Mavacamten for Hypertrophic Cardiomyopathy: Effectiveness and Value

Final Evidence Report and Meeting Summary

November 16, 2021

Prepared for

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None of the above authors disclosed any conflicts of interest defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care manufacturers or insurers.

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Jason H. Wasfy served as the lead author for the report. Molly Beinfeld led the systematic review and authorship of the comparative clinical effectiveness section in collaboration with Emily Nhan. Surrey M. Walton developed the cost-effectiveness model and authored the corresponding sections with assistance from Jyotirmoy Sarker. Melanie Whittington provided oversight of the cost-effectiveness analyses and developed the budget impact model. Steven D. Pearson and David M. Rind provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Laura Cianciolo, Maggie Houle, and Mrinmayee Joshi (University of Illinois at Chicago) for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at https://icer.org/.

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For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

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The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

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In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer.org/wp-content/uploads/2021/05/ICER_HCM_Stakeholder_List_050721.pdf.

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List of Acronyms and Abbreviations Used in this Report

AHRQ	Agency for Healthcare Research and Quality
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
cm	Centimeter
cMRI	Cardiac magnetic-resonance imaging
CPET	Cardiopulmonary exercise testing
evLY	Equal value of life years
FDA	Food and Drug Administration
HCM	Hypertrophic cardiomyopathy
HCMSQ [SoB]	Hypertrophic Cardiomyopathy Symptom Questionnaire [Shortness of Breath]
HOCM/OHCM	Hypertrophic obstructive cardiomyopathy
HRQoL	Health-related quality of life
hs-cTnI	High-sensitivity cardiac troponin I
ICD	Implantable cardioverter defibrillator
ICER	Institute for Clinical and Economic Review
IQR	Interquartile range
KCCQ [OS][CS]	Kansas City Cardiomyopathy Questionnaire [overall summary][clinical summary]
kg	Kilogram
L	Liter
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
mg	Milligram
mL	Milliliter
mm	Millimeter
mm Hg	Millimeter of mercury
MRI	Magnetic-resonance imaging
ms	Millisecond
N	Total number
n	Number
N/A	Not applicable
ng	Nanogram
NR	Not reported
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
P/I	Promising but inconclusive
PICOTS	Population, Intervention, Comparator, Outcomes, Timing, Setting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
$pV0_2$	Peak oxygen consumption
QALY	Quality-adjusted life year
SD	Standard deviation
SoC	Standard of care
US	United States
USPSTF	United States Preventive Services Task Force

Executive Summary

Hypertrophic cardiomyopathy (HCM) is a genetic disorder involving sarcomeres in heart muscle that can cause symptoms such as chest discomfort and shortness of breath, particularly with exertion. Additional symptoms can include palpitations, dizziness, and syncope (passing out). Although many patients with HCM have a normal life expectancy without symptoms, even patients without symptoms are at risk of sudden cardiac death. Apart from managing symptoms, key components of therapy include placement of implanted cardioverter defibrillators (ICDs) for patients at high risk of sudden death, and anticoagulation for patients who have both HCM and atrial fibrillation.

For patients with a specific subtype of HCM, hypertrophic obstructive cardiomyopathy (HOCM), obstruction of the left ventricular outflow tract (LVOT) can be an important contributor to exertional symptoms. The LVOT is the conduit through which blood exits the heart to the rest of the body. Among the effects of dynamic narrowing of the LVOT are increased pressure within the left ventricle, increased myocardial oxygen demand, and increased mitral regurgitation. While LVOT obstruction is one important target for therapy to reduce symptoms, there are other causes of symptoms that can also affect non-obstructive HCM patients. Those symptoms include diastolic dysfunction, microvascular angina (obstruction of small heart artery vessels), and irregular heart rhythms.

For HOCM patients with shortness of breath related to LVOT obstruction, medications can improve symptoms. Beta blockers and calcium channel blockers reduce the forcefulness of the heart's contraction, reducing the LVOT gradient, thus improving symptoms. However, beta blockers and calcium channel blockers have important side effects, including fatigue that can interfere with work or daily activities, dizziness, and sexual dysfunction.

When these first-line therapies are insufficient or not well tolerated, second-line treatment options include adding disopyramide or performing septal reduction procedures. Disopyramide has important side effects as well, and drug shortages limit access to the long-acting version. Septal reduction procedures include surgical myectomy (a type of open-heart surgery) or alcohol septal ablation, a controlled heart attack that reduces the thickness of the heart muscle causing LVOT obstruction. Those procedures can have substantial benefit, but they have a low but meaningful risk of death. Furthermore, clinical outcomes following these procedures may be worse outside centers of excellence. As such, there is substantial unmet need for the management of exertional symptoms in patients with symptomatic HOCM, particularly among patients that do not have good access to specialized centers.

A novel agent, mavacamten, has been tested in clinical trials. Mavacamten reduces adenosine triphosphatase activity in cardiac myosin heavy chain, one of the proteins in heart muscle cells, and thus reduces the contraction of the heart that can contribute to obstruction. A United States (US)

Food and Drug Administration (FDA) decision on approval of mavacamten is expected in early 2022. This report examines the comparative effectiveness and cost effectiveness of mavacamten in patients with symptomatic HOCM.

The key trial in such patients is EXPLORER, a Phase III randomized trial comparing mavacamten to placebo in 251 patients receiving first-line treatments. Mavacamten was more effective than placebo at meeting a primary composite endpoint of 1.5 mL/kg per min or greater increase in peak oxygen consumption (pVO_2) and at least one New York Heart Association (NYHA) class reduction or a 3.0 mL/kg per min or greater pVO_2 increase without NYHA class worsening (37% vs. 17%, p=0.0005). Among patients who completed the Kansas City Cardiomyopathy Questionnaire (KCCQ), the KCCQ overall summary score was more improved among patients assigned to mavacamten than placebo (+14.9 vs. +5.4, p<0.0001). Serious adverse events were uncommon in EXPLORER and similar between arms of the trial. Some clinical experts noted conceptual concerns about reductions in ejection fraction and myocardial thickness with mavacamten: these changes can be beneficial but could result in long-term harm if they persist or recover then worsen over time. Other clinical experts are much less concerned about this potential harm. In the absence of additional long-term evidence on mavacamten, we need to consider the potential for possible net harms, and we rate mavacamten in addition to usual care compared with usual care alone as *promising but inconclusive* ("P/I").

When comparing mavacamten with disopyramide, we are limited by the absence of head-to-head randomized trials and the absence of randomized trials of disopyramide. Disopyramide has known side effects and contraindications. Furthermore, data supporting use of disopyramide are relatively weak and potentially exaggerate the true treatment effect due to study design. On balance, we consider the evidence for mavacamten compared with disopyramide to be *promising but inconclusive* ("P/I") as well.

We lack randomized trials of septal reduction therapies either to each other, compared with no procedure, or compared with mavacamten. Observational data appear to show greater improvements in functional outcomes with such procedures than was seen in the EXPLORER trial, however, these procedures have a small risk of short-term serious adverse events including death. Overall, among patients who are eligible for a septal reduction procedure, net benefits are likely greater with a procedure than with mavacamten. However, we also believe the choice between a procedure with a short-term risk of death and mavacamten would be highly dependent on individual patient preferences. Given this, we are not assigning an evidence rating to this comparison: such decisions will need to be made on a case-by-case basis through discussions among patients, families, and clinicians.

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Mavacamten Plus Beta Blockers and Calcium Channel Blockers	Beta blockers and calcium channel blockers alone	P/I
Mavacamten Plus Beta Blockers and Calcium Channel Blockers	Disopyramide	P/I
Mavacamten Plus Beta Blockers and Calcium Channel Blockers	Septal reduction therapies	See discussion in Section 3.3

P/I: promising but inconclusive

For more information on the rationale for these evidence ratings, please see Section 3.3.

We created a semi-Markov model to estimate discounted lifetime time horizon costs, quality-adjusted life years (QALYs), life years, years in NYHA class I, and equal value of life years (evLYs) for mavacamten along with standard first-line therapies and several comparators. Table ES2 presents the base-case cost-effectiveness results.

Table ES2. Incremental Cost-Effectiveness Ratios for Mavacamten* in the Base Case

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Additional NYHA I Year
Mavacamten	Standard treatment	$1,200,000	Undefined	$1,200,000	$219,000
	Disopyramide	$1,500,000	Undefined	$1,500,000	$278,000
	Myectomy	Dominated	$5,600,000	N/A†	Dominated
	Septal ablation	Dominated	$7,000,000	N/A†	Dominated

evLY: equal value of life years, N/A: not applicable, NYHA: New York Heart Association, QALY: quality-adjusted life year

*Price assumed for mavacamten was a placeholder of $75,000 per year.

†Incremental cost per evLY gained not applicable due to fewer lifetime QALYs for mavacamten as compared to myectomy and septal ablation.

Mavacamten used along with standard first-line treatment was projected to generate higher amounts of QALYs than standard first-line treatment alone. However, at the placeholder cost of $75,000, the incremental cost-effectiveness ratio was well above standard thresholds ($1,200,000 per QALY). When compared with disopyramide, the incremental cost per QALY was even higher, and mavacamten was found to be dominated by both myectomy and septal ablation. From the cost-effectiveness analysis, we estimated the health-benefit price benchmark (HBPB) for mavacamten to be $12,000 to $15,000 annually. The actual cost effectiveness of mavacamten will depend on its price.

At the placeholder price of $75,000 per year, approximately 25% of eligible patients could be treated with mavacamten within five years before crossing the ICER potential budget impact threshold of $734 million per year. This could create a short-term potential budget impact that exceeds the potential threshold at this price. However, because this is based on a placeholder

price, ICER is not issuing an access and affordability alert. All eligible patients could be treated within five years without crossing the ICER potential budget impact threshold at the price to reach $150,000 per QALY.

Potential other benefits of mavacamten include more access to treatment options because septal reduction procedures are mainly available at specialized centers. When septal reduction procedures are performed at lower-volume centers, outcomes are worse although these differences could reflect both differences in quality and/or unmeasured confounding. There have also been national shortages of the long-acting form of disopyramide. In part based on the shortage as well as other issues including side effects and limited efficacy, few patients are actually taking disopyramide. However, some patients and patient groups emphasized that disopyramide is still an important treatment option. Finally, mavacamten will be a new option available for patients at points in their lives when they are making important life choices regarding education, work, and raising families, which could provide benefits over and above the improvement in QALYs calculated in the model.

Appraisal committee votes on questions of comparative effectiveness and value, along with key policy recommendations regarding pricing, access, and future research are included in the main report. Several key themes are highlighted below.

- All stakeholders have a responsibility to facilitate meaningful patient access to multidisciplinary centers of excellence for HCM in ways that do not exacerbate disparities.
- The manufacturer of mavacamten should commit to sponsoring research that will address the lack of data on the comparative effectiveness of mavacamten versus disopyramide and septal reduction procedures.
- The manufacturer of mavacamten should align the price of mavacamten with the explicit and transparent estimates of its treatment benefits for patients and families. Pricing should also be moderated to reflect the uncertainty about longer-term safety until such time as further outcomes data are generated.
- Payers should use the FDA label as the guide to coverage policy and engage clinical experts and diverse patient representatives in considering how to address coverage issues for which there is limited or no evidence at the current time.

1. Background

Hypertrophic cardiomyopathy (HCM) is a heart muscle disorder that can cause symptoms such as chest discomfort and shortness of breath, particularly with exertion. Although many patients with HCM have a normal life expectancy without symptoms, even patients without symptoms are at risk of sudden cardiac death. Patients with HCM who develop atrial fibrillation are at elevated risk of stroke.[1] The mechanisms that cause patients to have exertional symptoms are diverse and can include diastolic dysfunction (difficulty filling the heart with blood) and microvascular angina (obstruction of small heart artery vessels) as well as other causes.

HCM is a condition with different subtypes. For patients with hypertrophic obstructive cardiomyopathy (HOCM), which is one of the subtypes of HCM, narrowing and obstruction of the left ventricular outflow tract (LVOT) can occur with exertion or sometimes at rest. The LVOT is the conduit through which blood begins to exit the heart. Since this type of obstruction can interfere with the heart's pumping function, it is a major cause of exertional symptoms for patients with the HOCM subtype of HCM. However, not all exertional symptoms are caused by LVOT obstruction even among the subset of HCM patients with HOCM.

The underlying cause of HCM is dysfunction in proteins called sarcomeres that help cardiac muscle cells (myocytes) squeeze and pump blood.[2] The sarcomere dysfunction in HCM can lead to hypertrophy (thickening) of the heart. HCM can occur due to a number of heritable genetic defects affecting sarcomere proteins. Hypertrophy related to sarcomere dysfunction distinguishes HCM from other forms of cardiac conditions, such as hypertrophy caused by chronic high blood pressure, infiltrative disorders such as cardiac amyloidosis, or healthy adaptive hypertrophy from athletic training. As such, doctors often need to perform tests to distinguish HCM from other forms of hypertrophy; in some cases, the diagnosis can be difficult to make. Specific single-gene mutations in 15 genes have been identified as associated with HCM,[3] although patients can have the clinical appearance of HCM (phenotypic HCM) without an identified gene mutation.

Because of difficulties with detection, the observed prevalence of HCM varies in studies conducted with different methods. Asymptomatic patients may only be diagnosed with HCM when an imaging test is performed for a different reason. An estimate using echocardiographic screening suggested a prevalence of HCM of one in 500,[4] but screening with cardiac magnetic-resonance imaging (cMRI), which is more sensitive and specific for cardiac hypertrophy, found a prevalence of about one in 70.[5] Not all patients with HCM mutations develop hypertrophy. Guidelines for the treatment of patients with HCM were most recently published in 2020.[6] With appropriate selection of higher-risk patients for implantable cardioverter defibrillators (ICDs), which can shock the heart out of dangerous heart rhythms, the risk of sudden cardiac death has declined to 0.5% per year.[7] When patients develop atrial fibrillation, anticoagulation is generally recommended to prevent cardioembolic stroke regardless of conventional stroke risk factors. For HOCM patients with

exertional symptoms thought to be related to the LVOT gradient, principles of therapy involve reducing the magnitude of the LVOT gradient, which generally improves symptoms. Pharmacological approaches involve therapies that reduce cardiac contractility (negative inotropic agents) including beta blockers and calcium channel blockers.[8] For patients who still have symptoms or who are unable to tolerate these agents, adding disopyramide as a second-line agent and invasive strategies such as septal myectomy (open-heart surgery to remove a portion of heart muscle) or alcohol septal ablation (a controlled heart attack to reduce the heart muscle tissue in the obstructed area) are considered.[8] No randomized trial has compared surgical myectomy to septal ablation, but guidelines favor surgical myectomy in most patients.[6]

A novel agent, mavacamten, has been tested in clinical trials. Mavacamten is a direct myosin inhibitor and an oral medication administered once per day that directly reduces adenosine triphosphatase activity in cardiac myosin heavy chain, one of the proteins in heart muscle cells.[9] This is a key step in how heart muscle cells make energy for contracting the heart.[9]

A United States (US) Food and Drug Administration (FDA) decision on approval of mavacamten is expected in early 2022. Multispecialty guidelines were most recently revised in 2020 and, as such, do not yet specify the role of mavacamten in HCM.[10] Any use of mavacamten will likely occur in symptomatic HOCM patients who are refractory or intolerant to beta blocker and calcium channel blockers. Given that evidence does not yet exist comparing mavacamten to disopyramide, surgical myectomy, or septal ablation, clinical experts differ about the role of mavacamten as an alternative to those strategies. A randomized trial, VALOR-HCM (NCT04349072), is evaluating the use of mavacamten to reduce utilization of septal reduction procedures in patients who would otherwise be eligible for invasive therapies. As such, this trial is not designed to provide a direct comparison of up-front septal reduction procedures versus mavacamten.[11]

Given that the mechanism of action addresses the underlying pathophysiology of sarcomeric dysfunction, the cause of HCM, it remains conceptually possible that mavacamten may reduce symptoms for patients with HCM without obstruction. The MAVERICK-HCM trial demonstrated improvement in cardiac biomarkers, which are known surrogates for myocardial wall stress.[12] These therapeutic concepts are mechanistically appealing and could lead to further trials with clinical endpoints including symptoms. Other therapeutic concepts for HCM are in development and validation. For example, sacubitril/valsartan attenuates cardiac fibrosis and hypertrophy in a rat model of myocardial infarction.[13] Since these processes are key aspects of the pathophysiology of HCM, ongoing trials are evaluating the clinical effectiveness of sacubitril/valsartan in HCM without obstruction.[14] Additionally, other myosin inhibitors are being evaluated[15] with results of a Phase II trial of aficamten (REDWOOD-HCM, NCT04219826) recently reported at a conference in September 2021.

2. Patient and Caregiver Perspectives

ICER met virtually with patients with HCM, representatives from patient organizations, and clinical experts to understand patient and caregiver perspectives and unmet needs, contextual considerations, and outcomes important to patients with all types of HCM, including symptomatic HOCM. Dr. Jason H. Wasfy also participated in the 2020 American College of Cardiology Roundtable on Advances in Hypertrophic Cardiomyopathy to gain additional perspective.

Finally, to obtain more detailed information about patient, family, and caregiver perspectives, ICER conducted a national survey in partnership with the Hypertrophic Cardiomyopathy Association, the nation's most prominent organization providing support, advocacy, and education for patients with HCM. This survey encouraged free-text responses from HCM patients, allowing flexibility to express diverse perspectives. Responses were coded using qualitative methods to identify common themes and both common themes and direct patient quotes were reported. Of 641 total responses, 606 were from HCM patients, 29 were from caregivers and/or family members, and six were from patient advocates. Many patients and caregivers emphasized difficulties accessing specialized HCM centers, finding cardiology subspecialists knowledgeable about HCM, and difficulties with insurance. Patients reported substantial financial burdens associated with travel, co-payments, and high deductibles. Patients also reported a variety of symptoms including fatigue, exertional intolerance, and difficulty breathing. About a third of patients reported that their current treatments "work okay" and nearly a tenth report that their current treatments "do not work," suggesting a large unmet need related to symptoms. Many patients on treatments including beta blockers, calcium channel blockers, and disopyramide reported fatigue. Detailed information about the survey methods and both qualitative and quantitative results are presented in Section B.

The spectrum of severity of illness in HCM is wide, and many patients do not have severe symptoms (see Report Supplement Section B). For many other patients with HCM, the burden of disease can be severe. In addition to the relatively small risk of sudden cardiac death for most HCM patients, about one in six patients develop exertional symptoms.[16] Both patients with HCM generally and with HOCM specifically can have these exertional symptoms, and among patients with HOCM, a larger outflow tract gradient is associated with a higher likelihood of having symptoms.[16] Patients with HOCM also face anxiety, depression, and concerns about activities of daily living and social events. There is uncertainty about the extent to which exercise can increase the risk of sudden cardiac death for HOCM patients, and guidelines have shifted over time,[10] allowing recommendations for more athletic activity for HOCM patients. These changes have led to uncertainty and confusion among HOCM patients about optimal self-care. Since patients often have electrocardiograms and echocardiograms that mimic other conditions, including acute myocardial infarction and hypertensive heart disease, misdiagnosis is common and patients with HCM often have frustrations with the health care system. This can be minimized with care at large

high-volume centers of excellence, but many patients do not have access to these centers because of cost and location. The total cost of care for symptomatic patients with HOCM is greater than six times that of patients of similar age and gender.[17]

Patients and their representatives particularly highlighted exertional symptoms. Patients were most concerned with how symptoms impair everyday functioning and prevent them from living their lives. The cornerstones of therapy, beta blockers and calcium channel blockers, have important limitations. In the survey, one patient told us:

> "*I think the medications cause fatigue and brain fog that prompted me to take an early retirement from work as I felt I was not capable of performing my work tasks to full capability/commitment*."

For another patient, the fatigue caused by beta blockers made caring for her children more difficult:

> "*I was a single mom on beta blockers and had a hard time doing anything – my kids needed me to drive, make meals, etc., and sometimes I was just too tired*."

Patients also expressed concerns about representing functional status with New York Heart Association (NYHA) classification in part because of concerns about the term "heart failure." Furthermore, patients emphasized that there is a "good day, bad day" phenomenon in symptomatic HOCM, since symptoms can vary substantially from day-to-day, and this variation is not well described by NYHA class. Clinical experts expressed additional concerns with NYHA class, including that patients may underreport clinical symptoms. As such, objective patient-reported outcomes were preferred when possible. Patients also emphasized that HCM is not "traditional" heart failure, with very different treatments and prognoses even though some symptoms, including exertional dyspnea, are similar.

Some patients described the fear of sudden cardiac death. Although most patients have a normal life expectancy, early studies reported higher mortality rates. This fear has substantial effects on patients' life choices. Particularly when patients are diagnosed early in life, uncertainty and fear can lead to pressured life decisions about educational programs, marriage and relationships, and decisions about whether to have children. Patients reported concern about passing along genes associated with HCM to children. Patients also reported concerns about convincing children (who are sometimes adults at time of the patient's diagnosis) to receive screening. In addition, patients reported that the diagnosis of HOCM can lead to difficulties receiving life insurance, being admitted to educational programs, and receiving loans. In that context, patients reported feeling reluctant to discuss their condition for fear of being misunderstood. One patient told us, "I was living with a flopping, living fish in my chest and there was no one around to talk about it." Public focus on prominent athletes' deaths also takes away attention from other patient concerns, such as obstruction, exertional symptoms, and traditional heart failure in later-stage HCM.

Palpitations with arrythmias was a common source of concern for patients. Many patients reported feeling much worse when having irregular heart rhythms, and they reported fear about how to distinguish dangerous from less dangerous heart rhythms. Some patients and their friends and families consider buying automated electronic defibrillators, which are expensive, to reduce the risk of sudden cardiac death.

Patients with HOCM also reported substantial difficulties interacting with caregivers, clinics, and hospitals. According to the Hypertrophic Cardiomyopathy Association's Patient-Focused Drug Development Meeting report, "The underlying emotional toll for HCM patients can be intense and can cripple…a sense of wellbeing."[18] Given that HCM is a less common condition, many physicians do not understand how to manage it, and physicians sometimes overestimate risk. The electrocardiogram pattern for many patients with HCM can mimic a heart attack and, as such, many patients reported inappropriate escalations in care that would have been avoided with better access to HCM-specific expertise. Patients also reported worse access for non-cardiac ambulatory procedures (such as office-based colonoscopy) because of caregiver fear of cardiac complications. Fainting in public places is often a source of severe distress because patients need to advocate for themselves and give directions to both bystanders and emergency personnel given their unique circumstances.

A common concern was the organization and availability of centers of excellence. Access to procedural care for surgical myectomy and septal ablation is limited because these procedures are only performed at highly specialized centers. The excellent outcomes for these procedures represent care delivered at these centers and may not be generalizable to other settings. The Hypertrophic Cardiomyopathy Association has developed an assessment model that has identified 42 centers of excellence for HCM. Patients from rural areas, patients with less money to travel, and people of color may have disproportionally less access to these centers. Black patients in particular have less access to septal reduction therapies and genetic testing.[19] Furthermore, women are referred to subspecialty HCM care later than men.[20]

Many patients noted concern about underdiagnosis, since HCM can often be asymptomatic or misdiagnosed. Patients in different racial and socioeconomic groups have differential access to cardiac imaging used for diagnosis.

Patients and patient groups report concern about the financial burden to both patients and caregivers. Patients and patient groups are specifically concerned about the potential cost of mavacamten including cost-sharing arrangements such as co-payments. When caregivers are needed to provide care for HCM patients, they sometimes cannot work, exacerbating financial problems. Patients themselves are often underemployed because they fear moving to new jobs or communities because these moves could disrupt insurance, social supports, and access to caregivers.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic literature review assessing the evidence on mavacamten for symptomatic HOCM are detailed in Section D1 of the Report Supplement.

Scope of Review

We reviewed the clinical effectiveness of mavacamten plus usual care versus usual care alone, disopyramide, and septal reduction therapies. Usual care is defined as beta blockers and/or calcium channel blockers. We sought evidence on patient-important outcomes, including functional status and health-related quality of life (HRQoL). We also sought evidence on changes NYHA class, echocardiographic parameters, peak oxygen consumption (pVO_2), left ventricular ejection fraction (LVEF), and serum cardiac biomarkers. The full scope of the review is detailed in Section D1 of the Report Supplement.

Evidence Base

Mavacamten

Evidence informing our review of mavacamten in symptomatic HOCM was derived from one Phase III randomized controlled trial and one Phase II trial. Due to differences in trial design and outcomes assessed, the Phase II trial was not the primary focus of review and is described in detail in Section D2 of the Report Supplement. A randomized trial of mavacamten in symptomatic non-obstructive HCM, which is outside the scope of this review, is described in Section D2 of the Report Supplement.

EXPLORER-HCM was a multi-center Phase III trial that randomized 251 patients with HOCM in a 1:1 ratio to 5-15 mg oral mavacamten or placebo (Table 3.1).[24,25] Patients were eligible to participate if they were 18 years of age or older, met the criteria for HOCM based on current American College of Cardiology/American Heart Association guidelines,[6] and had documented LVEF ≥55% and NYHA class II-III symptoms. Patients were excluded if they were on current treatment with disopyramide or had been treated with septal reduction therapy (myectomy or septal ablation) within six months prior to screening. Randomization was stratified by four baseline clinical characteristics: NYHA class, beta blocker use, ergometer type (treadmill or bicycle), and consent for a cardiovascular MRI sub-study. All patients received mavacamten or placebo over a 30-week treatment period. Cardiopulmonary exercise testing (CPET) and post-exercise echocardiography were performed at screening and week 30, while resting echocardiography, electrocardiograms, and lab tests were performed every two to four weeks across 12 visits.

The primary outcome was a composite outcome of an objective physiological parameter as well as a clinician-estimated clinical measure to assess clinical response, defined as ≥1.5 mL/kg per min increase in pVO_2 *and* ≥1 NYHA class reduction *or* ≥3.0 mL/kg per min increase in pVO_2 *and* no worsening of NYHA class.[23]

Secondary outcomes included change from baseline to 30 weeks in post-exercise LVOT gradient, pVO_2, NYHA improvement, and HRQoL. Exploratory outcomes included N-terminal pro B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin I (hs-cTnl). Safety outcomes included treatment-emergent adverse events and serious adverse events.

Participants in the EXPLORER-HCM trial had a mean age of 58.5 years and were predominantly male and white (91%). In the mavacamten group, a minority of patients (9%) had undergone septal reduction therapy and all but 3% were taking background medication (beta blockers or calcium channel blockers). Most patients in both arms (72-74%) were classified as having NYHA class II symptoms at baseline. The study arms were balanced across baseline characteristics, with a few exceptions. The mavacamten arm included a greater percentage of female participants than the placebo arm (46% vs. 35%), fewer participants with a history of atrial fibrillation (10% vs. 18%), and had a higher mean NT-proBNP (777 vs. 616 ng/L) (Table 3.1). Additional information about the trial population is available in Table D4 and Table D14 of the Report Supplement.

The EXPLORER trial also included a five-year extension study (MAVA-LTE) to evaluate the long-term safety and efficacy of mavacamten. At the time of the report, only interim results from MAVA-LTE were available.[24]

Table 3.1. Selected Baseline Characteristics of the Randomized Controlled Trial of Mavacamten, Retrospective Study of Disopyramide, and Systematic Review of Septal Reduction Therapies[25-27]

	Randomized Controlled Trial of Mavacamten (EXPLORER)		Retrospective Study of Disopyramide (Sherrid 2005)		Systematic Review of Septal Reduction Therapies (Liebregts 2015)	
	Mavacamten (n=123)	Placebo (n=128)	Disopyramide (n=118)	Non-Disopyramide (n=373)	Septal Ablation (n=2,791)	Myectomy (n=2,013)
Age, Mean (SD)	58.5 (12.2)	58.5 (11.8)	47 (20)	43 (21)	56 (54-58)*†	47 (40-47)†
Female Gender, n (%)	57 (46)*	45 (35)	NR (49)	NR (47)	NR (49)*	NR (40)
Medical History, n (%):						
Atrial Fibrillation	12 (10)*	23 (18)	NR (20)	NR (18)	NR	NR
Septal Reduction Therapy	11 (9)	8 (6)	NR (28)	NR (18)	NR	NR
ICD	27 (22)	29 (23)	NR (5)	NR (2)	NR (3)	NR (10)
Background Therapy, n (%):						
Beta Blocker	94 (76)	95 (74)	NR (98)*	NR (70)	NR	NR
Calcium Channel Blocker	25 (20)	17 (13)	NR (32)	NR (27)	NR	NR
Neither	4 (3)	16 (13)	NR	NR	NR	NR
NYHA Class I, n (%)	0 (0)	0 (0)	14 (12)	NR	2.8 (2.8-3)†	2.9 (2.7-3.1)†
NYHA Class II, n (%)	88 (72)	95 (74)	59 (50)	NR		
NYHA Class III, n (%)	35 (28)	33 (26)	45 (38)	NR		

ICD: implantable cardioverter defibrillator, n: number, NR: not reported, NYHA: New York Heart Association, SD: standard deviation
*Indicates a statistically significant difference between groups.
†Reported value is weighted median (interquartile range).

Disopyramide

Evidence on disopyramide is very limited. To inform our review of disopyramide, we describe one retrospective study of 118 patients with HOCM treated with disopyramide at four US-based specialized HCM centers between 1990 and 1999 and 373 patients not treated with disopyramide during the same time period. Patients were followed for a mean of 4.2 years (±2.9 months).[26] At baseline, patients treated with disopyramide had a mean age of 47 years (±20), 28% had undergone septal reduction therapy, 98% were on beta blockers, and 50% had NYHA class II symptoms (Table 3.1). Additional baseline characteristics of this study and information about other studies of disopyramide are discussed in Section D2 of the Report Supplement.

Septal Reduction Therapies

Evidence to inform our review of septal reduction therapies (myectomy and septal ablation) came from existing systematic literature reviews. A 2015 review with meta-analysis pooled long-term outcomes from 24 studies comprising 16 myectomy cohorts (mean follow-up 7.4 years) and 11 septal ablation cohorts (mean follow-up 6.2 years).[27] Patients in the septal ablation cohorts were older than in the myectomy cohorts (56 years compared to 47, p=0.0009) and more likely to be female (49% female compared to 40%, p=0.058) (Table 3.1). Additional baseline characteristics and

systematic reviews of septal reduction therapy are discussed in Section D2 of the Report Supplement.

One major challenge in assessing comparative effectiveness for symptomatic HOCM is that while randomized data exist to compare mavacamten versus beta blockers and calcium channel blockers, there are not randomized data for comparisons of mavacamten versus either disopyramide or septal reduction therapies.

3.2. Results

Clinical Benefits

Mavacamten

Clinical Response

Clinical response was achieved by 45 (37%) patients in the mavacamten arm at 30 weeks compared to 22 (17%) in the placebo arm (p=0.0005).[21]

NYHA Class, LVOT Gradients, LVEF, and $pV0_2$

Thirty-two (27%) patients in the mavacamten group achieved NYHA class I status and all LVOT peak gradients <30 mm Hg at 30 weeks compared to one patient (1%) in the placebo group, a difference of 26.6% (95% confidence interval [CI]: 18.3-34.8) (Table 3.2).

Improvement in NYHA by at least one class at 30 weeks was reported in 80 (65%) patients in the mavacamten group and 40 (31%) in the placebo group (p<0.0001) (Table 3.2).[21] At baseline, no patients in either treatment arm had NYHA class I. By week 30, 49.6% of patients in the mavacamten group achieved NYHA class I status compared to 21.1% of patients in the placebo group. Furthermore, the proportion of patients with a NYHA class III status declined from 28.5% at baseline to 6.5% at 30 weeks in the mavacamten group and from 25.8% to 19.5% in the placebo group (Table 3.3). In the long-term extension study of mavacamten (MAVA-LTE), continued improvements in NYHA class were observed. At week 48, 29 of 49 (59%) patients on mavacamten reached NYHA class I.[24]

Changes in post-exercise and resting LVOT gradients from baseline to 30 weeks in the mavacamten and placebo groups are presented in Table 3.2. Improvements in resting LVOT gradient and Valsalva LVOT gradient were sustained out to 60 weeks in the long-term extension study (MAVA-LTE).[24]

Mean decrease in LVEF was -3.9% in the mavacamten group compared to -0.01% with placebo, a -4% difference (95% CI: -5.5 to -2.5) (Table 3.2).[21] These changes in LVEF were sustained in the long-term extension study (MAVA-LTE).[24]

Mean increase in pVO_2 was 1.4 mL/kg per min greater in the mavacamten group than in the placebo group (95% CI: 0.6-2.1; p=0.0006) (Table 3.2).[21]

Cardiac Biomarkers

Mean NT-proBNP declined from 777.4 ng/L at baseline to 163.1 ng/L at 30 weeks in the mavacamten group and increased from 615.7 ng/L at baseline to 645.9 ng/L at 30 weeks in the placebo group (proportion of geometric mean ratio between the two groups 0.202, 95% CI: 0.169-0.241) (Table 3.2).[21] NT-proBNP levels were sustained in the long-term extension study (MAVA-LTE). At week 60, median NT-proBNP was 153 ng/L.[24] Mean hs-cTnl started at 12.5 ng/L in both groups and declined to 7.4 ng/L in the mavacamten group at 30 weeks and remained constant at 12.6 ng/L in the placebo group (proportion of geometric mean ratio between the two groups 0.589, 0.500-0.693) (Table 3.2).[21]

Table 3.2. EXPLORER-HCM Key Trial Results[21]

Outcome at 30 Weeks	Mavacamten (n=123)	Placebo (n=128)
NYHA Class I and All LVOT Peak Gradients <30 mm Hg, n/N (%)	32/117 (27)	1/126 (1)
NYHA Class Improvement ≥1, n (%)	80 (65)	40 (31)
LVOT, Post-Exercise Peak Gradient <50 mm Hg, n/N (%)	75/101 (74)	22/106 (21)
LVOT, Post-Exercise, Change from Baseline Mean mm Hg (SD)	-47 (40)	-10 (30)
LVOT Gradient, Resting, Change from Baseline Mean mm Hg	-37.6	-5.2
LVEF, Resting, Change from Baseline, %	-3.9	-0.01
pVO_2 Change from Baseline, Mean mL/kg per min (SD)	1.4 (3.1)	-0.1 (3.0)
NT-proBNP, Geometric Mean, Change from Baseline, ng/mL	-614.3	30.2
Hs-CTnI, Geometric Mean, Change from Baseline, ng/L	-5.1	0.1

Hs-CTnI: High-Sensitivity Cardiac Troponin I, kg: kilogram, L: liter, LVEF: left ventricular ejection fraction, LVOT: left ventricular outflow tract, mL: milliliter, mm Hg: millimeter of mercury, NT-proBNP: N-terminal pro B-type natriuretic peptide, n: number, N: total number, ng: nanogram, NYHA: New York Heart Association, pVO2: peak oxygen consumption, SD: standard deviation

Table 3.3. Distribution of NYHA Class, Baseline, and 30 Weeks in the EXPLORER Trial[21]

	Mavacamten (n=123)		Placebo (n=128)	
	Baseline	**30 Weeks**	**Baseline**	**30 Weeks**
NYHA Class I (%)	0	49.6	0	21.1
NYHA Class II (%)	71.5	42.3	74.2	57.8
NYHA Class III (%)	28.5	6.5	25.8	19.5
Missing (%)	0	1.6	0	1.6

NYHA: New York Heart Association

Patient-Reported Quality of Life

In EXPLORER, patient health status (with a focus on symptoms, physical and social function, and quality of life) was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ), a validated cardiomyopathy-specific instrument,[28] and the HCM Symptom Questionnaire (HCMSQ) at baseline and weeks six, 12, 18, 30 (end of treatment), and 38 weeks (end of study, after an eight-week washout period).[29]

Greater improvements in KCCQ overall summary, clinical summary, physical limitation, and quality-of-life scores from baseline (positive is better) were observed for patients in the mavacamten group compared to the placebo group (Table 3.4). These changes at 30 weeks from baseline were all greater than the minimal clinically important difference, estimated to be between 4 and 6 points across all domains.[30] All improvements in KCCQ at 30 weeks reversed to baseline eight weeks after withdrawal of treatment during the washout period.[29]

Mean improvements in the HCMSQ-Shortness-of-Breath (HCMSQ-SoB) sub-score from baseline (negative is better) were -2.8±2.7 in the mavacamten group compared to -0.9±2.4 (least square mean difference -1.8, 95% CI: -2.4 to -1.2).[21]

Table 3.4. EXPLORER-HCM Change in Selected KCCQ Scores from Baseline[29]

Outcome at 30 Weeks	Mavacamten (n=92)	Placebo (n=88)	LSM Differences (95% CI)
Overall Summary Score, Mean (SD)	14.9 (15.8)	5.4 (13.7)	9.1 (5.5-12.8)
Clinical Summary Score, Mean (SD)	13.6 (14.4)	4.2 (13.9)	9.1 (5.5-12.7)
Physical Limitation Score, Mean (SD)	14.7 (17.0)	3.6 (15.4)	10.6 (6.2-14.8)
Quality of Life Score, Mean (SD)	18.8 (21.6)	8.3 (18.8)	9.6 (4.7-14.5)

CI: confidence interval, LSM: least square mean, n: number, SD: standard deviation

Disopyramide

In the retrospective study, of the 118 patients treated with disopyramide, 40 (34%) required major interventions (myectomy, septal ablation, or dual-chamber pacing) a mean of 2.0±2.1 years after initiating drug treatment because of inadequate symptom control, persistent gradients, drug intolerance, or withdrawal. Among patients who did not require an intervention and remained on treatment during the follow-up period, mean peak flow gradient decreased from 75 mm Hg (±30) at baseline to 40 mm Hg (±32) (p<00001), and mean NYHA class declined from 2.3 (±0.7) to 1.7 (±0.6) (p<0.0001). Among patients who required an intervention, disopyramide was not associated with improvements in NYHA class and modest improvements in peak LVOT gradient (Table 3.5). These outcomes were not reported in the non-disopyramide patients.[26]

Annualized all-cardiac death was 1.4% in the 118 disopyramide-treated patients and 2.6% in the 373 non-disopyramide-treated patients (p=0.07). Annualized sudden death was 1.0% in the disopyramide group and 1.8% in the non-disopyramide group (p=0.08).[26]

Table 3.5. Key Results of Retrospective Study of Disopyramide[26]

	Disopyramide without Intervention (n=78)		Disopyramide with Intervention (n=40)	
Outcome	**Baseline**	**Follow-Up**	**Baseline**	**Follow-Up**
Peak LVOT Gradient, Mean mm Hg (SD)	75 (33)	40 (32)	73 (35)	63 (31)
NYHA Class, Mean (SD)	2.3 (0.7)	1.7 (0.6)	2.3 (0.7)	2.3 (0.6)
NYHA Class Distribution, n (%)	I: 9 (12) II: 40 (51) III/IV: 29 (37)	I: 29 (37) II: 42 (54) III/IV: 7 (9)	NR	NR

LVOT: left ventricular outflow tract, mm Hg: millimeter of mercury, n: number, NR: not reported, NYHA: New York Heart Association, SD: standard deviation

Septal Reduction Therapies

In the 2015 systematic review with meta-analysis of septal reduction therapies, the pooled median percentage reduction in NYHA class after both septal ablation and myectomy was 45% and the median proportion of patients remaining in NYHA class III/IV was 8% after septal ablation and 5% after myectomy (p=0.43). Median LVOT gradient reduction was 71% after septal ablation and 77% after myectomy (p=0.63). More patients in the septal ablation cohorts required reintervention than in the myectomy cohorts (7.7% compared to 1.6%, p=0.001) (Table 3.6).[27] In a 2020 systematic review with meta-analysis of septal reduction therapies, the pooled mean difference in NYHA class before and after treatment was -1.16 (-1.43 to -0.90) after septal ablation, -1.51 (-1.69 to -1.33) for myectomy, and -1.31 (-1.69 to -1.33) across both therapies.[31]

Table 3.6. Selected Pooled Outcomes in Studies of Septal Reduction Therapies[27]

	Septal Ablation	Myectomy
NYHA, % Reduction, Weighted Median (IQR)	45 (45-50)	45 (44-48)
Remaining in NYHA III/IV, %, Weighted Median (IQR)	8 (8-8)	4.5 (4.5-12)
LVOT Gradient, mm Hg, % Reduction, Weighted Median (IQR)	71 (67-90)	77 (69-90)
Re-Intervention, Weighted Median (IQR)*	7.7 (4.2-11.1)	1.6 (0.6-2.6)

IQR: interquartile range, LVOT: left ventricular outflow tract, mm Hg: millimeter of mercury, NYHA: New York Heart Association
*Indicates a statistically significant difference between groups.

Harms

Mavacamten

In the EXPLORER trial, 88% of participants in the mavacamten group reported any treatment-emergent adverse event compared to 79% in the placebo arm. Common adverse events included ventricular tachycardia, atrial fibrillation, palpitations, cardiac failure, and angina. Eleven serious adverse events were reported by 10 (8%) patients in the mavacamten group versus 20 serious events reported by 11 (9%) in the placebo group. Serious adverse events leading to discontinuation

were reported by 1.6% of participants in the mavacamten group versus 0.8% in the placebo arm (Table 3.7).[21]

The study protocol required temporary treatment discontinuation for LVEF less than 50%, excessive QT interval, and mavacamten plasma concentration >1,000 ng/mL. During the study period, three patients on mavacamten and two patients on placebo temporarily discontinued due to LVEF decreases to less than 50% and an additional four patients on mavacamten had LVEF less than 50% at week 30. In three of the four patients, the LVEF returned to normal, and in one patient, severe systolic dysfunction developed after an atrial fibrillation ablation with complications. One of these patients in the mavacamten group had a procedural complication after ablation for atrial fibrillation and severe LVEF decrease, but partially recovered to LVEF 50% during the washout period. Three patients on mavacamten and three patients on placebo temporarily discontinued due to changes in QT interval. No patients discontinued due to mavacamten plasma levels. All patients who discontinued during the study period resumed treatment.[21]

In the long-term extension study of mavacamten (MAVA-LTE, n=224), no additional safety concerns were reported. Treatment-emergent adverse events were reported by 141 participants (62.9%). Serious adverse events were reported by 19 (8.5%), and two patients (0.9%) discontinued due to adverse events.[24]

Table 3.7. Overview of Safety Data for EXPLORER at 30 Weeks[24,34]

	Mavacamten (n=123)	Placebo (n=128)
Treatment-Emergent Adverse Events, n (%)	108 (88)	101 (79)
Serious Adverse Events, n (%)	10 (8)	11 (9)
Discontinuation, n (%)	4 (3.3)	3 (2.3)
Adverse Events Leading to Discontinuation, n (%)	2 (1.6)	1 (0.8)
Cardiac Serious Adverse Events, n (%)	4 (3.3)	4 (3.1)

n: number

Disopyramide

As an antiarrhythmic agent, disopyramide has known risks of proarrythmia. However, in a multi-center retrospective study of disopyramide, sudden cardiac death was similar in the disopyramide-treated patients (1.4%) and non-disopyramide-treated patients (2.6%, p=0.07). It is possible that there was selection bias with patients at greater risk of arrhythmia being less likely to receive disopyramide.[26] In a single-site retrospective study focusing on the safety of disopyramide, QT interval was prolonged by a mean 19 ms compared to baseline. The proportion of patients with QT prolongation ≥460 mg was 16% at baseline and 33% after disopyramide.[33]

Additional substantial concerns with disopyramide are drug-related side effects and treatment discontinuation.

Detailed harms of disopyramide were not reported in Sherrid 2005, however, eight patients (7%) discontinued due to intolerance, such as dry mouth (n=5) and prostatism (n=3).[26] In a single-site retrospective study, of 168 patients with HOCM who were started on disopyramide, 38 (23%) reported side effects. These side effects included anticholinergic effects (n=27), weakness and fatigue (n=50), and nausea (n=1). Eighteen (11%) discontinued the drug due to side effects. More information on harms of disopyramide is available in Table D30 of the Report Supplement.

Septal Reduction Therapies

The most important safety concern with septal reduction therapies is procedure-related harms. In a 2015 systematic with meta-analysis of septal reduction therapies, pooled peri-procedural mortality (<30 days) was 1.3% in the septal ablation cohorts and 2.5% in the myectomy cohorts (p=0.051). In addition, in-hospital outcomes are worse at lower-volume centers.[34] Peri-procedural adverse arrhythmic events, including sustained ventricular tachycardia and ventricular fibrillation, were 2.2% in the septal ablation cohorts and 1.0% in the myectomy cohorts (p=0.091). The need for permanent pacemaker implantation was higher in the septal ablation cohorts compared to the myectomy cohorts (10% vs. 4.4%, p=<0.001) (Table 3.8).[27]

Table 3.8. Pooled Safety Outcomes in Studies of Septal Reduction Therapies[27]

	Septal Ablation	Myectomy
Peri-Procedural Mortality (<30 Days), %, Weighted Mean (95% CI)	1.3 (0.7-1.8)	2.5 (1.4-3.6)
Peri-Procedural Adverse Arrhythmic Events, %	2.2	1.0
Cardiac Mortality, %, Weighted Mean	1.1	2.5
Permanent Pacemaker Implantation, %, Weighted Mean (95% CI)*	10 (7.8-12.1)	4.4 (2.6-6.2)

CI: confidence interval

Subgroup Analyses and Heterogeneity

In the EXPLORER trial, treatment effects for mavacamten across most subgroups were consistently indistinguishable from the average treatment effect with the exception that patients receiving concomitant beta blockers in addition to mavacamten were less likely than patients not on beta blockers to achieve the primary composite endpoint of complete response (30% vs. 59%). It is unclear whether this treatment interaction was related to a blunting of the effect of mavacamten or to how the primary endpoint was assessed since it included exercise testing.[21] There was no statistically significant difference in the primary endpoint for men versus women. Although outcomes are not reportedly separately by race, there were only six Black patients, one Native American or Alaska Native patient, and six Asian patients in the trial.

We sought evidence on the effectiveness of mavacamten in subgroups of interest such as in children, specific genetic variants of HOCM, and non-obstructive HCM, however, the evidence was

not available or not sufficient to assess effectiveness in these populations. Data from the MAVERICK trial on the effectiveness of mavacamten in non-obstructive HCM are described in Table D10 of the Report Supplement.[24]

In the retrospective study of disopyramide, modest improvements in peak gradient and no improvement in NYHA class were observed in the subgroup of patients who required invasive interventions compared to the subgroup of patients who stayed on drug treatment.[26]

In the 2015 systematic review with meta-analysis of septal reduction studies, septal ablation was associated with fewer peri-procedure complications than myectomy, but greater need for reintervention and permanent pacemaker implantation.[27]

Uncertainty and Controversies

While mavacamten improved physiologic parameters and symptoms in the EXPLORER trial, the available data are mostly short term, and symptomatic HOCM, once it appears, can last a lifetime. Clinical experts differed on whether the reductions in ejection fraction with mavacamten reflected beneficial improvements in cardiac function, including healthy remodeling, or worrisome changes that could be associated with clinical harm with longer observation times. Rapid loss of improvements in quality of life when mavacamten was stopped suggest that neither of these may be occurring, although any regression in physiological measurements (such as peak VO_2) is unclear. In a Phase II trial of a different myosin inhibitor, aficamten, one patient had transient reduction in LVEF.[15] Longer-term data are needed to understand if this has prognostic importance.

More than 90% of patients in EXPLORER were white leaving questions about the representativeness of the study population and the external validity of the results. Also, the mean age in the trial was 58.5, but treatment can be needed in younger patients. As such, the external validity of these results in real-world populations is uncertain. Trials have inclusion and exclusion criteria that are different than patients who receive a treatment in actual practice. Results from real-world use after FDA approval will help assess these potential concerns.

While patients and patient groups and some clinical experts have identified disopyramide as an important later-line medical therapy for HOCM and an important comparator for mavacamten,[35] it has not been studied in high-quality randomized trials, either against placebo or against mavacamten, limiting the ability to make direct or indirect comparisons of the agents. The largest retrospective multicenter analysis reports treatment effects for disopyramide among patients who did not have major interventions such as dual-chamber pacing or septal reduction therapy.[26] In addition, patients who received major interventions did not have improvement with disopyramide before receiving interventions. As such, the reported treatment effect among patients who did not receive interventions is larger than the actual treatment effect among all patients. In addition, this analysis reports changes in symptoms as measured by NYHA class when patients initially presented

for evaluation at a specialized HCM center (rather than immediately before starting disopyramide). Both of these effects likely exaggerate the reported efficacy of disopyramide in this analysis although the direction of bias is uncertain. Furthermore, patients enrolled in this retrospective, real-world analysis at four referral centers likely differ from patients enrolled in EXPLORER. These issues pose problems for the comparison of mavacamten to disopyramide.[35] Furthermore, long-acting disopyramide suffers from a drug shortage and in real-world practice, few patients are actually taking disopyramide.[36]

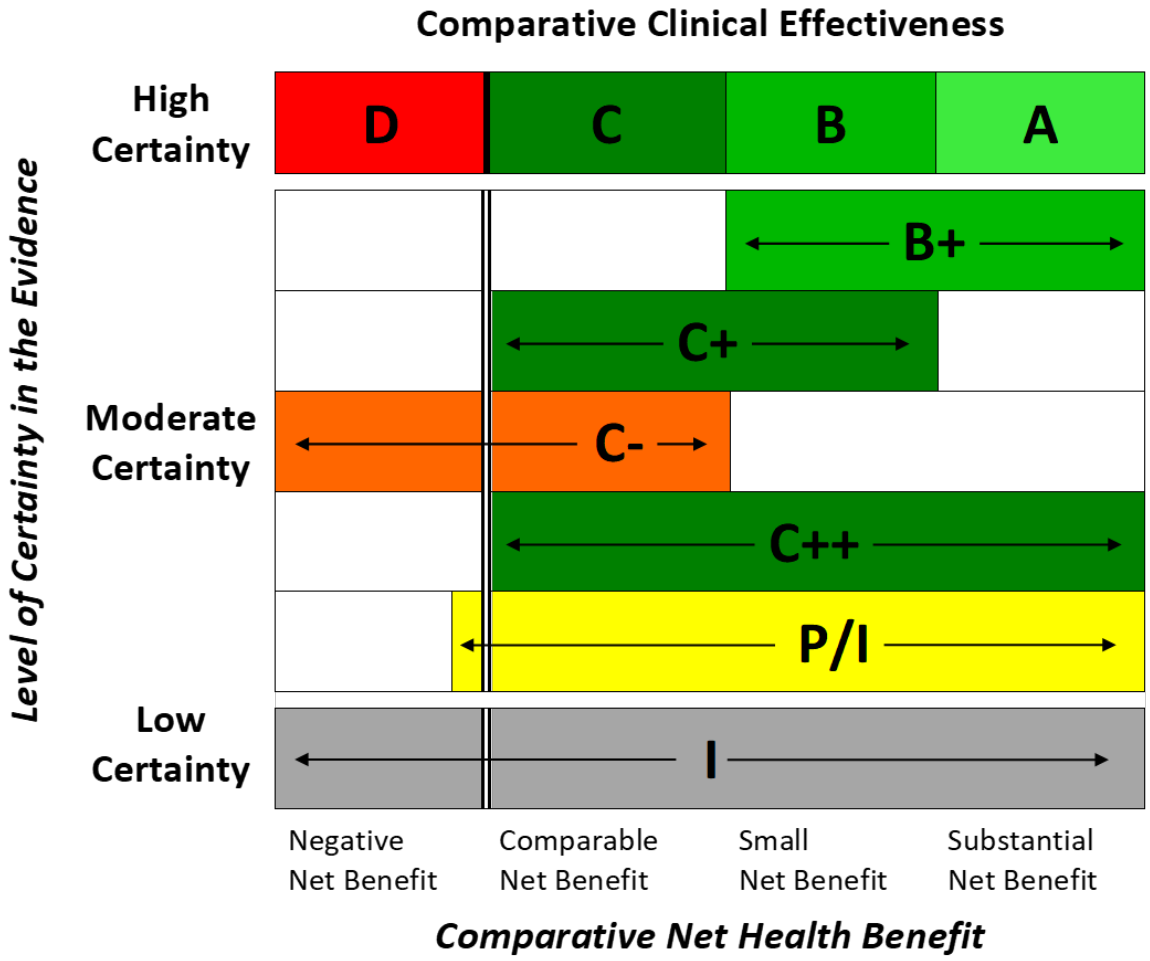
There are also no randomized data comparing surgical myectomy to septal ablation or comparing either type of septal reduction therapy to mavacamten. An ongoing randomized trial is examining whether mavacamten can reduce the need for septal reduction procedures,[11] but this does not directly assess the relative benefits of mavacamten and such procedures. Even in patients who are otherwise indifferent to the varying benefits and risks of a procedure or a medication, the lack of direct randomized evidence of the procedures versus mavacamten (or the procedures vs. one another) limits the ability to make rigorous comparisons. Furthermore, it is unclear whether the results of septal procedures at centers of excellence, where many patient series are from, can be generalized to other centers.

Patients treated with mavacamten who received cMRI during the trial demonstrated substantial regression in the pathological hypertrophic characteristic of this syndrome.[37] However, as mentioned above, symptoms of clinical dyspnea as measured by the KCCQ dropped from week 30 at the end of the trial to baseline by week 38, after eight weeks off study medication.[29] This discordance between 1) imaging results in the cMRI sub-study showing regression of hypertrophy and 2) patient-reported outcomes worsening after discontinuation of mavacamten raise concerns about the adequacy of imaging findings as surrogate outcomes. Furthermore, if any recurrence of hypertrophy occurs after stopping mavacamten, the clinical implication of that recurrence is unclear.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable" *- High certainty of a comparable net health benefit*
D= "Negative" *- High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" *- Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" *– Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

The randomized EXPLORER trial demonstrates that mavacamten improves exertional symptoms and quality of life in patients with symptomatic HOCM and had relatively few adverse effects during the trial period. This trial has reported data including patient-reported outcomes and physician-assessed outcomes, which are concordant with an objective measure of physiologic oxygen consumption. As such, EXPLORER presents a range of concordant, relevant patient outcomes with a strong study design (prospective randomized placebo-controlled trial) creating evidence for the efficacy of mavacamten. Taken alone, this information could have led to a better evidence rating. Importantly, however, with any new therapy there are concerns about adverse effects not detected during pre-approval trials. In our review, experts had starkly contrasting interpretations of the safety signals from EXPLORER. In particular, some experts worry that the reduction in LVEF and myocardial muscle thickness could lead to long-term harms rather than benefits.[35] Thus, in the absence of additional long-term evidence on mavacamten, we need to consider the potential for possible net harms, and we rate mavacamten in addition to usual care compared with usual care alone as *promising but inconclusive* ("P/I").

When comparing mavacamten with disopyramide, we are limited by the absence of head-to-head randomized trials and the absence of randomized trials of disopyramide. The best observational evidence on disopyramide appears to show similar benefits to mavacamten in those who continue taking it, but the study design could inflate the benefits of disopyramide: those who did not improve on it would be more likely to discontinue therapy. Additionally, disopyramide has known common side effects from its anticholinergic effects and the potential for serious harms from being pro-arrhythmic. The long-acting form suffers from a drug shortage and in practice, few patients take disopyramide. On balance, and considering the lack of long-term evidence on mavacamten, we consider the evidence for mavacamten compared with disopyramide to be *promising but inconclusive* ("P/I") as well.

We lack randomized trials of septal reduction therapies either to each other, compared with no procedure, or compared with mavacamten. Observational data appears to show greater improvements in functional outcomes with such procedures than was seen in the EXPLORER trial. However, these procedures carry risks of serious harms including death and the need for pacemakers to manage damage to the cardiac conduction system. Additionally, most data on these procedures comes from centers of excellence and it is uncertain how these results generalize when the procedures are done elsewhere. As discussed later in this report, modeling suggests greater quality-adjusted life year (QALY) gains with septal reduction procedures than with mavacamten. On balance, it seems likely that for patients who qualify for a septal reduction procedure, overall benefits are greater with a procedure than with mavacamten. However, this choice is highly dependent on patient preferences given the potential for short-term harms with procedures. Evidence-based medicine groups have considered that there can be rare situations in which assigning a preferred strategy is unhelpful given expected wide discrepancies in patient choices based on individual patient preferences. That is, the effects of common individual patient

preferences are so important that large variation will persist even with ideal comparative effectiveness evidence. We believe the tradeoffs between a more effective procedure for HOCM with a small but important short-term risk of death and a less effective medication are very preference dependent. Given this profound preference dependence, recommending a specific strategy is unhelpful. As such, we are not assigning an evidence rating to this comparison. These decisions will need to be made on a case-by-case basis through discussions among patients, families, and clinicians.

Table 3.9. Evidence Ratings

Treatment	Comparator	Evidence Rating
Mavacamten plus beta blockers and calcium channel blockers	Beta blockers and calcium channel blockers alone	P/I
Mavacamten plus beta blockers and calcium channel blockers	Disopyramide	P/I
Mavacamten plus beta blockers and calcium channel blockers	Septal reduction therapies	See discussion in text

P/I: promising but inconclusive

CTAF Votes

Table 3.10. CTAF Votes on Comparative Clinical Effectiveness

Question	Yes	No
Is the currently available evidence adequate to demonstrate that the net health benefit of mavacamten added to background therapy is superior to that provided by background therapy alone?	6	9
Is the currently available evidence adequate to demonstrate that the net health benefit of mavacamten is superior to that provided by disopyramide?	2	13

A majority of the panel voted that the evidence is not adequate to demonstrate that mavacamten plus background therapy is superior to background therapy alone. Panelists who voted with the majority cited the lack of long-term data and voiced concerns about potential adverse events, such as reductions in ejection fraction. Members who voted "Yes" noted EXPLORER's strong study design and the apparent improvements demonstrated in the trial in NYHA class, LVEF, pVO_2, cardiac biomarkers, and several patient-reported outcomes, such as the KCCQ.

A larger majority of the panel voted that the evidence is not adequate to demonstrate that mavacamten is superior to disopyramide due to the lack of head-to-head and randomized trials.

4. Long-Term Cost Effectiveness

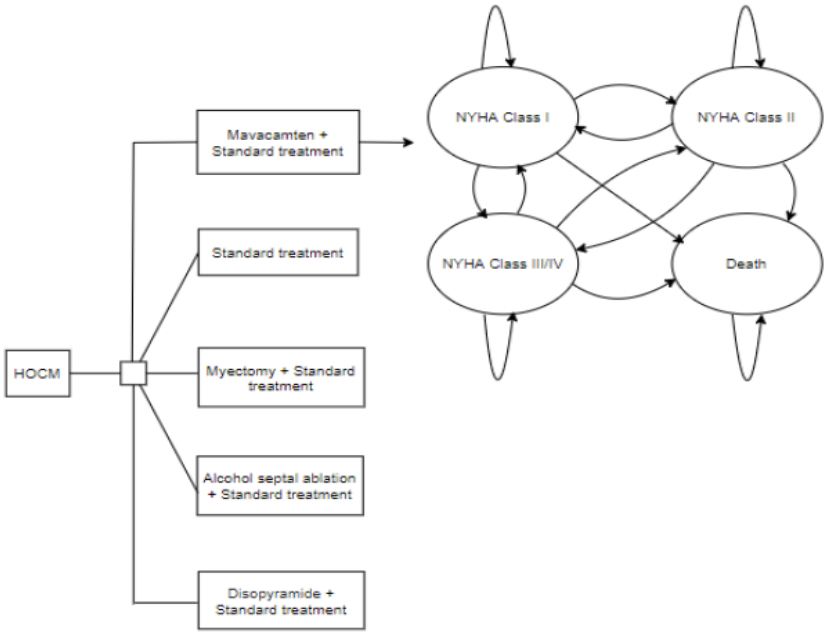
4.1. Methods Overview

The primary aim of this analysis was to estimate the incremental cost effectiveness of mavacamten used along with first-line standard of care treatments for patients with symptomatic HOCM. We developed a *de novo* semi-Markov model for this evaluation, informed by key clinical trials and prior relevant economic models. Costs and outcomes were discounted at 3% per year.

The model focused on an intention-to-treat analysis, with a hypothetical cohort of patients with symptomatic HOCM starting the model and being treated with mavacamten along with standard first-line therapy, standard first-line therapy alone, myectomy along with standard first-line therapy, septal ablation along with standard first-line therapy, or disopyramide along with standard first-line therapy. Model cycle length was four weeks based on available clinical data.

Figure 4.1 shows the treatment pathways and health states that form the Markov model. The model was programmed in Microsoft Excel 2016 (Redmond, WA). Treatment effects were characterized via observed changes in NYHA class post-treatment available from clinical trial data for mavacamten and standard first-line treatment and standard first-line therapy alone. Literature-based estimates of NYHA class changes for myectomy and standard first-line therapy, septal ablation with first-line therapy, and for disopyramide and standard first-line therapy were extrapolated to be comparable to the patient population in EXPLORER (see further detail below). Proportion of alive patients across NYHA class was assumed to be constant after Cycle 8 (week 32) in the mavacamten and standard first-line therapy and standard first-line therapy alone arms and past Cycle 1 (week four) in the myectomy and standard first-line therapy, septal ablation and standard first-line therapy, and disopyramide and standard first-line therapy arms. Based on discussions with clinical experts and a literature review, mortality rates, adjusted for age and gender, reflected US average all-cause mortality from the Centers for Disease Control and Prevention (CDC) and were assumed constant across NYHA class in this model. As such, the only mortality effect across treatments in the base-case model was associated with perioperative mortality from myectomy and septal ablation. A scenario analysis was also conducted that assigned higher mortality to patients in NYHA class III/IV. Patients remained in the model until they died.

Figure 4.1. Model Structure



HOCM: hypertrophic obstructive cardiomyopathy, NYHA: New York Heart Association

Various changes were made in response to public comments. First, several errors were identified in the model inputs, including an incorrect disutility for age and a switch of the perioperative mortality rates for septal ablation and myectomy. We had also reported undiscounted totals of time in NYHA class I. Additional detail surrounding costs was added to the input tables. We have updated the sensitivity analyses and they are shown separately for cost and QALYs and we have added a scenario analysis mentioned above considering increased mortality associated with NYHA class III/IV. Our base-case analysis continues to take a health care sector perspective (i.e., focuses on direct medical care costs only) and uses a lifetime time horizon. Unfortunately, data to conduct a formal societal perspective analysis were not available. However, we have also added several scenario analyses showing the impact of hypothetical employment effects of mavacamten and standard first-line therapy relative to first-line therapy alone.

4.2. Key Model Assumptions and Inputs

Table 4.1. Key Model Assumptions

Assumption	Rationale
Patient utilities were estimated via NYHA class with age decrements applied in the model using US average utilities across age.	Utilities were available by NYHA class from the EXPLORER trial but not by age, so we adjusted for age using US average differences by age.
We used a placeholder price of $75,000 per year for mavacamten.	The only available estimate for the price of mavacamten was a projected annual cost found online.
Mortality was the same across NYHA classes.	This assumption ensured that there were no relative mortality effects of the treatments, which was consistent with conversations with clinical experts and available literature regarding mortality in general in HOCM as well as relative effects of treatments on mortality. A scenario analysis that assigned higher mortality to patients in NYHA class III/IV tested this assumption.
We used transition rates across NYHA classes for mavacamten along with standard first-line therapy and for first-line therapy, based on those seen in weeks 26-30 to project NYHA class up to Cycle 8 in the model and then held the proportion of alive patients in each NYHA class constant.	The only available data to model NYHA class transitions in HOCM patients across time for mavacamten with first-line therapy and for first-line therapy alone were from EXPLORER. There were slight upward trends in NYHA I proportions between week 26 and week 30; however, there was also reason to believe NYHA class would begin to deteriorate at some point. As a middle ground assumption, we opted to hold the proportions of alive patients fixed across NYHA classes post Cycle 8.
The treatment effect of myectomy with standard first-line therapy, septal ablation with standard first-line therapy, and disopyramide along with standard first-line therapy occurred between weeks 0-4 and then the proportions of alive patients across NYHA classes in those arms were held constant.	The data on treatment effects for myectomy with standard first-line therapy, septal ablation with standard first-line therapy, and disopyramide with standard first-line therapy were based on longer time periods, years rather than weeks, making it impossible to know how rapid the treatment effects occurred or to know particular dynamics in the treatment effect that may have occurred over the first several months/years. It is possible that the treatment effects were larger or smaller in earlier time periods following the treatment in question than what was measured. It is also likely that eventually NYHA status would deteriorate across the lifetime. As a middle ground assumption, we opted to hold the proportion of alive patients across NYHA class constant after the first cycle in those two arms.
The model did not include discontinuation or serious adverse events.	Comparable data were not available for these aspects of the treatment courses other than directly between mavacamten with first-line therapy and first-line therapy alone where the rates of adverse events were very similar. Discontinuation was considered indirectly in the disopyramide treatment effect (see below) in a way consistent with how mavacamten was being modeled in terms of projections over a lifetime based on the trial data. Discontinuation over the long term in mavacamten was not available nor the extent to which discontinuation would result in surgical options. Minor disutility differences in comparing mavacamten and first-line therapy vs. first-line therapy alone are included. Substantial relative differences in adverse events associated with the treatments were not apparent in the literature other than perioperative mortality for myectomy and septal ablation, disutility from major surgery for myectomy and septal ablation, and higher use of pacemakers with septal ablation than myectomy, which were included in the model.

HOCM: hypertrophic obstructive cardiomyopathy, NYHA: New York Heart Association, US: United States

Table 4.2 below lists selected base-case model inputs along with the lower and upper values used in the deterministic sensitivity analyses. See the Report Supplement for more detailed descriptions of the model inputs.

Table 4.2. Model Inputs

Input Name	Treatment	Base Case	Lower Value	Upper Value
Epidemiological Inputs				
Age	--	58.00	34.00	82.00
Female	--	0.41	--	--
Clinical Inputs				
Mavacamten Treatment Effect (% NYHA I in Cycle 1)	Mavacamten	0.24	0.18	0.31
First-Line Treatment Effect	Standard	0.08	0.06	0.10
Myectomy Treatment Effect	Myectomy	0.77	0.58	0.96
Disopyramide Treatment Effect	Disopyramide	0.28	0.21	0.36
Septal Ablation Treatment Effect	Septal ablation	0.77	0.58	0.96
Quality-of-Life Inputs				
Utility of NYHA Class I for Mavacamten	Mavacamten	0.95	0.65	1.00
Utility of NYHA Class II for Mavacamten	Mavacamten	0.87	0.66	0.98
Utility of NYHA Class III and IV for Mavacamten	Mavacamten	0.71	0.56	0.84
Utility of NYHA Class I for SoC	Standard	0.95	0.65	1.00
Utility of NYHA Class II for SoC	Standard	0.85	0.65	0.97
Utility of NYHA Class III and IV for SoC	Standard	0.70	0.56	0.83
Utility of NYHA Class I for Other Comparators	Myectomy, septal ablation, and disopyramide	0.95	0.65	1.00
Utility of NYHA Class II for Other Comparators	Myectomy, septal ablation, and disopyramide	0.86	0.65	0.98
Utility of NYHA Class III and IV for Other Comparators	Myectomy, septal ablation, and disopyramide	0.71	0.56	0.83
Cost Inputs*				
Per Cycle Cost of Mavacamten	Mavacamten	$5,769	$4,694	$6,954
First Cycle Cost of Metoprolol	Metoprolol cycle 1	$38	$31	$46
Per Cycle Cost of Metoprolol	Metoprolol	$64	$52	$77
First Cycle Cost of Verapamil	Verapamil cycle 1	$49	$40	$59
Per Cycle Cost of Verapamil	Verapamil	$56	$46	$67
First Cycle Cost of Disopyramide	Disopyramide	$309	$252	$373
Per Cycle Cost of Disopyramide	Disopyramide	$413	$336	$497
Disopyramide Hospitalization Cost	Disopyramide	$8,559	$6,964	$10,316
Myectomy Procedure Cost	Myectomy	$122,759	$99,881	$147,960
Septal Ablation Procedure Cost	Septal ablation	$55,706	$45,325	$67,142

NYHA: New York Heart Association, SoC: standard of care

*All costs used in the model were updated to 2021 dollars based on the methods outlined in the ICER Reference Case.

Sensitivity and Threshold Analyses

We conducted deterministic one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We also performed threshold analyses for drug costs across a range of incremental cost-effectiveness ratios ($50,000, $100,000, $150,000, and $200,000 per QALY and evLYG) for mavacamten and first-line therapy relative to first-line therapy alone.

We included a scenario analysis that incorporates higher mortality for patients in NYHA class III/IV (hazard ratio [HR] 1.96) based on a meta-analysis of HCM patients.[38] We had also wanted to include a formal scenario analysis from a societal perspective but were unable to acquire the necessary data. We do consider several scenario analyses to examine the impact of potential differences from a societal perspective. First, we look at mavacamten and standard first-line therapy relative to standard first-line therapy alone where we model patients in NYHA class I as working full time and those in NYHA class II and class III/IV as being unemployed. In a second related scenario, we model mavacamten patients as all being employed and have all patients on first-line therapy alone as unemployed. In each case, we use average US wages ($27.07) across all occupations and 2,000 hours per year to model the annual financial gains for employed patients.[39]

4.3. Results

Base-Case Results

Tables 4.3 and 4.4 present the base-case results.

Table 4.3. Results for the Base Case for Each of the Treatments

Treatment	Total Drug Cost	Total Cost	QALYs	Life Years	NYHA I Years	evLY
Mavacamten*†	$1,258,000	$1,568,000	14.75	16.58	8.50	14.75‡
Standard Treatment	$12,600	$434,000	13.78	16.58	3.33	13.78
Disopyramide*	$116,000	$509,000	14.06	16.58	4.69	14.06
Septal Ablation*	$67,800	$297,000	14.97	16.40	12.49	14.97
Myectomy*	$135,000	$364,000	14.97	16.37	12.47	14.97

evLY: equal-value of life years, N/A: not applicable, NYHA: New York Heart Association, QALY: quality-adjusted life year

*Each of these treatments includes use of standard first-line therapy.

†Cost estimates for mavacamten were based on a placeholder price of $75,000 per year.

‡evLY for mavacamten is calculated as compared to standard treatment.

Table 4.4. Incremental Cost-Effectiveness Ratios for Mavacamten in the Base Case

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Additional NYHA I Year
Mavacamten*	Standard treatment	$1,200,000	Undefined	$1,200,000	$219,000
	Disopyramide	$1,500,000	Undefined	$1,500,000	$278,000
	Myectomy	Dominated	$5,600,000	N/A†	Dominated
	Septal ablation	Dominated	$7,000,000	N/A†	Dominated

evLY: equal-value of life years, N/A: not applicable, NYHA: New York Heart Association, QALY: quality-adjusted life year

*Incremental cost ratios are based on a placeholder price of $75,000 per year for mavacamten.

†Incremental cost per evLY gained not applicable due to fewer lifetime QALYs for mavacamten as compared to myectomy and septal ablation.

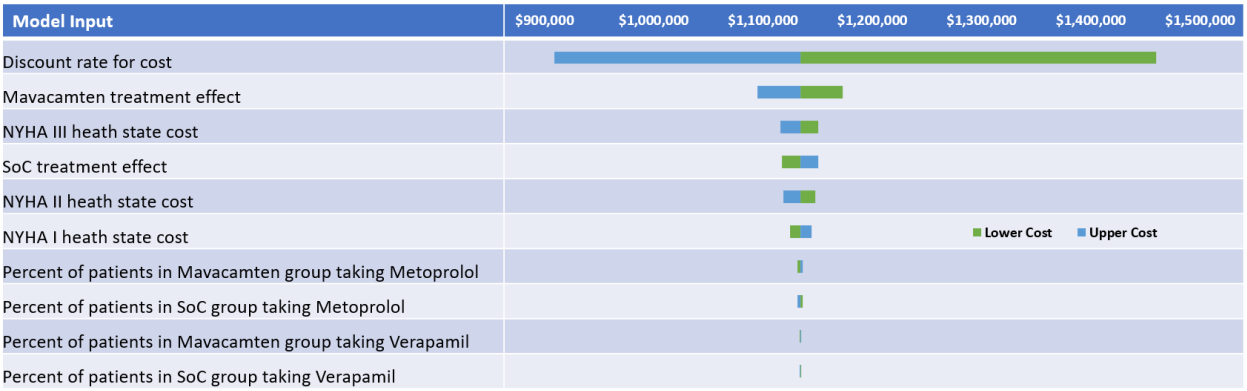
In the model, mavacamten along with standard first-line therapy was projected to produce more QALYs than standard first-line therapy alone but with very high additional costs when assuming a placeholder price of $75,000 per year for mavacamten. This resulted in an incremental cost per QALY well above standard thresholds. The incremental cost per QALY is even higher when comparing mavacamten to disopyramide. When compared to myectomy and septal ablation in terms of QALYs, mavacamten costs more and produced fewer QALYs. In terms of life years, due to procedural mortality, mavacamten produces more life years but at a very high cost per life year gained.

Sensitivity Analyses

One-way sensitivity analyses were conducted to measure the effect of uncertainty on projected incremental costs and QALYs between mavacamten with first-line therapy relative to first-line therapy alone. Figures 4.2A and 4.2B and Tables 4.5A and 4.5B present the results of these deterministic sensitivity analyses. Table 4.6 presents a summary of the probabilistic sensitivity analyses comparing mavacamten to standard treatment alone.

Given the lifetime horizon model, naturally, the incremental costs were sensitive to the discount rate though always sizable. The projected incremental costs were also relatively sensitive to potential variance in the treatment effects and NYHA-class-related costs although, once again, the projected incremental costs were always sizable. The incremental QALYs were relatively sensitive to the NYHA class utilities although, overall, mavacamten ranged from negative to relatively small gains in comparison with the incremental costs. Potential variance in the treatment effects of mavacamten with first-line therapy and first-line therapy alone had lesser effects on the QALYs than the utility scores of the NYHA.

Figure 4.2A. Tornado Diagram of Incremental Cost for Mavacamten versus Standard of Care



NYHA: New York Heart Association, SoC: standard of care

Table 4.5A. Inputs and Results for Mavacamten versus Standard of Care Incremental Cost Tornado Diagram

Input	Lower Cost	Upper Cost	Low-Input Value	High-Input Value
Discount Rate for Cost	$1,459,478	$909,141	0.01	0.05
Mavacamten Treatment Effect	$1,172,786	$1,094,769	0.18	0.31
NYHA III Heath State Cost	$1,150,089	$1,115,809	$2,299.24	$3,405.99
SoC Treatment Effect	$1,117,467	$1,150,088	0.06	0.10
NYHA II Heath State Cost	$1,147,666	$1,118,478	$1,663.84	$2,464.74
NYHA I Heath State Cost	$1,124,338	$1,144,176	$611.31	$905.57
Percent of Patients in Mavacamten Group Taking Metoprolol	$1,131,167	$1,136,388	0.57	0.95
Percent of Patients in SoC Group Taking Metoprolol	$1,136,319	$1,131,236	0.56	0.93
Percent of Patients in Mavacamten Group Taking Verapamil	$1,133,174	$1,134,381	0.15	0.25
Percent of Patients in SoC Group Taking Verapamil	$1,134,170	$1,133,385	0.10	0.16

NYHA: New York Heart Association, SoC: standard of care

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Figure 4.2B. Tornado Diagram of Incremental QALY for Mavacamten versus Standard of Care

NYHA: New York Heart Association, SoC: standard of care

Table 4.5B. Inputs and Results for Mavacamten versus Standard of Care Incremental QALY Tornado Diagram

Input	Lower QALY	Upper QALY	Low-Input Value	High-Input Value
Utility of NYHA Class II for SoC	2.91	-0.21	0.65	0.97
Utility of NYHA Class I for Mavacamten	-1.55	1.40	0.65	1.00
Utility of NYHA Class II for Mavacamten	-0.47	1.78	0.66	0.98
Utility of NYHA Class I for SoC	1.98	0.81	0.65	1.00
Utility of NYHA Class III and IV for SoC	1.50	0.52	0.56	0.83
Discount Rate for Outcomes	1.26	0.78	0.01	0.05
Mavacamten Treatment Effect	0.75	1.20	0.18	0.31
Utility of NYHA Class III and IV for Mavacamten	0.80	1.13	0.56	0.84
SoC Treatment Effect	1.09	0.86	0.06	0.10

NYHA: New York Heart Association, QALY: quality-adjusted life year, SoC: standard of care

Tables 4.6A and 4.6B below show the results of the probabilistic sensitivity analysis. The tables illustrate that extremely few and/or none of the simulations resulted in mavacamten along with first-line treatment being deemed cost effective relative to first-line therapy alone even at a willingness-to-pay threshold of $200,000 per QALY. The results were the same in looking at costs per evLY gained.

Table 4.6A. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Mavacamten versus Standard of Care

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY
Mavacamten	0.0%	0.0%	0.0%	0.0%

QALY: quality-adjusted life year

Table 4.6B. Probabilistic Sensitivity Analysis Cost per evLY Gained Results: Mavacamten versus Standard of Care

	Cost Effective at $50,000 per evLYG	Cost Effective at $100,000 per evLYG	Cost Effective at $150,000 per evLYG	Cost Effective at $200,000 per evLYG
Mavacamten	0.0%	0.0%	0.0%	0.0%

evLYG: equal value of life years gained

Scenario Analyses

Tables 4.7 and 4.8 show the incremental results when higher mortality for NYHA class III/IV is incorporated into the model. Again, we find that mavacamten plus standard of care had high incremental cost utility ratios relative to standard of care and to disopyramide plus standard of care and that it was dominated by the other arms.

Table 4.7. Results for the Scenario with Higher Mortality for NYHA Class III/IV

Intervention	Intervention Costs	Total Costs	QALYs	Life Years	NYHA I Years	evLY
Mavacamten	$1,242,000	$1,544,000	14.60	16.37	8.49	14.97
Standard Treatment	$12,100	$410,000	13.33	15.94	3.32	13.33
Disopyramide	$112,000	$485,000	13.68	16.04	4.69	13.68
Septal Ablation	$67,700	$295,000	14.92	16.33	12.49	14.88
Myectomy	$135,000	$361,000	14.92	16.30	12.47	14.89

evLY: equal value of life years, NYHA: New York Heart Association, QALY: quality-adjusted life year

Table 4.8. Incremental Cost-Effectiveness Ratios for Mavacamten in the Scenario with Higher Mortality for NYHA Class III/IV

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Additional NYHA I Year
Mavacamten	Standard treatment	$893,000	$2,600,000	$693,000	$219,000
	Disopyramide	$1,100,000	$3,100,000	$874,000	$279,000
	Myectomy	Dominated	$15,800,000	N/A*	Dominated
	Septal ablation	Dominated	$29,900,000	N/A*	Dominated

evLY: equal value of life years, N/A: not applicable, NYHA: New York Heart Association, QALY: quality-adjusted life year

*Incremental cost per evLY gained not applicable due to fewer lifetime QALYs for mavacamten as compared to myectomy and septal ablation.

Table 4.9 presents the incremental results of mavacamten and first-line therapy versus first-line therapy alone for the case when NYHA class I was associated with full employment and NYHA class II and III/IV were associated with no employment and also for an even more extreme case where mavacamten was associated with full employment in all NYHA classes and standard first-line therapy was associated with zero employment. In both, the incremental costs for QALYs remain above standard thresholds.

Table 4.9. Societal-Perspective-Related Scenario Analysis

Scenario	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Additional NYHA I Year
Full Employment for NYHA I and Not for Class II and Not /IV (Both Mavacamten and Standard Treatment Group)	$876,000	N/A	$876,000	$165,000
Full Employment for All Patients in Mavacamten Group and Not for Standard Treatment Group	$242,000	N/A	$242,000	$46,000

evLY: equal value of life years, N/A: not applicable, NYHA: New York Heart Association, QALY: quality-adjusted life year

Threshold Analyses

Tables 4.10A and 4.10B show per-year threshold costs for mavacamten that would be needed to achieve willingness-to-pay thresholds per QALY and per evLYG of $50,000, $100,000, $150,000, and $200,000.

Table 4.10A. QALY-Based Threshold Analysis Results

	Placeholder Cost	Price to Achieve $50,000 per QALY	Price to Achieve $100,000 per QALY	Price to Achieve $150,000 per QALY	Price to Achieve $200,000 per QALY
Mavacamten	$75,000	$9,600	$12,500	$15,400	$18,400

QALY: quality-adjusted life year

Table 4.10B. evLYG-Based Threshold Analysis Results

	Placeholder Cost	Price to Achieve $50,000 per evLYG	Price to Achieve $100,000 per evLYG	Price to Achieve $150,000 per evLYG	Price to Achieve $200,000 per evLYG
Mavacamten	$75,000	$9,600	$12,500	$15,400	$18,400

evLY: equal value of life years gained

Model Validation

We used several approaches to validate the model. First, we provided the preliminary model structure, methods, and assumptions to the manufacturer, patient organizations, and clinical experts. Based on feedback from these groups, we refined the data inputs used in the model, as needed. Second, we varied model input parameters to evaluate the face validity of changes in results. We also performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we also shared the model with Bristol Myers Squibb for external verification around the time of publishing the draft Evidence Report for this review. The model was also subject to numerous internal checks for logical functioning by changing the inputs and also several reviews of the inputs for accuracy.

Uncertainty and Controversies

There were only 30 weeks of data available for mavacamten in the EXPLORER trial on which to base projected treatment effects by NYHA class, and the EXPLORER data may not generalize to other patient populations. The utilities in the model across NYHA class also come from the trial and may not generalize to other HOCM patients. However, they were derived from HOCM patients, which we deemed to be an improvement over using utilities from more general heart failure populations. In addition, there were multiple comparators but insufficient data to conduct a network meta-analysis or other quantitative analyses controlling for treatment effects across baseline characteristics of patients in forming estimates for the comparators such as myectomy, septal ablation, and disopyramide relative to mavacamten. Further, the evidence for myectomy, septal ablation, and disopyramide comes from observational studies while the evidence for mavacamten and standard first-line therapy used in the modeling came from the EXPLORER trial.

The modeling of the treatment arms did not include discontinuation and subsequent use of other options. Though it is beyond the scope of this analysis, it is possible that greater or smaller proportions of patients on mavacamten may elect to have myectomy or septal ablation in the future as compared to standard first-line treatment alone and/or disopyramide along with standard first-line treatments. In terms of cost effectiveness, the procedures were dominant to mavacamten to begin with, but if mavacamten plus standard first-line therapy was associated with fewer follow-up procedures than standard first-line treatments alone that could impact the cost effectiveness of mavacamten and first-line therapy relative to first-line therapy alone. In addition, some mavacamten patients in the EXPLORER trial had previously undergone septal reduction procedures, which was not included in the model. Further, the procedural options involve tradeoffs between short-term mortality and long-term expected gains in QALYs that are not present in the pharmaceutical-only options.

Also, we were unable to include a societal perspective analysis using actual data. However, we did present several scenarios based on hypothetical data. Even under extreme assumptions, mavacamten was above commonly-cited thresholds from this hypothetical extreme societal perspective assuming the placeholder price for mavacamten. Further, we conducted the two additional scenario analyses to examine the impact of having treatment associated with employment.

Finally, available non-drug cost estimates by NYHA class are for a private payer and/or based on data from heart failure patients and we only had access to a placeholder cost for mavacamten.

4.4. Summary and Comment

Mavacamten used along with standard first-line treatment was projected to generate higher amounts of QALYs than standard first-line treatment alone. However, at the placeholder cost of $75,000, the incremental cost-effectiveness ratios were well above standard thresholds. When compared with disopyramide, the incremental cost per QALY was even higher, and mavacamten was found to be dominated by both myectomy and septal ablation. The sensitivity and scenario analyses suggested, using the placeholder price, that these findings were robust. However, the actual cost effectiveness of mavacamten will depend on its price.

5. Contextual Considerations and Potential Other Benefits

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the tables below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report, the appraisal committee voted on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review.

Table 5.1. Contextual Considerations

Contextual Consideration	Relevant Information
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	For many patients with symptomatic HOCM, the burden of disease can be very severe. In addition to exertional symptoms and the risk of sudden cardiac death, patients with HOCM also face anxiety, depression, concerns about activities of daily living and social events. There is uncertainty about the extent to which exercise can increase risk of sudden cardiac death for HOCM patients, and guidelines have shifted over time, leading to uncertainty and confusion among HOCM patients about optimal self-care. Since patients often have electrocardiograms and echocardiograms that mimic other conditions, including acute myocardial infarction and hypertensive heart disease, misdiagnosis is common and patients with HCM and HOCM often have frustrations with the health care system.
Magnitude of the lifetime impact on individual patients of the condition being treated	Patients with symptomatic HOCM are often at points in their lives when they are making important life choices regarding education, work, and raising families, which could provide benefits over and above the improvement in QALYs calculated in the model. The fear of death given the potential of malignant ventricular arrythmias is often present throughout life, causing a large burden to patients. Patients also report lifelong grief related to life decisions made because of fear of HCM-related complications.

HCM: hypertrophic cardiomyopathy, HOCM: hypertrophic obstructive cardiomyopathy, QALY: quality-adjusted life year

Table 5.2. Potential Other Benefits or Disadvantages

Potential Other Benefit or Disadvantage	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	Particularly when patients are diagnosed early in life, uncertainty and fear can lead to pressured life decisions about educational programs, marriage and relationships, and decisions about whether to have children. Patients reported concern about passing along genes associated with HCM to children. Some of those concerns about children are related to lack of treatment options for symptoms. Patients themselves are often underemployed because they fear moving to new jobs or communities because these moves could disrupt insurance, social supports, and access to caregivers. Symptoms of HCM or arrythmias related to HCM can interfere with work or social activities, affecting both career advancement and relationships.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	Patients also reported that the diagnosis of HCM can lead to difficulties receiving life insurance, being admitted to educational programs, and receiving loans. This can lead to underemployment since patients are reluctant to switch jobs, which often creates a shift in insurance policy. When caregivers are needed to provide care for HCM patients, they sometimes cannot work, exacerbating financial problems.
Society's goal of reducing health inequities	Mavacamten could provide more access to treatment options because septal reduction procedures are only available at specialized centers in specific cities.

HCM: hypertrophic cardiomyopathy, HOCM: hypertrophic obstructive cardiomyopathy

CTAF Votes

At the public meeting, CTAF deliberated and voted on the relevance of specific potential other benefits and contextual considerations on judgments of value for the interventions under review. The results of the voting are shown below. Further details on the intent of these votes to help provide a comprehensive view on long-term value for money are provided in the ICER Value Assessment Framework.

When making judgments of overall long-term value for money, what is the relative priority that should be given to any effective treatment for HOCM on the basis of the following contextual considerations?

Contextual Consideration	Very Low Priority	Low Priority	Average Priority	High Priority	Very High Priority
Acuity of need for treatment of individual patients based on the short-term risk of death or progression to permanent disability	2	3	7	3	0
Magnitude of the lifetime impact on individual patients of the condition being treated	0	0	4	10	1

A majority of the panel voted that a treatment for HOCM should be given average priority relative to other diseases. Panelists cited expert testimony, noting that the progression of disease is slow over time for most patients, and, on average, patients live a normal life expectancy with a low risk of death. However, panelists acknowledged that the lifetime impact of the disease is large as most patients live with HOCM and its attendant complications and high symptom burden for many years.

What are the effects of mavacamten on the following outcomes that inform judgment of the overall long-term value for money of mavacamten?

Potential Other Benefit or Disadvantage	Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
Patients' ability to achieve major life goals related to education, work, or family life	0	1	1	11	2
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0	1	2	11	1
Society's goal of reducing health inequities	0	1	8	5	1
Opportunity to improve access to treatment	0	0	6	8	1
Availability of a treatment with different timing and types of risks and benefits, relative to existing procedural and surgical options	0	0	1	9	5

A majority of the panel voted that mavacamten could have a potentially minor positive effect on patients' and caregivers' ability to achieve life goals related to education, work, or family life. These two votes were driven primarily by patient testimony, which highlighted the difficulties that patients and caregivers encounter throughout a lifetime. Among many such obstacles, patients stressed that individuals with HOCM have delayed or truncated their education, rethought marriage or children, and endured untenable jobs due to the impact of the disease on their social lives, insurance coverage and cost, and ability to conduct activities of daily living.

About half the panel voted that mavacamten would make no difference in reducing health inequities, but a bare majority did acknowledge that the drug may improve access to treatment. As stated in the most recent set of guidelines, centers of excellence play an essential role in HCM care; however, the distribution of these centers across the US is geographically unbalanced and there exist large swaths of the country without convenient access to specialists with expertise in HCM.[40] To access the highest level of care, many patients face burdensome and costly travel, and encounter difficulties taking time away from work or family obligations. Panelists noted that an oral treatment option could benefit these patients, especially in the era of telemedicine, which could encourage collaboration between a specialist at a center of excellence and a community cardiologist or primary care physician.

Lastly, although outcomes for myectomy are generally good and the risk of death is low, the procedure is invasive and requires significant aftercare. As such, a majority of the panel voted that the availability of an oral option with different risks and benefits compared to surgery may have a potentially minor or major positive effect on the disease. As advocates noted, surgery is not attainable or the best option for all patients, and access to an oral therapy may increase the number of patients who are adequately treated.

6. Health-Benefit Price Benchmarks

Health-benefit price benchmarks (HBPBs) for the annual cost of treatment are presented in Table 6.1 below. The HBPB for a drug is defined as the drug price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY gained or per evLY gained. For mavacamten, this range is $12,000 to $15,000 annually.

Table 6.1. Annual Health Benefit Price Benchmarks for Mavacamten

	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold
QALYs Gained	$12,000	$15,000
evLY Gained	$12,000	$15,000

evLY: equal value of life years, QALY: quality-adjusted life year

CTAF Votes

Value votes were not taken at the public meeting because a net price for mavacamten was not available.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Using results from the cost-effectiveness model, we estimated the potential budgetary impact of mavacamten for patients with symptomatic HOCM. We used the mavacamten price from the base-case analysis (placeholder price of $75,000 per year) and three annual threshold prices (at $50,000, $100,000, and $150,000 per QALY). Potential budget impact is defined as the total differential cost of using each new therapy rather than the relevant existing therapy for the treated population, calculated as differential health care costs (including intervention costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon.

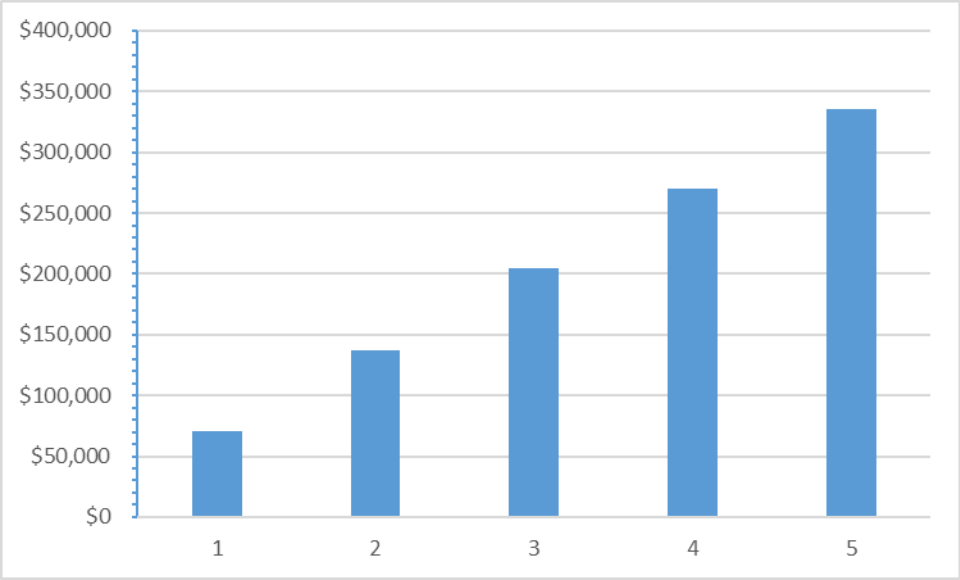
The analysis included the estimated number of individuals in the US who would be eligible for mavacamten. To estimate the size of the potential candidate population for treatment, we used inputs from best-available evidence. A study published in 2016 that examined a large claims database to calculate the prevalence of clinically-recognized HCM reported that diagnosed HCM occurred in one in 3,195 (i.e., 3.1 in 10,000) adult patients in the US.[41] Other literature has suggested that 70% of HCM patients have obstructive disease.[42] Applying these sources results in estimates of 2.2 in 10,000 patients who are diagnosed with symptomatic HOCM, or approximately 72,300 eligible patients in the US. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, or approximately 14,460 patients per year. In this potential budget impact analysis, we assumed that patients eligible for mavacamten would otherwise have been treated with standard treatment.

The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices within five years without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For 2021-2022, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $734 million per year for new drugs.

7.2. Results

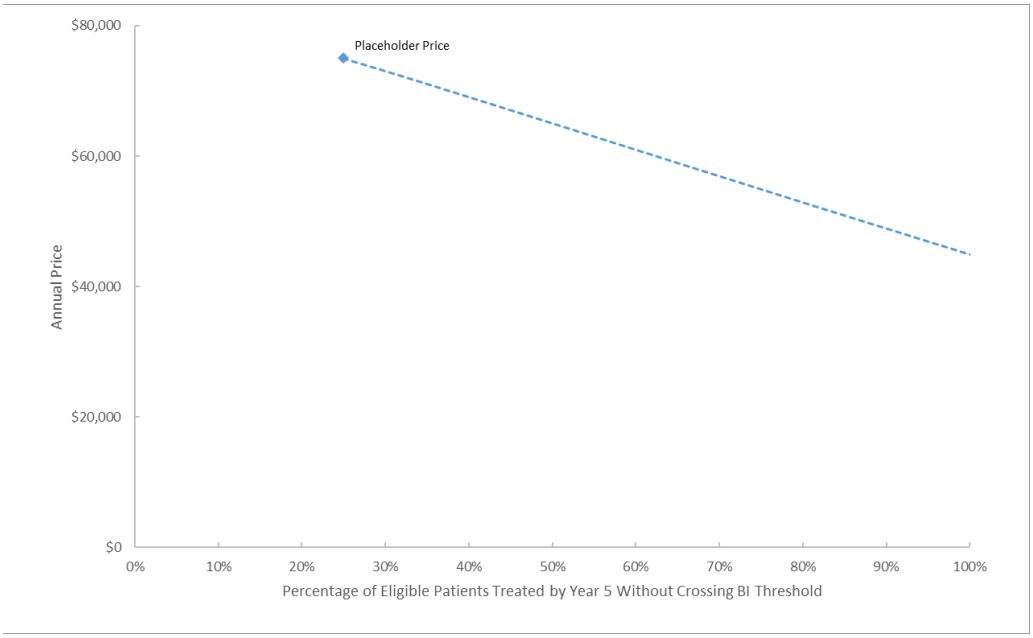
Figure 7.1 depicts the cumulative per-patient potential budget impact calculations for mavacamten as compared to standard therapy, based on a placeholder cost for mavacamten of $75,000 per year. The average potential budgetary impact for mavacamten was approximately $70,000 in year one, with cumulative net cost increasing each year to reach approximately $336,000 in year five.

Figure 7.1. Cumulative Net Cost per Patient Treatment with Mavacamten at Placeholder Price



Assuming the placeholder price of $75,000 per year, only 25% of the eligible patients could be treated within five years (assuming 20% uptake each year), before crossing the ICER potential budget impact threshold of $734 million per year. This could create a short-term potential budget impact that exceeds the potential threshold at this price. However, because this is based on a placeholder price, ICER is not issuing an access and affordability alert. All eligible patients could be treated within five years without crossing the ICER potential budget impact threshold at the price to reach $150,000 per QALY. Figure 7.2 depicts the potential budgetary impact of mavacamten.

Figure 7.2. Potential Budgetary Impact of Mavacamten in Symptomatic HOCM



BI: budget impact

8. Policy Recommendations

Following its deliberation on the evidence, CTAF engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on the use of mavacamten for symptomatic HOCM. The policy roundtable members included two patient advocates, two clinical experts, and two payers. The manufacturer declined to send a representative to participate in the policy roundtable. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

All Stakeholders

All stakeholders have a responsibility to facilitate meaningful patient access to multidisciplinary centers of excellence for HCM in ways that do not exacerbate disparities.

The most recent clinical guidelines developed by the American Heart Association/American College of Cardiology in 2020 for management of HCM explicitly recommend (class 2a) "consultation with or referral to" experienced multidisciplinary centers to aid in complex management decisions. Furthermore, for patients with HOCM, the guidelines strongly recommend that septal reduction procedures are performed in such centers (class 1).

Access to the expertise offered by these experienced multidisciplinary centers is critically important for several reasons. Although HCM is not a rare condition, many general cardiologists do not have deep expertise in diagnosis or management of HCM. HCM can mimic other disease conditions such as infiltrative cardiomyopathies and hypertensive heart disease, and even variants of normal (such as normal athlete's heart). Electrocardiograms for patients with HCM often mimic electrocardiograms for acute myocardial infarction (heart attack). As such, patients report unnecessary care escalations. In part because of these issues, patients report frustration interacting with care teams that do not have expertise in HCM. Furthermore, the diagnosis, monitoring, and management of patients with HCM often require specialized expertise in cardiac imaging and the interpretation of genetic data available only at specific centers. Lack of access to specialized centers can lead to health care disparities with respect to wealth, income, location, and race.

However, community-based physicians, including general cardiologists, also have an important role in the management of patients with HCM. Ideal care pathways could include regular care from an accessible local cardiologist with intermittent input from experts at centers of excellence. These ideal care pathways, however, are complicated by lack of access to telemedicine, restrictions on the practice of medicine between states, and payment policies limiting reimbursement for interprofessional (community physician to specialist physician) consultation.

To address these concerns:

Payers should take the following actions:

- Provide adequate reimbursement for telemedicine and interprofessional consultation between centers of excellence and community cardiologists to facilitate both access to care and appropriate subspecialist expertise when needed. Adequate reimbursement for telemedicine is also important both for initial consultation and ongoing monitoring for patients taking mavacamten.

- If payers restrict access to mavacamten to providers at specialized centers of excellence, they should work with the patient community as well as clinical experts to select these centers. Designations of centers of excellence should be meaningful. For example, provider self-attestation of expertise is unlikely to be meaningful and accurate. The HCM patient community has spent many years developing an understanding of which centers reflect the full spectrum of expertise and experience needed for excellent care of patients with HCM, and payers should collaborate with the patient community to leverage this work.

- Ensure that in the setting of promising short-term efficacy but long-term unresolved questions about safety, mavacamten is prescribed in centers with appropriate expertise and monitoring protocols. In the policy roundtable, both patients and clinical experts expressed safety concerns about the prospect of widespread use of mavacamten shortly after approval prior to the generation of longer-term data. If longer-term concerns about safety are resolved with time, however, any restrictions could be loosened to allow mavacamten to be prescribed in broader settings by a greater range of cardiologists.

Clinical specialty societies should take the following actions:

- Work with patient organizations to develop and validate standards for centers of excellence for HCM. For example, the Hypertrophic Cardiomyopathy Association has identified centers of excellence available on their website (www.4hcm.org/center-of-excellence). Aligning this type of list with input from professional societies could inform payer policy in a patient- and clinician-informed way.

- Work with payers, regulators, and patients to develop educational tools to improve knowledge about the management of HCM among community providers, including situations in which referral to a center of excellence is important.

- Continue to educate cardiologists about the critical importance of shared decision-making for all treatment options for HCM, including therapies to reduce LVOT gradient in patients with symptomatic HOCM. The 2020 guidelines recommend shared decision-making in HCM (class 1).

Organizations that provide health care should take the following actions:

- Develop and use platforms to share primary imaging data between community providers and centers of excellence to improve accuracy of diagnosis and appropriate utilization of treatments for HCM, including symptomatic HOCM. Both diagnosis and ongoing management for patients with HCM require relevant imaging and genetic counseling expertise.

- Restrict the performance of surgical myectomy and alcohol septal ablation to high-volume procedural centers with appropriate supportive services including cardiac critical care.

- Centers and providers with less expertise should establish referral pathways to and relationships with high-volume centers to ensure equity in access to patients (despite the restriction of the procedures to higher-volume centers). Since patients with HCM often seek emergency care in different settings, for example when traveling, emergency providers should have pathways to communicate with subspecialty experts in HCM when needed even when they are not physically available.

Manufacturers

The manufacturer of mavacamten should:

Commit to sponsoring research that will address the lack of evidence on the comparative effectiveness of mavacamten versus disopyramide and septal reduction procedures.

When patients with symptomatic HOCM have inadequate relief or intolerable side effects with beta blockers and calcium channel blockers, clinical guidelines support the use of disopyramide and or septal reduction procedures. After mavacamten is available, it will also become an important treatment option. Disopyramide has been approved for clinical use for many decades. The evidence evaluating the effectiveness of disopyramide is limited, but there are fewer concerns about long-term adverse effects because of more experience. As a practical matter, the short-acting form is difficult to use for patients because of a short half-life and four times per day daily dosing. However, the long-acting form, which can be given twice per day, is difficult to obtain because of drug shortages. If access to the long-acting form of disopyramide improves, it could provide a treatment option that works for many patients. Many of the patients with NYHA class III symptoms in the EXPLORER trial may also have been potential candidates for septal reduction therapies. Although VALOR-HCM will likely provide some important information for these patients, VALOR-HCM does not compare mavacamten to septal reduction procedures directly and as such, will not resolve the question of comparative effectiveness of mavacamten versus these procedures.

In that context, data are inadequate to inform important clinical choices such as:

1) Disopyramide versus mavacamten
2) Mavacamten versus alcohol septal ablation
3) Mavacamten versus surgical myectomy
4) Surgical myectomy versus alcohol septal ablation.

Although prospective, randomized trials with at least one to two years follow up would be ideal to establish evidence for these comparisons, some comparisons such as surgical myectomy versus alcohol septal ablation are likely never to occur. In that context, observational analyses with proper statistical methods to account for confounding and selection bias may be able to provide some information on the comparative effectiveness of these options.

Align the price of mavacamten with the explicit and transparent estimates of its treatment benefits for patients and families. Pricing should also be moderated to reflect the uncertainty about longer-term safety until such time as further outcomes data are generated.

- There is no available price for mavacamten. However, an analyst estimate suggests that the price of mavacamten could far exceed a price aligned with its value. Our analysis suggests an HBPB of $12,000-$15,000 per year. However, our estimate does not account for legitimate concerns about longer-term safety. In that context, an appropriate price after initial approval could be even lower.

- In 2020, Bristol Myers Squibb purchased MyoKardia. The purchase price for the smaller company should not be a basis of a price that is higher than a value-based price.

- A lower price would have several benefits for patients. First, it would likely expand access to mavacamten for patients who wish to try the medication early. Second, by expanding the proportion of patients who have access to the drug, it would allow a more rapid assessment of longer-term safety through post-approval monitoring with real-world evidence. Although there are known limitations to this type of observational data, a larger number of patients creates more statistical power to detect rarer side effects.

- If this type of longer-term evidence provides reassurance about longer-term safety, it would be appropriate to raise the price of mavacamten to the HBPB established in our analysis or to an even higher level should the effectiveness of the drug exceed early estimates.

Until rigorous evidence is available, avoid speculative suggestions about potential therapeutic benefits of novel treatment options.

The clinical evidence is inadequate to suggest that mavacamten may confer a survival benefit, irrespective of improvement in cardiac structure as measured by cMRI as well as improvements in

cardiac biomarkers. Particularly given the discordance between cMRI and patient-reported outcomes after mavacamten is stopped, there is substantial uncertainty about longer-term effects of the medication on cardiac structure and longer-term outcomes. Any suggestion that mavacamten reduces mortality at this point is speculative and carries the risk of creating false hope for this patient community.

Engage fully with patient groups, clinical experts, and independent entities seeking to produce transparent evaluations of the effectiveness and value of mavacamten.

Access to novel therapies for patients who will benefit at a price aligned with the benefits of that therapy is an important societal goal. This type of access can result from open communication between manufacturers, payers, and patients and their advocates. A representative of Bristol Myers Squibb delivered public comments at the public meeting on mavacamten but declined to participate in the policy roundtable. Avoiding this type of transparent public discussion does a disservice to the patient community and ultimately harms patient access to mavacamten.

All manufacturers of treatments for patients with HCM should be encouraged to assess patient-reported outcomes in clinical trials.

One of the important strengths of the EXPLORER study was that patient-reported outcomes were collected and a new patient-reported outcome specific to HCM was developed. These data complemented physiologic endpoints as well as clinician assessed measures of health status. Future trials should be encouraged to follow this example of including patient-reported outcomes, in particular when therapies are intended to improve subjective health status as opposed to "hard" event outcomes such as mortality.

Payers

Payers should use the FDA label as the guide to coverage policy and engage clinical experts and diverse patient representatives in considering how to address coverage issues for which there is limited or no evidence at the current time.

Given the significant uncertainty that will remain about the relative benefits and longer-term risks of mavacamten for different patients, it will be reasonable for payers to use prior authorization as a component of coverage policy. Prior authorization criteria should be based on the FDA label, clinical evidence and patient eligibility criteria from pivotal trials, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers and patients. Options for specific elements of coverage criteria within insurance coverage policy are discussed below.

Coverage Criteria

Age: Mavacamten is likely to be covered for adult patients (18 years or greater), in line with the inclusion criteria of the EXPLORER trial. There is greater uncertainty about both treatment effects and risks in younger patients, since the mean age in the trial was 58.5 years. However, younger adults were eligible for and included in the key trial.

Clinical Eligibility: Current evidence pertains to patients with symptomatic, obstructive HCM with LVOT gradients greater than or equal to 50 mmHg at rest after Valsalva maneuver or exercise.

Inclusion Criteria: When mavacamten is prescribed with the intent of improving symptoms in symptomatic HOCM, key clinical issues include establishing the presence of a LVOT gradient and excluding non-cardiac sources of exertional symptoms (such as pulmonary symptoms). Conditions that mimic HCM are common but are very unlikely to result in the subtype of HCM that causes obstruction. We are aware that therapeutic concepts are in development that eventually may lead to the use of mavacamten for HCM without obstruction. In that case, depending on the evidence available at the time, it may become reasonable to establish specific anatomic cutoffs for ventricular wall thickness. Overall, the distinction between HCM generally and conditions that mimic HCM are subtle and require interdisciplinary discussion among experts in cardiac imaging, genetics, and clinical cardiology. That integrative expertise is more helpful than specific anatomic cutoffs. For these reasons, it seems unreasonable for payers to establish specific cutoffs for left ventricular dimensions prior to approving mavacamten for symptomatic HOCM.

Although the diagnosis of HCM is subtle and often requires specialist expertise and, in some cases, confirmation through genetic testing, there are multiple important limitations to genetic testing. For example, some genetic variants that cause HCM are unknown. Secondly, of all the pathologic conditions (like hypertension and infiltrative cardiomyopathies) and non-pathologic conditions (athlete's heart) that can mimic HCM, they are unlikely to cause a hemodynamic gradient in the outflow tract. Since mavacamten is likely to be used in patients with symptomatic HOCM, rigorous establishment and confirmation of a hemodynamic outflow tract gradient is important. Conversely, in this situation, genetic testing will not be useful for establishing candidacy for mavacamten. For these reasons, it is unreasonable for payers to require genetic testing to confirm diagnosis prior to approval of mavacamten for symptomatic HOCM.

Exclusion Criteria: There are no specific medical comorbidities that would serve as exclusion criteria for mavacamten. Patients with permanent atrial fibrillation who are either not on anticoagulation for more than four weeks or not adequately rate controlled for more than six months, or any patients with paroxysmal atrial fibrillation were not included in the EXPLORER trial (see section on atrial fibrillation below). However, there is no specific contraindication to using mavacamten in patients with atrial fibrillation. Since atrial fibrillation is a common source of symptoms in patients with all types of HCM, distinguishing between symptoms related to outflow tract obstruction and

symptoms related to atrial fibrillation is important before attempting to reduce outflow tract obstruction with mavacamten.

Duration of Coverage and Renewal Criteria: Experts advised that patients initiated on mavacamten generally should have documented benefits within three months. Accordingly, patients generally should be reevaluated by clinicians within that timeframe (either in person or via telemedicine). Patients who remain on mavacamten should then again be reevaluated within one year.

Provider Restrictions: Both clinical experts and patients expressed concern about the safety of early widespread use of mavacamten in community-based settings outside of centers of excellence. As such, it seems reasonable to keep use of mavacamten very narrow within two to five years after FDA approval. As more safety data are available and clinicians gain more experience, it seems reasonable to widen provider access. This reflects a difficult balance between potentially concerning safety signals and patient access. Particularly given this balance, we encourage payers to collaborate with patient organizations to establish lists of preferred providers at centers of excellence. The Hypertrophic Cardiomyopathy Association has identified centers of excellence available on their website (www.4hcm.org/center-of-excellence).

Step Therapy

It is reasonable for payers to require an attempt to manage symptomatic HOCM with beta blockers and calcium channel blockers before approving mavacamten.

Patients in both the placebo and mavacamten arms of the EXPLORER trial could take beta blockers and calcium channel blockers. Very few patients enrolled in the trial were taking neither medication. As such, it is reasonable to require an attempt at managing symptoms with beta blockers and calcium channel blockers alone before approving mavacamten. Many patients report intolerable side effects with these medications. As such, intolerable side effects or contraindications are reasonable justifications for defining treatment failure of beta blockers and/or calcium channel blockers.

It is unreasonable for insurers to require either myectomy or septal ablation prior to approval of mavacamten.

Given that surgical myectomy and alcohol septal ablation involve very different trade-offs and risks for patients relative to an oral medication, it is unreasonable for insurers to require either myectomy or septal ablation prior to access to mavacamten. The comparative effectiveness of these treatment options is obscured by the absence of relevant trials. Even if more definitive evidence is established, the decision of an oral medication versus a procedure or surgery seems very dependent on the preferences and circumstances of an individual patient. Shared decision-making is appropriate in these situations.

Despite this recommendation, if insurers ever do require either surgical myectomy or septal ablation prior to coverage of mavacamten, they should recognize that patients lose considerable time from work while recuperating from these procedures and full consideration should be given to compensating patients for this lost time in some way.

Unless patients have better access to disopyramide, it seems unreasonable to consider requiring a trial of disopyramide prior to coverage of mavacamten. Further clinical evidence on the clinical benefits of disopyramide is also required to strengthen any consideration of this step therapy option.

Clinical experts disagreed about whether requiring a trial of disopyramide prior to approval of mavacamten would be reasonable. If the initial price of mavacamten is high, there would be more justification of the importance of a trial of disopyramide before mavacamten. Despite that, short-acting disopyramide requires onerous dosing every six hours. Long-acting disopyramide is a more reasonable option but is currently in a drug shortage, limiting access.

Clinical Investigators and Grant Funding Organizations

Researchers and funding agencies should ensure that future research assesses the potential benefits of treatment related to improved productivity and reductions in caregiver burden.

In determining a value-based price for a novel therapy, standard methods account for both increases in life expectancy and improvement in health status for patients. However, it is also reasonable to account for potential other benefits. Novel clinical innovations can provide additional benefits by easing caregiver burden and improving patient workforce productivity, but these benefits are often not measured. Unfortunately, these potential other benefits have not been well-captured in prior research. Patient-centered research that aims to quantify these potential other benefits would allow inclusion in decision-analytic models. Inclusion of this information in decision-analytic models would more fully capture the benefits of a novel therapy but also could potentially increase a value-based price estimate.

Further research should be targeted at evaluating the safety and benefits of mavacamten for patients with HOCM and atrial fibrillation.

Patients with permanent atrial fibrillation not on anticoagulation who are either not on anticoagulation for more than four weeks or not adequately rate controlled for more than six months, or any patients with paroxysmal atrial fibrillation were not included in the EXPLORER trial. In the setting of these exclusion criteria, only 12 patients (10%) in mavacamten arm of EXPLORER had even a history of atrial fibrillation. Atrial fibrillation is common in patients with HOCM, thromboembolic risk off anticoagulation is high, and because atrial fibrillation can exacerbate the hemodynamic gradient in the LVOT, atrial fibrillation often causes intolerable symptoms. In a

patient with symptomatic HOCM and atrial fibrillation, it is often difficult to distinguish between symptoms caused by atrial fibrillation and symptoms caused by the outflow tract gradient.

The comparative effectiveness and safety of mavacamten in many patients with atrial fibrillation is therefore unclear. More work is required to establish the efficacy and safety of mavacamten for patients with atrial fibrillation including paroxysmal atrial fibrillation.

Post-approval clinical registries should be established to detect rare side effects as well as assess the efficacy of mavacamten in more diverse populations.

Since the MAVA-LTE study uses the same population as the EXPLORER population, there is very limited representation among patients of color. Furthermore, this cohort that includes 224 patients will be underpowered to detect rarer side effects among all patients. Especially because there is a substantial concern about longer-term safety, clinical registries will be essential for detecting rarer adverse events and for assessing if the results of EXPLORER are extrapolatable to more diverse populations.

Patient Groups

Patient groups should continue to demonstrate leadership in defining clinical excellence and appropriate pricing.

- The Hypertrophic Cardiomyopathy Association has played a longstanding leadership role in advocacy for this patient community, including work generating educational information for patients and families, supporting research efforts, and identifying centers of excellence for HCM. Their actions serve as a model for other patient communities seeking to advance the best interests of patients today and in the future. Given the critical importance of centers for excellence for HCM generally, the Hypertrophic Cardiomyopathy Association should continue this involvement and seek to work with payers to find the right balance between breadth of access and quality of the care provided at diverse provider organizations.

- Hypertrophic Cardiomyopathy Association representatives and others have expressed concerns about the potential that the manufacturer will set a high price of mavacamten. The Hypertrophic Cardiomyopathy Association has established its credibility within its own community and with clinical experts. It has a powerful voice that will be used to advocate for appropriate access for patients to mavacamten and other new treatments. This group, and others, should fully exercise that voice and that power in support of responsible pricing that will advance the best interests of patients while sending a strong signal to innovators that they should develop robust evidence of benefits to patients to support their pricing. We hope that government, manufacturers, private payers, and other advocates will work

with the Hypertrophic Cardiomyopathy Association to facilitate their advocacy, which is critically important for patients with HCM.

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Report Supplement

A. Background: Supplemental Information

A1. Definitions

The outcomes in the key trials include the following variables:

- **Kansas City Cardiomyopathy Questionnaire (KCCQ)**[28]: This is a disease-specific patient-reported outcome specific for patients with heart failure. The instrument is based on a self-administered 23-item questionnaire that quantified patient-reported physical limitations, symptoms, self-efficacy, social interference, and quality of life. The original validation of the KCCQ demonstrated correlation between KCCQ scores and measures of physical limitation, clinician-measured estimate of functional status, another patient-reported measure of general health (the SF-36 scale), and clinical events such as death or hospitalization. The KCCQ ranges from 0-100, with higher scores indicating better health. The KCCQ overall summary score (KCCQ-OS) includes all health domains measured by KCCQ and the KCCQ clinical summary (KCCQ-CS) measures only physical limitations and total symptoms. The KCCQ-OS includes questions such as "*How well do you understand what things you are able to do to keep your heart failure symptoms from getting worse*?" that would be reflected in the KCCQ-OS but not the KCCQ-CS.

- **New York Heart Association (NYHA) Functional Classification**[43]: The NYHA classification is a clinician-assessed measure of functional status broadly applicable to patients with cardiac disease, including angina from coronary artery disease but also exertional intolerance from heart failure. Class I refers to patients with cardiac disease but without limitations of physical activity. Class II refers to patients with cardiac disease resulting in slight limitation of physical activity. Class III refers to patients with cardiac disease resulting in marked limitation of physical activity. Class IV refers to patients with cardiac disease resulting in inability to exert physically at all and/or the presence of symptoms at rest.

- **Peak $V0_2$**[44]: The maximal oxygen consumption of a patient estimated from peak work rate. This provides an objective, quantitative estimate of the functional capacity of a patient. Functional capacity can be limited by cardiac function but also other physiological processes including pulmonary function, the ability of the circulatory system to deliver oxygenated blood to muscle tissues, and other processes.

- **Left ventricular outflow tract (LVOT) gradient**: The LVOT gradient is the pressure gradient in the LVOT, the conduit through which blood passes from the left ventricle of the heart to the aorta. Patients with obstructive HOCM have gradients that cause pressure drops in the LVOT, impairing the ability of the heart to provide blood to the rest of the body.

A2. Potential Cost-Saving Measures in Symptomatic HOCM

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by mavacamten (e.g., need for septal myectomy of ablation), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of symptomatic HOCM beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with symptomatic HOCM that could be reduced, eliminated, or made more efficient. No suggestions were received.

B. Patient Perspectives: Supplemental Information

B1. Methods

ICER collaborated with the Hypertrophic Cardiomyopathy Association to conduct an online patient-input questionnaire to gather more insight on people living with and people who care for those living with HCM. Responders were recruited from social media and through a listserv of Hypertrophic Cardiomyopathy Association members. The survey results informed the scope of our review and helped focus our assessment on outcomes of most interest to patients and caregivers.

Because this survey consisted of qualitative, open-ended questions, responses were categorized and frequency of each category were quantified, summed, and then put into graphical or table form. Respondents could have more than one category assigned to their response and the categories are not all mutually exclusive; thus, the number of responses varies by question. Select individual unedited quotes are reported below to more fully capture narrative experiences of those living with HCM that were not fully captured by our quantitative summary. All responses were anonymous.

B2. Results

ICER received a total of 641 responses on the survey, including 606 patients, six patient advocates, and 29 caregivers/family members. We limited our summary below to 541 responses from patients that included information relevant to our review.

Experience with HCM

Type of HCM

While 14.3% and 12.5% of patients responded that the type of HCM that they live with is either obstructive and/or associated with a known, specific HCM gene variant, a large majority of patients (67.1%) did not know the subtype of HCM that they live with. Additionally, 2.4% of patients reported having HCM without obstruction. Since these categories were not mutually exclusive, patients could have reported they live with a known HCM gene variant and a specific HCM subtype (Table B1).

Table B1. HCM Type

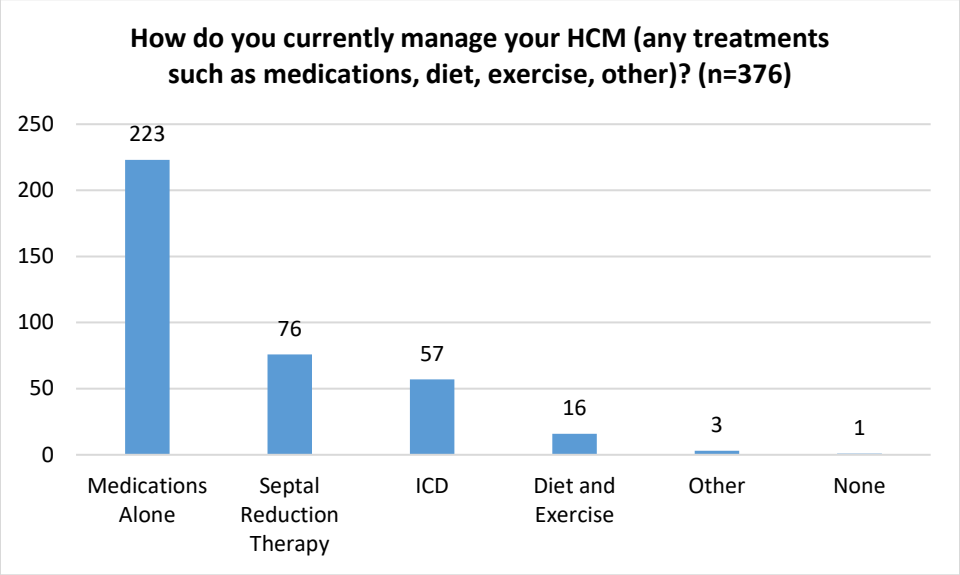
HCM Type (N=538)	n (%)
I Don't Know	361 (67.1%)
Obstructive	77 (14.3%)
Genotype	67 (12.5%)
Other	20 (3.7%)
Non-Obstructive	13 (2.4%)

n: number, N: total number

HCM Treatment and Management

A figure depicting patients' current management of HCM is below (Figure B1). Use of medications alone was reported by most patients (59%), followed by septal reduction therapy (20%), ICD (15%), and diet and exercise alone (4.3%).

Figure B1. Management of HCM



HCM: hypertrophic cardiomyopathy, ICD: implantable cardiac device, n: number

- "I try with diet and physical activity. I couldn't stand beta blockers. My doctor advises me to have a myectomy, but I really don't want open heart surgery. I have a lot of shortness of breath on activity, even walking, and forget walking up hill."

- "Twice daily Toprol XL (my body metabolizes it quickly for some reason and we found out the hard way that I get tachycardic if I take it only once daily) and an ICD for safety. I've experienced ventricular tachycardia and atrial fibrillation each a couple times (or just one several times, it was hard to tell) but never ventricular fibrillation, thankfully. My heart has behaved itself for almost 18 years. I have a lot of fatigue but no more cardiac events. I do what I can to keep stress to a minimum."

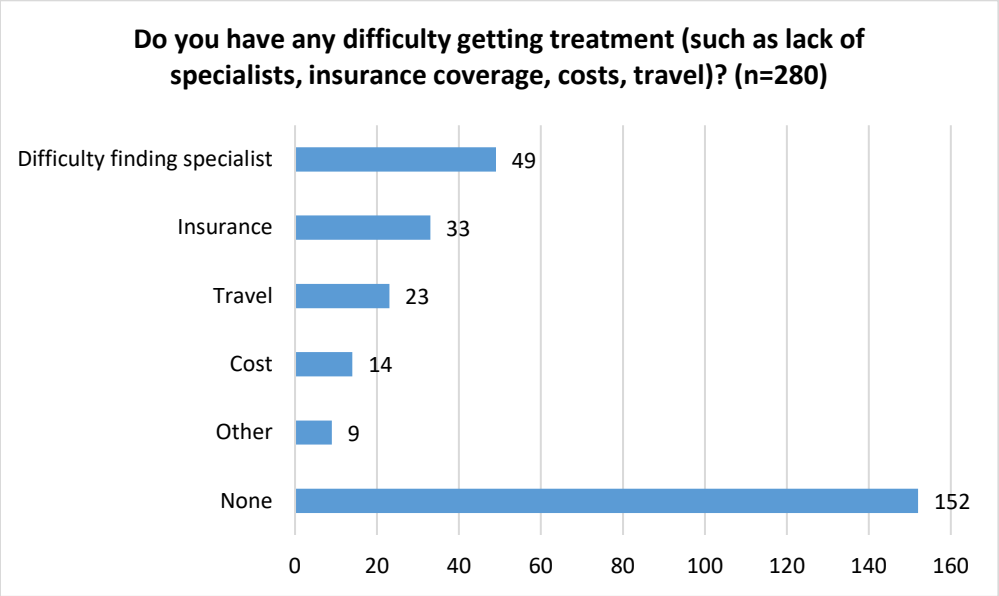
- "I have two sons that have each had a myectomy in their early and late 30s, and one also has a mechanical mitral valve at 23. Each of us have defibrillator/pacemaker."

- "Medications — fairly large doses of Norpace CR and metoprolol, as well as moderate exercises and lifestyle changes like not exercising after meals, eating small meals, avoiding being outside on hot days, and hydrating."

Treatment Access Issues

Barriers to acquiring treatment are demonstrated in Figure B2 below. Most patients (54%) reported no difficulties in getting treatment. The most cited barriers to treatment included: difficulty finding a specialist (18%), issues with insurance (12%), and travel (8%).

Figure B2. Difficulty Getting Treatment



n: number

- "We live in Illinois and have to travel to Cleveland for treatment. During my surgery, we stayed 21 days in a hotel. The lack of specialists and high-volume hospitals for this is very limited. Even in Chicago, the 'specialist' there told me I would need to get evaluated for transplant. Global knowledge is very challenging for care. Travel requirements for receiving quality care are burdensome... We had to open a credit card just for travel expenses for Cleveland. HMO insurance is free and 100% coverage with my husband's employer, they would not allow coverage of Cleveland with multiple appeals. For us to switch to PPO, my husband pays $330 per paycheck, percent of all services, and a $10,000 out-of-pocket deductible. We are actually in process of selling our home and downsizing due to drowning in medical debt from surgeries, checkups, and travel expenses."

- “The nearest center of excellence is more than six hours away. Travel is difficult during the months of October-May due to weather. The time off work that a trip requires is a situation as well. The money it costs for said travel is also a financial burden as I still have to pay for insurance, patient portion insurance doesn't cover as well as fuel, food, and a place to stay. It adds up quickly.”

- “I have two daughter who have HCM as well as myself. The cost of yearly screening and testing is a huge financial burden on our family as well as I’m sure other HCM families even after insurance.”

- “Yes, many cardiologists have not studied the disease as it is a sub-specialty. It is weird when the patient knows more than they. It worries me as I feel I always need to be alert to head off disaster. What if I appear unconscious in an ER or hospital? I don't generally feel safe away from Mayo Clinic.”

- “Yes. My insurance does not cover a center of excellence in HCM. As a result, I must stay informed about the latest evidence-based guidelines and advocate for myself. It’s exhausting and time consuming.”

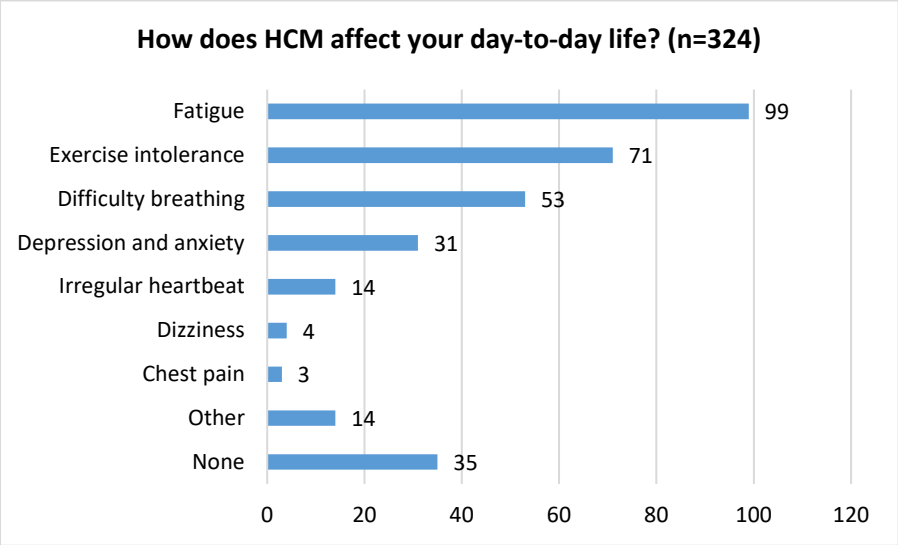
- “There are no cardiologists in my borough who understand HCM, so I was misdiagnosed for 54 years. Also, after my septal myectomy, there was no local cardiac rehab available to me and I could not go into a nursing facility because I wasn't old enough."

- “There is a severe shortage of Norpace CR, and I can only order it month-to-month from a pharmacy in New York at a co-pay of $280 per month plus mailing expense. Large pharmaceutical chains like CVS and Walgreens no longer carry it. I am on Medicare, and only one drug plan covers it at all. I have tried a generic that must be taken four times a day, and cut back on my dosage to save money. Neither worked for me. I live with the fear that I will no longer be able to obtain a medication I have been using successfully for more than 15 years.”

HCM Symptoms

Fatigue was the most reported symptom of HCM (30.6%), followed by exercise intolerance (21.9%), difficulty breathing (16.4%), and depression and anxiety (9.6%) (Figure B3).

Figure B3. How HCM Affects Day-to-Day Life



HCM: hypertrophic cardiomyopathy, n: number

- "Arrhythmias, exhaustion, retaining fluid in legs makes exercise/stairs/walking distances challenging, short of breath impacts everything, difficulty sustaining active sex life, difficultly being the active parent I wish to be for my kids."

- "My heart is continuing to get worse and I'm transitioning into congestive heart failure. For the first 10 to 15 years after my myectomy, I didn't feel that limited. The main issues were the defibrillator maintenance and battery replacements. But now I do have trouble breathing with a lot of exertion, so I am somewhat limited in recreational activities that I enjoyed like hiking. Also, I'm not supposed to shovel snow, so I have to hire somebody to do that. And I'm more restrictive in carrying heavy things than I used to be. As I have more restrictions, it's frustrating and humbling."

- "It has a huge impact on my life, and it affects my job. I can't walk more than 10 minutes without stopping to catch my breath, I can't work out like I used to, I am gaining weight, I can only walk up one flight of stairs at a time, I am embarrassed to be around people who may see me struggling to breathe – it keeps me secluded in my home. And what is most depressing is seeing how I am getting worse and can't stop it."

- "Breathlessness getting out of bed, washing my hair, etc. I work but have had to reduce to a sedentary job and decrease my hours. Can't do garden chores. Have to space out home duties (can't change all the sheets in the house in the same day)."

- "Have to be careful when working out for heart rate to stay within the given beats per minute. Some symptoms are debilitating, and I have to always be on my toes. It continuously plays on my mind so keeping stress levels down is not easy."

- "I become short of breath on exertion, especially going up stairs or uphill. I love to be active, but I lag behind my family and friends on walks and hikes. I use an electric bicycle, or I would not be able to bike ride with others."

Treatment Effects

Treatment Effectiveness

When asked about how well their treatments work, about half of patients reported that their treatments work well (50%), a third thought their treatments work okay (33%), and 9% thought their treatments don't work.

Table B2. Treatment Effectiveness

Treatment Effectiveness (N=341)	n (%)
They Work Well	172 (50.4%)
They Work Okay	114 (33.4%)
They Don't Work	31 (9.1%)
Other	24 (7.0%)

n: number, N: total number

- "Fairly well, but it is still worrisome knowing that something is wrong and feeling the symptoms of the HCM despite medically and lifestyle treatments."

- "I felt great after the myectomy in 2002. Prior to that I was on so much medication that I was always struggling from the side effects, even though I did work full-time and had a pretty active life. Once I had the myectomy, I did well for about 15 years, at which point my ejection fraction started to dip. For the most part, I still feel like I live a pretty normal life without too many restrictions, but as more medications are added due to my heart weakening, I'm starting to deal with side effects again."

- "I'm sure they are helping maintain my lower blood pressure but not so sure they are really helping my shortness of breath."

- "The drug treatments have been effective in slowing the increase in gradient. And reducing the LVOT disruption. However, the side effects of the treatments are about the side as the physical effects of the disease."

- "They keep my blood pressure under control, help prevent heart pain and keep my heart rate from being too fast. They work well, but are not a cure for the condition, they just help me manage with the condition."

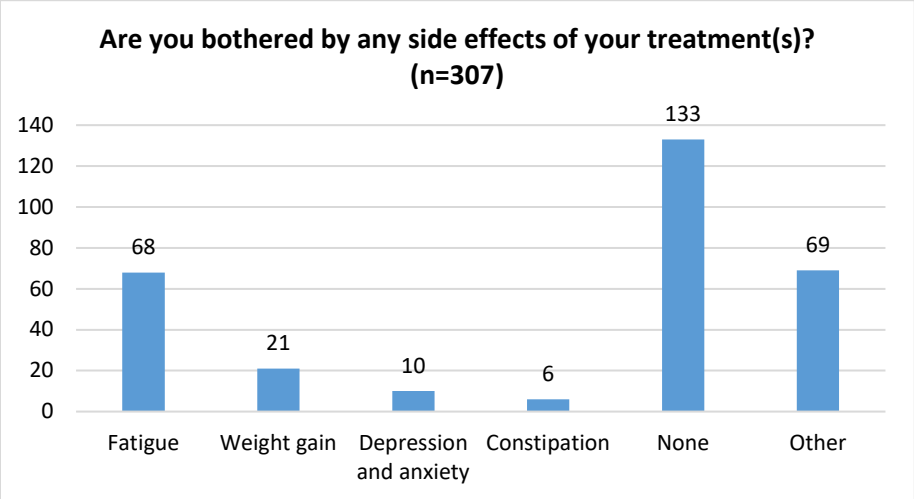
- "I am so much better than at my sickest, but very far from healthy. I don't know when I will have a bad day and no longer do a lot of the charitable work that I used to do out of fear that I will have heart issues and but someone at risk."

- "They have definitely decreased my angina and my arrhythmias. But they also contribute to my tiredness and possibly to my fluid retention."

Side Effects of Treatment

The most reported side effect of treatment was fatigue (22.1%), followed by weight gain (6.8%), and depression and anxiety (3.3%). The majority of patients reported that they had no side effects (Figure B4).

Figure B4. Treatment Side Effects



n: number

- "When I tried metoprolol, it made me really tired, lethargic, depressed, and gain weight, even on a very small dose. So, I gave up on beta blockers."

- "I'm 61 years old. I have little interest in the joys of life. I believe my meds are decreasing my interest in sex."

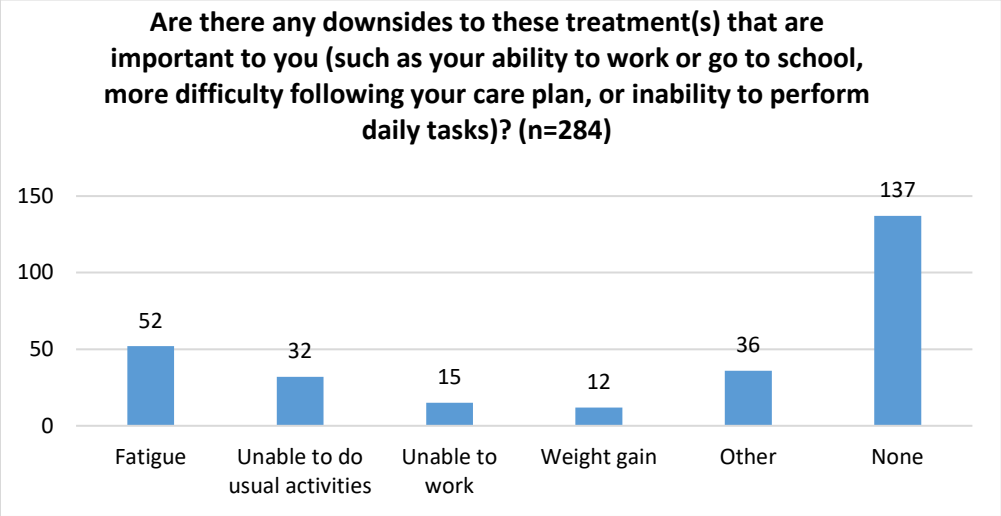
- "Yes, I think beta blockers and calcium channel blockers being taken to slow down the blood pressure may be having some side effects as I notice some swelling in ankles and feet sometimes."

- "Yes, prior to my myectomy, I felt like I was walking underwater. I was fatigued all the time, had digestive issues, memory problems. This had a lot to do with the high dosages I was on, 480 mg of Inderal, 800 mg of Norpace. After the myectomy, I wasn't on that much medication, and didn't really feel side effects. Now, being on IV medications, I am noticing them coming back, some issues with depression and anxiety, and some lowered sexual functioning."

Downsides to Treatment

Fatigue was the most reported downside to treatment for HCM (18.3%), followed by inability to perform unusual activities and inability to work (11.3% and 5.3%, respectively) (Figure B5). Most patients, however, reported "no" or "other downsides not listed" (12.7% and 48.2%, respectively).

Figure B5. Treatment Downsides



n: number

- "Daily tasks that involve bending over (laundry, cleaning floors) are still difficult. Limits on types of exercise are frustrating, but there are work arounds. Difficulty traveling by air and long car rides limit business opportunities and visits to family."

- "I have been on a do-not-work order for almost four years now due to my intolerance to medication and to help my heart not over working itself as my blood pressure drops when my heart rate rises, and I become very breathless and at times my hands and feet turn purple from lack of blood flow and swelling sucks."

- "The downside is really that I feel so dependent on these medications for survival and to get through my daily activities. The side effects don't disrupt my routine, but managing the medications and the HCM is very stressful and takes its toll on me and my family."

- "Being 100% dependent on a device is challenging. I always have to think about keeping magnets or other electronics away from the ICD."

- "I think the medications cause fatigue and brain fog that prompted me to take an early retirement from work as I felt I was not capable of performing my work tasks to full capability/commitment."

- "Yes, can't always perform daily tasks. Worry about driving. Always check to see if there is a shoulder I can pull off into. What if there is no shoulder? What if I have atrial fibrillation? I have become a lethal weapon. I try to make all appointments in the morning. I have cataract surgery coming up, but I worry. What if I go into atrial fibrillation? At home, I would drop to the floor. I may be flipping a hamburger one minute and on the floor the next."

- "I was a single mom on beta blockers and had a hard time doing anything – my kids needed me to drive, make meals, etc. and sometimes I was just too tired."

Impact of Treatment On Caregivers

About a third (33%) of patients reported that treatments had no impact on caregivers, while 22% reported that treatments had a large impact and 10% reported that treatments had a small impact (Table B3).

Table B3. Treatment Caregiver Impact

Treatment Caregiver Impact (N=257)	n (%)
Large Impact	56 (21.8%)
Small Impact	25 (9.7%)
No Impact	84 (32.7%)
Not Applicable	76 (29.6%)
Other	16 (6.2%)

n: number, N: total number

- "As a patient, because medications lower your heart rate and thereby everything, on specific days you might become more quiet and not as functioning and this could add physical and mental burden to your caregiver. As a patient and depending on the dosage of your medications, you are not as active or capable to satisfy your partner physically or sexually or engage in activities that might bring joy to both of you and as a family."

- "My condition itself has been enormously stressful to my family. My septal myectomy has improved their lives as I can function better now. I don't tell them how bad I am feeling."
- "Financial impact on the family has been intense – we max out co-pays and deductibles EVERY year. We don't take vacations and we must go without things others take for granted. My husband and family members worry about my health causing stress and lots of trips to doctors, hospitals and 'rescue' calls when I am not feeling well, which disrupts normal life."
- "No impact at this time to caregivers since the device was implanted in Minneapolis in 2012. I am independent and ambulatory. No caregiver needed."

C. Clinical Guidelines

Guidelines relevant to treatment of patients, including those with symptomatic HOCM have been published by a joint committee in the US as well as other non-US based organizations. Key elements focusing on the management of symptoms in HCM including HOCM from these guidelines are summarized below. The guidelines address many other topics relevant to HCM, including HOCM, including risk stratification for sudden cardiac death, genetic testing, and diagnostic imaging.

American College of Cardiology and American Heart Association[6]

In 2020, the joint committee on clinical practice guidelines of the American College of Cardiology and the American Heart Association issued a report on diagnosis and treatment for all patients with HCM, including those with symptomatic HOCM. These guidelines emphasize the importance of shared decision making for testing and treatment options. They explicitly recommend (level 2a) consultation with or referral to comprehensive HCM centers for complex management decisions. When indicated, the guidelines recommend (class 1) that septal reduction procedures including surgical myectomy and septal ablation are performed at these specialized centers.

With respect to pharmacological therapies for patients with HOCM and exertional limitations, such as shortness of breath, the guidelines recommend beta blockers as first-line therapy (class 1). For patients for whom beta blockers are ineffective or poorly tolerated, centrally-acting calcium channel blockers are recommended (class 1). For patients with persistent severe symptoms attributable to left ventricular outflow obstruction, either adding disopyramide or performing a septal reduction procedure is recommended (class 1). For patients with clinical fluid retention, cautious use of diuretics, avoiding dehydration can be considered (class 2b). Vasodilating blood pressure agents including angiotensin-converting enzyme inhibitors, dihydropyridine calcium channel blockers (such as amlodipine), and digoxin are reasonable to consider stopping, given that they can worsen left ventricular outflow tract obstruction (class 2b). Finally, in patients with severe shortness of breath at rest, very high left ventricular outflow tract gradients (>80-100 mm Hg), or low blood pressure, calcium channel blockers are contraindicated because of potential harm (class 3).

For patients who remain severely symptomatic because of LVOT gradients despite medical therapy, guidelines support septal reduction therapy (class 1). Patients who are at acceptable surgical risk and/or who have other surgical heart disease (such as intrinsic structural mitral valvular dysfunction) should receive surgical myectomy (class 1). Conversely, patients who are at elevated surgical risk should receive alcohol septal ablation (class 1). It is also reasonable to consider surgical myectomy for patients with severe progressive pulmonary hypertension or mitral regurgitation, left atrial enlargement with atrial fibrillation, poor functional capacity due to LVOT obstruction, or

young adults with very high resting LVOT gradients (>100 mm Hg) (class 2b). Any type of septal reduction, including alcohol septal ablation and surgical myectomy, is contraindicated for patients with HCM who are asymptomatic and have normal exercise capacity (class 3).

European Society of Cardiology

The European Society of Cardiology convened a task force for diagnosis and management of hypertrophic cardiomyopathy and most recently issued guidelines in 2014.[45]

For patients with symptomatic HOCM, guidelines recommend beta blockers first and then calcium channel blockers for those patients who are intolerant to beta blockers (class 1). Unlike American guidelines, which offer disopyramide or septal reduction therapies next as a choice, the European Society of Cardiology guidelines explicitly recommend disopyramide for patients with persistent symptoms (class 1). Verapamil is explicitly favored in European guidelines over diltiazem (class 2a). Unlike American guidelines, which recommend that disopyramide is used only with beta blockers or calcium channel blockers (due to the risk of enhanced atrioventricular nodal conduction if atrial fibrillation develops), the European guidelines allow the consideration of disopyramide as monotherapy (class 2b). For patients with clinical congestion judicious use of diuretics can be considered (class 2b).

For patients with resting or provoked gradients of 50 mm Hg or greater and who have NYHA class III-IV symptoms despite maximum tolerated medical therapy, European guidelines recommend septal reduction therapies by highly experienced operators within expert multidisciplinary teams (class 1). While surgical myectomy is favored (class 1) when there is concurrent cardiac surgical disease, European guidelines emphasize uncertainty about the comparative effectiveness of septal ablation versus myectomy.

For patients with HOCM, the guidelines recommend generally against the use of arterial and venous dilators (class 2a) and more strongly against digoxin (class 3) since these agents can worsen LVOT obstruction. The guidelines also emphasize that restoration of sinus rhythm or better rate control is recommended before considering invasive septal reduction therapies (class 2a).

National Institute for Health and Care Excellence

In 2004, the United Kingdom's National Institute for Health and Care Excellence cites "adequate" evidence to support the use of septal ablation for patients with symptomatic HOCM as an alternative to surgical myectomy.[46]

Ludwig Boltzmann Institute for Health Technology Assessment

In 2013, the Ludwig Boltzmann Institute for Health Technology Assessment in Austria issued a report recommending that septal ablation only be performed in highly-specialized centers and all patients with the procedure be enrolled in procedural registries.[47]

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS (Population, Intervention, Comparator, Outcomes, Timing, Setting)

Population

The population of focus for the review is adults with symptomatic HOCM. As data allowed, we planned to review any available data in children with symptomatic HOCM. We also separately reviewed available evidence for the intervention in patients with symptomatic HCM without obstruction.

Interventions

The intervention of interest is mavacamten in addition to usual care.

Comparators

Mavacamten was compared with usual care. This included comparisons with adding mavacamten to existing therapy as estimated by the placebo arms of clinical trials, but also comparisons with alternative therapies including medications typically used later than first line (e.g., disopyramide) and septal reduction procedures (surgical myectomy and septal ablation).

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Symptoms of HOCM such as exertional intolerance, fatigue, shortness of breath, dizziness, arrhythmia, chest discomfort, mental acuity (with particular attentiveness to patient-reported outcomes)
    - Requirement for exercise restriction
    - Anxiety and depression
    - Overall mortality
    - Sudden cardiac death
    - Need for implantation of ICD
    - Heart failure
    - Rate of septal reduction therapy (septal ablation or myectomy)

    - Atrial fibrillation and stroke
    - Adverse events including:
        - Treatment-emergent adverse events and serious adverse events
- Other Outcomes
    - Peak oxygen consumption (pVO_2 exercise capacity)
    - Post-exercise LVOT gradient and resting LVOT gradient
    - Left ventricular ejection fraction
    - NYHA functional class
    - Cardiac biomarkers such as NT-proBNP and hs-cTnl

Timing

Evidence on intervention effectiveness and harms were derived from studies of any duration.

Settings

All relevant settings were considered, with a focus on outpatient settings in the US.

Table D1. PRISMA 2009 Checklist

Checklist Items		
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of Bias in Individual Studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.
Risk of Bias Across Studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of Bias Within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).

Checklist Items		
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of Bias Across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of Evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for symptomatic HOCM followed established best research methods. We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[48] The PRISMA guidelines include a checklist of 27 items, which are described further in Table D1.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE) as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and

other grey literature when the evidence met ICER standards (for more information, see https://icer.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/). Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data (https://icer.org/guidelines-on-icers-acceptance-and-use-of-in-confidence-data-from-manufacturers-of-pharmaceuticals-devices-and-other-health-interventions/).

Table D2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials

1	Exp Cardiomyopathy, Hypertrophic/
2	(((hypertroph* or obstruct*) adj3 (cardiomyopath* or subaortic stenosis or Asymmetric*)) or hcm or hocm or ihss or Symptomatic obstructive hypertrophic cardiomyopathy).ti,ab.
3	1 OR 2
4	(Mavacamten).ti,ab
5	('myk 461' OR myk461).ti,ab
6	('sar 439152' OR sar439152).ti,ab
7	4 OR 5 OR 6
8	3 AND 7
9	(addresses or autobiography or bibliography or biography or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt
10	8 NOT 9
11	animals.mp. not (humans and animals).sh.
12	10 NOT 11
13	limit 12 to English language

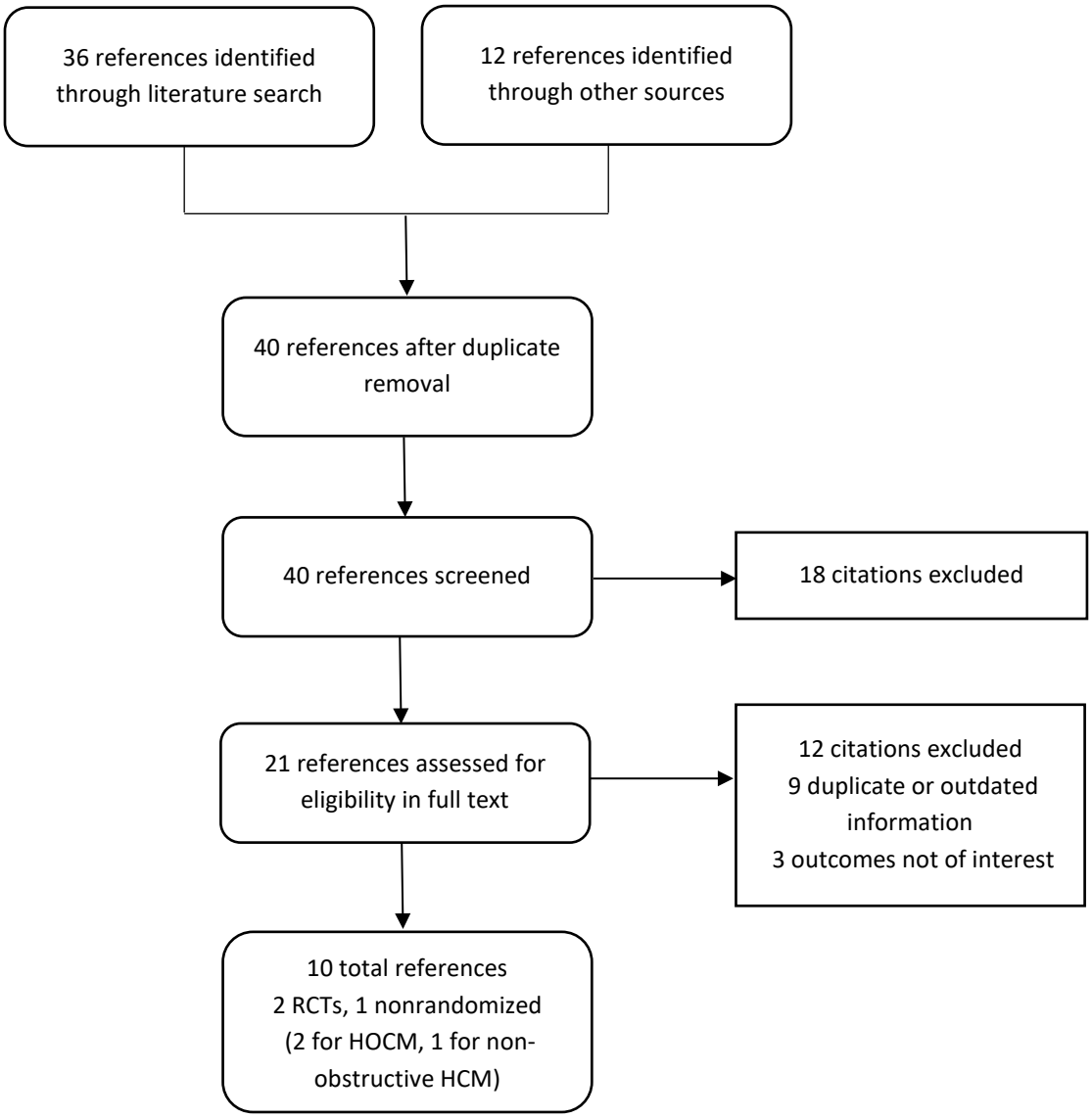
*Search last updated on August 30, 2021.

Table D3. Search Strategy of EMBASE SEARCH

#1	'hypertrophic obstructive cardiomyopathy'/exp OR 'hypertrophic obstructive cardiomyopathy'
#2	cardiomyopathy OR 'hypertrophic obstructive' OR 'cardiomyopathy, obstructive' OR 'hypertrophic cardiomyopathy, obstructive' OR 'myocardiopathy, obstructive' OR 'obstructive cardiomyopathy' OR 'obstructive hypertrophic myocardiopathy' OR 'obstructive myocardiopathy' OR 'hypertrophic cardiomyopathy' OR (((hypertroph* OR obstruct*) NEAR/3 (cardiomyopath* OR 'subaortic stenosis' OR Asymmetric*)) OR hcm OR hocm OR ihss):ti,ab
#3	#1 OR #2
#4	Mavacamten/exp OR mavacamten
#5	('myk 461' OR myk461 OR 'sar 439152' OR sar439152):ti,ab
#6	#4 OR #5
#7	#3 AND #6
#8	('case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#9	#7 NOT #8
#10	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#11	#9 NOT #10
#12	#11 AND [english]/lim

*Search last updated on August 30, 2021.

Figure D1. PRISMA Flowchart Showing Results of Literature Search for Mavacamten



Study Selection

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

Data Extraction and Quality Assessment

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of randomized controlled trials and comparative cohort studies, using the categories "good," "fair," or "poor" (see Table F2).[49] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention-to-treat analysis is used for randomized controlled trials.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention-to-treat analysis is done for randomized controlled trials.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For randomized controlled trials, intention-to-treat analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.[49,50]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. We performed an assessment of publication bias for mavacamten using the clinicaltrials.gov database of trials. We selected studies which would have met our inclusion criteria and for which no findings have been published and did not find any evidence of publication bias.

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables and synthesized qualitatively in the body of the review. Due to insufficient evidence and lack of comparative data on disopyramide and septal reduction therapy, we did not perform any network meta-analyses comparing mavacamten with these comparators. Additionally, we did not perform any pairwise meta-analyses due to differences in study design, population characteristics, and outcomes between the mavacamten trials. We instead descriptively made these comparisons in the main report of the review and supplement.

D2. Additional Clinical Evidence

Evidence Base

Mavacamten

The main report focused primarily on outcomes of mavacamten in patients with symptomatic, obstructive HCM. In this section, we also describe outcomes in patients with symptomatic non-obstructive HCM.

Symptomatic Obstructive HCM

In addition to the pivotal Phase III EXPLORER trial and related long-term extension study (MAVA-LTE, which is described in the sections above), we also identified a Phase II trial of mavacamten for patients with HOCM, PIONEER-HCM[52] and a Phase II trial of mavacamten for patients with non-obstructive HCM (MAVERICK-HCM).[12]

Selected baseline characteristics of EXPLORER are below in Table D4.

Table D4. Selected Baseline Characteristics of EXPLORER-HCM[21]

	Mavacamten (n=123)	Placebo (n=128)
Age, Mean (SD)	58.5 (12.2)	58.5 (11.8)
Female Gender, n (%)*	57 (46)	45 (35)
Race, n (%):		
White	115 (93)	114 (89)
Black or African American	1 (1)	5 (4)
Native American or Alaskan Native	0	1 (1)
Asian	4 (3)	2 (2)
Unknown	3 (2)	6 (5)
Medical History, n (%):		
HOCM Gene Variant, n/N	28/90 (31)	22/100 (22)
Family History of HOCM	33 (27)	36 (28)
Atrial Fibrillation*	12 (10)	23 (18)
Septal Reduction Therapy	11 (9)	8 (6)
ICD	27 (22)	29 (23)
Background HOCM Therapy, n (%):		
Beta Blocker	94 (76)	95 (74)
Calcium Channel Blocker	25 (20)	17 (13)
Neither	4 (3)	16 (13)
NYHA Class II, n (%)	88 (72)	95 (74)
NYHA Class III, n (%)	35 (28)	33 (26)
pVO_2, Mean mL/kg Per Min (SD)	18.9 (4.9)	19.9 (4.9)
NT-proBNP, Geometric Mean, ng/L (CV%)*	777 (136)	616 (108)
Hs-CTnI, Geometric Mean, ng/L (CV %)	12.5 (208)	12.5 (373)
Echocardiographic Parameters:		
LVEF Mean, % (SD)	74 (6)	74 (6)
Maximum LV Wall Thickness, Mean mm (SD)	20 (4)	20 (3)
LVOT Gradient, Rest, Mean mm Hg (SD)	52 (29)	51 (32)
LVOT Gradient, Valsalva, mm Hg (SD)	72 (32)	74 (32)
LVOT Gradient, Post-Exercise, mm Hg (SD)	86 (34)	84 (36)

CV: coefficient of variation, HOCM: hypertrophic obstructive cardiomyopathy, Hs-CTnI: high-sensitivity cardiac troponin I, ICD: implantable cardiac device, kg: kilogram, L: liter, LF: left ventricular, LVEF: left ventricular ejection fraction, LVOT: left ventricular outflow tract, mm: millimeter, mm Hg: millimeter of mercury, n: number, N: total number, ng: nanogram, NT-proBNP: N-terminal pro B-type natriuretic peptide, NYHA: New York Heart Association, pVO_2: peak oxygen consumption, SD: standard deviation

*Indicates a statistically significant difference between groups.

PIONEER was a prospective, open-label multi-center study conducted at five sites in the US with two sequential cohorts totaling 21 patients (Table D12).[52] Patients were eligible to participate if they were 18-70 years old, had HCM, with LV wall thickness ≥15 mm at time of initial diagnosis or ≥13 mm with a positive family history of HCM, LVEF ≥55%, resting LVOT gradient ≥30 mm Hg and post-exercise peak LVOT gradient ≥50 mm Hg, and NYHA class II or higher.[53]

In cohort A, patients were taken off concomitant beta-blockers, calcium-channel blockers, and disopyramide two weeks prior to treatment with a high dose of mavacamten (10 or 15 mg per day depending on body weight). In cohort B, patients were allowed to continue use of beta blockers

and were started on a lower dose of mavacamten (2 mg per day, increasing to 5 mg per day at four weeks depending on resting LVOT gradient). Patients were followed for 12 weeks on treatment followed by a four-week washout period. The primary outcome was change in post-exercise LVOT gradient at 12 weeks compared to baseline. Secondary outcomes included post-exercise LVOT gradient less than 30 mm Hg, change in numerical rating dyspnea score, change in pVO_2, change in Valsalva LVOT gradients, and resting LVEF. Exploratory outcomes included NYHA class, KCCQ-OS, and NT-proBNP.

Participants in PIONEER-HCM had a mean age of 56 in cohort A and 58 in cohort B, were predominantly male (64% in cohort A and 50% in cohort B), and the majority were on beta-blockers prior to treatment with mavacamten (82% in cohort A and 90% in cohort B) (Table D5).

Table D5. Selected Baseline Characteristics of PIONEER-HCM[52]

	Cohort A (n=11)	Cohort B (n=10)
Age, Mean (range)	56 (22-70)	58 (26-67)
Female Gender, n (%)*	4 (36)	5 (50)
Background HOCM Therapy, n (%):		
Beta Blocker	9 (82)	9 (90)
Calcium Channel Blocker	1 (9)	0 (0)
Disopyramide	5 (45)	0 (0)
NYHA Class II, %	64	50
NYHA Class III, %	36	50
Echocardiographic Parameters:		
Interventricular Septum Thickness (SD), Mean, cm	1.7 (0.2)	1.5 (0.2)
Systolic Anterior Motion of Mitral Valve, n (%)	11 (100)	9 (90)
Left Atrial Volume Index (SD), Mean, mL/m^2	30 (10)	41 (20)
Mitral Regurgitation Present, n (%)	11 (100)	10 (100)

cm: centimeter, HOCM: hypertrophic obstructive cardiomyopathy, m: meter, mL: milliliter, n: number, NYHA: New York Heart Association, SD: standard deviation

Symptomatic Non-Obstructive HCM

MAVERICK-HCM was a Phase II multi-center, double-blind, randomized controlled trial of two doses of mavacamten compared to placebo in patients with symptomatic, non-obstructive HCM.[12] Fifty-nine patients were randomized to three groups: 200 ng/mL mavacamten (n=19), 500 ng/mL mavacamten (n=21) or placebo (n=19). Patients were eligible to participate if they were adults with a diagnosis of symptomatic non-obstructive HCM, defined as being NYHA function class II/III, an elevated NT-proBNP, LVEF ≥55%, and left ventricular wall thickness ≥15 mm or ≥13 mm with family history of HCM. Participants were excluded if they had resting or Valsalva and/or exercise LVOT gradient >30mm Hg. Participants were allowed to continue use of beta blockers or calcium channel blockers during the study period. Primary outcomes were safety and tolerability. Exploratory outcomes included clinical response, defined as a composite measure of 1.5 mL/kg per min or greater increase in pVO_2 *and* at least one NYHA class reduction *or* a 3.0 mL/kg per min or greater increase in pVO_2 *and* no worsening in NYHA class, pVO_2 change from baseline, and NYHA class.[54]

Participants in MAVERICK-HCM had a mean age of 58 and 50 in the mavacamten 200 ng/mL arm and 500 ng/mL arms, respectively, and 54 in the placebo arm (Table D6). The majority (62-63%) were taking beta blockers at baseline and were in NYHA class II (68-86%). Mean resting LVEF at baseline was 66-69%.

Table D6. Selected Baseline Characteristics of MAVERICK-HCM[12]

	Group 1 200 ng/mL Mavacamten (n=19)	Group 2 500 ng/mL Mavacamten (n=21)	Placebo (n=19)
Age, Mean (SD)	58 (14)	50 (15)	54 (18)
Female Gender, n (%)	9 (47)	12 (57)	13 (68)
Background HOCM Therapy, n (%):			
Beta Blocker	12 (63)	13 (62)	12 (63)
Calcium Channel Blocker	5 (26)	5 (24)	3 (16)
Neither	3 (16)	3 (14)	4 (21)
NYHA Class II, %	79	86	68
NYHA Class III, %	21	14	32
Pathogenic or Likely Pathogenic HCM Gene Variant, n/N (%)	7/14 (50)	7/14 (50)	8/12 (67)
Echocardiographic Parameters:			
LVEF, % (SD)	68 (5)	69 (6)	66 (8)
Maximal LV Wall Thickness, mm	21 (3)	20 (5)	19 (4)
Peak LVOT Gradient, mm Hg (SD)	8 (3)	9 (4)	8 (3)
pVO_2, Mean, mL/kg/min (SD)	20 (5)	21 (7)	18 (5)
NT-proBNP, Geometric Mean, pg/mL (Range)	889 (747-1575)	763 (606-1261)	914 (770-1558)
CTnI, Geometric Mean, ng/L (Range)	0.024 (0-0.503)	0.023 (0.016-0.080)	0.02 (0.013-0.119)

CTnI: cardiac troponin I, HCM: hypertrophic cardiomyopathy, HOCM: hypertrophic obstructive cardiomyopathy, kg: kilogram, L: liter, LV: left ventricular, LVEF: left ventricular ejection fraction, LVOT: left ventricular outflow tract, mL: milliliter, mm: millimeter, mm Hg: millimeter of mercury, n: number, ng: nanogram, NT-proBNP: N-terminal pro B-type natriuretic peptide, NYHA: New York Heart Association, pg: picogram, pVO2: peak oxygen consumption, SD: standard deviation

Disopyramide

The main report discusses the primary source of data to inform our comparison of mavacamten to disopyramide, a multicenter retrospective study of observational data.[26] Three additional studies were identified, all single center retrospective studies.[54,55] One of these focused primarily on safety outcomes.[33]

Baseline characteristics of a multi-center retrospective study of disopyramide are provided in Table D7.

Table D7. Selected Baseline Characteristics in Retrospective Study of Disopyramide[26]

	Disopyramide (n=118)	Non-Disopyramide (n=373)
Age at Initial Evaluation, Mean (SD)	47 (20)	43 (21)
Female Gender (%)	49	47
Medical History, (%):		
Atrial Fibrillation at Initial Evaluation	20	18
Syncope or Pre-Syncope*	47	26
Dyspnea*	82	60
Septal Reduction Therapy	28	18
ICD	5	2
Background HOCM Therapy (%):		
Beta Blocker*	98	70
Calcium Channel Blocker	32	27
NYHA Class at Initial Evaluation, Mean (SD)*	2.3 (0.7)	1.9 (0.8)
LV Outflow Gradient, Mean mm Hg (SD)*	74 (35)	62 (32)

HOCM: hypertrophic obstructive cardiomyopathy, ICD: implantable cardiac device, LV: left ventricular, mm Hg: millimeter of mercury, n: number, NYHA: New York Heart Association, SD: standard deviation

*Indicates a statistically significant difference between groups.

Septal Reduction Therapies

The main report discusses the primary source of data to inform our comparison of mavacamten to septal reduction therapies, a 2015 systematic literature review with meta-analysis of long-term outcomes of septal ablation and myectomy.[27] Baseline characteristics of this systematic review are provided in Table D8. A more recent systematic review with meta-analysis reported on pooled short and long-term outcomes of septal reduction therapies, primarily all-cause mortality, cardiovascular mortality, reintervention, and complications,[57] while another reported improvements other outcomes such as symptoms of HOCM (NYHA class) and LVOT gradient.[31]

Table D8. Pooled Baseline Characteristics of Septal Reduction Therapy Studies[27]

	Septal Ablation (n=2,791)	Myectomy (n=2,013)
Age, Weighted Median (IQR)*	56 (54-58)	47 (40-47)
Female Gender (%)	49.4 (45-49.4)	40.1 (37-49)
Medical History, (%):		
Syncope or Pre-Syncope (%)	16 (15-26)	21 (21-29)
ICD (%)	3 (3-5)	10 (10-10)
NYHA Class, Weighted Median (IQR)	2.8 (2.8-3)	2.9 (2.7-3.1)
LVOT Gradient, mm Hg, Weighted Median (IQR)	78 (78-104.4)	93 (67.3-103)

ICD: implantable cardioverter defibrillator, IQR: interquartile range, LVOT: left ventricular outflow tract, LVWT: left ventricular wall thickness, mm: millimeter, mm Hg: millimeter of mercury, n: number, NYHA: New York Heart Association

*Indicates a statistically significant difference between groups.

Effectiveness

Mavacamten

Symptomatic Obstructive HCM

LVOT Gradients, LVEF, $PV0_2$, and NT-proBNP

The main report summarizes primary and secondary outcomes in the pivotal Phase III randomized controlled trial of mavacamten (EXPLORER).

In the Phase II trial (PIONEER), post-exercise, resting, and Valsalva LVOT gradients improved from baseline to week 12 in both cohort A and cohort B (Table D9). Resting LVEF declined 15% (-23 to -6) from baseline to week 12 in cohort A and 6% (-10 to -1) in cohort B. Mean pVO_2 increased 4 mL/kg/min (1 to 6) from baseline to week 12 in cohort A and a mean of 2 mgL/kg/min (0.03 to 3) in cohort B. Median NT-proBNP levels decreased 425 pg/mL in cohort A and 81 pg/mL in cohort B (Table D9).

Table D9. Selected Primary, Secondary and Exploratory Outcomes of PIONEER-HCM[52]

	Cohort A (n=11)	Cohort B (n=10)
Post Exercise LVOT Gradient, Mean Change from Baseline, mm Hg (SD)	-90 (-138 to -41) (n=8)	-25 (-47 to -3) (n=9)
Resting LVOT Gradient, Mean Change from Baseline, mm Hg (SD)	-48 (-72 to -23) (n=10)	-49 (-83 to -14)
Valsalva LVOT Gradient, Mean change from Baseline, mm Hg (SD)	-85 (-114 to -56) (n=10)	-47 (-82 to -12)
Resting LVEF, Mean Change from Baseline, % (SD)	-15 (-23 to -6) (n=10)	-6 (-10 to -1)
pVO_2, Mean Change from Baseline, mL/kg/min (95% CI)	4 (1 to 6) (n=10)	2 (0.3 to 3)
NT-proBNP Level, Median Change from Baseline, pg/mL (IQR)	-425 (-748 to -68) (n=10)	-81 (-637 to -16) (n=9)

kg: kilogram, LVEF: left ventricular ejection fraction, LVOT: left ventricular outflow tract, mL: milliliter, mm Hg: millimeter of mercury, n: number, NT-proBNP: N-terminal pro B-type natriuretic peptide, pg: picogram, pVO_2: peak oxygen consumption, SD: standard deviation

NYHA Class

The main report presents details on NYHA class outcomes in the pivotal Phase III randomized controlled trial of mavacamten (EXPLORER). In the Phase II trial (PIONEER), mean NYHA class declined -0.9 (-1.4 to -0.04) from baseline to week 12 in cohort A and -1.0 (-1.3 to -0.7) in cohort B.[52]

More detailed outcomes from both the EXPLORER and PIONEER trail are provided in Tables D19-D20.

HRQoL

The main report provides details on HRQoL outcomes in the pivotal Phase III randomized controlled trial of mavacamten (EXPLORER).

In the Phase II trial (PIONEER), mean KCCQ overall summary score, a measure of overall health, improved 14 points (7 to 22) from baseline to 12 weeks in cohort A and 16 points (0.3 to 32) in cohort B.[52]

Details on HRQoL outcomes from EXPLORER and PIONEER are provided in Tables D24-D25.

Symptomatic Non-Obstructive HCM

LVEF, $PV0_2$, and Cardiac Biomarkers

In the Phase II trial (MAVERICK), mean LVEF decreased 2% (-5 to 0.4) from baseline to week 16 in the lower-dose mavacamten group (200 ng/mL, Group 1, n=19) and 6% (-10 to -1) in the higher-dose mavacamten group (500 ng/mL, Group 2, n=21) and 2% (-5 to 0.2) in the placebo group (n=19) (Table D10). Mean pVO_2 increased 0.4 mL/kg/min (-1.4 to 2) from baseline to week 16 in Group 1 and 0.1 mL/kg/min (-1.8 to 2) in Group 2 and 0.6 (-0.6 to 1.8) in the placebo group. Mean NT-proBNP decreased 47% from baseline to week 24 in Group 1, 58% in Group 2 and 0.7% in the placebo group (p=0.01 and 0.001, respectively). Mean cTnI decreased 23% from baseline to week 16 in Group 1, 41% in Group 2 and increased 4% in the placebo group (p=0.09 and 0.003, respectively) (Table D10).[12]

Table D10. Change from Baseline in Selected Outcomes in the MAVERICK Trial[12]

	Group 1 200ng/mL Mavacamten (n=19)	Group 2 500ng/mL Mavacamten (n=21)	Placebo (n=19)
LVEF, Mean Change from Baseline (%) (95% CI)	-2 (-5 to 0.4)	-6 (-10 to -1)	-2 (-5 to 0.2)
pVO_2, Mean Change from Baseline, mL/kg/min (95% CI)	0.4 (-1 to 2)	0.1 (-2 to 2)	0.6 (-0.6 to 2)
NT-proBNP, Geometric Mean, Change from Baseline pg/mL (%) **cTnI, Geometric Mean, Change from Baseline ng/L (%)**	-47 -23	-58 -41	-0.7 4
≥1 NYHA Class Mean Change from Baseline (%) (95% CI)	53 (29 to 76)	33 (15 to 57)	37 (16 to 62)
Mean NYHA Class Change from Baseline (95% CI)	-0.6 (-1 to -0.2)	-0.3 (-0.5 to -0.3)	-0.4 (-0.8 to -0.1)
KCCQ-OSS Mean Change from Baseline (95% CI)	0.4 (-5 to 5)	6 (1 to 11)	6 (-3 to 15)
KCCQ-CSS Mean Change from Baseline (95% CI)	0.1 (-4 to 5)	6 (1 to 10)	4 (-4 to 13)

CI: confidence interval, CTnI: cardiac troponin I, KCCQ-CS: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score, KCCQ-OS: Kansas City Cardiomyopathy Questionnaire Overall Summary Score, kg: kilogram, LVEF: left ventricular ejection fraction, mL: milliliter, n: number, NT-proBNP: N-terminal pro B-type natriuretic peptide, NYHA: New York Heart Association, pVO_2: peak oxygen consumption

NYHA Class

In the MAVERICK trial, the proportion of patients who improved at least one NYHA class from baseline to week 12 was 53% in Group 1 and 33% in Group 2 and 37% in the placebo group. Mean NYHA class decreased 0.6 points (-1 to -0.2) from baseline to week 16 in Group 1, 0.3 points (-0.5 to -0.3) in Group 2, and 0.4 points (-0.8 to -0.1) in the placebo group (p=0.4 and 0.5, respectively) (Table D10).[12]

HRQoL

In the MAVERICK trial, KCCQ-OS, and clinical summary score (KCCQ-CS) mean change from baseline to week 12 are shown in Table D10. Mean KCCQ-OS increased 0.4 points in Group 1, 6 points in Group 2 and 6 points in the placebo group (p=0.5 and 0.5, respectively). Mean KCCQ-CS increased 0.1 points in Group 1, 6 points in Group 2, and 4 points in the placebo group (p=1 and 0.4, respectively).[12]

Disopyramide

The main report discusses data from the primary source of outcomes data for disopyramide, a multi-site retrospective study.[26] We also identified two additional single-site retrospective studies of disopyramide. In a single-site registry-based study of second-line treatments for HOCM, among

221 patients on disopyramide, mean resting gradient decreased from 63mm Hg (±45) at baseline to 25mm Hg (±32) at follow-up (p<0.0001). Of the 221 patients started on disopyramide, 80 (36%) underwent septal reduction over the 4.5-year study period. Among 141 patients on disopyramide who did not undergo septal reduction and remained on disopyramide, mean NYHA class decreased from 2.7 (±0.6) at initial evaluation to 1.9 (±0.5) at last evaluation (p<0.0001).[58]

In a more recent single-site retrospective study focused primarily on safety, 74 patients (44%) discontinued disopyramide due to side effects (11%) or lack of symptom improvement (33%) over a five-year period. Fifty-five patients underwent septal reduction therapy (eight septal ablation and 47 myectomy).[33]

Septal Reduction Therapies

The main report discusses data from the primary source of outcomes data for septal reduction therapies, a 2015 systematic review with meta-analysis.[27] Additional selected outcomes data from 2020 systematic review with meta-analysis was also discussed in the main report.[31]

Harms

Mavacamten

The main report provides details on harms in the pivotal Phase III randomized controlled trial of mavacamten (EXPLORER).

In the Phase II trial (PIONEER), mavacamten was well tolerated; most adverse events were mild (80%) or moderate (19%). The most common adverse events related to mavacamten were a decrease in LVEF (n=3) and atrial fibrillation (n=5). One patient in cohort A experienced a serious adverse event (atrial fibrillation leading to hospitalization) and discontinued treatment.[52]

Details on adverse events from EXPLORER and PIONEER are provided in Tables D27-D28.

Disopyramide

The main report discusses adverse events from the primary sources of data for harms of disopyramide, a multi-center retrospective study as well as a single-site retrospective study focused on safety.[29,35]

Septal Reduction Therapies

The main report discusses adverse events from the primary source of data for septal reduction therapies.[27]

Subgroup Analyses and Heterogeneity

The main report discusses available subgroup analyses in the setting of obstructive HCM.

The data on mavacamten in the setting of symptomatic non-obstructive HCM is substantially weaker compared to in the setting of symptomatic obstructive HCM. Improvements in cardiac biomarkers such as NT-proBNP and cTnI with mavacamten in the MAVERICK trial in patients with non-obstructive HCM point to potential benefits of the drug, but improvements in patient-important outcomes such as NYHA class or HRQoL were not observed although the study was not adequately powered for these clinical endpoints.[12]

Uncertainties and Controversies

The MAVERICK-HCM trial (discussed in Section D2) is a Phase II trial that enrolled 59 patients and assessed the effectiveness of mavacamten in non-obstructive HCM patients. Although the trial did not demonstrate a difference in an exploratory composite functional endpoint that includes symptoms, identical to the primary endpoint in EXPLORER-HCM, there were improvements in biomarkers including NT-proBNP and troponin. Non-obstructive symptomatic HCM patients have fewer alternatives for reducing symptoms, since there is not a conceptual basis to support therapies directed at reducing the LVOT gradient. As such, clinicians and patients may use mavacamten to reduce symptoms in non-obstructive HCM patients simply on the conceptual basis of reducing wall stress, even if this indication is not within the FDA label for mavacamten. Phase III trials that are statistically powered for clinical outcomes could assess the effectiveness of mavacamten for symptomatic HCM patients without obstruction.

D3. Evidence Tables

Table D11. Study Quality Table[15,24]

Trial	Comparable Groups	Non-Differential Follow-Up	Patient/ Investigator Blinding	Clear Definition of Intervention	Clear Definition of Outcomes	Selective Outcome Reporting	Measurements Valid	Intention-to-Treat Analysis	Approach to Missing Data	USPSTF Rating
Population: Symptomatic Obstructive HCM										
EXPLORER-HCM	Yes, with exception to gender, AF rates, and mean NT-proBNP	Yes	Yes	Yes	Yes	No	Yes	Yes	NRI for primary composite endpoint; week 26 timepoint used for NYHA if week 30 endpoint was missing	Good
Population: Symptomatic Non-Obstructive HCM										
MAVERICK-HCM	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Good

AF: atrial fibrillation, HCM: hypertrophic cardiomyopathy, NR: not reported, NRI: non-responder imputation, NT-proBNP: N-terminal pro B-type natriuretic peptide, NYHA: New York Heart Association, USPSTF: United States Preventive Services Task Force

Table D12. Study Design: Mavacamten[1,15,24,27,34,51,52,58-60]

Trial (NCT)	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
Symptomatic Obstructive HCM					
EXPLORER-HCM NCT03470545	Phase III DB, PC, RCT, MC Location: global	N=251 Patients ages 18+ with symptomatic HOCM	Individualized doses of 2.5, 5, 10, or 15 mg (n=123) or placebo (n=128) administered orally 30-week treatment	Inclusion Criteria • Age 18 and greater, body weight ≥45 kg • Has adequate acoustic windows to enable accurate TTEs • Diagnosed with HOCM consistent with current ACCF/AHA and European Society of Cardiology guidelines and has documented LVEF ≥55% and NYHA class II or III • Has documented O_2 saturation at rest ≥90% at screening • Able to perform an upright CPET and has a respiratory exchange ratio (RER) ≥1.0 at screening per central reading Exclusion Criteria • Cardiac hypertrophy that mimics HOCM • History of syncope or sustained V-tach with exercise, resuscitated sudden cardiac arrest or ICD discharge for life-threatening ventricular arrhythmia within 6 months • Has paroxysmal, intermittent AF or persistent or permanent AF not on anticoagulation for at least 4 weeks and/or not controlled within 1 year • Treatment with disopyramide or ranolazine • Any dose adjustment of β-blockers, verapamil, or diltiazem treatment • Has LVOT gradient with Valsalva maneuver <30 mm Hg • Has been successfully treated with invasive septal reduction (surgical myectomy or septal ablation) within 6 months • ICD placement within 6 months • Has pulmonary disease that limits exercise capacity or systemic arterial oxygen saturation • Prior treatment with cardiotoxic agents such as doxorubicin or similar	Percentage of Participants Achieving A Clinical Response: Primary: • 1.5 mL/kg per min or greater increase in pVO_2 and at least one NYHA class reduction or a 3.0 mL/kg per min or greater pVO_2 increase without NYHA class worsening Secondary: • Change in post-exercise LVOT gradient • Change in pVO_2 • Change in NYHA class • Change in KCCQ-CSS • Change in HCMSQ-SoB

Trial (NCT)	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
MAVA-LTE NCT03723655	Phase III Long-term extension trial Location: global	Patients ages 18+ who completed either MAVERICK-HCM or EXPLORER-HCM trials	Mavacamten 5 mg/d, with dose adjustments (2.5, 5, 10, or 15 mg) at weeks 4, 8, and 12 if needed	Inclusion Criteria • Patients who successfully complete either MyoKardia's MAVERICK-HCM or EXPLORER-HCM clinical trials • Has a body weight greater than 45 kg • Has adequate acoustic windows to enable accurate TTEs • Has documented LVEF ≥ 50% by echocardiography core laboratory read of screening TTE at rest • Has safety laboratory parameters (chemistry, hematology, coagulation, and urinalysis) within normal limits Exclusion Criteria • Has any ECG abnormality that poses a risk to participant safety • Has a history of syncope or a history of sustained ventricular tachycardia with exercise between Parent Study EOS Visit and screening visit • Has a history of resuscitated sudden cardiac arrest or known history of appropriate ICD discharge for life-threatening ventricular arrhythmia between Parent Study EOS Visit and screening visit • Currently or planned treatment with disopyramide or ranolazine • Has any acute or serious comorbid condition (e.g., major infection or hematologic, renal, metabolic, GI, or endocrine dysfunction) that could interfere with study • History of clinically significant malignant disease that developed since enrollment in the Parent Study. • Has participated in a clinical trial with any investigational drug, except for MAVERICK-HCM or EXPLORER-HCM	Primary: Frequency and severity of TEAS and SAEs (252 weeks)

Trial (NCT)	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
PIONEER-HCM NCT02842242 Heitner 2021	Phase II open-label, MC, pilot study Location: U.S.	N=21 Patients ages 18-70 with symptomatic HCM and LVOT obstruction	Cohort A: Mavacamten 10 to 20 mg/d, without background medications Cohort B: Mavacamten 2 to 5 mg/d, with β-blockers allowed 12-week treatment	<u>Inclusion Criteria</u> • Diagnosed with HCM, with LV wall thickness ≥15 mm at time of initial diagnosis or ≥13 mm with a positive family history of HCM • Age 18-70 • BMI 18-37 kg/m2 • Documented LVEF ≥55% at the screening visit as determined by the investigator and the investigational site's echocardiography laboratory • Resting LVOT gradient ≥30 mm Hg and post-exercise peak LVOT gradient ≥50 mm Hg NYHA functional class II or higher <u>Exclusion Criteria</u> • History of sustained V-tach or syncope with exercise • Active infection • Persistent AF or AF at screening or history of paroxysmal AF with resting rate document > 100 bpm within 1 year of screening • Has QTc Fridericia (QTcF) > 500 ms, or any other ECG abnormality considered by the investigator to pose a risk to subject safety • Aortic stenosis or fixed subaortic obstruction • History of LV systolic dysfunction (LVEF < 45%) at any time during their clinical course • History of obstructive coronary artery disease • Part A: Ongoing therapy with beta blockers, calcium channel blockers, or disopyramide • Part B: Ongoing therapy with calcium channel blockers or disopyramide • Prior treatment with cardiotoxic agents such as doxorubicin or similar, or current treatment with antiarrhythmic drugs that have negative inotropic activity, e.g., flecainide or propafenone.	<u>Primary:</u> • Change in post-exercise peak LVOT gradient from baseline to Week 12 <u>Secondary:</u> • Change in dyspnea symptom score from baseline to week 12 • Change in LVEF 2D and 3D, global longitudinal strain, and LV fractional shortening from baseline to week 12 • Change in post-exercise peak LVOT gradient from week 12 to week 16 • Change in pVO_2 and VE/VCO2 from baseline to week 12 • Plasma PK profile of mavacamten (16 weeks) • Proportion of subjects achieving an LVOT gradient response of post-exercise peak gradient <30 mm Hg (12 weeks)

Trial (NCT)	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
PIONEER-OLE NCT03496168	Phase II, ongoing 3-year prospective, open-label, multicenter study Location: US	N=13 Patients ages 18+ with symptomatic HOCM previously enrolled in PIONEER-HCM	starting dose: 5 mg/d; titration at Week 6 to an individualized dose (5, 10, or 15 mg)	Inclusion Criteria • Completed Study MYK-461-004 -Body weight > 45 kg • Has safety laboratory parameters (chemistry and hematology) within normal limits Exclusion Criteria • Has QTcF >480 ms or any other ECG abnormality • Since enrollment into Study MYK-461-004, has developed obstructive coronary artery disease or known moderate or severe aortic valve stenosis • Since enrollment into Study MYK-461-004, has developed any acute or serious comorbid condition (e.g., major infection or hematologic, renal, metabolic, GI, or endocrine dysfunction) • Has a positive serologic test at Screening for human immunodeficiency virus, hepatitis C virus, or hepatitis B virus • Since enrollment into Study MYK-461-004 has developed clinically significant malignant disease	Frequency and severity of adverse events: • LVOT Gradient • E/e at Week 24 • LA Volume Index (LAVi) at Week 24 • NT-proBNP at Week 24 • Interventricular Septal Thickness (IST) at Week 24 • LVEF at Week 24 • NYHA Class Improvement
Symptomatic Non-Obstructive HCM					
MAVERICK-HCM NCT03442764	Phase 2 DB, MC, PC, RCT Location: US	N=59 Patients ages 18+ with body weight ≥45 kg with symptomatic non-OHCM and preserved LVEF	Group 1: Starting dose mavacamten 5 mg/d, adjusted at week 6 (2.5, 5, 10, or 15 mg) according to 200 ng/mL target PK Group 2: Starting dose	Inclusion Criteria • Diagnosed with HCM (hypertrophied and non-dilated left ventricle in absence of systemic or other known cause), with LV wall thickness ≥15 mm at Screening or ≥13 mm with a positive family history of HCM. • Age 18 and greater, body weight ≥45 kg • Documented LVEF ≥55% at Screening • LVOT gradient <30 mm Hg • NYHA functional class II or III • Elevated NT-proBNP at rest Exclusion Criteria • History of syncope, sustained ventricular tachycardia with exercise, resuscitated sudden cardiac arrest or ICD discharge	Primary: • Safety and tolerability at Week 16 (AEs, TEAEs, etc.) Exploratory Endpoints at Week 16: • Composite functional endpoint (1.5 mL/kg per min or greater increase in peak oxygen consumption (pVO_2) and at least one NYHA class

Trial (NCT)	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
			mavacamten 5 mg/d, adjusted at week 6 (2.5, 5, 10, of 15 mg) according to 500 ng/mL target PK Placebo	• Has AF at Screening • Treatment with disopyramide, a combination of beta blockers and verapamil or combination of beta blockers and diltiazem • Has been treated with invasive septal reduction (surgical myectomy or septal ablation) within 6 months • Resting or post-exercise LVOT >30mm Hg unless treated by septal reduction • Has QTc Fridericia (QTcF) >480 ms or any other ECG abnormality considered to pose a risk to participant safety • History of obstructive coronary artery disease or myocardial infarction within past 6 months • Has pulmonary disease that limits exercise capacity or systemic arterial oxygen saturation	reduction or a 3.0 mL/kg per min or greater pVO_2 increase without NYHA class worsening) • pVO_2 change from baseline

3D: three-dimensional, AF: atrial fibrillation, AE: adverse event, ACCF: American College of Cardiology Foundation, AHA: American Heart Association, CPET: cardiopulmonary exercise testing, d: day, DB: double-blind, ECG: electrocardiogram, EOS: end of study, HCM: hypertrophic cardiomyopathy, HOCM: hypertrophic obstructive cardiomyopathy, ICD: implantable cardioverter-defibrillator, KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score, kg: kilogram, LV: left ventricular, LVEF: left ventricular ejection fraction, LVOT: left ventricular outflow tract, m: meter, MC: multi-center, mg: milligram, mL: milliliter, mm: millimeter, mm Hg: millimeter of mercury, ms: millisecond, n: number, NCT: National Clinical Trial number, NT-proBNP: N-terminal pro B-type natriuretic peptide, NYHA: New York Heart Association, O_2: oxygen, PC: placebo-controlled, PK: pharmacokinetic, pVO_2: peak oxygen consumption, RCT: randomized controlled trial, RER: respiratory exchange ratio, TTE: transthoracic echocardiogram, VE: ventilation, VCO_2: volume of exhaled carbon dioxide

Table D13. Study Design: Comparators[29,30]

Trial & Author	Study Design & Location	N	Treatment	Inclusion & Exclusion Criteria	Key Outcomes
Disopyramide					
Sherrid et al. 2005	Retrospective, multicenter, observational study Location: US, Poland, UK	N=491 Patients with HOCM	Disopyramide with initial dose of 200 or 250 mg/day and dose adjustments every 2 weeks if needed (n=118) No disopyramide treatment (n=373)	Inclusion Criteria • Patients with HCM consecutively treated at one of the four HCM centers from 1990-1999 • Outflow obstruction at rest (gradient ≥30 mm Hg) Exclusion Criteria NR	• Need for non-pharmacologic intervention (e.g., septal reduction therapy and pacing) • LVOT gradient at rest • Mean NYHA functional class • Mortality rates
Septal Reduction Therapy (Septal Myectomy and Septal Ablation)					
Liebregts et al. 2015	Systematic literature review of studies looking at septal ablation or septal myectomy in HCM patients Location: Varies	N=4,804 (24 studies) Patients with HOCM undergoing septal ablation or septal myectomy	Septal ablation (n=2,013; 11 cohorts) Septal myectomy (n=2,791; 16 cohorts)	Inclusion Criteria for Studies • Having at least 5 HOCM patients undergoing septal ablation and/or septal myectomy • Mean follow-up at least 5 years Exclusion Criteria for Studies • Other ablative media than ethanol • Enrollment of primarily patients who underwent rescue ablation or rescue myectomy after failed previous septal reduction therapy • Enrollment of primarily patients who underwent combined procedures, have a high risk of sudden death, or children	Short-term outcomes: • Mortality rates • Necessity of pacemaker implantation • AEs Long-term outcomes • Mortality rates • AEs • LVOT gradient reduction • NYHA class reduction • Need for reintervention

AE: adverse events, d: day, HOCM: hypertrophic obstructive cardiomyopathy, HCM: hypertrophic cardiomyopathy, LVOT: left ventricular outflow gradient, mg: milligram, mm Hg: millimeter of mercury, n: number, N: total number, NR: not reported, NYHA: New York Heart Association

Table D14. Baseline Characteristics: Phase III Trials[24,27]

Trial		EXPLORER-HCM		MAVA-LTE (EXPLORER-HCM Cohort)
Arms		Mavacamten	Placebo	Mavacamten
N		123	128	224
Age, Mean (SD)		58.5 (12.2)	58.5 (11.8)	60.3 (11.8)
Sex, n (%)	Men	66 (54)	83 (65)	135 (60.3)
	Women	57 (46)	45 (35)	89 (39.7)
Race, n (%)	White	115 (93)	114 (89)	NR
	Black or African American	1 (1)	5 (4)	NR
	Native American or Alaskan Native	0	1 (1)	NR
	Asian	4 (3)	2 (2)	NR
	Unknown	3 (2)	6 (5)	NR
Region, n (%)	USA	53 (43)	55 (43)	NR
	Spain	17 (14)	16 (13)	NR
	Poland	16 (13)	16 (13)	NR
	Other	37 (30)	41 (32)	NR
BMI, Mean kg/m² (SD)		29.7 (4.9)	29.2 (5.6)	NR
Heart Rate, Mean bpm (SD)		63 (10.1)	62 (10.6)	NR
Blood Pressure, Mean mm Hg (SD)	Systolic Blood Pressure	128 (16.2)	128 (14.6)	NR
	Diastolic Blood Pressure	75 (10.8)	76 (9.9)	NR
NYHA Functional Class, n (%)	Class I	NA	NA	13 (5.8)
	Class II	88 (72)	95 (74)	146 (65.2)
	Class III	35 (28)	33 (26)	65 (29)
Mavacamten Dose Assignment, n (%)	2 mg/d	NA	NA	NR
	5 mg/d	123 (100)	NA	NR
	10 mg/d (≤60 kg), 15 mg/d if (60 kg)	NA	NA	NR
pVO_2, Mean mL/kg per Min (SD)		18.9 (4.9)	19.9 (4.9)	NR
HCM Genetic Testing Performed, n (%)		90 (73)	100 (78)	NR
Pathogenic or Likely Pathogenic HCM Gene Variant, n/N (%)		28/90 (31)	22/100 (22)	NR
Medical History, n (%)	Family History of HCM	33 (27)	36 (28)	NR
	Atrial Fibrillation	12 (10)	23 (18)	NR
	Septal Reduction Therapy	11 (9)	8 (6)	NR
	Hypertension	57 (46)	53 (41)	NR
	Hyperlipidemia	27 (22)	39 (30)	NR
	Coronary Artery Disease	12 (10)	6 (5)	NR

Trial		EXPLORER-HCM		MAVA-LTE (EXPLORER-HCM Cohort)
Arms		Mavacamten	Placebo	Mavacamten
N		123	128	224
	Obesity	15 (12)	14 (11)	NR
	Type 2 Diabetes	6 (5)	7 (6)	NR
	Asthma	17 (14)	11 (9)	NR
	Chronic Obstructive Pulmonary Disease	2 (2)	3 (2)	NR
Background HCM Therapy, n (%)	B-blocker	94 (76)	95 (74)	169 (75.4)
	Calcium Channel Blocker	25 (20)	17 (13)	37 (16.5)
	Neither B-blocker nor Calcium Channel Blocker	4 (3)	16 (13)	NR
	Disopyramide	NA	NA	NR
NT-proBNP, Geometric Mean, ng/L (CV%)		777 (136)	616 (108)	Median: 785* IQR: 323 to 1586
High-Sensitivity Cardiac Troponin I, Geometric Mean, ng/L (CV%)		12.5 (208)	12.5 (373)	NR
KCCQ OSS, Mean (SD)		NR	NR	NR
NRS Dyspnea, Mean (SD)		NR	NR	NR
VE/VCO_2, Mean (SD)		NR	NR	NR
Echocardiographic Parameters	LVEF Mean, % (SD)	74 (6)	74 (6)	74 (5.9)
	Resting LVEF Mean, % (SD)	NR	NR	NR
	Exercise LVEF Mean, % (SD)	NR	NR	NR
	Maximum LV Wall Thickness, Mean mm (SD)	20 (4)	20 (3)	NR
	LVOT Gradient, Rest, Mean mm Hg (SD)	52 (29)	51 (32)	48.1 (31.6)
	LVOT Gradient, Valsalva, Mean mm Hg (SD)	72 (32)	74 (32)	69.5 (33.2)†
	LVOT Gradient, Post-Exercise, Mean mm Hg (SD)	86 (34)	84 (36)	NR
	Interventricular Septum Thickness, Mean cm (SD)	NR	NR	NR
	Systolic Anterior Motion of Mitral Valve, n (%)	NR	NR	NR
	LAVI, Mean mL/m^2 (SD)	40 (12)	41 (14)	37.9 (12.5)‡
	Mitral Regurgitation Present, n (%)	NR	NR	NR
	Left Atrial Diameter, Mean mm (SD)	42 (5)	42 (6)	NR

bpm: beats per minute, cm: centimeter, d: day, HCM: hypertrophic cardiomyopathy, KCCQ-OSS: Kansas City Cardiomyopathy Questionnaire Overall Summary Score, kg: kilogram, L: liter, LAVI: left atrial volume index, LV: left ventricular, LVEF: left ventricular ejection fraction, LVOT: left ventricular outflow tract, m: meter, mg: milligram, mL: milliliter, mm: millimeter, mm Hg: millimeter of mercury, n: number, N: total number, NA: not applicable, NR: not reported, NRS: numerical rating scale, NT-proBNP: N-terminal pro B-type natriuretic peptide, NYHA: New York Heart Association, pVO_2: peak oxygen consumption, VE: ventilation, VCO_2: volume of exhaled carbon dioxide, SD: standard deviation

*N=223, †N=221, ‡N=216

Table D15. Baseline Characteristics: Phase II Trials[51,52,58-60]

Trial		PIONEER-HCM		PIONEER-OLE		
Arms		Cohort A	Cohort B	Cohort A	Cohort B	Mavacamten (Overall)
N		11	10	5	8	13
Age, Mean (SD)		56, range: 22-70	58, range: 26-67	NR	NR	57.8
Sex, n (%)	Men	7 (64)	5 (50)	NR	NR	9 (69.2)
	Women	4 (36)	5 (50)	NR	NR	4 (31.8)
Race, n (%)	White	11 (100)	9 (90)	NR	NR	NR
	Black or African American	0	1 (10)	NR	NR	NR
	Native American or Alaskan Native	0	0	NR	NR	NR
	Asian	0	0	NR	NR	NR
	Unknown	0	0	NR	NR	NR
Region, n (%)	USA	11 (100)	12 (100)	NR	NR	NR
	Spain	0	0	NR	NR	NR
	Poland	0	0	NR	NR	NR
	Other	0	0	NR	NR	NR
BMI, Mean kg/m² (SD)		29.7 (4.1)	32.3 (5.4)	NR	NR	NR
Heart Rate, Mean bpm (SD)		76 (10)	62 (8)	NR	NR	NR
Blood Pressure, Mean mm Hg (SD)	Systolic Blood Pressure	136 (13)	132 (14)	NR	NR	NR
	Diastolic Blood Pressure	75 (8)	77 (15)	NR	NR	NR
NYHA Functional Class, n (%)	Class I	NA	NA	NR	NR	NR
	Class II	7 (64)	5 (50)	NR	NR	NR
	Class III	4 (36)	5 (50)	NR	NR	NR
Mavacamten Dose Assignment, n (%)	2 mg/d	NA	10 (100)	NR	NR	NR
	5 mg/d	NA	NA	NR	NR	NR
	10 mg/d (≤60 kg), 15 mg/d if (60 kg)	11 (100)	NA	NR	NR	NR
pVO_2, Mean mL/kg per min (SD)		20.7 (7.4)	19.4 (4.6)	NR	NR	NR
HCM Genetic Testing Performed, N (%)		NR	NR	NR	NR	NR
Pathogenic or Likely Pathogenic HCM Gene Variant, n/N (%)		5/21 (23.8)		NR	NR	NR
Medical History, n (%)	Family History of HCM	NR	NR	NR	NR	NR
	Atrial Fibrillation	NR	NR	NR	NR	NR
	Septal Reduction Therapy	NR	NR	NR	NR	NR
	Hypertension	NR	NR	NR	NR	NR
	Hyperlipidemia	NR	NR	NR	NR	NR
	Coronary Artery Disease	NR	NR	NR	NR	NR
	Obesity	NR	NR	NR	NR	NR
	Type 2 Diabetes	NR	NR	NR	NR	NR
	Asthma	NR	NR	NR	NR	NR
	Chronic Obstructive Pulmonary Disease	NR	NR	NR	NR	NR

Trial		PIONEER-HCM		PIONEER-OLE		
Arms		Cohort A	Cohort B	Cohort A	Cohort B	Mavacamten (Overall)
N		11	10	5	8	13
Background HCM Therapy, n (%)	B-Blocker	9 (82)	9 (90)	NR	NR	12 (92.3)
	Calcium Channel Blocker	1 (9)	0 (0)	NR	NR	NR
	Neither B-blocker nor Calcium Channel Blocker	NR	NR	NR	NR	NR
	Disopyramide	5 (45)	0 (0)	NR	NR	NR
NT-proBNP, Geometric Mean, pg/mL (SD)		930 (647)	1834 (3209)*	NR	NR	1836 (2886)
High-Sensitivity Cardiac Troponin I, Geometric Mean, ng/L (CV%)		NR	NR	NR	NR	NR
KCCQ OSS, Mean (SD)		65 (16)	61 (26)	NR	NR	74.1 (18.4)
NRS Dyspnea, Mean (SD)		4.9 (1.6)	4.0 (2.6)	NR	NR	NR
VE/VCO_2, Mean (SD)		32.2 (5.4)	32.3 (4.4)	NR	NR	NR
Echocardiographic Parameters	LVEF Mean, % (SD)	NR	NR	69.4 (5.6†)	73.6 (3.8†)	72 (4.9)
	Resting LVEF Mean, % (SD)	70 (7)	75 (5)	NR	NR	NR
	Exercise LVEF Mean, % (SD)	76 (8)	76 (8)	NR	NR	NR
	Maximum LV Wall Thickness, Mean mm (SD)	NR	NR	NR	NR	11.7 (2.2)‡
	LVOT Gradient, Rest, Mean mm Hg (SD)	60 (28)	86 (63)	NR	NR	67.3 (42.8)
	LVOT Gradient, Valsalva, Mean mm Hg (SD)	97 (32)	100 (65)	75.7 (30.7†)¶	97 (29.7†)	89.9 (30.7)
	LVOT Gradient, Post-Exercise, Mean mm Hg (SD)	103 (50)*	86 (43)*	NR	NR	127.5 (33.4)#
	Interventricular Septum Thickness, Mean cm (SD)	1.7 (0.2)	1.5 (0.2)	NR	NR	16.7 (2.8)
	Systolic Anterior Motion of Mitral Valve, n (%)	11 (100)	9 (90)	NR	NR	NR
	LAVI, Mean mL/m^2 (SD)	30 (10)	41 (20)	NR	NR	40.9 (16.4)
	Mitral Regurgitation Present, n (%)	11 (100)	10 (100)	NR	NR	NR
	Left Atrial Diameter, Mean mm (SD)	NR	NR	NR	NR	NR

bpm: beats per minute, cm: centimeter, d: day, HCM: hypertrophic cardiomyopathy, KCCQ-OSS: Kansas City Cardiomyopathy Questionnaire Overall Summary Score, kg: kilogram, L: liter, LAVI: left atrial volume index, LV: left ventricular, LVEF: left ventricular ejection fraction, LVOT: left ventricular outflow tract, m: meter, mg: milligram, mL: milliliter, mm: millimeter, mm Hg: millimeter of mercury, n: number, N: total number, NA: not applicable, NR: not reported, NRS: numerical rating scale, NT-proBNP: N-terminal pro B-type natriuretic peptide, NYHA: New York Heart Association, pg: picogram, pVO_2: peak oxygen consumption, VE: ventilation, VCO_2: volume of exhaled carbon dioxide, SD: standard deviation
*N=9, †Digitized estimate, ‡LV posterior wall thickness, ¶N=4, #N=12

Table D16. Baseline Characteristics: MAVERICK-HCM[12]

Trial		MAVERICK-HCM			
Arms		Group 1 Mava (~200 ng/mL)	Group 2 Mava (~500 ng/mL)	Pooled Mavacamten	Placebo
N		19	21	40	19
Age, Mean (SD)		58.3 (13.7)	50.0 (14.7)	54.0 (14.6)	53.8 (18.2)
Sex, n (%)	Men	10 (52.6)	9 (42.9)	19 (47.5)	6 (31.6)
	Women	9 (47.4)	12 (57.1)	21 (52.5)	13 (68.4)
Race, n (%)	White	17 (89.5)	18 (85.7)	35 (87.5)	17 (89.5)
	Black or African American	1 (5.3)	1 (4.8)	2 (5.0)	0
	Native American or Alaskan Native	NR	NR	NR	NR
	Asian	1 (5.3)	0	1 (2.5)	0
	Unknown	0	2 (9.5)	2 (5.0)	2 (10.5)
Region, n (%)	USA	19 (100)	21 (100)	40 (100)	19 (100)
	Spain	NR	NR	NR	NR
	Poland	NR	NR	NR	NR
	Other	NR	NR	NR	NR
BMI, Mean kg/m² (SD)		28.8 (4.1)	29.8 (6.1)	29.3 (5.2)	31.0 (4.9)
Heart Rate, Mean bpm (SD)		NR	NR	NR	NR
Blood Pressure, Mean mm Hg (SD)	Systolic Blood Pressure	NR	NR	NR	NR
	Diastolic Blood Pressure	NR	NR	NR	NR
NYHA Functional Class, n (%)	Class I	NA	NA	NA	NA
	Class II	15 (78.9)	18 (85.7)	33 (82.5)	13 (68.4)
	Class III	4 (21.1)	3 (14.3)	7 (17.5)	6 (31.6)
Mavacamten Dose Assignment, n (%)	2 mg/d	NA	NA	NA	NA
	5 mg/d	19 (100)	21 (100)	40 (100)	NA
	10 mg/d (≤60 kg), 15 mg/d if (60 kg)	NA	NA	NA	NA
pVO_2, Mean mL/kg per Min (SD)		19.5 (5.2)	21 (6.6)	20.4 (6)	17.9 (5.1)
HCM Genetic Testing Performed, n (%)		14 (73.7)	14 (66.7)	28 (70.0)	12 (63.2)
Pathogenic or Likely Pathogenic HCM Gene Variant, n/N (%)*		7/14 (50.0)	7/14 (50.0)	14/28 (50.0)	8/12 (66.7)
Medical History, n (%)	Family History of HCM	NR	NR	NR	NR
	Atrial Fibrillation	NR	NR	NR	NR
	Septal Reduction Therapy	NR	NR	NR	NR
	Hypertension	NR	NR	NR	NR
	Hyperlipidemia	NR	NR	NR	NR
	Coronary Artery Disease	NR	NR	NR	NR
	Obesity	NR	NR	NR	NR

Trial		MAVERICK-HCM			
Arms		Group 1 Mava (~200 ng/mL)	Group 2 Mava (~500 ng/mL)	Pooled Mavacamten	Placebo
N		19	21	40	19
	Type 2 Diabetes	NR	NR	NR	NR
	Asthma	NR	NR	NR	NR
	Chronic Obstructive Pulmonary Disease	NR	NR	NR	NR
Background HCM Therapy, n (%)	B-Blocker	12 (63.2)	13 (61.9)	25 (62.5)	12 (63.2)
	Calcium Channel Blocker	5 (26.3)	5 (23.8)	10 (25)	3 (15.8)
	Neither B-Blocker nor Calcium Channel Blocker	3 (15.8)	3 (14.3)	6 (15)	4 (21.1)
	Disopyramide	NR	NR	NR	NR
NT-proBNP, Geometric Mean, pg/mL (95% CI)		889 (747 to 1,575)	763 (606 to 1,261)	821 (790 to 1,293)	914 (770 to 1,558)
High-Sensitivity Cardiac Troponin I, Geometric Mean, ng/mL (95% CI)		0.024 (0 to 0.503)	0.023 (0.016 to 0.08)	0.023 (0 to 0.253)	0.02 (0.013 to 0.119)
KCCQ OSS, Mean (SD)		NR	NR	NR	NR
NRS Dyspnea, Mean (SD)		NR	NR	NR	NR
VE/VCO_2, Mean (SD)		NR	NR	NR	NR
Echocardiographic Parameters	LVEF Mean, % (SD)	68 (5.2)	69.4 (5.8)	68.7 (5.5)	66.4 (7.7)
	Resting LVEF Mean, % (SD)	NR	NR	NR	NR
	Exercise LVEF Mean, % (SD)	NR	NR	NR	NR
	Maximum LV Wall Thickness, Mean mm (SD)	20.9 (3)	20.4 (4.8)	20.6 (4)	18.8 (3.5)
	LVOT Gradient, Rest, Mean mm Hg (SD)	8.1 (3.3)	9.4 (3.6)	8.8 (3.5)	7.8 (2.5)
	LVOT Gradient, Valsalva, Mean mm Hg (SD)	NR	NR	NR	NR
	LVOT Gradient, Post-Exercise, Mean mm Hg (SD)	NR	NR	NR	NR
	Interventricular Septum Thickness, Mean cm (SD)	NR	NR	NR	NR
	Systolic Anterior Motion of Mitral Valve, n (%)	NR	NR	NR	NR
	LAVI, Mean mL/m^2 (SD)	40.3 (16.1)	34.5 (8.9)	37.3 (13)	40.8 (15.2)
	Mitral Regurgitation Present, n (%)	NR	NR	NR	NR
	Left Atrial Diameter, Mean mm (SD)	NR	NR	NR	NR

bpm: beats per minute, cm: centimeter, d: day, CI: confidence interval, HCM: hypertrophic cardiomyopathy, KCCQ-OSS: Kansas City Cardiomyopathy Questionnaire Overall Summary Score, kg: kilogram, LAVI: left atrial volume index, LV: left ventricular, LVEF: left ventricular ejection fraction, LVOT: left ventricular outflow tract, m: meter, mg: milligram, mL: milliliter, mm: millimeter, mm Hg: millimeter of mercury, n: number, N: total number, NA: not applicable, NR: not reported, NRS: numerical rating scale, NT-proBNP: N-terminal pro B-type natriuretic peptide, NYHA: New York Heart Association, pVO_2: peak oxygen consumption, VE: ventilation, VCO_2: volume of exhaled carbon dioxide, SD: standard deviation
*Gene mutation of 40 with genetic testing.

Table D17. Baseline Characteristics: Disopyramide[26]

Trial		Sherrid et al. 2005			
Arms		Disopyramide	Disopyramide without Intervention	Disopyramide with Intervention	Non-Disopyramide
N		118	78	40	373
Age at Initial Evaluation, Mean Years (SD)		47 (20)	48 (20)	44 (20)	43 (21)
Duration of Follow-Up, Mean Years (SD)		4.2 (2.9)	NR	NR	6.5 (5.2)
Gender, n (%)	Male	60 (51)	NR	NR	198 (53)
	Female	58 (49)	34 (44)	22 (55)	175 (47)
NYHA Functional Class, Mean (SD)		2.3 (0.7)	2.3 (0.7)	2.3 (0.7)	1.9 (0.8)
NYHA Functional Class Distribution, n (%)	Class I	14 (12)	9 (11.5)	NR	NR
	Class II	59 (50)	40 (51.3)	NR	NR
	Class III or Class IV	45 (38)	29 (37.2)	NR	NR
Disopyramide Dose, Mean mg/day (SD)		432 (181)	425 (169)	445 (201)	NA
Medical History, n (%)	Syncope or Pre-Syncope	55 (47)	NR	NR	97 (26)
	Dyspnea	97 (82)	NR	NR	224 (60)
	NSVT	21 (18)	NR	NR	63 (17)
	Family History of SCD	18 (15)	NR	NR	56 (15)
	AF at Initial Evaluation	24 (20)	NR	NR	67 (18)
	Septal Myectomy	22 (19)	NR	NR	34 (9)
	Septal Ablation	11 (9)	NR	NR	34 (9)
	DDD Pacemaker	13 (11)	NR	NR	52 (14)
	MV Surgery	NR	NR	NR	NR
	All Interventions Combined	40 (34)	NR	NR	104 (28)
	ICD	6 (5)	NR	NR	7 (2)
LVOT Gradient, Mean mm Hg (SD)		74 (35)	75 (33)	73 (35)	62 (32)
MAX LV Wall Thickness, Mean mm (SD)		21.9 (5.5)	21.1 (5)	23.1 (6)	23.7 (6.4)
Coronary Stenosis >70%, n (%)		8 (7)	NR	NR	7 (2)
Background Therapy, n (%)	Beta Blocker	116 (98)	NR	NR	261 (70)
	Calcium Channel Blocker	38 (32)	NR	NR	101 (27)
	Amiodarone	12 (10)	NR	NR	112 (30)

AF: atrial fibrillation, DDD: dual chamber, ICD: implantable cardioverter-defibrillator, mg: milligram, mm Hg: millimeter of mercury, MV: mitral valve, n: number, N: total number, NA: not applicable, NR: not reported, NSVT: non-sustained ventricular tachycardia, NYHA: New York Heart Association, SCD: sudden cardiac death, SD: standard deviation

Table D18. Baseline Characteristics: Septal Reduction Therapy[27]

Trial		Liebregts et al. 2015	
Arms		**Septal Ablation**	**Surgical Myectomy**
N		**2,013**	**2,791**
Age at Initial Evaluation, Weighted Median Years (IQR)		56 (54 to 58)	47 (40 to 47)
Duration of Follow-Up, Mean Years (SD)		6.2	7.4
Gender, Weighted Median % (IQR)	**Male**	NR	NR
	Female	49.4 (45 to 49.4)	40.1 (37 to 49)
NYHA Functional Class, Weighted Median (IQR)		2.8 (2.8 to 3)	2.9 (2.7 to 3.1)
NYHA Functional Class Distribution, n (%)	**Class I**	NR	NR
	Class II	NR	NR
	Class III or Class IV	NR	NR
Disopyramide Dose, Mean mg/day (SD)		NA	NA
Medical History, Weighted Median % (IQR)	**Syncope or Pre-Syncope**	16 (15 to 26)	21 (21 to 29)
	Dyspnea	NR	NR
	NSVT	NR	NR
	Family History of SCD	NR	NR
	AF at Initial Evaluation	NR	NR
	Septal Myectomy	NR	NR
	Septal Ablation	2.5 (2 to 2.6)*	NA
	DDD Pacemaker	NR	NR
	MV Surgery	NA	7.1 (0.0 to 26)
	All Interventions Combined	NR	NR
	ICD	3 (3 to 5)	10 (10 to 10)
LVOT Gradient, Weighted Median mm Hg (IQR)		78 (78 to 104.4)	93 (67.3 to 103)
MAX LV Wall Thickness, Weighted Median mm (IQR)		21 (20.3 to 21)	22.1 (21.9 to 23.5)
Coronary Stenosis >70%, n (%)		NR	NR
Background Therapy, n (%)	**Beta Blocker**	NR	NR
	Calcium Channel Blocker	NR	NR
	Amiodarone	NR	NR

AF: atrial fibrillation, DDD: dual chamber, ICD: implantable cardioverter-defibrillator, mg: milligram, mm Hg: millimeter of mercury, MV: mitral valve, n: number, N: total number, NA: not applicable, NR: not reported, NSVT: non-sustained ventricular tachycardia, NYHA: New York Heart Association, SCD: sudden cardiac death, SD: standard deviation

*Alcohol, ml.

Table D19. Efficacy Outcomes: Phase III Trials[24,27]

Trial		EXPLORER-HCM				MAVA-LTE				
Arms		Mavacamten	Placebo	Mavacamten	Placebo	EXPLORER-HCM Cohort				
N		123	128	123	128	224				
Timepoint		14 Weeks		30 Weeks		12 Weeks	24 Weeks	36 Weeks	48 Weeks	60 Weeks
Composite Measure Response n (%)	Either ≥1.5 mL/kg per Min Increase in pVO_2 and NYHA Class Improvement ≥1 OR ≥3 mL/kg per Min Increase in pVO_2 and No Worsening in NYHA Class	NR	NR	45 (37)	22 (17)	NR	NR	NR	NR	NR
	≥1.5 mL/kg per Min Increase in pVO_2 and NYHA Class Improvement ≥1	NR	NR	41 (33)	18 (14)	NR	NR	NR	NR	NR
	≥3 mL/kg per Min Increase in pVO_2 and No Worsening in NYHA Class	NR	NR	29 (24)	14 (11)	NR	NR	NR	NR	NR
	Both ≥3 mL/kg per Min Increase in pVO_2 and NYHA Class Improvement ≥1	NR	NR	25 (20)	10 (8)	NR	NR	NR	NR	NR
NYHA Class I & All LVOT Peak Gradients <30 mm Hg, n/N (%)		NR	NR	32/117 (27)	1/126 (1)	NR	NR	NR	NR	NR
Post-Exercise LVOT Peak Gradient <50 mm Hg, n/N (%)		NR	NR	75/101 (74)	22/106 (21)	NR	NR	NR	NR	NR
Post-Exercise LVOT Peak Gradient <30 mm Hg, n/N (%)		NR	NR	64/113 (57)	8/114 (7)	NR	NR	NR	NR	NR
Post-Exercise LVOT Gradient Change from Baseline, Mean (SD)		NR	NR	-47 (40)*	-10 (30)†	NR	NR	NR	NR	NR
Resting LVOT Gradient Change from Baseline, Mean mm Hg (SD)		NR	NR	-37.6	-5.2	-30.5#	-33.5ɣ	-37.9††	-37.7##	-24.1 (30.6)ɣɣ
Valsalva LVOT Gradient Change from Baseline, Mean mm Hg (SD)		NR	NR	-47.6	-11.2	-36.4#	-42.7ɣ	-51.6††	-47.7##	-42.6 (38.1)ɣɣ

Trial		EXPLORER-HCM				MAVA-LTE				
Arms		Mavacamten	Placebo	Mavacamten	Placebo	EXPLORER-HCM Cohort				
N		123	128	123	128	224				
Timepoint		14 Weeks		30 Weeks		12 Weeks	24 Weeks	36 Weeks	48 Weeks	60 Weeks
Resting LVEF Change from Baseline, % (95% CI)		NR	NR	-3.9	-0.01	-3.9§	-6.2**	-7.1‡‡	-7.9§§	-7.6 (6.9)***
pVO_2 Change from Baseline, Mean mL/kg per Min (SD)		NR	NR	1.4 (3.1)‡	-0.1 (3.0)¶	NR	NR	NR	NR	NR
NYHA Class Improvement ≥1, n (%)		NR	NR	80 (65)	40 (31)	NR	NR	NR	35 (71)##	NR
NYHA Class Mean Change from Baseline (95% CI)		NR	NR	NR	NR	NR	NR	NR	NR	NR
NYHA Functional Class Distribution, n (%)	Class I	39 (31.7)	21 (16.4)	61 (49.6)	27 (21.1)	72 (45.3)§	NR	NR	29 (59.2)##	NR
	Class II	68 (55.3)	82 (64.1)	52 (42.3)	74 (57.8)	74 (46.5)§	NR	NR	16 (32.7)##	NR
	Class III	4 (3.3)	19 (14.8)	8 (6.5)	25 (19.5)	13 (8.2)§	NR	NR	4 (8.2)##	NR
VE/VCO_2 Mean Change from Baseline (95% CI)		NR	NR	-2.6 (-3.6 to -1.5)	NR	NR	NR	NR	NR	NR
NRS Dyspnea Score Mean Change from Baseline (95% CI)		NR	NR	NR	NR	NR	NR	NR	NR	NR
NT-proBNP Level Change from Baseline, Median (IQR), pg/mL (95% CI)		NR	NR	-614.3	30.2	-600#	-605**	-632¶¶	-655##	-356 (-1073 to -148)ᵞᵞ
Hs-CTnI Change from Baseline, Geometric Mean, ng/L		NR	NR	-5.1	0.1	NR	NR	NR	NR	NR

CI: confidence interval, IQR: interquartile range, kg: kilogram, LVEF: left ventricular ejection fraction, LVOT: left ventricular outflow tract, mL: milliliter, mm Hg: millimeter of mercury, n: number, N: total number, NR: not reported, NRS: numerical rating scale, NT-proBNP: N-terminal pro B-type natriuretic peptide, NYHA: New York Heart Association, pg: picogram, pVO_2: peak oxygen consumption, VE: ventilation, VCO_2: volume of exhaled carbon dioxide, SD: standard deviation

*N=117, †N=122, ‡N=120, ¶N=125, #N=162, §N=159, ᵞN=110, **N=108, ††N=97, ‡‡N=93, ¶¶N=94, ##N=49, §§N=47, ᵞᵞN=23, ***N=22

Table D20. Efficacy Outcomes: Phase II Trials[51,59,60]

Trial		PIONEER-HCM				PIONEER-OLE							
Arms		Cohort A	Cohort B	Cohort A	Cohort B	Cohort A		Cohort B		Mavacamten (Overall)			
N		11*	10	11*	10	5		8		13			
Timepoint		12 Weeks		16 Weeks		12 Weeks	24 Weeks	12 Weeks	24 Weeks	12 Weeks	24 Weeks	36 Weeks	48 Weeks
Composite measure response n (%)	Either ≥1.5 mL/kg per Min Increase in pVO_2 and NYHA Class Improvement ≥1 OR ≥3 mL/kg per Min Increase in pVO_2 and No Worsening in NYHA Class	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	≥1.5 mL/kg per Min Increase in pVO_2 and NYHA Class Improvement ≥1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	≥3 mL/kg per Min Increase in pVO_2 and No Worsening in NYHA Class	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Both ≥3 mL/kg per Min Increase in pVO_2 and NYHA Class Improvement ≥1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NYHA Class I & All LVOT Peak Gradients <30 mm Hg, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Post-Exercise LVOT Peak Gradient <50 mm Hg, n/N (%)		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Trial		PIONEER-HCM				PIONEER-OLE							
Arms		Cohort A	Cohort B	Cohort A	Cohort B	Cohort A		Cohort B		Mavacamten (Overall)			
N		11*	10	11*	10	5		8		13			
Timepoint		12 Weeks		16 Weeks		12 Weeks	24 Weeks	12 Weeks	24 Weeks	12 Weeks	24 Weeks	36 Weeks	48 Weeks
Post-Exercise LVOT Peak Gradient <30 mm Hg, n/N (%)		8/11 (72.7)	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Post-Exercise LVOT Gradient Change from Baseline, Mean (95% CI)		-89.5 (-138.3 to -40.7)†	-25 (-47.1 to -3.0)‡	-45.1 (-91.2 to 1.0)†	-3.5 (-27.5 to 20.5)‡	NR	NR	NR	NR	NR	NR	NR	NR
Resting LVOT Gradient Change from Baseline, Mean mm Hg (95% CI)		-47.8 (-72.2 to -23.4)	-48.5 (-82.8 to -14.1)	29.5 (-63.1 to 4.2)	-9.1 (-30.0 to 11.7)	NR	NR	NR	NR	NR	-55.7 (SD: 42.3)	-54.4 (SD: 59.2)	-73.6 (SD: 45.5)
Valsalva LVOT Gradient Change from Baseline, Mean mm Hg (95% CI)		-84.7 (-113.8 to -55.7)	-47.1 (-82.1 to -12.1)	-60.6 (-91.8 to -29.4)	-9.5 (-38.5 to 19.6)	-47.8	-53¶	-77.8	-76.9#	-67.4	-68.3§ (SD: 28.9)	-52.1 (SD: 41)	-73.6 (SD: 45.1)
Resting LVEF Change from Baseline, % (95% CI)		-14.6 (-23.1 to -6.2)	-5.5 (-9.8 to -1.2)	-6.2 (-12.2 to -0.2)	-2.8 (-7.5 to 2.0)	-4.4	-4.8¶	-4.5	-3.1#	-4.5	-2.5 (SD: 3.7)	-3.6 (SD: 3.7)	-2.6 (SD: 7.2)
pVO_2 Change from Baseline, Mean mL/kg per Min (95% CI)		3.5 (1.2 to 5.9)	1.7 (0.03 to 3.3)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NYHA Class Improvement ≥1, n (%)		NR	NR	NR	NR	NR	NR	NR	NR	NR	10 (76.9)	NR	NR
NYHA Class Mean Change from Baseline (95% CI)		-0.9 (-1.4 to -0.4)	-1.0 (-1.3 to -0.7)	-0.4 (-1.0 to 0.2)	-0.4 (-0.8 to -0.03)	NR	NR	NR	NR	NR	NR	NR	NR
NYHA Functional Class	Class I	7 (70)	6 (60)	4 (44)‡	1 (10)	NR	NR	NR	NR	NR	7 (70)ɣ	NR	3 (50)#
	Class II	2 (20)	3 (30)	3 (33)‡	7 (70)	NR	NR	NR	NR	NR	3 (30)ɣ	NR	3 (50)#

Trial		PIONEER-HCM				PIONEER-OLE							
Arms		Cohort A	Cohort B	Cohort A	Cohort B	Cohort A		Cohort B		Mavacamten (Overall)			
N		11*	10	11*	10	5		8		13			
Timepoint		12 Weeks		16 Weeks		12 Weeks	24 Weeks	12 Weeks	24 Weeks	12 Weeks	24 Weeks	36 Weeks	48 Weeks
Distribution n (%)	Class III	1 (10)	1 (10)	2 (22)‡	2 (20)	NR	NR	NR	NR	NR	0 (0)ɣ	NR	0 (0)#
VE/VCO_2 Mean Change from Baseline (95% CI)		-2.2 (-6.1 to 1.7)	-2.5 (-4.3 to -0.7)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
NRS Dyspnea Score Mean Change from Baseline (95% CI)		-3.1 (-4.1 to -2.1)	-3.0 (-5.0 to -1.0)	-2.2 (-4.6 to 0.2)	-0.8 (-2.3 to 0.7)	NR	NR	NR	NR	NR	NR	NR	NR
NT-proBNP Level Change from Baseline, Median (IQR), pg/mL (95% CI)		-425 (-748 to -68)	-81 (-637 to -16)‡	-629.5 (-804 to 158)	240 (4 to 311)	NR	NR	NR	NR	-1658 (SD: -2695)	-1689 (SD: 2816)	-2243 (SD: 3282)	-3638 (SD: 3947)
Hs-cTnI Change from Baseline, Geometric Mean, ng/L		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

CI: confidence interval, IQR: interquartile range, kg: kilogram, LVEF: left ventricular ejection fraction, LVOT: left ventricular outflow tract, mL: milliliter, mm Hg: millimeter of mercury, n: number, N: total number, NR: not reported, NRS: numerical rating scale, NT-proBNP: N-terminal pro B-type natriuretic peptide, NYHA: New York Heart Association, pg: picogram, pVO_2: peak oxygen consumption, VE: ventilation, VCO_2: volume of exhaled carbon dioxide, SD: standard deviation

*N=10 for all reported outcomes unless otherwise stated, †N=8, ‡N=9, ¶N=4, #N=6, §N=12, ɣN=10

Table D21. Efficacy Outcomes: MAVERICK-HCM[12]

Trial		MAVERICK-HCM			
Arms		Group 1 Mava (~200 ng/mL)	Group 2 Mava (~500 ng/mL)	Pooled Mavacamten	Placebo
N		19	21	40	19
Timepoint		16 Weeks			
Composite Measure Response n (%)	Either ≥1.5 mL/kg per Min Increase in pVO_2 and NYHA Class Improvement ≥1 OR ≥3 mL/kg per Min Increase in pVO_2 and No Worsening in NYHA Class	3 (15.8) (95% CI: 3.4 to 39.6)	6 (28.6) (95% CI: 11.3 to 42.2)	9 (22.5) (95% CI: 10.8 to 38.5)	4 (21.1) (95% CI: 6.1 to 45.6)
	≥1.5 mL/kg per Min Increase in pVO_2 and NYHA Class Improvement ≥1	NR	NR	NR	NR
	≥3 mL/kg per Min Increase in pVO_2 and No Worsening in NYHA Class	NR	NR	NR	NR
	Both ≥3 mL/kg per Min Increase in pVO_2 and NYHA Class Improvement ≥1	NR	NR	NR	NR
NYHA Class I & All LVOT Peak Gradients <30 mm Hg, n/N (%)		NR	NR	NR	NR
Post-Exercise LVOT Peak Gradient <50 mm Hg, n/N (%)		NR	NR	NR	NR
Post-Exercise LVOT Peak Gradient <30 mm Hg, n/N (%)		NR	NR	NR	NR
Post-Exercise LVOT Gradient Change from Baseline, Mean (SD)		NR	NR	NR	NR
Resting LVOT Gradient Change from Baseline, Mean mm Hg (SD)		NR	NR	NR	NR
Valsalva LVOT Gradient Change from Baseline, Mean mm Hg (SD)		NR	NR	NR	NR
Resting LVEF Change from Baseline, % (SD)		-2.3 (5.3)	-5.61 (9.65)	-4.09 (8.02)	-2.31 (4.94)
pVO_2 Change from Baseline, Mean mL/kg per min (SD)		0.36 (3.12)	0.12 (3.76)	0.22 (3.44)	0.58 (2.39)
NYHA Class Improvement ≥1, n (%)		10 (52.6); (95% CI: 28.9 to 75.6)	7 (33.3); (95% CI: 14.6 to 57)	17 (42.5); (95% CI: 27 to 59.1)	7 (36.8); (95% CI: 16.3 to 61.6)
NYHA Class Mean Change from Baseline (SD)		-0.6 (0.7)	-0.3 (0.6)	-0.4 (0.7)	-0.4 (0.6)
NYHA Functional Class Distribution, n (%)	Class I	NR	NR	NR	NR
	Class II	NR	NR	NR	NR
	Class III	NR	NR	NR	NR
VE/VCO_2 Mean Change from Baseline (95% CI)		NR	NR	NR	NR
NRS Dyspnea Score Mean Change from Baseline (95% CI)		NR	NR	NR	NR
NT-proBNP Level Change from Baseline, Median (IQR), pg/mL (95% CI)*		-47.1	-57.1	-53.2	-0.7
Hs-CTnI Change from Baseline, Geometric Mean, ng/L*		-23.4	-41	-34	3.8

CI: confidence interval, IQR: interquartile range, kg: kilogram, LVEF: left ventricular ejection fraction, LVOT: left ventricular outflow tract, mL: milliliter, mm Hg: millimeter of mercury, n: number, N: total number, NR: not reported, NRS: numerical rating scale, NT-proBNP: N-terminal pro B-type natriuretic peptide, NYHA: New York Heart Association, pg: picogram, pVO_2: peak oxygen consumption, VE: ventilation, VCO_2: volume of exhaled carbon dioxide, SD: standard deviation
*Percent change.

Table D22. Efficacy Outcomes: Disopyramide[26]

Trial		Sherrid et al. 2005	
Arms		**Disopyramide without Intervention**	**Disopyramide with Intervention**
N		**78**	**40**
Timepoint		**3.1 ± 2.6 years**	**NR**
Intervention Type, n (%)	**Septal Myectomy**	NA	22 (55)
	Septal Ablation	NA	10 (25)
	Dual-Chamber Pacemakers	NA	8 (20)
LVOT Peak Gradient Change from Baseline, Mean mm Hg		-35*	-10*
Re-Intervention, Weighted Median (IQR)		NR	NR
NYHA Class Change from Baseline, Mean (SD)		-0.6*	0
NYHA Class Distribution, n (%)	**Class I**	29 (37.2)*	NR
	Class II	42 (53.8)*	NR
	Class III/IV	7 (9.0)*	NR

IQR: interquartile range, LVOT: left ventricular outflow tract, n: number, N: total number: NA: not applicable, NR: not reported, NYHA: New York Heart Association, SD: standard deviation

*Statistically significant.

Table D23. Efficacy Outcomes: Septal Reduction Therapy[27]

Trial		Liebregts et al. 2015	
Arms		**Septal Ablation**	**Surgical Myectomy**
N		**2,013**	**2,791**
Timepoint		**Follow-up***	
Intervention Type, n (%)	**Septal Myectomy**	NR	NR
	Septal Ablation	NR	NR
	Dual-Chamber Pacemakers	NR	NR
LVOT Peak Gradient Change from Baseline, Weighted Median % (IQR)		-71 (-67 to -90)	-77 (-69 to -90)
Re-Intervention, Weighted Median % (95% CI)		7.7 (4.2 to 11.1)	1.6 (0.6 to 2.6)
NYHA Class Change from Baseline, Weighted Median % (IQR)		-45 (-45 to -50)	-45 (-44 to -48)
NYHA Class Distribution, Weighted Median % (95% CI)	**Class I**	NR	NR
	Class II	NR	NR
	Class III/IV	8 (8 to 8)	4.5 (4.5 to 12)

CI: confidence interval, IQR: interquartile range, LVOT: left ventricular outflow tract, n: number, N: total number: NR: not reported, NYHA: New York Heart Association, SD: standard deviation

*Timepoints varied between studies in this systematic literature review.

Table D24. Patient-Reported Outcomes: Phase III Trials[1,24,27]

Trial		EXPLORER-HCM		MAVA-LTE
Arms		Mavacamten	Placebo	EXPLORER-HCM Cohort
N		123*	128‡	224
Timepoint		30 weeks		NR
KCCQ-CSS Mean Change from Baseline (SD)		13.6 (14.4)	4.2 (13.7)	NR
KCCQ-OSS Mean Change from Baseline (SD)		14.9 (15.8)	5.4 (13.7)	NR
KCCQ-PLS Mean Change from Baseline (SD)		14.7 (17)	3.6 (15.4)	NR
Magnitude of Clinical Change in KCCS-CSS, n (%)	Clinically Worse	9 (10)	22 (25)	NR
	No significant Change	19 (21)	27 (31)	NR
	Small but Clinically Important Improvement	16 (17)	12 (14)	NR
	Moderate to Large Clinical Improvement	15 (16)	16 (18)	NR
	Large to Very Large Improvement	33 (36)	11 (13)	NR
Magnitude of clinical change in KCCS-OSS, n (%)	Clinically Worse	8 (9)	20 (23)	NR
	No Significant Change	18 (20)	28 (32)	NR
	Small but Clinically Important Improvement	17 (18)	9 (10)	NR
	Moderate to Large Clinical Improvement	16 (17)	18 (20)	NR
	Large to Very Large Improvement	33 (36)	13 (15)	NR
HCMSQ-SoB Mean Change from Baseline (SD)		-2.8 (2.7)†	-0.9 (2.4)	NR

HCMSQ-SoB: Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath sub-score, KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score, KCCQ-OSS: Kansas City Cardiomyopathy Questionnaire Overall Summary Score, KCCQ-PLS: Kansas City Cardiomyopathy Questionnaire Physical Limitation Score, n: number, N: total number, NR: not reported, SD: standard deviation

*N=92 for all reported KCCQ outcomes unless otherwise stated, †N=85, ‡N=88 for all reported KCCQ outcomes unless otherwise stated, ¶N=86

Table D25. Patient-Reported Outcomes: Phase II Trials[51,59]

Trial		PIONEER-HCM				PIONEER-OLE		
Arms		Cohort A	Cohort B	Cohort A	Cohort B	Mavacamten (Overall)		
N		11	10	11	10	13		
Timepoint		12 Weeks		16 Weeks		24 Weeks	36 Weeks	48 Weeks
KCCQ-CSS Mean Change from Baseline (SD)		NR	NR	NR	NR	NR	NR	NR
KCCQ-OSS Mean Change from Baseline (SD)		14.4* (95% CI: 7.3 to 21.5)	16.0 (95% CI: 0.3 to 31.6)	-0.4* (95% CI: -1.0 to 0.2)	-0.4 (95% CI: -0.8 to -0.03)	15.3 (18.5)	NR	16.3 (24.2)
KCCQ-PLS Mean Change from Baseline (SD)		NR	NR	NR	NR	NR	NR	NR
Magnitude of Clinical Change in KCCS-CSS, n (%)	Clinically Worse	NR	NR	NR	NR	NR	NR	NR
	No Significant Change	NR	NR	NR	NR	NR	NR	NR
	Small but Clinically Important Improvement	NR	NR	NR	NR	NR	NR	NR
	Moderate to Large Clinical Improvement	NR	NR	NR	NR	NR	NR	NR
	Large to Very Large Improvement	NR	NR	NR	NR	NR	NR	NR
Magnitude of Clinical Change in KCCS-OSS, n (%)	Clinically Worse	NR	NR	NR	NR	NR	NR	NR
	No Significant Change	NR	NR	NR	NR	NR	NR	NR
	Small but Clinically Important Improvement	NR	NR	NR	NR	NR	NR	NR
	Moderate to Large Clinical Improvement	NR	NR	NR	NR	NR	NR	NR
	Large to Very Large Improvement	NR	NR	NR	NR	NR	NR	NR
HCMSQ-SoB Mean Change from Baseline (SD)		NR	NR	NR	NR	NR	NR	NR

CI: confidence interval, HCMSQ-SoB: Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath sub-score, KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score, KCCQ-OSS: Kansas City Cardiomyopathy Questionnaire Overall Summary Score, KCCQ-PLS: Kansas City Cardiomyopathy Questionnaire Physical Limitation Score, n: number, N: total number, NR: not reported, SD: standard deviation
*N=10.

Table D26. Patient-Reported Outcomes: MAVERICK-HCM[12]

Trial		MAVERICK-HCM			
Arms		Group 1 Mava (~200 ng/mL)	Group 2 Mava (~500 ng/mL)	Pooled Mavacamten	Placebo
N		19	21	40	19
Timepoint		16 weeks			
KCCQ-CSS Mean Change from Baseline (SD)		0.11 (7.67)	5.66 (10.01)	3.37 (9.41)	4.34 (16.05)
KCCQ-OSS Mean Change from Baseline (SD)		0.35 (8.71)	6.24 (10.73)	3.82 (10.24)	6.02 (17.63)
KCCQ-PLS Mean Change from Baseline (SD)		NR	NR	NR	NR
Magnitude of Clinical Change in KCCS-CSS, n (%)	Clinically Worse	NR	NR	NR	NR
	No Significant Change	NR	NR	NR	NR
	Small but Clinically Important Improvement	NR	NR	NR	NR
	Moderate to Large Clinical Improvement	NR	NR	NR	NR
	Large to Very Large Improvement	NR	NR	NR	NR
Magnitude of Clinical Change in KCCS-OSS, n (%)	Clinically Worse	NR	NR	NR	NR
	No Significant Change	NR	NR	NR	NR
	Small but Clinically Important Improvement	NR	NR	NR	NR
	Moderate to Large Clinical Improvement	NR	NR	NR	NR
	Large to Very Large Improvement	NR	NR	NR	NR
HCMSQ-SoB Mean Change from Baseline (SD)		NR	NR	NR	NR

HCMSQ-SoB: Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath sub-score, KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score, KCCQ-OSS: Kansas City Cardiomyopathy Questionnaire Overall Summary Score, KCCQ-PLS: Kansas City Cardiomyopathy Questionnaire Physical Limitation Score, n: number, N: total number, NR: not reported, SD: standard deviation

Table D27. Adverse Events: Phase III Trials[24,27,34]

Trial		EXPLORER-HCM		MAVA-LTE (EXPLORER-HCM Cohort)
Arms		Mavacamten	Placebo	Mavacamten
N		123	128	224
Timepoint		30 weeks		60 weeks
≥ 1 AE, n (%)		NR	NR	NR
≥ 1 TEAE, n (%)		108 (88)	101 (79)	141 (62.9)
≥1 SAE, n (%)		10 (8)	11 (9)	19 (8.5)
AE Severity, n (%)	Mild	NR	NR	82 (36.6)¶
	Moderate	NR	NR	45 (20.1)¶
	Serious/Severe	NR	NR	13 (5.8)¶
Study Drug-Related AEs, n (%)		NR	NR	20 (8.9)¶
Discontinuation, n (%)		4 (3.3)	3 (2.3)	NR
AEs Leading to Treatment Discontinuation, n (%)		2 (1.6)	1 (0.8)	2 (0.9)
Mavacamten Dose Adjustment, n (%)	2.5 mg	NR	NR	NR
	5 mg	NR	NR	NR
	10 mg	NR	NR	NR
	15 mg	NR	NR	NR
Cardiac SAEs, n (%)		4 (3.3)	4 (3.1)	9 (4)#
Atrial Fibrillation, n (%)		8 (6.5)	9 (7)	11 (4.9)
Atrial Flutter, n (%)		NR	NR	NR
Heart Failure, n (%)		NR	NR	2 (0.9)
Systolic Dysfunction, n (%)		NR	NR	NR
Dyspnea, n (%)		NR	NR	10 (4.5)
Syncope, n (%)		2 (2)	1 (1)	NR
Stress Cardiomyopathy, n (%)		2 (2)	0	NR
Palpitations, n (%)		7 (5.7)	9 (7.0)	NR
Coronary Artery Disease, n (%)		NR	NR	NR
Cardiac Failure, n (%)		2 (1.6)	3 (2.3)	NR
Cardiac Failure Congestive, n (%)		0	1 (1)	NR
Ventricular Tachycardia, n (%)		36 (32)*†	38 (33)‡	NR
Angina Pectoris, n (%)		1 (0.8)	5 (3.9)	NR

AE: adverse event, mg: milligram, n: number, N: total number, NR: not reported, SAE: serious adverse event, TEAE: treatment-emergent adverse event

*Based on week 26 outcomes, †N=113, ‡N=117, ¶Based on teaes, #cardiovascular drug-related events

Table D28. Adverse Events: Phase II Trials[51,52,59]

Trial		PIONEER-HCM		PIONEER-OLE
Arms		Cohort A	Cohort B	Mavacamten (Overall)
N		11	10	13
Timepoint		16 weeks		55 weeks
≥ 1 AE, n (%)		NR	NR	11 (84.5)
≥ 1 TEAE, n (%)		NR	NR	NR
≥1 SAE, n (%)		1 (9)	NR	NR
AE Severity, (%)*	Mild	76%	85%	74.5%
	Moderate	23%	15%	14.9%
	Serious/Severe	2%	0%	6.4%
Study Drug-Related AEs, n (%)		21%		NR
Discontinuation, n (%)		2 (18)	0	NR
AEs Leading to Treatment Discontinuation, n (%)		2%	0%	NR
Mavacamten Dose Adjustment, n (%)	2.5 mg	NR	NR	NR
	5 mg	NR	NR	NR
	10 mg	NR	NR	NR
	15 mg	NR	NR	NR
Cardiac SAEs, n (%)		NR	NR	NR
Atrial Fibrillation, n (%)		3 (27)	1 (10)	NR
Atrial Flutter, n (%)		NR	NR	NR
Heart Failure, n (%)		NR	NR	NR
Systolic Dysfunction, n (%)		NR	NR	NR
Dyspnea, n (%)		2 (18)	0	NR
Syncope, n (%)		NR	NR	NR
Stress Cardiomyopathy, n (%)		NR	NR	NR
Palpitations, n (%)		1 (9.1)	0	NR
Coronary Artery Disease, n (%)		NR	NR	NR
Cardiac Failure, n (%)		1 (9.1)	0	NR
Cardiac Failure Congestive, n (%)		NR	NR	NR
Ventricular Tachycardia, n (%)		1 (9.1)	4 (40)	NR
Angina Pectoris, n (%)		0	2 (20)	NR

AE: adverse event, mg: milligram, n: number, N: total number, NR: not reported, SAE: serious adverse event, TEAE: treatment-emergent adverse event
*Percentages based on numerical instances of each severity of AEs and not number of patients who experienced them.

Table D29. Adverse Events: MAVERICK-HCM[12]

Trial		MAVERICK-HCM			
Arms		Group 1 Mava (~200 ng/mL)	Group 2 Mava (~500 ng/mL)	Pooled Mavacamten	Placebo
N		18	21	39	19
Timepoint		24 weeks			
≥1 AE, n (%)		NR	NR	NR	NR
≥1 TEAE, n (%)		16 (88.9)	19 (90.5)	35 (89.7)	13 (68.4)
≥1 SAE, n (%)		2 (11.1)	2 (9.5)	4 (10.3)	4 (21.1)
AE Severity, n (%)	Mild	76%			
	Moderate	21%			
	Serious/Severe	NR	NR	NR	NR
Study Drug-Related AEs, n (%)		NR	NR	NR	NR
Discontinuation, n (%)		3 (15.8)*	3 (14.3)	6 (15)¶	0
AEs Leading to Treatment Discontinuation, n (%)		NR	NR	NR	NR
Mavacamten Dose Adjustment, n (%)	2.5 mg	1 (5.6)	NA	NR	NA
	5 mg	15 (83.3)	4 (19.0)	NR	NA
	10 mg	2 (11.1)	9 (42.9)	NR	NA
	15 mg	NA	8 (38.0)	NR	NA
Cardiac SAEs, n (%)		NR	NR	NR	NR
Atrial Fibrillation, n (%)‡		0	3 (14.3)	3 (7.7)	1 (5.3)
Atrial Flutter, n (%)†		0	0	0	1 (5.3)
Heart Failure, n (%)		NR	NR	NR	NR
Systolic Dysfunction, n (%)†		0	1 (4.8)	1 (2.6)	0
Dyspnea, n (%)‡		1 (5.6)	3 (14.3)	4 (10.3)	3 (15.8)
Syncope, n (%)		NR	NR	NR	NR
Stress Cardiomyopathy, n (%)		NR	NR	NR	NR
Palpitations, n (%)‡		1 (5.6)	5 (23.8)	6 (15.4)	3 (15.8)
Coronary Artery Disease, n (%)†		0	0	0	1 (5.3)
Cardiac Failure, n (%)		NR	NR	NR	NR
Cardiac Failure Congestive, n (%)		NR	NR	NR	NR
Ventricular Tachycardia, n (%)		NR	NR	NR	NR
Angina Pectoris, n (%)†		0	0	0	1 (5.3)

AE: adverse event, mg: milligram, n: number, N: total number, NR: not reported, SAE: serious adverse event, TEAE: treatment-emergent adverse event
*N=19, †Based on SAEs, ‡Based on TEAEs, ¶N=40

Table D30. Adverse Events: Disopyramide[26]

Trial		Sherrid et al. 2005	
Arms		**Disopyramide**	**Non-Disopyramide**
N		**118**	**373**
Timepoint		**3.1 ± 2.6 years**	**NR**
Discontinuation, n (%)		8 (7)	NR
Pacemaker Implantation, % (95% CI)		NR	NR
Tamponade, % (95% CI)		NR	NR
Sustained Ventricular Tachycardia, % (95% CI)		NR	NR
Ventricular Fibrillation, % (95% CI)		NR	NR
Total Adverse Arrhythmic Events, % (95% CI)		NR	NR
Periprocedural Death, n (%)		NR	NR
Sudden Cardiac Death, n (%)		4 (3.4)	NR
Aborted Sudden Cardiac Death, n (%)		NR	NR
Surgery-Related Death, n (%)		NR	2 (0.5)
Cardiac Mortality, % (95% CI)		NR	NR
Non-Cardiac Mortality, n (%)		NR	NR
All-Cause Mortality, % (95% CI)		NR	NR
Annualized Death Rate, %	**Non-Cardiac**	1.4	1.2
	Non-Sudden Cardiac	0.4	0.9
	Sudden Cardiac	1	1.8
	All-Cause Cardiac	1.4	2.6
	All Deaths	2.8	3.8
Atrial Fibrillation, n (%)		17 (14)	63 (17)
Stroke, n (%)		4 (3)	7 (2)
ICD Shock, n (%)		NR	NR

CI: confidence interval, ICD: implantable cardioverter-defibrillator, n: number, N: total number, NR: not reported

Table D31. Adverse Events: Septal Reduction Therapy[27]

Trial		Liebregts et al. 2015*			
Arms		Septal Ablation	Surgical Myectomy	Septal Ablation	Surgical Myectomy
N		2,013	2,791	2,013	2,791
Timepoint		Short-term (<30 days)*		Long-term (after 30 days)	
Discontinuation, n (%)		NR	NR	NR	NR
Pacemaker Implantation, % (95% CI)		10 (7.8 to 12.1)	4.4 (2.6 to 6.2)	NR	NR
Tamponade, % (95% CI)		0.6 (0.1 to 1.1)	1.0 (0 to 2.0)	NR	NR
Sustained Ventricular Tachycardia, % (95% CI)		0.8 (0.2 to 1.4)	0.4 (0.0 to 1.4)	NR	NR
Ventricular Fibrillation, % (95% CI)		0.8 (0.2 to 1.4)	0.3 (0 to 0.8)	NR	NR
Total Adverse Arrhythmic Events, % (95% CI)		2.2 (1.1 to 3.3)	1.0 (0.1 to 1.8)	NR	NR
Periprocedural Death, n (%)		20 (1)	61 (2.2)	NR	NR
Sudden Cardiac Death, n (%)		NR	NR	36 (1.8)	78 (2.8)
Aborted Sudden Cardiac Death, n (%)		NR	NR	4 (0.2)	15 (0.5)
Surgery-Related Death, n (%)		NR	NR	NR	NR
Cardiac Mortality, n (%)		1.1% (95% CI: 0.6 to 1.6)	2.5% (95% CI: 1.3 to 3.6)	76 (3.8)	175 (6.3)
Non-Cardiac Mortality, n (%)		NR	NR	65 (3.2)	85 (3)
All-Cause Mortality, n (%)		1.3% (95% CI: 0.7 to 1.8)	2.5% (95% CI: 1.4 to 3.6)	191 (9.5)	302 (10.8)
Annualized Death Rate, %	Non-Cardiac	NR	NR	NR	NR
	Non-Sudden Cardiac	NR	NR	NR	NR
	Sudden Cardiac	NR	NR	0.41†	0.49†
	All-Cause Cardiac	NR	NR	0.5	0.74
	All Deaths	NR	NR	1.52 (95% CI: 1.12 to 1.91)	1.44 (95% CI: 1.13 to 1.76)
Atrial Fibrillation, n (%)		NR	NR	NR	NR
Stroke, % (95% CI)		0.3 (0 to 0.8)	0.9 (0.3 to 1.6)	NR	NR
ICD Shock, n (%)		NR	NR	14 (0.7)	11 (0.4)

CI: confidence interval, ICD: implantable cardioverter-defibrillator, n: number, N: total number, NR: not reported
*All short-term timepoint data (with exception to periprocedural death) presented as % (CI).
†Aborted sudden cardiac death rate.

D4. Ongoing Studies

Table D32. Ongoing Studies

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy (VALOR-HCM) MyoKardia, Inc. NCT04349072	Phase III, double-blind, multicenter, placebo-controlled, RCT Estimated enrollment: 100	Arm 1 Mavacamten Arm 2 Placebo	Inclusion Criteria • 18 years old and older and body weight >45 kg • Diagnosed with HOCM • Referred or under active consideration for and willing to have SRT procedure • Has documented LVEF ≥60% and oxygen saturation at rest ≥90% Key Exclusion Criteria • Persistent or permanent atrial fibrillation and subject not on anticoagulation for ≥4 weeks prior to screening and/or not adequately rate controlled ≤6 months prior to screening • Previously treated with invasive septal reduction (surgical myectomy or septal ablation) • For individuals on beta blockers, calcium channel blockers, or disopyramide, any dose adjustment of these medications <14 days prior to screening or an anticipated change in regimen during the first 16 weeks of the study	Primary Outcome • Number of subjects who decide to proceed with SRT and number of subjects who remain eligible for SRT at week 16 Secondary Outcomes • Number of subjects who decide to proceed with SRT and number of subjects who remain eligible for SRT at week 32 • Change from baseline to week 16 in the mavacamten group vs. placebo group in NYHA class • Change from baseline to week 16 in the mavacamten group vs. placebo group in KCCQ-23 • Change from baseline to week 16 in the mavacamten group compared with the placebo group in NT-	December 2024

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
			• Any medical condition that precludes upright exercise stress testing • Paroxysmal, intermittent atrial fibrillation with atrial fibrillation present at screening • Prior treatment with cardiotoxic agents, such as doxorubicin or similar	proBNP and cardiac troponin • Change from baseline to week 16 in the mavacamten group vs. placebo group in LVOT gradient	
A Long-Term Safety Extension Study of Mavacamten in Adults Who Have Completed MAVERICK-HCM or EXPLORER-HCM MyoKardia, Inc. NCT03723655	Phase II/III, long-term safety extension study	Mavacamten 5 mg/day, with dose adjustments at weeks 4, 8, and 12 if needed	Key Inclusion Criteria • Has completed MAVERICK-HCM or EXPLORER-HCM • Has a body weight >45 kg • Has adequate acoustic windows to enable accurate TTEs • Has documented LVEF ≥50% Key Exclusion Criteria • Has any ECG abnormality that could pose a risk to participant safety • Has a history of syncope or a history of sustained ventricular tachyarrhythmia with exercise, resuscitated sudden cardiac arrest or known history of appropriate ICD discharge for life-threatening ventricular arrhythmia • Currently treated with disopyramide or ranolazine or treatment with disopyramide or ranolazine is planned during the study	• Frequency and severity of TEAEs and SAEs [Timeframe: 252 weeks]	

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion Date
			• Has any acute or serious comorbid condition (e.g., major infection or hematologic, renal, metabolic, gastrointestinal, or endocrine dysfunction) that could interfere with the study		
Extension Study of Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy Previously Enrolled in PIONEER (PIONEER-OLE) MyoKardia, Inc. NCT03496168	Phase II, multicenter, open-label extension study	Mavacamten 5 mg/day, with individualized dose adjustments (5, 10, or 15 mg) at week 6 if needed	Key Inclusion Criteria • Completed Study MYK-461-004. Prior participation in a non-interventional observational study is allowed • Body weight >45 kg at screening Key Exclusion Criteria • Has QTcF >500 ms or any other ECG abnormality that could pose a risk to subject safety • Has developed obstructive coronary artery disease (>70% stenosis in one or more arteries), known moderate or severe aortic valve stenosis, any acute or serious comorbid condition (e.g., major infection or hematologic, renal, metabolic, gastrointestinal, or endocrine dysfunction) that interfere with the study	• Frequency and severity of AEs and SAEs [Timeframe: up to 260 weeks]	November 9, 2023

AE: adverse event, ECG: electrocardiogram, HCM: hypertrophic cardiomyopathy, HOCM: hypertrophic obstructive cardiomyopathy, ICD: implantable cardioverter-defibrillator, KCCQ: Kansas City Cardiomyopathy Questionnaire, kg: kilogram, LVEF: left ventricular ejection fraction, mg: milligram, ms: millisecond, NT-proBNP: N-terminal pro B-type natriuretic peptide, RCT: randomized controlled trial, SAE: serious adverse event, SRT: septal reduction therapy, TEAE: treatment-emergent adverse event, TTE: transthoracic echocardiogram
Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies).

D5. Previous Systematic Reviews and Technology Assessments

We did not identify any previous systematic literature reviews on mavacamten in HOCM.

E. Long-Term Cost Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1. Impact Inventory

Sector	Type of Impact (Add Additional Domains, As Relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if Quantified), Likely Magnitude & Impact (if Not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X		
	Health-related quality of life effects	X		
	Adverse events	X		
Medical Costs	Paid by third-party payers	X		
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	☐	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	N/A	☐	
	Unpaid caregiver-time costs	N/A	☐	
	Transportation costs	N/A	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	N/A	X	
	Cost of unpaid lost productivity due to illness	N/A	X	
	Cost of uncompensated household production	N/A	☐	
Consumption	Future consumption unrelated to health	N/A	☐	
Social services	Cost of social services as part of intervention	N/A	☐	
Legal/Criminal Justice	Number of crimes related to intervention	N/A	☐	
	Cost of crimes related to intervention	N/A	☐	
Education	Impact of intervention on educational achievement of population	N/A	☐	
Housing	Cost of home improvements, remediation	N/A	☐	
Environment	Production of toxic waste pollution by intervention	N/A	☐	
Other	Other impacts (if relevant)	N/A	☐	

N/A: not applicable
Adapted from Sanders et al.[62]

Target Population

The population of focus for the economic evaluation included symptomatic HOCM patients in the US, incorporating demographics at onset of treatment similar to those seen in the EXPLORER trial. The mean age and percent female shown below were used to calculate per cycle mortality rates based on CDC statistics for the US.

Table E2. Baseline Population Characteristics

	Mavacamten and Comparators
Mean Age	58
% Female	41%
Source	EXPLORER

Treatment Strategies

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows:

- Mavacamten used along with standard first-line treatment.

The comparator(s) for mavacamten along with first-line therapy will be:

- Standard first-line treatment of HOCM (beta blockers and calcium channel blockers)
- Disopyramide used along with standard first-line treatment
- Myectomy used along with standard first-line treatment
- Septal ablation used along with standard first-line treatment.

Table E3. Treatment Regimen Recommended Dosage

Generic Name	Mavacamten	Disopyramide	Metoprolol	Verapamil
Brand Name	--	Generic	Generic	Generic
Manufacturer	Bristol Myers Squibb	--	--	--
Route of Administration	Oral	Oral	Oral	Oral
Dosing (Initial and Final Average)	*5-[redacted] mg per day	400-800 mg per day	50-250 mg per day	180-240 mg per day

mg: milligram

*The dose does not impact costs in the mavacamten arm as a per-year placeholder price is used.

Table E4. First-Line Drug Use by Arm

Intervention	Mavacamten	First Line	Disopyramide	Myectomy	Septal Ablation
Metoprolol	76%	74%	98%	75%	75%
Verapamil	20%	13%	32%	8.25%*	8.25%*
Source	EXPLORER	EXPLORER	Sherrid et al.	EXPLORER, literature, and assumption	EXPLORER and assumption

*16.5% in the initial cycle only, then 8.25% beyond where the 50% reduction after treatment is an assumption consistent with evidence in available small studies on myectomy and assumed to be the same for septal ablation.[9,10]

Model Inputs

Clinical Inputs

Key clinical inputs included transitions between NYHA class and mortality. The best-available evidence was reviewed for inclusion in the model. The base-case treatment effects influenced NYHA class transitions and, for mavacamten and standard first-line care and standard first-line care alone, came from a Phase III clinical trial of mavacamten. Treatment effects of disopyramide along with first-line treatment, myectomy with first-line treatment and septal ablation with standard first line treatment, came from key literature sources.[1,2]

Transition Probabilities and Treatment Effects

Transitions between NYHA class for mavacamten with first-line therapy and for first-line therapy alone were derived from those seen in EXPLORER clinical trial data up to Cycle 8. For mavacamten and standard first-line therapy and first-line therapy alone, clinical trial data were used directly in Cycles 0 and 1 (weeks 0 and four). For weeks four through 12 in the model, the transition rates were fitted cycle by cycle to match clinical trial data available at week 14 using an assumption of a constant weekly exponential rate. For weeks 12 through 24 in the model, the transitions were based on information available from weeks 14 through 26 in the clinical trial data. For weeks 28 and 32, the transition rates were based on transitions observed between weeks 26 and 30 in EXPLORER trial data. Following Cycle 8, the proportions of live patients across NYHA class were held constant.

For disopyramide along with standard first-line therapy, baseline, and week four distributions across NYHA class were based on data in Sherrid et al. where the distribution across NYHA class in week four in the model is as seen in disopyramide patients who remained on treatment for several years in 66% of the patients and assumed to be 0 in 34% of the patients as 34% of the patients in the Sherrid study had eventually opted for surgical options. Following Cycle 1 (week four) in the disopyramide along with standard first-line therapy arm, we held the proportions of alive patients across NYHA classes constant. The disopyramide and standard first-line therapy patients also had

their mortality modeled based on US CDC mortality rates corresponding to the average age and percent female characteristics seen in the EXPLORER trial patients.

Myectomy patients and septal ablation were modeled having the same baseline distribution of NYHA class as the mavacamten patients in EXPLORER. For the treatment effect of myectomy along with first-line therapy and septal ablation with standard first-line therapy in the model, the percent of patients in week four in NYHA class I is such that it makes the percent reduction in the average NYHA class between Cycles 0 and 1 (weeks 0 and four) equal to the percent reduction seen in the Liebregts meta-analysis (55% reduction), keeping the relative percent of those remaining in NYHA class II and NYHA class III/IV in the same proportion as that seen in the mavacamten population in week four. Simultaneously, between weeks 0 and four, 1.3% of the myectomy patients and 1.1% of the septal ablation patients were be modeled as dying from the procedure based on rates from studies in years later than 2000 as shown in Liebregts. Following week four, the relative portion of alive patients across NYHA class was held constant, and mortality is based on average demographic characteristics seen in EXPLORER.

Specific treatment effects are shown via NYHA class below in Table E6 for disopyramide and standard first-line therapy and myectomy and standard first-line therapy. Septal ablation and standard first-line therapy had the same treatment effect in Cycle 1 consistent with results in Liebregts.

Table E5. Specific Treatment Effects

Clinical Inputs			
Input Name	**Base Case (Percent in NYHA I in Cycle 1)**	**Lower Value**	**Upper Value**
Mavacamten Treatment Effect*	0.24	0.18	0.31
Standard First-Line Therapy Treatment Effect	0.08	0.06	0.10
Myectomy Treatment Effect*	0.77	0.58	0.96
Disopyramide Treatment Effect*	0.28	0.21	0.36
Septal Ablation Treatment Effect*	0.77	0.58	0.96

NYHA: New York Heart Association
*With standard first-line therapy.

Discontinuation

Discontinuation was not included in the model as there was no long-term evidence suggesting an appropriate estimate for mavacamten, and as first-line therapy tends to be used for life in this patient population. We did make an adjustment in the treatment effect for disopyramide described above that is related to discontinuation in those patients, however, in the model, technically, no one discontinues.

Mortality

Mortality estimates were sourced from the CDC and reflected US average mortality rates adjusted for age and gender as reflected by the overall averages of baseline characteristics of patients seen in the clinical trial. Based on conversations with clinical experts and available evidence, mortality was assumed to be constant across NYHA class as there is not enough evidence from the trial to warrant projecting mortality effects for mavacamten along with first-line therapy relative to other treatments, although this assumption was tested in a scenario analysis. Note that for myectomy and septal ablation, as stated above, there is an initial increase in mortality based on mortality rates associated with the procedure.[2]

Adverse Events

In EXPLORER, 8% of patients experienced a serious adverse event in the mavacamten arm and 9% in the standard-of-care/placebo arm.[3] As the rate of serious adverse events across the arms was very similar and because we have limited data to compare serious adverse events with the other comparators, we did not include additional costs or disutilities of serious adverse events in the model. However, utility impacts of the serious adverse events would have been captured in the utility scores used across NYHA class for mavacamten and standard of care (see Health State Utilities section below). For the disopyramide, myectomy, and septal ablation arms, we do not include impacts of adverse events in the model (although there is a surgical disutility for myectomy and septal ablation and there are total cost estimates used from the literature that would include costs of adverse events for those procedures) and we use an average of the utility scores for each NYHA class seen in EXPLORER to project the treatment effect of changes in NYHA class to changes in QALYs.

Heterogeneity and Subgroups

There is insufficient evidence to warrant or allow modeling of subgroups within the treatments or comparators.

Health State Utilities

Health state utilities were based on manufacturer-submitted data for NYHA class I, II, and III/IV. We used consistent health state utility values across treatments evaluated in the model. The utilities were taken directly from the patients in the trial and, as such, they include disutilities from the small difference in adverse events seen in the trial. Consequently, we did not add additional disutilities for serious adverse events in the model. No head-to-head data are available to compare adverse event rates in mavacamten and first-line therapy versus disopyramide and first-line therapy and/or myectomy or septal ablation with first-line therapy. It was reported that 7% of patients on disopyramide experienced adverse side effects leading to discontinuation, which is similar to the

adverse event rates of 8% and 9% seen in EXPLORER. Given available data, we elected to use an average of the utilities for placebo and mavacamten for the utilities by NYHA class for the other comparators. The utility scores are based on the EQ-5D administered to the patients in EXPLORER.[4] In addition, we applied an average disutility by age of 0.0007 per year, which reflects average age decrements seen in the EQ-5D in the US.[5] For myectomy, a disutility of 0.086 is applied for the first six cycles matching available numbers for coronary artery bypass surgery patients versus US average utilities for similarly aged patients using the EQ-5D.[6] For septal ablation, a one cycle disutility of 0.04 is applied.[63] Further, for myectomy and septal ablation there is a 0.05 lifetime disutility applied to 4% and 10% of patients respectively reflecting different rates of pacemaker placement related to those procedures as seen in the literature.[27]

Table E6. Health State Utilities

Input Came	Treatment	Base Case	Lower Value	Upper Value
Utility of NYHA Class I for Mavacamten	Mavacamten	0.95	0.65	1.00
Utility of NYHA Class II for Mavacamten	Mavacamten	0.87	0.66	0.98
Utility of NYHA Class III and IV for Mavacamten	Mavacamten	0.71	0.56	0.84
Utility of NYHA Class I for SoC	Standard	0.95	0.65	1.00
Utility of NYHA Class II for SoC	Standard	0.85	0.65	0.97
Utility of NYHA Class III and IV for SoC	Standard	0.70	0.56	0.83
Utility of NYHA Class I for Comparators	Myectomy, septal ablation, disopyramide	0.95	0.65	1.00
Utility of NYHA Class II for Comparators	Myectomy, septal ablation, disopyramide	0.86	0.65	0.98
Utility of NYHA Class III and IV for Comparators	Myectomy, septal ablation, disopyramide	0.71	0.56	0.83
Disutility of Pacemaker	Myectomy and septal ablation	0.05	0.04	0.05
Disutility of Septal Ablation Procedure	Septal ablation (1 cycle)	0.04	0.03	0.05
Disutility of Myectomy Procedure	Myectomy (6 cycles)	0.09	0.07	0.10

NYHA: New York Heart Association, SoC: standard of care

Drug Utilization

Patients in all the arms were modeled as using beta blockers represented by metoprolol and calcium channel blockers represented by verapamil according to usual doses for extended-release versions of those drugs associated with adult hypertension.[7,8] For myectomy and septal ablation patients, post-myectomy use of verapamil will be reduced by 50% based on available pre-post studies of myectomy.[9,10] See Table E7 for the doses used and Table E8 for the proportions using first-line treatment in the model.

The following inputs were used to model drug utilization and associated costs:

- Duration of treatment
- Schedule of doses for each drug in each regimen
- Protocol/label dosage for the indication.

Cost Inputs

Drug Costs

For mavacamten, we used a placeholder price based on market analyst estimates.[11] For disopyramide, metoprolol, and verapamil, we calculated the average wholesale acquisition cost (WAC) based on generic formulations in Red Book (see Table E9). Other than an initial hospitalization associated with disopyramide (see Table E10), no administration costs were included because all drugs included in the model are orally administered.

Table E7. Drug Costs

Input Name	Treatment	Base Case	Lower Value	Upper Value
Per Cycle Cost of Mavacamten	Mavacamten	$5,769	$4,694	$6,954
First Cycle Cost of Metoprolol	Metoprolol cycle 1	$38	$31	$46
Per Cycle Cost of Metoprolol	Metoprolol	$64	$52	$77
First Cycle Cost of Verapamil	Verapamil cycle 1	$49	$40	$59
Per Cycle Cost of Verapamil	Verapamil	$56	$46	$67
First Cycle Cost of Disopyramide	Disopyramide cycle 1	$309	$252	$373
Per Cycle Cost of Disopyramide	Disopyramide	$413	$336	$497

*All costs used in the model were updated to 2021 dollars based on the methods outlined in the ICER Reference Case.

Non-Drug Costs

Non-drug costs were modeled based on NYHA class derived from data provided by Bristol Myers Squibb for NYHA class I and II, which reflect non-symptomatic HOCM and symptomatic HOCM patients, respectively, and were projected from the NYHA class II to NYHA class III proportionally based on proportional differences across those classes seen in general heart failure patients in a recent model.[12]

In addition, there were echocardiograph costs at week 0, week eight, and week 16 applied to the mavacamten and first-line treatment arm, in addition to having those done initially and every two years for all of the comparators (see Table E10). There are also two days of hospital costs applied to disopyramide upon treatment initiation, and the cost used for myectomy and septal ablation reflects total costs associated inclusive of the surgery costs as well as inpatient, surgical, outpatient and emergency room use in six months following those surgeries in a recent claims data analysis.[64]

Table E8. Non-Drug Costs

Cost Inputs*				
Input Name	**Treatment**	**Base Case**	**Lower Value**	**Upper Value**
Disopyramide Hospitalization	Disopyramide hospitalization	$8,559	$6,964	$10,316
Myectomy Procedure Cost	Myectomy	$122,759	$99,881	$147,960
Septal Ablation Procedure Cost	Septal ablation	$55,706	$45,325	$67,142
Echocardiogram Cost	Transthoracic TTE (93308)	$101	$82	$121
NYHA I Heath State Cost	NYHA I heath state cost			
NYHA II Heath State Cost	NYHA II heath state cost			
NYHA III Heath State Cost	NYHA III heath state cost	$2,826	$2,299	$3,406

NYHA: New York Heart Association, TTE: transthoracic echocardiogram
*All costs used in the model were updated to 2021 dollars based on the methods outlined in the ICER Reference Case.

E2. Results

Description evLY Gained Calculations

The cost per evLY gained considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLY gained in cases where the life expectancy was different across treatment arms.

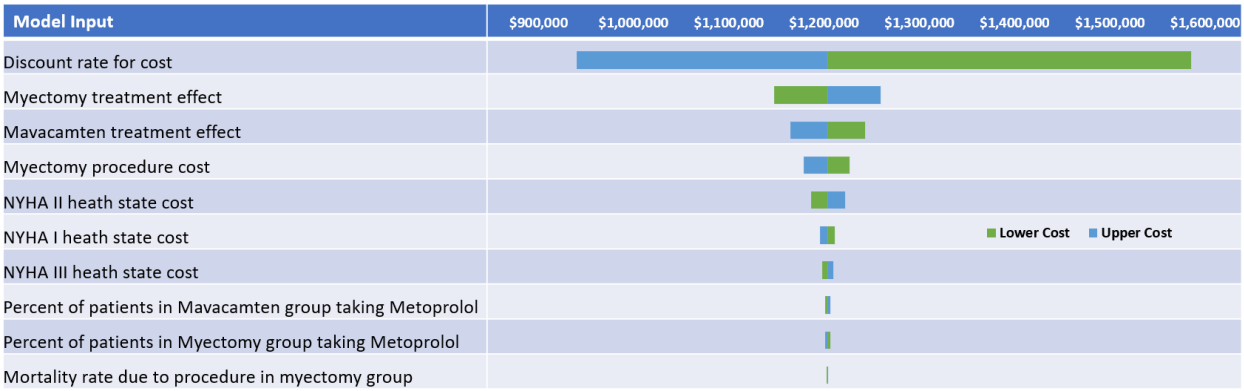
1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy. [65]
2. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLYG).
3. We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the equal value of life years (evLY) for that cycle.
4. If no life years were gained using the intervention versus the comparator, evLYs are equivalent to QALYs
5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.
6. We use the same calculations in the comparator arm to derive its evLY.

Finally, the evLY gained is the incremental difference in evLY between the intervention and the comparator arms.

E3. Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per addition QALY. Figures E1A and E1B and Tables 9A and 9B show the tornado diagrams for mavacamten versus myectomy in terms of costs and then in terms of QALYs. As this is a lifetime model, the incremental costs are sensitive to the discount rate. Varying the treatment effects (increasing the proportion in NYHA I) also has a moderate impact. The treatment effects and NYHA utility scores have a relatively large effect on projected incremental QALYs. Overall, however, the sensitivity analyses demonstrated robust findings that at a price of $75,000 per year, the incremental ratios would be above standard thresholds. These analyses were repeated for the other comparators with similar findings displayed below.

Figure E1A. Tornado Diagram of Incremental Cost for Mavacamten versus Myectomy



NYHA: New York Heart Association

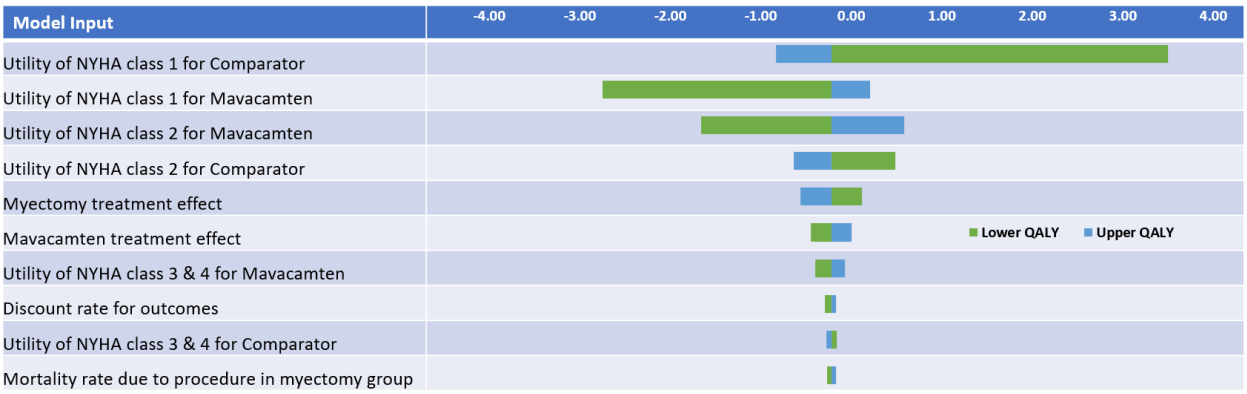
Table E9A. Inputs and Results for Mavacamten versus Myectomy Incremental Cost Tornado Diagram

Input	Lower Cost	Upper Cost	Low Input Value	High Input Value
Discount Rate for Cost	$1,584,965	$940,538	0.01	0.05
Myectomy Treatment Effect	$1,147,719	$1,259,440	0.58	0.96
Mavacamten Treatment Effect	$1,242,588	$1,164,572	0.18	0.31
Myectomy Procedure Cost	$1,226,457	$1,178,379	$99,881.32	$147,959.69
NYHA II Heath State Cost	$1,186,641	$1,222,239	$1,663.84	$2,464.74
NYHA I Heath State Cost	$1,210,829	$1,195,594	$611.31	$905.57
NYHA III Heath State Cost	$1,198,253	$1,209,448	$2,299.24	$3,405.99
Percent of Patients in Mavacamten Group Taking Metoprolol	$1,200,969	$1,206,190	0.57	0.95
Percent of Patients in Myectomy Group Taking Metoprolol	$1,206,122	$1,201,037	0.56	0.94
Mortality Rate Due to Procedure in Myectomy Group	$1,202,793	$1,204,366	0.01	0.02

NYHA: New York Heart Association, SoC: standard of Care

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Figure E1B. Tornado Diagram of Incremental QALY for Mavacamten versus Myectomy



NYHA: New York Heart Association

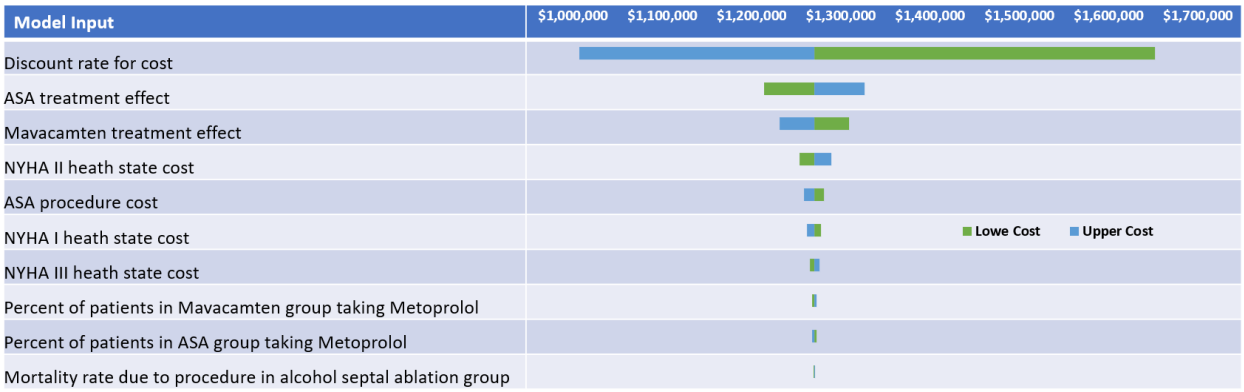
Table E9B. Inputs and Results for Mavacamten versus Myectomy Incremental QALY Tornado Diagram

Input	Lower QALY	Upper QALY	Low Input Value	High Input Value
Utility of NYHA Class I for Comparator	3.50	-0.83	0.65	1.00
Utility of NYHA Class I for Mavacamten	-2.75	0.20	0.65	1.00
Utility of NYHA Class II for Mavacamten	-1.66	0.58	0.66	0.98
Utility of NYHA Class II for Comparator	0.48	-0.63	0.65	0.98
Myectomy Treatment Effect	0.12	-0.56	0.58	0.96
Mavacamten Treatment Effect	-0.45	0.01	0.18	0.31
Utility of NYHA Class III and IV for Mavacamten	-0.40	-0.07	0.56	0.84
Discount Rate for Outcomes	-0.29	-0.17	0.01	0.05
Utility of NYHA Class III and IV for Comparator	-0.16	-0.27	0.56	0.83
Mortality Rate Due to Procedure in Myectomy Group	-0.27	-0.17	0.01	0.02

NYHA: New York Heart Association, QALY: quality-adjusted life year

Figure E2 shows the tornado diagram for mavacamten versus septal ablation. Similar findings as described above.

Figure E2A. Tornado Diagram of Incremental Cost for Mavacamten versus Septal Ablation



ASA: alcohol septal ablation, NYHA: New York Heart Association

Table E10A. Inputs and Results for Mavacamten versus Septal Ablation Incremental Cost Tornado Diagram

Input	Lowe Cost	Upper Cost	Low Input Value	High Input Value
Discount Rate for Cost	$1,651,393	$1,007,202	0.01	0.05
ASA Treatment Effect	$1,214,174	$1,326,121	0.58	0.96
Mavacamten Treatment Effect	$1,309,156	$1,231,140	0.18	0.31
NYHA II Heath State Cost	$1,253,243	$1,288,770	$1,663.84	$2,464.74
ASA Procedure Cost	$1,280,529	$1,258,712	$45,324.87	$67,142.21
NYHA I Heath State Cost	$1,277,443	$1,262,112	$611.31	$905.57
NYHA III Heath State Cost	$1,264,826	$1,276,010	$2,299.24	$3,405.99
Percent of Patients in Mavacamten Group Taking Metoprolol	$1,267,538	$1,272,758	0.57	0.95
Percent of Patients in ASA Group Taking Metoprolol	$1,272,696	$1,267,600	0.56	0.94
Mortality Rate Due to Procedure in ASA Group	$1,269,482	$1,270,814	0.01	0.01

ASA: alcohol septal ablation, NYHA: New York Heart Association, SoC: standard of Care

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Figure E2B. Tornado Diagram of Incremental QALY for Mavacamten versus Septal Ablation

ASA: alcohol septal ablation, NYHA: New York Heart Association

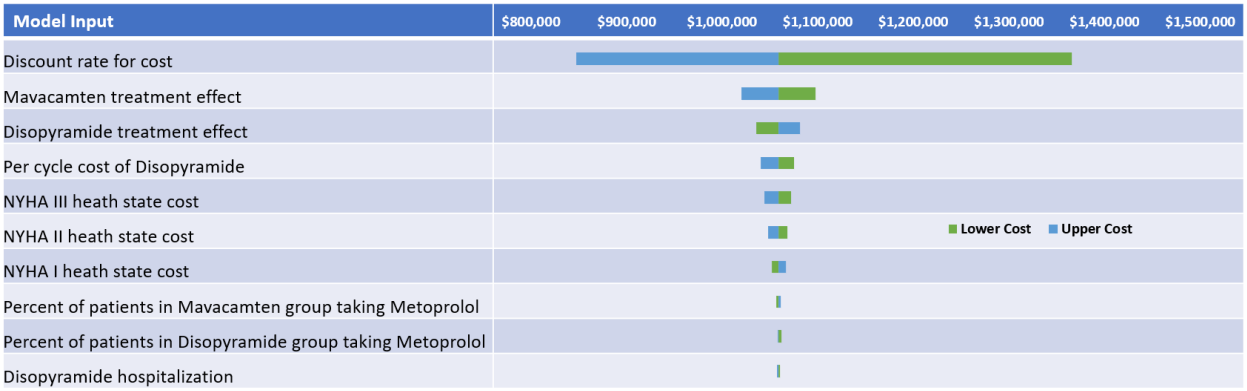
Table E10B. Inputs and Results for Mavacamten versus Septal Ablation Incremental QALY Tornado Diagram

Input	Lowe QALY	Upper QALY	Low Input Value	High Input Value
Utility of NYHA Class I for Comparator	3.50	-0.83	0.65	1.00
Utility of NYHA Class I for Mavacamten	-2.75	0.21	0.65	1.00
Utility of NYHA Class II for Mavacamten	-1.66	0.59	0.66	0.98
Utility of NYHA Class II for Comparator	0.49	-0.63	0.65	0.98
ASA Treatment Effect	0.12	-0.56	0.58	0.96
Mavacamten Treatment Effect	-0.45	0.01	0.18	0.31
Utility of NYHA class III and IV for Mavacamten	-0.39	-0.06	0.56	0.84
Utility of NYHA class III and IV for Comparator	-0.16	-0.27	0.56	0.83
Discount Rate for Outcomes	-0.28	-0.17	0.01	0.05
Mortality Rate Due to Procedure in ASA Group	-0.26	-0.18	0.01	0.01

ASA: alcohol septal ablation, NYHA: New York Heart Association, SoC: standard of Care
*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Figures E3A and E3B and Table E11 describe the one-way sensitivity analyses for mavacamten versus disopyramide.

Figure E3A. Tornado Diagram of Incremental Cost for Mavacamten versus Disopyramide



NYHA: New York Heart Association

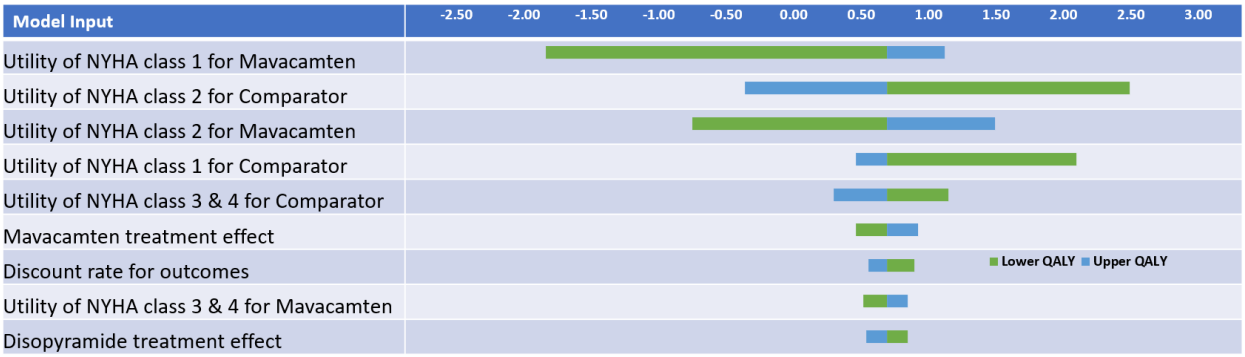
Table E11A. Inputs and Results for Mavacamten versus Disopyramide Incremental Cost Tornado Diagram

Input	Lower Cost	Upper Cost	Low Input Value	High Input Value
Discount Rate for Cost	$1,365,337	$847,335	0.01	0.05
Mavacamten Treatment Effect	$1,097,781	$1,019,765	0.18	0.31
Disopyramide Treatment Effect	$1,035,926	$1,081,621	0.21	0.36
Per Cycle Cost of Disopyramide	$1,075,272	$1,040,599	$335.65	$497.22
NYHA III Heath State Cost	$1,071,779	$1,044,447	$2,299.24	$3,405.99
NYHA II Heath State Cost	$1,068,255	$1,048,329	$1,663.84	$2,464.74
NYHA I Heath State Cost	$1,051,832	$1,066,420	$611.31	$905.57
Percent of Patients in Mavacamten Group Taking Metoprolol	$1,056,163	$1,061,384	0.57	0.95
Percent of Patients in Disopyramide Group Taking Metoprolol	$1,062,139	$1,058,499	0.74	1.00
Disopyramide Hospitalization	$1,060,368	$1,057,016	$6,963.60	$10,315.56

NYHA: New York Heart Association, SoC: standard of care

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Figure E3A. Tornado Diagram of Incremental QALY for Mavacamten versus Disopyramide



NYHA: New York Heart Association

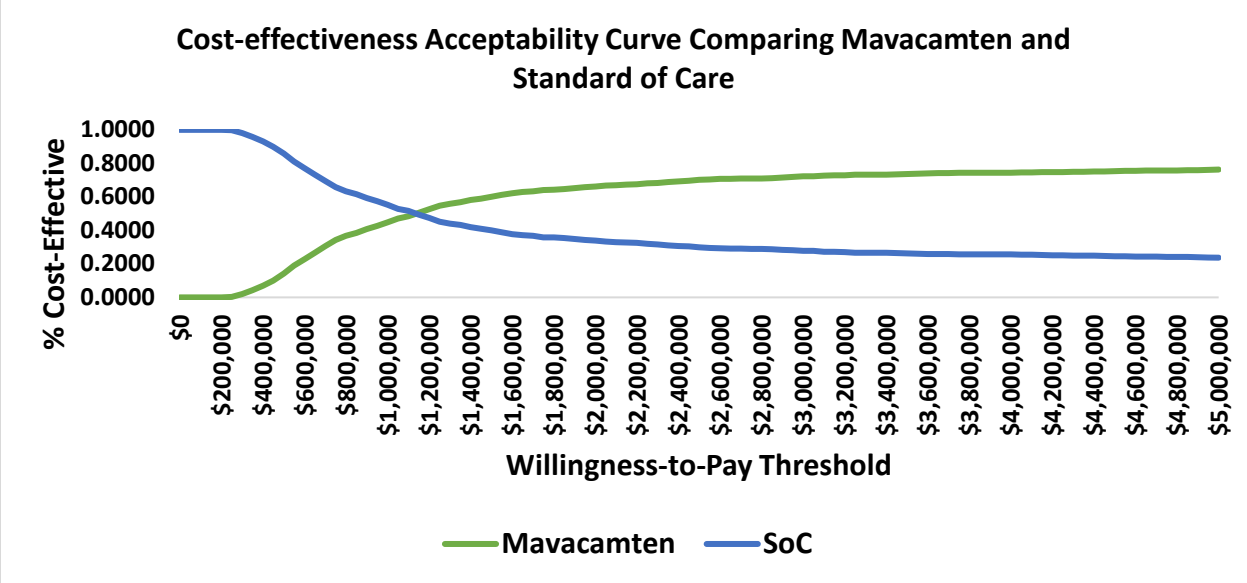
Table E11B. Inputs and Results for Mavacamten versus Disopyramide Incremental QALY Tornado Diagram

Input	Lower QALY	Upper QALY	Low Input Value	High Input Value
Utility of NYHA Class I for Mavacamten	-1.84	1.12	0.65	1.00
Utility of NYHA Class II for Comparator	2.49	-0.36	0.65	0.98
Utility of NYHA Class II for Mavacamten	-0.75	1.50	0.66	0.98
Utility of NYHA Class I for Comparator	2.10	0.46	0.65	1.00
Utility of NYHA Class III and IV for Comparator	1.15	0.30	0.56	0.83
Mavacamten Treatment Effect	0.46	0.92	0.18	0.31
Discount Rate for Outcomes	0.89	0.55	0.01	0.05
Utility of NYHA Class III and IV for Mavacamten	0.52	0.84	0.56	0.84
Disopyramide Treatment Effect	0.85	0.54	0.21	0.36

NYHA: New York Heart Association, QALY: quality-adjusted life year

Figures E4-E7 show results of the probabilistic sensitivity analyses for mavacamten plus standard first-line therapy versus all the comparators. At willingness-to-pay threshold levels under $200,000 per QALY essentially none of the simulations project mavacamten to be cost effective. Even at extremely high willingness-to-pay thresholds the proportion of simulations was not much above half for mavacamten plus first-line therapy being cost effective. All of these incorporated the placeholder price of mavacamten as its average cost.

Figure E4. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Acceptability Curves for Mavacamten and Standard of Care



SoC: standard of care

Figure E5. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Acceptability Curves for Mavacamten and Disopyramide

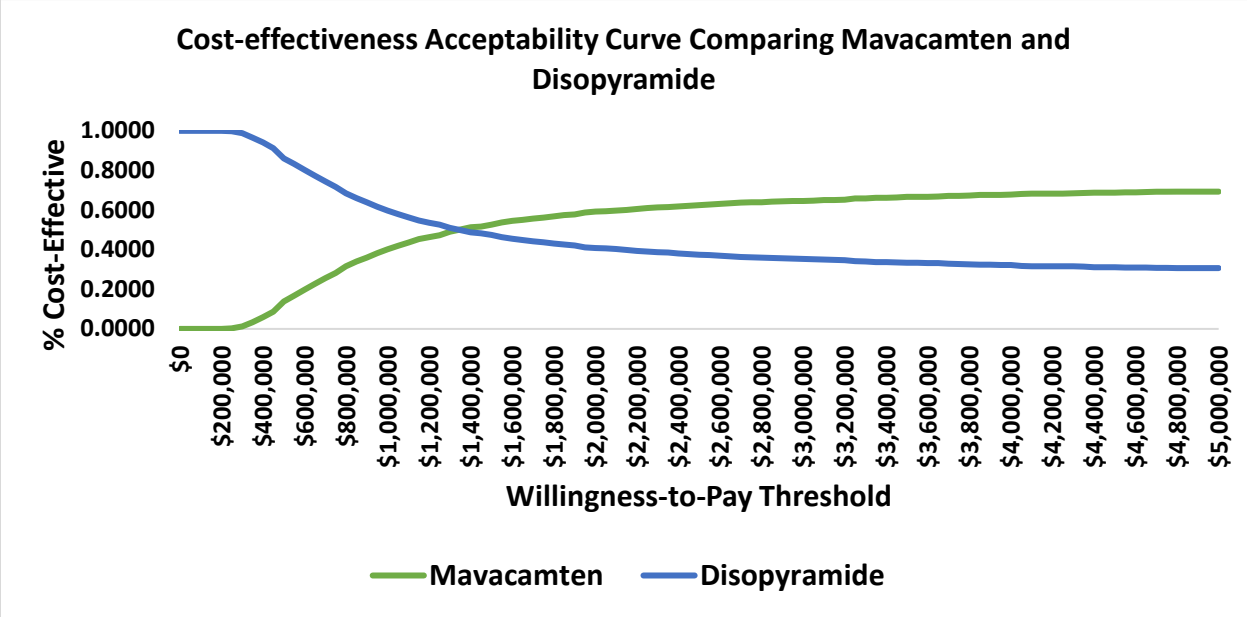


Figure E6. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Acceptability Curves for Mavacamten and Myectomy

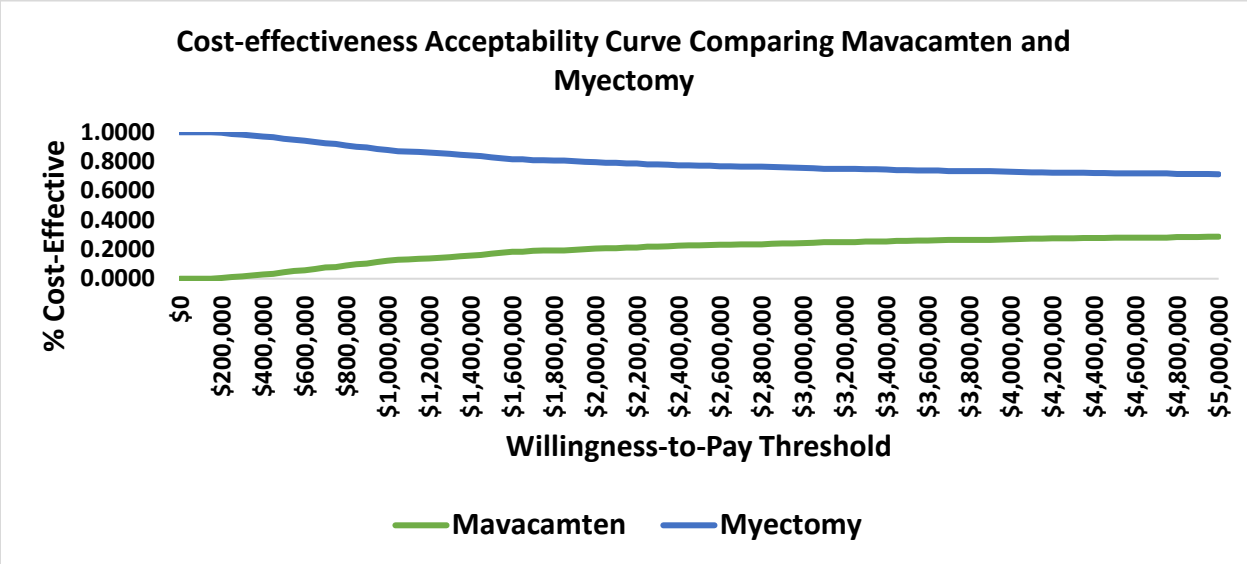
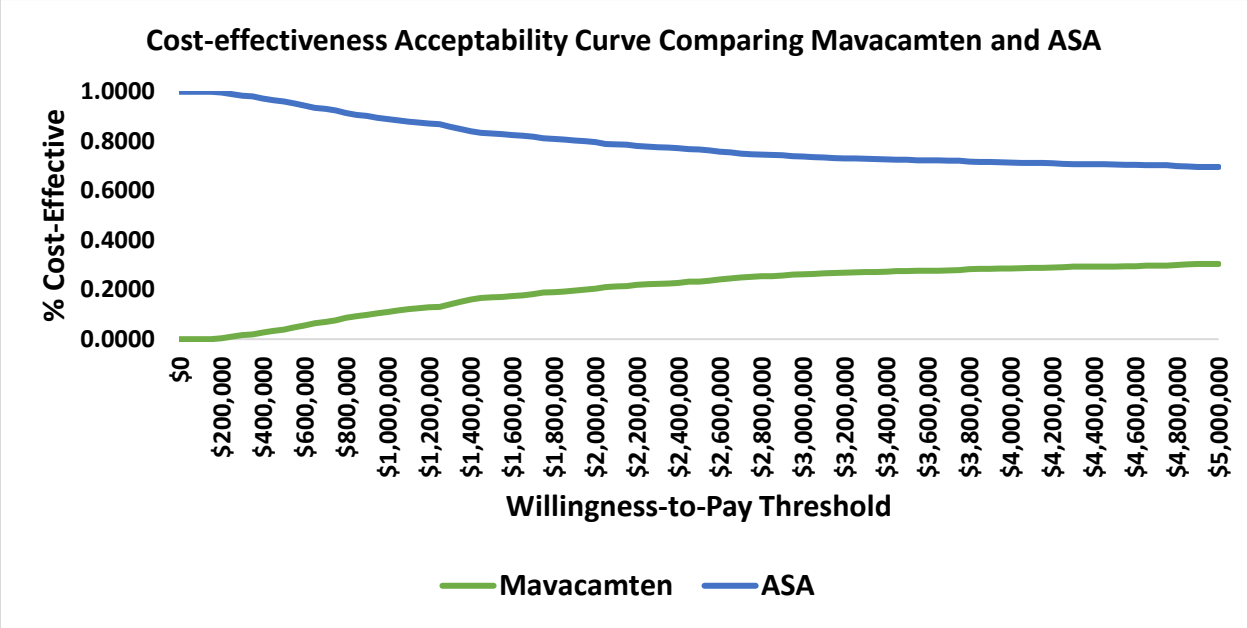


Figure E7. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Acceptability Curves for Mavacamten and Septal Ablation



ASA: alcohol septal ablation

E4. Scenario Analyses

We included a scenario using a higher mortality rate for patients in NYHA class III/IV. We also included a scenario where NYHA class I was associated with full employment and the other classes with no employment in comparing mavacamten and first-line therapy with first-line therapy alone. In addition, we included a scenario where mavacamten and first-line therapy was associated with full employment and first-line therapy alone was associated with having no employment. In all of them, the incremental cost-effectiveness ratio was higher than standard threshold values.

E5. Model Validation

Prior Economic Models

There were no prior published cost-effectiveness models for HOCM patients. Some of the model inputs were informed by heart failure models available in the literature. In particular, Zueger et al. 2018 used a heart failure model based on NYHA class to project the cost effectiveness of various treatments for heart failure. Our model incorporated the percent difference in non-treatment costs between patients in NYHA II and NYHA III/IV seen in that model in projecting non-treatment related costs for HOCM patients. Our model was also informed by discussions and data provided academic in confidence by modelers employed by Bristol Myers Squibb. However, that model has yet to be published.

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using mavacamten rather than standard therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[65,66] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (https://icer.org/our-approach/methods-process/value-assessment-framework/), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2021-2022, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $734 million per year for new drugs.

G. Public Comments

This section includes summaries of the public comments prepared for the CTAF public meeting on Friday, October 22, 2021. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. One speaker did not submit summaries of their public comments.

A video recording of all comments can be found here. Conflict of interest (COI) disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

John Whang, MD, FACC, Bristol Myers Squibb
Vice President, US Medical for Cardiovascular and Established Brands

Obstructive HCM is a debilitating and life-changing disease, sometimes with symptoms limiting even routine daily activities, substantially impairing health-related quality of life. Currently, there are no available medications that target the underlying pathophysiology of HCM. Surgical intervention can be the final option for patients with symptoms refractory to first-line medications. Therefore, there is a substantial unmet need for novel disease-specific therapies that improve quality of life and potentially slow or reverse disease progression, mitigating the need for surgical intervention.

Mavacamten is currently under FDA review for the treatment of symptomatic obstructive hypertrophic cardiomyopathy, also known as HCM. Mavacamten represents the first pharmacological breakthrough for HCM in nearly 35 years, and if approved, would be the first-in-class myosin inhibitor, specifically targeting the underlying pathophysiology of HCM. In EXPLORER-HCM, all primary and secondary endpoints were met with statistical significance, including clinically meaningful improvements in symptoms, peak oxygen consumption, and quality of life, with emerging data suggesting regression of some of the HCM-induced abnormalities in heart muscle structure and function, which is consistent with mechanistic, preclinical data. Mavacamten's safety profile, as reported in the peer-review literature, was generally comparable to that of placebo in EXPLORER-HCM.

From the outset, BMS is concerned that ICER's review is premature given the fast-evolving evidence for mavacamten. Should mavacamten receive FDA approval, additional data will become available through peer-reviewed publications.

However, even within the specified criteria of this review, ICER's methods remain fundamentally flawed due to two major design decisions:

1) Choice of treatment comparators
2) Assumptions about mortality and disease progression.

1) ICER's comparison of septal reduction therapy (SRT) and disopyramide with mavacamten is incorrect and misleading.

The SRT patient population in the ICER model was based on the mavacamten arm of EXPLORER-HCM, in which 72% of patients had NYHA class II symptoms at baseline. The ICER assumption that all of these patients with NYHA class II symptoms would receive SRT is inconsistent with the current AHA/ACC 2020 and ESC 2014 guidelines.

As for the disopyramide arm, the baseline NYHA class distribution was based on the Sherrid et al. paper, which means the patient population in the disopyramide arm differed from the other treatment arms in terms of baseline disease severity, quality of life, and health care cost.

Furthermore, as acknowledged by ICER, there is insufficient data for a scientifically valid and rigorous comparison of the different treatments. Despite recognizing this limitation, ICER proceeded with an inappropriate comparison between the randomized clinical trial evidence on mavacamten[9] and real-world observational evidence on SRT and disopyramide because the true treatment effectiveness of SRT and disopyramide relative to mavacamten are unknown.

2) ICER ignores well-documented evidence on mortality and disease progression in obstructive HCM.

As seen in the literature, mortality risk increases with higher NYHA class in HCM. The base-case model assumed there is no difference in mortality risk by NYHA class. While ICER's scenario analysis attempted to account for this difference in mortality risk, the analysis was based on a sample in which most patients had non-obstructive disease, yet mortality risks in obstructive and non-obstructive disease are known to be different.

Contradictory to patient experience and cumulative literature, there is no disease progression in any patient after week 32 in ICER's model. While HCM is a heterogenous disease with varied clinical presentation, ICER's model focuses on symptomatic obstructive HCM, and mainly in patients with baseline refractory symptoms despite standard first-line treatment. These patients will likely experience disease progression over their remaining lifetime. Any model that doesn't accurately reflect disease progression cannot accurately predict treatment efficacy.

Conclusion

BMS is concerned with this premature and flawed evaluation given the fast-evolving evidence for mavacamten and the inappropriate choice of disopyramide and SRT as comparators. ICER's model was further based on invalid clinical assumptions—most notably on mortality and disease progression—that underestimate the disease burden and unmet need that patients face and undermine ICER's ability to accurately estimate treatment health benefits. These and other issues were detailed to ICER by patients, providers, and professional organizations, and were largely ignored. BMS is reiterating and expanding on these concerns today.

Dr. Whang is a full-time employee of Bristol Myers Squibb.

Billur Ternar Dowse, MSc
Retired, Patient Advocate

I am a patient with HOCM, who had to retire early after I was diagnosed four years ago. I presented my perspectives from a patient's point of view as well as an informed expert with over 25 plus years of experience in pricing, access, drug evaluations, and outcomes both in the academic medical center and in the pharma industry. I am also a Board Director at HCMA, and our work is purely voluntary. Please correct your slide about my "conflicts of interest." Every meeting we attend and advice/ideas we share are completely provided "free of charge." On Oct 22, I had stated that I have endocarditis, well since then I had major complications. I am providing my comments after coming home from the hospital. I thank ICER for giving me an extension until Nov 15.

As a patient: My HOCM manifested itself after a sudden uncontrollable asthma attack. Five months after my diagnosis due to my severe symptoms, and the fast progression of my HOCM, I had to retire early from my job. I was given strict medical orders regarding my limitations. Started on medication therapy which became a cocktail of medications, and into dose escalations to control my symptoms. As a person who never had to take beta blockers and calcium channel blockers before in her life, not only it was very difficult for me to initially handle the impact of these medications and the impact of the daily HOCM symptoms, but it was also quite difficult to describe what it does to the quality of life of a person. It took a good three years to understand what triggered some of the symptoms, and how to cope with them. The way HOCM manifested itself, I had to make major lifestyle changes. This had a major economic impact on my family and my life plans.

Social and Indirect Costs: Comprehensive models need to determine what is a meaningful improvement when a new medication is added; and if the magnitude of improvement is meaningful enough to improve the quality of life of the patients. ICER highlights these in Section 5, "Contextual Considerations," and lists all the attributes as a must to be considered when evaluating the "value and effectiveness of mavacamten." I highlighted my major concerns regarding the models in previous feedback sessions. On Oct 22, I emphasized again without including "social and indirect costs" in any of the models and assumptions, and even having reworded your questions, there is insufficient (or no) data available to answer them. I do not feel adequate data appears in the ICER report to achieve a meaningful patient-centric opinion on the value of mavacamten. With so many clinical unknowns, and with so many inaccurate non-real-world pricing assumptions and utilization rates, especially your budget impact model is opening the doors for barriers to access.

When deciding the value of mavacamten, please consider the following:

It is an "Add-on therapy." Please stop talking about the potential of this being a stand-alone therapy without any real-world or Phase IV data being available.

This is a novel first-in-class drug. The clinical trial data is based on a limited time, and under 300 patients are being treated worldwide, however, results are promising for some of the HOCM patients. Please stop expanding the patient base to all HCM or other heart failure patients when there is no data available.

Access and affordability are essential to learning about the benefits of this drug. More studies and actual patient experiences are needed to fully understand the long-term benefits of the medicine. Adherence to treatment protocols should not be hindered due to cost.

By assigning arbitrarily chosen high price points (it is an orphan drug), you are telling payers to engage in cost-sharing schemes, knowingly as a society, we are pushing patients either to bankruptcy or "go fund me" options. Is this what we call "American medical innovation and advancement of care?"

HCM is not all the same. Only specialized cardiologists should determine who the appropriate patient population is to administer this drug and when.

HOCM patients want to live the best quality of life possible with a chronic, life-threatening heart condition. When determining the "value of mavacamten," you must find a balance in cost, benefit, affordability, and access to ensure all who need it can benefit from it. We are talking about patients' lives.

Thank you!

Billur T. Dowse has collaborated with the Hypertrophic Cardiomyopathy Association, which receives 20% of its sponsorship for educational programming from Bristol Myers Squibb/MyoKardia.

Pastor Kent Sperry, MDiv
Patient Advocate

My name is Kent Sperry. I live in Beulah, North Dakota, where I pastor Prince of Peace Lutheran Church. And I was diagnosed with HCM about 11 years ago.

Even though my father was diagnosed with it a couple of years before me, and even though the doctors knew what to look for, I was repeatedly told that I was fine even after experiencing the symptoms of this disease. It took a doctor who was new to my area, who had been working at Mayo Clinic and was opening his own practice, to identify it.

Not long after my diagnosis, I moved to North Dakota. I immediately established myself as the patient of a cardiologist an hour away from home for ongoing monitoring and treatment. There was no one closer I could see. But, about a year later, when my symptoms suddenly became worse for no apparent reason, he refused to even make me an appointment. It was then that I sought treatment at Mayo Clinic and became familiar with the work of the HCMA.

I learned very quickly how important it is to have a specialist who works with this disease on a regular basis. The care that I now receive is wonderful, even though it's not convenient in the least. Receiving this care means that I have to drive about nine hours one way. It necessitates that I take the time off of work to do so. And it usually involves a stay of several days in a motel.

This trip is made on a regular basis not only for me. Shortly after my first contact with Mayo Clinic, I was gene tested. The gene responsible for my condition was identified. And this enabled us to test my six children to see which of them inherited this gene.

It meant a fight with my insurance company to have this approved. But we learned that three of my six children have this gene. This means that not only am I seen at Mayo Clinic to monitor and treat my condition. My children are also monitored there on a regular basis so that we can know if they develop HCM and treat it from the beginning.

Some years we've been able to make this trip and to see our doctors at the same time. Other times, however, it's meant more than one trip.

As uncertainty is the name of the game with HCM, I recently experienced a worsening of my condition. For several years, my condition was stable and successfully treated with medication. We changed the dose a few times to keep me feeling well. But my doctor didn't believe I would ever need more aggressive treatment.

However, about a year ago, my symptoms drastically worsened. My medication was increased one last time. I was told that I was maxed out on that drug, and it still wasn't doing the job. After being

seen once again at Mayo, it was discovered that my septum had grown 8-9 mm and that I was now severely obstructed. So, something had to be done.

My options were to join the trial of the very medication being discussed today. However, because of the distance and the requirements of the trial, it was determined that it would be very difficult for me to take part in it. I could try a different medication in combination with the one I was already on, but my doctor believed the chances of this helping me to be slim. The last option presented to me, and the one he recommended, was surgery.

About five weeks ago, I traveled to Mayo to have a septal myectomy. Again, this involved the long drive, a longer stay in the motel (especially for my wife), and surgery itself.

Had it been easier, I believe that I would have joined the trial. Had the drug been available, I more than likely would've tried it before submitting to surgery. After all, the emotional toll of putting yourself in a position to have your chest cut open, your heart stopped, and a chunk of your heart removed is great. Even knowing it was the right thing to do, the worry that it caused as I awaited the procedure was intense. And this was true even knowing that I had a fantastic surgeon at a great hospital, and that the risks in a high-volume center are very low.

From my experience, getting proper medical care for HCM can be both difficult and expensive. Even with the help that insurance provides, this remains the case. While I've made the necessary sacrifices to obtain the proper care for myself and my children, I believe it important to have needed medical treatments that are accessible for everyone who is struggling with this condition. And my hope is that, should they develop HCM, my children will be able to affordably access the needed care.

No financial conflicts of interest to disclose.

Nikora Groomes, JD
Patient Advocate

My name is Nikora Groomes, and I am an African American mother, lawyer, and caregiver to twins. My twin son Asaun Groomes has HOCM, and his twin sister could ultimately assess positive for HCM. We hold our breath every three years when she gets tested for HCM. In my profession in health care law, I have written the evidence of coverage for health benefits, rx riders, and cost shares for health plans for Maryland, District of Columbia, and Virginia.

When my son was diagnosed with this disease at 15 years old, I immediately was inundated with numerous appointments for MRI, EKGs, and my son was also placed in a special study at NIH to explore his heart genetic mutation. All of this was an enormous amount of time, paperwork, and coordination of care through referrals and appeals. If I were not educated this would have been an even bigger nightmare.

My son had a scholarship to play basketball at a private school since eighth grade and traveled the country in the Amateur Athletic league (AAU) to play basketball. One horrific asthma attack on the basketball court found his HCM and saved his life. We were lucky enough to have his HCM diagnosed because the facts are "that young African Americans athletes die of Hypertrophic Cardiomyopathy more than any other subgroup. Therefore, lifesaving medication must be reachable and affordable to diverse and marginalized communities and the care must be able to be attainable to underrepresented individuals.

My son initially was cared for at Children's Hospital because that is what the health plan directed. Children's care plan was to do experimental test on my son after fibrosis in his heart was detected. Before agreeing to this experimental surgical treatment on my son, I researched and found the organization HCMA. This organization informed me about Centers of Excellence for individuals with HCM. My husband and I decided our son were not going to be a guinea pig experimented on. His diagnosis already puts his life at risk and an experimental surgery could have killed him sooner. We switched Asaun's care to a "COE," which now required an hour drive to receive care.

As a caregiver, I have had to endure the possibility of losing my child to this disease, so I was going to fight for him to get the best medical care. One such fight was that the doctors provided my son with medication and indicated he also needed a portable defibrillator. His disease had not progressed enough for an implantable device. The evidence of coverage indicated my health plan covered the defibrillator however I got pushback from the health plan that it was not covered. I continued to push for this lifesaving device. I was so worried because the average price point of the defibrillator is thousands of dollars out of pocket. After appeals and numerous calls, I won the fight and a defibrillator shipped to my home, but I paid the ultimate price and lost my job. I then had to frantically find insurance and utilized the health care exchanges to ensure my family and myself would have insurance at a specified price point.

My son is now a freshman in college. With college, we had to work with accessibility services on campus and utilize the Americans with Disabilities Act to make college safer for my son. He required a single room and several defibrillators added to campus. We also had to create an emergency plan in case he has a SCA. This is the kind of advocacy a mother has to do for her sick child. Co-pays, coinsurance four medication or doctor visits are always evaluated and needed as more care at any given time could be needed. FMLA/Family Medical Leave Act is always necessary as a parent of a child with a genetic heart disease. My son's life matters and if you can provide a medication that is attainable and reachable for him it would be lifesaving. Further, by age 26 my son will have to muster enough strength to get his own medical plan with a preexisting condition and be able to get health care to sustain his life. Do no harm here and create this medication at a price point that is reachable for all and able to make a lifesaving difference for my son and others with this disease.

Thank you for taking the time to hear our story. We simply need adequate access to your medication.

No financial conflicts of interest to disclose.

Lisa Salberg, Hypertrophic Cardiomyopathy Association
Founder and CEO

I submit these comments after the seven months of work on the review of mavacamten, a novel therapy under review by the FDA for the treatment of hypertrophic obstructive cardiomyopathy. I am the Founder and CEO of the HCMA, a patient advocacy organization in operation since 1996 – 4hcm.org. From 1989 to 2005, I was employed as the health plan administrator for a private plan. I come from a 100+ year history of HCM in my family. I am an HCM survivor of a stroke, endocarditis, five implantable defibrillators, multiple medical therapies, clinical trials, and a heart transplant. Twenty-six years ago, my sister Lori's sudden death at the age of 36 began my work to create the Hypertrophic Cardiomyopathy Association. Lori was a casualty of HCM mismanagement. I currently have eight family members with HCM; the HCMA – my larger family, serves over 15,000 families in 52 nations. The HCMA has helped develop and support 43 HCMA recognized Center of Excellence programs, with 16 on the path to review.

HCM used to only be in the headlines when a young athlete died, creating the narrative that this was a fatal problem only for young athletes. The reality is that this is a common genetic disorder impacting as many as one in 250 people worldwide, which is an estimated one million Americans, with highly variable presentations from mild to severely debilitating; sadly, only about 15% of those with HCM are in treatment for it today. HCM has had over 75 names since 1959, with each specific anatomical variation of the expression of hypertrophy leading to nomenclature confusion.

What HCM patients want and need is to live the best quality of life possible with a chronic, life-threatening heart condition. They want proven treatments options that are meaningful to them and provide some stability in symptoms, leading to a more predictable quality of life. Mavacamten's trial results show that this is achievable for some of them.

Today, we have no labeled indication drugs designed explicitly for HCM targeting the underlying mechanism for HCM. That is why this review has been convened because mavacamten is a very different drug as it targets this previously untreated mechanism – myosin heads within the sarcomere. Data related to the use of off-label use of disopyramide in HCM must be approached with the complete understanding that the name brand – NORPACE CR has not had a stable supply history over the last ten years and is currently "OUT OF STOCK" worldwide. The generic requires dosing every six to eight hours, which creates a challenge for young adults.

Patients have been left to manage with drugs developed for other forms of heart disease, which has proved challenging. Other treatment options such as surgical myectomy and catheter-based treatments such as alcohol septal ablation are proven therapeutic options when performed at high-volume centers. Patients may want to use medical therapy over invasive options for many reasons – childcare, work, major life events, caring for elderly parents, career implications, to name a few. From an economic point, these treatments are highly effective for their cost – yet they have risks.

HCM is not all the same. HCM spectrum disorders include mimickers, including Danon's, Fabry, amyloidosis, Noonan syndrome, and others, some of which have their own labeled medications. We feel it is critically important for future therapeutics to be administered with the guidance of COE's to ensure the proper patient selection and monitoring into the Phase IV aspect of the study. We need the suitable patients to get the right treatments at the right time.

We are very early in our understanding of the role of these agents in the HCM population, and the data is limited at this time, with under 300 patients worldwide being treated. We find ourselves here to discuss the economic impact of an agent into our community and do so from a position we feel is absent of the total effect to the patient community. We do not know yet how this novel medication will truly serve many patients.

We know the ICER report has not addressed many of the “contextual considerations,” which four patients issued public comments on at the meeting. I assure you patients want access to mavacamten once it is available. They want the chance to try a drug designed for them, which the early data suggests may be life-changing for many. The "right to try" applies beyond unapproved therapies, we believe that when it comes to myosin inhibitors, this concept must apply once it hits the market. We want to ensure HCM patients an opportunity to have access to myosin inhibitors like mavacamten with favorable review and formulary placement once to market.

When I first became engaged with ICER, the methods explained sounded very strong. We appreciated being involved early and frankly welcomed the opportunity to help improve the process.

We had over 600 patients reply to ICERS “survey.” The survey was formatted to ask what it was like to have HCM; it was not well designed to answer the question of economic burden, treatment wishes, or the value of therapeutic options. The ICER draft report stated that there was not ample data to evaluate to determine the impact on patients. If there were an attempt to look to the economic impact of HCM on patients and families, the survey conducted would have been specifically worded to gain understanding, in short, the survey was not well aligned with the community's needs, and five patients were given a total of 30 minutes to fill these gaps in knowledge at a public meeting. This seems inadequate. Patients want and need to live the best quality of life possible with a chronic, life-threatening heart condition—HCM—the ability to have treatment options that are meaningful to them and provide some stability in symptoms, leading to a more predictable quality of life.

I caution reviewers and payers fully understand how variable New York Heart Association class can be in HCM patients. NYHA class is a moment in time and varies significantly in the lives of HCM patients with reasons that have not been well defined in the literature. Our social media closed community has over 7,500 participants: This post from 10/19/21 explains what patients experience daily “Last week I could hardly walk without feeling like I was going to pass out, and all I did was

huff and puff Spend most of my days in bed. The palpitations were nonstop. So two days ago, I felt great went to target today and walked the whole store." We hear this type of comment daily. Drugs like mavacamten may provide stability in symptom burden, which would be a welcomed change for the HCM community.

We welcome myosin inhibitors to the community and hope to be priced, placed favorably on formularies, and market access to ALL patients who may benefit from it, not simply the top 1%. We all want affordable drugs for many diseases, and it is essential to understand that HCM has long been ignored and patients left without meaningful drug options. The cost associated with bringing this to market has been steep, and we, the patient community, cannot ignore the risks taken by the developer nor the risk taken by the new owner of the drug to bring this to the patients. We are all in this together. We must find a balance in cost, benefit, affordability, and access to ensure all who can benefit have the chance to try, without payers pushing the prices to the backs of patients and families struggling to survive physically and economically.

I look forward to sharing my experience with the ICER team in the near future to help identify more effective ways to ensure future reviews are improved to include a more realistic view of the economic impact to patients, families, and all Americans. Thank you for your time and consideration.

The Hypertrophic Cardiomyopathy Association receives 20% of its sponsorship for educational programming from Bristol Myers Squibb/MyoKardia.

H. Conflict of Interest Disclosures

Tables H1 through H3 contain COI disclosures for all participants at the Friday, October 22, 2021 public meeting of CTAF.

Table H1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants	
Molly Beinfeld, MPH, Senior Research Lead, Evidence Synthesis, ICER*	**David Rind, MD, MSc**, Chief Medical Officer, ICER*
Laura Cianciolo, Program Manager, ICER*	**Jyotirmoy Sarker, MPharm, MBA, MBiotech**, Graduate Student, Pharmacy Systems, Outcomes, and Policy, University of Illinois at Chicago*
Maggie Houle, Program and Event Coordinator, ICER*	**Surrey M. Walton, PhD, MA**, Professor, Pharmacy Systems, Outcomes, and Policy; Assistant Director, Center for Pharmacoepidemiology and Pharmacoeconomic Research, University of Illinois at Chicago*
Emily Nhan, Research Assistant, ICER*	**Jason H. Wasfy, MD, MPhil**, Associate Professor, Harvard Medical School; Medical Director, Massachusetts General Hospital Physicians Organization; Director of Outcomes Research, Massachusetts General Hospital Heart Center*
Rasheed Mohammed, PharmD, MPH, Health Technology Assessment Fellow, ICER*	**Melanie Whittington, PhD**, Associate Director of Health Economics, ICER*
Steven D. Pearson, MD, MSc, President, ICER	

*None of the above authors disclosed any conflicts of interest defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care manufacturers or insurers.

Table H2. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Milind Desai, MD, MBA, Director of Clinical Operations, Hypertrophic Cardiomyopathy Center, Cleveland Clinic	Dr. Desai served as an investigator for the VALOR study of mavacamten sponsored by Bristol Myers Squibb/MyoKardia.
Martin Maron, MD, Director, Hypertrophic Cardiomyopathy Center and Research Institute, Tufts Medical Center	Dr. Maron served as a site investigator for a Phase I study of mavacamten and currently serves as a steering committee member for a Phase II study of a second-generation myosin inhibitor sponsored by Cytokinetics.
Gwendolyn Mayes, JD, MMSc, Founder and Chief Concept Officer, GwenCo Health	Gwendolyn Mayes serves as a consultant to the Hypertrophic Cardiomyopathy Association, which receives 20% of its sponsorship for educational programming from Bristol Myers Squibb/MyoKardia. She also consults for Edwards Lifesciences, Paragonix, and Natural Cycles.
Carla McSpadden, RPh, BCGP, MBA, Director, Clinical Formulary Strategies, Humana	Carla McSpadden is a full-time employee of Humana.
Lisa Salberg, Founder and CEO, Hypertrophic Cardiomyopathy Association	The Hypertrophic Cardiomyopathy Association receives 20% of its sponsorship for educational programming from Bristol Myers Squibb/MyoKardia.
John Watkins, PharmD, MPH, BCPS, Residency Program Director, Premera Blue Cross	John Watkins is a full-time employee of Premera Blue Cross.

Table H3. CTAF Member Participants and COI Disclosures

Participating Members of CTAF	
Ralph G. Brindis, MD, MPH, MACC, FSCAI, FAHA, Clinical Professor of Medicine, UCSF*	**Elizabeth J. Murphy, MD, DPhil**, Professor of Clinical Medicine, UCSF; Chief, Division of Endocrinology and Metabolism, Zuckerberg San Francisco General Hospital*
Felicia Cohn, PhD, Bioethics Director, Kaiser Permanente, Orange County; Clinical Professor of Bioethics, Department of Medicine, University of California, Irvine School of Medicine*	**Kathryn A. Phillips, PhD**, Professor of Health Economics and Health Services Research; Director and Founder, UCSF Center for Translational and Policy Research on Personalized Medicine; Department of Clinical Pharmacy/School of Pharmacy, UCSF Institute for Health Policy Studies, and UCSF Comprehensive Cancer Center*
Robert Collyar, Patient Advocate in Research*	**Rita F. Redberg, MD, MSc, FACC**, Cardiologist and Professor of Medicine and Women's Cardiovascular Services at UCSF*
Kimberly Gregory, MD, MPH, Vice Chair, Women's Healthcare Quality & Performance Improvement, Cedars-Sinai Medical Center*	**Richard Seiden, JD**, Patient Advocate, Retired Partner, Foley & Lardner LLP*
Paul Heidenreich, MD, MS, Professor of Medicine, Stanford University School of Medicine*	**Alexander Smith, MD, MPH**, Professor of Medicine, UCSF
Jeffrey Hoch, PhD, Associate Director, Center for Healthcare Policy and Research, UC Davis*	**Joanna Smith, LCSW, MPH, CHA**, Chief Executive Officer, Healthcare Liaison, Inc.*
Sei Lee, MD, Associate Professor of Medicine, Division of Geriatrics, UCSF*	**Anthony Sowry,** Patient Advocate and Lead Volunteer, California, National Patient Advocate Foundation; Senior Vice President, Maritime Container Shipping (Retired)*
Joy Melnikow, MD, Director of the Center for Healthcare Policy and Research and Professor of Family and Community Medicine at UCD*	

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.