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Mavacamten Treatment for Symptomatic Obstructive Hypertrophic Cardiomyopathy

Interim Results From the MAVA-LTE Study, EXPLORER-LTE Cohort

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ABSTRACT

BACKGROUND Data assessing the long-term safety and efficacy of mavacamten treatment for symptomatic obstructive hypertrophic cardiomyopathy are needed.

OBJECTIVES The authors sought to evaluate interim results from the EXPLORER-Long Term Extension (LTE) cohort of MAVA-LTE (A Long-Term Safety Extension Study of Mavacamten in Adults Who Have Completed EXPLORER-HCM; NCT03723655).

METHODS After mavacamten or placebo withdrawal at the end of the parent EXPLORER-HCM (Clinical Study to Evaluate Mavacamten [MYK-461] in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy; NCT03470545), patients could enroll in MAVA-LTE. Patients received mavacamten 5 mg once daily; adjustments were made based on site-read echocardiograms.

RESULTS Between April 9, 2019, and March 5, 2021, 231 of 244 eligible patients (94.7%) enrolled in MAVA-LTE (mean age: 60 years; 39% female). At data cutoff (August 31, 2021) 217 (93.9%) remained on treatment (median time in study: 62.3 weeks; range: 0.3-123.9 weeks). At 48 weeks, patients showed improvements in left ventricular outflow tract (LVOT) gradients (mean change ± SD from baseline: resting: −35.6 ± 32.6 mm Hg; Valsalva: −45.3 ± 35.9 mm Hg), N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (median: −480 ng/L; Q1-Q3: −1,104 to −179 ng/L), and NYHA functional class (67.5% improved by ≥1 class). LVOT gradients and NT-proBNP reductions were sustained through 84 weeks in patients who reached this timepoint. Over 315 patient-years of exposure, 8 patients experienced an adverse event of cardiac failure, and 21 patients had an adverse event of atrial fibrillation, including 11 with no prior history of atrial fibrillation. Twelve patients (5.2%) developed transient reductions in site-read echocardiogram left ventricular ejection fraction of <50%, resulting in temporary treatment interruption; all recovered. Ten patients discontinued treatment due to treatment-emergent adverse events.

CONCLUSIONS Mavacamten treatment showed clinically important and durable improvements in LVOT gradients, NT-proBNP levels, and NYHA functional class, consistent with EXPLORER-HCM. Mavacamten treatment was well tolerated over a median 62-week follow-up. (J Am Coll Cardiol HF 2024;12:164–177) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Hypertrophic cardiomyopathy (HCM) is a myocardial disorder associated with sarcomeric dysfunction mediated by excess myosin-actin cross-bridges, which results in hypercontractility, impaired relaxation, and increased energy utilization.[1-4] While most patients achieve normal life expectancy, a subset of patients with HCM with progressive disease may experience cardiac failure due to left ventricular outflow tract (LVOT) obstruction, diastolic dysfunction, and/or systolic dysfunction; atrial fibrillation, with an increased risk of systemic thromboembolism and stroke; angina; or sudden cardiac death from ventricular tachyarrhythmias.[2] The majority (~70%) of patients with HCM have dynamic LVOT obstruction or obstructive HCM, defined as an LVOT gradient of ≥30 mm Hg at rest or when provoked with the Valsalva maneuver or exercise.[5,6] LVOT obstruction is an underlying cause of symptoms such as dyspnea and chest pain, leading to reduced quality of life in patients with obstructive HCM.[2]

Current treatment guidelines for obstructive HCM are focused on symptom management. Medications such as beta blockers, non-dihydropyridine calcium-channel blockers (verapamil and diltiazem), and disopyramide offer variable relief of symptoms and outflow obstruction.[5,7] Invasive septal reduction therapies, such as septal myectomy or alcohol septal ablation, are effective methods to reduce LVOT obstruction; however, they are specialized procedures not easily accessible for all patients.[5,8] Thus, there is a major unmet need for effective medical management of patients with obstructive HCM.

Mavacamten is a first-in-class, small-molecule, selective, allosteric, reversible cardiac myosin inhibitor approved by the U.S. Food and Drug Administration for the treatment of adults with symptomatic NYHA functional class II to III obstructive HCM.[9-11] The efficacy and safety of mavacamten in patients with symptomatic obstructive HCM was assessed in the randomized, double-blind, placebo-controlled, phase 3 EXPLORER-HCM (Clinical Study to Evaluate Mavacamten [MYK-461] in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy).[11,12] In this pivotal trial, 30 weeks of mavacamten treatment led to significant reductions in LVOT gradients and improvements in exercise capacity, NYHA functional class, and patient-reported health status. Mavacamten had a similar safety profile to placebo. There were 9 patients (7 receiving mavacamten and 2 receiving placebo) previously described who had a transient LV ejection fraction (LVEF) of <50%.[11] Nevertheless, data assessing the long-term safety and efficacy of mavacamten treatment for symptomatic obstructive HCM are needed.

MAVA-LTE (A Long-Term Safety Extension Study of Mavacamten in Adults Who Have Completed EXPLORER-HCM) is an ongoing 5-year active-treatment study designed to assess the long-term safety and efficacy of mavacamten. Patients with obstructive HCM who completed EXPLORER-HCM, including the 8-week washout period, and enrolled into MAVA-LTE comprised the EXPLORER-LTE cohort of MAVA-LTE. Here, we report the first cumulative interim results of treatment with mavacamten from the EXPLORER-LTE cohort of MAVA-LTE.

SEE PAGE 178

ABBREVIATIONS AND ACRONYMS

HCM = hypertrophic cardiomyopathy

LAVI = left atrial volume index

LV = left ventricular

LVEF = left ventricular ejection fraction

LVOT = left ventricular outflow tract

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

PK = pharmacokinetic

QTcF = QT interval corrected using Fridericia's formula

SAE = serious adverse event

SAM = systolic anterior motion

TEAE = treatment-emergent adverse event

METHODS

STUDY DESIGN, PATIENTS, AND DOSING. Full inclusion and exclusion criteria for patients enrolled in EXPLORER-HCM (NCT03470545) have been published previously.[11,12] Patients who completed EXPLORER-HCM were screened for eligibility prior to enrolling in the EXPLORER-LTE cohort of MAVA-LTE (NCT03723655). Patients (n = 231) were enrolled at 29 sites across the United States (n = 95; 41.1%) and at 37 non-U.S. sites (n = 136; 58.9%). Patients signed informed consent for participation in the EXPLORER-LTE cohort of MAVA-LTE within 90 days of completing the EXPLORER-HCM end-of-study visit or with study sponsor approval if beyond the 90-day window. At the end of 30 weeks of treatment in the EXPLORER-HCM study, there was an 8-week post-treatment withdrawal phase for all patients. Between the end-of-study of EXPLORER-HCM at week 38 and the beginning of MAVA-LTE, the patients were not on

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

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TABLE 1 Demographic and Disease Characteristics Data at Week 38 of EXPLORER-HCM and Baseline Demographic and Disease Characteristics for the EXPLORER-LTE Cohort of MAVA-LTE and for the Same Cohort

	Week 38 of EXPLORER-HCM (n = 231)[a]	EXPLORER-LTE Cohort (n = 231)
Demographics		
Age, y	58.6 ± 11.8[b]	60.0 ± 11.9
Male	140 (60.6)	140 (60.6)
BMI, kg/m^2	29.45 ± 5.5 (n = 164)	29.7 ± 5.2 (n = 229)
Background HCM therapy		
Beta-blocker	175 (75.8)	175 (75.8)
Calcium-channel blocker[c]	39 (16.9)	38 (16.5)
NYHA functional class		
I	17 (7.4)	14 (6.1)[d]
II	132 (57.1)	152 (65.8)
III	58 (25.1)	65 (28.1)
NT-proBNP, ng/L	830 (359-1,528) (n = 167)	783 (326-1,593) (n = 230)
History of atrial fibrillation		
Yes	28 (12.1)	40 (17.3)
Echocardiography parameters		
Resting LVEF, %	74.2 ± 6.2 (n = 170)	74.0 ± 5.9 (n = 230)
LVOT gradients, mm Hg		
Resting	47.9 ± 32.0 (n = 170)	48.3 ± 31.9
Valsalva	68.4 ± 34.0 (n = 169)	69.5 ± 33.3 (n = 228)
E/e′ ratio		
Lateral	14.9 ± 7.25 (n = 163)	14.8 ± 7.3 (n = 224)
Septal	19.9 ± 7.3 (n = 162)	20.2 ± 7.9 (n = 225)
LAVI, mL/m^2	38.6 ± 14.5 (n = 164)	38.3 ± 13.0 (n = 227)
Systolic anterior motion present		
Yes	111 (65.7) (n = 169)	179 (78.5) (n = 228)
Mitral regurgitation present[e]		
Yes	166 (97.6) (n = 170)	215 (93.5) (n = 230)

Values are n (%), mean ± SD, or median (Q1-Q3). [a]Due to the COVID-19 pandemic, a large number of patients were not able to attend the week 38 end-of-study visit and had a phone interview instead; therefore, some measures were not evaluated for those patients. [b]Age is based on EXPLORER-HCM baseline, not at week 38. [c]Calcium-channel blocker includes only diltiazem and verapamil. [d]Patients were assessed as belonging to NYHA functional class I at baseline in the extension study following the parent study. [e]Owing to the challenges in quantifying the degree and severity of mitral regurgitation in HCM, it was only indicated as present or absent.

BMI = body mass index; E/e′ = ratio between early mitral inflow velocity and mitral annular early diastolic velocity; EXPLORER-HCM = Clinical Study to Evaluate Mavacamten [MYK-461] in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy; EXPLORER-LTM = Clinical Study to Evaluate Mavacamten [MYK-461] in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy-Long-Term Extension; HCM = hypertrophic cardiomyopathy; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; MAVA-LTE = A Long-Term Safety Extension Study of Mavacamten in Adults Who Have Completed EXPLORER-HCM; ND = not determined; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

study, and there was no data collection. Following the week 38 withdrawal in EXPLORER-HCM, if patients enrolled in MAVA-LTE within 4 weeks, the values from the week 38 visit were used as the baseline for the MAVA-LTE study. If the period off the study drug between the week 38 visit of EXPLORER-HCM and starting MAVA-LTE was >4 weeks, then rescreening assessments were performed. The range of time between the week 38 visit of EXPLORER-HCM and starting LTE was 3 to 359 days (in part due to delays during the COVID-19 pandemic in 2020). At baseline in MAVA-LTE, medical history was obtained to collect current medication information and any new medical conditions, and this information is summarized in Table 1.

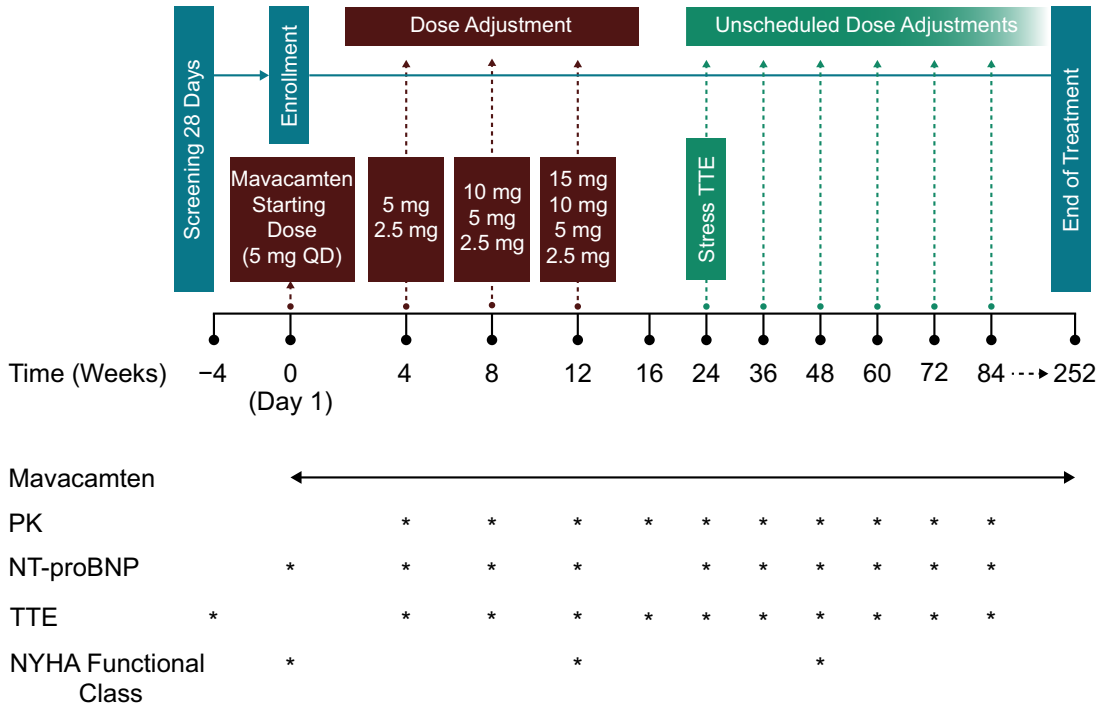
Key inclusion criteria included completion of week 38 of EXPLORER-HCM; age of ≥18 years; documented resting LVEF of ≥50%; safety laboratory parameters within normal limits; and no pregnancy or lactation. Stable background cardiomyopathy monotherapy with beta blockers or with verapamil or diltiazem was permitted. Disopyramide was not allowed, and the background therapy dose could be adjusted or discontinued after week 24. The data cutoff date for this interim analysis was August 31, 2021.

The study design and schedule of assessments are illustrated in Figure 1. All patients enrolled in the EXPLORER-LTE cohort of MAVA-LTE received mavacamten treatment at a starting dosage of 5 mg once daily. Dosing assignments from the parent study (ie, mavacamten or placebo) remained double-blinded in MAVA-LTE until the parent study was unblinded to the sponsor. Dose adjustments were made based on evaluation of LVOT gradient with the Valsalva maneuver and resting LVEF using site-read echocardiogram readings (echocardiograms were also sent to the core laboratory for review). Assessments and same-day dose adjustments were performed at weeks 4, 8, and 12 to individualized, blinded doses of mavacamten 2.5, 5, 10, or 15 mg. A site-read stress echocardiogram was also performed at week 24 to evaluate the postexercise LVOT gradient; dose increase was allowed per investigator request if the postexercise LVOT gradient was ≥50 mm Hg. At any visit after week 24, Valsalva LVOT gradient of >30 mm Hg could also be considered for increasing the mavacamten dose, provided that LVEF was ≥50%. Echocardiograms were also obtained at each visit and sent to a core laboratory for review.

Prespecified criteria for temporary treatment interruption were defined as LVEF of <50% (based on site-read echocardiogram), mavacamten plasma trough concentration of ≥1,000 ng/mL, or a >15% increase in QT interval corrected using Fridericia's formula (QTcF) above the baseline value (or a QTcF of ≥520 ms if the QRS interval was narrow [<120 ms] or a QTcF of ≥550 ms if the QRS interval was wide [≥120 ms]). If values no longer met withholding criteria at the follow-up visit, patients were restarted at 1 dose level lower than their previous dose at a second follow-up visit. If patients were already receiving the 2.5-mg dose at the time of interruption, treatment was permanently discontinued. LVEF of <30% was a criterion for permanent discontinuation.

This study was conducted in accordance with the principles stated in the Declaration of Helsinki, the

FIGURE 1 Study Design and Schedule of Assessments



NT-proBNP = N-terminal pro-B-type natriuretic peptide; PK = pharmacokinetic; QD = once daily; TTE = transthoracic echocardiogram.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice guidelines, U.S. Title 21 Code of Federal Regulations, and all applicable laws and regulations of the countries in which the study was conducted. An independent Ethics Committee or Institutional Review Board reviewed and approved the study protocol and other relevant documents. All patients provided written informed consent.

STUDY ASSESSMENTS. The scheduled timepoints of assessments are indicated in Figure 1. Assessments at baseline only included echocardiograms read by the central laboratory (Brigham and Women's Hospital, Boston, Massachusetts, USA) to preserve the blinded nature of the study when transitioning from EXPLORER-HCM.

Assessments to evaluate efficacy included site- and central-read echocardiograms to measure resting and Valsalva LVOT gradients and LVEF; NYHA functional class; and plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration. The primary outcome of the study was the long-term safety assessment of mavacamten and included the frequency and severity of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). Blood samples were collected at all visits to measure NT-proBNP and mavacamten plasma concentrations (except for day 1). Additional efficacy assessments (from central-read echocardiograms) included markers related to ventricular filling pressure (the ratio between early mitral inflow velocity and mitral annular early diastolic velocity [E/e′], both lateral and septal) and diastolic function (left atrial volume index [LAVI]); mitral valve systolic anterior motion (SAM); and presence or absence of mitral regurgitation. Concordance between LVOT Valsalva gradient values (above or below 30 mm Hg) and LVEF values (above or below 50%) from site- vs central-read echocardiograms was also assessed. Given that this study was not powered to evaluate specific efficacy-related hypotheses, all efficacy assessments were exploratory.

Owing to site-visit restrictions during the COVID-19 pandemic in 2020, patients who were unable to attend a clinic visit for a period of >2 weeks from the last onsite visit during the initial 12-week dose-

titration phase were instructed to stop taking mavacamten. These patients could re-enter the study once they were able to access the clinic, but a rescreening visit was required. In the efficacy analyses, only data from the re-enrollment period were included for the 28 patients who enrolled more than once into the study for this reason.

STATISTICAL ANALYSES. All efficacy and safety analyses were performed on the intention-to-treat and safety (all patients who received at least 1 dose of study drug) populations, respectively. No formal sample size calculation was performed.

For efficacy analyses, descriptive statistics for each echocardiogram parameter were provided by timepoint (site and central readings) for the number of patients who had reached that timepoint at the time of data cutoff and for change from baseline (central reading only), including the 95% CI; no formal statistical testing was performed. For safety analyses, statistics were also descriptive, and no hypothesis testing was planned or conducted.

RESULTS

BASELINE CHARACTERISTICS. Of the 244 patients who completed study in EXPLORER-HCM, 231 (94.7%) enrolled in MAVA-LTE (first patient, first visit: April 9, 2019; last patient, first visit: March 5, 2021), including 8 of the 9 patients who experienced an LVEF of <50% in the parent study. At the data cutoff for interim analysis (August 31, 2021), 11 patients had permanently discontinued the study, and 3 additional patients had permanently discontinued treatment but were still enrolled in the study for safety assessment while completing follow-up. Reasons for discontinuation are listed in Supplemental Table 1.

In total, 116 patients (50.2%) had received placebo in the parent study. The mean (range) time from the EXPLORER-HCM end-of-study visit (week 38) to day 1 of MAVA-LTE was 66.5 (IQR: 3-359) days. The median (range) follow-up duration at the cutoff date of this interim analysis was 62.3 (IQR: 0.3-123.9) weeks. In total, 205 patients (88.7%) and 67 patients (29.0%) had reached ≥48 weeks and ≥84 weeks of treatment, respectively.

Baseline demographics and disease characteristics of the EXPLORER-HCM patients enrolled in MAVA-LTE are shown in **Table 1**. The mean age was 60.0 years, and 39.4% were female. Background therapy was common, with 75.8% of patients receiving beta blockers and 16.5% receiving non-dihydropyridine calcium-channel blockers (verapamil or diltiazem); 7.8% had no background therapy. The majority of patients had hypercontractile LV function and LVOT obstruction at baseline, with a mean central-read LVEF of 74%, a mean resting LVOT gradient of 48.3 mm Hg (range: 4.8-161.3 mm Hg), and a mean Valsalva LVOT gradient of 69.5 mm Hg (range: 9.2-172.7 mm Hg).

At baseline, 217 patients (93.9%) had NYHA functional class II or III symptoms, and the median NT-proBNP concentration was 782.5 ng/mL (Q1-Q3: 326-1,593 ng/mL; normal laboratory range: <124 ng/mL).

EFFICACY ASSESSMENTS. Reductions in resting and Valsalva LVOT gradients were observed with mavacamten beginning as early as week 4, with the majority of patients having substantial reduction in LVOT gradients, as assessed by site-read and confirmed by central-read echocardiograms (**Central Illustration**). The mean change ± SD from baseline in resting LVOT gradient (central read) was −35.6 ± 32.6 mm Hg at week 48 and −32.8 ± 30.8 mm Hg at week 84. The mean change ± SD from baseline in Valsalva LVOT gradient (central read) was −45.3 ± 35.9 mm Hg at week 48 and −46.4 ± 35.8 mm Hg at week 84. At week 48, which corresponds to the NYHA functional class assessment timepoint per protocol and with the largest sample size at this data cutoff, 14 of 206 patients (6.8%) had a resting LVOT gradient of >30 mm Hg, and 22 of 206 patients (10.7%) had a Valsalva LVOT gradient of >50 mm Hg; 7 patients were included in both categories. Of the 14 patients with a resting LVOT of >30 mm Hg, 5, 8 and 1 were assessed as NYHA functional class I, II, and III, respectively. Of the 8 patients assessed as NYHA functional class II, 6 had improved from baseline NYHA functional class III, and 2 had remained in their baseline class. Of the 22 patients with a Valsalva LVOT of >50 mm Hg, 10, 10, and 2 were NYHA functional class I, II and III, respectively. Of the 10 patients assessed as NYHA functional class II, 5 had improved from baseline NYHA functional class III, and 5 had remained in their baseline class. In addition, 56 of 66 patients (85%) assessed at week 84 achieved a Valsalva LVOT gradient of ≤30 mm Hg.

Decreases in mean resting LVEF were observed at week 4 and plateaued by week 16 (**Central Illustration**). Mean LVEF was similar from week 48 through week 84; the mean change ± SD from baseline in LVEF at week 48 was −7.0% ± 8.3%, as assessed by central-read echocardiograms. From week 4 to week 84, central-read mean LVEF values

(range: 66%-71%) were slightly higher than site-read values (range: 64%-66%) and within the range of variability of the measure.

Additional echocardiographic parameters showed sustained improvements with mavacamten treatment. At week 48, decreases in lateral and septal E/e′, were observed, suggesting reduction of LV filling pressure, with mean change ± SD from baseline values of −3.5 ± 4.9 and −4.3 ± 6.6, respectively. Consistent with these improvements in diastolic function parameters, at week 48, there was a reduction in LAVI (mean ± SD: −6.8 ± 8.4 mL/m^2) compared with baseline. Moreover, of the patients with evaluable assessments (central read) at baseline and at week 48, 77.7% (157 of 202 patients) had SAM at baseline, and 94.5% (190 of 201) had any mitral regurgitation at baseline, compared with 19.8% (40 of 202) and 74.1% (149 of 201), respectively, at week 48.

NT-proBNP levels decreased from baseline (783 ng/L; Q1-Q3: 326-1,593) by week 4 and were sustained through week 84 (**Central Illustration**). The median change from baseline in NT-proBNP concentration was −480 ng/L (Q1-Q3: −1,104 to −179 ng/L) at week 48, with 42.4% and 50.0% of patients having normalized NT-proBNP levels (<124 ng/L) by week 48 and week 84, respectively.

These improvements in echocardiographic measures and biomarkers were accompanied by improvement in NYHA functional class as assessed at week 12 and week 48 (**Figure 2**). At baseline (n = 231), 6.1%, 64.9%, and 29.0% of patients were classified as NYHA functional class I, II, and III, respectively. A majority of patients with a week 12 assessment (113 of 192; 58.9%) had an improvement of ≥1 NYHA functional class and 7 (3.6%) worsened compared with baseline, including 5 patients who had returned to their baseline NYHA functional class by week 48 (Supplemental Table 2). Of the 206 patients assessed at week 48, 139 (67.5%) improved by ≥1 NYHA functional class relative to baseline. Sixty-four patients (31.1%) had no change in NYHA functional classification, and 3 (1.5%) worsened by 1 class.

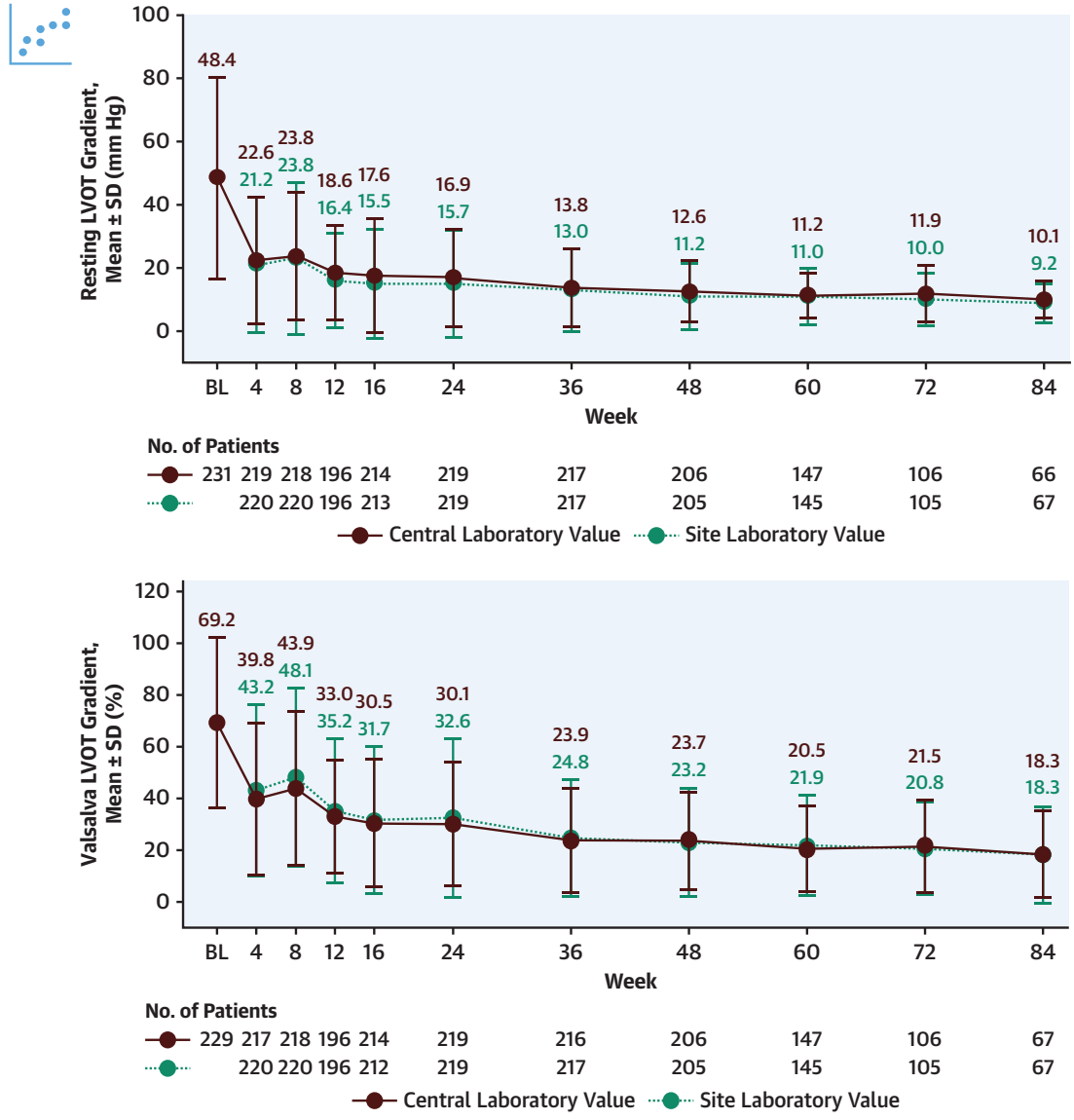
Site-read echocardiogram values, which were used for dosing decisions at weeks 4, 8, and 12, were generally consistent and in agreement with central-read values. Overall, when comparing site- and central-read values for Valsalva LVOT gradient of ≥30 mm Hg or <30 mm Hg, there was a >90% concordance rate, with the proportion of patients with discrepant results being 3.0% to 13.3% across week 4 through week 84. Site- and central-read values for LVEF of ≥50% or <50% were also highly consistent with a 99% concordance rate. Discrepancies were found for 15 of 1,841 assessments (0.8%) involving 13 of 229 patients (5.7%) with a mix of site- or core-read values being above or below the 50% boundary.

SAFETY AND TOLERABILITY. Dosing and treatment exposure. At the interim analysis data cutoff, 220 patients (95.2%) remained in study in the EXPLORER-LTE cohort, and 217 remained on treatment. Per-protocol-defined dose adjustments yielded 28.3%, 25.9%, 29.3%, and 16.1% of patients receiving 2.5, 5, 10, and 15 mg of daily mavacamten, respectively, after 48 weeks, with minimal change by week 84 (25.4%, 32.8%, 26.9%, and 13.4%, respectively). For all patients in the EXPLORER-LTE cohort, the duration of exposure at this data cutoff was 317 patient-years (315 patient-years when adjusted for interruptions in dosing), indicating high retention in the study and compliance (99.6% of patients had a compliance rate of ≥80%) and few short-duration interruptions. At week 16 (the follow-up visit after the last dose adjustment at week 12), 215 patients (98.6%) had mavacamten plasma trough concentrations of <1,000 ng/mL, and 3 (1.4%) had values of ≥1,000 ng/mL (Supplemental Table 3). Overall, these data indicated that the echocardiogram-guided dose strategy can safely and effectively achieve target mavacamten concentrations in the vast majority of patients without pharmacokinetic-guided dosing, as was done in the parent EXPLORER-HCM study.

At data cutoff, 16 patients and 1 patient had reduced their baseline beta-blocker and calcium-channel blocker doses by ≥50%, respectively. Four patients discontinued beta-blockers, and 4 patients discontinued calcium-channel blockers; following discontinuation, vital signs, site-read Valsalva LVOT gradients, and LVEF values remained stable.

Treatment-emergent adverse events. Altogether, 895 TEAEs were reported for 201 patients (87.0%), of which 625 of 895 (69.8%) and 225 of 895 (25.1%) were mild and moderate in severity, respectively (**Table 2**). Fatigue was the most frequently reported TEAE (10.4%; 24 of 231 patients), followed by dizziness (10.0%; 23 of 231 patients), hypertension (10.0%; 23 of 231 patients), and atrial fibrillation (9.1%; 21 of 231 patients) (**Table 3**), while cardiac failure was reported in 3.5% (8 of 231) of patients. Of the 21 patients who experienced an adverse event of atrial fibrillation, 11 patients (4.8%) had new onset of atrial fibrillation, and 10 patients had a prior history of atrial fibrillation. At the data cutoff date, adverse events of atrial fibrillation had resolved in 16 of 21 patients (76%). Five of 21 patients (24%) who experienced an adverse event of atrial fibrillation had a simultaneous transient LVEF reduction below 50% (adverse events of atrial fibrillation had resolved in 4 of these 5 patients

CENTRAL ILLUSTRATION **Longer-Term Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy With Mavacamten Shows Sustained Improvements and Is Well Tolerated**



Rader F, et al. J Am Coll Cardiol HF. 2024;12(1):164–177.

BL values represent those from the beginning of MAVA-LTE, not the beginning of the parent study. BL echocardiograms were read at the central laboratory only as a precaution to preserve the blinded nature of the study when transitioning from EXPLORER-HCM. The number of patients reflects the number of evaluable results for those having reached the stated follow-up time in weeks at the time of the data cut-off (median follow-up: 62.3 weeks). Not all patients had evaluable data at BL. BL = baseline; EXPLORER-HCM = Clinical Study to Evaluate Mavacamten [MYK-461] in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; MAVA-LTE = A Long-Term Safety Extension Study of Mavacamten in Adults Who Have Completed EXPLORER-HCM; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

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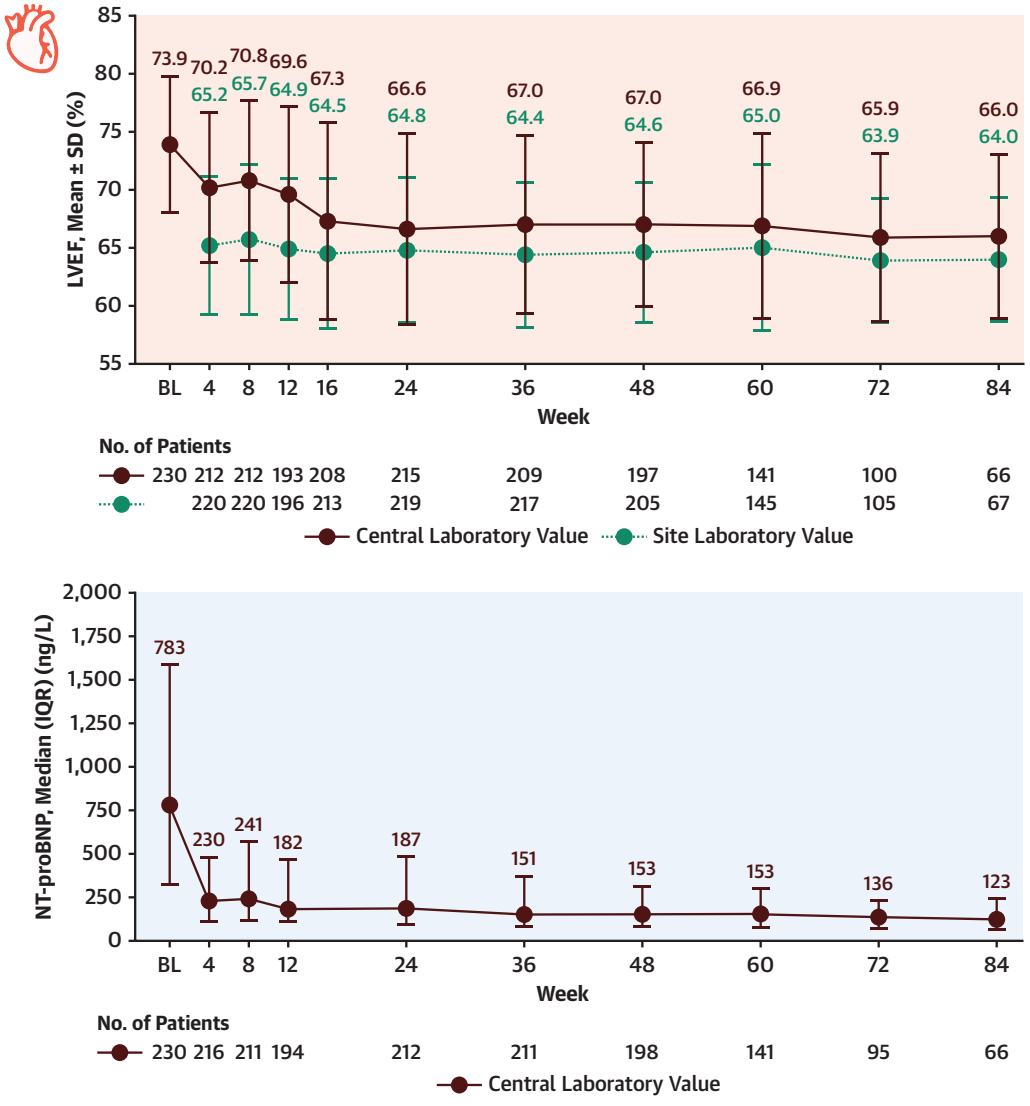
CENTRAL ILLUSTRATION Continued

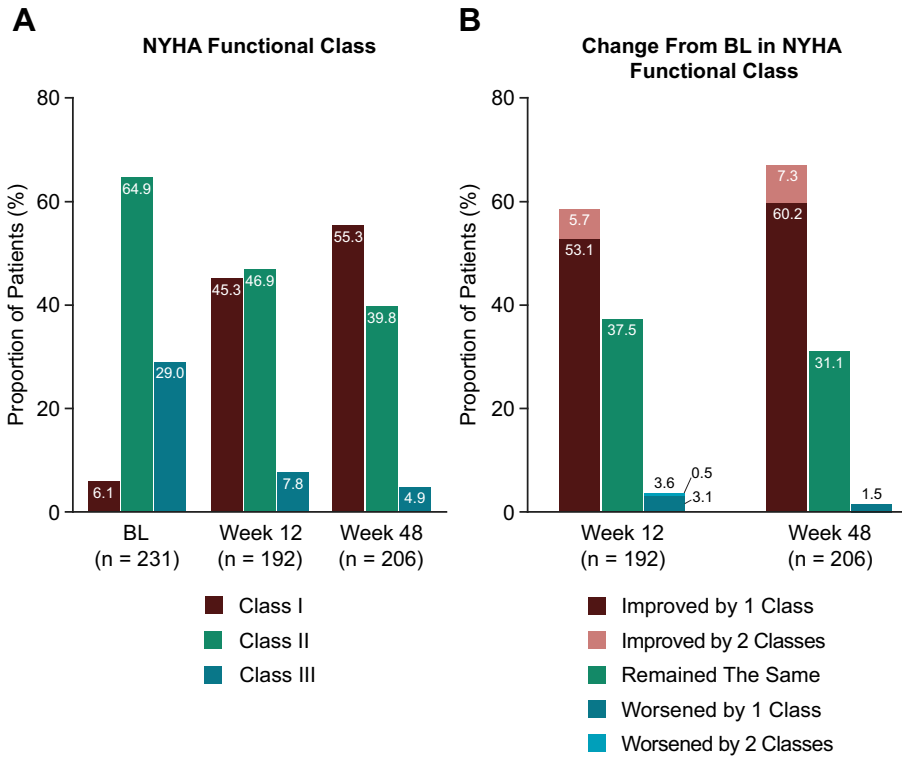


- LVEF reductions <50% occurred in 5% of patients. In most cases, the reductions were transient, reversible, and not associated with adverse events, and treatment was resumed.
- The proportion of patients with serious adverse events of atrial fibrillation in the EXPLORER cohort of MAVA-LTE (3%) was similar to that reported in the mavacamten (2%) and placebo (3%) arms of EXPLORER-HCM.

Rader F, et al. J Am Coll Cardiol HF. 2024;12(1):164–177.

at the data cutoff date) (Supplemental Table 4). When analyzed according to the patients' drug exposure time (per 100 patient-years), the most common TEAEs remained the same events as those determined by unadjusted incidence (fatigue: 8.02; dizziness: 7.51; hypertension:7.49; and atrial fibrillation: 6.89). The exposure-adjusted incidences per 100 patient-years for other cardiac-related TEAEs were as follows: palpitations: 3.51; decreased ejection fraction: 2.53; and cardiac failure: 2.52. Eighty-four TEAEs in 40 patients

FIGURE 2 NYHA Functional Class in the EXPLORER-LTE Cohort



(A) Distribution of NYHA functional class at baseline, week 12, and week 48. (B) Change in NYHA functional class from BL to week 12 and week 48. BL = baseline; EXPLORER-LTE = Clinical Study to Evaluate Mavacamten [MYK-461] in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy–Long-Term Extension.

TABLE 2 Summary of TEAEs and SAEs

	Patients	Total Events
Any TEAE	201 (87.0)	895
Mild	87 (37.7)	625
Moderate	89 (38.5)	225
Severe	21 (9.1)	41
Drug-related TEAEs	40 (17.3)	84
Cardiovascular drug-related TEAEs of clinical interest	19 (8.2)	25
SAEs	34 (14.7)	56
Cardiovascular serious TEAEs of clinical interest	15 (6.5)	20
Drug-related serious TEAEs	5 (2.2)	5[a]
Death	3 (1.3)	3[b]

Values are n (%) or n. [a]Includes cardiac failure (n = 3) and decreased left ventricular ejection fraction (n = 2). [b]Owing to bacterial endocarditis (n = 1), cardiac arrest (n = 1), and acute myocardial infarction (n = 1; sudden death without an autopsy performed); all unrelated to treatment.

SAE = serious adverse event; TEAE = treatment-emergent adverse event.

TABLE 3 Incidence and Exposure-Adjusted Incidence of TEAEs

	Patients	Exposure-Adjusted Incidence per 100 Patient-Years
Patients with ≥1 TEAE[a]	201 (87.0)	70.8
Fatigue	24 (10.4)	8.02
Dizziness	23 (10.0)	7.51
Hypertension	23 (10.0)	7.49
Atrial fibrillation	21 (9.1)	6.89
Headache	19 (8.2)	6.19
Nasopharyngitis	19 (8.2)	6.45
Back pain	15 (6.5)	4.78
COVID-19 infection	14 (6.1)	4.45
Dyspnea	14 (6.1)	4.52
Pain in extremity	13 (5.6)	4.19
Ejection fraction decrease[b]	8 (3.5)	2.53
Cardiac failure	8 (3.5)	2.52

Values are n (%) or n. [a]TEAEs of any grade in ≥5% of patients, except for ejection fraction decrease and cardiac failure, for which the proportions of patients were lower than 5%. [b]Reported TEAEs of ejection fraction decrease are not always associated with an echocardiographic measure of LVEF of <50%.

TEAE = treatment-emergent adverse event.

TABLE 4 Clinical Profile of Patients Who Experienced an LVEF of <50%

Patient #	LVEF at Event	LVEF at Last Assessment	Dose at Event	Dose at Last Assessment	Intercurrent Illness at Event	Permanent Treatment Discontinuation
1	45% (wk 36)	56% (wk 120)	10 mg	5 mg (wk 120)	No	No
2[a]	35% (wk 60)	51% (wk 65)	10 mg	NA	Atrial flutter	Yes
3	45% (wk 36)	60% (wk 52)	2.5 mg	NA	Exacerbated hypertension	Yes
4	48% (wk 24) 42% (wk 26)	60% (wk 33)	10 mg	NA	AF	Yes
5[a]	45% (wk 7)	65% (wk 260)	5 mg	NA	AF, atrial flutter	Yes
6	39% (wk 58)	NA[b]	10 mg	NA[b]	No	No
7	44% (wk 16) 48% (wk 42)	64% (wk 84)	15 mg 10 mg	5 mg (wk 84)	AF Atrial flutter	No
8	41% (wk 54)	54% (wk 60)	10 mg	5 mg (wk 60)	No	No
9	43% (wk 48) 49% (wk 52)	61% (wk 55)	10 mg	NA	AF	Yes[c]
10	48% (wk 36)	63% (wk 48)	10 mg	5 mg (wk 48)	AF	No
11	45% (wk 16)	56% (wk 84)	10 mg	5 mg (wk 84)	No	No
12	48% (wk 16)	63% (wk 84)	10 mg	5 mg (wk 84)	No	No

[a]Serious adverse event of reduced ejection fraction. [b]The assessment at wk 58 was the last assessment included in the current data cutoff; however, the patient continued receiving mavacamten, and their LVEF was 63% at wk 96. [c]Patient later re-enrolled.

AF = atrial fibrillation; LVEF = left ventricular ejection fraction; NA = not applicable.

(17%) were considered drug related by the investigator, 25 of which—experienced by 19 patients (8.2%)—were cardiovascular events of clinical interest (eg, major adverse cardiovascular events, atrial fibrillation, syncope/presyncope [broad/narrow], cardiac failure, and QTc prolongation). Details on patients who experienced an adverse event coded as cardiac failure are presented in Supplemental Table 5.

Serious adverse events. Of the 895 TEAEs, 56 were reported as SAEs in 34 patients (14.7%), including 20 cardiovascular events of clinical interest in 15 patients (6.5%). The exposure-adjusted incidence of cardiovascular SAEs was 4.8 per 100 patient-years. SAEs of atrial fibrillation were reported in 8 of 231 patients (3%), including 5 patients with a medical history of atrial fibrillation. The exposure-adjusted incidence of SAEs of atrial fibrillation was 2.5 per 100 patient-years. Five patients (2%) experienced an SAE that was considered by the investigator to be drug related (3 for cardiac failure, including a patient with right ventricular dysfunction, and 2 for decreased ejection fraction [Supplemental Table 6]). All 5 events resolved; 3 patients remained in the study, whereas 2 patients permanently discontinued the study (described later) (Supplemental Table 6).

TEMPORARY TREATMENT INTERRUPTIONS. Twenty-five patients (10.8%) experienced 29 qualifying events that triggered temporary treatment interruptions due to the following reasons: increase in QTcF interval of >15% from baseline; mavacamten plasma trough concentration of ≥1,000 ng/mL; and LVEF of <50% based on site-read echocardiograms. At the data cutoff, 20 of these 25 patients (80%) remained on study treatment. Seven patients (3.0%) had a temporary treatment interruption due to QTcF prolongation; notably, 4 of these 7 patients were receiving concurrent known QTcF-prolongation agents (eg, amiodarone), whereas 1 patient had a dosing error and concurrent mavacamten concentration of ≥1,000 ng/mL (1,330 ng/mL). Nine patients (3.9%) had a mavacamten concentration of ≥1,000 ng/mL, including the previously mentioned patient with prolonged QTcF (Supplemental Table 3) and the 3 patients with values of ≥1,000 ng/mL at week 16 mentioned earlier. Elevated mavacamten concentration did not consistently precede or coincide with the development of LVEF of <50%, with only 2 patients with mavacamten concentration of ≥1,000 ng/mL having an LVEF of <50%. Of the 12 patients (5.2%) in total who met the criteria for a temporary treatment interruption due to LVEF of <50% (range: 35-49%), 6 had intercurrent illness at the time of reduced LVEF (5 with atrial fibrillation/flutter and 1 with exacerbated hypertension) (**Table 4**). All 12 patients recovered with an LVEF of >50%, including 7 who resumed mavacamten treatment and 5 who permanently discontinued treatment and the study, of whom 1 re-enrolled.

PERMANENT TREATMENT DISCONTINUATION. In total, 10 patients of the 201 who experienced at least 1

TEAE experienced TEAEs that led to permanent treatment discontinuation. Reasons for permanent treatment discontinuation included: LVEF of <50%, determined by the investigator as a TEAE of decreased ejection fraction (n = 2); cardiac failure (n = 1); cardiac arrest leading to death (sudden and unwitnessed) (n = 1); acute myocardial infarction (sudden death without an autopsy performed) (n = 1), muscular weakness (n = 1); systemic lupus erythematosus (n = 1); fatigue (n = 1); bacterial endocarditis leading to death (n = 1); and prolonged QTcF (n = 1). Of these 10 patients, 1 with an LVEF of <50% and 1 with prolonged QTcF discontinued the study and later re-enrolled. Erroneous overdosing due to a site error was determined to be the cause of the cardiac failure SAE (LVEF of 29%, which later recovered) while admitted to the hospital for a concomitant SAE of pneumonia.

As reported, there were 3 deaths in the study. One patient with a medical history of atrial fibrillation, left bundle branch block, dizziness, implantable cardioverter-defibrillator, aortic stenosis, and essential hypertension died of a cardiac arrest. The patient had an event of atrial fibrillation 5 minutes before the terminal event. The cause of death, per the death certificate, was congestive cardiac failure as a consequence of atrial fibrillation and coronary artery disease. The cause of the second death, per the death certificate, was presumed to be acute myocardial infarction; the cause of death, per the investigator, was attributed to cardiac arrhythmia, which was thought to be related to the underlying disease. A subsequent follow-up with the investigator confirmed that the most likely cause of death was sudden cardiac death; however, the precise cause of death cannot be confirmed because of the lack of postmortem. The third death was due to cardiac arrest secondary to multisystem organ failure induced by hemorrhagic shock due to acute gastrointestinal bleeding. The death followed a complicated hospital course involving bacterial endocarditis, and cardiac surgery including mitral valve replacement, myectomy, and maze procedure. All 3 deaths were deemed by the study investigators to be unrelated to mavacamten (**Table 2**).

DISCUSSION

This interim analysis from the EXPLORER cohort of the MAVA-LTE study represents the largest and longest report of mavacamten use in obstructive HCM (315 patient-years of exposure). A large proportion of EXPLORER-HCM patients continued in the MAVA-LTE study, indicating that most patients who participated in EXPLORER-HCM were willing to receive mavacamten treatment in the MAVA-LTE study. Consistent with the results from the parent study, EXPLORER-HCM, patients treated with mavacamten showed: 1) improvements in resting and Valsalva LVOT gradients within 4 weeks of treatment with mavacamten, which were sustained up to week 84; 2) improvements in E/e′, LAVI, SAM, and mitral regurgitation at week 48 and beyond; 3) considerable reductions in NT-proBNP; and 4) clinically meaningful improvements in NYHA functional class at weeks 12 and 48. Furthermore, the exposure-adjusted TEAE rate was similar to that observed in a prior analysis (data cutoff: May 27, 2020; follow-up range: 4-48 weeks),[13] and, consistent with the known mechanism of action of mavacamten, modest reversible reductions in LVEF were observed, but these plateaued, and occurrences of LVEF below 50% through week 84 happened in approximately 5% of patients.

The reductions in LVOT gradients and improvements in diastolic function suggest that mavacamten is associated with consistent hemodynamic improvements in patients with HCM.[9,14] Mavacamten, therefore, may serve as a more durable treatment option for patients with obstructive HCM than the current treatment paradigm of beta blockers, calcium-channel blockers, and disopyramide, which results in incomplete symptom management control and can have diminished efficacy over time.[5,7,15] Furthermore, some patients have begun to decrease or discontinue their background HCM therapy while maintaining stable clinical status. Although further data timepoints are needed to assess how improvements in LVOT gradients and diastolic function affect the long-term prognosis for patients with obstructive HCM, improvements in echocardiographic measures and NYHA functional classification in the EXPLORER-LTE cohort of MAVA-LTE show that mavacamten treatment effectively reduces eligibility for septal reduction therapy (eg, maintaining LVOT gradients of <50 mm Hg and NYHA functional class I or II), consistent with the results from the VALOR-HCM study (NCT04349072).[16] The data presented here do not support that residual gradient is responsible for persistent symptoms. Although approximately 45% of patients were assessed as NYHA functional class II or III at week 48, 37 of 82 (45.1%) NYHA functional class

II patients improved from baseline class III, and 44 of 82 (53.7%) remained NYHA functional class II without further progression of NYHA functional class over this timeframe. Furthermore, <5% of patients remained in class III, a status considered for septal reduction therapy if LVOT gradient is also >50 mm Hg.[2,4] Due to the heterogeneity of symptoms and symptom burden associated with HCM, it is not expected that mavacamten treatment will alleviate all the symptoms in all patients.

Effectiveness (reduction in LVOT gradient) and safety (maintenance of normal LVEF) assessment by echocardiogram for optimal dosing of mavacamten were generally consistent and in agreement between site and central readings. This observation is particularly notable given the global nature of the study, in which 65 sites in 13 countries were involved in gathering and assessing patient data. Discrepant site- and central-read echocardiograms for LVEF of ≥50% or <50% were only reported for 15 assessments (0.8%), and site-read LVEF measurements were consistently lower than central readings, suggesting that site readings were more conservative with a greater safety margin.

Although safety surveillance in this study included monitoring of the pharmacokinetic (PK) levels of mavacamten and the QTcF interval as a precaution, no patient permanently discontinued mavacamten solely for PK of ≥1,000 ng/mL, although 2 with high levels presented with simultaneous LVEF of <50%. Furthermore, only 1 patient permanently discontinued mavacamten for QTcF prolongation, and this was in the context of amiodarone coadministration; the patient later re-enrolled. Altogether, the additional PK monitoring did not meaningfully affect patient management beyond that provided by regular clinical and echocardiographic monitoring. Indeed, echocardiogram assessments, which are already part of routine clinical care for patients with HCM, were sufficient for monitoring safety and guiding clinical decisions related to mavacamten treatment. By following an echocardiogram-guided dose-titration strategy, the vast majority of patients across all study visits achieved mavacamten plasma concentrations of ≤700 ng/mL.[11,12] Further, using this approach, only 12 patients (5.2%) developed an LVEF of <50%, of whom 2 had concurrent mavacamten plasma trough concentrations of ≥1,000 ng/mL; all patients recovered with an LVEF of >50% after discontinuing mavacamten, temporarily or permanently. The current study data support the conclusion that use of echocardiography-guided dosing by the practitioner in routine clinical practice is reliable and practical. In addition, echocardiographic examinations of a patient's cardiac function and symptom status enable a broader assessment for the etiology of symptoms in the setting of HCM; moreover, results from site-read echocardiograms can be readily available to manage dose adjustment accordingly and expeditiously.

Given that HCM is a chronic condition, pharmacologic treatment not only needs to be well tolerated over long-term treatment exposure but should also maintain stable efficacy over long periods of time. Most TEAEs (>94%) were mild or moderate in severity, with <3% of patients experiencing serious drug-related TEAEs. Moreover, many of the TEAEs (eg, atrial fibrillation, cardiac failure, sudden death) reported in patients receiving mavacamten are also associated with HCM and should be viewed within the overall disease state of the patient.[2] Importantly, the total patient-years of exposure should be considered when examining the safety profile of mavacamten in studies with different durations. Indeed, by numbers, severity, and standard of care, the exposure-adjusted TEAE rate was the same as or less than that observed in a prior analysis.[13] In addition, the exposure-adjusted incidence of serious cardiovascular adverse events reported in the EXPLORER cohort of MAVA-LTE (4.8 per 100 patient-years) was similar to that in EXPLORER-HCM (5.6 per 100 patient-years).[11] However, this observation should be interpreted in the context of a single-arm study. Events of LVEF of <50% occurred with no greater frequency than previously reported, based on patient-years of exposure, supporting the important notion that long-term exposure to mavacamten does not lead to a progressive reduction in LVEF.[11] In all such cases, LVEF recovered without further sequelae. Importantly, the proportion of patients experiencing adverse events of atrial fibrillation in the EXPLORER-HCM cohort of MAVA-LTE (9.1%) was similar to that in the placebo arm of EXPLORER-HCM (7.0%) over a shorter treatment period and was not higher than the rate of atrial fibrillation in an HCM population reported in a large retrospective study (18%).[17] Furthermore, the proportion of patients with an SAE of atrial fibrillation in the current study (3%) was similar to that reported in the placebo (3%) and mavacamten (2%) groups of EXPLORER-HCM.[11] Longer-term assessments of cardiovascular safety profile are needed, including further follow-up data and real-world experience to clarify if mavacamten potentiates or mitigates the development of atrial

fibrillation and the extent to which it can be associated with concomitant transient systolic dysfunction. Forthcoming data from future data cutoffs of this ongoing 5-year MAVA-LTE study will help to further substantiate these findings.

STUDY LIMITATIONS. The present findings should be interpreted in the context of some limitations. First, the dose-blinded, active treatment design of this long-term extension study, which does not include a control arm for comparison, can potentially introduce bias, especially when reporting subjective efficacy outcomes, such as NYHA functional class. However, the current results are consistent with the findings from the parent randomized, placebo-controlled study. Second, this is a cumulative interim analysis; as such, the results may evolve as the study progresses and more data are included in the analysis. Third, these results are from participating investigators and centers with expertise in HCM care, and generalizability of echocardiogram performance to nonspecialized centers cannot be made. Future observations from real-world studies such as DISCOVER-HCM (A Prospective Registry Study to Assess Real-World Patient Characteristics, Treatment Patterns, and Longitudinal Outcomes in Patients Receiving Mavacamten and Other Treatments for Symptomatic Obstructive Hypertrophic Cardiomyopathy; NCT05489705]) will be helpful. Finally, the population that enrolled from the parent study was predominantly White, as in the parent study.

CONCLUSIONS

These cumulative results from an interim analysis of the EXPLORER-LTE cohort of the MAVA-LTE study demonstrate that mavacamten over a median treatment duration of 62 weeks reduces LVOT gradients, relieving outflow obstruction below the level defining obstructive HCM (eg, <30 mm Hg) in most patients with HCM while treated. Mavacamten also improves diastolic function, reduces cardiac wall stress, and improves NYHA functional class in a clinically meaningful way over a sustained period. The safety and tolerability profile of long-term mavacamten treatment was consistent with that seen in EXPLORER-HCM. Evaluation of safety data in this study supports a site-read echocardiography-guided dose-titration and monitoring strategy for mavacamten as a novel therapy with evidence of advantageous cardiac remodeling for patients with obstructive HCM. Further studies should address the implications of gradient reduction and improved diastolic parameters on long-term prognosis.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Mavacamten targets the underlying pathophysiology of obstructive HCM by selectively and reversibly inhibiting cardiac myosin through binding to its allosteric site. Mavacamten was shown to improve exercise capacity, LVOT gradients, and symptoms after 30 weeks of treatment in the EXPLORER-HCM study. The ongoing 5-year MAVA-LTE study is evaluating longer-term safety and efficacy of mavacamten treatment.

COMPETENCY IN PATIENT CARE: Current treatment guidelines recommend pharmacologic therapies, such as beta blockers, non-dihydropyridine calcium-channel blockers, and disopyramide, to mitigate symptoms in patients with obstructive HCM. Mavacamten is a new alternative for medical care of symptomatic obstructive HCM and is associated with sustained improvements in LVOT gradients and NT-proBNP levels up to 84 weeks of treatment and in NYHA functional class up to 48 weeks of treatment. An echocardiogram-guided dose strategy can safely and effectively achieve target mavacamten concentrations in the vast majority of patients.

TRANSLATIONAL OUTLOOK: This interim analysis from the EXPLORER cohort of MAVA-LTE provides the longest report of mavacamten use in >200 patients and 315 patient-years exposure. Although reassuring findings regarding safety, cardiac function, and cardiac structure are being reported in this median 62-week interim analysis, future data from the ongoing 5-year MAVA-LTE will provide valuable information on the longer-term efficacy and safety profile of mavacamten.

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KEY WORDS efficacy, long-term outcomes, LVOT gradient, NT-proBNP, NYHA functional class, safety

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