Journal of the American Heart Association

ORIGINAL RESEARCH

Safety and Efficacy of Mavacamten and Aficamten in Patients With Hypertrophic Cardiomyopathy

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BACKGROUND: Cardiac myosin inhibitors were recently developed to address the underlying pathophysiology of hypertrophic cardiomyopathy and to improve symptoms and quality of life. In this review, we evaluated the pharmacologic profile and clinical outcomes for mavacamten and aficamten, 2 cardiac myosin inhibitors investigated in symptomatic hypertrophic cardiomyopathy.

METHODS AND RESULTS: Using a systematic search, 10 clinical trials with safety and efficacy data for either drug in obstructive hypertrophic cardiomyopathy (oHCM) and nonobstructive hypertrophic cardiomyopathy were included. Additionally, we included data from regulatory agencies. Both drugs demonstrated substantial benefit in reducing left ventricular outflow tract obstruction (Valsalva left ventricular outflow tract gradients improved by −45 mm Hg or better), symptom burden (placebo-corrected New York Heart Association class improvement ≥1 of at least 30%), and cardiac biomarkers (geometric mean ratio of 0.2 for N-terminal pro-B-type natriuretic peptide) while improving exercise parameters (improved placebo-corrected peak oxygen consumption of at least 1.4 to 1.8 mL/kg per minute) in patients with oHCM. Both drugs were generally well-tolerated, although patients on mavacamten had higher rates of treatment interruption (partly protocol-driven, 8.7% versus 0.5%, respectively, in oHCM) due to left ventricular ejection fraction reduction, atrial fibrillation (11.5 versus 4.1 per 100 patient-years, respectively, in oHCM), and heart failure (1.7 versus 0.0 per 100 patient-years, respectively, in oHCM) compared with aficamten. These comparisons are limited by a shorter exposure duration to aficamten, and longer follow-up is needed. The data in nonobstructive hypertrophic cardiomyopathy are derived from phase II trials, with phase III trials ongoing.

CONCLUSIONS: Mavacamten and aficamten represent effective medications for the treatment of symptomatic oHCM.

Key Words: aficamten ■ cardiac myosin inhibitors ■ mavacamten ■ symptomatic hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common inherited heart disease in the world, which if left untreated carries significant morbidity.[1] Conventional pharmacological therapies, including β-blockers, nondihydropyridine calcium channel blockers, and disopyramide are guideline-recommended for the treatment of symptomatic obstructive HCM (oHCM).[2] However, despite these therapies, symptoms frequently persist, which represents an ongoing unmet medical need.[3–5] In nonobstructive HCM (nHCM), there is an arguably even greater medical need for effective medications to improve symptoms

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This article was sent to Sula Mazimba, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.038758

For Sources of Funding and Disclosures, see page 23.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In this review of 2 cardiac myosin inhibitors, mavacamten and aficamten, both medications are safe and efficacious in symptomatic hypertrophic cardiomyopathy.
- Based on review of the 10 clinical trials assessed, patients on mavacamten had higher rates of atrial fibrillation, heart failure, and treatment interruption due to left ventricular ejection fraction <50% compared with aficamten, although comparisons are limited by a shorter exposure duration to aficamten.

What Are the Clinical Implications?

- Phase III trials are ongoing in nonobstructive hypertrophic cardiomyopathy.

Nonstandard Abbreviations and Acronyms

CMI	cardiac myosin inhibitor
CSS	Clinical Summary Score
CYP	cytochrome p450
DDI	drug–drug interaction
FDA	Food and Drug Administration
HCM	hypertrophic cardiomyopathy
KCCQ	Kansas City Cardiomyopathy Questionnaire
LSMD	least-squares mean difference
nHCM	nonobstructive hypertrophic cardiomyopathy
NYHA	New York Heart Association
oHCM	obstructive hypertrophic cardiomyopathy
pVO_2	peak oxygen consumption
TEAE	treatment-emergent adverse events

and exercise capacity. In nHCM, only β-blockers and nondihydropyridine calcium channel blockers are guideline-recommended based on limited data.[2] Although patients with persistent symptoms despite pharmacologic therapy in oHCM may undergo septal reduction therapy, those options are not available to patients with nHCM. In this context, cardiac myosin inhibitors (CMIs) emerged as potent oral small molecules that directly target the cardiac sarcomere by binding to α and β isoforms of cardiac myosin to produce a dose-dependent reduction in myosin adenosine triphosphatase activity rate, resulting in decreased myosin-actin cross-bridges and improving the underlying pathological hypercontractility seen in HCM.[6–8]

Two CMIs to date, mavacamten and aficamten, have shown efficacy and safety in randomized and open-label clinical trials.[9–26] Mavacamten is already approved by numerous regulatory agencies for the treatment of symptomatic oHCM, but due to its associated reduction in left ventricular ejection fraction (LVEF), heart failure risk, drug–drug interactions (DDIs), and inconsistent pharmacokinetic to pharmacodynamic relationship, rigorous safety monitoring programs have been recommended or enforced.[27–29] Of note, pharmacokinetics refers broadly to the absorption, distribution, metabolism, and excretion of drugs. More specifically in the context of CMI clinical trials, we refer to pharmacokinetics as the drug concentration. Pharmacodynamics refers to the effect of a drug on the body, and in the context of these clinical trials, we define pharmacodynamics specifically as the effect these CMIs have on LVEF. As such, the US Food and Drug Administration (FDA) instituted a strict Risk Evaluation and Mitigation Strategies program to mandate a specific approach to prescribing and monitoring mavacamten.[29] Despite these limitations, mavacamten represents a significant improvement and a step forward in the care of patients with oHCM. Mavacamten currently represents a second-line medical option for treating patients with symptomatic oHCM who remain symptomatic despite β-blockers or calcium channel blockers.[2] In contrast, mavacamten is not currently approved for use in patients with symptomatic nHCM.

Aficamten is the second-in-class CMI that has been shown to be safe and effective in multiple clinical trials.[20–26,30] Aficamten has a shorter half-life than mavacamten, a consistent pharmacokinetic/pharmacodynamic profile (drug concentration as it relates to effect on LVEF), and is metabolized through multiple CYP (cytochrome P450) enzymes leading to infrequent DDIs.[20,22,26,30,31] Mavacamten and aficamten have distinct chemical structures and different binding sites at the sarcomere level.[30,32] Given its more recent development, long-term safety data are relatively limited for aficamten, and it remains under regulatory review. Over a relatively short period, there has been a tremendous degree of investigation into both CMIs, and the wealth of data generated by these trials require further appraisal. In this review, we summarize the safety and efficacy outcome measures reported in 10 clinical trials of mavacamten and aficamten.

METHODS

All supporting data used to generate this review are available within the article, its supplementary material, or in the referenced articles. A systematic search of PubMed, Cochrane-CENTRAL, and ClinicalTrials.gov

from inception to June 11, 2024 was used to identify all clinical and randomized controlled trials associated with the use of CMIs in HCM. Search included the keywords aficamten, mavacamten, cardiac myosin inhibitor, CK-3773274/CK-274 (aficamten synonyms), MYK-461 (mavacamten synonym), and hypertrophic cardiomyopathy. All identified phase II to III clinical and randomized controlled trials with available safety and efficacy data for either aficamten or mavacamten in both oHCM and nHCM were included. Preclinical, phase I, observational, or retrospective studies were excluded, as were post hoc analyses, meta-analyses, or review articles. The details about study selection (including a Preferred Reporting Items for Systematic Reviews and Meta-Analyses-style flow diagram) and the quality of evidence for the selected trials are available in Figure S1 and Table S1. We conducted additional review of conference proceedings where data were presented from ongoing, selected clinical trials. Data were extracted from the most recent publication, abstract, or conference proceedings and were supplemented with available FDA and European Medicines Agency clinical and statistical reviews as needed.[28,29]

Efficacy outcome measures included resting and Valsalva left ventricular outflow tract (LVOT) gradients, peak oxygen consumption (pVO_2), ventilation/carbon dioxide production slope, septal reduction therapy eligibility at follow-up, improvement in New York Heart Association (NYHA) class ≥1 functional class, Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels, and cardiac troponin levels. Safety outcome measures included frequency of treatment-emergent adverse events (TEAE), serious adverse events, LVEF <50%, heart failure (defined individually for each trial), atrial fibrillation, dizziness, syncope, and death.

For the purposes of this review, the Results and Discussion sections will primarily highlight data from completed phase III clinical trials in oHCM and phase II trials in nHCM so as to minimize comparing studies from trials of different phases. For information on institutional review board approval, please refer to each referenced trial individually. All trial participants provided written, informed consent according to trial protocols outlined by each referenced trial.

Statistical Analysis

Due to significant heterogeneity in study design (including inclusion criteria, follow-up, and dosing strategies), small sample size, and outcome measures, no formal statistical analysis or a quantitative meta-analysis was performed, and exhaustive efforts were taken to account for trial heterogeneity in our qualitative assessments. Rates of events of interest for safety outcome measures were calculated per 100 patient-years using median follow-up duration (if unavailable, total follow-up duration was used). Data are reported as mean±SD, median (interquartile range), or number (percentage), unless otherwise specified.

RESULTS

Ten phase II to III clinical trials totaling 901 unique patients (n=524 for mavacamten trials, n=377 for aficamten trials) were included: PIONEER-HCM (Pilot Study Evaluating MYK-461 in Subjects With Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction; NCT02842242), PIONEER-OLE (Open Label Extension Study of Mavacamten [MYK-461] in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy Previously Enrolled in PIONEER; NCT03496168), EXPLORER-HCM (Clinical Study to Evaluate Mavacamten [MYK-461] in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy; NCT03470545), VALOR-HCM (A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy; NCT04349072), EXPLORER-CN (A Study to Evaluate the Efficacy and Safety of Mavacamten in Chinese Adults With Symptomatic Obstructive HCM; NCT05174416), MAVERICK-HCM (The Study of Mavacamten in Adults With Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy; NCT03442764), MAVA-LTE (A Long-Term Safety Extension Study of Mavacamten in Adults Who Have Completed MAVERICK-HCM or EXPLORER-HCM; NCT03723655), REDWOOD-HCM (Randomized Evaluation of Dosing With CD-274 in Obstructive Outflow Disease in HCM; NCT04219826), FOREST-HCM (Follow-Up, Open-Label, Research Evaluation of Sustained Treatment With Aficamten in HCM; NCT04848506), and SEQUOIA-HCM (Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM; NCT05186818).[9–26] Table 1 summarizes active and completed clinical trials for mavacamten and aficamten.

Baseline Characteristics

Table 2 provides baseline characteristics for 3 completed, randomized, double-blinded, placebo-controlled phase III clinical trials (EXPLORER-HCM, VALOR-HCM, and SEQUOIA-HCM).[11,12,25] These trials enrolled patients with oHCM with a mean age ranging from 58.5 to 60.4 years, and sex distribution was balanced. All trials included symptomatic patients with NYHA class II to III symptoms except for VALOR-HCM, which selected for patients referred for septal reduction therapy who largely had NYHA class III or IV symptoms (92.9% of patients). In contrast, 27.1% and 24.1% of patients had NYHA class ≥III symptoms

Table 1. Completed and Active Clinical Trials for Mavacamten and Aficamten in Hypertrophic Cardiomyopathy Classified According to Clinical Trial Type and Phase

Trial Name	Design	Inclusion criteria	Exclusion criteria	Dose and concurrent drugs	Primary outcome	Secondary outcomes
Mavacamten						
Observational, prospective cohort study						
DISCOVER-HCM NCT05489705 N=1500 (estimated) Duration: up to 5 y Status: active	Observational, prospective cohort study	oHCM, LVEF ≥55%, NYHA II-IV, receiving CCB, disopyramide, BB or mavacamten, or a combination thereof	HCM phenocopy, fixed obstruction of outflow tract, prior SRT within 6 mo, naive to treatment for oHCM, previously or currently enrolled in LTE study of mavacamten	Mavacamten with BB, CCB, and disopyramide allowed	Incidence of new or worsening heart failure due to LVEF ≤50%	MACE, other treatment-emergency adverse events, all-cause and cardiovascular mortality, peak resting and provoked LVOT peak gradients, LVEF, KCCQ, EQ-5D-5L questionnaire, NT-proBNP, cardiac troponin
Mavacamten Pregnancy Surveillance Program NCT05939700 N=20 (estimated) Duration: up to 1 y Status: active	Observational, prospective cohort study	Exposure to ≥1 dose mavacamten any time during pregnancy or breastfeeding, 15 y old or older	None	Mavacamten	Live, full-term, pre-term or stillbirths, spontaneous or elective abortions, pregnancy complications, major and minor congenital malformations, small for gestational age, premature delivery, and post-natal growth and development deficiency	
Phase II Trials						
PIONEER-HCM NCT02842242 N=21 Duration: 12 wk Status: completed[9]	Open-label, phase 2 study	oHCM, NYHA II/III, LVEF ≥55% at screening visit	Exertional syncope within the past 6 mo, history of sustained VT, history of LVEF <45%, persistent or uncontrolled paroxysmal atrial fibrillation, history of obstructive CAD	Cohort A (n=11): 10–20 mg mavacamten without background medications Cohort B (n=10): 2–5 mg mavacamten with BB allowed	Change in post-exercise peak LVOT gradient	Resting and Valsalva LVOT gradient, pVO_2, VE/VCO_2, dyspnea numeric rating scale, LVEF, NYHA class, KCCQ-OSS, NT-proBNP
PIONEER-OLE NCT03496168 N=13 Duration: up to 260 wk Status: completed (preliminary data published)[10]	Open-label, phase 2 study	Completed PIONEER-HCM	Since enrollment in PIONEER-HCM: obstructive CAD, moderate to severe aortic stenosis, acute or serious comorbid condition or clinically significant malignancy	5–15 mg mavacamten with BB and CCB allowed	Frequency and severity of adverse events and serious adverse events	
MAVERICK-HCM NCT03442764 N=59 Duration: 16 wk Status: completed[15]	Double-blind, placebo-controlled, phase 2 randomized-control trial	nHCM, LVEF ≥55%, NYHA II/III, NT-proBNP ≥300 ng/L at rest	History of syncope, sustained VT, obstructive CAD, MI, or invasive SRT within 6 mo, history of resuscitated sudden cardiac death, clinically significant malignancy within 10 y, persistent or permanent atrial fibrillation that is uncontrolled or not on anticoagulation	2.5–15 mg with target mavacamten plasma concentration of 200 or 500 ng/mL vs placebo with BB or CCB allowed	Percentage of patients who experience at least one treatment-emergent or serious adverse events	Composite of pVO_2 ≥1.5 mL/kg/min + NYHA class reduction by 1 or pVO_2 ≥3.0 mL/kg/min without NYHA class reduction
MAVA-LTE NCT03723655 N=282 (estimated) Duration: up to 252 wk Status: active (preliminary data published)[16–19]	Double-blind, parallel, phase 2/3 randomized trial	Competed parent study, LVEF ≥50%, non-pregnant, non-lactating, oHCM for EXPLORER Cohort*, nHCM for MAVERICK Cohort†	History of syncope or sustained VT or sudden cardiac arrest, any acute or serious comorbid condition or clinically significant malignancy	Explorer Cohort*: 2.5–15 mg mavacamten with BB or CCB allowed Maverick Cohort†: 2.5–15 mg with target mavacamten plasma concentrations of either 200 or 500 ng/mL	Frequency and severity of treatment-emergent and serious adverse events	

(*Continued*)

Table 1. Continued

Trial Name	Design	Inclusion criteria	Exclusion criteria	Dose and concurrent drugs	Primary outcome	Secondary outcomes
Phase III Trials						
EXPLORER-HCM NCT03470545 N=251 Duration: 30 wk Status: completed[11]	Double-blind, placebo-controlled, phase 3 randomized control trial	oHCM, NYHA II/III, LVEF ≥55%, able to perform upright CPET, SpO_2 ≥90%	History of syncope or sustained VT within 6 mo, HCM phenocopy, persistent or uncontrolled paroxysmal atrial fibrillation, history of resuscitated sudden cardiac arrest	2.5–15 mg mavacamten with BB and CCB allowed compared to placebo	Percentage with: 1) pVO_2 ≥1.5 mL/kg/min + NYHA class reduction ≥1, or 2) pVO2 ≥3.0 mL/kg/min without NYHA class reduction	Peak post-exercise LVOT gradient, pVO_2, NYHA class reduction ≥1, KCCQ, HCMSQ score
VALOR-HCM NCT04349072 N=112 Duration: 16 and 56 wk Status: completed[12,13]	Double-blind, placebo-controlled, phase 3 randomized-control trial	oHCM, referred or under active consideration for SRT within past 12 mo, LVEF ≥60%, SpO_2 ≥90%	Persistent or permanent atrial fibrillation either uncontrolled or not on anticoagulation, previously treated with SRT, inability to perform upright CPET, paroxysmal atrial fibrillation present at screening visit	2.5–15 mg mavacamten vs placebo with BB, CCB, and disopyramide allowed	Composite of decision to proceed with SRT and SRT-guideline eligible	NYHA class reduction ≥1, KCCQ-CSS, NT-proBNP, cardiac troponin, peak post-exercise LVOT gradient
EXPLORER-CN NCT05174416 N=81 Duration: 30 and 78 wk Status: active (preliminary data published)[14]	Double-blind, placebo-controlled, phase 3 randomized-control trial (2:1 mavacamten: placebo)	oHCM, LVEF ≥55%, NYHA II/III, non-pregnant, non-lactating	History of successful SRT, obstructive CAD, moderate or severe aortic stenosis, constrictive pericarditis, clinically significant congenital heart disease, history of syncope or sustained VT in past 6 mo, paroxysmal atrial fibrillation present at screening, acute or serious comorbid condition or clinically significant malignancy	1–15 mg mavacamten vs placebo with BB or CCB allowed	Change in peak Valsalva LVOT gradient	Peak resting LVOT gradient, proportion of patients achieving Valsalva LVOT peak gradient <30 mmHg and <50 mmHg, NYHA class reduction ≥1, NT-proBNP, cardiac troponin, left ventricular mass index
HORIZON-HCM NCT05414175 N=38 Duration: 30 wk Status: active	Open-label, single-arm, phase 3 study	oHCM, NYHA II/III, LVEF ≥60%	HCM phenocopy, history of syncope, sustained VT, or successful SRT within past 6 mo, history of resuscitated sudden cardiac arrest, paroxysmal atrial fibrillation at time of screening, ICD placement within 2 mo, persistent or permanent atrial fibrillation that is uncontrolled or not on anticoagulation	Mavacamten	Post-exercise peak LVOT gradient	KCCQ-CSS, NYHA class reduction ≥1, NT-proBNP, cardiac troponins
MEMENTO NCT06112743 N=100 (estimated) Duration: 48 wk Status: active	Double-blind, placebo-controlled, phase 3b/4 randomized control trial	oHCM, LVEF ≥55%, NYHA II/III	HCM phenocopy, history of obstructive CAD or MI, history of resuscitated sudden cardiac arrest or life-threatening ventricular arrhythmia within 6 mo, ICD or pacemaker or other contraindication for cardiac MRI	Mavacamten vs placebo	Composite of decrease in left atrial volume index of ≥5 mL/m^2 and left ventricular mass index of ≥5 g/m^2	NYHA class reduction ≥1, left atrial volume index, left ventricular mass index, MACE and MACE-expended event incidence, treatment-emergency adverse and serious adverse events and all-cause mortality
NCT06253221 N=40 (estimated) Duration: 28 and up to 56 wk Status: active	Double-blind, placebo-controlled phase 3 trial	Symptomatic oHCM, children 12–17 y old	HCM phenocopy, LVEF <50% in prior 6 mo, planned escalation in HCM therapy	Mavacamten or placebo	Change in peak Valsalva LVOT gradient	Peak resting and post-exercise LVOT gradient, maximal wall thickness, E/e', pVO_2, NYHA class reduction ≥1, mitral regurgitation grade improvement ≥ 1, treatment emergent and serious adverse events, QT interval, LVEF ≤30% and ≤50%, pharmacokinetics

(*Continued*)

Table 1. Continued

Trial Name	Design	Inclusion criteria	Exclusion criteria	Dose and concurrent drugs	Primary outcome	Secondary outcomes
ODYSSEY-HCM NCT05582395 N=420 (estimated) Duration: up to 48 and 120 wk Status: active	Double-blind, placebo-controlled, phase 3 randomized control trial	nHCM, NYHA II/III	HCM phenocopy, history of unexplained syncope or sustained VT within 6 mo	Mavacamten vs placebo	Change from baseline in KCCQ-CSS and change in pVO_2	VE/VCO_2, NT-proBNP, cardiac troponin, HCMSQ, time to first MACE-plus events
Aficamten						
Phase II Trials						
REDWOOD-HCM NCT04219826 N=41 (Cohorts 1–2) N=13 (Cohort 3) N=41 (Cohort 4) Duration: 10 wk Status: completed[20–22]	Double-blind, placebo-controlled, phase 2 randomized control (Cohorts 1–2) or open-label (Cohorts 3–4) trial	oHCM (Cohorts 1–3), nHCM (Cohort 4), NT-proBNP >300 ng/L (Cohort 4), LVEF ≥60%, NYHA II/III	Aortic stenosis or fixed subaortic obstruction, HCM phenocopy, history of LVEF <45%, history of obstructive CAD or MI, treated with SRT (Cohorts 1–3), paroxysmal atrial fibrillation or flutter present at screening, history of syncope or sustained VT within 6 mo	Cohort 1: 5–15 mg aficamten vs placebo; Cohort 2: 10–30 mg aficamten vs placebo; Cohort 3: 5–15 mg aficamten with disopyramide required; Cohort 4: 5–15 mg aficamten. For all, BB and CCB allowed	Incidence of reported adverse events	LVEF <50% incidence, incidence of serious adverse events, resting and Valsalva peak LVOT gradient (for oHCM patients)
FOREST-HCM NCT04848506 N=600 (estimated) Duration: up to 5 y Status: active (preliminary data reported)[23,24]	Open-label, phase 2 study	Completion of REDWOOD-HCM, LVEF ≥55%	Appropriate ICD shock within 30 d, received mavacamten treatment within 56 d, since prior trial completion: development of new-onset paroxysmal or permanent atrial fibrillation requiring rhythm-restoring treatment within 30 d, confirmed LVEF <40% requiring dose interruption on prior study	5–20 mg aficamten with BB, CCB, and disopyramide allowed	Incidence of adverse events	Incidence of serious adverse events, LVEF <50%, peak resting LVOT gradient
Phase III Trials						
SEQUOIA-HCM NCT05186818 N=282 Duration: 24 wk Status: completed[25,26]	Double-blind, placebo-controlled, phase 3 randomized clinical trial	oHCM, NYHA II/III, LVEF ≥60%, hemoglobin ≥10 g/dL, respiratory exchange ratio ≥1.05 and pVO_2 ≤90% predicted on screening CPET	HCM phenocopy, moderate-severe aortic stenosis or mitral regurgitation, LVEF <45%, history of SRT, inability to exercise on a treadmill or bicycle, history of syncope or sustained VT within 6 mo, paroxysmal atrial fibrillation present during screening period, paroxysmal or permanent atrial fibrillation if not rate controlled or on anticoagulation or received rhythm-restoring treatment within 6 mo	5–20 mg aficamten vs placebo with BB, CCB, and disopyramide allowed	pVO_2 change	KCCQ-CSS, NYHA class reduction ≥1, peak post-Valsalva LVOT gradients, total workload change during CPET, duration of SRT eligibility
ACACIA-HCM NCT06081894 N=420 Duration: 72 wk Status: active	Double-blind, placebo-controlled, phase 3 randomized clinical trial	nHCM, LVEF ≥60%, NYHA II/III, respiratory exchange ratio ≥1.00 and pVO2 ≤90% at screening CPET, KCCQ-CSS between 30–85, NT-proBNP ≥300 (sinus rhythm) or ≥900 (atrial fibrillation) ng/L	HCM phenocopy, moderate-severe aortic stenosis or mitral regurgitation, LVEF <45%, history of SRT within 6 mo, inability to exercise on a treadmill or bicycle, history of syncope or sustained VT within 6 mo, history of paroxysmal or persistent atrial fibrillation if uncontrolled, not on anticoagulation or received rhythm-restoring therapy within 3 mo, SpO_2 <90% or DBP >100 at screening	5–20 mg aficamten vs placebo	KCCQ-CSS	Change in composite of two Z-scores of pVO_2 and VE/VCO_2, NYHA class reduction ≥1, NT-proBNP, left atrial volume index, time to first MACE

(*Continued*)

Table 1. Continued

Trial Name	Design	Inclusion criteria	Exclusion criteria	Dose and concurrent drugs	Primary outcome	Secondary outcomes
MAPLE-HCM NCT05767346 N=170 (estimated) Duration: 24 wk Status: active	Double-blind, active-comparator, phase 3 randomized clinical trial	oHCM, NYHA II/III, hemoglobin ≥10 g/dL, off mavacamten for at least 8 wk	HCM phenocopy, moderate-severe aortic stenosis or mitral regurgitation, LVEF <45%, history of SRT within 6 mo, inability to exercise on a treadmill or bicycle, history of syncope or sustained VT within 6 mo, history of paroxysmal or persistent atrial fibrillation or flutter, SpO_2 <90%, SBP >160, or HR >100 at screening, current or recent therapy with disopyramide	5–20 mg aficamten or 50–200 mg metoprolol succinate	Change in pVO_2	NYHA class reduction ≥1, KCCQ-CSS, left ventricular mass index, left atrial volume index, NT-proBNP, peak post-Valsalva LVOT gradient
NCT06116968 N=44 (estimated) Duration: at least 1 y Status: active	Open-label, phase 3 study	Completion of prior aficamten trial, LVEF ≥55%	Appropriate ICD shock within 30 d, received mavacamten treatment, since prior trial completion: development of new-onset paroxysmal or permanent atrial fibrillation requiring rhythm-restoring treatment within 30 d, confirmed LVEF <40% requiring dose interruption on prior study, history of SRT	5–20 mg aficamten	Incidence of reported adverse events, serious adverse events, or LVEF <40%	

For the purposes of this table, all clinical trials planned but not actively enrolling participants were excluded. Additionally, all observational, retrospective studies and all phase I clinical trials were excluded. Clinical trials were identified by the search strategy included in Figure S1. ACACIA-HCM indicates phase 3 trial to evaluate the efficacy and safety of aficamten compared with placebo in adults with symptomatic nHCM; BB, β-blocker; CAD, coronary artery disease; CCB, calcium channel blockers; CPET, cardiopulmonary exercise testing; CSS, Clinical Summary Score; DBP, diastolic blood pressure; DISCOVER-HCM, Deliver Insights in Hypertrophic Cardiomyopathy and Observation Outcomes in Real World; E/e', ratio of peak early mitral inflow velocity over early diastolic mitral annular velocity; EQ-5D-5L, EuroQol 5-dimension 5-level; EXPLORER-CN, A Study to Evaluate the Efficacy and Safety of Mavacamten in Chinese Adults With Symptomatic Obstructive HCM; EXPLORER-HCM, Clinical Study to Evaluate Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy; FOREST-HCM, Follow-Up, Open-Label, Research Evaluation of Sustained Treatment With Aficamten in HCM; HCM, hypertrophic cardiomyopathy; HCMSQ, HCM symptom questionnaire; HORIZON-HCM, A Study of Mavacamten in Obstructive Hypertrophic Cardiomyopathy; HR, heart rate; ICD, implantable cardioverter-defibrillator; KCCQ, Kansas City cardiomyopathy questionnaire; LTE, long-term extension; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MACE, major adverse cardiovascular event; MAPLE-HCM, Metoprolol vs Aficamten in Patients With LVOT Obstruction on Exercise Capacity in HCM; MAVA-LTE, A Long-Term Safety Extension Study of Mavacamten in Adults Who Have Completed MAVERICK-HCM or EXPLORER-HCM; MAVERICK-HCM, The Study of Mavacamten in Adults With Symptomatic Nonobstructive Hypertrophic Cardiomyopathy; MEMENTO, A Study to Evaluate Mavacamten Impact on Myocardial Structure in Participants With Symptomatic Obstructive Hypertrophic Cardiomyopathy; MI, myocardial infarction; MRI, magnetic resonance imaging; nHCM, non-obstructive HCM; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; ODYSSEY-HCM, A Study of Mavacamten in Non-Obstructive Hypertrophic Cardiomyopathy; oHCM, obstructive HCM; OSS, Overall Summary Score; PIONEER-HCM, Pilot Study Evaluating MYK-461 in Subjects With Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction; PIONEER-OLE, Open Label Extension Study of Mavacamten (MYK-461) in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy Previously Enrolled in PIONEER; pVO_2, peak oxygen consumption; REDWOOD-HCM, Randomized Evaluation of Dosing With CD-274 in Obstructive Outflow Disease in HCM; SBP, systolic blood pressure; SEQUOIA-HCM, Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM; SpO_2, blood oxygen saturation; SRT, septal reduction therapy; VALOR-HCM, A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy; VE/VCO_2, ventilation/carbon dioxide production slope; and VT, ventricular tachycardia.

*Cohort of patients with oHCM previously enrolled in the EXPLORER-HCM trial.

†Cohort of patients with nHCM previously enrolled in the MAVERICK-HCM trial.

in EXPLORER-HCM and SEQUOIA-HCM, respectively. Patients in SEQUOIA-HCM were more likely to be non-White (20.1%) compared with VALOR-HCM and EXPLORER-HCM (10.7% versus 8.8%, respectively) and had lower rates of β-blocker usage (61.3%) than VALOR-HCM and EXPLORER-HCM (75.0% versus 75.3%, respectively). pVO_2 baseline levels were also lower in the SEQUOIA-HCM trial related to its design (18.4±4.4 versus 18.6±4.5 mL/kg per minute in the aficamten versus placebo arms, respectively) compared with the EXPLORER-HCM trial (18.9±4.9 versus 19.9±4.9 mL/kg per minute in the mavacamten versus placebo arms, respectively).[11,25,33] Otherwise, baseline characteristics including resting and Valsalva LVOT gradients, cardiac biomarkers, echocardiographic features, and KCCQ-Clinical Summary Scores (CSS) were comparable among these phase III clinical trials.

Efficacy Data

Efficacy data based on CMI (mavacamten or aficamten) are summarized in Table 3 for oHCM and Table S2 for nHCM.

Table 2. Baseline Characteristics for Three Completed, Phase III Randomized Controlled Trials Identified in Hypertrophic Cardiomyopathy

	Mavacamten				Aficamten	
	EXPLORER-HCM[11]		VALOR-HCM[12–13]		SEQUOIA-HCM[25–26]	
	Placebo (n=128)	Mavacamten (n=123)	Placebo (n=56)	Mavacamten (n=56)	Placebo (n=140)	Aficamten (n=142)
Age—years	58.5±11.8	58.5±12.2	60.9±10.6	59.8±14.2	59±13.3	59.2±12.6
Sex						
Male	83 (64.8)	66 (53.7)	28 (50)	29 (51.8)	81 (57.9)	86 (60.6)
Female	45 (35.2)	57 (46.3)	28 (50)	27 (48.2)	59 (42.1)	56 (39.4)
Ethnicity						
Hispanic or Latino	4 (3.1)	8 (6.5)	1 (1.8)	0		
Not Hispanic or Latino	119 (93.0)	114 (92.7)	54 (96.4)	56 (100.0)		
Unknown	5 (3.9)	1 (0.8)	1 (1.8)	0		
Race						
White	114 (89.1)	115 (93.5)	52 (92.9)	48 (85.7)	115 (82.1)	108 (76.1)
Black	5 (3.9)	1 (0.8)	0	3 (5.4)	0	3 (2.1)
Asian	2 (1.6)	4 (3.3)	0	2 (3.6)	25 (17.9)	29 (20.4)
Native American or Alaskan Native	1 (0.8)	0				
Unknown	6 (4.7)	3 (2.4)				
Not Specified			4 (7.1)	3 (5.4)	0	2 (1.4)
Medical History						
Family history of HCM	36 (28.1)	33 (26.8)	15 (26.8)	17 (30.4)	34 (24.3)	41 (28.9)
Hypertension	53 (41.4)	57 (46.3)	34 (60.7)	36 (64.3)	70 (50.0)	75 (52.8)
Atrial fibrillation	23 (18.0)	12 (9.8)	8 (14.3)	11 (19.6)	21 (15.0)	23 (16.2)
Coronary artery disease	6 (4.7)	12 (9.8)			16 (11.4)	19 (13.4)
Background HCM therapy						
Beta-blocker	95 (74.2)	94 (76.4)	39 (69.6)	45 (80.4)	87 (62.1)	86 (60.6)
Calcium-channel blocker	17 (13.3)	25 (20.3)	23 (41.1)	16 (28.6)	36 (25.7)	45 (31.7)
Disopyramide	0	0	8 (14.3)	14 (25.0)	20 (14.3)	16 (11.3)
None	16 (12.5)	4 (3.3)	3 (5.4)	3 (5.4)	22 (15.7)	19 (13.4)
NYHA functional class						
II	95 (74.2)	88 (71.5)	4 (7.1)	4 (7.1)	106 (75.7)	108 (76.1)
III	33 (25.8)	35 (28.4)	52 (92.9)	52 (92.9)	33 (23.6)	34 (23.9)
IV	0	0			1 (0.7)	0
KCCQ-CSS—points	65.7±19.6	67.2±17.2	65.6±19.9	69.5±16.3	74±18	76±18
NT-proBNP—ng/L	616 (108)*	777 (136)*	743 (275-1196)†	724 (291-1913)†	692 (335-1795)†	818 (377-1630)†
Echocardiographic Values						
Resting peak LVOT gradient—mmHg	51±32	52±29	46.3±30.5	51.2±31.4	55.3±32.1	54.8±27
Valsalva peak LVOT gradient—mmHg	74±32	73±32	76.2±29.9	75.3±30.8	83.3±32.7	82.9±32
LVEF—%	74±6	74±6	68.3±3.2	67.9±3.7	74.8±6.3	74.8±5.5
pVO_2—mL/kg/min	19.9±4.9	18.9±4.9			18.6±4.5	
≤18.4 mL/kg/min					67 (47.9)	74 (52.1)
>18.4 mL/kg/min					73 (52.1)	68 (47.9)

All data are reported as mean±standard deviation or number (percentage) unless otherwise specified. Studies selected were identified as completed at the time of our systematic search (e.g., June 11, 2024; please see Figure S1 for more details regarding search strategy). EXPLORER-HCM indicates Clinical Study to Evaluate Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy; HCM, hypertrophic cardiomyopathy; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire—Clinical Summary Score; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; pVO_2, peak oxygen consumption; SEQUOIA-HCM, Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM; and VALOR-HCM, A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy.

*Geometric mean (coefficient of variation %).

†Median (interquartile range).

Table 3. Efficacy Data for Mavacamten and Aficamten in Obstructive Hypertrophic Cardiomyopathy

Trial	Patients	Drug	Duration, Wk	Resting LVOT, mm Hg	Valsalva LVOT, mm Hg	pVO_2, mL/kg/min	VE/VCO_2	SRT Eligibility*	NYHA Class (Improved ≥1)	KCCQ (OSS† vs CSS‡)	NT-proBNP, ng/L	hs-cTnI, ng/L	LVEF, %
Mavacamten Trials													
PIONEER-HCM[9]	21	Mavacamten High-Dose (n=11)	12	BL: 60±28	BL: 97±32	BL: 20.7±7.4	BL: 32.2±5.4		64%	BL: 65±16†	BL: 930±647		BL: 70±7
				Δ: −48±34§	Δ: −85±41§	Δ: 3.5±3.3§	Δ: −2.2±5.5§			Δ: 14±10†,§	Δ: −459±722§		Δ: −15 (−23 to - 6)‖
		Mavacamten Low-Dose (n=10)		BL: 86±63	BL: 100±65	BL: 19.4±4.6	BL: 32.3±4.4		90%	BL: 61±26†	BL: 1834±3209		BL: 75±5
				Δ: −48±48§	Δ: −47±49§	Δ: 1.7±2.3§	Δ: −2.5±2.5§			Δ: 16±22†,§	Δ: −1195±2770§		Δ: −6 (−10 to −1)‖
PIONEER-OLE[10]	13	Mavacamten	48	BL: 67±43	BL: 90±31				69%	BL: 72±19†	BL: 594 (351–1168)		BL: 72±5
				Δ: −53±41	Δ: −66±30					Δ: 16±18†	Δ: −472 (−2467 to −197)		Δ: −2±6
			96	Δ: −56±47	Δ: −63±41				77%	Δ: 16±18†	Δ: −463 (−2441 to −195)		Δ: −6±8
			180	Δ: −50±55	Δ: −70±41				77%	Δ: 17±16†	Δ: −498 (−2184 to −76)		Δ: −6±9
EXPLORER-HCM[11]	251	Placebo (n=128)	30	BL: 51±32	BL: 74±32	BL: 19.9±4.9	BL: 32.4±6.2§		31%	Δ: 4±14‡	BL: 616 (108)¶	BL: 13 (373)¶	BL: 74±6
				Δ: −5#	Δ: −11#	Δ: −0.1±3.0	Δ: 0.4±4.1§				Δ: 1.02§,**	Δ: 0.99§,**	Δ: 0#
		Mavacamten (n=123)		BL: 52±29	BL: 72±32	BL: 18.9±4.9	BL: 33.6±6.2§		65% (P<0.0001)	Δ: 13±14 (P<0.0001)‡	BL: 777 (136)¶	BL: 13 (208)¶	BL: 74±6
				Δ: −38#	Δ: −48#	Δ: 1.4±3.1 (P=0.0006)	Δ: −2.4±4.6 (P<0.0001)§				Δ: 0.2 (P<0.0001)§,**	Δ: 0.58 (P<0.0001)§,**	Δ: −4#
VALOR-HCM[12,13]	112	Placebo (n=56)	16	BL: 46±30	BL: 76±30			BL: 56 (100%)	21%	BL: 66±20‡	BL: 743 (275–1196)	BL: 13 (6–26)	BL: 68±3
				Δ: −2±27	Δ: 0±30			Follow-Up: 43 (76.8%)		Δ: 1.9±12‡	Δ: 40 (−155 to 203)	Δ: 0.1 (−2 to 3)	Δ: 0±4
		Mavacamten (n=56)		BL: 51±31	BL: 75±31			BL: 56 (100%)	63%	BL: 70±16‡	BL: 724 (291–1913)	BL: 17 (7–32)	BL: 68±4
				Δ: −36±29	Δ: −45±29			Follow-Up: 10 (17.9%) (P<0.001)		Δ: 10±16 (P<0.001)‡	Δ: −399(−1146 to −138) (P<0.001)	Δ: −9 (−18 to −2) (P<0.001)	Δ: −3±6 (P=ns)
	108	Placebo-to-Mavacamten (n=52)	56	BL: 47±29	BL: 79±30			BL: 52 (100%)	73%	BL: 67±19‡	BL: 706 (372–1318)	BL: 13 (7–27)	BL: 68±2
				Δ: −33 (−42 to −25)‖	Δ: −55 (−66 to −43)‖			Follow-Up: 10 (19.2%)		Δ: 12 (7–16)‡,‖	Δ: −423 (−624 to −252)††	Δ: −6 (−12 to −3)††	Δ: −4 (−6 to −2)‖
		Mavacamten (n=56)		Δ: −34 (−44 to −25)‖	Δ: −46 (−57 to −35)‖			Follow-Up: 5 (8.9%)	93%	Δ: 14 (10–18)‡,‖	Δ: −376 (−723 to −225)††	Δ: −7 (−10 to −2)††	Δ: −4 (−6 to −3)‖

(*Continued*)

Table 3. Continued

Trial	Patients	Drug	Duration, Wk	Resting LVOT, mm Hg	Valsalva LVOT, mm Hg	pVO_2, mL/kg/min	VE/VCO_2	SRT Eligibility*	NYHA Class (Improved ≥1)	KCCQ (OSS† vs CSS‡)	NT-proBNP, ng/L	hs-cTnI, ng/L	LVEF, %
EXPLORER-CN[14]	81	Placebo (n=27)	30	BL: 73±32	BL: 100±41				15%	BL: 84±17‡	BL: 1250 (160)¶	BL: 39 (443)¶	BL: 77±7
				Δ: 6±34	Δ: 21±46					Δ: −5±3‡,‡‡	Δ: 0.9**	Δ: 1.4**	
		Mavacamten (n=54)		BL: 75±35	BL: 107±43				59% (P<0.001)	BL: 82±17‡	BL: 811 (138)¶	BL: 34 (325)¶	BL: 78±7
				Δ: −51±36	Δ: −58±46					Δ: 5±2 (P<0.001)‡,‡‡	Δ: 0.2 (P<0.001)**	Δ: 0.4 (P<0.001)**	
MAVA-LTE: Explorer Cohort[17–19]	231	Mavacamten	12	BL: 48±32	BL: 69±33				59%		BL: 783 (326–1593)		BL: 74±6
				Δ: −30#	Δ: −36#								
			48	Δ: −36±33	Δ: −45±36				68%		Δ: −480 (−1104 to −179)		Δ: −7±8
			84	Δ: −33±31	Δ: −46±36								
			120	Δ: −35±33	Δ: −47±37				76%		Δ: −458 (−1104 to −566)		Δ: −9±7
			180	Δ: −40±33	Δ: −55±34				78%		Δ: −562 (−1163 to −209)		Δ: −11±9
Aficamten Trials													
REDWOOD-HCM[20]	41	Placebo (n=13)	10	BL: 52±27	BL: 85±21				31%		BL: 532 (129–958)	BL: 8 (3–38)	BL: 75±6
				Δ: −8#	Δ: −9#						Δ: 65 (179)¶	Δ: −2%§§	Δ: 0#
		Aficamten Cohort 1 (n=14)		BL: 54±25	BL: 74±25				43%		BL: 490 (192)¶ Δ: −325 (145)¶ (P<0.001)	BL: 16 (7–83)	BL: 73±6
				Δ: −41 (P=0.0003)#	Δ: −36 (P=0.001)#							Δ: −18% (P=0.29)§§	Δ: −6 (P=0.007)#
		Aficamten Cohort 2 (n=14)		BL: 58±36	BL: 82±37				64%			BL: 8 (5–19)	BL: 75±6
				Δ: −43 (P=0.0004)#	Δ: −52 (P<0.0001)#							Δ: −26% (P=0.097)§§	Δ: −11 (P<0.0001)#
REDWOOD-HCM Cohort 3[21]	13	Aficamten	10	BL: 50±25	BL: 78±27				85%		BL: 1108 (668–2572)	BL: 10 (8–22)	BL: 74±8
				Δ: −27±22 (P<0.0001)	Δ: −28±32 (P<0.0001)						Δ: −43%§§	Δ: −9%§§	Δ: −5 (P=0.018)#
FOREST-HCM[23]	46	Aficamten	48	BL: 52±33	BL: 82±35			BL: 19 (41.3%)	82%		BL: 668 (160)¶		BL: 69±5
				Δ: −40±34	Δ: −53±39			Follow-Up: 1 (2.2%)			Δ: −63%§§		Δ: −5±6

(*Continued*)

Table 3. Continued

Trial	Patients	Drug	Duration, Wk	Resting LVOT, mm Hg	Valsalva LVOT, mm Hg	pVO_2, mL/kg/min	VE/VCO_2	SRT Eligibility*	NYHA Class (Improved ≥1)	KCCQ (OSS† vs CSS‡)	NT-proBNP, ng/L	hs-cTnI, ng/L	LVEF, %
SEQUOIA-HCM[25]	282	Placebo (n=140)	24	BL: 55±32	BL: 83±33	BL: 18.6±4.5		114 (94–135)‖‖	24%	BL: 74±18‡	BL: 692 (335–1795)	BL: 12 (8–25)	BL: 75±6
					Δ: 2 (−4 to 8)‖	Δ: 0.0 (−0.5 to 0.5)‖				Δ: 5 (3–7)‡,‖	Δ: 1.0**		
		Aficamten (n=142)		BL: 55±27	BL: 83±32	BL: 18.4±4.4		37 (27–46) (*P*<0.001)‖‖	59% (*P*<0.001)	BL: 76±18‡	BL: 818 (377–1630)	BL: 13 (8–34)	BL: 75±6
					Δ: −48 (−54 to −41) (*P*<0.001)‖	Δ: 1.8 (1.2–2.3) (*P*<0.001)‖				Δ: 11 (9–14) (*P*<0.001)‡,‖	Δ: 0.2**		

All values provided are mean±SD or median (interquartile range) unless otherwise denoted. Δ indicates change from baseline; BL, baseline; CSS, Clinical Summary Score; EXPLORER-CN, A Study to Evaluate the Efficacy and Safety of Mavacamten in Chinese Adults With Symptomatic Obstructive HCM; EXPLORER-HCM, Clinical Study to Evaluate Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy; FOREST-HCM, Follow-Up, Open-Label Research Evaluation of Sustained Treatment With Aficamten in HCM; hs-cTnI, high-sensitivity cardiac troponin I; KCCQ, Kansas City Cardiomyopathy Questionnaire; 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 MAVERICK-HCM or EXPLORER-HCM; NS, non-significant; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; OSS, Overall Summary Score; PIONEER-HCM, Pilot Study Evaluating MYK-461 in Subjects With Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction; PIONEER-OLE, Open Label Extension Study of Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy Previously Enrolled in PIONEER; pVO_2, peak oxygen consumption; REDWOOD-HCM, Randomized Evaluation of Dosing With CD-274 in Obstructive Outflow Disease in HCM; SEQUOIA-HCM, Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM; SRT, septal-reduction therapy; VALOR-HCM, A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy; and VE/VCO_2, ventilation/carbon dioxide production slope.

*Follow-up data include those still eligible for SRT, those who underwent SRT, or SRT status not evaluable, imputed as meeting criteria, unless otherwise specified.

†Included study reported KCCQ-OSS scores.

‡Included study reported KCCQ-CSS scores.

§Information supplemented with Food and Drug Administration clinical and statistical review.[29]

‖Mean (95 % CI).

¶Geometric mean (coefficient of variation %).

#Difference between the mean baseline value and the mean follow-up duration value.

**Geometric mean ratio.

††Median (95 % CI).

‡‡Least squares mean±SE.

§§Relative reduction.

‖‖Total duration of SRT eligibility during the treatment period in days expressed as mean (95 % CI).

Obstructive HCM

LVOT Obstruction

Both drugs led to substantial reductions in resting and Valsalva LVOT gradients (Table 3).[9–14,17–21,23,25,26] These reductions were evident as early as 4 weeks for mavacamten (first scheduled assessment), with the reported maximum effect occurring by 12 to 16 weeks of treatment.[11,12] For aficamten, LVOT gradient reductions occurred as early as 2 weeks (first scheduled assessment), with the reported maximum effect occurring within 4 to 8 weeks of treatment.[25] Resting and Valsalva LVOT gradients for mavacamten decreased from baseline by −37.6 and −47.6 mm Hg, respectively, by week 30 for the EXPLORER-HCM trial, by −36.0±28.8 and −45.2±28.5 mm Hg, respectively, by week 16 for the VALOR-HCM trial, and by −51.5±36.0 and −57.9±45.6 mm Hg, respectively, by week 30 for the EXPLORER-CN trial. For aficamten, Valsalva LVOT gradient decreased from baseline by a mean of −48 mm Hg (95% CI, −54 to −41); P<0.001) by week 24 for the SEQUOIA-HCM trial.

Exercise Capacity

Both mavacamten and aficamten improved pVO_2 in the EXPLORER-HCM and SEQUOIA-HCM trials, respectively (Table 3).[11,25] Mavacamten had an effect size of 1.4 mL/kg per minute least-squares mean difference [LSMD] (95% CI, 0.6–2.1 mL/kg per minute). Aficamten had an effect size of 1.8 mL/kg per minute LSMD (95% CI, 1.2–2.3 mL/kg per minute). Using the coprimary end point in the EXPLORER-HCM trial of change in pVO_2 ≥1.5 mL/kg per minute with an improvement of ≥1 NYHA class or change in pVO_2 ≥3 mL/kg per minute without worsening NYHA class, 19.4% (95% CI, 8.7%–30.1%) of patients in 30 weeks of treatment met the coprimary end point in EXPLORER-HCM. For aficamten, 28.7% of patients in 24 weeks of treatment met the same coprimary end point of the EXPLORER-HCM trial in the SEQUOIA-HCM trial.[34]

In SEQUOIA-HCM, aficamten was shown to improve pVO_2 independent of β-blocker use, where patients not on a β-blocker had an improvement in pVO_2 of 1.9 mL/kg per minute LSMD (95% CI, 1.0–2.9 mL/kg per minute) compared with 1.6 mL/kg per minute LSMD (95% CI, 0.6–2.5 mL/kg per minute) in patients taking a β-blocker ($P_{interaction}$>0.05).[25,34] In EXPLORER-HCM, patients taking mavacamten not on a β-blocker had a mean change in pVO_2 of 2.2±3.0 mL/kg per minute compared with 1.1±3.1 mL/kg per minute in patients taking a β-blocker ($P_{interaction}$=0.01).[11]

Symptom Burden

KCCQ scores and NYHA class improved significantly in all trials (Table 3). In SEQUOIA-HCM, the effect size for improvement in KCCQ-CSS scores was 7 points LSMD (95% CI, 5–10; P<0.001).[25] For mavacamten, the effect size on KCCQ-CSS was 9.1 points LSMD (95% CI, 5.5–12.7; P<0.0001) in EXPLORER-HCM, and 9.4 points (treatment difference 95% CI, 4.9–14.0; P<0.001) during the placebo-controlled duration of VALOR-HCM. However, in EXPLORER-HCM, 22% and 12% of patients had KCCQ-CSS scores missing at baseline and at week 30, respectively. The FDA conducted sensitivity analyses to account for this degree of missingness, and reported that although there was no tipping point found in the analyses, the effect size for improvement in KCCQ-CSS scores was 4.9 points LSMD (95% CI, 1.3–8.4; P=0.0072) if baseline scores were missing at random, and 5.3 points LSMD (95% CI, 1.7–8.5; P=0.0038) if baseline scores were not missing at random.[29] In SEQUOIA-HCM, 0% and 2.1% of patients had KCCQ-CSS scores missing at baseline and at week 24, respectively, and VALOR-HCM had 0% and 3.6% of KCCQ-CSS scores for patients missing at baseline and at week 16, respectively.[12,25] In VALOR-HCM, the placebo change in KCCQ-CSS was only 1.9±12.0 points, which is divergent from what was seen in both EXPLORER-HCM and SEQUOIA-HCM (4.2±13.7 points and 5 points [95% CI, 3–7], respectively). In the EXPLORER-CN trial, patients on mavacamten had a 5.0-point improvement (SE, 2.1; P<0.001) in KCCQ-CSS scores during the placebo-controlled duration of the trial, but due to a reduction of KCCQ-CSS by 5 points in the placebo group, the effect size was 10.2 points LSMD (95% CI, 4.4–16.1; P<0.001), and missingness was not reported.[11,12,14]

In the VALOR-HCM trial, the treatment difference in improvement in NYHA class ≥1 in those on mavacamten compared with placebo was higher (41.1% [95% CI, 24.5%–57.7%]; P<0.001) compared with the EXPLORER-HCM trial (34% [95% CI, 22%–45%]; P<0.0001) and the SEQUOIA-HCM trial (34.2 [95% CI, 23.4–45.0]; P<0.001). Of note, as above, the mavacamten arm of the VALOR-HCM trial also had a higher percentage of patients with NYHA class III or IV symptoms (92.9%) compared with EXPLORER-HCM (28.5%) or the aficamten arm of the SEQUOIA-HCM trial (23.9%).

Nonobstructive HCM

In nHCM, MAVERICK-HCM was placebo-controlled, whereas MAVA-LTE, REDWOOD-HCM Cohort 4, and FOREST-HCM were open-label studies (Table S2).[15,16,22,24] Both drugs reduced NT-proBNP from baseline, by −435 ng/L (P=0.0005) and −437 (−792 to −201) for mavacamten in MAVERICK-HCM (over 16 weeks) and MAVA-LTE (over 120 weeks), respectively, and by −512 ng/L (P<0.0001) and −666 ng/L (−1244 to −232 ng/L) (P<0.0001) for aficamten in REDWOOD-HCM Cohort 4 (over 10 weeks) and FOREST-HCM (over 36 weeks), respectively. Aficamten

showed improvement in KCCQ-CSS scores (increase of 11±15 points and 14±13 points from baseline in REDWOOD-HCM Cohort 4 [over 10 weeks] and FOREST-HCM [over 36 weeks], respectively) and NYHA class (55% and 79% of patients had an improvement by ≥1 in REDWOOD-HCM Cohort 4 [over 10 weeks] and FOREST-HCM [over 36 weeks], respectively), albeit in an open-label fashion.[22,24] In MAVERICK-HCM, following 16 weeks of treatment, mavacamten improved NYHA class ≥1 in 43% of patients compared with 37% for placebo (P=0.68), and improved KCCQ-CSS scores by 3±9 points compared with 4±16 points for placebo (P=0.96).[15] In MAVA-LTE, mavacamten improved NYHA class ≥1 in 62% during 120 weeks of follow-up, whereas KCCQ-CSS scores were not reported.[16]

Safety Data

Safety data for the percentage of patients who incurred an event of interest during the trial duration are summarized in Table 4 for oHCM and Table S3 for nHCM. Table 5 (for oHCM) and Table S4 (for nHCM) summarize total number of safety events incurred and includes event rates to account for the variable duration of treatment and number of subjects.[9–26]

Obstructive HCM

Treatment-Emergent Adverse Events and Serious Adverse Events

EXPLORER-HCM and VALOR-HCM reported 87.8% and 73.2% of patients on mavacamten experiencing a TEAE over 30 and 16 weeks of treatment, respectively, compared with 78.9% and 60.7% of patients on placebo, respectively (Tables 4 and 5).[11,12] In SEQUOIA-HCM, patients on aficamten reported a TEAE in 73.9% of patients compared with 70.7% of patients on placebo over 24 weeks of treatment.[25] Dizziness was common in the EXPLORER-HCM trial compared with other trials, with 26.8% of patients on mavacamten reporting dizziness compared with 18.0% on placebo, whereas in VALOR-HCM, 7.1% of patients on mavacemten experienced dizziness compared with 5.5% on placebo.[11,12,29] In EXPLORER-HCM, 1.6% and 5.7% of patients on mavacamten experienced a serious adverse event or any adverse event of syncope, respectively, compared with 1.8% of patients experiencing syncope in VALOR-HCM.[11,12,29] In the aficamten arm, SEQUOIA-HCM reported 4.2% of patients experienced dizziness with no reports of syncope.[26]

In the long-term extension trial for mavacamten, MAVA-LTE: Explorer Cohort, TEAEs and serious adverse events occurred in 98.7% and 27.3% of patients, respectively, over a median follow-up of 166 weeks.[19] Of the 117 serious adverse events, 10 were considered related to the study drug (n=3 for cardiac failure, n=5 for LVEF decrease, n=2 for atrial fibrillation or atrial flutter). Long-term extension data for TEAEs and serious adverse events for aficamten from the FOREST-HCM trial are forthcoming.

Heart Failure, LVEF Reduction

In the completed phase III trials, 1.3% of patients were reported to have developed heart failure on mavacamten.[11,12] In EXPLORER-HCM, there were 2 episodes of stress-induced cardiomyopathy in patients receiving mavacamten. In both patients, these events were deemed unrelated to mavacamten therapy. Both had coronary angiograms that did not show evidence of epicardial coronary artery disease. In 1 patient, LVEF was 40% (no baseline provided) and in another, LVEF was 35% (baseline LVEF of 92%). Following the event, both patients resumed treatment without recurrence of cardiac adverse events and enrolled in the MAVA-LTE trial.[29] In MAVA-LTE, 5.6% of patients on mavacamten were reported to develop heart failure without a concurrent reduction in LVEF <50%, whereas 0.4% of patients developed heart failure with a concurrent reduction in LVEF <50% over a median follow-up of 166 weeks.[19] To date, no patients receiving aficamten in oHCM have been reported to develop heart failure or stress cardiomyopathy.[20,21,23,25]

In EXPLORER-HCM, 5.7% of patients on mavacamten had an LVEF <50% over 30 weeks, whereas in VALOR-HCM, 3.6% had an LVEF <50% over 16 weeks of treatment.[11,12] For aficamten, the rate of LVEF <50% was 3.5% in SEQUOIA-HCM over 28 weeks of treatment.[25] MAVA-LTE reported an LVEF <50% in 8.7% of patients on mavacamten over a median follow-up of 166 weeks, whereas FOREST-HCM reported an LVEF <50% in 2 patients (4.3%) on aficamten who completed 48 weeks of treatment.[19,23]

Atrial Fibrillation

EXPLORER-HCM and VALOR-HCM reported 7.7% and 7.1% of patients developed atrial fibrillation on mavacamten, respectively, during the placebo-controlled duration of the trials compared with 6.5% and 0% on placebo, respectively.[11,12] SEQUOIA-HCM reported 2.8% of patients developed atrial fibrillation on aficamten compared with 2.9% on placebo.[25] Of note, 33 events of atrial fibrillation occurred in the EXPLORER Cohort of MAVA-LTE, of which 18 were new-onset atrial fibrillation over a 166-week median follow-up.[19] FOREST-HCM reported 1 event of alcohol-induced atrial fibrillation but has not provided the total number of patients who experienced atrial fibrillation.[23]

In total, among 414 patients on mavacamten with oHCM, there were a total of 53 events of atrial fibrillation, with an event rate of 11.5 per 100 patient-years (Tables 4 and 5). Among 188 patients on aficamten

Table 4. Safety Data for Mavacamten and Aficamten in Obstructive Hypertrophic Cardiomyopathy: Comparison of Patients With Adverse Events

Trial	Patients	Drug	Total Follow-Up Duration, Wk	TEAE, %	AFib TEAE, %	Dizziness, %	SAE, %	AFib SAE, %	Syncope, %	Heart Failure, %	Death, %	LVEF Drop Events <50%, %	Alternative Explanation for LVEF Drop	LVEF Drop with Temporary [or Permanent] Discontinuation, %
PIONEER-HCM9	21	Mavacamten High-Dose (n=11)	16		3 (27.3%)	1 (9.1%)	1 (9.1%)	0			0	4 (36.4%)	1*	
		Mavacamten Low-Dose (n=10)			1 (10.0%)	3 (30.0%)	0	0			0	0	0	
		Total Mavacamten (n=21)			4 (19.0%)	4 (19.0%)	1 (4.8%)	0			0	4 (19.0%)	1*	
PIONEER-OLE[10]	13	Mavacamten	211	13 (100.0%)	1 (7.7%)		5 (38.5%)	0	0	1 (7.7%)	0	1 (7.7%)	0	1 (7.7%) [0]
EXPLORER-HCM[11]	251	Placebo (n=128)	30	101 (78.9%)	9 (7.0%)	23 (18.0%)†	11 (8.5%)	4 (3.1%)	1 (0.8%)	3 (2.3%)	1 (0.8%)	2 (1.6%)	NS‡	2 (1.6%) [0]
		Mavacamten (n=123)		108 (87.8%)	8 (6.5%)	33 (26.8%)†	10 (8.1%)	2 (1.6%)	2 (1.6%)	2 (1.6%)§	0	7 (5.7%)		3 (2.4%) [0]
VALOR-HCM[12–13]	112	Placebo (n=56)	16	34 (60.7%)	0	3 (5.5%)	1 (1.8%)	0	0		0	0	NS‖	0
		Mavacamten (n=56)		41 (73.2%)	4 (7.1%)	4 (7.1%)	3 (5.4%)	2 (3.6%)	1 (1.8%)		0	2 (3.6%)		2 (3.6%) [0]
	108	Placebo-to-Mava (n=52)	56				6 (11.5%)	0		1 (1.9%)	1 (1.9%)	5 (9.6%)		2 (3.8%) [3 (5.7%)]
		Mavacamten (n=56)					4 (7.1%)	3 (5.4%)		0	0	7 (12.5%)		7 (12.5%) [0]
		Total Mavacamten (n=108)¶					10 (9.3%)	3 (2.8%)		1 (0.9%)	1 (0.9%)	12 (11.1%)		9 (8.3%) [3 (2.8%)]
EXPLORER-CN[14]	81	Placebo (n=27)	30	24 (88.9%)	0	2 (7.4%)	0	0		0	0	0	0	0
		Mavacamten (n=54)		45 (83.3%)	2 (3.7%)	7 (13.0%)	4 (7.4%)	2 (3.7%)		0	0	0	0	0
MAVA-LTE: EXPLORER Cohort[17–19]	231	Mavacamten	180	228 (98.7%)#	33 (14.3%)#	41 (17.7%)#	63 (27.3%)#			14 (6.1%)#	5 (2.2%)#	20 (8.7%)#	NS**	15 (6.5%) [5 (2.2%)]#
Total Mavacamten (n=414)										**18 (4.3%)**	**6 (1.4%)**	**44 (10.6%)**		**28 (6.8%) [8 (1.9%)]**
REDWOOD-HCM[20]	41	Placebo (n=13)	12	(88%)	1 (7.7%)		1 (7.7%)	0		1 (7.7%)	0	0	0	0
		Aficamten Cohort 1 (n=14)		21 (75.0%)	0		1 (7.1%)	0		0	0	0	0	0
		Aficamten Cohort 2 (n=14)			0		1 (7.1%)	0		0	0	2 (14.3%)	NS††	0
		Total Aficamten (n=28)			0		2 (7.1%)	0		0	0	2 (7.1%)		0
REDWOOD-HCM Cohort 3[21]	13	Aficamten	12		0		0	0		0	0	0	0	0

(*Continued*)

Table 4. Continued

Trial	Patients	Drug	Total Follow-Up Duration, Wk	TEAE, %	AFib TEAE, %	Dizziness, %	SAE, %	AFib SAE, %	Syncope, %	Heart Failure, %	Death, %	LVEF Drop Events <50%, %	Alternative Explanation for LVEF Drop	LVEF Drop with Temporary [or Permanent] Discontinuation, %
FOREST-HCM[23]	46	Aficamten	48									2 (4.3%)	1 (2.2%)[‡‡]	1 (2.2%) [0]
SEQUOIA-HCM[25,26]	282	Placebo (n=140)	28	99 (70.7%)	4 (2.9%)	2 (1.4%)	13 (9.3%)	1 (0.7%)	1 (0.7%)	1 (0.7%)	0	1 (0.7%)	NS[§§]	0
		Aficamten (n=142)		105 (73.9%)	4 (2.8%)	6 (4.2%)	8 (5.6%)	1 (0.7%)		0	0	5 (3.5%)		0
Total Aficamten (n=188)										**0**	**0**	**9 (4.8%)**		**1 (0.5%) [0]**

AFib indicates atrial fibrillation; EXPLORER-CN, A Study to Evaluate the Efficacy and Safety of Mavacamten in Chinese Adults With Symptomatic Obstructive HCM; EXPLORER-HCM, Clinical Study to Evaluate Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy; FOREST-HCM, Follow-Up, Open-Label Research Evaluation of Sustained Treatment With Aficamten in HCM; LVEF, left ventricular ejection fraction; MAVA-LTE, A Long-Term Safety Extension Study of Mavacamten in Adults Who Have Completed MAVERICK-HCM or EXPLORER-HCM; NS, not specified; PIONEER-HCM, Pilot Study Evaluating MYK-461 in Subjects With Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction; PIONEER-OLE, Open Label Extension Study of Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy Previously Enrolled in PIONEER; REDWOOD-HCM, Randomized Evaluation of Dosing With CD-274 in Obstructive Outflow Disease in HCM; SAE, serious adverse event; SEQUOIA-HCM, Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM; TEAE, treatment-emergent adverse event; and VALOR-HCM, A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy.

*1 patient with LVEF drop unrelated to mavacamten and no further description given.

†Based on information gathered from the US Federal Drug Administration (FDA) Clinical and Statistical Review of Mavacamten.[29]

‡Not specified whether LVEF drops were related to drug. Occurred during treatment period in 5 patients (2 placebo, 3 mavacamten) prompting temporary treatment discontinuation with subsequent normalization of LVEF, after which treatment was resumed. Four patients in mavacamten arm had LVEF drop at week 30, 3 of which recovered in 8-week washout period. 1 patient had a severe LVEF drop following atrial fibrillation ablation during washout period followed by partial recovery to LVEF of 50%.

§Notably, it did not appear to include patients with reported stress cardiomyopathy.

‖Not specified whether LVEF drops were related to the drug, but most appear to be related based on the description. In one patient, LVEF<50% on two repeat measures prompted permanent discontinuation. One patient had heart failure with AFib; LVEF normalized after cardioversion and drug discontinuation. One patient died shortly after being noted with LVEF <30%, prompting drug discontinuation. In nine other patients, all patients had improvement of LVEF on lower drug doses. None of these 9 were symptomatic.

¶Summation of total mavacamten events includes summation of the placebo-to-mavacamten group and mavacamten group for the entirety of the 56-week duration.

#Data included up to week 180, based on manuscript with reported data cutoff for interim analysis of August 31, 2023.[19]

**Not specified whether LVEF reductions were related to study drug. 2, 5, 12, and 3 patients were receiving mavacamten doses of 2.5, 5, 10, and 15 mg, respectively. 40% of the patients had intercurrent atrial fibrillation or flutter at the time of the event.[19] Based on data included up to week 120 with reported data cutoff for interim analysis of May 31, 2022, 5 of the 13 patients who had an LVEF <50% had an alternative explanation. The median dose associated with LVEF drop <50% was 10 mg. 6 patients had intercurrent illness at the LVEF reduction event (5 AFib/AFlutter, 1 exacerbated hypertension), but it was not specified whether these intercurrent illnesses were mavacamten-related or not. All patients LVEF recovered >50% after drug discontinuation. Of note, two patients with LVEF drop were noted to have mavacamten concentration ≥1000 ng/mL.[17]

††Not specified whether LVEF drops were related to the drug. One patient required a per-protocol dose reduction for an LVEF of 43% with a resultant increase in LVEF; one patient had an LVEF of 49% at the end of treatment.

‡‡One patient developed recurrent alcohol-induced atrial fibrillation; temporary treatment discontinuation occurred at the time of cardioversion and rhythm control.

§§Not specified whether LVEF drops were related to the drug, although all patients had a return to baseline LVEF after the washout of the trial drug.

Table 5. Safety Data for Mavacamten and Aficamten in Obstructive Hypertrophic Cardiomyopathy: Comparison of Adverse Event Rates (Per 100 Patient-Years)

Trial	Patients	Drug	Follow-Up Duration*	Median Follow-Up*	TEAE Events	TEAE ER*	AFib TEAE Events	TEAE AFib ER*	SAE Events	SAE ER*	AFib SAE Events	SAE AFib ER*	Heart Failure Events†	Heart Failure ER*	LVEF Reduction <50% Events	LVEF Reduction ER*
PIONEER-HCM[9]	21	Mavacamten High-Dose (n=11)	16		62	1832			1	29.5	1	29.5			4	118.2
		Mavacamten Low-Dose (n=10)			59	1918			0	0.0	0	0.0			0	0.0
		Total Mavacamten (n=21)			121	1873	5‡	77.4	1	15.5	1	15.5			4	61.9
PIONEER-OLE[10]	13	Mavacamten	211	201	144	287	1	2.0	6	11.9	0	0.0	1	2.0	1	2.0
EXPLORER-HCM[11]	251	Placebo (n=128)	30		425	576	9§	12.2	20	27.1	4§		3§	4.1	2	2.7
		Mavacamten (n=123)			419	590	8§	11.3	11	15.5	2§		2§	2.8	7	9.9
VALOR-HCM[12–13]	112	Placebo (n=56)	16		93	540	0§	0.0	1	5.8	0	0.0			0	0.0
		Mavacamten (n=56)			123	714	4§	23.2	4	23.2	2§	11.6			2	11.6
	108	Placebo-to-Mava (n=52)	56						6§	10.7	0§	0.0	1§	1.8	5	8.9
		Mavacamten (n=56)							4§	6.6	3§	5.0	0§	0.0	7	11.6
		Total Mavacamten (n=108)‖							10§	8.6	3§	2.6	1§	0.9	12	10.3
EXPLORER-CN[14]	81	Placebo (n=27)	30		82	526	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Mavacamten (n=54)			165	530	2	6.2	8	25.7	2	6.4	0	0.0	0	0.0
MAVA-LTE: EXPLORER Cohort[17–19]	231	Mavacamten	120¶ 180**	62.3¶ 166**	1870**	254**	33§,**	4.5**	117**	15.9**	8§,¶	2.9¶	14§,**	1.9**	20**	2.7**
Total Placebo (n=211)					**600**	**560**	**9**	**7.4**	**21**	**18.0**	**4**	**3.3**	**3**	**3.4**	**2**	**1.6**
Total Mavacamten (n=414)					**2842**	**488**	**53**	**11.5**	**153**	**15.2**	**16**	**3.6**	**18**	**1.7**	**44**	**7.8**
REDWOOD-HCM[20]	41	Placebo (n=13)	12		40	1333	1	33.3	5	166.7	0	0.0	1	33.3	0	0.0
		Aficamten Cohort 1 (n=14)			33	1021	0	0.0	1	31.0	0	0.0	0	0.0	0	0.0
		Aficamten Cohort 2 (n=14)			26	805	0	0.0	1	31.0	0	0.0	0	0.0	2	61.9
		Total Aficamten (n=28)			59	913	0	0.0	2	31.0	0	0.0	0	0.0	2	31.0
REDWOOD-HCM Cohort 3[21]	13	Aficamten	12				0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FOREST-HCM[23]	46	Aficamten	48												3	7.1
SEQUOIA-HCM[25–26]	282	Placebo (n=140)	28				4§	5.3	13§	17.2	1§	1.3	1§	1.3	1	1.3
		Aficamten (n=142)					4§	5.2	8§	10.5	1§	1.3	0	0.0	5	6.5

(*Continued*)

Table 5. Continued

Trial	Patients	Drug	Follow-Up Duration*	Median Follow-Up*	TEAE Events	TEAE ER*	AFib TEAE Events	TEAE AFib ER*	SAE Events	SAE ER*	AFib SAE Events	SAE AFib ER*	Heart Failure Events†	Heart Failure ER*	LVEF Reduction <50% Events	LVEF Reduction ER*
Total Placebo (n=153)					40	1333	5	7.7	18	29.9	1	1.2	2	4.0	1	1.2
Total Aficamten (n=188)					59	913	4	4.1	10	12.9	1	1.0	0	0.0	10	9.3

AFib indicates atrial fibrillation; ER, event rate; EXPLORER-CN, A Study to Evaluate the Efficacy and Safety of Mavacamten in Chinese Adults With Symptomatic Obstructive HCM; EXPLORER-HCM, Clinical Study to Evaluate Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy; FOREST-HCM, Follow-Up, Open-Label Research Evaluation of Sustained Treatment With Aficamten in HCM; LVEF, left ventricular ejection fraction; MAVA-LTE, A Long-Term Safety Extension Study of Mavacamten in Adults Who Have Completed MAVERICK-HCM or EXPLORER-HCM; NS, not specified; PIONEER-HCM, Pilot Study Evaluating MYK-461 in Subjects With Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction; PIONEER-OLE, Open Label Extension Study of Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy Previously Enrolled in PIONEER; REDWOOD-HCM, Randomized Evaluation of Dosing With CD-274 in Obstructive Outflow Disease in HCM; SAE, serious adverse event; SEQUOIA-HCM, Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM; TEAE, treatment-emergent adverse event; and VALOR-HCM, A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy.

*Of note, all event rates were calculated utilizing the median patient follow-up duration as able. If the median follow-up duration was not reported or could not be calculated, total follow-up duration was used as a surrogate. Follow-up durations were measured in weeks. Calculations are represented per 100 patient-years.

†Heart failure (or cardiac failure) was reported as specified in each individual trial. Some trials appeared to define cardiac failure as SAEs of heart failure leading to hospitalization, whereas other trials included non-serious TEAEs of cardiac failure as well.

‡Reported as five events that were possibly related to mavacamten. It is unclear whether additional events of atrial fibrillation occurred that were deemed unrelated to mavacamten.

§Based on the number of patients reported with the event of interest. It may not be accounting for events that may have occurred multiple times in the same patient.

‖Summation of total mavacamten events includes summation of the placebo-to-mavacamten group and mavacamten group for the entirety of the 56-week duration.

¶Data included up to week 120, based on manuscript with reported data cutoff for interim analysis of August 31, 2021.[18]

**Data included up to Week 180, based on publication with reported data cutoff of August 31, 2023.[19]

with oHCM, there were 4 events of atrial fibrillation, with an event rate of 4.1 per 100 patient-years.

Treatment Dose Adjustments and Discontinuation

In EXPLORER-HCM, 10 (8.1%) patients (7 [5.7%] due to LVEF <50% and 3 [2.4%] due to QT interval corrected for heart rate using Fridericia's formula prolongation) on mavacamten had temporary treatment discontinuation over 30 weeks of treatment.[11] Additionally, 2 (1.6%) patients permanently discontinued mavacamten due to adverse events of new-onset syncope and new-onset atrial fibrillation. EXPLORER-HCM also reported 17 (13.8%) patients who required dose reductions due to elevated mavacamten pharmacokinetic levels, 3 (2.4%) of whom also had concurrent LVEF <50%. In total, 26 (21.1%) patients on mavacamten in EXPLORER-HCM had dose-titration or temporary or permanent discontinuation of mavacamten.[29] In VALOR-HCM, 2 (3.6%) patients and 12 (11.1%) patients were reported to require temporary drug discontinuation due to LVEF <50% over 16 and 56 weeks, respectively.[12] Three (2.8%) patients required permanent discontinuation of mavacamten, 2 (1.9%) of whom had LVEF <30%, and 1 (0.9%) of whom had an LVEF <50% on 2 separate instances over 56 weeks of treatment. In SEQUOIA-HCM, no treatment discontinuations due to instances of LVEF <50% occurred in the 28 weeks of safety data, whereas 7 (4.9%) patients required echocardiography-guided down-titration of aficamten (per protocol for LVEF 40%–49%, aficamten was down-titrated rather than discontinued).[25] Additionally, only 1 (0.7%) patient permanently discontinued aficamten related to an adverse event (paranoia) in SEQUOIA-HCM. Notably, dosing was determined by site-read echocardiograms in SEQUOIA-HCM compared with core laboratory-read echocardiograms in EXPLORER-HCM and VALOR-HCM.

In the EXPLORER Cohort of MAVA-LTE, over a median follow-up of 166 weeks, 20 (8.7%) patients required treatment discontinuation of mavacamten for an LVEF <50%, 6 (2.6%) of whom had an LVEF <40%, and 5 (2.2%) of whom permanently discontinued treatment and were not re-enrolled at a later date. In total, 20 (8.7%) patients underwent permanent treatment discontinuation. Additionally, a total of 10 (4.3%) patients required temporary treatment discontinuation due to elevated mavacamten pharmacokinetic levels >1000 ng/mL before its removal from the trial protocol as a stoppage criterion.[19] In the FOREST-HCM trial, 1 (2.2%) patient had a temporary dose interruption in the setting of an LVEF <50% and alcohol-induced atrial fibrillation.[23] In all trials of aficamten, pharmacokinetic level has not been used for clinical decision-making. As such, there are no data on interventions related to pharmacokinetics in aficamten trials.

In total, trials of mavacamten in patients with oHCM showed that there were 36 instances of temporary (n=28) or permanent (n=8) discontinuation of mavacamten in 414 total patients due to LVEF reductions.[9–14,17–19] It is unclear how many of these events occurred in the same individual. Trials of aficamten in patients with oHCM demonstrated 1 incidence prompting temporary (and no incidents prompting permanent) treatment discontinuation in the setting of LVEF reductions. Drug levels (pharmacokinetics) were not used for clinical decision-making in any of the aficamten trials, and there were no reported episodes of dose adjustments or treatment discontinuation from QT interval corrected for heart rate using Fridericia's formula prolongation for patients on aficamten.[20,21,23,25]

Death

There were 5 (2.2%) deaths in MAVA-LTE and 1 (0.9%) in VALOR-HCM while receiving mavacamten.[13,16] In MAVA-LTE, all 5 deaths were deemed to be unrelated to mavacamten (due to bacterial endocarditis at week 16, acute myocardial infarction at approximately week 57, cardiac arrest at week 73, progression of liver metastases and cholangitis [week unspecified], and intracranial hemorrhage [week unspecified]).[16,19,29] In VALOR-HCM, 1 (0.9%) patient died of sudden cardiac death at approximately week 57, within 1 week after the last dose of mavacamten in the setting of an LVEF <30%.[13] This patient was felt to be asymptomatic without signs of heart failure at their week 56 follow-up, and mavacamten was permanently discontinued. Three days later, they were evaluated by a pulmonologist for mild asthma, and 4 days later they died due to sudden cardiac death with autopsy showing pulmonary fibrosis and pneumonia without evidence of myocardial infarction or aortic dissection. In oHCM, there were no patients on aficamten therapy who died.[20,21,23,25]

Nonobstructive HCM

Treatment-Emergent Adverse Events

A higher proportion of patients reported TEAEs (89.7%) and dizziness (17.9%) in the mavacamten arm of MAVERICK-HCM compared with placebo (68.4% experienced TEAEs and 5.3% experienced dizziness) (Tables S3 and S4).[15] In MAVA-LTE: MAVERICK Cohort, nearly all (97.7%) patients reported TEAEs on mavacamten therapy.[16] In REDWOOD-HCM Cohort 4 and FOREST-HCM, 2 open-label studies of aficamten in nHCM, 68.3% and 88.2% of patients reported TEAEs, respectively.[22,24] In REDWOOD-HCM Cohort, 49.8% of patients reported dizziness, and 2.9% of patients reported dizziness in FOREST-HCM.

Heart Failure, LVEF Reduction, and Treatment Dose Discontinuations

In nHCM using predetermined drug level (pharmacokinetic) targets, MAVERICK-HCM had a 12.8% incidence of LVEF <45% (compared with none in placebo) over 16 weeks of treatment, whereas the incidence of LVEF <50% was as high as 27.3% over a median follow-up of 146 weeks for the long-term extension of MAVERICK-HCM (MAVA-LTE: MAVERICK Cohort).[15,16] In mavacamten trials in nHCM, there were 17 instances of temporary (n=11) or permanent (n=6) discontinuation of mavacamten related to reductions in LVEF in 40 patients receiving mavacamten in MAVERICK-HCM and 44 patients (overlapping) receiving mavacamten in the MAVERICK Cohort of MAVA-LTE. For aficamten in nHCM, 7.3% and 5.9% of patients developed an LVEF <50% over 10 and 36 weeks of treatment in REDWOOD-HCM Cohort 4 and FOREST-HCM, respectively, using a purely echocardiogram-guided strategy without the use of pharmacokinetics.[22,24] Of these, only 1 (2.4%) patient required temporary (and none required permanent) treatment discontinuation related to the reductions in LVEF. All of the events of LVEF <50% in aficamten trails of nHCM occurred in the setting of atrial fibrillation.

Atrial Fibrillation

In MAVERICK-HCM over a 24-week safety period, 7.7% of patients on mavacamten had atrial fibrillation compared with 5.3% on placebo.[15] In the MAVERICK Cohort of MAVA-LTE, rates of atrial fibrillation were not reported. In REDWOOD-HCM Cohort 4 (12 weeks), 2.4% of patients had atrial fibrillation, and in the FOREST-HCM trial (36 weeks), 5.1% of patients had atrial fibrillation.[22,24]

Death

No deaths have been reported in patients on mavacamten therapy in nHCM.[15,16] There was 1 (2.4%) death in REDWOOD-HCM Cohort 4 in a patient receiving aficamten. The patient, who had a history of aborted sudden cardiac death and long-QT syndrome before participation in the study, experienced a fatal arrhythmia at week 6 that was not terminated by the patient's internal-cardioverter defibrillator. The patient had a visit a few days before the event where all assessments were conducted per protocol without unexpected findings. This was reported as unrelated to aficamten.[22]

DISCUSSION

Both mavacamten and aficamten showed significant benefit in reducing LVOT obstruction, symptom burden, and cardiac biomarkers while improving exercise capacity in oHCM.[9–14,17–21,23,25,26] Although both drugs show a promising safety profile, mavacamten trials appeared to have more frequent events of dizziness, syncope, heart failure, atrial fibrillation, and LVEF reductions <50% prompting temporary or permanent

treatment discontinuation. The similarities in the enrolled populations in phase III trials and the reasonably close follow-up duration allow for rigorous comparisons of safety and efficacy. However, although both drugs have 5-year long-term extension trials ongoing, due to the earlier development of mavacamten, there is longer exposure to it compared with aficamten. As such, the data presented here should be put in context of different treatment-exposure times. Additionally, it should be noted that despite exhaustive efforts undertaken to account for slight variations in treatment duration, length of follow-up, study design, and included patient populations when comparing these trials, cross-trial comparisons are inherently fraught with limitations. As CMIs gain favor in the treatment of HCM, head-to-head trials in oHCM and nHCM may be necessary to confirm differences in efficacy and safety between the 2 drugs.

Efficacy

The 2 pivotal trials of mavacamten and aficamten (EXPLORER-HCM and SEQUOIA-HCM, respectively) used cardiopulmonary exercise testing and NYHA class as part of their primary and secondary end points.[11,25] In these trials, both CMIs showed substantial improvement in exercise capacity and symptom burden in oHCM. However, in the SEQUOIA-HCM trial, aficamten's placebo-corrected effect size on categorical pVO_2 and NYHA class change was 28.7% compared with 19.4% for mavacamten in the EXPLORER-HCM trial.[11,34] These differences are driven by the higher effect size of aficamten on pVO_2 (LSMD of 1.8 [95% CI, 1.2–2.3] mL/kg per minute) compared with mavacamten (LSMD of 1.4 [95% CI, 0.6–2.1] mL/kg per minute). The higher LSMD and narrower confidence interval meant a larger proportion of patients improved their pVO_2 to ≥1.0 mL/kg per minute on aficamten, which is the accepted minimum clinical change associated with reduction in the risk for all-cause and cardiovascular mortality and all-cause hospitalizations among patients with heart failure and in HCM.[35–37] Although it may not be practical, a head-to-head clinical trial would be needed to confirm these differences in effect size. Nevertheless, improvements in exercise capacity and symptom burden for both CMIs were significantly more robust than those demonstrated for placebo on the background of conventional pharmacologic therapies (disopyramide was not allowed in EXPLORER-HCM).[3–5] The observed large effect size of CMIs on symptoms, function, and quality of life will likely have downstream benefits in improving adherence and compliance to these therapies in real-world settings.

Additionally, a distinct observation in the SEQUOIA-HCM trial is that the improvement in pVO_2 was consistent across all subgroups including patients on β-blockers at baseline.[25] In EXPLORER-HCM, patients on β-blockers derived less benefit from mavacamten compared with patients not on β-blockers.[11] This could simply be a chance finding in EXPLORER-HCM due to the small sample size (62 patients [24.7%] were not on β-blocker therapy) compared with SEQUOIA-HCM (109 patients [38.7%] were not on β-blocker therapy), or it may signal a possible heterogeneity of treatment effect based on concomitant β-blocker use, which is currently the recommended first-line therapy in oHCM.[2,38] The FDA review of mavacamten focused on this heterogeneity of effect based on β-blocker use in EXPLORER-HCM and concluded that it was unclear if this was a true treatment effect or not.[29] More studies are needed to confirm these findings and to better understand the relationship between mavacamten and β-blocker use, because the guidelines currently recommend mavacamten as a second-line therapy in patients who continue to be symptomatic on β-blockers or calcium channel blockers.[2,39]

Both CMIs led to significant improvement in LVOT gradients in oHCM, where Valsalva LVOT gradient on mavacamten improved by −65% and −60% for EXPLORER-HCM and VALOR-HCM, respectively, compared with −58% for aficamten in SEQUIOA-HCM.[11,12,25] The magnitude of improvement in LVOT gradients appeared consistent across trials and was maintained throughout the maintenance periods of these trials.

In terms of patient-reported outcomes, KCCQ-CSS improved significantly across all CMI phase III trials.[11,12,14,25] As presented in the Results at length, there are certain nuances to the interpretation of KCCQ-CSS data from various trials, including completeness of data, as well as placebo group response. For example, KCCQ-CSS decreased by almost 5 points in the placebo cohort of EXPLORER-CN, whereas it remained unchanged or improved in placebo cohorts of EXPLORER-HCM and SEQUOIA-HCM. HCM is a chronic illness that does not typically progress rapidly over a short period of time, and patients who use oral placebo typically report improvement rather than decline. The findings across trials are reassuring that patients generally feel better on CMIs. Further responder analyses are required to understand the drivers of improved patient-reported outcomes and if reduction in LVOT gradient is the primary driver of that improvement.

In nHCM, the CMI safety and efficacy data are derived from small phase II trials and open-label extension from these trials. Arguably, patients with symptomatic nHCM are the most in need of a therapy that improves their symptoms and exercise capacity. The 2024 guidelines recommend β-blockers as first-line therapy for symptomatic nHCM.[2] However, this is based on extrapolation of data from oHCM, where a

recent trial showed that metoprolol reduces LVOT gradients and improves symptoms without improvements in filling pressures, exercise capacity, or pVO_2.[2,3] As such, in nHCM, the current available therapies do not have robust evidence behind their use.[2,40,41]

In the available phase II trial data, patients on mavacamten in MAVERICK-HCM did not have an improvement in NYHA class or KCCQ-CSS scores compared with placebo.[15] However, its long-term extension study, MAVA-LTE: MAVERICK Cohort, has demonstrated higher rates of improvement in NYHA class (62% of patients with NYHA class ≥1) over longer-term exposure, although in an open-label fashion.[16] For aficamten, in the open-label trials REDWOOD-HCM Cohort 4 and its extension in FOREST-HCM, KCCQ-CSS scores improved by 11±15 points and 14±13 points over 10 and 36 weeks, respectively, which is comparable to the improvements seen in the phase III clinical trials on both CMIs in oHCM, not accounting for placebo effect, which ranges between 3 and 6 points in oHCM.[11,12,14,22,24,25] Additionally, NYHA class improvement ≥1 occurred in 55% and 79% of patients in REDWOOD-HCM Cohort 4 and FOREST-HCM over 10 and 36 weeks of treatment, respectively.[22,24] These results from the phase II trials are encouraging, and when combined with the safety and effectiveness of CMIs in oHCM, they paint the pathway forward for the use of CMIs in nHCM. Two large phase III CMI trials are ongoing in nHCM, ODYSSEY-HCM (A Study of Mavacamten in Non-Obstructive Hypertrophic Cardiomyopathy; NCT05582395) with mavacamten, and ACACIA-HCM (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults with Symptomatic nHCM; NCT06081894) with aficamten, which will define CMI efficacy (including assessments of symptom burden and exercise capacity) and safety in this population. Given the significant unmet need in nHCM, the collective data to date and those being generated will hopefully address these needs.

Safety

CMIs mechanism of action is enabled by reducing the pathological hypercontractility in HCM, which results in a modest reduction in LVEF.[6] However, it is likely the individual CMI's properties drive the incidence of exaggerated or unpredictable LV response. Based on available data, aficamten may have a more favorable safety profile compared with mavacamten based on its metabolism and its predictable drug level to LVEF reduction (pharmacokinetic/pharmacodynamic) relationship.[26] Table S5 provides a thorough comparison of available pharmacology data for mavacamten and aficamten that demonstrate aficamten's wider therapeutic window, shorter half-life, and more favorable CYP profile with reduced DDI potential as compared with mavacamten.[27,30,42,43]

Mavacamten is metabolized mainly by CYP2C19 and CYP3A4, with a relatively long half-life (6–9 days in normal CYP2C19 metabolizers and up to 23 days for poor metabolizers) and elimination time (approximately 45 days in normal CYP2C19 metabolizers and up to 115 days in poor metabolizers), which also introduces complexities related to frequent DDIs (Figure S2).[27,28,44] For this reason, all mavacamten trials (except VALOR-HCM and the amended MAVA-LTE) required pharmacokinetic monitoring (eg, assessment of mavacamten plasma concentrations) to guide dosing adjustments. In VALOR-HCM, the incidence of LVEF <50% was higher than that in EXPLORER-HCM.[11,13] Although patients in VALOR-HCM were referred for septal reduction therapy, the baseline characteristics of patients in VALOR-HCM were similar to patients in EXPLORER-HCM, except for a higher prevalence of NYHA class III symptoms (92.9% versus 27.1%, respectively). Having NYHA class III symptoms is not a reliable, repeatable measure of disease severity when compared with patients with NYHA class II symptoms.[45] An objective measure, NT-proBNP, was similar among patients receiving mavacamten in VALOR-HCM (median NT-proBNP of 724 ng/L) and EXPLORER-HCM (geometric mean of 777 ng/L) at baseline. Due to the impractical implementation of drug level (pharmacokinetic) monitoring clinically, the FDA and other regulators have not required it for therapeutic monitoring of mavacamten. Rather, regulators recommended surrogates such as intense echocardiography-guided monitoring and forced down-titration protocol using Valsalva LVOT gradient in the first 8 weeks of starting mavacamten (FDA) or CYP2C19 genotyping before therapy initiation (European Medicines Agency).[28,29] Of note, pharmacokinetic/pharmacodynamic data from EXPLORER-HCM, VALOR-HCM, and MAVA-LTE have not been published with the trials data.

The recommendation for CYP2C19 genotyping from the European Medicines Agency is predicated largely on surrogate data rather than clinical events. First, CYP2C19 poor metabolizers have shown higher maximum concentrations and areas under the curve after a single dose of mavacamten compared with normal metabolizers, which theoretically increases their risk for deleterious side effects.[29] Additionally, PIONEER-HCM demonstrated that mavacamten plasma concentrations ≥1000 ng/mL were associated with exaggerated reductions in LVEF beyond what was required to eliminate the LVOT gradient.[9] As such, concern remains that poor metabolizers may be at increased risk for systolic dysfunction after receiving mavacamten given their prolonged elimination time and the FDA review suggesting that EXPLORER-HCM demonstrated evidence for possible cumulative effects of mavacamten exposure.[29] In EXPLORER-HCM, 2 patients (1 of whom was 1 of only 5 CYP2C19 poor metabolizers

included in the study) demonstrated elevated mavacamten plasma concentrations and a LVEF <50% at week 30 despite no up-titration of mavacamten being allowed after week 14.[11,29] Among the 10 patients with a mavacamten level (pharmacokinetics) ≥1000 ng/mL prompting temporary treatment discontinuation in the MAVA-LTE: EXPLORER Cohort, 6 were CYP2C19 intermediate metabolizers, and 2 had a concurrent reduction in LVEF <50%.[29] Despite these data, clinical mavacamten level (pharmacokinetic) monitoring was discontinued in the amended MAVA-LTE, and the latest long-term follow-up data did not show a significant increase in the incidence of LVEF <50% events.[18,19]

EXPLORER-CN assessed mavacamten safety and efficacy under pharmacokinetic parameters in a Chinese oHCM population with higher rates of intermediate-to-poor CYP2C19 metabolizer status (60.5% of the total patients in comparison with the 27.5% of total patients in the EXPLORER-HCM trial).[14,29] In this 30-week study, only 1 patient (a CYP2C19 intermediate metabolizer) developed mavacamten pharmacokinetic levels ≥1000 ng/mL, and no patients developed an LVEF <50%. However, the dosing regimen for EXPLORER-CN was adapted to enable a safer strategy compared with EXPLORER-HCM and VALOR-HCM. Patients in EXPLORER-CN were started on a lower dose (2.5 mg) of mavacamten (compared with 5 mg in the other trials) and were allowed doses as low as 1 mg (compared with a minimum of 2.5 mg in the other trials). Patients in EXPLORER-CN also achieved lower overall doses at the study end. In EXPLORER-CN, 59% of patients were on a dose of 5-mg or less by the end of the study at week 30, and no patients were at a dose of 15-mg. In contrast, 49% and 45% of patients in EXPLORER-HCM and VALOR-HCM were on dose ≤5 mg by the end of the study at week 30 and week 16, respectively, and 11% and 21% were at a dose of 15 mg, respectively.[11,12,14,46] As such, although EXPLORER-CN did demonstrate safety of use for mavacamten in a population at higher risk for toxicity, its dosing regimen impacts study comparability and extrapolation of the effect of mavacamten on functional capacity.

Aficamten was shown to have a consistent linear drug level to LVEF effect (pharmacokinetic/pharmacodynamic relationship), as was confirmed in multiple trials, with multiple metabolism pathways significantly reducing its DDI potential and to date eliminating any need for metabolizer genotyping and exhaustive medications review, which simplifies the prescribing process for physicians.[26,30] Additionally, aficamten has a shorter half-life (3.5 days), which allows for more rapid up-titration of the study drug, where phase III clinical trials allowed dose increases every 2 weeks for aficamten compared with every 4 to 6 weeks for mavacamten.[11,12,14,25,30] These properties of aficamten might enable a simpler implementation approach in clinical practice. The safety of aficamten was demonstrated in both the SEQUOIA-HCM trial, where 5 (3.5%) patients had an LVEF <50% without aficamten discontinuation, and in subsequent integrated safety analyses, where safety profiles were similar for aficamten compared with placebo and were consistent over an extended duration of treatment.[34,47] Aficamten trials did not use clinical pharmacokinetic monitoring, which cross-trial comparisons should take into account when evaluating safety. In this setting, VALOR-HCM represents a more practical comparative to SEQUOIA-HCM than EXPLORER-HCM. In the EXPLORER-HCM trial, 14 (11.4%) patients underwent dose adjustments based on pharmacokinetic monitoring without a concurrent LVEF reduction. It is unknown if mavacamten's safety profile and incidence of LVEF <50% would have been similar if these pharmacokinetic-based dose adjustments did not take place. In VALOR-HCM, where no pharmacokinetic monitoring was used, 9 (8.3%) patients (of whom 7 [12.5%] were in the original mavacamten group and 2 [3.8%] were in the placebo crossover group) on mavacamten had an LVEF <50% over 32 weeks of treatment.[48]

Atrial fibrillation is another frequently encountered complication of HCM.[49] Among clinical trials, patients enrolled in aficamten trials appeared to have a reduced incidence of atrial fibrillation compared with patients enrolled in mavacamten trials. It remains unclear if these are random chance findings due to small samples and excessive visits and monitoring in clinical trials, or if there is an association between a specific CMI's properties and atrial fibrillation. Longer-term follow-up and accumulating exposure data will help elucidate these observations. Previous studies have shown left atrial volume index independently predicts atrial fibrillation occurrence.[38] Thus, the improvement in left atrial volume index in those taking mavacamten (baseline, 40±12 mL/m^2; mean change, −7.5 mL/m^2 [95% CI, −9.0 to −6.1 mL/m^2]) compared with placebo (baseline, 41±14 mL/m^2; mean change, −0.1 mL/m^2 [95% CI, −1.6 to 1.5 mL/m^2]; P<0.0001) in the EXPLORER-HCM trial should theoretically help reduce the occurrence of atrial fibrillation.[50] However, despite improvements in left atrial volume index, the atrial fibrillation event rate on mavacamten was higher compared with placebo in mavacamten trials (11.5 events versus 7.4 events per 100 patient-years, respectively) and compared with patients on aficamten (4.1 events per 100 patient-years). Interestingly, the atrial fibrillation rate on placebo (7.7 events per 100 patient-years) in aficamten trials was essentially the same as placebo in the mavacamten trials.[9–26]

Additionally, atrial fibrillation events were somewhat common in patients in the MAVA-LTE: EXPLORER Cohort, with 33 (14.3%) patients affected over a median

follow-up time of 166 weeks, and the VALOR-HCM trial, with 4 (7.1%) patients on mavacamten affected (while no patients on placebo had atrial fibrillation) over a median follow-up of 16 weeks.[12,19] To date, no studies have assessed if certain factors, such as mavacamten dose or CYP2C19 metabolizer status, could have an association, or if these rates of atrial fibrillation are simply a reflection of the significant burden of disease in this population and the frequent assessment required for these patients during mavacamten initiation. In a small study on human surgical atrial samples, mavacamten inhibited the α-myosin heavy chain found in the atria in a similar rate to the β-myosin heavy chain found in the ventricle. This reduced atrial twitch amplitude would lead to depressed atrial contractility.[51] To date, similar assessments of atrial α-myosin heavy chain affinity have not been conducted for aficamten, which, as stated above, has different myosin binding sites than mavacamten. Whether this reduced atrial twitch amplitude may potentiate the development of atrial fibrillation and the differences in atrial fibrillation incidence between CMIs is unknown. Longer-term follow-up on aficamten in oHCM will help clarify this relationship. A recent observational study of a cohort of oHCM patients taking mavacamten had higher rates of new-onset atrial fibrillation than what was reported in phase III clinical trials, although such preliminary data require multicenter studies to confirm them.[50]

Compared with placebo, TEAEs, dizziness, syncope, and heart failure appeared to occur at higher rates on mavacamten compared with aficamten among the clinical trials included, although longer follow-up from the long-term extension studies is needed. In total, 26.8%, 7.1%, and 13.0% of patients reported dizziness on mavacamten during the placebo-controlled duration in EXPLORER-HCM, VALOR-HCM, and EXPLORER-CN, respectively.[11,12,14,29] In contrast, 4.2% of patients reported dizziness on aficamten in SEQUOIA-HCM.[25] It is unclear why rates of dizziness were so substantial in EXPLORER-HCM compared with other mavacamten trials, but it appears its long-term extension trial reports rates of dizziness more similar to that of the other trials, where 17.7% of patients reported dizziness over a median follow-up of 166 weeks in MAVA-LTE: EXPLORER Cohort.[19] Similarly, syncope occurred at a rate of 5.7% on mavacamten in EXPLORER-HCM (versus 1.6% in placebo), whereas it was not reported in SEQUOIA-HCM (low-frequency events <2% were not reported).[26,29] Heart failure also occurred at a low rate on mavacamten (4.3% of patients in oHCM and 2.3% of patients in nHCM) and on aficamten (no patients in oHCM and 2.4% of patients in nHCM). Death was rare in CMI trials, and none were attributable to the investigational product.[9–26]

Preclinical data showed that mavacamten led to teratogenicity in 2 animal species at clinically relevant exposure doses (an estimated equivalent human dose of 15 mg/d).[52] Based on these data, the FDA suggested mavacamten has a high probability of fetal teratogenicity, prompting the recommendation of contraception use in women of reproductive potential during treatment and for 4 months after the final dose.[29] It remains to be seen if aficamten has the potential for fetal teratogenicity. These are important considerations given the significant number of patients with HCM who are of reproductive age.[53]

From the limited evidence to date, a deep understanding of the relationship between a CMI, the target dose, and its safety and efficacy are required to translate its use to routine clinical practice. In regard to use of CMIs in nHCM, a recent update from the MAVERICK MAVA-LTE cohort reported a 27% rate of reduction of LVEF <50% while on mavacamten over approximately 2.5 years of follow-up and using pharmacokinetic targets in tightly-controlled trial settings.[16] Although these reductions appear to be reversible and many patients are rechallenged with mavacamten, these safety concerns arise in the setting of only mixed efficacy in the 2 mavacamten studies available for nHCM.

Aficamten was trialed in 2 open-label clinical trials in nHCM in the same patient population using site-read echocardiography without pharmacokinetic targets or monitoring. In REDWOOD-HCM Cohort 4, 7.3% of patients (all with underlying atrial fibrillation) had an LVEF <50% over 10 weeks of treatment, whereas 5.9% of patients (also in the setting of atrial fibrillation) had LVEF <50% over 36 weeks of treatment in the FOREST-HCM trial.[15,24] Both mavacamten and aficamten safety and efficacy in nHCM are being evaluated in 2 large phase III trials.

Ultimately, the specific CMI regulatory label will have significant impact on the degree of uptake and use of each individual CMI. The current mavacamten label issued by the FDA is cumbersome to physicians and patients but is designed to optimize the safe use of mavacamten in light of the clinical trials' design and findings.[6,29] Based on the data presented in this study, the risk of LVEF <50% and heart failure on mavacamten is low in the first few months of starting mavacamten, with the risk increasing over time related to prolonged exposure and potential accumulation of mavacamten. As such, the current FDA-mandated initiation phase of mavacamten will not necessarily capture the majority of LVEF <50% events or heart failure. How a risk evaluation and mitigation strategies program or an intense monitoring strategy might be enforced for aficamten is yet to be seen.

Limitations

Cross-trial comparisons represent a limitation of this review. However, baseline characteristics of the included trials, especially the phase III trials, are reasonably

comparable and should allow for efficacy and safety assessments. The open-label trials had different follow-up durations, which can influence the interpretation of proportionality, which is why event rates were provided. Finally, this was a qualitative review without a meta-analysis due to the small number of trials and significant heterogeneity between trials.

CONCLUSIONS

Both mavacamten and aficamten are safe medications that show benefit in reducing LVOT obstruction, symptom burden, and cardiac biomarkers while improving exercise capacity in patients with symptomatic oHCM. Although trials of both mavacamten and aficamten show substantial improvement in pVO_2 with overlapping CIs, the limited available data suggest a larger effect size in the aficamten trials on pVO_2 and the coprimary outcome of categorial pVO_2 and NYHA class improvement compared with the mavacamten trials. Aficamten also appears to have an overall improved safety profile in indirect comparisons, with minimal expected DDIs as well as lower rates of heart failure, atrial fibrillation, and treatment interruption due to LVEF reductions (partly protocol-driven) compared with mavacamten, although this comparison is limited by shorter follow-up times in trials of aficamten to date. Data from ongoing 5-year long-term open-label extension trials will further inform our understanding of differences in efficacy and safety for these medications. Once commercially available, and although logistically difficult, a head-to-head comparison of mavacamten and aficamten in oHCM could further our understanding of the similarities and differences between these medications. Data from the ongoing MAPLE-HCM trial (Metoprolol vs Aficamten in Patients with LVOT Obstruction on Exercise Capacity in HCM; NCT05767346) will provide evidence of the role of aficamten versus metoprolol as a first-line therapy in oHCM. The next frontier will focus on asymptomatic patients with oHCM with the goal of achieving reverse remodeling and prevention of long-term complications. In nHCM, phase II studies have been encouraging, but further evidence is required from the ongoing phase III trials to open the door for the first ever evidence-based therapy for patients with nHCM. These future directions and goals for CMIs might allow us to get to a uniform therapy for all patients with HCM regardless of underlying phenotype.

ARTICLE INFORMATION

Received September 7, 2024; accepted January 15, 2025.

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Sources of Funding

None.

Disclosures

R.B.-V. reports grants from Sanofi, and Bristol-Myers Squibb Company, travel fees from Bristol-Myers Squibb Company, and advisor fees from Bristo-Myers Squibb Company, Pfizer, Alnaylam, Sanofi, and Cytokinetics. P.G.-P. reports speaking fees from Alnylam Pharmaceuticals, AstraZeneca, Bristol-Myers Squibb Company, Bridgebio, Intellia, Ionis Pharmaceuticals, NovoNordisk, and Pfizer, consulting fees from Biomarin, Bristol-Myers Squibb Company, Bayer, Cytokinetics, Rocket Pharmaceuticals, Lexeo, Pfizer, Edgewise, Bridgebio, Daiichi Sankyo, Neuroimmune, Alnylam Pharmaceuticals, AstraZeneca, NovoNordisk, ATTRalus, Intellia, Idoven, General Electric, and Alexion, and research/educational support to his institution from Pfizer, Bridgebio, NovoNordisk, AstraZeneca, Intellia and Alnylam Pharmaceuticals. I.O. received research grants from Bristol-Myers Squibb Company, Cytokinetics, Amicus, Genzyme, Shire Takeda, Menarini international, Chiesi, Boston Scientific, and personal fees from Bristol-Myers Squibb Company, Cytokinetics, Amicus, Genzyme, Shire Takeda, Menarini International, Chiesi, Boston Scientific, Tenaya, Rocket Pharma, Lexeo. A.T.O. has consulted for BioMaron Pharmaceuticals, Bristol Myers Squibb Company, Cytokinetics, Edgewise Therapeutics, Lexeo, Lexicon Pharmaceuticals, Pfizer, Renovacor, Stealth, and Tenaya. C.J.C. has been a speaker for Roche Diagnostics International. S.D.S. has received research grants from Alexion, Alnylam, Applied Therapeutics, AstraZeneca, Bellerophon, Bayer, Bristol-Myers Squibb Company, Boston Scientific, Cytokinetics, Edgewise, Eidos/Bridgebio, Gossamer, GSK, Ionis, Lilly, National Institutes of Health/National Heart, Lung, and Blood Institute, Novartis, NovoNordisk, Respicardia, Sanofi-Pasteur, Tenaya, Theracos, US2. AI, and has consulted for Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Bristol-Myers Squibb Company, Cardior, Cardurion, Corvia, Cytokinetics, GSK, Lilly, Novartis, Roche, Theracos, Quantum Genomics, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, and Valo. M.S.M. has consulted for BioMaron Pharmaceuticals, Cytokinetics, Edgewise, and Imbria. A.M. reports research grants from Pfizer, Ionis, Attralus, and Cytokinetics, and personal fees from Cytokinetics, Bristol-Myers Squibb Company, Eidos, Pfizer, Ionis, Lexicon, Alnylam, Attralus, Haya, BioMarin, and Tenaya. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S5
Figures S1–S2

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