. Although ethnic diversity was rather limited, the patients in the trial were from North America, Europe, Israel, and China. The clinical profile of the trial population included patients with typical characteristics of obstructive HCM, including those with a range of left ventricular outflow tract gradients and left ventricular wall thicknesses, and was inclusive of all conventional HCM background therapy use.[1,3,6,16,17,19]

This trial further underscores the benefits of cardiac myosin inhibitor drug therapy in patients with obstructive HCM, which were similar to the recent findings seen with mavacamten.[20-22] However, the unique pharmacologic properties of aficamten provide some notable distinctions between aficamten and mavacamten. The shorter half-life of aficamten enables more rapid dose escalation, which results in the ability to identify an effective dose within weeks, providing timely clinical benefit.[23,24] The incidence of a left ventricular ejection fraction of less than 50% was low with aficamten, occurring in 5 patients (3.5%), and could be attributed to a shallow dose–response relationship.[24] In addition, no patient in the aficamten group who had a left ventricular ejection fraction of less than 50% had an interruption of treatment or an exacerbation of heart failure. Furthermore, the return to baseline measures of the left ventricular outflow tract gradient, symptoms, and the left ventricular ejection fraction after the washout period reflects a rapid reversal of the pharmacodynamic effects.

Limitations of this trial include the relatively short treatment period, precluding assessment of longer-term cardiovascular outcomes. However, the improvement in exercise capacity with aficamten exceeded the previously observed minimal clinically important difference in peak oxygen uptake (1 ml/kg/min),[27] and previously reported improvements that were not as pronounced as those observed in this trial have been associated with enhanced survival among patients with heart failure without HCM.[31]

Among patients with symptomatic obstructive HCM, treatment with aficamten resulted in a significantly greater improvement in peak oxygen uptake than placebo.

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

APPENDIX

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