Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from Bristol-Myers Squibb**:**
   a. Submission
   b. Submission addendum
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2. **Clarification questions and company responses**
   a. Main response
   b. Appendix A
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3. **Patient group, professional group and NHS organisation submissions** from:
   a. Cardiomyopathy UK
   b. British Cardiovascular Society
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   d. Norfolk & Norwich University Hospitals NHS Foundation Trust
   e. St George's University Hospitals NHS Foundation Trust

4. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre (SHTAC)

5. **External Assessment Report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Juan Pablo Kaski, Associate Professor in Paediatric Inherited Cardiology and Consultant Paediatric Cardiologist – clinical expert, nominated by British Congenital Cardiac Association
   b. Sunil Nair, Consultant Cardiologist & lead for inherited and acquired heart muscle diseases – clinical expert, nominated by Norfolk and Norwich University Hospitals NHS Foundation Trust

8. **Technical engagement responses from stakeholders:**

a. Cardiomyopathy UK
b. Associated of Inherited Cardiac Conditions
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9. **External Assessment Report critique of company response to technical engagement** prepared by Southampton Health Technology Assessments Centre (SHTAC)

10. **NICE Managed Access feasibility assessment**

11. **Corrected company technical engagement response cost-effectiveness results** from Bristol Myers-Squibb

12. **Expert personal perspective from Laura Kelly – patient expert,** nominated by Cardiomyopathy UK

13. **Expert personal perspective from Sanjeev Patel** – Innovative Medicines Fund (IMF) clinical lead for NHS England

14. **Updated PAS and cost-effectiveness results** from Bristol Myers-Squibb

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Document B

Company evidence submission

June 2022

File name	Version	Contains confidential information	Date
		Yes	**19 July 2022**

Contents

Tables and figures

Abbreviations

ACM	all-cause mortality
AE	adverse event
AF	atrial fibrillation
ANCOVA	analysis of covariance
ASA	alcohol septal ablation
ATP	adenosine triphosphate
ATPase	adenosine triphosphatase
AV	atrioventricular
BB	beta blocker(s)
BMI	body mass index
BNF	British National Formulary
CCB	calcium channel blocker(s)
CEM	cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CMR	cardiac magnetic resonance
CPET	cardiopulmonary exercise testing
CSR	clinical study report
CSS	clinical summary score
CV	cardiovascular
COV	coefficient of variation
DBL	database lock
DSA	deterministic sensitivity analysis
EC	European Commission
ECG	electrocardiogram
EHR	electronic health records
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
ESC	European Society of Cardiology
HCM	hypertrophic cardiomyopathy
HCMSQ	HCM Symptom Questionnaire
HCMSQ-SoB	HCM Symptom Questionnaire Shortness-of-Breath
HCRU	healthcare resource utilisation
HF	heart failure
HR	hazard ratio
HRQoL	health-related quality of life
hs-cTnI	high sensitivity cardiac troponin I
ICD	implantable cardioverter-defibrillator
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
IRR	incidence rate ratio
ITT	intention to treat

IXRS	interactive response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	left atrium/atrial
LAVI	left atrial volume index
LGE	late gadolinium enhancement
LS	least squares
LTE	long-term extension
LV	left ventricle/ventricular
LVEF	left ventricular ejection fraction
LVMI	left ventricular mass index
LVOT	left ventricular outflow tract
LVOTO	left ventricular outflow tract obstruction
LY	life years
LYG	life years gained
MHRA	Medicines and Healthcare products Regulatory Agency
N	No
NA	not applicable
ND	not determined
NHB	net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	not reported
NYHA	New York Heart Association
NT-proBNP	*N*-terminal pro–B-type natriuretic peptide
OS	overall summary score
PAS	patient access scheme
PD	pharmacodynamics
PGIC	Patients Global Impression of Change
PGIS	Patients Global Impression of Severity
PK	pharmacokinetics
PPPY	per patient per year
PRO	patient reported outcomes
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
pVO_2	peak oxygen consumption
QALY	quality-adjusted life year
QTcF	QT interval with Fridericia correction
Q1	first quarter
Q3	third quarter
RCT	randomised controlled trial
RER	respiratory exchange ratio
ROBINS-I	Risk of Bias in Non-Randomized Studies of Interventions
RR	relative risk
RWE	real-world evidence
SAE	serious adverse event
SAM	systolic anterior motion

SCD	sudden cardiac death
SD	standard deviation
SE	standard error
SHaRe	Sarcomeric Human Cardiomyopathy Registry
SLR	systematic literature review
SmPC	Summary of Product Characteristics
SRT	septal reduction therapies
UTI	urinary tract infection
TEAE	treatment emergent adverse event
TIA	transient ischaemic attack
TTE	transthoracic echocardiogram
WPAI:SHP	Work Productivity and Activity Impairment Specific Health Problem Questionnaire
WTP	willingness to pay
Y	yes

B.1 Decision problem, description of the technology and clinical care pathway

- This submission compares mavacamten in combination with standard care to individually optimised standard care without mavacamten, for the treatment of [redacted], where standard care comprises beta blockers (BB) and calcium channel blockers (CCB)
- Although the first descriptions of obstructive HCM were published more than 60 years ago,[8] there are no current pharmacological therapeutic options specifically indicated for symptomatic, obstructive HCM, highlighting the unmet need for targeted, effective therapies in this patient population.
  - Obstructive HCM is a chronic, progressive disease of the heart muscle
  - Due to debilitating symptoms, patients with obstructive HCM often experience impaired quality of life with impacts on social functioning, economic productivity and psychological wellbeing.
  - Obstructive HCM is associated with an increased risk of cardiovascular complications and mortality.
  - Currently used pharmacological therapies were not designed for the treatment of HCM and many are used 'off-label' on an empirical basis; they have variable effectiveness and a range of side effects.[2,9,11,12]
- Mavacamten is an innovative medicine, the first therapy that has demonstrated efficacy and safety in a large randomised controlled trial for obstructive HCM. It has been shown to significantly reduce symptoms and improve function in patients with symptomatic, obstructive HCM, leading to a meaningful impact on patient quality of life.[3,14]
  - Mavacamten is a first-in-class, oral, allosteric modulator of cardiac myosin;
  - Mavacamten is designed to modify the underlying pathophysiology in obstructive HCM;
  - The highly innovative nature of mavacamten has been recognised with the award of a Promising Innovative Medicines (PIM) designation on 21 August 2021 by the Medicines and Healthcare products Regulatory Agency (MHRA).[21]

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. The decision problem that the submission addresses is summarised in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with symptomatic obstructive hypertrophic cardiomyopathy (NYHA class II-III)	[redacted]	N/A
Intervention	Mavacamten in combination with standard care	Mavacamten in combination with standard care	N/A
Comparator(s)	• Individually optimised standard care without mavacamten • Standard care is defined as: o Beta-blockers o Non-dihydropyridine calcium channel blockers o Disopyramide, alone or in combination with either beta-blockers or non-dihydropyridine calcium channel blockers	• Individually optimised standard care without mavacamten • Standard care is defined as: o Beta-blockers o Non-dihydropyridine calcium channel blockers	Advice received from UK clinical experts is that disopyramide is rarely used for treatment of symptomatic obstructive hypertrophic cardiomyopathy (HCM) in clinical practice in England and Wales due both to the considerable side-effects that many patients find difficult to tolerate, and the phenomenon of tachyphylaxis (a loss of clinical benefit over time).[19] Tachyphylaxis has been reported to occur in a significant percentage of patients,[15] with clinical advice indicating that loss of effect is observed over a period of ~9 months.[19] Furthermore, UK clinical experts have indicated that disopyramide is currently difficult to obtain, which is further limiting its use in clinical practice.[20] As a result of these limitations, disopyramide does not form part of standard care and should not be considered a relevant comparator.
Outcomes	The outcome measures to be considered include:	The outcome measures to be considered include:	Although patients with HCM have a higher risk of mortality compared with the

	• response rates • mortality • cardiovascular events • cardiovascular related mortality • exercise capacity • oxygen consumption • patient-reported symptom severity • change in NYHA class • change in left ventricular ejection fraction • adverse effects of treatment • health-related quality of life	• response rates, given as proportion of patients with complete response (B.2.6.1.4) • mortality (modelled) • exercise capacity, given by cardiopulmonary exercise test (CPET) parameters, particularly peak oxygen consumption (pVO_2), which forms part of the composite primary outcome and a separate secondary endpoint in the pivotal trial (B.2.6.1.1 and B.2.6.1.2) • oxygen consumption; pVO_2 measured by CPET), which forms part of the composite primary outcome and a separate secondary endpoint in the pivotal trial (B.2.6.1.1 and B.2.6.1.2) • patient-reported symptom severity, assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ)-23, HCM Symptom Questionnaire Shortness-of-Breath (HCMSQ-SoB) and EQ-5D (B.2.6.1.3) • change in NYHA class, which forms part of the composite primary outcome and a separate secondary endpoint in the pivotal trial (B.2.6.1.1 and B.2.6.1.2) • change in left ventricular ejection fraction (B.2.6.1.4) • adverse effects of treatment (B.2.10) • health-related quality of life (B.2.6.1.3).	general population,[25,26] the annual all-cause mortality rate in patients with HCM is <1%.[7] This low event rate does not permit inclusion of mortality or cardiovascular (CV) mortality as trial endpoints, as the timescales required to accumulate enough events to power the trial would be prohibitive. The same limitation applies to CV events. Therefore, these endpoints are not presented in B.2. The Company have addressed the lack of trial mortality data by using NYHA class as a surrogate for mortality in the cost-effectiveness model, deriving hazard ratios for mortality by NYHA class from real-world data from patients with obstructive HCM (see section B.3.3.5). No such data have been identified to permit an analysis of CV mortality or CV events, therefore evidence is not provided in this submission for these outcome measures.

B.1.2 Description of the technology being evaluated

A description of the technology being appraised in this submission (mavacamten) is presented in Table 2. The draft summary of product characteristics (SmPC) for mavacamten is presented in Appendix C.

Table 2. Technology being evaluated

UK approved name and brand name	Mavacamten (CAMZYOS®)
Mechanism of action	Mavacamten is a first-in-class, selective, allosteric, reversible inhibitor of cardiac myosin. The early pathophysiological mechanisms underlying HCM are hypercontractility of the heart muscle during systole and impaired diastolic relaxation, leading to an increased risk of HF, AF, stroke, ventricular arrhythmias and sudden cardiac death, in addition to debilitating daily symptoms.[1,2,27] Mavacamten binds reversibly to cardiac myosin and inhibits the myosin ATPase activity. This stabilises myosin in the weakly-bound state, thereby reducing the number of myosin heads bound to actin, normalising the hypercontractility and enabling diastolic relaxation. Mavacamten targets the underlying pathophysiology of HCM to improve cardiac function and reduce symptoms. See B.1.3.3.1 for details.
Marketing authorisation/CE mark status	A regulatory submission was made to the EMA on [redacted]. The earliest point at which an opinion from CHMP is anticipated is [redacted]. The earliest point at which an EC decision is anticipated is [redacted]. [redacted]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The anticipated wording of the licensing indication is: "CAMZYOS is indicated [redacted]"
Method of administration and dosage	Mavacamten is administered as a once-daily oral capsule. Dosing: 2.5, 5.0, 10.0 or 15.0 mg, once daily, according to the following posology: The recommended starting dose is 5 mg orally once daily. [redacted]

	[redacted] (Appendix C)
Additional tests or investigations	[redacted] (Appendix C)
List price and average cost of a course of treatment	Proposed list price (provisionally approved by DH, pending MA approval): £[redacted] per pack (2.5 mg capsules x28) £[redacted] per pack (5.0 mg capsules x28) £[redacted] per pack (10 mg capsules x28) £[redacted] per pack (15 mg capsules x28) Average cost of a course of treatment is: £[redacted] per patient per year All prices exclusive of VAT.
Patient access scheme (if applicable)	The Company are proposing a simple discount PAS, to give fixed net prices of: £[redacted] per pack (2.5 mg capsules x28) £[redacted] per pack (5.0 mg capsules x28) £[redacted] per pack (10 mg capsules x28) £[redacted] per pack (15 mg capsules x28) This would result in a net price of £[redacted] per patient per year. All prices exclusive of VAT.

AF: atrial fibrillation; ATPase: adenosine triphosphatase; CHMP: Committee for Medicinal Products for Human Use; DH: Department of Health; EC: European Commission; EMA: European Medicines Agency; HCM: hypertrophic cardiomyopathy; HF: heart failure; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; MHRA: Medicines and Healthcare products Regulatory Agency; PAS: patient access scheme; VAT: value added tax

B.1.3 Health condition and position of the technology in the treatment pathway

- HCM is a chronic, progressive cardiac disease characterised by hypercontractility and hypertrophy of the heart muscle, which can result in impaired function, debilitating symptoms and increased risk of serious complications.[1,2]
- An estimated two thirds of HCM patients have the obstructive form i.e. have left ventricular outflow tract obstruction (LVOTO).[2]
- Patients with obstructive HCM are at risk of a range of adverse outcomes and the development of debilitating symptoms that impair quality of life.
  - LVOTO is associated with an increased risk of disease progression, arrhythmias, stroke, heart failure and mortality.[2,4-7]
  - The major burden of disease in HCM lies in the morbidity and associated symptoms – fatigue, dyspnoea, chest pain, palpitations, syncope – that impact on patient quality of life, mental health and activities of daily living.[10]
- In the UK, patients with symptomatic, obstructive HCM are managed empirically with pharmacological therapies indicated for other conditions.[2] Many patients find their symptoms are not adequately managed by current standard medical care.[10]
  - BB and CCB can be effective in some patients, but can be associated with significant side effects and tolerability issues.[12,15]
  - Disopyramide is a second-line therapy for patients who remain symptomatic despite BB or CCB.[2,16] Due to significant side effects, tachyphylaxis and lack of availability, it is rarely used in clinical practice in England and Wales.[2,12,15,17-20]
  - Septal reduction therapies (SRTs) are invasive procedures to reduce septal hypertrophy and relieve LVOTO and can be effective but are associated with a range of complications and are generally only considered for patients with moderate to severe symptoms that cannot be managed medically. SRT is not commonly performed, due to contraindications, patient preference and requirement for specialist centres.[2,22] SRTs do not cure the underlying condition and patients may require reintervention and/or ongoing medical therapy.[22-24]
  - There are no existing approved therapies that target the underlying pathophysiology of obstructive HCM.
- There is a substantial unmet need for a targeted therapy that relieves patient's symptoms and improves function to positively impact quality of life and prevent disease progression.
  - Current pharmacological treatments for obstructive HCM provide a degree of symptomatic relief but do not target the underlying cause of HCM nor alter disease course.
- Mavacamten is an innovative, first-in-class, oral therapy designed to target the hypercontractility underlying HCM pathology in order to improve cardiac function and reduce symptoms.

B.1.3.1 Disease background

B.1.3.1.1 Overview

Cardiomyopathies, of which HCM is a form, are a group of chronic diseases of the heart muscle that alter the structure and impair the function of the heart,[2] and are distinct from cardiac diseases that are caused by coronary artery disease, hypertension, valvular disease or congenital heart disease.[28] Obstructive HCM is one of two forms of HCM and represents approximately two thirds of HCM cases, with the remaining one third having the non-obstructive form of the disease.[2] Both forms of HCM are characterised by excessive heart muscle contraction (hypercontractility), ventricular hypertrophy and impaired ventricular relaxation,[27] while obstructive HCM has an additional pathophysiological feature known as left ventricular outflow tract obstruction (LVOTO). LVOTO exacerbates disease progression and symptoms and heightens the risks of complications in obstructive HCM patients, including cardiac arrhythmias, heart failure (HF), stroke and mortality.[1,2]

B.1.3.1.2 Aetiology and pathophysiology

Some obstructive HCM patients have a genetic cause of disease, which is inherited in an autosomal dominant fashion.[29] The majority of causal mutations are found in a number of genes encoding proteins found in the cardiac sarcomere, which is the contractile unit of muscle.[7,27,30,31] A sarcomere is composed of overlapping thick and thin myofilaments.[32] Sarcomere shortening is driven by myosin (thick filament) hydrolysing adenosine triphosphate (ATP) in order to bind to actin (thin filament), forming a cross-bridge between actin and myosin. This is followed by a 'power stroke' in which changes in the configuration of the myosin head move the actin thin filament towards the centre of the sarcomere, shortening the sarcomere and resulting in muscle contraction. Known genetic mutations that cause HCM directly alter sarcomere structure and function, resulting in an increased number of cross-bridges forming between actin and myosin. This results in hypercontractility of the cardiac muscle (Figure 1), which is considered to be the primary driver of pathology in obstructive HCM.

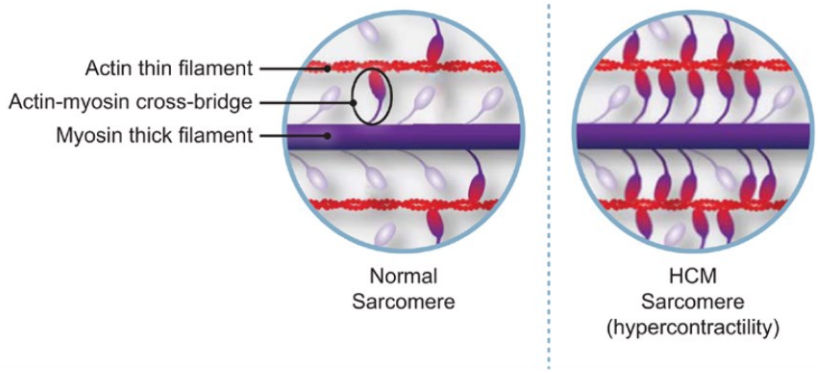


Figure 1. Dysfunctional sarcomere structure and function in HCM

HCM-associated mutations in sarcomeric genes may result in excess actin-myosin crossbridge formation compared to normal sarcomeres, leading to cardiac muscle hypercontractility and hypertrophy. Adapted from Ho et al 2020.[33] HCM: hypertrophic cardiomyopathy.

The pathophysiology of obstructive HCM is complex and multifactorial. The sarcomeric dysfunction and consequent cardiac hypercontractility described above drives the development of cardiac hypertrophy and impairs diastolic relaxation, which have been identified as some of the earliest signs of the disease.[34-36] As the disease progresses, there may be further cardiac remodelling, featuring progressive, pathological hypertrophy with disordered cardiomyocytes that can lead to increased fibrosis, resulting in a small, stiff ventricle.[7,27] These structural and functional changes ultimately result in the range of characteristic pathophysiological manifestations often seen in obstructive HCM: LVOTO, diastolic dysfunction, myocardial ischaemia, mitral regurgitation and arrhythmias.[7]

The defining characteristic of obstructive HCM is the LVOTO, which is defined as when the peak pressure gradient of the left ventricular outflow tract (LVOT) is ≥ 30 mmHg.[2,7] LVOTO results from hypertrophy of the septum causing or exacerbating abnormalities of the mitral valve. In brief, the anatomical changes at the basal septum cause the mitral valve to move anteriorly towards the septum during contraction (systole). This systolic anterior motion (SAM) of the valve leaflet creates an obstruction at the LVOT (Figure 2).[2,7,27] The obstruction impedes blood flow into the aorta, resulting in increased systolic left ventricular (LV) pressure, reduced stroke volume, and mitral regurgitation. The immediate consequence is a reduction in the efficiency of the heart, while over time, LVOTO exacerbates the hypertrophy and myocardial ischaemia, driving further pathology.

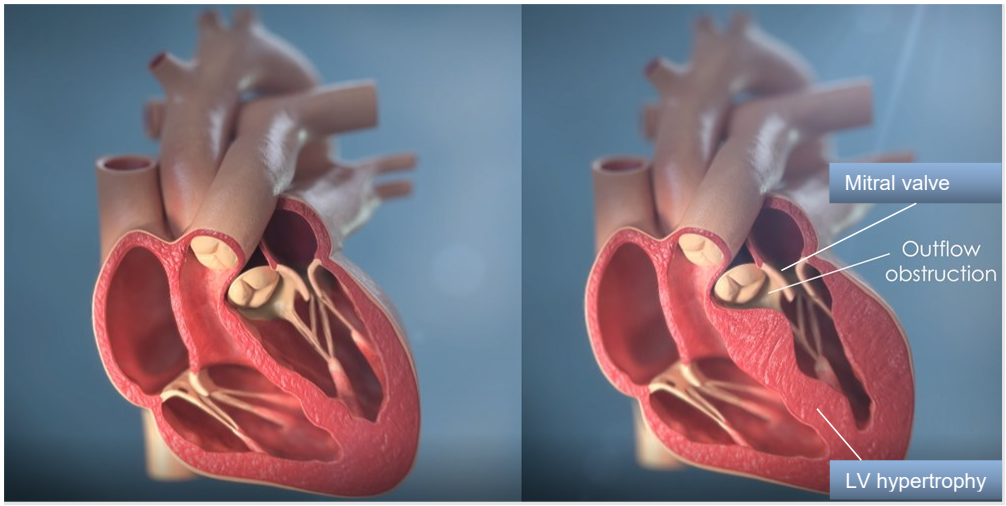


Figure 2. Normal heart and obstructive HCM heart

Normal heart on the left; obstructive HCM heart on the right, with septal hypertrophy leading to obstruction of the left ventricular outflow tract. Adapted from Hypertrophic Cardiomyopathy, Mayo Clinic.[37] HCM: hypertrophic cardiomyopathy; LV: left ventricular.

The degree of obstruction is sensitive to contractility (how hard and fast the heart is beating), preload (ventricular filling at the end of diastole) and afterload (which is affected by blood pressure). All of these are dynamic and alter in response to extrinsic stimuli, and thus LVOTO is also dynamic, and can change with daily activities including exercise, food and alcohol consumption.[2] Some patients with obstructive HCM experience LVOT gradients at rest; one cohort study measured resting gradients ≥ 50 mmHg in 37% HCM patients.[38] Other symptomatic HCM patients have gradients < 30 mmHg at rest but, due to the dynamic nature of LVOTO, manifest LVOT gradients when provoked by exercise or the Valsalva manoeuvre. The burden of disease associated with LVOTO is discussed further in section B.1.3.1.3.4.

B.1.3.1.3 Natural history and burden of disease

Obstructive HCM is a chronic, progressive disease that can manifest at any age. The natural history is highly variable, where some patients have few symptoms while others experience progressive impairment of cardiac function with substantial morbidity and quality of life burden. The 2020 AHA/ACC guidelines[7] state that *"among referral-based cohorts of patients with HCM, 30% to 40% will experience adverse events, including: 1) sudden death events; 2) progressive limiting symptoms because of LVOTO or diastolic dysfunction; 3) HF symptoms associated with systolic*

dysfunction; 4) Atrial fibrillation (AF) with risk of thromboembolic stroke." HCM, and particularly LVOT obstruction, is associated with an increased risk of long-term cardiac complications and mortality. Together, this has a considerable impact on quality of life (B.1.3.1.3.1), as well as a substantial morbidity (B.1.3.1.3.2) and mortality (B.1.3.1.3.3) burden, which is exacerbated by LVOTO (B.1.3.1.3.4).

B.1.3.1.3.1 Symptoms and health-related quality of life burden

In patients with symptomatic, obstructive HCM, the complex pathophysiology outlined above ultimately results in a heart that is progressively failing to function adequately, causing a range of symptoms related to circulatory deficit (fatigue, dizziness), cardiac remodelling (chest pain, palpitations) and respiratory dysfunction (breathlessness).[14] Clinically, the severity of functional limitation due to symptoms in obstructive HCM is assessed using the New York Heart Association (NYHA) classification system (Table 3),[39] which is widely used in clinical practice to assess patients with HCM.[2,7,20]

Table 3. NYHA classification system

NYHA class	Description	Symptoms at rest	Symptoms on ordinary activity
Class I	no limitation of physical activity	ordinary physical activity does not cause symptoms	
Class II	slight limitation of physical activity	Comfortable at rest	Ordinary physical activity results in symptoms such as undue fatigue, palpitations, breathlessness
Class III	marked limitation of physical activity	Comfortable at rest	Less than ordinary physical activity causes fatigue, palpitations, breathlessness
Class IV	unable to carry on any physical activity without discomfort	Symptoms when resting	Symptoms and discomfort increase with any physical activity

NYHA: New York Heart Association. Adapted from Classes of Heart Failure, American Heart Association.[39]

These symptoms worsen over time in the absence of effective treatment.[4] Obstructive HCM can be a life-altering disease, with patients requiring lifelong follow-up to monitor and manage their progressive symptoms, cardiac function and rhythm and risk of adverse events (AEs).

In 2020, the Hypertrophic Cardiomyopathy Association (HCMA) held an externally led patient-focused drug development meeting to hear patient and caregiver perspectives on living with or caring for those with HCM.[10] The report included the

following key themes and accounts of the burden of disease and impact on daily living:

Key theme: Patients report the most burdensome symptom of HCM is living with shortness of breath, followed by fatigue, exercise intolerance, palpitations, and fainting. While this can cause patients to limit many forms of exercise…it can also impact simple activities of daily living such as ironing, house cleaning, and getting dressed.

Key theme: HCM patients make lifestyle changes including diet changes, adjustments in work schedules, and most often, changes in exercise and social interactions to accommodate for burdensome symptoms and fatigue. Symptoms can occur due to HCM itself or as a side effect of medications.

Key theme: Regardless of age, the overall impact of living with HCM is reflected in the emotional and psychological toll patients experience…This can lead to chronic anxiety, depression, isolation, failed relationships, and lost job opportunities.

Key theme: The inheritability/genetics of the condition leaves many parents feeling guilty about passing the gene to their children…There are generational effects on families as the loss of a parent can lead to a variety of challenges in the family structure…and create financial strain due to consequences of the loss of parental or spousal income.

Patients spoke eloquently about their frustrations and disappointments at not being able to hold a job, tend to their children, or complete simple tasks such as bathing, cooking, and dressing. Along with the uncertainty is the angst of not knowing whether the immediate change in function is short-lived or a serious digression that will require additional testing, medications, and treatments.

"I never know what my day will hold! Activities just shopping can completely do me in. I used to be such an active person. Now I am so limited. My husband and I used to dirt bike and motorcycle together and I can no longer join him. I can feel fine and then just like a flash I can have a horrible day." – Lisa

Many patients spoke to the difficulties in finding the right "combination" of treatment options. Patients varied on whether treatments and lifestyle changes had had any impact on them, if at all.

"The current treatments just aren't enough. As patients, we've become accustomed to the thought of only ever being able to get treatment for symptoms . . . but we're tired of that. We want more than just symptom relief." – Wendy

"We really need better medications with side effects that are at least tolerable and medications that are not cumulatively toxic. People diagnosed with HCM can lead relatively normal lives for over 50 years so it is not acceptable to rely on medications that will poison us quickly." – Sara[10]

A conceptual model to capture the patient experience of both obstructive and non-obstructive HCM has been developed, based on insights from patients, clinical experts and a targeted literature review.[14] This model found that fatigue (74%), shortness of breath upon exertion (73%), and light-headedness (70%) were the

symptoms most commonly experienced, while only 21% patients reported no limitation of physical activity. 84% patients with obstructive disease reported four or more HCM symptoms, with 43% reporting symptoms consistent with NYHA class III or IV, representing moderate to severe disease.[14] Concept elicitation interviews conducted as part of the same study reported the most common impacts on patients' lives as limitations to physical activities (78%), emotional impacts (78%), feeling anxious or depressed (78%), and impacts on work (63%).[14]

Patients with HCM are encouraged to consider a range of lifestyle adjustments to accommodate their condition.[2,7] Patients are strongly recommended to avoid competitive sports, while recreational activities may also be restricted based on an individual's symptoms and risk profile, and patients whose jobs involve strenuous activity may require modifications.[2] The dynamic nature of LVOTO is reflected in the daily life of patients, where the degree of obstruction and related symptoms can vary seemingly spontaneously, and can be provoked by exertion (standing, walking), dehydration, meals or alcohol consumption.[11,38] Consequently, patients with obstructive HCM often need to make lifestyle modifications to avoid these provoking factors.[2] For women with HCM, particularly those with LVOTO, pregnancy is associated with increased risk for both mother and foetus, and requires monitoring and careful management; patients who have severe, symptomatic LVOTO may be advised against pregnancy.[2]

These restrictions in activities of daily living required to manage symptoms highlights the lack of alternative therapy options. For example, key themes in the HCMA Voice of the Patient Report were that *"While [symptoms] can cause patients to limit many forms of exercise (e.g., team sports, hiking, biking, etc.) it can also impact simple activities of daily living such as ironing, house cleaning, and getting dressed."* and *"HCM patients make lifestyle changes including diet changes, adjustments in work schedules, and most often, changes in exercise and social interactions to accommodate for burdensome symptoms and fatigue. Symptoms can occur due to HCM itself or as a side effect of medications"*.[10]

This patient-based evidence highlights the impact that obstructive HCM symptoms have on daily life, and in particular, the lifestyle modifications made to accommodate

the impact of these symptoms. Patients also emphasised the psychological burden and guilt of living with a genetic condition. The effect of cardiomyopathy on emotional wellbeing of both patients and their family, friends and caregivers has been highlighted in a survey by Cardiomyopathy UK. The majority of patients and family/friends/carers felt that having cardiomyopathy affected their mental health or emotional wellbeing all or most of the time (22% and 28.6%, respectively, or some of the time (32.5% and 37.1%, respectively).[40]

The daily symptoms experienced by patients with symptomatic obstructive HCM impact on social participation, economic productivity and psychological wellbeing. As a result, patients have reduced health-related quality of life (HRQoL), health status and functionality.[14]

B.1.3.1.3.2 Morbidity burden and cardiac complications

A major burden of disease in HCM lies in the morbidity associated with disease progression and development of complications. Analysis of 4,591 patients with HCM from the Sarcomeric Human Cardiomyopathy Registry (SHaRe), an international registry of longitudinal databases from high-volume HCM centres, found that patients diagnosed aged < 40 years had a 77% (95% CI: 72, 80) cumulative incidence of a composite of cardiac arrest, cardiac transplantation, appropriate implantable cardioverter defibrillator (ICD) therapy, all-cause death, AF, stroke, NYHA class III/IV symptoms by 60 years of age.[25]

HF has been described as *"the predominant cause of disease-related morbidity and mortality and, therefore, greatest unmet treatment need"* in patients with HCM.[7] HF has been estimated to occur in up to 45% of HCM patients.[25,41] The hypertrophied LV in HCM patients becomes small and stiff, reducing the ability of the heart to supply blood to the body, resulting in the breathlessness, fatigue and chest pain characteristic of HF.

Other complications of HCM include ventricular arrhythmias and AF. The primary clinical manifestations of ventricular arrhythmias are palpitations, presyncope, and syncope, and ventricular arrhythmias can cause sudden cardiac death (SCD).[27] The SHaRe study estimated a lifetime cumulative incidence of malignant ventricular

arrhythmias in HCM of 32% (95% confidence interval [CI] 23–40),[25] while in an electronic health records (EHR) study of 1,375 patients with HCM in England, the incidence rate ratio (IRR) for ventricular arrythmia was 23.53 (95% CI 12.67, 43.72) in patients with HCM compared to matched controls.[42] AF is common in patients with HCM across all ages. In the SHaRe study, among patients diagnosed at a young age (< 40 years), the risk of developing AF was 62% (95% CI 56–67) by 60 years of age.[25] The English EHR study estimated an IRR for AF of 3.80 (95% CI 3.04, 4.75) in patients with HCM compared to matched controls.[42] AF is a significant risk factor for stroke.

B.1.3.1.3.3 Mortality burden

Compared with the general population, patients with HCM have an estimated two- to threefold greater risk of mortality. Data from SHaRe indicate that the mortality of the patients with HCM is approximately three times higher than that of the US general population at matched ages[25] while a similar analysis of a European cohort demonstrated patients with HCM have increased mortality across all ages compared with the general population (standardised mortality ratio 2.0, 95% CI: 1.48, 2.63).[26]

B.1.3.1.3.4 Impact of LVOTO on clinical burden

The presence of obstruction has been shown to be an important prognostic factor in patients with HCM. LVOTO is associated with an increased risk of disease progression, long-term cardiac complications and mortality.[4,7,25] LVOTO causes increased LV systolic pressure, which exacerbates the ongoing progression of the other pathophysiological features of HCM i.e. hypertrophy, myocardial stiffening and fibrosis.[4] In turn, these lead to heightened risk of HF, diastolic dysfunction, arrhythmias and mortality. The impact of LVOTO on clinical burden is summarised in Figure 3.

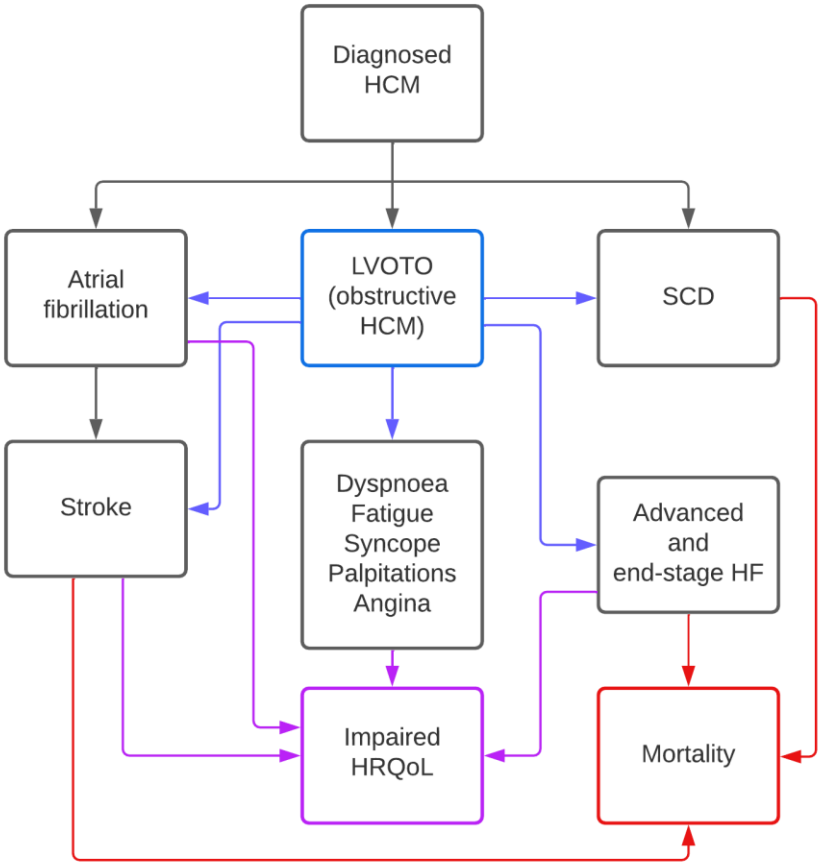


Figure 3. Impact of LVOT obstruction on clinical burden

Patients with HCM are at risk of developing a range of comorbidities and complications, including AF, stroke, HF and SCD. The presence of LVOTO, which characterises obstructive HCM, can cause a range of debilitating, chronic and progressive symptoms that seriously impair HRQoL. LVOTO also increases the risk of disease progression and development of comorbidities such as AF, stroke, HF and SCD.[4,7,25] Note that some aspects of HCM pathophysiology (e.g. ventricular arrhythmias, pulmonary hypertension, diastolic dysfunction) have been omitted for clarity.
HCM: hypertrophic cardiomyopathy; HF: heart failure; HRQoL: health-related quality of life; LVOTO: left ventricular outflow tract obstruction; SCD: sudden cardiac death.

The majority of obstructive HCM patients will experience some symptoms of HF,[11,16] which develops primarily due to the high LV systolic pressures caused by LVOTO.[11] In a cohort of 573 patients with HCM who were in NYHA class I or II at baseline and were followed up for a median of 6.8 years, 10% of patients with non-obstructive disease progressed to NYHA class III/IV compared to 20% of patients with provocable LVOTO and 38% of patients with resting LVOTO.[43] There are limited data specific to arrhythmias in obstructive HCM, however one study reported a higher proportion of AF in patients with obstruction (27%) compared to those without (18%; p <0.01).[4]

The presence of LVOTO in patients with HCM is significantly associated with increased mortality. In a study of 1,101 patients with HCM, LVOTO at rest was independently associated with an increased risk of HCM-related death (relative risk [RR] 1.6, p = 0.02) compared to non-obstructive HCM.[4] In an international meta-analysis in 12,146 patients with HCM, obstruction was a significant prognostic factor for all-cause death (HR 1.56 [95% CI 1.29, 1.90]),[5] while in an English study of 917 adult patients with HCM, five-year survival from all-cause mortality (ACM)/transplantation was lower in the 288 patients with LVOTO compared to patients without, and severe LVOTO (≥ 90 mmHg) was a significant predictor of SCD on multivariate analysis (RR 3.82, 95% CI 1.6–9.2, p = 0.005).[6]

Higher NYHA class is associated with greater risk of mortality in patients with obstructive HCM.[44,45] Using EHR data, an increased risk of ACM was demonstrated in patients with obstructive HCM with higher NYHA class (Figure 4).[44]

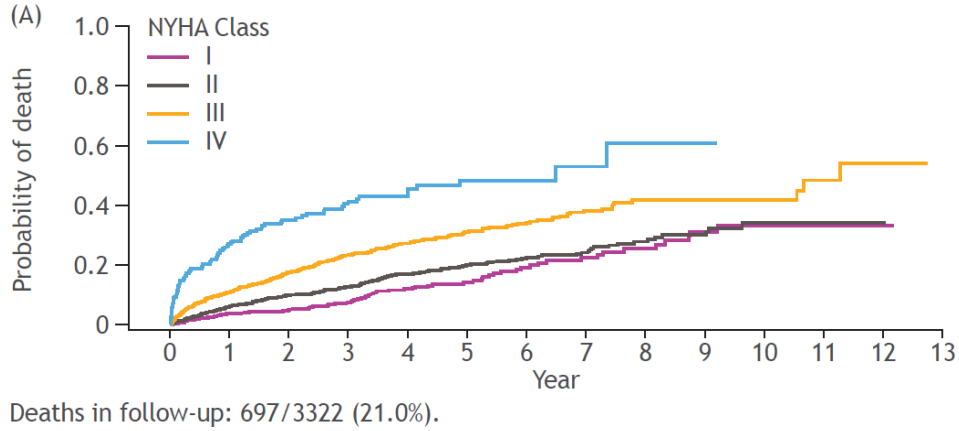


Figure 4. Risk of ACM by NYHA class in obstructive HCM

Figure reproduced from Wang et al 2022.[44] ACM: all-cause mortality; HCM: hypertrophic cardiomyopathy; NYHA: New York Heart Association.

B.1.3.1.4 Epidemiology

The most commonly cited prevalence estimate for HCM is 1 in 500 (0.2%),[1] based on a 1995 cohort study by Maron *et al.* that screened 4,111 people randomly selected from the US general population for unexplained maximum left ventricular wall thickness (MLVWT) ≥ 15 mm,[46] which satisfies the clinical definition of HCM.[2] A recent study of cardiac magnetic resonance (CMR) images from 29,826 UK Biobank participants also evaluated the prevalence of HCM based on MLVWT ≥ 15 mm.[47]

The UK Biobank is a population-based, prospective cohort study that enrolled 500,000 individuals aged 40–69 years. The results of the CMR screening indicate an HCM prevalence of 0.11%.[47] This study is larger, more contemporary and more representative of UK demographics than Maron *et al*., 1995. While imaging evidence for unexplained MLVWT ≥ 15 mm satisfies the clinical definition of HCM, it does not necessarily represent the prevalence of diagnosed HCM in real-world populations, due to the variability in HCM presentation,[2] which means a proportion of people who are mutation carriers and/or have unexplained LV hypertrophy nevertheless do not experience any signs or symptoms of disease.

The proportion of patients with the obstructive form is estimated to be around two thirds of HCM patients. Although studies that assess only resting gradients report obstruction in approximately one third of diagnosed HCM patients,[2,4,6] this is likely to be an underestimate of the number of patients who have LVOTO because it does not account for patients who have provoked gradients. Studies that assess gradients provoked by exercise or Valsalva manoeuvre have reported peak LVOT gradients ≥ 30 mmHg in up to 70% of patients,[7,38] leading to the conclusion that around two thirds of HCM patients have LVOTO at rest or when provoked by exercise.[2,38] Of these, there are few data to indicate the proportion who are symptomatic (i.e. NYHA class II–IV), but estimates range from 50–84%.[10,14,16,48]

HCM can present at any age, including in childhood and adolescence, although there are a range of estimates of the mean±standard deviation (SD) age at diagnosis (48±17 years;[45] 51±16 years;[49] 61.0±14.8 years[44]). It is notable that HCM affects a younger demographic than many other CV diseases – for example, the average age of HF diagnosis is 77.[50] The prevalence of HCM is similar between sexes, although women are less frequently diagnosed than men.[7] The 2014 European Society of Cardiology (ESC) guidelines outline evidence that the prevalence is similar across racial groups.[2] Studies in the US setting indicate that there may be racial disparities in incidence,[51] but the generalisability of these to the UK is unclear.

B.1.3.2 Clinical pathway of care

The indication for this submission is patients with obstructive HCM, therefore the outlined clinical pathway of care focuses on treatments specific to this population.

B.1.3.2.1 Diagnosis and monitoring of obstructive HCM

Diagnosis of HCM in adults is defined by a wall thickness ≥ 15 mm in one or more segments of the LV, that cannot be explained by loading conditions, or wall thickness ≥ 13 mm in first-degree relatives of patients with diagnosed HCM.[2] This is typically ascertained by cardiac imaging, either echocardiography or CMR.[2]

Echocardiography is considered central to the diagnosis and monitoring of HCM, not only for assessment of LV wall thickness, but also for detection and monitoring of LVOTO, which is important for management of symptoms and SCD risk.[2] The diagnostic criteria for obstructive HCM is a peak LVOT pressure gradient ≥ 30 mmHg at rest or during physiological provocation such as Valsalva manoeuvre, standing or exercise.[2] Therefore, 2D and Doppler echocardiography should be performed while the patient performs the Valsalva manoeuvre. If this does not evoke a gradient in a symptomatic patient, an exercise stress echocardiogram is recommended.[2]

Cardiopulmonary exercise testing (CPET) measures respiratory gases during exercise, and assesses the cardiovascular, respiratory and skeletal muscle components of exercise performance, and can thus be used to quantify the impact of obstructive HCM on exercise capacity. It is recommended for use in patients with HCM where available;[2] certain parameters including peak oxygen consumption (pVO_2) have been shown to be prognostic indicators of mortality in HCM.[13]

B.1.3.2.2 Management of obstructive HCM

There are no UK-specific guidelines on management of HCM. Current guidance relevant to the UK includes:

- 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy.[2]
- Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the ESC. 2019.[16]
- 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy.[7]
- National Institute for Health and Care Excellence (NICE): Non-surgical reduction of the myocardial septum [IPG40], 2004.[52]

The NICE scope also includes NG106 (Chronic heart failure in adults: diagnosis and management (2018)[50]) as relevant to the decision problem, however it should be noted that this guideline does not explicitly mention HCM (or subtypes) or HCM-related HF. The majority of the treatment recommendations in NG106 are not relevant to patients with obstructive HCM; the recommended treatments for patients with HF with reduced ejection fraction (EF) are typically not indicated for patients with obstructive HCM, who generally have preserved EF and whose treatment focuses on management of symptoms associated with LVOTO.[2,16]

The HCM guidelines listed above state that the goal of existing treatments for patients with symptomatic, obstructive HCM is to manage the symptoms associated with LVOTO (B.1.3.1.3.1).[2,7] There is no evidence that these therapies alter the natural history of the disease. The recommendations presented by the guidelines for obstructive HCM are empiric, based largely on expert opinion and data from non-randomised studies and retrospective, observational studies leading to 'by consensus' recommendations, as there are few randomised controlled trials (RCTs) specifically evaluating patients with HCM.[2,7,11] In particular, the AHA/ACC 2020 guidelines highlight unmet needs for patients with HCM encompassing the lack of RCT trial data to identify strategies to improve functional capacity, attenuate disease progression and reduce adverse outcomes, noting that the low event rate and slow disease progression represents a challenge requiring novel trial designs and tools to assess meaningful endpoints such as quality of life.[7] Consistent with this, the Committee for Medicinal Products for Human Use (CHMP) has identified HCM as a patient population with high unmet medical need.[53]

The current treatment pathway for patients with obstructive HCM is outlined in Figure 5, which was synthesised from both the recommendations in the ESC 2014 guidelines[2] and has been validated by clinical experts.[19]

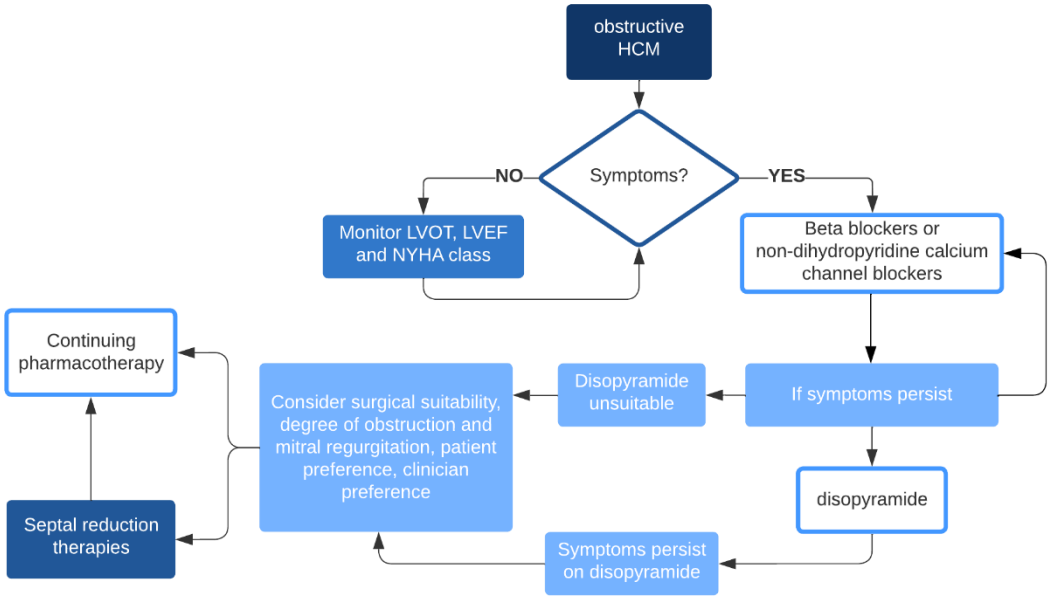


Figure 5. Overview of the management of obstructive HCM

HCM: hypertrophic cardiomyopathy; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; NYHA: New York Heart Association.

B.1.3.2.3 Pharmacological treatments

There are no current pharmacological therapeutic options specifically designed to treat symptomatic, obstructive HCM. Selected pharmacological therapies, described below, are used empirically, highlighting the unmet need for targeted therapies in this indication. In the HCMA Voice of the Patient report, patients noted the challenge of adhering to therapies not originally designed to target HCM, with the report stating that "*A common theme was the lack of HCM-specific medications available to patients for modification of the disease resulting in having to rely upon a wide variety of treatment courses based primarily on symptoms. Patients face medications with side effects that, themselves, cause adverse conditions. HCM-specific pharmaceuticals targeted to the underlying disease pathology and a more wholistic approach to care are needed*" and concluding that *"…most patients are treated as symptoms arise with drugs and devices that were not designed with HCM in mind which can lead to off target effects that compromise quality of life"*.[10]

B.1.3.2.3.1 Beta blockers

Non-vasodilating BB are currently the initial treatment for patients with obstructive HCM,[2,54] however, their benefits are variable and restricted to symptom relief rather than modification of disease progression.[2] The symptomatic relief is thought to be mediated by the negative chronotropic and inotropic effects of BB; reduction or limitation in heart rate improves LV filling and reduced force of contraction (particularly the effect of limiting exercise-induced increases in contractile force) can reduce the LVOT gradient and associated symptoms.[15]

BB have been shown to be effective at reducing exercise-induced LVOTO in some patients. However, there is variation in the response; in a study of 27 patients with HCM and exercise-induced LVOTO, the LVOTO was almost abolished in 52% of patients, substantially reduced in 33% of patients, and unchanged in 15% following 12 ± 4 months of BB treatment.[55] Severe LVOTO persisted in 22% of patients.[55] Consistent with the mechanism of action, BB therapy also tends to be less effective in patients with severe LVOTO at rest,[15] and Maron (2018) notes that "progressively increasing [BB] dosage in patients with rest obstruction is rarely effective in reducing gradient or symptoms".[11]

BB are also associated with side effects such as fatigue, reduced exercise capacity, asthma, depression, decreased atrioventricular (AV) conduction and hypotension[12] which can impact tolerability as well as reducing the likelihood of treatment adherence. The effect of longer-term BB therapy on patients with HCM remains poorly understood, and there is no conclusive evidence on how BB influence the natural history or outcomes of HCM.[11,15,16]

B.1.3.2.3.2 Non-dihydropyridine calcium channel blockers

The non-dihydropyridine CCBs verapamil and diltiazem are recommended as alternatives to BB when BB therapy is contraindicated or ineffective, or patients are intolerant,[2] however, are considered less effective than BB at reducing resting or severe exercise-induced LVOT gradients due to their vasodilating properties.[12,15] The reported benefits are predominantly mediated by their negative inotropic and chronotropic effects, resulting in increased LV filling time and improved blood flow to subendocardial layers of the LV.[15]

Whilst they have demonstrated benefit in symptomatic patients with HCM,[56-58] these therapies should be used with caution in patients with significant LVOTO, elevated pulmonary wedge pressure, and low systemic blood pressure, since a decrease in blood pressure associated with treatment could induce an increase in LVOTO and precipitate pulmonary oedema.[2,54] Similarly to BB, CCB are associated with variable efficacy, side effects and tolerability issues, including ankle oedema, and decreased AV conduction,[12] and there is limited evidence that CCB alter natural history or outcomes; of four small, prospective trials enrolling a total of 55 HCM patients, three indicated that diltiazem improved LV diastolic parameters and one showed beneficial effects on myocardial ischaemia.[15] Note that BB in combination with CCB is not considered standard care in the UK.

B.1.3.2.3.3 Disopyramide

Disopyramide is a class 1A antiarrhythmic therapy (sodium channel blocker). Its benefits in patients with HCM result from its negative inotropic effect on the ventricular myocardium which reduces contractility and attenuates pressure gradients in patients with LVOTO.[12,15] Disopyramide is considered a second-line therapy that may be prescribed in combination with BB therapy or verapamil (a CCB) in patients who remain symptomatic despite BB or CCB.[2,16]

However, disopyramide is associated with parasympathetic side effects, such as dry eyes and mouth, urinary hesitancy or retention, and constipation, as well as QTc prolongation, which are dose-limiting[2,12] and may reduce treatment compliance. Whilst disopyramide efficacy and safety in patients with HCM have been demonstrated in a large multicentre registry study,[59] the therapy can demonstrate tachyphylaxis over the course of several months.[12,15,18] Expert clinical advice indicates that it is therefore rarely used in clinical practice in England and Wales and, furthermore, is currently difficult to obtain, further limiting its use.[19,20] This is supported by an analysis of data from the Clinical Practice Research Datalink (CPRD) Gold database commissioned by the Company, which indicates that only [redacted] patients with a record of obstructive HCM between 2009 and 2020 in the CPRD in England have been prescribed disopyramide subsequent to their diagnosis.

The limitations associated with disopyramide (i.e. side effects, tachyphylaxis, lack of availability) mean that patients whose symptoms are inadequately controlled with first line therapies may nevertheless not progress to disopyramide, but instead remain symptomatic with a significant unmet therapeutic need.

B.1.3.2.4 Non-pharmacological septal reduction therapies

Non-pharmacological therapies for obstructive HCM involve invasive techniques to reduce the septal hypertrophy and thus relieve the LVOTO. The two approaches used are septal myectomy and alcohol septal ablation (ASA), which are collectively referred to as septal reduction therapies (SRT). SRT is indicated for the treatment of drug-refractory symptoms and is commonly reserved for patients with moderate-to-severe symptoms (NYHA class III–IV).[2]

Septal myectomy is a surgical procedure that involves removing a portion of muscle from the ventricular septum, and permits revision of other anatomical abnormalities e.g., of the mitral valve or papillary muscles, if required. ASA involves injection of alcohol into a septal branch of the left anterior descending coronary artery to create a localised infarct in the ventricular septum, replacing the hypertrophied tissue with a thinner scar. ASA provides an alternative to myectomy for patients who are not suitable surgical candidates e.g. due to age, comorbidities, as it does not require sternotomy; however, it does require suitable anatomy,[2,7,22] and clinical advice indicates that a minority of patients are eligible.[60]

When performed in experienced, specialised centres, SRT can be effective in reducing obstruction, improving LV outflow and reducing symptoms; myectomy is reported to abolish or significantly reduce LVOT gradient in > 90% of cases and ASA has similar outcomes,[22] resulting in improved exercise capacity and a reduction in symptoms.[2] However, there is a range of peri- and post-procedural complications associated with each approach, including surgical mortality, AV block, ventricular septal defect and aortic regurgitation.[2,22] A large proportion of myectomy patients develop left bundle branch block (38.8% in 2,159 patients from one cohort study),[61] while ASA is associated with a ~10% risk of AV block resulting in the requirement for a permanent pacemaker.[22] SRT may also form a risk factor for developing LV systolic dysfunction.[62] Although reported rates of mortality are ~1–3%,[2,22] most data

come from large, specialised centres, therefore may not be representative of results from less experienced clinics; for example, early mortality has been reported to be 3.8% in high volume centres and 15.6% in low volume centres.[63] A recent systematic review and meta-analysis reported long-term ACM (8.72 vs. 7.84%, p = 0.42), short-term ACM (1.12 vs. 1.27%, p = 0.93), cardiovascular (CV) mortality (2.48 vs. 3.66%, p = 0.26), SCD (1.78 vs. 0.76%, p = 0.20) and stroke (0.36 vs. 1.01%, p = 0.64) associated with surgical myectomy versus ASA, respectively.[24]

It should also be noted that as SRT does not address the underlying myocardial disease, residual or recurrent obstruction may occur[23] and underlying diastolic dysfunction with associated symptoms may also remain. ASA, in particular, is associated with a requirement for reintervention.[22] The meta-analysis described above found that ASA was associated with a higher rate of reinterventions than myectomy (10.1 vs. 0.27%, p < 0.001),[24] while other studies have reported reintervention rates of 7–20%.[22] In an advisory board on SRT, experts indicated that ~20% SRT procedures require repeat procedures or additional interventions, typically with symptoms returning or worsening to the point that additional pharmacologic or intervention is required around 4–6 months after the original procedure.[60]

Due to the lack of randomised, comparative evidence, recommendations around SRT are based on expert consensus, with shared decision-making taking into account individual patient circumstances and preferences encouraged. Clinical advice is that myectomy is favoured over ASA, particularly for younger patients, and that over half of SRT-eligible patients typically undergo the intervention, indicating that a substantial proportion of eligible patients choose not to. An audit by the British Cardiovascular Intervention Society recorded 59 ASA procedures performed in the UK in 2019–20.[64] Overall, despite the efficacy of the procedures, SRTs are only performed in a small proportion of patients, due to a combination of contraindications, patient preference, and variation in clinical practice between centres; due to the risks associated with both procedures, SRTs should only be performed in experienced centres,[2] which limits their availability to some patients.

B.1.3.2.5 Parallel treatment pathways

Note that in addition to the assessment and treatment of LVOTO and associated symptoms, ESC 2014 guidelines state that all patients with HCM should be evaluated for other complications and risk factors and treated accordingly.[2] These include atrial tachyarrhythmias, particularly AF, and risk of SCD, which may be managed with an ICD.[2] Although LVOTO affects the risk of developing these complications, these are considered parallel treatment pathways and are not relevant to the decision problem.

B.1.3.2.6 Summary of current pathway of care

Currently available pharmacological treatment options offer limited and variable relief in symptoms for patients with obstructive HCM, especially in patients with more advanced disease. Pharmacologic management with agents developed for other indications (i.e. BB, CCB) lacks randomised, prospective trials in the obstructive HCM population to inform on the benefit-risk and long-term tolerability of these agents when used for patients with obstructive HCM. Furthermore, because no currently approved treatments target the underlying pathophysiology of the disease, there are no options available to slow, halt or reverse disease progression. Interventional procedures i.e. SRT can offer good efficacy for patients with obstructive HCM, however are associated with risk of complications, mortality and potential need for reintervention, which, along with cost and availability considerations, limit their use in clinical practice.

Thus, there is considerable unmet need for a safe and effective pharmacological therapy for the treatment of symptomatic, obstructive HCM, that targets the underlying pathophysiology in order to improve cardiac function and relieve the substantial symptom burden, freeing patients from the limitations on daily physical activities, emotional impact, mental health burden, impact on work and productivity and lifestyle modifications required to control symptoms, that impair patient quality of life throughout the patient's lifetime.[10,14,40]

B.1.3.3 Role of mavacamten in therapy

The technology being appraised in this submission is mavacamten for the treatment of symptomatic obstructive HCM. Mavacamten is a first in class, oral, allosteric

modulator of cardiac myosin which reduces hypercontractility, a key part of the pathogenesis of HCM.[65] Due to the gradual nature of pathological progression, there may be a window of opportunity to implement disease-modifying therapies that can prevent or delay cardiac remodelling as well as slow or halt disease progression.[7,25]

B.1.3.3.1 Mechanism of action of mavacamten

Mavacamten is an oral, small molecule modulator of cardiac myosin.[66] Myosin together with actin comprise the main proteins within the sarcomere (Figure 6). HCM-associated mutations in genes encoding sarcomere proteins result in excess force generation by the sarcomere, resulting in hypercontractility of the cardiac muscle (Figure 6),[33,36] which leads to hypertrophy and the cascade of pathophysiological consequences outlined in sections B.1.3.1.2 and B.1.3.1.3. Mavacamten targets this pathophysiological process by binding to and inhibiting cardiac myosin (an ATPase).[36,67] It stabilises the off-actin state of myosin by reversibly inhibiting the binding of myosin to actin. This leads to a reduction in sarcomere force production and therefore reduced hypercontractility (Figure 6), without impeding the ability of myosin to detach from actin – a vital step required for diastolic relaxation. The reversibility of mavacamten means that decreases in left ventricular ejection fraction (LVEF) as a result of myosin inhibition are reversible upon drug washout (see B.2.6.1.4).

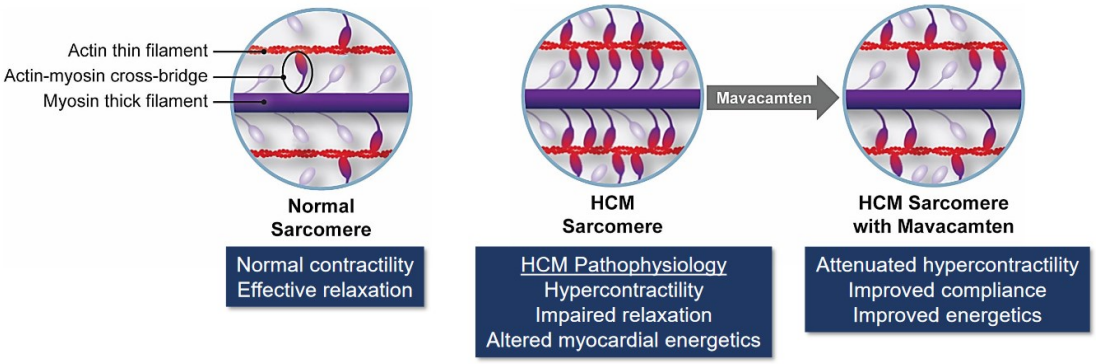


Figure 6. Mavacamten mechanism of action

Figure reproduced from Ho et al., 2020[33] HCM: hypertrophic cardiomyopathy

Mavacamten has specificity for the β-cardiac myosin isoform and is inactive in skeletal muscle and smooth muscle.[67] Mavacamten normalises the function of

myosin in hypercontractile cardiac muscle, regardless of the presence or absence of gene mutation.[66] This reduction in cardiac contractility appears to reduce hypertrophy and consequently ameliorates dynamic LVOTO in patients with obstructive HCM.[3,68]

B.1.3.3.2 Place of mavacamten in treatment of symptomatic obstructive HCM

Although the first descriptions of obstructive HCM were published more than 60 years ago,[8] there are no current pharmacological therapeutic options specifically indicated for symptomatic, obstructive HCM, and there is no evidence that existing therapies alter the disease course (B.1.3.2). Currently, selected pharmacological therapies are used 'off-label' on an empirical basis, and have variable effectiveness and a range of side effects (B.1.3.2).[2,11,12] SRT can be effective, but is associated with a range of complications and is generally only considered for patients with moderate to severe symptoms that cannot be managed medically. SRT is not commonly performed, due to contraindications, patient preference and requirement for specialist centres.[2,22] Furthermore, SRT is associated with a ~1% risk of short-term mortality,[24] and ASA, in particular, has reintervention rates of 7–20%.[22]

Consequently, many patients find their symptoms are not adequately managed by current standard medical care.[10] This highlights the unmet need for a targeted, effective therapy in this patient population that relieves symptoms and improves function to positively impact quality of life and prevent disease progression. Mavacamten used in combination with standard care provides functional and symptomatic improvement to patients whose symptoms are inadequately controlled by BB or CCB.

Mavacamten is an innovative, first-in-class, oral therapy designed to target the hypercontractility underlying HCM pathology in order to improve cardiac function and reduce symptoms. The highly innovative nature of mavacamten has been recognised with the award of a PIM designation by the Medicines and Healthcare products Regulatory Agency (MHRA). This indicates that mavacamten is a promising candidate treatment fulfilling the following criteria:

1a. the condition should be life-threatening or seriously debilitating

1b. the condition should have high unmet need (no method of treatment, diagnosis of prevention available or existing methods have serious limitations)

2. the medicinal product is likely to offer major advantage over methods currently used in the UK

3. the potential adverse effects of the medicinal product are likely to be outweighed by the benefits, allowing for the reasonable expectation of a positive benefit risk balance.[21]

Mavacamten is the first targeted therapy that has demonstrated efficacy and safety in a large, placebo-controlled RCT for obstructive HCM. Mavacamten has been shown to significantly reduce symptoms and improve function and quality of life in patients with symptomatic, obstructive HCM.[3,14]

B.1.4 Equality considerations

No equality issues have been identified or are anticipated.

B.2 Clinical effectiveness

Summary of clinical evidence

Key evidence

Evidence for the efficacy and safety of mavacamten in combination with standard care compared to individually optimised standard care alone was primarily derived from the pivotal RCT, EXPLORER-HCM[3], with support from the EXPLORER-LTE cohort of the MAVA-LTE long-term extension study.[9]

- The EXPLORER-HCM trial met its primary endpoint, with mavacamten demonstrating clinically meaningful improvements in NYHA class (symptoms) and functional capacity (peak oxygen consumption [pVO_2])[3]
- Treatment with mavacamten was associated with meaningful clinical and statistical improvements in all secondary endpoints compared to placebo, where:[3]
    - 34% more patients improved ≥ 1 NYHA class than patients allocated to placebo
    - exercise capacity measured by pVO_2 was increased; a measure which is prognostic for mortality in obstructive HCM[13]
    - post-exercise LVOT gradient was reduced
    - Quality of life improved, as shown by patient-reported outcomes
- Mavacamten demonstrated sustained benefits and efficacy in pre-specified subgroups[3]
- Mavacamten was generally well-tolerated, with a safety profile similar to placebo[3]
- Interim data from the EXPLORER-LTE cohort were consistent with those observed in the EXPLORER-HCM parent study, indicating that these benefits appear to be sustained through the first year of treatment and beyond.

Other supporting evidence

- In addition, two RWE studies, an expert elicitation study and advisory boards are used as supporting evidence for the burden of disease:
    - Mortality in patients with obstructive HCM from EHR data
    - Mortality in patients with obstructive HCM from the SHaRe registry
    - Structured expert elicitation study
    - UK and global clinical and health economic advisory boards

B.2.1 Identification and selection of relevant studies

B.2.1.1 Systematic literature review

A systematic literature review (SLR) was conducted to identify efficacy and safety data regarding the treatment of obstructive HCM. Full details of the methods employed to identify and select the relevant clinical evidence are summarised in Appendix D. In brief, Embase®, MEDLINE® (In-Process) (via ProQuest), the Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews were searched from database inception to 2 August 2021, with an updated search performed on 3 December 2021. Relevant conferences were also searched for abstracts between 2019 and 2021 (see Appendix D for details).

In total, the SLR identified 197 publications reporting on 191 studies describing treatments for obstructive HCM, of which 21 investigated pharmacological treatments, with 15 of those evaluating mavacamten and/or relevant comparators i.e. BB/CCB. Of the 15 publications evaluating relevant pharmacological treatments, seven provided randomised evidence:

- Six publications reported on one RCT evaluating the effectiveness of mavacamten in symptomatic obstructive HCM, EXPLORER-HCM.[3,69-73]

- One publication, Masini et al (1981), described a randomised crossover study evaluating the efficacy of pindolol (a BB) and verapamil (a CCB).[74] As this did not provide direct comparative evidence with mavacamten, and as direct evidence comparing mavacamten with both BB and CCB is available from the large, high quality, pivotal phase III EXPLORER-HCM trial, EXPLORER-HCM was considered the most appropriate source of evidence and data from Masini et al was not considered relevant.

The remaining eight publications evaluating pharmacological treatments were non-randomised studies, of which four evaluated mavacamten (the PIONEER-HCM and PIONEER-OLE studies).[75-78]

B.2.2 List of relevant clinical effectiveness evidence

B.2.2.1 List of relevant clinical trial evidence

Two relevant studies providing information on the clinical benefits of mavacamten in combination with standard care and individually optimised standard care alone in patients with symptomatic (NYHA class II or III) obstructive HCM were identified in the SLR:

1. Evidence is primarily derived from the pivotal EXPLORER-HCM (MYK-461-005; NCT03470545) trial, a phase III, double-blind, randomised study of mavacamten versus placebo in addition to individually optimised standard care (Table 4).[3,68-70,73,79-81] EXPLORER-HCM included a CMR imaging substudy[68] (Appendix M).

2. Longer-term supporting evidence is also presented from MAVA-LTE (MYK-461-007; NCT03723655), a long-term safety extension study of mavacamten in adults with HCM who have completed MAVERICK-HCM or EXPLORER-HCM (Table 4).[9,73] Data from patients with non-obstructive HCM (i.e. those from MAVERICK-HCM) are not relevant to this indication. Therefore, the subsequent sections present data from the EXPLORER-LTE cohort of MAVA-LTE i.e. only those patients who had previously been enrolled in EXPLORER-HCM. Henceforth, this is referred to as the EXPLORER-LTE cohort. The data presented from the EXPLORER-LTE cohort in B.2 are from the interim analysis based on the most recent database lock (DBL; August 2021);[9] note that the publication on this DBL was not identified in the SLR because it was published after 3 December 2021. Additional clinical data from an earlier DBL (October 2020) are included in Appendix M for completeness.[72]

The SLR also identified publications describing PIONEER-HCM and PIONEER-OLE. PIONEER-HCM was a phase II open-label study[75] and therefore was not considered to represent the best available evidence, given that data are available from the pivotal phase III EXPLORER-HCM study.[3] Therefore, PIONEER-HCM[75] and the associated long-term extension (LTE) study, PIONEER-OLE,[77] are not described further in the main submission; a summary, along with an overview of the full mavacamten clinical trial programme, can be found in Appendix M.

Table 4. Clinical trial effectiveness evidence

Study	EXPLORER-HCM[3,68,70,79,80]		MAVA-LTE[9,82]	
Study design	A phase III, double-blind, randomised, placebo-controlled, multicentre, international, parallel-group study to evaluate the safety, tolerability, and efficacy of mavacamten once-daily compared with placebo over 30 weeks		A phase II/III open-label, single arm, long-term safety extension study as a follow-on from both EXPLORER-HCM and MAVERICK-HCM	
Population	• Patients with symptomatic (NYHA class II–III) obstructive HCM		• Patients entering from the parent study EXPLORER-HCM had symptomatic (NYHA class II–III) obstructive HCM, at the time of enrolment into EXPLORER-HCM • Patients entering from the parent study MAVERICK-HCM had symptomatic, non-obstructive HCM, NYHA class II–III at the time of enrolment into MAVERICK-HCM [note that data from these patients are not used to support this submission and will not be covered in sections B.2.3–B.2.10]	
Intervention(s)	Mavacamten		Mavacamten	
Comparator(s)	Placebo		NA (single-arm study)	
Indicate if trial supports application for marketing authorisation	Yes	✓	Yes	✓
	No		No	
Indicate if trial used in the economic model	Yes	✓	Yes	✓
	No		No	
Rationale if study not used in the model	NA		NA	
Reported outcomes specified in the decision problem (**bold** indicates outcomes incorporated into the model)	• response rates • exercise capacity • oxygen consumption • **patient-reported symptom severity** • **change in NYHA class** • change in LVEF • **adverse effects of treatment** • **health-related quality of life**		• **patient-reported symptom severity** • **change in NYHA class** • change in LVEF • **adverse effects of treatment**	
All other reported outcomes	• Post-exercise LVOT peak gradient • Echocardiographic indices of cardiac structure, systolic and diastolic function		• LVOT gradients (resting and Valsalva) • Echocardiographic indices of cardiac structure, systolic and diastolic function	

Study	EXPLORER-HCM[3,68,70,79,80]	MAVA-LTE[9,82]
	• NT-proBNP • hs-cTnI • Cardiac rhythm patterns • Daily step count and other accelerometer parameters • Change in HCM risk prediction model • Pharmacokinetics • CMR measurements (LVMI, LGE, cellular hypertrophy, LA volume and function, LV function)	• NT-proBNP • Pharmacokinetics

CMR: cardiac magnetic resonance; HCM: hypertrophic cardiomyopathy; hs-cTnI: high sensitivity cardiac troponin I; LA: left atrium; LGE: late gadolinium enhancement; LTE: long-term extension; LV: left ventricular; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; LVOT: left ventricular outflow tract; NA: not applicable; NT-proBNP: *N*-terminal pro–B-type natriuretic peptide; NYHA: New York Heart Association.

B.2.2.2 List of relevant evidence from real-world studies and expert opinion

The updated NICE user guide (January 2022) requests details on additional and supporting evidence, including expert elicitation, expert opinion, real-world evidence (RWE) or natural history data used to support any severity assumptions. Although supporting evidence was not used for severity assumptions in this submission, a summary of the RWE and expert elicitation evidence commissioned for and used in this submission is provided here for completeness:

1. An RWE EHR study has been undertaken to derive the association between NYHA class and outcomes including mortality in patients with obstructive HCM. The results of this study were published by Wang *et al.,* 2022.[44]

2. An RWE registry study has been undertaken to provide additional supporting evidence for the association between NYHA class and ACM, in patients with obstructive HCM, using SHaRe registry data. The results of this study were published by Lakdawala *et al*., 2021;[45] details of additional analyses are in Appendix N.

3. Four advisory boards have been conducted:

    i. Worldwide HCM clinical experts and health economics experts (July 2021). The purpose was to discuss the evidence base, positioning and modelling approach.[83]
    ii. UK HCM clinical experts and UK health economics experts (September 2021). The purpose was to align the Company's initial approach for this submission with clinical and health economic opinion, to discuss how clinical data could be best represented in the economic modelling and to discuss the appropriateness of the proposed model framework.[19]
    iii. Worldwide HCM specialists (December 2021). The purpose was to understand their experience of SRT.[60]
    iv. UK HCM clinical experts (March 2022). The purpose was to obtain insight on and validation of clinical assumptions used in the cost-effectiveness model (CEM).[20]

4. An expert elicitation study has been conducted to gain clinical feedback on HCM epidemiology and typical healthcare resource use in the UK. Full methodology and results are reported in Appendix O.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

Comparative summaries of the trial design and methodology for EXPLORER-HCM and the EXPLORER-LTE cohort are presented in Table 5 and detailed below. For additional details of the methodology, please see the trial protocols.[84,85]

Table 5. Comparative summary of trial methodology: EXPLORER-HCM and the EXPLORER-LTE cohort

Trial acronym	EXPLORER-HCM[3,85]	EXPLORER-LTE cohort[82,86]
Trial design	A phase III, double-blind, randomised, placebo-controlled, multicentre, international, parallel-group study to evaluate the safety, tolerability, and efficacy of mavacamten once-daily compared with placebo over 30 weeks.	A phase II/III open-label, single-arm, long-term safety extension study; EXPLORER-LTE cohort enrolled from EXPLORER-HCM

Eligibility criteria for participants	**Key inclusion criteria:**
	• Adults aged at least 18 years
	• Body weight ≥ 45 kg
	• Diagnosed with obstructive HCM, satisfying both the following criteria:
	  o Unexplained LV hypertrophy with LV wall thickness ≥ 15 mm at time of initial diagnosis or ≥ 13 mm with a positive family history of HCM
	  o LVOT peak gradient ≥ 50 mmHg at rest, after Valsalva manoeuvre or post-exercise
	• LVEF ≥ 55% at rest
	• LVOT gradient with Valsalva manoeuvre ≥ 30 mmHg
	• Resting oxygen saturation ≥ 90%
	• Adequate acoustic windows to enable accurate TTE
	• NYHA class II or III
	• Able to perform upright CPET and has RER ≥ 1.0
	Key exclusion criteria:
	• History of syncope or sustained ventricular tachyarrhythmia with exercise within 6 months prior to screening
	• QTcF > 500 ms
	• AF at screening
	• Underwent SRT within 6 months prior to screening or planned SRT during the study
	• Current or planned treatment with disopyramide, ranolazine, or a combination of beta-blockers and verapamil or diltiazem
	• ICD placement within 2 months before screening or planned ICD placement during the study
		Key inclusion criteria:
		• Has completed the Parent Study, EXPLORER-HCM
		• Adults aged at least 18 years
		• Body weight ≥ 45 kg
		• LVEF ≥ 50% at rest
		• Adequate acoustic windows to enable accurate TTEs.
		• Safety laboratory parameters (chemistry, haematology, coagulation, and urinalysis) within normal limits
		Key exclusion criteria:
		• History of syncope or sustained ventricular tachyarrhythmia with exercise between the EXPLORER-HCM end of study (EOS) visit and the MAVA-LTE screening visit
		• Current or planned treatment with disopyramide, ranolazine, or a combination of BB and verapamil or diltiazem
		• Persistent or permanent AF not on anticoagulation for ≥ 4 weeks prior and/or not adequately rate-controlled

Settings and locations where the data were collected	90 clinical sites worldwide, including in Belgium, Czech Republic, Denmark, France, Germany, Israel, Italy, Netherlands, Poland, Portugal, Spain, **UK**, USA	Belgium, Czech Republic, Denmark, France, Germany, Israel, Italy, Netherlands, Poland, Portugal, Spain, **UK**, USA

Trial acronym	EXPLORER-HCM[3,85]	EXPLORER-LTE cohort[82,86]
Intervention	Mavacamten: one 2.5, 5, 10, or 15 mg capsule, once daily, by oral administration	Mavacamten: one 2.5, 5, 10 or 15 mg capsule, once daily, by oral administration
Comparator	Placebo to match mavacamten capsule, once daily, by oral administration	NA
Permitted and disallowed concomitant medications	Background cardiomyopathy therapy (BB or non-dihydropyridine CCB [verapamil or diltiazem]) was allowed. Participants were on optimal medical therapy as determined by the investigator and informed by HCM treatment guidelines. Dual therapy with BB and CCB (verapamil or diltiazem) was not permitted. Disopyramide and ranolazine were disallowed as concomitant medications.	Background cardiomyopathy therapy (BB or non-dihydropyridine CCB [verapamil or diltiazem]) was allowed. Participants were on optimal medical therapy as determined by the investigator and informed by HCM treatment guidelines. Dual therapy with BB and CCB (verapamil or diltiazem) was not permitted. Prior or concomitant treatment with cardiotoxic agents such as doxorubicin or similar was prohibited. Use of disopyramide or ranolazine was prohibited from 14 days before screening to the EOS.
Primary outcome	The primary efficacy endpoint was clinical response at Week 30, defined as achieving one of the following: • An improvement of ≥ 1.5 mL/kg/min in pVO_2 as determined by CPET and a reduction of ≥ 1 NYHA class, or • An improvement of ≥ 3.0 mL/kg/min in pVO_2 with no worsening in NYHA class	The primary objective is to assess the long-term safety and tolerability of mavacamten in patients with obstructive HCM previously enrolled in EXPLORER-HCM. Safety assessments included medical history, physical examinations, electrocardiograms (ECGs), vital signs, adverse events and safety laboratory results.
Other outcomes used in the economic model/specified in the scope	• response rates • exercise capacity • oxygen consumption • patient-reported symptom severity • change in NYHA class • change in left ventricular ejection fraction • adverse effects of treatment • health-related quality of life	• patient-reported symptom severity • change in NYHA class • change in left ventricular ejection fraction • health-related quality of life
Pre-planned subgroups	Selected efficacy endpoints were analysed for subgroups of patients with the following characteristics at baseline: • BB use (yes vs no) • Type of ergometer (treadmill vs exercise bicycle) • NYHA class (II vs III)	

Trial acronym	EXPLORER-HCM[3,85]	EXPLORER-LTE cohort[82,86]
	• Consent for CMR substudy (yes vs no) • Sex (male vs female) • Age in years (≤ 49 vs 50–64 vs ≥ 65 years) • BMI (< 30 vs ≥ 30) • Race (white vs not white) • Region (US vs ex-US) • Presence of HCM pathogenic mutation (pathogenic/likely pathogenic vs variant of uncertain significance [VUS] vs negative]) • Time from obstructive HCM diagnosis (≤ 5 years vs > 5 years) • Calcium channel blocker use (yes vs no) • SRT history (yes vs no) • Implanted ICD (yes vs no) • History of hypertension (yes vs no) • Resting LVEF (< 75% vs ≥ 75%) • Resting LVOT peak gradient (≤ 50 mmHg vs > 50 mmHg) • Resting LVOT peak gradient (≤ 30 mmHg vs > 30 mmHg) • Left atrial volume index (≤ 39 mL/m2 vs > 39 mL/m2) • E/e'(lateral, septal, average) (≤ 14 vs > 14) • E/e'(lateral, septal, average) >14 or cTnI > ULN vs others • NT-proBNP (≤ 710 ng/L vs > 710 ng/L) • hs-cTnI (< 15.6 ng/L vs > 15.6 ng/L for females and < 34.2 ng/L vs > 34.2 ng/L for males) • Creatinine clearance (< 60 mL/min vs ≥ 60 mL/min)	

BB: beta blockers; BMI: body mass index; CCB: calcium channel blocker; CMR: cardiac magnetic resonance; CPET: cardiopulmonary exercise testing; cTnI: cardiac troponin I; ECG: electrocardiogram; HCM: hypertrophic cardiomyopathy; hs-cTnI: high sensitivity cardiac troponin I; LA: left atrium; LGE: late gadolinium enhancement; LV: left ventricular; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; LVOT: left ventricular outflow tract; NA: not applicable; NT-proBNP: N-terminal pro–B-type natriuretic peptide; NYHA: New York Heart Association; pVO_2: peak oxygen consumption; RER: respiratory exchange ratio; SRT: septal reduction therapies; TTE: transthoracic echocardiogram; ULN: upper limit of normal.

B.2.3.1 Trial design and methodology

B.2.3.1.1 EXPLORER-HCM study design

EXPLORER-HCM (NCT03470545) is a phase III, double-blind, randomised, parallel-group trial conducted between May 30, 2018 and July 12, 2019. EXPLORER-HCM was developed to evaluate the safety and efficacy of mavacamten compared with placebo in participants with symptomatic (NYHA class II–III) obstructive HCM.[3,33,85] The study design is outlined in Figure 7 and a summary of the design and methodology presented in Table 5. The study comprised three periods:

1. Screening period (day -35 to day 1), during which patients were assessed against the eligibility criteria;
2. Double-blind treatment period (day 1 [randomisation] to week 30/end of treatment [EOT]), which included 10 scheduled clinic visits;
3. Post-treatment follow-up period (week 30/EOT to week 38/end of study [EOS]), which included a telephone appointment at week 38 and clinic visit at week 38. This post-treatment follow-up period applied only to participants who were receiving study drug after week 22.[3,33,85] Patients remained blinded to their treatment allocation during the follow-up period.

Eligible patients were randomised via an interactive response technology (IXRS) in a ratio of 1:1 to receive either once daily mavacamten or placebo for 30 weeks. Randomisation was double-blinded and stratified by NYHA functional classification (mavacamten: [redacted] ([redacted]%) class II, [redacted] ([redacted]%) class III; placebo: [redacted] ([redacted]%) class II, [redacted] ([redacted]%) class III), current treatment with BB (mavacamten: [redacted] ([redacted]%); placebo: [redacted] ([redacted]%)), planned type of ergometer used during the study (mavacamten: [redacted] ([redacted]%) treadmill, [redacted] ([redacted]%) exercise bicycle; placebo: [redacted] ([redacted]%) treadmill, [redacted] ([redacted]%) exercise bicycle), and consent for the CMR substudy (mavacamten: [redacted] ([redacted]%); placebo: [redacted] ([redacted]%)).[3,33,85]

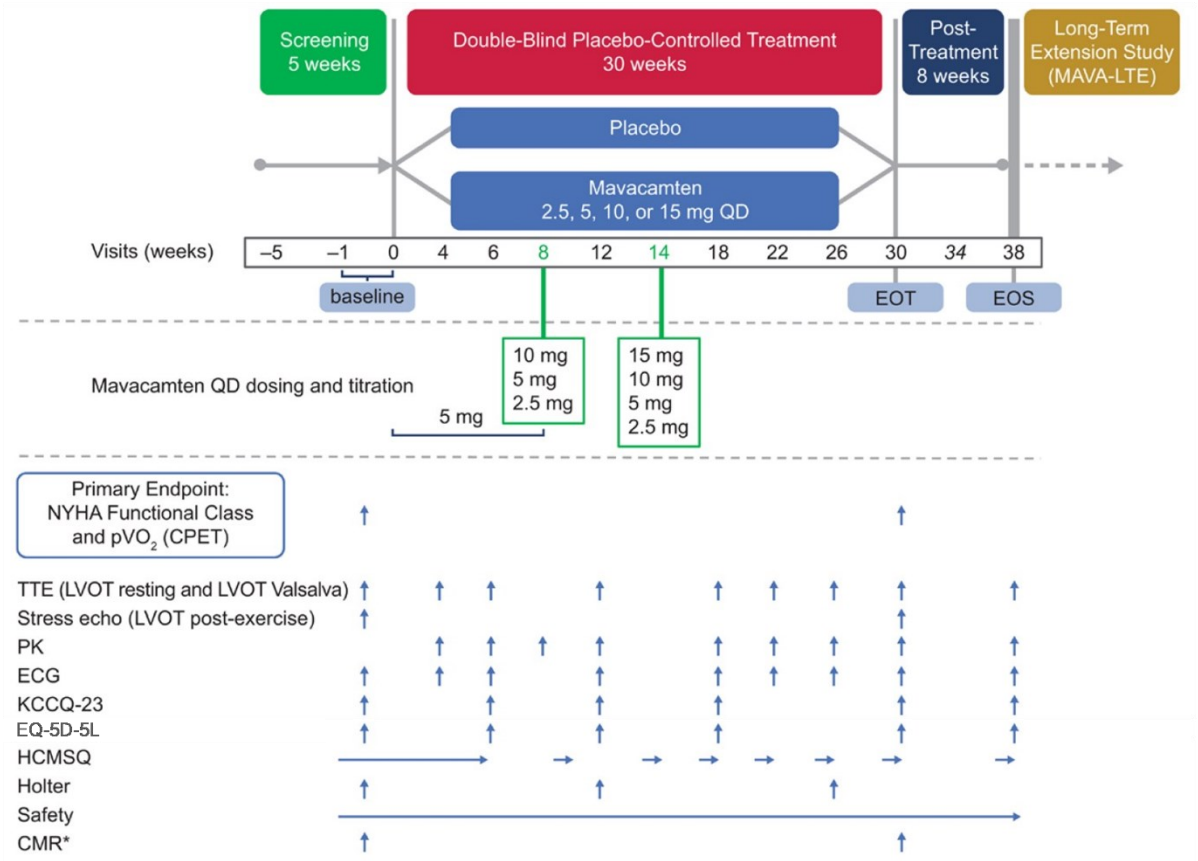


Figure 7. EXPLORER-HCM study schematic

Adapted from Ho et al, 2020[33] *CMR: cardiac magnetic resonance; CPET: cardiopulmonary exercise testing; ECG: electrocardiogram; EOT: end of treatment; EOS: end of study;HCMSQ: hypertrophic cardiomyopathy symptoms questionnaire; KCCQ-23: Kansas City Cardiomyopathy Questionnaire; LVOT: left ventricular outflow tract; NYHA: New York Heart Association; PK: pharmacokinetics; pVO_2: peak oxygen consumption; QD: once daily; TTE: transthoracic echocardiography.

During the study, transthoracic echocardiography (TTE) to evaluate resting and Valsalva LVOT gradient, electrocardiograms (ECGs), safety assessments, pharmacokinetic (PK)/pharmacodynamic (PD) assessment and patient reported outcomes (PRO) were conducted every 2–6 weeks, while CPET and post-exercise TTE were done at screening and EOT.[3,33,85] The starting dose of mavacamten was 5 mg once daily. At weeks 8 and 14, patients were evaluated for dose adjustments to achieve a LVOT gradient < 30 mm Hg and a mavacamten plasma concentration between 350 ng/mL and 700 ng/mL. After week 14 no further up-titrations were permitted, but down-titrations were permitted at week 6 and after week 14 if PK/PD criteria were met. Possible doses were 2.5, 5, 10, or 15 mg, once daily. The pre-specified criteria for treatment interruption or discontinuation of study drug included resting LVEF < 50%, QTcF (QT interval with Fridericia correction) prolongation or

mavacamten plasma trough concentration ≥ 1,000 ng/mL.[3,33,85] EXPLORER-HCM endpoints are provided in Table 6.

Table 6. Study endpoints in EXPLORER-HCM

EXPLORER-HCM trial outcomes	
Primary endpoint	Composite functional response at week 30, defined as achieving: 1. An improvement of ≥ 1.5 mL/kg/min in pVO_2 as determined by CPET and a reduction of ≥ 1 NYHA class **or** 2. An improvement of ≥ 3.0 mL/kg/min in pVO_2 with no worsening in NYHA class.
Secondary endpoints	• Change from baseline to week 30 in postexercise LVOT peak gradient • Change from baseline to week 30 in pVO_2 determined by CPET • Proportion of patients who had at least 1 class of improvement from baseline in NYHA class at week 30 • Change from baseline to week 30 in patient-reported health status as assessed by the KCCQ-23 CSS • Change from baseline to week 30 in patient-reported severity of HCM symptoms as assessed by the HCMSQ SoB domain score Other secondary endpoints included: • Safety and tolerability endpoints • PK characteristics of mavacamten
Exploratory endpoints	Prespecified exploratory efficacy endpoints included change from baseline to week 30 in: • Proportion of patients with a complete response (all LVOT gradients < 30 mmHg and NYHA class I status) • Proportion of patients with improvement in LVOT gradients (< 30 mmHg; < 50 mmHg) • Proportion of patients with absence of SAM at week 30 of those who had SAM at baseline • Proportion of patients with absence of mitral regurgitation at week 30 of those who had mitral regurgitation at baseline • Multiple TTE parameters: LVEF, resting and Valsalva LVOT gradients, LVESVI, LVEDVI, LVSV, heart rate, cardiac output, e' lateral, e' septal, E/e' later, E/e' septal, LAVI, LV wall thickness, LVMI. • Serum concentrations of cardiac biomarkers (NT-proBNP, hs-cTnI) • Additional PROs: EQ-5D-5L, WPAI:SHP, PGIC, PGIS • Cardiac rhythm patterns • Accelerometer parameters, including daily step count • HCM risk prediction model

CPET: cardiopulmonary exercise testing; CSR: clinical study report; HCM: hypertrophic cardiomyopathy; HCMSQ SoB: hypertrophic cardiomyopathy symptoms questionnaire – shortness of breath; hs-cTnI: high sensitivity cardiac troponin I; KCCQ-23 CSS: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LAVI: left atrial volume index; LV: left ventricle/ventricular; LVEF: left ventricular ejection fraction; LVEDVI: left ventricular end-diastolic volume index; LVESVI: left ventricular end-systolic volume index; LVMI: left ventricular mass index; LVOT: left ventricular outflow tract; LVSV: left ventricular stroke volume; NT-proBNP: N-terminal pro B-type natriuretic peptide; NYHA: New York Heart Association; PGIC: Patients Global Impression of Change; PGIS: Patients Global Impression of Severity; PK: pharmacokinetic; PRO: patient-reported outcome; pVO_2: peak oxygen consumption; SAM: systolic anterior motion; TTE: transthoracic echocardiogram; WPAI:SHP: Work Productivity and Activity Impairment Specific Health Problem Questionnaire.
Source: EXPLORER-HCM CSR[80]

B.2.3.1.1.1 Justification of trial endpoint design and selection

The primary endpoint in EXPLORER-HCM was a composite endpoint assessing the effect of treatment on both function and feel, by incorporating a physiological measure of exercise capacity (pVO_2; see section B.1.3.2.1) and a physician-assessed component (NYHA class; see section B.1.3.1.3.1). This novel composite endpoint was designed based on consultation with HCM experts, patients and regulatory authorities to provide a comprehensive assessment of relevant treatment benefits for patients with obstructive HCM.

Reduced functional capacity with exercise limitation is common in patients with HCM.[87-89] Changes in functional capacity can be monitored using CPET, which is a direct, objective and reproducible measure of exercise capacity and thus, physiological functional status.[87] CPET allows for the analysis of respiratory gas exchange at rest, during exercise and during recovery.[88] Improvements in these measures, specifically peak oxygen consumption (pVO_2), have been shown to correlate with improvements in quality of life, as well as predicting both short- and long-term clinical outcomes (e.g. mortality [all-cause and CV], heart transplant, and a composite of death, heart transplant and functional deterioration leading to hospitalisation for SRT) in obstructive HCM[13,88] and an improvement in $pVO_2 \geq 1$ mL/kg/min is considered clinically meaningful.[13] The CHMP guideline on clinical investigation of medicinal products for the treatment of chronic HF states that exercise capacity may be considered as a primary endpoint in patient populations with high unmet medical need, including HCM.[53]

In current clinical practice, many patients with obstructive HCM remain symptomatic despite standard care (i.e. BB/CCB), but will not progress to advanced therapies (i.e. disopyramide, SRT) due to contraindications, lack of access or patient choice not to undergo invasive techniques with associated morbidity and mortality risks (see B.1.3.2.2). Therefore, another relevant measurement of mavacamten efficacy is change in symptoms. NYHA classification is the established standard assessment tool used in both research studies and in routine clinical practice[2,7,19] for classifying the functional status of patients with cardiovascular disease, particularly HF, but also cardiomyopathies, including HCM. For an individual patient, a reduction in NYHA class of one or more represents a clinically meaningful improvement in health status.

As well as being widely used and understood in clinical practice, an increase in NYHA class is associated with adverse outcomes in HCM[5,7,45] and has been shown to predict HRQoL as assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ).[90]

The components of the composite primary endpoint are evaluated as individual secondary endpoints. The other physiological secondary endpoint was change in postexercise LVOT gradient, which is an objective measure of the level of LVOTO, a key pathophysiological feature of obstructive HCM that is prognostic for disease progression and mortality.[4,5,7] The secondary endpoints also include PROs; the Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-23 CSS) and the HCM Symptom Questionnaire-Shortness-of-Breath (HCMSQ-SoB) subscore. The KCCQ is a valid, reliable and responsive PRO instrument[91] that has been validated for use in patients with symptomatic obstructive HCM.[92] The KCCQ-23 clinical summary score represents a combination of the total symptom score and physical limitation domains, providing a patient-reported parallel to the physician-assessed NYHA class.[70] KCCQ has been used to evaluate HRQoL in patients with HCM,[90] and correlations between KCCQ scores and NYHA class, and KCCQ score and pVO_2, have been demonstrated in patients with HCM.[93] The HCM Symptom Questionnaire (HCMSQ) is a novel, HCM-specific PRO tool developed to assess the key symptoms of HCM; dyspnoea, fatigue, palpitations, chest pain, dizziness.[85]

PRO data were also collected using the generic EQ-5D instrument as an exploratory endpoint. These data are presented here and used in the economic model in line with the NICE reference case. However, it is anticipated that certain aspects of the patient experience with obstructive HCM will not be fully captured by a generic PRO questionnaire; for example, symptoms are often labile, varying day-to-day or even hour-by-hour, and may be provoked by e.g. consumption of a large meal, or alcohol.[2] Therefore, the EQ-5D data are supplemented by data from the KCCQ and HCMSQ instruments described above, which have greater disease specificity.

B.2.3.1.2 EXPLORER-LTE cohort study design

The MAVA-LTE study is an ongoing dose-blinded, five-year safety extension study that was developed to evaluate the long-term safety and tolerability of mavacamten,

including in the EXPLORER-LTE cohort of patients who had completed EXPLORER-HCM (NCT03723655).[84] The study design is outlined in Figure 8 and a summary of the design and methodology presented in Table 5.

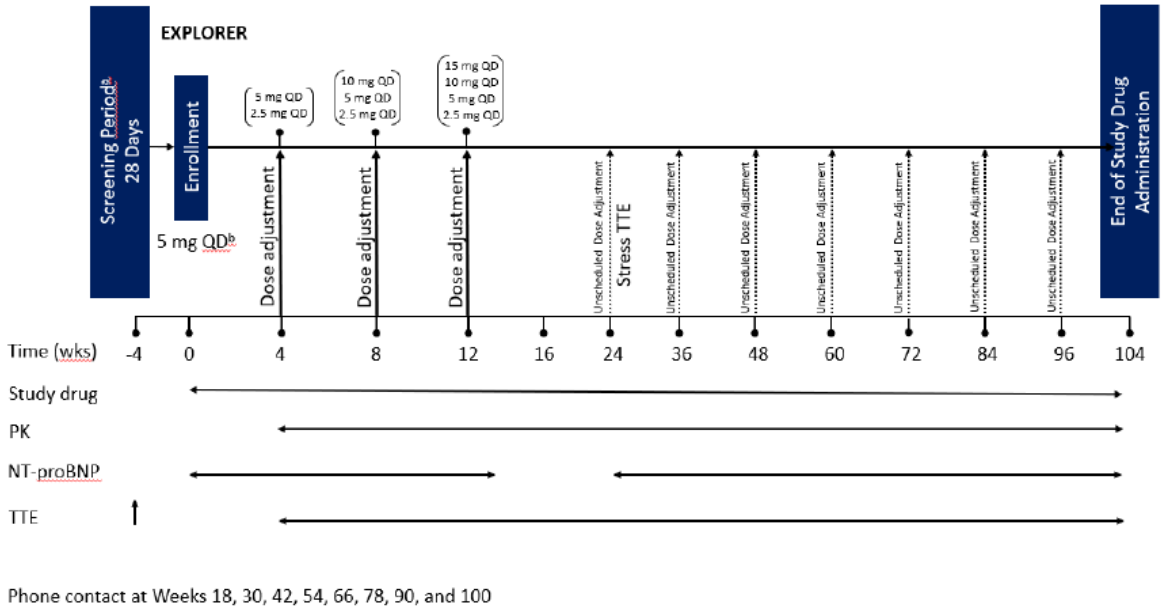


Figure 8. Study design of the EXPLORER-LTE cohort

Figure reproduced from MAVA-LTE Interim CSR October 2020 DBL (Figure 1)[82]
[a] Assessments from EXPLORER-HCM Week 38 (EOS) Visit may have served as Screening assessments, if the patient began Screening into Study MYK-461-007 within 28 days of the Week 38 Visit.
[b] Patients received mavacamten immediate-release capsules at a starting dose of 5 mg QD unless otherwise noted in Protocol Amendment 2.
CSR: clinical study report; NT-proBNP: N-terminal pro B-type natriuretic peptide; PK: pharmacokinetics; QD: once daily; TTE: transthoracic echocardiogram (resting and with Valsalva manoeuvre).

Patients could enter the EXPLORER-LTE cohort from either the mavacamten or placebo arm of the parent EXPLORER-HCM trial. Prior to enrolment in the LTE, all patients underwent an 8-week post-treatment wash-out period in the parent study plus a variable time lapse to day 1 of the LTE. All patients in the EXPLORER-LTE cohort initiated mavacamten treatment at 5 mg once daily irrespective of prior treatment in the parent study, unless at EXPLORER-HCM EOT the patient had a dose of 5 mg and mavacamten plasma concentration ≥ 700 ng/mL, in which case the starting dose in the LTE was 2.5 mg mavacamten, with scheduled dose adjustments in weeks 4, 8 and 12 as required, based on LVEF and Valsalva LVOT gradient assessed by echocardiography. Unscheduled dose adjustments following study visits from week 24 onwards are permitted, based on post-exercise LVOT gradient.

Temporary discontinuation criteria included LVEF < 50%, increased QTcF > 15% and mavacamten plasma trough concentration ≥ 1,000 ng/mL.[82,84]

The primary objective of MAVA-LTE, including for the EXPLORER-LTE cohort, is the evaluation of long-term safety. Secondary efficacy and pharmacodynamic endpoints are frequency of cardiac transplantation and change from baseline in: echocardiographic parameters of systolic and diastolic function; resting and Valsalva LVOT gradients; NYHA class; N-terminal pro–B-type natriuretic peptide (NT-proBNP). Additional exploratory endpoints include cardiac structural and functional parameters evaluated by CMR, PROs, PK/PD analysis, accelerometery and high sensitivity cardiac troponin I (hs-cTnI).[82,84]

B.2.3.2 Study populations

In EXPLORER-HCM, a total of 429 potential patients were screened and 251 patients were randomised (123 patients in mavacamten group, 128 patients in placebo group), forming the intention to treat (ITT) population. All 251 randomised patients received at least one dose of study drug and were also included in the safety population (Table 7).[80] Full details of patient disposition can be found in the clinical study report (CSR).[80]

Table 7. EXPLORER-HCM study populations

	Mavacamten	Placebo
ITT population[a]	123 (100)	128 (100)
Safety population[b]	[redacted]	[redacted]
PK population[c]	[redacted]	[redacted]
CMR substudy population[d]	[redacted]	[redacted]

[a] The ITT population is defined as all randomised patients regardless of whether they receive study drug or not. Patients are analysed by randomised treatment assignment.
[b] The safety population is defined as all randomised patients who received at least 1 dose of study drug (mavacamten or placebo). Patients are analysed by actual treatment received.
[c] The PK population is defined as all randomised patients who receive at least 1 dose of mavacamten and have at least 1 detectable mavacamten plasma concentration.
[d] The CMR substudy population is defined as all patients who consent to participate in the CMR substudy and have CMR scans available at both day 1 and week 30. Patients are analysed by randomised treatment assignment.
Source: EXPLORER-HCM CSR[80]
CMR: cardiac magnetic resonance; CSR: clinical study report; ITT: intention to treat; PK: pharmacokinetic.

As of the data cut-off for the interim analysis (August 2021), 231 patients were enrolled from EXPLORER-HCM into the EXPLORER-LTE cohort, with 217 remaining on treatment at the time of the DBL. The mean time from the end of the EXPLORER-HCM study to LTE day 1 was 66.5 days (range: 3–359 days).[9]

Disaggregated patient disposition data for the August 2021 DBL were not available at the time of submission; disaggregated patient disposition data for the October 2020 DBL can be found in Appendix M.

B.2.3.3 Baseline characteristics

In EXPLORER-HCM, the mean age of patients was 58.5 years (range: 18–82 years), the majority of patients were white (91.2%) and male (59.4%).[3] There were some small differences in baseline characteristics typical of an RCT, but none are considered clinically meaningful or likely to influence the outcomes of the trial. The majority of patients had NYHA class II symptoms (73%) and were taking a BB or CCB (92%). Eleven (9%) patients in the mavacamten arm and eight (6%) patients in the placebo arm had prior SRT. Baseline measures of heart rate, systolic and diastolic blood pressure, pVO_2 and echocardiographic parameters were similar between the two arms.[3,80]

In the EXPLORER-LTE cohort, at the interim data analysis cut-off (31 August 2021), the baseline mean patient age was 60.0 years and 39.4% were female (Table 8). 94% patients had NYHA class II or III symptoms at baseline and 92% were on either BB or CCB as background therapy.[9]

Table 8. Baseline characteristics of patients in EXPLORER-HCM and the EXPLORER-LTE cohort

Characteristic	EXPLORER-HCM[3,80]		EXPLORER-LTE cohort (N = 231)[9]
	Mavacamten (N = 123)	Placebo (N = 128)	
Age, mean years (SD)	58.5 (12.2)	58.5 (11.8)	60.0 (11.9)
Female sex, n (%)	57 (46)	45 (35)	91 (39.4)
Race, n (%)			
White	115 (93)	114 (89)	NR**
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)	
Region, n (%)			
USA	53 (43)	55 (43)	NR**
Spain	17 (14)	16 (13)	
Poland	16 (13)	16 (13)	
Other	37 (30)*	41 (32)*	
Ex-USA sites	-	-	
NYHA			
Class I	-	-	14 (6.1)
Class II	88 (72)	95 (74)	152 (65.8)
Class III	35 (28)	33 (26)	65 (28.1)
Medical history, n (%)			NR††
Family history of HCM	33 (27)	36 (28)	
AF	12 (10)	23 (18)	
SRT	11 (9)	8 (6)	
Hypertension	57 (46)	53 (41)	
Hyperlipidaemia	27 (22)	39 (30)	
Coronary artery disease	12 (10)	6 (5)	
Obesity	15 (12)	14 (11)	
Type 2 diabetes	6 (5)	7 (6)	
Asthma	17 (14)	11 (9)	
Chronic obstructive pulmonary disease	2 (2)	3 (2)	
pVO_2, mL/kg/min, mean (SD)	18.9 (4.9)	19.9 (4.9)	NR††
NT-proBNP, ng/L, geometric mean (CV%)	777 (136)*	616 (108)*	NR**
NT-proBNP, ng/L, median (IQR)	NR	NR	783 (326, 1593) [n = 230]

Characteristic	EXPLORER-HCM[3,80]		EXPLORER-LTE cohort (N = 231)[9]
	Mavacamten (N = 123)	Placebo (N = 128)	
Background therapy, n (%)			
BB	94 (76)	95 (74)	175 (75.8)
CCB	25 (20)	17 (13)	38 (16.5)
Neither BB nor CCB	4 (3.3)	16 (12.5)	NR
Implantable cardioverter-defibrillator, n (%)	27 (22%)	29 (23%)	NR††
HCM genetic testing performed, n (%)	90 (73)	100 (78)	NR††
Pathogenic/likely pathogenic HCM gene variant, n/N tested (%)	28/90 (31)	22/100 (22)	
BMI, kg/m^2, mean (SD)	29.7 (4.9)	29.2 (5.6)	NR**
Heart rate, beats per minute, mean (SD)	63 (10.1)	62 (10.6)	NR**
Systolic blood pressure, mmHg, mean (SD)	128 (16.2)	128 (14.6)	NR††
Diastolic blood pressure, mmHg, mean (SD)	75 (10.8)	76 (9.9)	NR††
pVO_2, mL/kg/minute, mean (SD)	18.9 (4.9)	19.9 (4.9)	NR††
High-sensitivity cardiac troponin I, geometric mean, ng/L (COV%)	12.5 (208)‡	12.5 (373)‡	NR††
Echocardiographic parameters			
LVEF, %	74 (6)	74 (6)	74.0 (5.9) [n = 230]
Maximum LV wall thickness, mm	20 (4)	20 (3)	NR††
LVOT gradient, rest, mmHg	52 (29)	51 (32)	48.3 (31.9)
LVOT gradient, Valsalva, mmHg	72 (32)	74 (32)	69.5 (33.3) [n = 228]
LVOT gradient, post-exercise, mmHg	86 (34)§	84 (36)§	NR††
Left atrial volume index, mL/m^2	40 (12)¶	41 (14)¶	NR††
Left atrial diameter, mm	42 (5)‖	42 (6)‖	NR††

*Other comprised Israel, Germany, France, Czech Republic, Denmark, Netherlands, Portugal, Italy, Belgium, and the UK (ordered by number of patients).
†Data missing for three patients in the mavacamten group and two patients in the placebo group. The variation number (COV%) is the coefficient of variation, which is defined as the ratio of the SD to the mean.
‡Data missing for three patients in the mavacamten group and nine patients in the placebo group.
§Data missing for one patient in the mavacamten group and one patient in the placebo group.
¶Data missing for one patient in the mavacamten group.
‖Data missing for five patients in each group.
**Reported for October 2020 DBL; see Appendix M
††Baseline characteristics not currently available for the EXPLORER-LTE cohort.[72,82]
AF: atrial fibrillation; BMI: body mass index; CCB: calcium channel blocker; COV: coefficient of variation; HCM: hypertrophic cardiomyopathy; IQR: interquartile range; LV: left ventricular; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; NR: not reported; NT-proBNP: N-terminal pro B-type natriuretic peptide; NYHA: New York Heart Association; pVO_2: peak oxygen consumption; SD: standard deviation; SRT: septal reduction therapies.

B.2.3.4 Expert elicitation

As outlined in section B.2.2.2, due to the relative paucity of published evidence identified in the SLRs, an expert elicitation exercise was conducted to gain clinical feedback on HCM epidemiology and typical healthcare resource use in the UK. Details of the methodology can be found in Appendix O. In addition, four advisory boards were held.[19,20,60,83]

B.2.3.5 Real-world evidence studies

In order to address evidence gaps highlighted by both the clinical and economic SLRs, two RWE studies were conducted, as outlined in section B.2.2.2. Methods and results of the SHaRe analysis can be found in Appendix N and Lakdawala *et al*, 2021,[45] and methods and results of the EHR study are published by Wang *et al.* 2022.[44]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

A summary of the statistical methodology for EXPLORER-HCM is provided in Table 9 and for the EXPLORER-LTE cohort in Table 10 and further details can be found in the SAPs.[94,95 96]

Table 9. Statistical analysis summary for EXPLORER-HCM

	EXPLORER-HCM[80,94]
Analysis populations	Six analysis populations were defined in this study: • ITT Population: all randomised participants regardless of whether they received study drug, with analyses conducted according to the randomised treatment assignment • Per Protocol Population: all randomised participants who reached week 30 visit and completed all efficacy assessments, with analyses conducted by actual treatment received • Safety Analysis Population: all randomised participants who received at least 1 dose of study drug, with analyses conducted by actual treatment received • PK Analysis Population: all randomised participants who received at least 1 dose of study drug and had at least 1 evaluable mavacamten plasma drug concentration • PK/PD Analysis Population: all randomised participants who received at least 1 dose of study drug, had at least 1 evaluable mavacamten plasma drug concentration, and had post-baseline PD data; at least one 1 post-baseline PD data point must coincide temporally with an evaluable mavacamten plasma drug concentration • CMR Substudy Population: all participants who consented to participate in the CMR substudy
General considerations	Descriptive summary statistics for continuous variables included the number of participants, mean, SD or SE, median, minimum, and maximum. Nominal categorical variables were summarised using counts and percentages. Ordinal variables may be analysed as continuous variables as if they were continuously scaled.
Statistical analysis of primary endpoint	The estimates of treatment group differences and the 95% CIs based on normal approximation were provided. The CMH test for categorical data was used to test the statistical significance of the association between composite functional endpoint (responder vs nonresponder) and treatment group (mavacamten vs placebo). Unstratified analysis using a Chi-square test was performed as a sensitivity analysis.
Statistical analysis of key secondary endpoints	Five secondary endpoints were defined and were tested sequentially in the order given in Table 6. All continuous variables were summarised by descriptive statistics at baseline and postbaseline time points and changes from baseline to postbaseline time points. Between-group comparisons were based on analysis of covariance or a mixed-model for repeated measures for continuous variables and based on CMH tests for categorical data. Contingent upon significance in the primary endpoint, each of the secondary efficacy endpoints were tested sequentially. All statistical tests were conducted at a 2-sided significance level of 0.05.
Statistical analysis of safety endpoints	All randomised patients who received at least one dose of study drug were included in the Safety Population. Safety data were summarised by treatment group and included all data collected from the first dose of study drug up to the date of the last dose of study drug plus 56 days (i.e., 8 weeks) (i.e., treatment emergent). In some cases, safety data are also presented for the treatment period (day 1 to week 30) allowing for comparison of rates between the mavacamten and placebo groups. Pre-treatment AEs (i.e., those with onset from the time of providing informed consent up to the first dose of study drug) were also collected. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0.

Statistical analysis of exploratory endpoints	Exploratory endpoints were summarised by treatment group and visit. Estimates of between-group mean differences and differences in response rates and 95% CIs based on normal approximation were provided. Plasma concentrations of mavacamten were summarised by treatment group, and the relationships between changes from baseline in postexercise LVOT gradient, LVEF, pVO_2, and NT-proBNP versus mavacamten plasma concentration were evaluated.
Sample size and power calculation	Approximately 220 participants were planned to be randomised, with 110 participants in each of the two groups. Randomisation was stratified for NYHA functional classification (II or III), current treatment with BB (yes/no), type of ergometer (treadmill or exercise bicycle), and consent for the CMR substudy (yes or no). The sample size was calculated to provide adequate power to determine the superiority of mavacamten in improving pVO_2 and NYHA functional class relative to placebo. The sample size was estimated to provide 96% power to detect a 25% difference between treatment groups for the primary endpoint. The proposed sample size of 110 participants per arm provided 96% power at two-sided 5% statistical significance level.
Patient withdrawals	Participants who terminated early or could not be assessed for the clinical response at the end of 30-week dosing period were considered as non-responders.

AE: adverse event; CI: confidence interval; CMH: Cochran-Mantel-Haenszel; CMR: cardiac magnetic resonance; ITT: intention to treat; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; NT-proBNP: N-terminal pro-B type natriuretic peptide; NYHA: New York Heart Association; PD: pharmacodynamic; PK: pharmacokinetic; pVO_2: peak oxygen consumption; SD: standard deviation; SE: standard error.

Table 10. Statistical analysis summary for the EXPLORER-LTE cohort

	EXPLORER-LTE cohort[82,95]
Analysis populations	The analysis populations defined for this interim analysis were: • ITT Population: all randomised participants regardless of whether they received study drug, with analyses conducted according to the randomised treatment assignment • Safety Analysis Population: all randomised participants who received at least 1 dose of study drug, with analyses conducted by actual treatment received • PK Analysis Population: all randomised participants who received at least 1 dose of study drug and had at least 1 evaluable mavacamten plasma drug concentration
General considerations	The primary analysis for this interim analysis was conducted using data collected from 27 September 2018 through 30 October 2020, by which time the study sponsor was unblinded to treatment assignment in the parent study and dose adjustments in the current study. Data collected through 30 October 2020 were cleaned and locked prior to analysis. Continuous variables were summarised by number of patients (N), mean, SD, median, minimum, and maximum, and categorical variables were summarised by counts and percentages. Unless otherwise stated, denominators for percentages were the number of patients in the analysis population with non-missing variable of interest for the column of interest. Body surface area was derived using the Du Bois method (Dubois and Dubois 1916).

	Statistical tests were conducted at a 2-sided significance level of 0.05, unless otherwise noted. All confidence intervals were constructed based on the normal approximation unless otherwise noted.
Statistical analysis of primary objective (safety)	All safety analyses were performed using the Safety Analysis Population data set with the following common rules applied: • The baseline value was defined generally as the last available value before the first administration of study drug, excluding ECG measurements, which were determined at day 1 in the EXPLORER-LTE cohort • The analysis of the safety variables was descriptive, and no hypothesis testing was planned or conducted.
Statistical analysis of other endpoints	All efficacy and PD analyses were performed on the ITT Analysis Population data set. Analyses for echocardiographic indices of cardiac structure as well as systolic and diastolic ventricular function and NYHA functional class were specified in the SAP. Descriptive statistics for each echocardiography parameter were provided by timepoint and change from baseline, including the 95% CIs. Echocardiographic parameters were analysed, as appropriate, using a MMRM to evaluate the change from baseline for select timepoints of interest. The model included time as a fixed effect and subject as a random effect. Baseline value of the endpoint of interest, timepoint (as a categorical variable), and the interaction between treatment and time point were included. “Subject” was treated as a random effect, and a compound symmetric variance covariance component was used. All post-baseline data through the observation period are included unless otherwise specified. Comparisons to baseline were based on the least squared mean difference obtained from the MMRM and are presented with associated 2-sided 95% CI. Statistical significance of the difference versus baseline was evaluated at the 2-sided 0.05 level. Mean (±SD) over time, line plots for select resting echocardiography parameters are provided. Plasma concentrations of mavacamten were determined and summarized using descriptive statistics. Select PK/PD analysis were generated as exploratory analyses using the PK Population data set.
Sample size and power calculation	Since the general analytical approach for this LTE study was observational and descriptive, no formal sample size calculation was performed. Up to 250 participants with obstructive HCM who completed EXPLORER-HCM were to be enrolled in this study.

CI: confidence interval; ECG: electrocardiogram; HCM: hypertrophic cardiomyopathy; ITT: intention to treat; LTE: long-term extension; MMRM: mixed-effect model with repeated measures; NYHA: New York Heart Association; PD: pharmacodynamic; PK: pharmacokinetic; SAP: statistical analysis plan; SD: standard deviation.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of the pivotal EXPLORER-HCM trial was conducted using the University of York, Centre for Reviews and Dissemination (2008) checklist (Table 11).

Table 11. Quality assessment checklist for EXPLORER-HCM

Study questions	EXPLORER-HCM Grade (yes/no/not clear/NA)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in dropouts between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination[97]).
ITT: intention-to-treat; NA: not applicable.

Quality assessment of the EXPLORER-LTE cohort in the long term extension safety study was conducted using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool. No confounding of the effect of intervention was expected in this study, therefore the risk of bias due to confounding was determined to be low.

The complete quality assessments are available in Appendix D. It should be noted that the quality assessment of EXPLORER-HCM, which was conducted as part of a global SLR, concluded that the groups were not similar at the outset in terms of prognostic factors. Although there were some small differences in baseline characteristics between the two arms (section B.2.3.3), none of these differences are considered clinically significant and are not likely to have prognostic implications over the 30-week duration of the trial. Therefore, it is likely that the outcomes measured in the trial are robust to these differences and the quality of the trial can be considered appropriate to inform decision making.

The EXPLORER-HCM trial and the LTE can be considered to closely reflect routine clinical practice in England. Details on this and other aspects of the generalisability of the trial can be found in section B.2.12.4.

B.2.6 Clinical effectiveness results of the relevant studies

Evidence for the clinical efficacy of mavacamten is derived primarily from EXPLORER-HCM, a phase III, placebo-controlled RCT,[3] supplemented by interim data from the August 2021 DBL of the EXPLORER-LTE cohort.[9]

B.2.6.1 EXPLORER-HCM: efficacy results

All efficacy analyses were based on the ITT population unless otherwise noted. The EXPLORER-HCM trial met its primary endpoint, with mavacamten demonstrating clinically meaningful improvements in NYHA class and exercise capacity (pVO_2). This is supported by the consistency of mavacamten's sustained benefits and efficacy in pre-specified subgroups. Clinically meaningful and statistically significant improvements were also observed across all secondary endpoints.

B.2.6.1.1 Primary efficacy endpoint

A greater proportion of patients in the mavacamten group compared with the placebo group achieved the primary endpoint (37% vs 17%, respectively; p = 0.0005; Figure 9 and Table 12). While only 8% of placebo patients had a ≥ 3.0 mL/kg/min increase in pVO_2 and ≥ 1 NYHA class improvement, 20% of mavacamten-treated patients had both. This combination represents the most stringent components of the composite primary functional endpoint, therefore the results indicate that patients receiving mavacamten obtained significant and clinically meaningful benefits in measures of symptoms and function (B.2.3.1.1.1).[3,80]

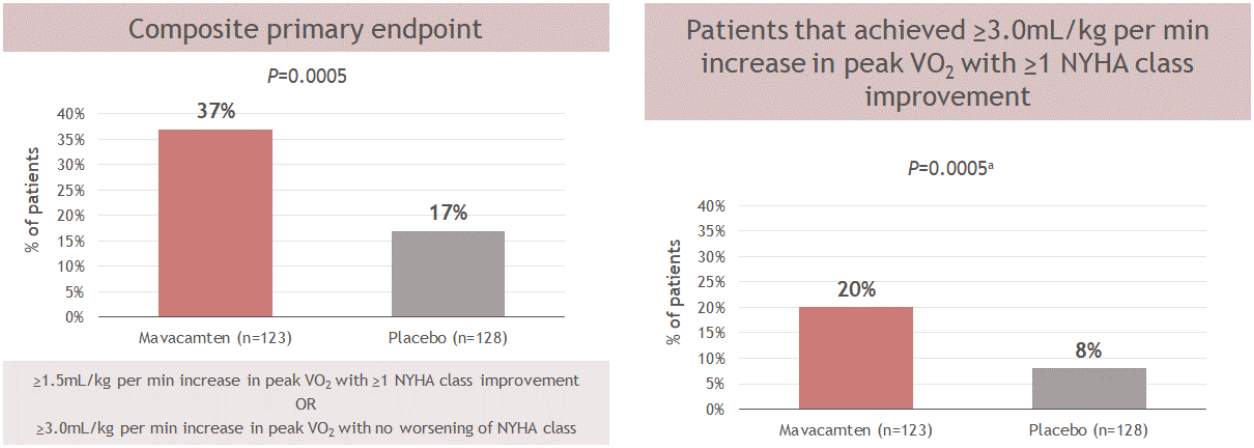


Figure 9. Proportion of patients achieving the composite primary endpoint in EXPLORER-HCM

[a]p value not alpha-controlled. CI: confidence interval; NYHA: New York Heart Association; pVO_2: peak oxygen consumption.

The between group difference for patients who achieved the composite functional endpoint was statistically significant based on both the primary analysis that considered baseline stratification factors (odds ratio [OR] [redacted] [95% CI [redacted], [redacted]], p = 0.0005) and the unstratified sensitivity analysis (OR [redacted] [95% CI [redacted], [redacted]], p = 0.0005).[3,80]

Table 12. EXPLORER-HCM composite primary functional endpoint at week 30

	Mavacamten (N = 123)	Placebo (N = 128)	Mavacamten vs placebo (95% CI)[a]
Primary endpoint			
Either ≥1.5 mL/kg per min increase in pVO_2 with ≥1 NYHA class improvement or ≥3.0 mL/kg per min increase in pVO_2 with no worsening of NYHA class,[b] n (%)	45 (37)	22 (17)	19.4 (8.7, 30.1)
Components of composite primary endpoint			
≥1.5 mL/kg per min increase in pVO_2 with ≥1 NYHA class improvement[b]	41 (33)	18 (14)	19.3 (9.0, 29.6)
≥3.0 mL/kg per min increase in pVO_2 with no worsening of NYHA class[b]	29 (24)	14 (11)	12.6 (3.4, 21.9)
Both ≥3 mL/kg/min in pVO_2 and an improvement of ≥1 NYHA class[e]	25 (20)	10 (8)	12.5 (4.0, 21.0)

[a] The 95% CIs of the response differences between mavacamten and placebo groups are based on normal approximation.
[b] Missing NYHA class at Week 30 was imputed using available NYHA class at Week 26. After the imputation, the subjects whose response status at Week 30 was still missing were classified as nonresponders.
[c] The analysis was stratified on NYHA class, BB use, and exercise type (based on IXRS). Odds ratio was estimated using Cochran-Mantel-Haenszel method. Odds ratio > 1 indicates better outcome when comparing to placebo. P-value and 95% CI were derived using the exact method.
[d] Unstratified analysis is performed as sensitivity analysis. P value and 95% CI is derived from Pearson's Chi-square test.
[e] These are the most stringent pVO_2 and NYHA class components of the composite functional endpoint.

CI: confidence interval; IXRS: interactive response system; NYHA: New York Heart Association; pVO_2: peak oxygen consumption.

B.2.6.1.2 Secondary efficacy endpoints: physician-assessed outcomes

Mavacamten-treated patients demonstrated statistically significant improvements for all physician-assessed secondary outcomes. A significant reduction in post-exercise LVOT peak gradient ($p < 0.0001$) (Figure 10), improvement in pVO_2 ($p = 0.0006$) and increased proportion with improvement of ≥ 1 NYHA class ($p < 0.0001$ for stratified and unstratified analyses) was seen from baseline to week 30 compared with placebo (Table 13).[3,80] This indicates that mavacamten improves exercise capacity and reduces dynamic LVOTO, and provides further evidence for a meaningful symptomatic and functional benefit. Baseline values for each of the evaluated parameters were similar for the mavacamten and placebo groups.

Table 13. Changes from baseline to week 30 in physician-assessed secondary endpoints

Change from baseline to week 30 in:	Mavacamten mean (SD)[a]	Placebo mean (SD)[a]	Mavacamten vs placebo (95% CI)[b]	p value
LVOT peak gradient, mmHg	-47 (40)	-10 (30)	-35.6 (-43.2, -28.1)[c]	< 0.0001
pVO_2, mL/kg/min	1.4 (3.1)	-0.1 (3.0)	1.4 (0.6, 2.1)	0.0006[b]
Improved by ≥ 1 NYHA class from baseline to week 30[d], n (%)	80 (65)	40 (31)	34 (22, 45)	< 0.0001

[a] The number analysable (n) for secondary endpoints based on availability of baseline and Week 30 data was as follows. LVOT peak gradient (n/N): mavacamten 117/123, placebo 122/128. pVO_2 (n/N): mavacamten 120/123, placebo 125/128.
[b] 95% CIs of response differences between the mavacamten and placebo groups based on normal approximation
[c] Mean difference estimate, 95% CIs and p values are from the ANCOVA which controls for treatment group, baseline value of the endpoint of interest and the 3 stratification factors (BB use, NYHA class, ergometer type based on IXRS).
[d] Missing NYHA class at Week 30 was imputed using available NYHA at Week 26. After imputation, patients whose response status at Week 30 was still missing were classified as nonresponders.
CI: confidence intervals; subscore; IXRS: interactive response system; LVOT: left ventricular outflow tract; NYHA: New York Heart Association; pVO_2: peak oxygen consumption; SD: standard deviation

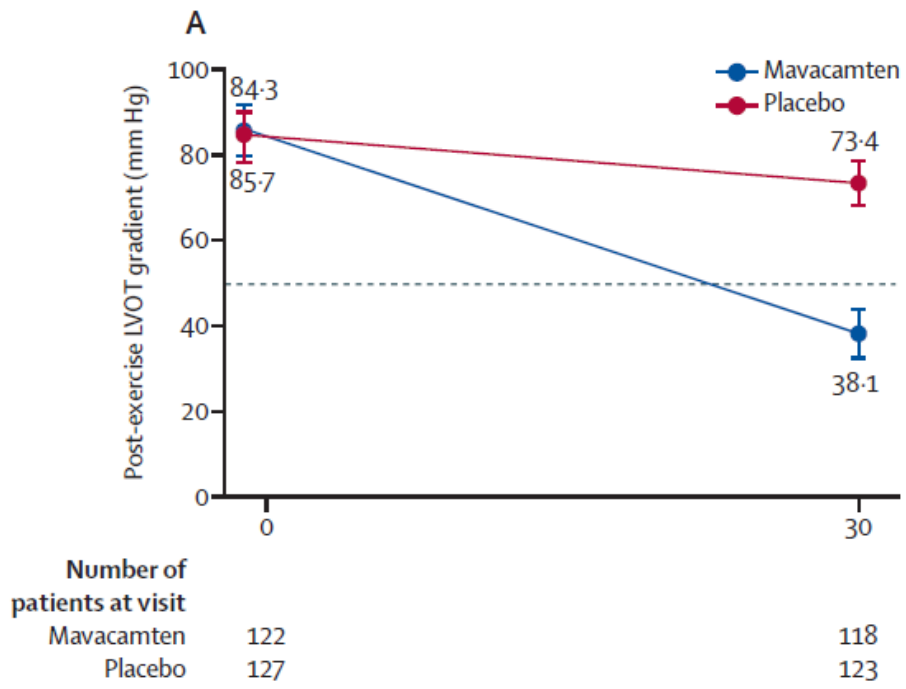


Figure 10. Changes from baseline to week 30 in mean postexercise LVOT gradient

Figure reproduced from Olivotto et al 2020, figure 1A.[3] Error bars are 95% CI. The dashed lines represent the threshold for guideline-based invasive intervention (LVOT gradient > 50 mmHg). CI: confidence intervals; LVOT: left ventricular outflow tract.

B.2.6.1.3 Secondary and exploratory efficacy endpoints: patient-reported outcomes

Rapid and sustained improvements in quality of life evaluated by KCCQ-23 and HCMSQ-SoB were observed with mavacamten compared to placebo.

The improvement in both KCCQ-23 overall summary score (OS) and KCCQ-23 CSS was greater in the mavacamten group, with significant separation seen between the groups after 6 weeks and maintained throughout the 30 weeks of treatment ($p < 0.001$ for all timepoints from 6 weeks, except KCCQ-OS at 30 weeks where $p < 0.0001$) (Figure 11, Table 14). The proportion of patients with an increase of ≥ 10 points, which represents a moderate to very large clinical improvement, was 52% in the mavacamten arm compared to 31% in the placebo arm for KCCQ-CSS, and 53% compared to 35% for KCCQ-OS, respectively. After treatment ended at week 30, the scores in the mavacamten group declined towards that seen in the placebo group.[70]

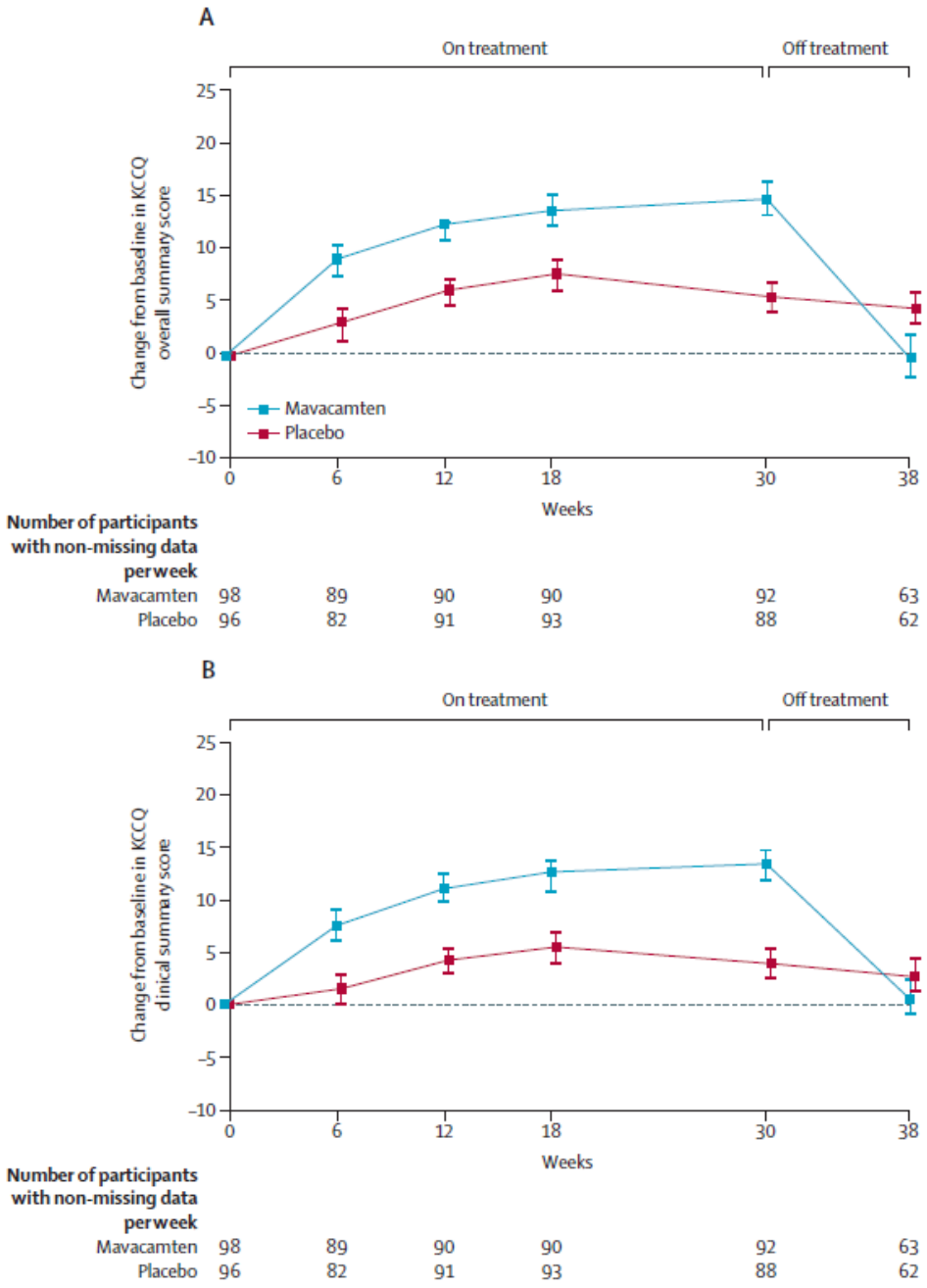


Figure 11. Mean change from baseline in KCCQ-23 OS and KCCQ-23 CSS

Figure reproduced from Spertus et al 2021, Figure 1.[70] CSS: clinical summary score; KCCQ-23: Kansas City Cardiomyopathy Questionnaire; OS: overall summary score.

Significant improvement was seen in patient-reported shortness of breath, as assessed by the HCMSQ-SoB, during treatment with mavacamten (Figure 12, Table 14). Note

that decreases in HCMSQ-SoB subscore represent reduced shortness of breath, indicating symptomatic improvement. The mean improvement from baseline was greater in the mavacamten arm compared to placebo at week 30 ($p < 0.0001$), with effects observed as early as 4 weeks.[3] A decrease from baseline ≥ 2.5 points in HCMSQ-SoB domain score was the threshold for a within-patient clinically meaningful response.[69] At week 30, 50.0% of patients in the mavacamten group had achieved a clinically meaningful response from baseline in HCMSQ-SoB domain score compared with 21.3% in the placebo group.[69]

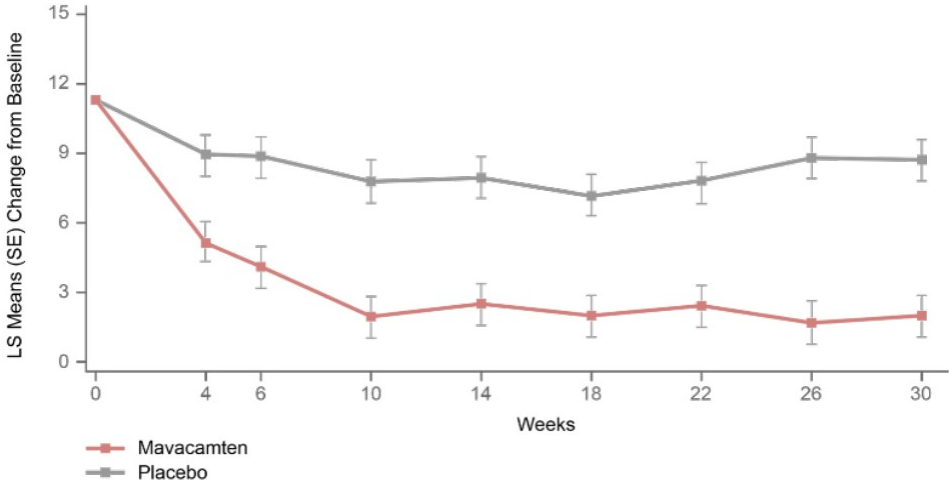


Figure 12. Change in HCMSQ-SoB score from baseline to week 30

HCMSQ-SoB: HCM Symptom Questionnaire Shortness-of-Breath; LS: least squares; SE: standard error.

HRQoL was also assessed using the EQ-5D-5L instrument as an exploratory endpoint. Patients receiving mavacamten had significantly greater 30-week improvement in EQ-5D-5L index score (unadjusted difference 0.075 [95% CI 0.028–0.122], $p = 0.002$) and EQ-VAS score (unadjusted difference 7.8 [95% CI 2.0–13.6], $p = 0.009$) compared with placebo (Table 14). In post hoc analyses of the proportions of patients experiencing at least the meaningful change threshold (MCT), a significantly higher proportion of patients receiving mavacamten showed meaningful improvements in EQ-5D-5L compared to placebo, regardless of the MCT value used.[79] Additionally, mean utilities significantly decreased with higher NYHA functional class but were similar within the

same NYHA class between arms (NYHA class I: mavacamten = 0.950, placebo = 0.952; NYHA class II: mavacamten = 0.866, placebo = 0.850; NYHA class III/IV: mavacamten = 0.708, placebo = 0.704).[79]

Table 14. Changes from baseline to week 30 in patient-reported outcomes

Change from baseline to Week 30 in:	Mavacamten mean (SD)[a]	Placebo mean (SD)[a]	Mavacamten vs placebo (95% CI)	p value[b]
KCCQ-23 CSS	13.6 (14.4)	4.2 (13.7)	9.1 (5.5, 12.7)	< 0.0001
KCCQ-23 OS	14.9 (15.8)	5.4 (13.7)	9.1 (5.5, 12.8)	< 0.0001
HCMSQ-SoB subscore	-2.8 (2.7)	-0.9 (2.4)	-1.8 (-2.4, -1.2)	< 0.0001
EQ-5D-5L index score	0.084	0.009	0.075 (0.028, 0.122)	0.002
EQ-VAS score	8.5	0.7	7.8 (2.0, 13.6)	0.009

[a] The number analysable (n) for secondary endpoints based on availability of baseline and Week 30 data was as follows. KCCQ-23 CSS and OS (n/N): mavacamten 92/123, placebo 88/128. HCMSQ-SoB (n/N): mavacamten 85/123, placebo 86/128. EQ-5D-5L index score and EQ-VAS (n/N): mavacamten 96/123, placebo 89/128.
[b] Based on Mixed Model for Repeated Measurements with data up to Week 30 which includes baseline value, treatment group, visit, interaction between treatment group and visit, and the 3 stratification factors (BB use, NYHA class, exercise type based on IXRS) as fixed effect, and patient as random effect.
EQ-5D-5L index score calculated according to the US-based value set.[79]
Sources: KCCQ-23 CSS and HCMSQ-SoB,[3] KCCQ-23 OS,[70] EQ-5D-5L and EQ-VAS.[79]
CI: confidence intervals; HCMSQ-SoB: HCM Symptom Questionnaire Shortness-of-Breath; IXRS: interactive response system; KCCQ-23 CSS: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; KCCQ-23 OS: Kansas City Cardiomyopathy Questionnaire Overall Summary Score; NYHA: New York Heart Association; SD: standard deviation.

B.2.6.1.4 Additional exploratory endpoints

Improvements in CPET parameters, which represent aspects of exercise capacity, were observed with mavacamten compared to placebo (Table 15). Mean baseline values for all evaluated CPET parameters were similar for the mavacamten and placebo groups. Compared with placebo, mavacamten significantly improved peak VO_2, peak V_E/VCO_2, peak circulatory power, peak metabolic equivalents of task, peak exercise time, peak $PETCO_2$, V_E/VCO_2 slope and ventilatory power, indicating a benefit in exercise performance. The beneficial effects of mavacamten on submaximal exertional tolerance parameters may indicate improvements in patient symptoms during activities of daily living. There was no significant difference between treatment groups in peak respiratory exchange ratio (RER), indicating that patients attained their peak exercise in both groups.[80,98]

Table 15. Changes from baseline in exploratory CPET parameters

CPET parameter	Mavacamten		Placebo		LS mean difference (95% CI)	p value
	Change from baseline to Week 30		Change from baseline to Week 30			
	n	Mean (SD)	n	Mean (SD)		
Peak VE/VCO_2	120	-1.9 (3.7)	125	0.5 (3.8)	-2.2 (-3.1, -1.3)	< 0.0001
Peak MET	120	0.4 (0.9)	125	-0.0 (0.9)	0.4 (0.2, 0.6)	<0.001
Peak $PETCO_2$	110	1.7 (3.4)	113	-0.4 (3.0)	2.0 (1.12, 2.79)	< 0.0001
Peak circulatory power	119	414.1 (972.0)	124	-17.9 (869.1)	372.9 (153.1, 592.6)	0.001
Peak RER	120	[redacted]	125	[redacted]	0.02 (-0.003, 0.040)	0.09
VE/VCO_2 slope	120	-2.4 (4.6)	125	0.4 (4.1)	-2.6 (-3.6, -1.5)	< 0.001
Ventilatory power	122	0.7 (1.4)	121	-0.03 (1.2)	0.6 (0.3, 0.9)	<0.001
Ventilatory threshold	106	0.7 (2.5)	116	0.1 (2.6)	0.6 (-0.03, 1.2)	0.06

The LS means (95% CI) and the p values are from a mixed model for repeated measurements with data up to Week 30, which includes baseline value, treatment group, visit, interaction between treatment group and visit, and the three stratification factors (BB use, NYHA class, exercise type based on IXRS) as fixed effect and patient as random effect.
Source: Wheeler et al 2022[98] and EXPLORER-HCM CSR[80]
CI: confidence interval; CPET: cardiopulmonary exercise testing; CSR: clinical study report; IXRS: interactive response system; LS: least squares; MET: metabolic equivalents of task; $PETCO_2$: partial pressure of end tidal CO_2; RER: respiratory exchange ratio; SD: standard deviation; VE/VCO_2: volume expired/CO_2 production; VO_2: oxygen consumption.

A greater proportion of patients in the mavacamten group achieved a complete response (NYHA class I and all LVOT peak gradients < 30 mmHg), compared with the placebo group (27% versus 1%, respectively; difference 26.6 [95% CI 18.3, 34.8], p < 0.0001).[80] The proportion of patients achieving NYHA class I at week 30 compared to baseline in the mavacamten and placebo arms is illustrated in Figure 13.

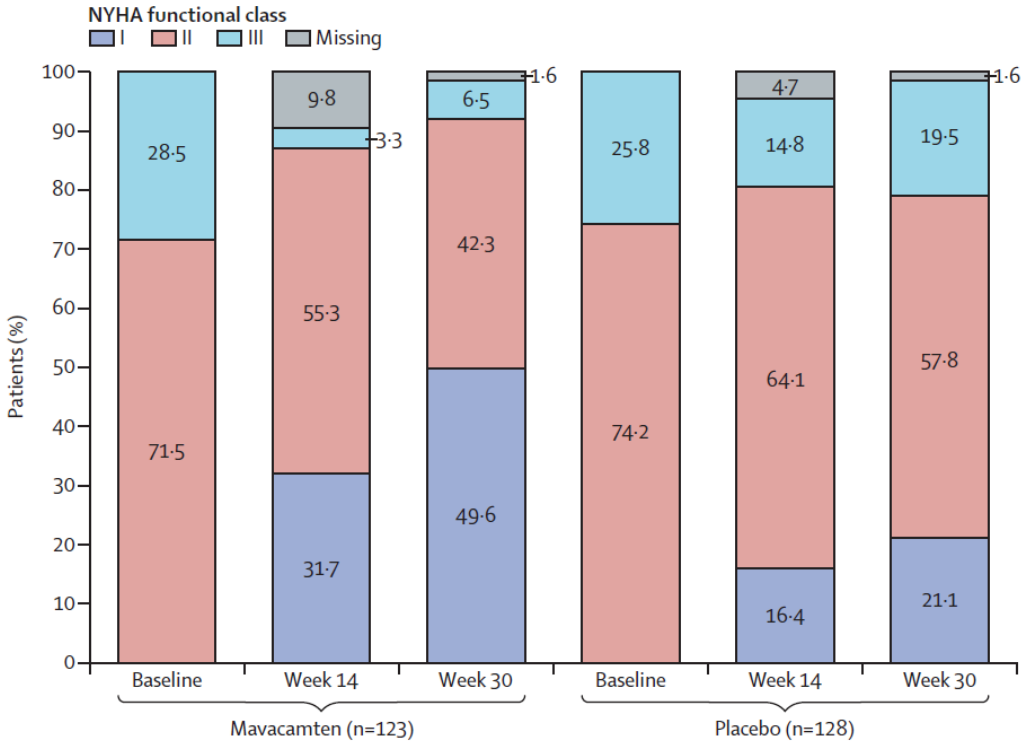


Figure 13. Percentage of patients in each NYHA functional class at baseline, week 14 and week 30 for mavacamten vs placebo groups

Figure reproduced from Olivotto et al 2020, Figure 2.[3] NYHA: New York Heart Association.

At baseline, mean (SD) LVEF was similar and hypercontractile for the mavacamten 74% (5.8%) and placebo 74% (5.9%) groups (Figure 14).[3,80] There was a small mean (SD) decrease in LVEF (-4% [7.7%]) during 30 weeks of treatment in the mavacamten group compared with placebo (-0.01 [6.8]) (Figure 14).[3,80] [redacted].[80] This indicates that mavacamten's effect on LVEF is small and reversible.

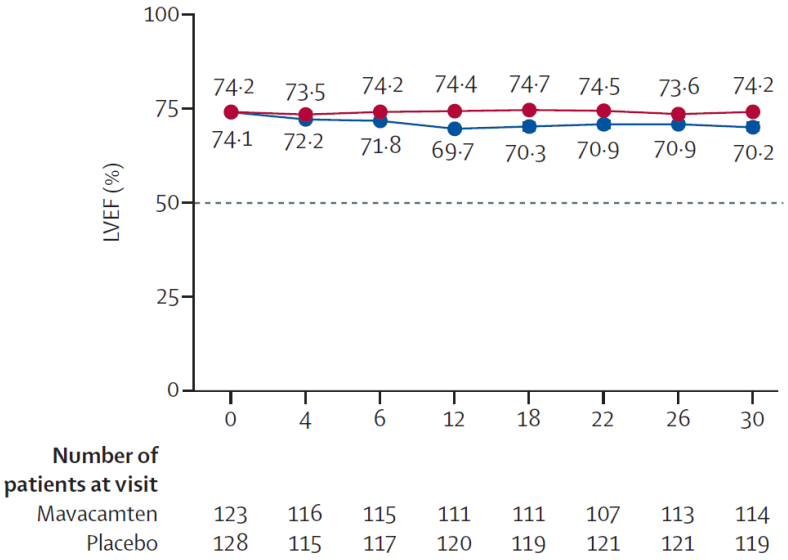


Figure 14. LVEF over time for mavacamten versus placebo

Figure reproduced from Olivotto et al 2020, Figure 1B.[3] Error bars are 95% CI. The dashed line represents the protocol threshold for temporary discontinuation of study drug. CI: confidence intervals; LVEF: left ventricular ejection fraction.

Note that for brevity, only two exploratory TTE endpoints, which are considered most relevant to the outcomes specified in the decision problem, are presented and discussed in full here. Results for the other exploratory endpoints can be found in the EXPLORER-HCM CSR[80] and results of the CMR imaging substudy are published in Saberi *et al.* 2021[68] (see also Appendix M).

B.2.6.2 EXPLORER-LTE cohort: efficacy results

For this interim analysis, efficacy endpoints were collected from the start of the study through 31 August 2021. Clinical benefits were consistent with those observed in the EXPLORER-HCM parent study, demonstrating clinically important improvements in LVOT gradients, NYHA class and NT-proBNP levels at and beyond 48 weeks in patients with symptomatic obstructive HCM. Data for the efficacy outcomes most relevant to the decision problem are presented in sections B.2.6.6.1, B.2.6.6.2; additional outcomes can be found in Rader et al 2022.[9]

B.2.6.2.1 Change in NYHA class

Improvements in NYHA class were observed through week 48 (Figure 15). At week 48, 67.5% (139/206) patients improved by at least one NYHA class, with 15 (7.3%) patients improving by two NYHA classes.[9]

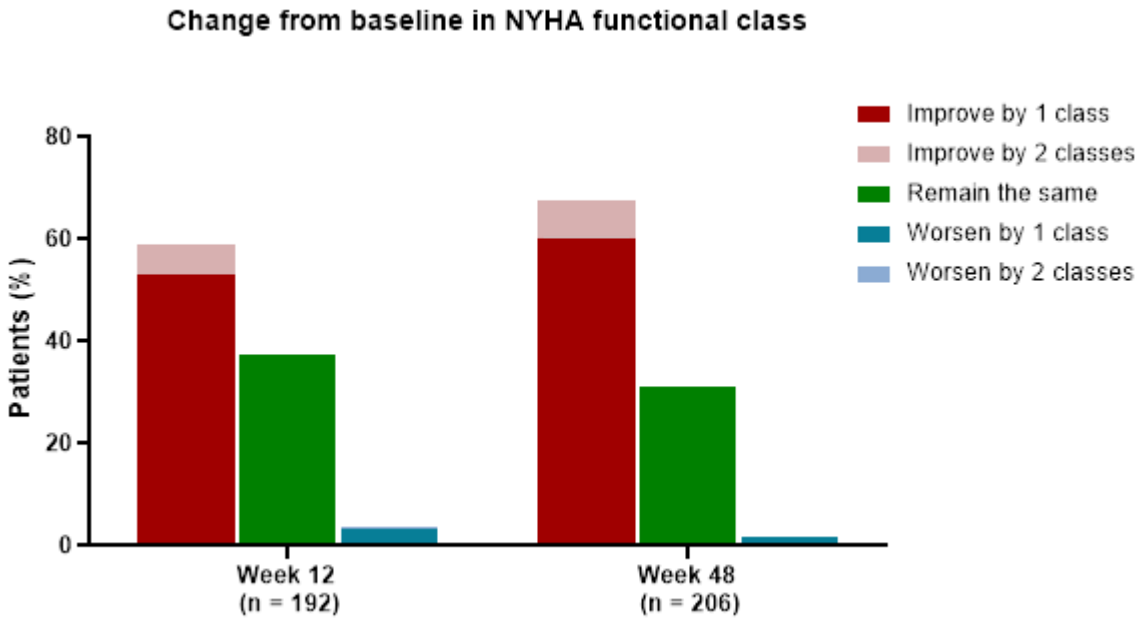


Figure 15. EXPLORER-LTE cohort changes in NYHA class

Note: NYHA class assessed at weeks 12 and 48; next assessment is at week 108. Baseline values at the beginning of MAVA-LTE, not the beginning of the parent study. Figure reproduced from Rader et al 2022.[9] Based on interim analysis up to August 2021. NYHA: New York Heart Association.

Patients entered the EXPLORER-LTE cohort from both the mavacamten and placebo arms of the parent trial, EXPLORER-HCM, following a washout period. An ad hoc analysis of NYHA class at each time point, stratified by the arm of the parent trial, was performed. No difference with respect to the treatment arm allocation in the parent trial was found ([redacted]Figure 16).

Figure 16. NYHA class at day 1, week 12, week 48 and week 108 for the EXPLORER-LTE cohort, stratified by arm of the parent study

'Mavacamten in HCM' and 'Placebo in HCM' refer to the groups of patients in the EXPLORER-LTE cohort who entered the single-arm study from the mavacamten and placebo arms of the EXPLORER-HCM parent trial, respectively. HCM: hypertrophic cardiomyopathy; LTE: long-term extension; NYHA: New York Heart Association

B.2.6.2.2 LVEF and LVOT gradients

Echocardiography was used to evaluate changes in LVEF and LVOT gradients (resting and Valsalva). Mavacamten was associated with rapid and sustained improvement in resting and Valsalva LVOT gradients, sustained for up to 84 weeks, while maintaining LVEF > 50% (Figure 17 and Figure 18).[9]

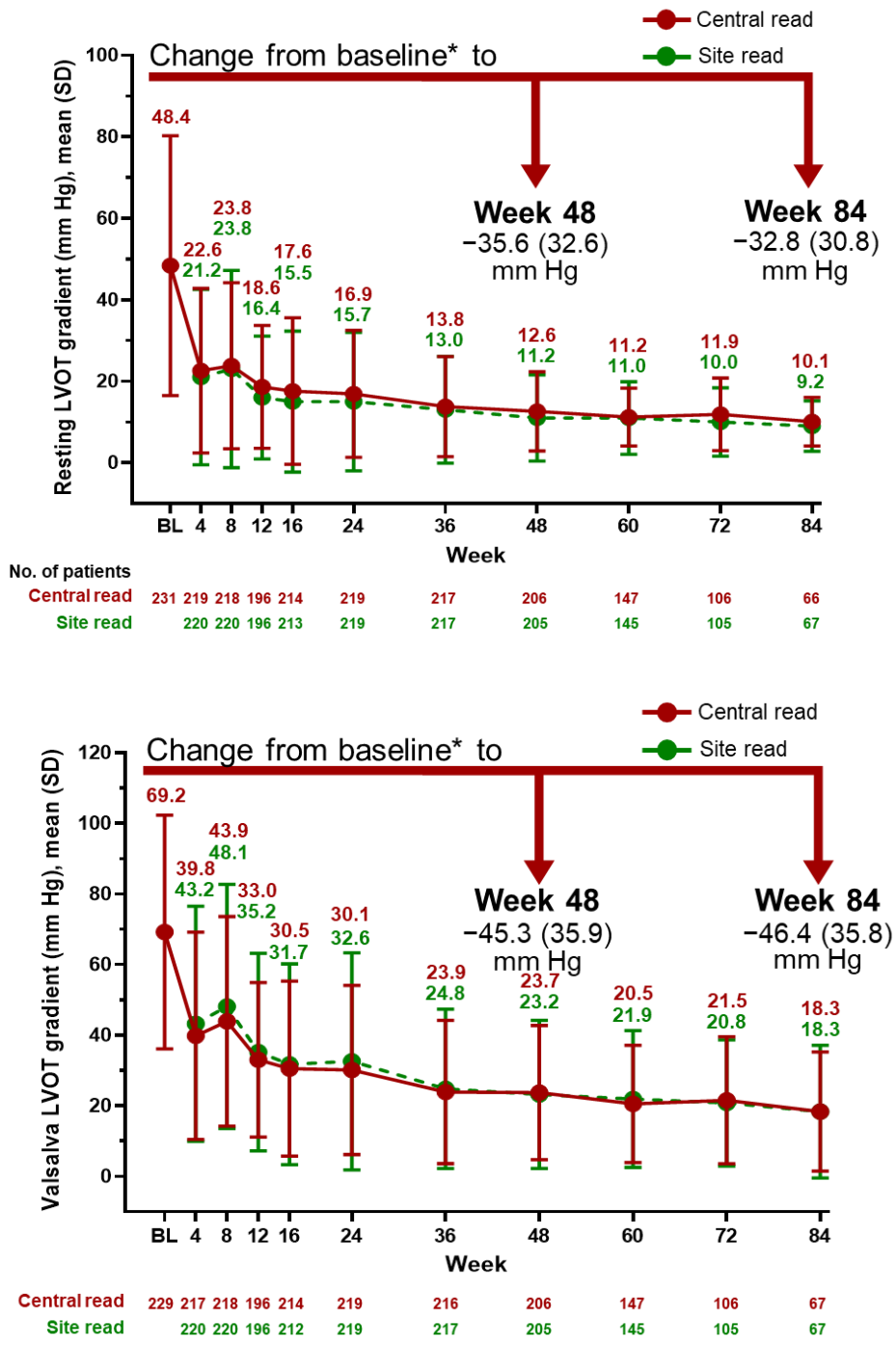


Figure 17. Resting and Valsalva LVOT gradients over time in the EXPLORER-LTE cohort

Figure reproduced from Rader et al 2022.[9] Based on interim analysis up to August 2021. Data from EXPLORER-HCM are not shown. Baseline values represent those from the beginning of MAVA-LTE, not the beginning of the parent study. *Change from baseline are only summarized for patients with a value at both baseline visit and specific post-baseline visits.
BL: baseline; LVOT: left ventricular outflow tract; SD: standard deviation.

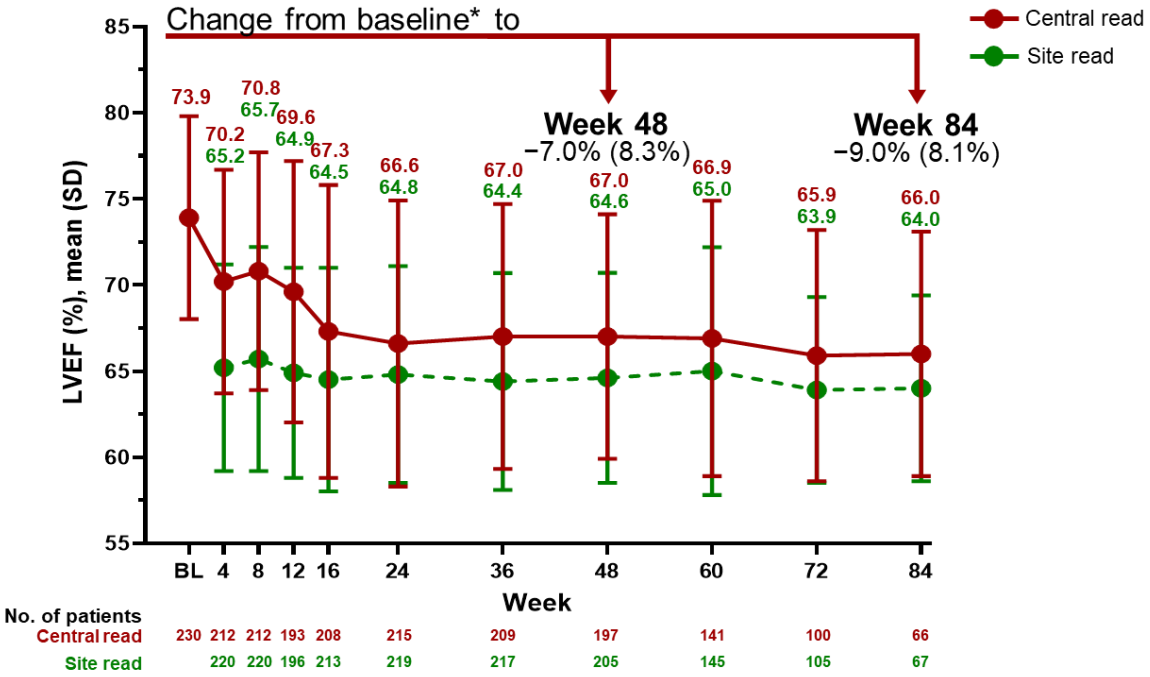


Figure 18. Resting LVEF over time in the EXPLORER-LTE cohort

Figure reproduced from Rader et al 2022.[9] Based on interim analysis up to August 2021. Data from EXPLORER-HCM are not shown. Baseline values represent those from the beginning of MAVA-LTE, not the beginning of the parent study. *Change from baseline are only summarized for patients with a value at both baseline visit and specific post-baseline visits.
BL: baseline; LVEF: left ventricular ejection fraction; SD: standard deviation.

B.2.7 Subgroup analysis: EXPLORER-HCM

Efficacy endpoints in EXPLORER-HCM were analysed by predefined subgroups, including those used as stratification factors as well as other demographics and baseline characteristics. Mavacamten showed a consistent benefit for the primary endpoint across the subgroups (Figure 19).

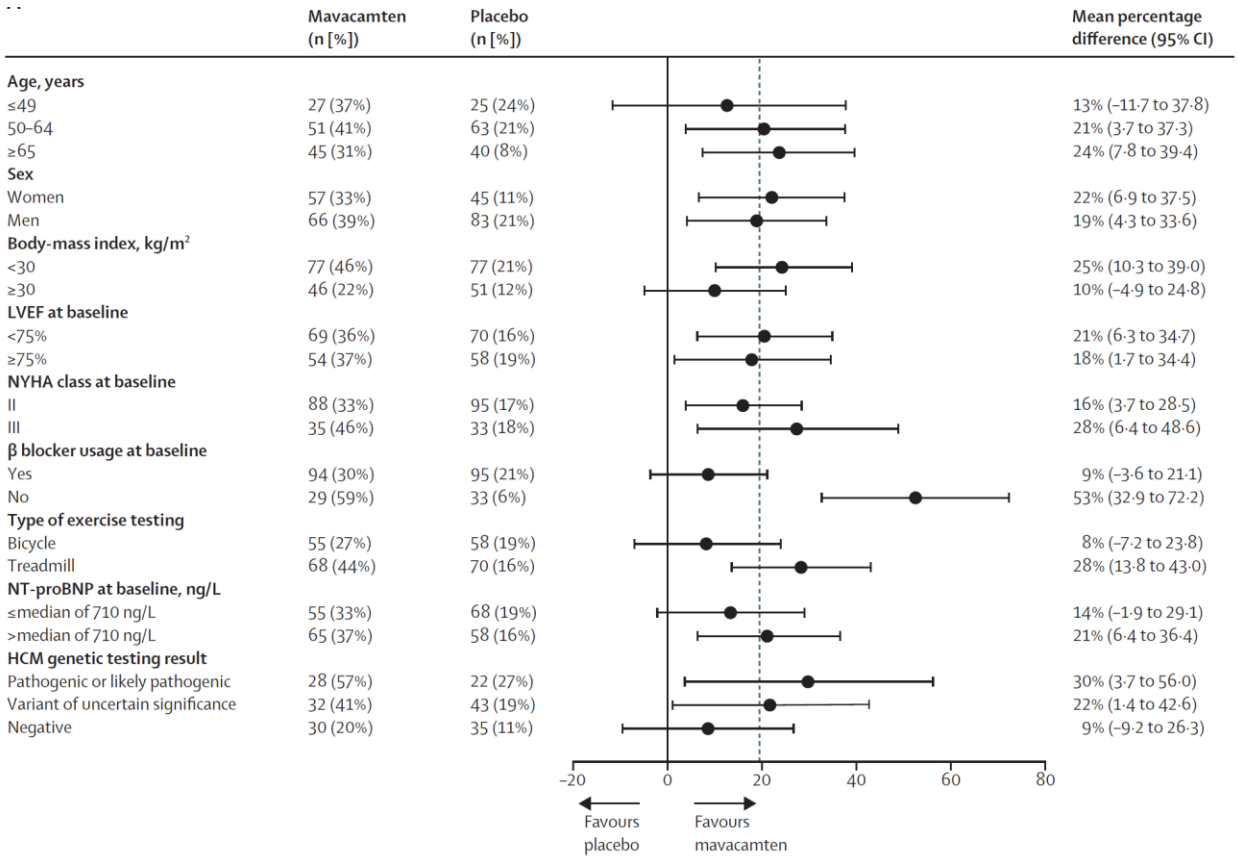


Figure 19. Forest plot of the primary endpoint by prespecified subgroups for mavacamten versus placebo

Figure reproduced from Olivotto et al. 2020.[3] Mean difference in patients meeting the primary endpoint. The dashed vertical line (overall effect) represents the between-treatment group difference in the overall study cohort (19%) and the solid vertical line (no effect) indicates no difference between treatment groups. Patients with a non-evaluable primary endpoint were considered as non-responders. CI: confidence interval; HCM: hypertrophic cardiomyopathy; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro B-type natriuretic peptide; NYHA: New York Heart Association.

B.2.7.1 Subgroup analysis by BB use: EXPLORER-HCM and the EXPLORER-LTE cohort

In EXPLORER-HCM subgroup analysis (Figure 19), an interaction was observed with BB use at baseline; improvements were observed in both groups but the magnitude of the treatment effect was greater for patients who were not using BB compared with those who were (between-group difference 53% [95% CI 32.9, 72.2] versus 9% [95% CI -3.6, 21.1], respectively). Therefore, subgroup analysis by BB use at baseline was

performed for a range of outcomes for both the EXPLORER-HCM study and the EXPLORER-LTE cohort (Table 16).[73]

Table 16. BB subgroup analysis on key outcomes from EXPLORER-HCM and the EXPLORER-LTE cohort

Outcome	EXPLORER-HCM				EXPLORER-LTE cohort			
	BB: Y		BB: N		BB: Y		BB: N	
	Mavacamten	Placebo	Mavacamten	Placebo	Mavacamten			
	Week 30				Week 12	Week 48	Week 12	Week 48
pVO_2, mL/kg/min	1.1 (3.1)	0.1 (3.2)	2.2 (3.0)	-0.5 (2.4)	ND	ND	ND	ND
VE/VCO_2 slope	-2.4 (4.5)	0.6 (4.1)	-2.7 (4.9)	-0.1 (4.4)	ND	ND	ND	ND
LVOT resting gradient, mmHg	-37.5 (30.1)	-5.1 (27.5)	-42.2 (27.9)	-6.8 (29.7)	-29.1 (30.3)	-27.9 (28.3)	-32.6 (39.4)	-25.2 (50.1)
LVOT Valsalva, mmHg	-50.0 (36.8)	-10.4 (30.3)	-46.3 (25.6)	-17.3 (32.8)	-35.5 (34.4)	-39.2 (35.1)	-37.9 (36.0)	-36.6 (46.6)
NYHA improvement, % of patients	65	35	66	21	63	73	50	63
KCCQ CSS score	14.2 (14.3)	3.3 (13.7)	11.0 (15.0)	6.3 (13.8)	ND	ND	ND	ND

Source: Jacoby et al 2021.[73] Data presented are mean (SD) change from baseline unless otherwise stated. BB: beta blocker; HCM: hypertrophic cardiomyopathy; KCCQ CSS: Kansas City Cardiomyopathy Questionnaire clinical summary score; LTE: long-term extension; LVOT: left ventricular outflow tract; N: no; ND: not determined; NYHA: New York Heart Association; SD: standard deviation; Y: yes

Mean (SD) change from baseline at EXPLORER-HCM week 30 in pVO_2, a component of the composite primary functional endpoint, was smaller for patients using BB compared with those who were not using BB (1.1 [3.1] versus 2.2 [3.0] mL/kg/min).[73] BB are well established to have a blunting effect on heart rate and, therefore, certain heart rate-dependent parameters assessed by CPET, including pVO_2.[99,100] Consistent with this, baseline mean (SD) peak heart rate with exercise tended to be lower for the subgroup of patients using BB compared with those not using BB (119 beats/min versus 138 beats/min, respectively).[3] Similarly, mean (SD) baseline pVO_2 by CPET tended to be lower for the BB subgroup compared with the non-BB subgroup. This accounts for the interaction with BB use observed for the treatment effect on pVO_2 and hence the composite primary outcome.

In contrast, heart rate independent parameters of CPET, e.g. VE/VCO_2 slope, showed an improvement with mavacamten treatment compared with placebo regardless of BB use.[73] Furthermore, secondary endpoints, including change in postexercise LVOT peak

gradient, NYHA class and KCCQ-23 CSS showed consistent benefit for mavacamten compared with placebo across the evaluated subgroups, irrespective of BB use (Table 16).[73]

B.2.8 Meta-analysis

No meta-analysis was performed for mavacamten in combination with standard care compared to individually optimised standard care without mavacamten because direct evidence comparing the efficacy of the intervention and relevant comparators was available from a single head-to-head RCT and there is no additional comparative evidence with which to conduct a meta-analysis (section B.2.2).

B.2.9 Indirect and mixed treatment comparisons

The intervention (mavacamten in combination with standard care) and comparators (individually optimised standard care comprising BB, CCB) considered have been evaluated within a single RCT, therefore no indirect or mixed treatment comparisons were required.

B.2.10 Adverse reactions

Safety data for mavacamten for the treatment of symptomatic (NYHA II–III) obstructive HCM are available from EXPLORER-HCM and the EXPLORER-LTE cohort of the MAVA-LTE long-term extension study. In general, mavacamten presented with an acceptable safety profile and was well tolerated. The safety profile among subgroups was consistent with the overall study population. Overall, frequencies of AEs, serious adverse events (SAEs) and cardiac AEs were similar in the mavacamten and placebo arms of EXPLORER-HCM, and no new safety signals have been observed in the interim analysis of the long-term extension. Note that no new safety signals were identified in the interim analysis of VALOR-HCM.[101]

B.2.10.1 EXPLORER-HCM: extent of exposure

Duration of study drug exposure is summarised in Table 17.[80]

Table 17. Exposure to study treatment (safety population)

	Mavacamten (N = 123)	Placebo (N = 128)
Duration of exposure (weeks)[a]		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Adjusted duration of exposure (weeks)[b]		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

a Duration of exposure in weeks is the interval between first dose date and last dose date and calculated as (the last dose date – the first dose date +1)/7.
b Adjusted duration of exposure is the duration of exposure with adjustment for the period of protocol-specified dose interruptions (i.e., triggered by IXRS or due to a TEAE).
Source: EXPLORER-HCM CSR[80]
CSR: clinical study report; IXRS: interactive response system; Q1: first quarter; Q3: third quarter; SD: standard deviation; TEAE: treatment-emergent adverse event.

B.2.10.2 EXPLORER-HCM: overall treatment-emergent adverse events

A greater proportion of patients in the mavacamten group compared with the placebo group experienced any treatment-emergent adverse event (TEAE) ([redacted]% vs [redacted]%, respectively) during the treatment-emergent period (day 1 to week [redacted]).[80] A smaller proportion of patients in the mavacamten group compared with the placebo group had treatment interruptions due to TEAEs ([redacted]% vs [redacted]%). [redacted] patients in the mavacamten group ([redacted]%) had TEAEs that resulted in discontinuation of study drug and the study ([redacted]). The most commonly reported TEAEs (≥ 10% of patients) in each treatment group are summarised in Table 18. The full list of TEAEs, by treatment and preferred term, can be found in the EXPLORER-HCM CSR.[80]

Table 18. TEAEs reported in ≥ 10% patients in each treatment group

	Mavacamten (N = 123) n (%)	Placebo (N = 128) n (%)
Dizziness	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]

a Headache was reported for < 10% patients in the placebo group (10 patients, 7.8%).
For each preferred term, a patient is counted only once if the patient reported 1 or more events. A TEAE is any AE that occurred after the first dose of study drug through the last dose of study drug + 56 days. AE terms are mapped to the appropriate preferred term according to MedDRA, v21.0. The relatedness of study drug was determined by the investigator and collected in the eCRF. Source: EXPLORER-HCM CSR[80]
AE: adverse event; CSR: clinical study report; eCRF: electronic case record form; HCM: hypertrophic cardiomyopathy; TEAE: treatment-emergent adverse event.

B.2.10.3 EXPLORER-HCM: TEAEs by relationship to study drug

The rates of treatment-related TEAEs (as assessed by the investigator) were comparable for the mavacamten and placebo groups ([redacted] patients, [redacted]% vs [redacted] patients [redacted]%) (Table 19).[80]

Table 19. Treatment-related TEAEs reported for ≥ 1 patient in either treatment group (safety population)

	Mavacamten (N = 123) n (%)	Placebo (N = 128) n (%)
Number of patients with at least one study drug related TEAE	[redacted]	[redacted]
AF	[redacted]	[redacted]
Palpitations	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Presyncope	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]

For each preferred term, a patient is counted only once if the patient reported 1 or more events. A TEAE is any AE that occurred after the first dose of study drug through the last dose of study drug + 56 days. AE terms are mapped to the appropriate preferred term according to MedDRA, v21.0. The relatedness of study drug was determined by the investigator and collected in the eCRF. Source: EXPLORER-HCM CSR[80]

AE: adverse event; AF: atrial fibrillation; CSR: clinical study report; eCRF: electronic case record form; HCM: hypertrophic cardiomyopathy; TEAE: treatment-emergent adverse event.

B.2.10.4 EXPLORER-HCM: SAEs

The proportion of patients who had SAEs during the on-treatment period (day 1 to week 30) was similar for the mavacamten and placebo groups (10 patients, 8% vs 11 patients, 9%) (Table 20).[3] One patient in the placebo group had a TEAE of sudden death; this was the only treatment-related SAE reported in the study.

Table 20. Treatment-emergent SAEs during the on-treatment period (day 1 to week 30; safety population)

	Mavacamten (N = 123) n (%)	Placebo (N = 128) n (%)
Total number of treatment-emergent SAEs	11	20
Patients with ≥ 1 treatment-emergent SAE	10 (8)	11 (9)
AF	2 (2)	4 (3)
Stress cardiomyopathy	2 (2)	0
Cardiac failure congestive	0	1 (1)
Sudden death	0	1 (1)
Urinary tract infection	0	2 (2)
Diverticulitis	1 (1)	0
Gastroenteritis viral	0	1 (1)
Infection	1 (1)	0
Contusion	1 (1)	0
Forearm fracture	1 (1)	0
Dehydration	0	1 (1)
Rheumatoid arthritis	0	1 (1)
Cholesteatoma	0	1 (1)
Prostate cancer	0	1 (1)
Syncope	2 (2)	1 (1)
Transient ischaemic attack	0	1 (1)
Vocal cord polyp	0	1 (1)

Source: Olivotto et al., 2020[3]
AF: atrial fibrillation; CSR: clinical study report; HCM: hypertrophic cardiomyopathy; SAE: serious adverse event

B.2.10.5 EXPLORER-LTE cohort: safety summary

No new safety signals have been identified in the interim data from the EXPLORER-LTE cohort (Table 21).[9] Exposure-adjusted incidence per 100 patient-years was 70.8 for any TEAE, 2.52 for cardiac failure and 2.53 for decreased LVEF. By numbers, severity and system organ class, the exposure-adjusted TEAE rate was the same or less compared to previous analysis.[9] At the time of the August 2021 DBL, 26 (11%) patients had temporary treatment interruptions per protocol. Overall, 20/26 (77%) patients remained on study treatment following the temporary interruption. Permanent treatment discontinuations due to TEAEs are outlined in Table 22. Additional safety data from the October 2020 DBL are presented in Appendix M.

Table 21. Cumulative AEs for the EXPLORER-LTE cohort

	EXPLORER-LTE cohort (N = 231) n (%)
Any TEAE*	201 (87.0)
Mild	87 (37.7)
Moderate	89 (38.5)
Severe	21 (9.1)
Drug-related TEAEs	40 (17.3)
CV ECI drug-related TEAEs	19 (8.2)
SAEs (drug-related and unrelated)	34 (14.7)
CV ECI SAEs	15 (6.5)
Drug-related SAEs	5 (2.2)†
Deaths	3 (1.3)‡

*The most common TEAEs of any grade occurring in ≥ 5% of patients were fatigue (10.4%), dizziness (10.0%), hypertension (10.0%), headache (8.2%), nasopharyngitis (8.2%), AF (9.1%), back pain (6.5%), COVID-19 infection (6.1%), dyspnoea (6.1%), and pain in extremity (5.6%); †Includes cardiac failure (3) and decreased LVEF (2); ‡Due to bacterial endocarditis (1), cardiac arrest (1), and acute myocardial infarction (1), all unrelated to treatment.
AE: adverse event; AF: atrial fibrillation; CV: cardiovascular; ECI: event of clinical interest; LTE: long-term extension; LVEF: left ventricular ejection fraction; SAE: serious adverse event; TEAE: treatment-emergent adverse event. Source: Rader et al 2022.[9]

Table 22. TEAEs leading to permanent treatment discontinuation in the EXPLORER-LTE cohort

TEAEs leading to permanent treatment discontinuation*	EXPLORER-LTE cohort (N = 231) n (%)
TEAEs	10 (4.3)
LVEF <50%	2‡
Cardiac failure	1‡†
Cardiac arrest	1#
Acute myocardial infarction	1
Muscular weakness	1
Systemic lupus erythematosus	1
Fatigue	1
Bacterial endocarditis	1
Prolonged QTcF	1

*Two patients terminated participation in the study and were subsequently re-enrolled; both TEAEs (LVEF <50%; prolonged QTcF) leading to therapy interruption were related to the study drug; ‡All three patients recovered with LVEF>50%; †TEAE of cardiac failure (was attributed to erroneous dosing and in-hospital echocardiogram showed LVEF of 40%); patient experienced cardiac failure event while admitted in the hospital due to an SAE of pneumonia; #Cardiac arrest was a sudden unwitnessed event. LTE: long-term extension; LVEF: left ventricular ejection fraction; QTcF: QT interval corrected by Fridericia's formula; TEAE: treatment-emergent adverse event. Source: Rader et al 2022.[9]

B.2.11 Ongoing studies

The long-term extension study MAVA-LTE, which includes the EXPLORER-LTE cohort, is ongoing. Results from an interim analysis of the August 2021 DBL are presented in

sections B.2.6, B.2.7 and B.2.10. The estimated primary completion date is September 2025.[86] Further interim analyses are expected in the 12 months following submission.

Another ongoing study is VALOR-HCM (NCT04349072), a multicentre, phase III, double-blind, placebo-controlled, randomised study of mavacamten versus placebo in adult patients with symptomatic obstructive HCM who are guideline-eligible and willing to undergo SRT.[96] The primary endpoint is a composite of the decision to proceed with SRT prior to or at week 16 or remaining guideline-eligible for SRT at week 16, while secondary efficacy endpoints include change (from baseline to week 16 in the mavacamten group vs placebo) in post-exercise LVOT gradient, NYHA, KCCQ-CSS, NT-proBNP and cardiac troponin. On 16 February 2022, it was announced that VALOR-HCM had met its primary endpoint, based on an interim DBL;[101] 17.9% (10/56) patients in the mavacamten arm had proceeded with SRT or remained guideline-eligible for SRT at week 16, compared to 76.8% (43/56) patients in the placebo arm.[102] In this interim analysis, no new safety signals were observed, in a study population where 92.9% were NYHA class III or higher at baseline.[101,102] Selected AEs (mavacamten vs placebo) included ejection fraction < 50% (2 [3.6%]) vs 0 [0%]), AF (4 [7.1%] vs 0 [0%]), non-sustained ventricular tachycardia (0 [0%] vs 5 [9.1%]), chest pain (2 [3.6%] vs 3 [5.5%]), fatigue (5 [8.9%] vs 2 [3.6%]), nausea (4 [7.1%] vs 1 [1.8%]), headache (2 [3.6%] vs 5 [9.1%]) and rash (4 [7.1%] vs 0 [0%]).[102] The results of this initial interim analysis of the primary and secondary endpoints were presented at ACC 2022.[102] Further results are expected to be available within the post-submission appraisal period.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings from the clinical evidence

The clinical evidence supporting the use of mavacamten for the treatment of symptomatic, obstructive HCM was primarily derived from EXPLORER-HCM,[3,68-70,73,79-81] supported by interim results from the EXPLORER-LTE cohort.[72,82]

EXPLORER-HCM is a phase III, randomised, double-blind, multi-centre, placebo-controlled study designed to capture the effect of mavacamten versus placebo on

exercise capacity and clinical symptoms. Across multiple measures of symptoms and function evaluated in the EXPLORER-HCM study, the results demonstrate that myosin inhibition with mavacamten reduces dynamic LVOT obstruction, improves symptoms and exercise capacity and reduces biomarkers of cardiac stress. Mavacamten was associated with a tolerable safety profile (B.2.10).[3,68-70,73,79-81]

The principal findings from EXPLORER-HCM were:

- A significantly greater proportion of mavacamten-treated patients met the primary composite endpoint compared to placebo (37% versus 17%, p = 0.0005), demonstrating a clinically meaningful combined benefit in both symptoms, assessed by NYHA class, and function, assessed by pVO_2.[3]
- Mavacamten was associated with meaningful clinical and statistically significant improvements in all secondary endpoints, including:
    - 65% mavacamten-treated patients improved by one or more NYHA class compared to 31% patients receiving placebo (p < 0.0001).[3]
    - Patients treated with mavacamten demonstrated a statistically significant increase in exercise capacity, measured by pVO_2,[3] a measure which is prognostic for mortality in obstructive HCM.[13]
    - Treatment with mavacamten led to a statistically significant reduction in postexercise LVOT gradient compared to placebo[3]
- 27% of patients on mavacamten (32 patients) achieved complete response, defined as NYHA class I and all LVOT gradients < 30 mmHg, versus <1% on placebo (1 patient), representing a meaningful improvement in both function and feel to benefit patients.[3]
- Symptom burden in HCM, particularly obstructive HCM, has profound impact on patient quality of life. The most frequent symptoms in patients with obstructive HCM are shortness of breath and chest pain, with resulting reduced exercise tolerance.[14] Statistically significant and clinically meaningful improvements in KCCQ-23 CSS and HCMSQ-SoB were reported by patients receiving mavacamten, compared to placebo.[3,69,70]

The interim results of the EXPLORER-LTE cohort, showed that the clinical efficacy measures were consistent with those observed in the EXPLORER-HCM parent study, while LVEF was maintained in the normal range, indicating that these benefits appear to be sustained through the first year of treatment and beyond.[72]

Furthermore, interim results from VALOR-HCM have shown that the trial has met its primary endpoint; fewer patients on mavacamten treatment were eligible for or chose to undergo SRT procedures at week 16.[101,102]

In general, mavacamten presented with an acceptable safety profile and was well tolerated, compared to placebo. The safety profile among subgroups was consistent with the overall study population. Overall, frequencies of AEs, SAEs and cardiac AEs were similar in the mavacamten and placebo arms of EXPLORER-HCM, and no new safety signals have been observed in the interim analysis of the long-term extension or the interim analysis of VALOR-HCM.[9,101,102]

Together these data demonstrate that mavacamten relieves symptoms and improves function in patients with symptomatic, obstructive HCM and is not associated with an increased frequency of AEs when used in combination with standard care.

B.2.12.2 Strengths and limitations of the clinical evidence base

B.2.12.2.1 Strengths of the clinical evidence

Overall, the clinical evidence provides an appropriate base to inform the assessment of clinical effectiveness and cost-effectiveness of mavacamten in combination with standard care, compared with individually optimised standard care alone, where standard care represents BB or non-dihydropyridine CCB (NB. for patients intolerant or non-responsive to both, this may include no background therapy).

B.2.12.2.1.1 Study design and population

EXPLORER-HCM is a well-designed, phase III, randomised, placebo-controlled trial that provides direct evidence for the efficacy of mavacamten versus appropriate comparators in a patient population directly relevant to the indication. The patient cohort

was large (123 in the mavacamten arm, 128 in the placebo arm), and baseline demographics and disease characteristics were well balanced between the arms.[3] Generalisability to UK clinical practice is good (see B.2.13.4 for more details). EXPLORER-HCM is the largest RCT conducted in patients with obstructive HCM, and provides high-quality evidence for efficacy and safety of mavacamten that is lacking for current medical therapies.

B.2.12.2.1.2 Improvements in functional status, physiological parameters and symptoms

Mavacamten was associated with a combined benefit in both symptoms and function.[3] Improvements in NYHA class and pVO_2 associated with mavacamten were both statistically significant compared to placebo, and clinically meaningful.[3] At week 30, 27% of patients on mavacamten reported no symptoms (NYHA class I) and were below the guideline-based definition of obstruction (all LVOT gradients < 30 mmHg), compared to 1% in the placebo arm (B.2.6.2.4).[3]

According to IPG40,[52] invasive therapies i.e. SRT may be considered for treating LVOTO in patients who remain symptomatic despite drug treatment, while the ESC 2014 guidelines state that invasive treatment to reduce LVOTO should be considered in patients with an LVOTO gradient of ≥ 50 mmHg, moderate-to-severe (NYHA III–IV) symptoms and/or recurrent exertional syncope in spite of maximally tolerated drug therapy.[2] Therefore, the marked improvements in NYHA class and in postexercise LVOT gradients with mavacamten, compared with placebo,[3] suggest that treatment with mavacamten may reduce the need for invasive therapies for patients with obstructive HCM. This is supported by the report that VALOR-HCM has met its primary endpoint (a composite of the number of patients who decided to proceed with SRT prior to or at week 16 and the number of patients who remained SRT-guideline eligible),[101] and promising indications of beneficial cardiac remodelling seen in the CMR substudy.[68]

Statistically significant and clinically meaningful improvements in PROs in EXPLORER-HCM were reported by patients receiving mavacamten, compared to placebo, which returned to baseline following study drug washout,[69,70,79,80] indicating the mavacamten

provides substantial benefit in terms of the heavy symptom and HRQoL burden experienced by patients with obstructive HCM (B.2.6.3.2).

B.2.12.2.2 Limitations of the evidence base

One limitation of the trial data is that it was not feasible to collect data on endpoints such as mortality, CV mortality or CV events; although patients with obstructive HCM are at an increased risk of mortality and CV events, the event rate of these outcomes is low in the context of the duration of a clinical trial, therefore directly evaluating the impact of mavacamten on these outcomes would not be feasible to conduct. Therefore, it is necessary to use intermediate endpoints such as NYHA class to infer the effect of mavacamten on mortality (see also B.3.3.5). Various studies indicate that NYHA class is prognostic for mortality in patients with HCM,[4-6,44,45] including data from two large, RWE studies indicating that the risk of mortality increases with worse NYHA class in patients with obstructive HCM.[44,45] The range of supporting evidence suggests this association can be considered robust.

Another potential limitation with respect to study endpoints is that as NYHA classes are broadly defined, with four classes representing a disease impact ranging from asymptomatic (NYHA I) to profoundly disabled (NYHA IV), each class can encompass a degree of heterogeneity. Therefore the use of NYHA class may underestimate the benefit of mavacamten, as patients may experience functional improvements without changing classification. Despite these limitations, NYHA class remains the assessment tool of choice among clinical experts, therefore the use of this endpoint is entirely reflective of clinical practice. Furthermore, the benefit of mavacamten as assessed by improvement in NYHA class is supported by evidence demonstrating the benefit of mavacamten treatment on a range of physiological endpoints directly relevant to obstructive HCM (LVOT gradient, exercise capacity measured by pVO_2, biomarkers, CMR imaging) as well as more granular, disease-relevant PROs (KCCQ, HCMSQ).

Finally, the EXPLORER-HCM trial does not provide comparative evidence against disopyramide or against SRT. However, as described in sections B.1.1 and B.1.3.2, these are not considered to be relevant comparators for this indication or setting.

These limitations should be considered within the context of the study strengths and the high unmet need in this patient population.

B.2.12.3 Relevance of the evidence base to the decision problem

EXPLORER-HCM is a randomised, controlled trial evaluating the efficacy of mavacamten versus placebo on a background of standard care in patients with symptomatic (NYHA class II–III), obstructive HCM. This is directly relevant to the decision problem, both in terms of population and comparator (noting that EXPLORER-HCM did not include disopyramide as part of standard care, which does not align with the scope but is in line with UK clinical practice according to clinical expert advice).

B.2.12.4 External validity of study results to patients in routine clinical practice

Patients enrolled in EXPLORER-HCM can be considered broadly representative of UK clinical practice in terms of baseline characteristics. In EXPLORER-HCM, the mean age was 58.5 years, 41% patients were female and 91% were white, which is highly comparable to the HCM cohort identified in a large cohort study of electronic health records in England from 1997–2010 (mean age 55.8 years, 41% female, 91.3% white).[42] Thus, the EXPLORER-HCM population is demographically similar to HCM patients in English clinical practice. Although published data on obstructive HCM patient demographics have not been identified, an analysis of CPRD data has indicated that among [redacted] patients with obstructive HCM in England, the mean age was [redacted] years and [redacted]% were female (note that it was not possible to estimate the racial demographics due to data missingness), which closely matches the EXPLORER-HCM cohort.

The EXPLORER-HCM trial compared mavacamten to placebo, on a background of standard medical care of BB, non-dihydropyridine CCB or no medical therapy. Clinical experts have advised that this is representative of the standard care received by the majority of symptomatic, obstructive HCM patients in UK clinical practice.

The outcomes assessed in EXPLORER-HCM are of direct relevance to the indication. Obstructive HCM is a disease with high symptomatic burden and risk of serious

complications, which are linked to the presence of LVOT obstruction. Efficacy endpoints in EXPLORER-HCM demonstrated the benefit of mavacamten on functional status and symptom burden (NYHA class, PROs) and relevant physiological parameters with prognostic implications (LVOT gradient, pVO_2), as well as providing evidence of beneficial cardiac remodelling (TTE, CMR substudy, biomarkers). Given the high unmet need described in B.1.3, improvements in these endpoints are expected to translate to meaningful clinical benefits and improvements in quality of life, encompassing emotional and social benefits and improved productivity, for patients with symptomatic, obstructive HCM.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify studies evaluating the cost-effectiveness of treatments for obstructive HCM. Full details of the methods employed are summarised in Appendix G. In brief, searches were conducted on 2 August 2021, with an updated search performed on 3 December 2021. No publications that presented cost-effectiveness analysis for treatments for obstructive HCM were identified.

B.3.2 Economic analysis

As discussed above, no cost-effectiveness studies of interventions in obstructive HCM were identified to inform the economic analysis presented in this submission (Appendix G). Therefore, a de novo economic model was developed in Microsoft Excel® to address the decision problem. The model was developed following the NICE Process and Methods Guide to Health Technology Evaluations [PMG36] (2022) and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) decision modelling guidelines.[103,104] The economic case presented in this submission is based on conventional cost-utility analysis, assessing the use of mavacamten in combination with standard care (comprising BB or CCB) versus standard care (i.e. BB or CCB monotherapy) alone, for the treatment of symptomatic, obstructive HCM, taking into account a simple patient access scheme (PAS) discount for mavacamten.

B.3.2.1 Patient population

This analysis evaluates the cost-effectiveness of mavacamten in patients with symptomatic (NYHA II–III) obstructive HCM (i.e. the ITT population of the EXPLORER-HCM trial) and therefore aligns with the population defined in the decision problem (B.1.1) and the anticipated marketing authorisation (B.1.2). No relevant subgroups have been identified for consideration, which aligns with the decision problem (B.1.1).

B.3.2.2 Model structure

B.3.2.2.1 Overview of model structure and approach

A Markov model was developed, comprising five mutually exclusive and collectively exhaustive health states representing disease severity; these health states were defined by NYHA classes I, II, III and IV, with a death state accessible from all other health states (Figure 20). The use of a Markov model was deemed appropriate as it can capture the disease progression and patient heterogeneity amongst obstructive HCM patients with a manageable number of health states. Furthermore, a targeted search of cost-effectiveness analyses in other CV diseases identified that a Markov model was the most commonly used framework, demonstrating a precedent for this approach in related indications.[105-107] This Markov structure was then incorporated into a treatment sequencing model (B.3.3.4).

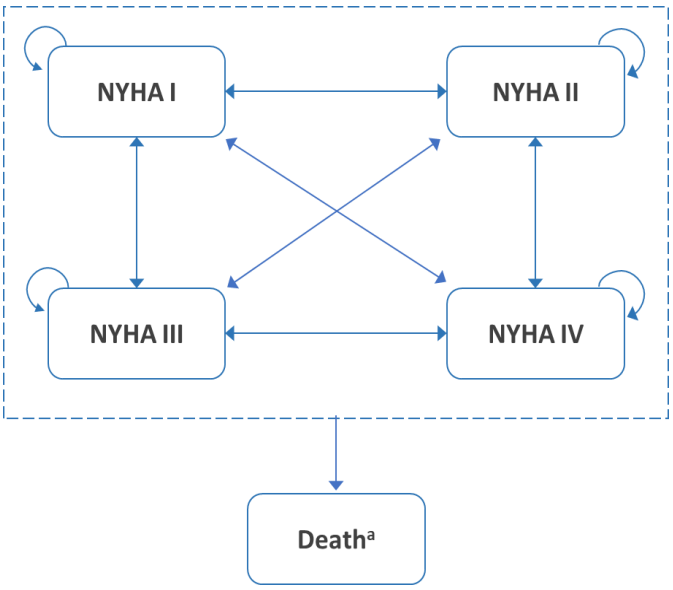


Figure 20. Outline model structure

[a] Death state is accessible from all non-death health states
NYHA: New York Heart Association.

B.3.2.2.2 Health states

Initially, health states based on the primary composite endpoint of the EXPLORER-HCM trial (i.e., NYHA class and pVO_2) were explored and discussed during a global HTA advisory board meeting, which included experts from the UK.[83] However, modelling pVO_2 was not considered feasible, primarily due to the lack of clinically-defined cut-off points for changes in pVO_2 to inform model transitions. Additionally, NYHA class was collected at higher frequency in EXPLORER-HCM than pVO_2 (NYHA class every 2–4 weeks; pVO_2 at baseline and week 30), therefore provided higher granularity.

Health states were therefore defined based on NYHA class. NYHA class is a component of the primary endpoint and a key standalone secondary endpoint in EXPLORER-HCM (B.2.3.1.1), and is widely used in treatment guidelines and in clinical practice for assessment of patients with obstructive HCM.[2,7,19] Furthermore, a NYHA class-based model is a well-established framework for modelling CV diseases and has previously been accepted by NICE in technologies that evaluated interventions for heart disease (TA314, TA696).[106,107] In addition, a published SLR of CEMs for HF found that among 64 studies identified, most publications (n = 40) used NYHA class-based Markov health states, further supporting the use of NYHA class to model disease severity in CV disease.[105]

In the model, all patients enter in either NYHA class II or III health states, in alignment with the decision problem and anticipated marketing authorisation for mavacamten (B.1.2), which is based on the eligibility criteria of the EXPLORER-HCM trial. In EXPLORER-HCM, the number of patients moving to NYHA class IV was very small, irrespective of the treatment arm. Given the limited data available from EXPLORER-HCM trial to inform the transition probabilities to NYHA class IV separately (Appendix M), initially a combined NYHA III/IV health state was considered. However, since the clinical prognosis of NYHA IV patients is expected to be substantially different to that for NYHA III patients, it was decided to keep them as separate health states. At each cycle, patients can transition to any other NYHA class health state or stay in the same health

state based on treatment-specific transition probabilities (B.3.3.2). All patients are at a health state-specific risk of death in each model cycle (B.3.3.5). CV outcomes, such as HF, transplant or stroke are not modelled separately because they are assumed to be captured by the overarching NYHA-based health states.

B.3.2.2.3 Features of the economic analysis

The analysis was conducted from the perspective of the NHS and Personal Social Services (PSS), and costs and quality-adjusted life years (QALYs) were discounted at a rate of 3.5% per annum, consistent with the NICE reference case.[103]

During the first 30 weeks of model, variable cycle lengths have been used, in line with clinical assessment time points of the EXPLORER-HCM trial (Figure 7). This allows for the transition probabilities derived from the trial assessments to be directly applied in the model. After week 30, a cycle length of 28 days has been employed. This aligns with the anticipated dosage of mavacamten (i.e. 28-day cycles, each pack with 28 capsules; one per day). A half-cycle correction was applied to account for state transitions occurring during a cycle. Due to the chronic nature of obstructive HCM, a lifetime horizon (up to age 100 years) was considered appropriate to capture all the relevant differences in costs and utilities between the treatments being compared. Shorter horizons were explored in scenario analyses (section B.3.9.3).

A summary of the model features is presented in Table 23. As mavacamten is first-in-class and the first drug to be evaluated for obstructive HCM, no previous NICE TAs have been identified in this indication.

Table 23. Features of the economic analysis

Factor	Current evaluation	
	Chosen values	**Justification**
Time horizon	Lifetime (up to age 100 years)	Reflects the chronic nature of the indication and maximum life expectancy of patients with symptomatic, obstructive HCM
Cycle length	Aligned with EXPLORER-HCM trial assessment periods until week 30; 28 days thereafter	Allows transition rates derived from the trial assessments to be directly applied in the model until week 30. Thereafter, aligns with the anticipated dosage of mavacamten
Discounting	3.5%	As per NICE reference case
Perspective	NHS/PSS	As per NICE reference case
Treatment waning effect?	None	Expert opinion indicated that this should be considered only if there is a plausible physiological mechanism that would lead us to expect loss of efficacy, with clinicians noting that there is no a priori reason to expect this for mavacamten.[19] This is supported by the clinical trial data, which shows a sustained treatment effect out to 108 weeks (**Figure 16).[19]
Source of utilities	EXPLORER-HCM provides EQ-5D-5L data that has been mapped to EQ-5D-3L and used to derive utility inputs by NYHA class.	As per NICE reference case (EQ-5D instrument used with 5L mapped to 3L; HRQoL reported directly by patients; mapped using UK preference data).
Source of costs	Per the NICE reference case, costs were sourced from NHS reference costs, BNF, PSSRU for all inputs. No reference case costs were identified for SRT, therefore these costs are informed by expert elicitation.	As per NICE reference case with the exception of expert elicitation (Appendix O) used to inform SRT costs, as no published sources of costs for these procedures were identified.

BNF: British National Formulary; HCM: hypertrophic cardiomyopathy; HRQoL: health-related quality of life; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NYHA: New York Heart Association; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; SRT: septal reduction therapies

B.3.2.3 Intervention technology and comparators

The decision problem defines the intervention as ‘mavacamten in combination with standard care’. As discussed in B.1.1, this submission considers standard care to be BB or CCB. Therefore, the modelled intervention is mavacamten + BB/CCB, as per the anticipated marketing authorisation (B.1.2). The modelled comparator, representing standard care, is BB/CCB monotherapy, as detailed in section B.1.1.

Data for the intervention and comparator arms are taken from the mavacamten and placebo arms of the EXPLORER-HCM trial, respectively. This appropriately reflects current and anticipated UK clinical practice. In the model, propranolol was chosen as representative of BBs; no guidelines were identified specifying if any BB should be preferentially used in this population, but this choice is not expected to impact the cost-effectiveness results given the low acquisition costs of BB as a class. In line with clinical practice guidelines, verapamil and diltiazem were included as non-dihydropyridine CCB.[2]

Consistent with the chronic, lifelong nature of obstructive HCM, patients in the modelled mavacamten arm are assumed to continue on treatment unless they satisfy one of the conditions for discontinuation, which are discontinuation due to AEs and discontinuation due to lack of response (B.3.3.3). Discontinuation due to lack of response is in line with the draft SmPC.

B.3.3 Clinical parameters and variables

Evidence to describe the effectiveness of mavacamten in combination with standard care for the treatment of symptomatic (NYHA II–III) obstructive HCM, compared to standard care alone, is primarily derived from the EXPLORER-HCM trial, supplemented with data from the EXPLORER-LTE cohort (B.3.3.2). Evidence for the effect on mortality was derived from real-world studies (B.3.3.5). Evidence for the use and efficacy of subsequent therapies was derived from the published literature and expert elicitation (B.3.3.4).

Due to the paucity of published evidence, expert elicitation was used to inform the frequency and efficacy of SRT (B.3.3.4). As detailed in Appendix O, this expert elicitation study was based on a modified Delphi methodology, which was used to gain quantitative feedback from a UK-based group of clinicians (n = 10) with expertise in treating obstructive HCM. During the panel discussion it became clear that two of the respondents are considered ‘structural interventionalists’ i.e. they specialise in the use of SRT for the treatment of obstructive HCM. Both participants noted that they probably

do not represent the norm and were likely to treat patients of a more severe presentation. Additionally, it was noted that as SRT is a specialist intervention that forms part of treatment escalation, patients were often referred to the structural interventionalists by the other clinicians, introducing a risk of double counting. Therefore, the data used in the model are from the experts excluding the two structural interventionalists (n = 8).

B.3.3.1 Patient parameters

Baseline patient parameters are informed by the baseline characteristics of EXPLORER-HCM and included sex, age and proportion of patients in each NYHA class (Table 24). The modelled population is considered generalisable to symptomatic obstructive HCM patients in the UK (B.2.12.4).

Table 24. Baseline patient characteristics and NYHA class distribution

Parameter	Value	Source
Male, %	59.4	EXPLORER-HCM[3]
Mean age, years	59.0	
Baseline distribution of patients within each NYHA class health state		
NYHA I	0.0	EXPLORER-HCM[3]
NYHA II	72.9	
NYHA III	27.1	
NYHA IV	0.0	
NYHA: New York Heart Association		

B.3.3.2 Transition probabilities

Clinical data from EXPLORER-HCM and the EXPLORER-LTE cohort were primarily used to inform the transition probabilities for the intervention and comparator arms. Short-term transition probabilities were calculated directly from NYHA class data from the clinical trials, using data available over the longest possible time period (B.3.3.2.1 and B.3.3.2.2). However, follow-up was substantially less than the lifetime time horizon of the model, therefore necessary assumptions were made about the long-term efficacy (B.3.3.2.3).

B.3.3.2.1 Mavacamten short-term transition probabilities

Transition probabilities for the intervention arm were computed from the EXPLORER-HCM mavacamten arm data for the period until week 30 (Table 25).

The rationale for this choice is that although a proportion of patients entered the EXPLORER-LTE cohort from the mavacamten arm of EXPLORER-HCM, at week 30 (EOT) of EXPLORER-HCM, treatment with mavacamten was discontinued for an average of 16 weeks, until the baseline assessment for the EXPLORER-LTE cohort. Specifically, between weeks 30 (EOT) and 38 (EOS) of EXPLORER-HCM, there was a washout period, and between week 38 and the baseline assessment for the EXPLORER-LTE cohort, patients were not receiving any study drug, although patients remained on their background standard care therapy. This off-treatment period resulted in a deterioration of NYHA class (Figure 21). The similar and sustained treatment benefit observed in all patients in the EXPLORER-LTE cohort (Figure 22) suggests the deterioration in NYHA class between week 30 and 38 is due to the loss of mavacamten treatment effect upon drug washout, which is supported by the reversibility of mavacamten's mechanism of action (B.1.3.3.1). Therefore, the longest continuous data on mavacamten efficacy is available from baseline to week 30 of EXPLORER-HCM.

Figure 21. NYHA distribution at weeks 30 and 38 of EXPLORER-HCM and at baseline of the EXPLORER-LTE cohort, by treatment arm in EXPLORER-HCM

BB: beta blockers; CCB: calcium channel blocker; HCM: hypertrophic cardiomyopathy; LTE: long-term extension; NYHA: New York Heart Association.

Figure 22. Evolution of NYHA class distribution of the mavacamten arm in EXPLORER-HCM (to 30 weeks) and the full EXPLORER-LTE cohort

Note that only 13 patients are observed at week 108 in the data cut used for the analysis.
BB: beta blockers; CCB: calcium channel blocker; HCM: hypertrophic cardiomyopathy; LTE: long-term extension; NYHA: New York Heart Association.

An alternative approach could have been to use data from patients in the EXPLORER-LTE cohort who had been on placebo in EXPLORER-HCM (i.e. initiating mavacamten

for the first time in the EXPLORER-LTE cohort) to further inform the short-term transition probabilities for the modelled mavacamten + BB/CCB arm. However, the frequency of NYHA assessment time points was different between the EXPLORER-LTE cohort and the EXPLORER-HCM trial, therefore, the statistical approaches required to combine these two datasets was considered likely to introduce a greater degree of uncertainty than using solely the EXPLORER-HCM data. However, when comparing the general evolution of the proportion of patients in each NYHA class for the mavacamten arm of EXPLORER-HCM and all patients in the EXPLORER-LTE cohort (i.e. regardless of treatment arm allocation in the EXPLORER-HCM) this is very similar, suggesting a similar treatment benefit from mavacamten in the two studies (Figure 22). Also, this treatment benefit is sustained throughout the EXPLORER-LTE cohort data up to week 108 (Figure 22), although it should be noted that in the most recent DBL only 13 patients have an assessment at week 108.

Therefore, including only data from baseline to week 30 was deemed as the most appropriate approach to model the effect of mavacamten on disease severity and to avoid the distortion introduced by the washout and off-treatment period prior to entering the EXPLORER-LTE cohort.

B.3.3.2.2 BB/CCB monotherapy short-term transition probabilities

The short-term transition probabilities for the comparator (BB/CCB monotherapy) arm in the base case were derived from the placebo arm of EXPLORER-HCM, where placebo + standard medical therapy is assumed to represent BB/CCB monotherapy. The longest available data were used to inform disease progression for patients with obstructive HCM receiving standard care, that is, data from the EXPLORER-HCM baseline up to the baseline assessment of the EXPLORER-LTE cohort, as explained in greater detail below.

The baseline assessment for the EXPLORER-LTE cohort from the October 2020 DBL was on average (mean) 59.7 days (SD = 56.1; range: 3–262) after the end of study assessment of EXPLORER-HCM (week 38 EOS).[72] The baseline assessment for the EXPLORER-LTE cohort from the August 2021 DBL was on average (mean) 66.5 days

(range: 3–359) after the end of study assessment of EXPLORER-HCM (week 38 EOS).[9] As a modelling assumption, the time from the EXPLORER-HCM EOS to the EXPLORER-LTE cohort baseline assessment is approximated as 8 weeks, and as such is henceforth referred to as week 46. The use of data up to week 46 to inform the efficacy in the comparator arm was considered the most appropriate approach for the base case as it represents the longest identified continuous data on the efficacy of standard care medical therapies. However, some uncertainty could be introduced by the variability in time between the EXPLORER-HCM EOS and the EXPLORER-LTE cohort baseline, therefore to address the impact of this uncertainty, short-term transition probabilities up to week 38 were used in a scenario analysis (B.3.9.3).

Table 25 presents the base case transition probabilities by NYHA class at each cycle/assessment timepoint during the short-term period for the intervention and comparator. Missing data due to missed NYHA class assessments were imputed using the last observation carried forward approach.

Table 25. Short-term transition probabilities

Week	To / From	Mavacamten + BB/CCB, %				BB/CCB monotherapy, %			
		NYHA I	NYHA II	NYHA III	NYHA IV	NYHA I	NYHA II	NYHA III	NYHA IV
Baseline to week 4	NYHA I*	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							
	NYHA IV*	[redacted]							
Week 4 to 6	NYHA I	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							
	NYHA IV	[redacted]							
Week 6 to 8	NYHA I	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							
	NYHA IV	[redacted]							
Week 8 to 12	NYHA I	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							

	NYHA IV	[redacted]							
Week 12 to 14	NYHA I	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							
	NYHA IV	[redacted]							
Week 14 to 18	NYHA I	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							
	NYHA IV	[redacted]							
Week 18 to 22	NYHA I	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							
	NYHA IV	[redacted]							
Week 22 to 26	NYHA I	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							
	NYHA IV	[redacted]							
Week 26 to 30	NYHA I	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							
	NYHA IV	[redacted]							
Week 30 to 38	NYHA I	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							
	NYHA IV	[redacted]							
Week 38 to 46#	NYHA I	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							
	NYHA IV	[redacted]							

*No transition probability data for NYHA I and IV were available from EXPLORER-HCM for week 0 (i.e., baseline) to week 4 since the trial included only patients who were NYHA class II or III at baseline.
Week 46 refers to day 0 of EXPLORER-LTE cohort NYHA distribution.
NA represents a timepoint within the trial in which no patients were assessed to be within the defined NYHA class.
BB: beta-blocker; CCB: calcium channel blocker; HCM: hypertrophic cardiomyopathy; LTE: long-term extension; NYHA: New York Heart Association.

B.3.3.2.3 Long-term transition probabilities

In the base case, no interstate transitions between NYHA classes are modelled in the long term. Patients in the mavacamten + BB/CCB arm retain the NYHA class attained at

the end of week 30 as the main response measure and remain in the same health state throughout the time horizon, unless they escalate to SRT or move to the death state. Patients in the BB/CCB monotherapy arm retain the NYHA class attained at the end of week 46 (the baseline assessment of the EXPLORER-LTE cohort), on the same assumption.

Although there is longer-term efficacy data (up to 108 weeks) for patients on mavacamten from the EXPLORER-LTE cohort, it was not considered appropriate to compute transition probabilities for the mavacamten + BB/CCB arm based on the LTE data for the reasons discussed in section B.3.3.2.1. Therefore, the long-term data were used to validate the long-term transition probabilities but did not directly inform the modelled efficacy. This may be considered a conservative assumption, as potential additional benefit of mavacamten beyond 30 weeks is not captured.

The choice of long-term transition probabilities in the base case is justified by the stabilisation of NYHA class distribution observed towards the later periods of the EXPLORER-HCM trial for mavacamten patients (Figure 23). A similar pattern was observed in the EXPLORER-LTE cohort, as shown in the bottom panel of Figure 22.

Figure 23. NYHA class distribution in EXPLORER-HCM and the baseline assessment of the EXPLORER-LTE cohort, by treatment arm allocation in EXPLORER-HCM

This figure was built using the total number of observations at a given assessment timepoint, which is lower in later timepoints due to the fact that some patients are censored. The last bar corresponds to the baseline assessment of the EXPLORER-LTE cohort, which the assessment at day 0 has been defined as week 46. BB: beta blockers; CCB: calcium channel blockers; HCM: hypertrophic cardiomyopathy; LTE: long-term extension; NYHA: New York Heart Association.

By modelling no NYHA transitions in either arm in the long-term (unless patients escalate treatment, see section B.3.3.4.1) in the base case, the model assumes there is no underlying disease progression within either arm. Although a simplified assumption, there is a paucity of evidence available to inform transition probabilities over a longer time horizon for both mavacamten and standard care. Indeed, no evidence of an impact

of standard care on disease progression was found in the clinical SLR, and natural history data are also sparse. Given its mechanism of action, clinical advisors were in agreement that mavacamten is likely to slow disease progression relative to standard care,[20] and as such, the assumption of a lack of progression in both arms is expected to be conservative, favouring standard care.

An alternative approach to modelling long-term effectiveness, where the last observed set of transition probabilities would be carried forward throughout the model's time horizon, was discussed in a UK advisory board meeting.[19] This approach was not considered appropriate by the experts consulted because the implication would be an indefinite and recursive treatment benefit, in addition to that already achieved at week 30. Although additional benefit for mavacamten was observed in the EXPLORER-LTE cohort post week 30 (Figure 22), it is unlikely that continued benefit would accrue indefinitely, and this approach was considered to lack face validity.

B.3.3.3 Discontinuation of mavacamten

In the model, patients in the intervention arm can discontinue mavacamten due to SAEs (B.3.3.3.1) or lack of response (B.3.3.3.2). Inputs for discontinuation of mavacamten were sourced from EXPLORER-HCM, and are listed in Table 26.[108]

Table 26. Inputs for discontinuation of mavacamten

Parameter	NYHA I	NYHA II	NYHA III	NYHA IV	Source
Discontinuation due to AEs and non-compliance					
Discontinuation at week 30, %	1.6	1.6	1.6	1.6	EXPLORER-HCM[3]
Annual discontinuation in post-trial period, %	2.8	2.8	2.8	2.8	Assumption based on EXPLORER-HCM
Discontinuation based on lack of NYHA class improvement from baseline					
Discontinuation at week 30 due to no response, %	0.0	[redacted]	100.0	100.0	EXPLORER-HCM[3]
AEs: adverse events; HCM: hypertrophic cardiomyopathy; NYHA: New York Heart Association					

The distribution of subsequent treatments is outlined in Table 27. In the base case, all patients who discontinue mavacamten (which can occur from week 30 onwards) receive

BB/CCB monotherapy in the cycle following discontinuation. Patients can then continue on BB/CCB monotherapy or escalate to subsequent treatments (section B.3.3.4). To explore the impact of this assumption, a range of scenarios were conducted (B.3.9.3).

Table 27. Base case distribution of treatments following mavacamten discontinuation

Subsequent treatment	NYHA I	NYHA II	NYHA III	NYHA IV
BB/CCB monotherapy, %	100	100	100	100
Disopyramide + BB/CCB, %	0	0	0	0
SRT + BB/CCB, %	0	0	0	0
BB: beta blocker; CCB: calcium channel blocker; NYHA: New York Heart Association; SRT: septal reduction therapies				

B.3.3.3.1 Discontinuation of mavacamten due to SAEs

End of trial period (week 30): It was assumed that no patients in the intervention arm discontinued mavacamten during first 30 weeks, but a proportion of patients discontinued mavacamten at the end of the trial period (i.e. week 30) due to the incidence of SAEs. The EXPLORER-HCM trial reported a discontinuation rate of 1.6% due to SAEs over the 30 weeks (Table 26). This rate was implemented in the model at the end of the trial period as a one-off proportion, applied evenly across all NYHA health states.[3]

After week 30: A constant proportion of patients in the model discontinue mavacamten due to SAEs. It was assumed that the discontinuation rate of mavacamten would be similar to that observed in EXPLORER-HCM, therefore an annual discontinuation rate of 2.8% has been applied evenly, regardless of NYHA class, derived by scaling the trial discontinuation of 1.6% over 30 weeks to an annual rate (Table 26).[3] To explore the impact of the discontinuation assumptions, two scenarios were explored; one in which all patients remained on mavacamten in the post-trial period, and one in which the annual discontinuation rate was halved to 1.4% (section B.3.9.3).

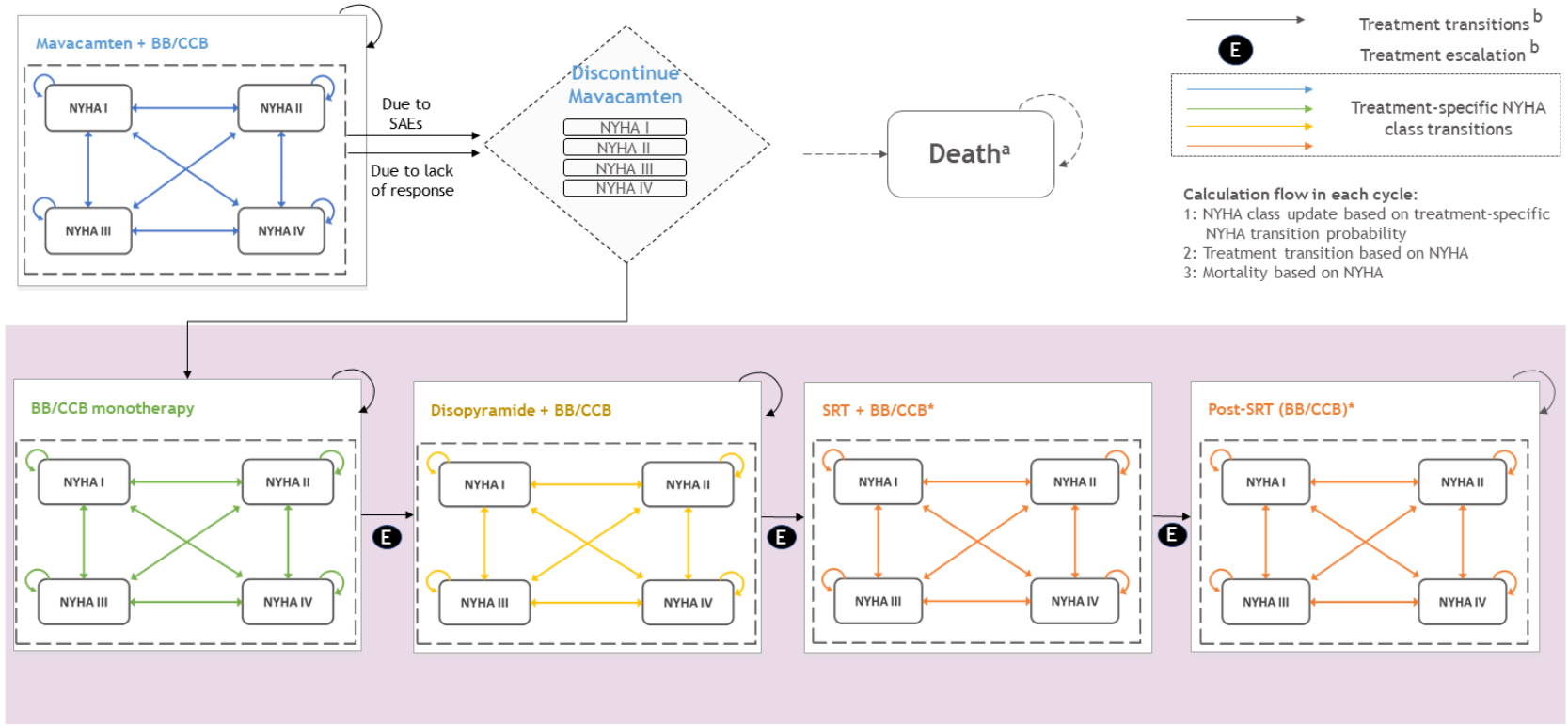
B.3.3.3.2 Discontinuation of mavacamten due to lack of response

The draft SmPC recommends considering discontinuation of mavacamten [redacted] (Appendix C). To align with this, the base case models discontinuation from mavacamten due to lack of response at week 30; lack of response is defined as no NYHA class improvement at week 30 compared to baseline. The proportion of patients in each NYHA class who discontinue due to lack of response was derived from EXPLORER-HCM (Table 26). Due to the assumption of no NYHA class transitions post week 30 for mavacamten (section B.3.3.2.3), no further discontinuation due to lack of response occurs in the base case. This assumption of discontinuation was validated by clinical expert advice; most clinicians felt that patients should not continue on treatment without deriving a clinical benefit, and indicated that discontinuation due to failure to meet the secondary endpoint after 30 weeks is clinically justified in terms of the current evidence base.[19]

B.3.3.4 Subsequent treatments

The Markov structure described in B.3.2.2.1 was incorporated into a treatment sequencing model (Figure 24), aligning with the treatment pathway described in B.1.3.2. This approach was validated in a clinical advisory board.[19,20]

Figure 24. Schematic of treatment sequencing model



[a]Death state is accessible from all non-death health states.
[b]Treatment transitions are based on NYHA classes.
*Treatment with SRT procedure was modelled as an event (tracked using tunnel state). Hence, patients treated with SRT were moved to post-SRT state after one cycle.
Pink shaded box highlights the treatment pathway as outlined in the ESC guidelines.
BB: beta blocker; CCB: calcium channel blocker; NYHA: New York Heart Association; SAE: serious adverse event; SRT: septal reduction therapy.

Patients in the modelled intervention and comparator arms remain on their initial treatment (B.3.2.3) for the first 30 weeks, aligning with the EXPLORER-HCM trial (B.2.3.1.1).

At the end of week 30 and at each subsequent cycle:

- patients in the comparator arm can remain on their initial therapy or escalate to subsequent therapies, as per the ESC guidelines[2] (B.1.3.2);
- patients in the intervention arm can remain on their initial therapy or discontinue mavacamten treatment (B.3.3.3) and remain on BB/CCB monotherapy. Patients who discontinue mavacamten are then subject to the same modelled subsequent therapies.

A NYHA class-specific proportion of patients escalates to subsequent therapy each cycle (Table 28). The same probability of escalation applies regardless of whether patients initiate in the comparator arm or initiate in the mavacamten arm and then discontinue mavacamten.

In the base case, patients who experience escalation receive disopyramide + BB/CCB as the first subsequent therapy combination. Disopyramide is modelled as a short-term therapy prior to SRT, meaning that all patients who escalate to disopyramide + BB/CCB then discontinue disopyramide and undergo SRT. The proportion of patients who escalate from BB/CCB monotherapy to disopyramide is therefore directly linked to the rate of SRT procedures. No published data on SRT rates by NYHA class were identified, therefore this was informed by the expert elicitation exercise (Appendix O). Clinicians estimated the proportion of patients who would receive SRT per NYHA class (NYHA I: [redacted]%; II: [redacted]%; III: [redacted]%; IV: [redacted]%; Appendix O). These proportions were then adjusted dynamically in the model based on the mean NYHA-adjusted overall survival to derive annual rates of SRT, which were used to derive the annual proportion of patients who escalate from BB/CCB monotherapy to disopyramide + BB/CCB (Table 28).

This assumption is based on expert clinical advice that disopyramide is not typically used as a long-term therapy due to the tolerability issues and tachyphylaxis (B.1.3.2.3.3). As supported by insights from a UK advisory board meeting, it was assumed that all patients will be escalated to SRT at 9 months post-disopyramide initiation.[19] This assumption has been tested in scenario analyses (section B.3.9.3).

Treatment with SRT is modelled as an incident event, with patients undergoing an SRT-dependent NYHA class health state transition on event occurrence, and incurring incident costs and mortality associated with the procedure. Patients treated with SRT move to a post-SRT state after one cycle. Modelling SRT as a tunnel state to a post-SRT state allows for incorporation of different transition probabilities and other key inputs pre- and post-SRT, in turn reflecting the differences in clinical profiles of the patients more accurately. In the post-SRT state, patients revert back to BB/CCB monotherapy.

Table 28. Proportions of patients who undergo NYHA class-dependent treatment escalation

Treatment	NYHA I	NYHA II	NYHA III	NYHA IV	Source
Annual escalation from BB/CCBs monotherapy* (%)	[redacted]	[redacted]	[redacted]	[redacted]	Expert elicitation study (Appendix O)
Annual escalation from BB/CCB + disopyramide# (%)	[redacted]	[redacted]	[redacted]	[redacted]	Expert elicitation study(Appendix O)

*Escalation rates from BB/CCB monotherapy were adjusted dynamically based on mean survival by each NYHA class.
#The assumption that all patients escalate from disopyramide to SRT at 9 months results in an annual escalation rate above 100%.
BB: beta-blocker; CCB: calcium channel blocker; NYHA: New York Heart Association; SRT: septal reduction therapy.

B.3.3.4.1 Efficacy of subsequent treatments

Transition probabilities representing the efficacy of subsequent therapies were applied in the model based on the following assumptions:

Disopyramide + BB/CCB: It was assumed that patients receiving disopyramide + BB/CCB retain their NYHA class from the time of treatment initiation. This assumption

was made due to a paucity of evidence to inform disopyramide efficacy in this indication.

SRT + BB/CCB: No published evidence in a UK setting describing the efficacy of SRT was identified. Therefore, efficacy estimates for SRT used in the base case analysis were collected via the expert elicitation process (Appendix O), excluding the two experts regarded as structural interventionalists.

The clinical SLR identified one published study describing the efficacy of SRT based on NYHA class was identified in a Ukrainian population (Knyshov *et al*., 2013).[109] In this study, a total of 42 patients received either myectomy or septal ablation with a mean baseline age of 29 or 34 years, respectively. The applicability of this study to the UK setting was considered questionable, therefore this was not used in the base case. However, as this was the only study identified in which clear transition probabilities between states could be calculated, this was explored in scenario analysis (B.3.9.3).

Treatment with SRT was modelled as an event; incident transition probabilities were applied (Table 29) and patients moved to a post-SRT state after one cycle.

Table 29. Transition probabilities for patients receiving SRT + BB/CCB

Option	To / From	Transition probabilities, %			
		NYHA I	NYHA II	NYHA III	NYHA IV
Base case					
Expert elicitation study (Appendix O)	**NYHA I**	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA II	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]
Scenario					
Knyshov et al. (2013)[109]	**NYHA I**	100.0	0.0	0.0	0.0
	NYHA II	33.3	66.7	0.0	0.0
	NYHA III	0.0	85.7	14.3	0.0
	NYHA IV	0.0	0.0	33.3	66.7

BB: beta blocker; CCB: calcium channel blocker; NYHA: New York Heart Association; SRT: septal reduction therapy

Patients in the post-SRT state were assumed to remain in the same health state throughout the time horizon due to a paucity of long-term efficacy data identified in the literature.

B.3.3.5 Modelling mortality

General population ACM rates were obtained from the latest (i.e., 2018–2020) UK life tables published by the Office for National Statistics.[110] These rates reflect the average mortality rates of the UK population, adjusted for the EXPLORER-HCM age and sex distribution.

As described in Table 1, data were not available from EXPLORER-HCM to directly inform mortality associated with the intervention or comparator, and no relevant alternative studies were identified in the clinical SLR. As HCM is associated with increased mortality relative to the general population (B.1.3.1.3.3), it is a relevant outcome, therefore alternative data were sought to inform the model. It is well established in both obstructive HCM and related indications that there is a relationship between NYHA class and mortality (B.1.3.1.3.4); this was also supported by expert clinical opinion.[20] Furthermore, mavacamten is designed to improve the cardiac dysfunction associated with the underlying pathophysiology of obstructive HCM, and a beneficial impact of mavacamten on cardiac function, clinically meaningful improvements in cardiac injury biomarkers and structural improvements in heart anatomy are supported by data from EXPLORER-HCM and the CMR substudy (Appendix M).[3,68] Therefore, it is anticipated that mavacamten may attenuate disease progression, thereby reducing the mortality associated with more advanced disease. However, no mortality data specific to the intervention or comparator technologies in obstructive HCM, particularly NYHA class-specific mortality, were identified in the established literature.

To address this evidence gap, the Company undertook two RWE studies to describe the mortality in obstructive HCM patients by NYHA class. Further details can be found in Wang *et al*., 2022,[44] Lakdawala *et al*., 2021[45] and Appendix N. In brief, one was an EMR study that identified 3,322 obstructive HCM patients within a US-based cardiac

cohort who had at least one NYHA class assessment after HCM diagnosis, which allowed mortality to be stratified by NYHA class and adjusted for age, sex and race.[44] The other study used registry data from SHaRe and identified 2,495 patients with obstructive HCM and at least one NYHA class assessment; 1-year unadjusted RR estimates from this study have been published by Lakdawala *et al.* 2021,[45] while adjusted analyses are currently unpublished (Appendix N).

It was assumed that the mortality of patients in NYHA class I was the same as the general population. In the base case, hazard ratios (HRs) from the EMR study[44] were used to reflect the excess mortality associated with NYHA class II, III and IV compared to class I (Table 30). These were considered more suitable to inform the modelling than the SHaRe data because NYHA classes III and IV could not be disaggregated in the SHaRe data. The unadjusted and adjusted SHaRe data analyses have been explored in scenario analysis (B.3.9.3), with the composite NYHA class III/IV HR applied to both health states in the model. This assumption is likely to overestimate the mortality because the HR for the combined NYHA III/IV class is driven by the much higher mortality in NYHA class IV patients. Note also that HRs are preferred over RRs as HR estimates account for both number and timing of events (i.e., time to event analysis) whereas RR considers only total number of events.

Table 30. Mortality relationship between NYHA classes relative to NYHA class I

NYHA class	HRs from Wang *et al.* 2022[44] (base case)	Unadjusted 1-year RRs from SHaRe analysis[45] (Lakdawala *et al.* 2021[45]) (scenario)	Adjusted HRs from SHaRe analysis (Appendix N) (scenario)
I	Reference class (ACM) i.e. 1.00		
II vs I	1.51	2.38	[redacted]
III vs I	2.77	9.38*	[redacted]
IV vs I	7.09		

*Composite III/IV HR applied to both III and IV classes separately.
ACM: all-cause mortality; HR: hazard ratio; SHaRe: Sarcomeric Human Cardiomyopathy Registry; NYHA: New York Heart Association; RR: relative risk

In addition to the NYHA-based mortality rates, the model captured mortality associated with SRT. A published SLR and meta-analysis by Bytyçi et al. 2020 reported a short-term mortality risk of 1.12% and 1.27% in patients receiving alcohol-ablation therapy and myectomy, respectively.[24] Based on this, a weighted average of 1.2% was utilised as a one-off surgical mortality in the SRT tunnel state.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

HRQoL data were collected in the EXPLORER-HCM trial using the EQ-5D-5L instrument (B.2.6.1.3). Assessments were made at baseline (day 1), weeks 6, 12, 18, 30 (EOT) and 38 (EOS).

B.3.4.2 Mapping

Details of the utility analysis are given in Appendix P. In brief, the EQ-5D-5L data were mapped to the EQ-5D-3L using the Hernandez-Alava and Pudney crosswalk method,[111] estimated on the EEPRU dataset,[112] in alignment with the NICE 2022 methods update.[103] The EQ-5D-3L value set proposed by Dolan was then applied to generate the EQ-5D-3L utility values.[113]

To account for the repeated nature of the data and explore the influence of demographic characteristics and time from treatment on the utility values, linear mixed effects models for repeated measures were used to derive the health state utility values ranging from 0 to 1. Once the optimal model was selected, least square mean estimates of the EQ-5D-3L utility values along with the corresponding standard errors (SE) were calculated for each health state.

The preferred random intercept model specification featured a random intercept at the subject level. In addition, only binary indicators for current NYHA class were statistically significant in the model. Treatment arm was not found to be a statistically significant variable, meaning that the treatment effect is well captured by NYHA class and indicating that it is appropriate to use health state (NYHA)-specific utility values across

both treatment arms in the CEM. This finding does not contradict the trial data showing that patients in the mavacamten arm experienced greater improvements in utility compared to those in the placebo arm; analysis indicates that the increases in utility seem to originate from improvements in NYHA class, which were more frequent in the mavacamten arm (Appendix P).

NYHA class I was used as the reference category. Due to the small number of observations in NYHA class IV, it was not possible to estimate a utility value for those patients: two of the three NYHA class IV observations were at timepoints when EQ-5D was not assessed and the remaining observation had missing values for some of the modelled covariates and was not retained. The trial utility values associated with NYHA classes I, II and III are presented in Table 31.

Table 31. Utility values from EXPLORER- HCM

NYHA class	Utility value, mean (SE)
I	[redacted]
II	[redacted]
III	[redacted]
SE: standard error; NYHA: New York Heart Association	

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify studies evaluating HRQoL associated with treatments for symptomatic, obstructive HCM. Full details of the SLR can be found in Appendix H. The SLR identified 11 publications that investigated HRQoL in patients with obstructive HCM: five studies provided utilities in patients who underwent SRT, five provided utilities in patients who underwent pacing and one study reported utilities measured in EXPLORER-HCM. Note that none of the five studies reporting HRQoL related to SRT used the EQ-5D, therefore these were not used to inform SRT-related utility in the model.

B.3.4.4 Adverse reactions

The incidences of serious AEs derived from the mavacamten and placebo arms of EXPLORER-HCM were used to inform the probabilities of AEs in the modelled

intervention and comparator arms, respectively (Table 32). Specifically for the subsequent therapies disopyramide or SRT, it is acknowledged that both are associated with side-effects and AEs, however, given the limited quantifiable evidence on these, as a conservative assumption specific AEs in the model were assumed to be the same as the placebo arm of EXPLORER-HCM (although note that mortality associated with SRT is modelled (B.3.3.5)). This is likely to be a conservative assumption given the side effects associated with disopyramide and the range of AEs associated with SRT, as described in B.1.3.2.3.3 and B.1.3.2.4. For each modelled AE, the trial-derived 30-week probability was converted to a 4-weekly incidence rate, which was applied across the remaining time horizon. Sudden death was not included to avoid double counting with the mortality inputs (B.3.3.5).

Table 32. Incidence of modelled AEs

AE	Intervention arm: mavacamten + BB/CCB (%)		Comparator arm: BB/CCB monotherapy (%)		Disopyramide + BB/CCB(%)	Post-SRT: BB/CCB monotherapy (%)
	n (%)	4-week rate (%)	n (%)	4-week rate (%)		
Syncope	2 (1.6)	0.22	1 (0.8)	0.10	0.10	0.10
TIA	0 (0.0)	0.00	1 (0.8)	0.10	0.10	0.10
Cardiac failure congestive	0 (0.0)	0.00	1 (0.8)	0.10	0.10	0.10
Viral gastroenteritis	0 (0.0)	0.00	1 (0.8)	0.10	0.10	0.10
UTI	0 (0.0)	0.00	2 (1.6)	0.21	0.21	0.21
Source	EXPLORER-HCM[3]		EXPLORER-HCM[3]		Assumption	Assumption

Mavacamten arm: N=123; comparator arm: N=128.
AE: adverse event; BB, beta-blocker; CCB, calcium channel blocker; SRT, septal reduction therapy; TIA: transient ischaemic attack; UTI: urinary tract infection

Disutility associated with AEs was not included in model due to the potential double counting of AE impact within the underlying utilities observed in the trial. Further details on modelled AEs can be found in section 0.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Of the studies identified in the SLR, only the publication describing HRQoL from EXPLORER-HCM was relevant to the intervention and comparator arms in the model. Thus, trial-based (i.e., EXPLORER-HCM) utilities, which reflect the actual experience of obstructive HCM patients in different NYHA classes being treated with mavacamten and/or BB/CCB monotherapy, were considered most appropriate for the model. This is in line with the NICE reference case.[12] The health state utility values chosen for the cost-effectiveness analysis are summarised in Table 33.

Table 33. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (SE)	95% CI	Reference in submission	Justification
NYHA I	[redacted]*	[redacted]	B.3.4.1 and B.3.4.2	Trial utilities from EXPLORER-HCM were used for NYHA classes I–III. These were considered the most appropriate data to inform the CEM as they were evaluated in a patient population relevant to the indication. Comparison with utilities identified in the literature for NYHA class in other CV disease areas suggest that the utilities used in the CEM are a reasonable reflection of HRQoL in patients experiencing symptoms associated with NYHA classes I–III.
NYHA II	[redacted]*	[redacted]		
NYHA III	[redacted]*	[redacted]		
NYHA IV	[redacted]*	[redacted]	Assumption	No data were identified to inform the utility value for NYHA class IV therefore the utility was assumed to be the same as NYHA class III. This is a conservative assumption that may favour the comparator arm, as patients in the comparator arm spend longer in higher NYHA class health states.

*Note than an age-related utility decrement was applied using the method published by Ara and Brazier, 2010.[114]

CEM: cost-effectiveness model; CI: confidence interval; CV: cardiovascular; HCM: hypertrophic cardiomyopathy; HRQoL: health-related quality of life; NYHA: New York Heart Association; SE: standard error.

Due to the small number of EQ-5D assessments for patients in NYHA class IV in EXPLORER-HCM, it was not possible to calculate trial-based utilities for this health

state. No relevant alternative sources of utility values for NYHA class IV were identified in the literature. Therefore, it is assumed that NYHA class IV patients had the same utilities as NYHA class III. This is likely to overestimate the real utility values for NYHA class IV patients, which is a conservative assumption that potentially favours the comparator arm.

The utility value of [redacted] associated with NYHA I is higher than the utility computed using the model proposed by Ara and Brazier (2010),[114] which predicted a counterfactual general population utility of 0.848. This may be accounted for by the nature of the indication. As described in section B.1.3.1.2, LVOTO can be influenced by extrinsic factors such as meals, alcohol consumption and physical activity. Therefore, patients with symptomatic, obstructive HCM may modify their lifestyle substantially to accommodate their symptoms and, through a process of adaptation, may then perceive their baseline utility as closer to population norms. Subsequent treatment effect after entering the trial means patients report increased utility compared to their baseline, leading to higher utilities than the general population norm in those patients who are now truly asymptomatic (B.1.3.1.3.1). This phenomenon was described by one clinical expert as patients “didn’t know what they couldn’t do until they had been treated, and so felt disproportionately good”.

Additionally, a comparison with existing literature reporting EQ-5D utilities by NYHA class in other disease areas indicates that utility values higher than general population are a common finding in patients in NYHA class I or equivalent functional status:

- Berghammer et al. (2013) computed EQ-5D-3L utilities using the Danish value set for both symptomatic and asymptomatic patients with congenital heart disease. The average EQ-5D utility was 0.91 among asymptomatic patients.[115] Since NYHA I patients are broadly asymptomatic, it is reasonable to consider them comparable to the asymptomatic patients of Berghammer et al.
- An EQ-5D-5L value set developed by Gandhi et al (2021) specifically to represent the preferences of patients with heart disease estimates the utility of patients in NYHA I at 0.960 (SD = 0.093).[116]

The utilities of NYHA I patients in the EXPLORER-HCM trial are very similar to those from the asymptomatic patients of Berghammer et al ([redacted] vs 0.91) and slightly lower than those reported by Gandhi et al (0.960 vs [redacted]), despite similar average patient age in both studies.

To account for the natural decline in HRQoL associated with increasing age, age-related utility decrements were estimated in the model, using the regression equation published by Ara and Brazier et al. (2010).[114]

Although no alternative utilities directly relevant to the indication were identified in the SLR, a search for utilities stratified by NYHA class in other CV indications identified a publication by Göhler *et al*.,[117] which published utilities for patients with chronic HF following acute myocardial infarction, therefore these were used in a scenario analysis (B.3.9.3)

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify studies evaluating healthcare resource utilisation (HCRU) associated with symptomatic, obstructive HCM. Full details of the SLR can be found in Appendix I. In brief, electronic databases, relevant conference proceedings and websites were searched on 2 August 2021, with an updated search performed on 3 December 2021. The SLR found 27 publications that met the eligibility criteria. Of these, only two were relevant to the UK setting,[118,119] and both reported resource use related to SRT only, unstratified by NYHA class, therefore were not adequate to inform the model. This evidence gap was addressed using the expert elicitation exercise summarised in sections B.2.2.2 and B.3.3 and detailed in Appendix O, which provided estimates of HCRU by NYHA class.

For each modelled cost category, unit costs were multiplied by the frequency of a certain type of resource used within each cycle. The cost per cycle was then multiplied by the distribution of patients in each health state per cycle to calculate the total costs.

All costs are expressed in 2021 Great British Pounds (GBP). Costs were inflated to 2021 GBP when appropriate based on UK Consumer Prices Index data.[120]

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Mavacamten acquisition costs

The acquisition costs of mavacamten are outlined in Table 34. Note that [redacted]. No administration costs are modelled because mavacamten is an oral tablet, self-administered. A simple discount PAS has been applied, resulting in a fixed net price of £[redacted], which corresponds to a net price of £[redacted] per patient per year (PPPY).

Table 34. Mavacamten acquisition costs

Form	Pack size	Dosing schedule	List price	PAS price	Source
Tablet	28	2.5 mg, once per day*	£[redacted] per pack (2.5 mg capsules x28)#	£[redacted] per pack (2.5 mg capsules x28)#	Dosing: draft SmPC Cost: BMS
		5 mg, once per day*	£[redacted] per pack (5.0 mg capsules x28)#	£[redacted] per pack (5.0 mg capsules x28)#	
		10 mg, once per day*	£[redacted] per pack (10 mg capsules x28)#	£[redacted] per pack (10 mg capsules x28)#	
		15 mg, once per day*	£[redacted] per pack (15 mg capsules x28)#	£[redacted] per pack (15 mg capsules x28)#	

*Dose titration outlined in Table 2 and detailed in the draft SmPC (Appendix C).
#[redacted]. This PAS discount results in a net price of £[redacted] per patient per year
PAS: patient access scheme; SmPC: Summary of Product Characteristics

The impact on cost of missing doses or protocol-driven temporary discontinuation of mavacamten has been modelled using the adherence rate of [redacted]% from EXPLORER-HCM.

B.3.5.1.2 Comparator and subsequent therapy acquisition costs

Costs for comparators (BB/CCB) and subsequent medical therapy (disopyramide) were estimated using data from the drug labels and the British National Formulary (BNF; accessed February 2022).[121] No published sources of SRT costs were identified, therefore these costs were informed by expert elicitation (see B.2.2.2, B.2.3.3 and B.3.5.2 for details). Costs are summarised in Table 35. No administration costs were modelled because the medical therapies are oral formulations that can be self-administered, and the full costs of SRT were assumed to be captured within the one-off cost used derived from the expert elicitation.

Table 35. Costs of modelled comparators and subsequent therapies

Treatment	Form	Pack size	Dosing	Cost	Source
Propranolol (BB)	10 mg tablet	28	10 mg, three times daily	£0.25 per pack	Costs: eMIT[122] Posology: BNF, June 2022[123]
Verapamil (CCB)	80 mg tablet	84	80 mg, three times daily	£1.51 per pack	Costs: eMIT[122] Posology: BNF, June 2022[124]
Diltiazem (CCB)	60 mg modified release tablet	84	60 mg, three times daily	£9.03 per pack	Costs: eMIT[122] Posology: BNF, June 2022[121]
Disopyramide	100 mg capsule	100	300 mg, daily	£12.95 per pack	Costs: eMIT[122] Posology: BNF, June 2022[125]
ASA	Modelled as one-off procedure			£[redacted] per procedure	Expert elicitation (Appendix O)
Septal myectomy	Modelled as one-off procedure			£[redacted] per procedure	

*Dose titration outlined in Table 2 and detailed in the draft SmPC (Appendix C). ASA: alcohol septal ablation; BB: beta-blocker; BNF: British National Formulary; CCB: calcium channel blocker.

The market share of the treatment options within each class were used to calculate a weighted cost (Table 36). The distribution between BB and CCB were informed by the EXPLORER-HCM trial (Table 24). Within the CCB class, the proportion of patients receiving diltiazem and verapamil was assumed to be 50% each, while the market share of ASA and septal myectomy were obtained based on crude pooling of the expert

elicitation responses (Appendix O). The impact of alternative market shares for SRT have been explored in scenario analyses (B.3.9.3).

Table 36. Market shares of comparators and subsequent therapies

Treatment	Proportion of patients (%)	Source
Proportion of patients on BB or CCB		
BB	81.8	EXPLORER-HCM[3]
CCB	18.2	
Market share of CCB		
Diltiazem	50.0	Assumption
Verapamil	50.0	
Market share of SRT		
ASA	[redacted]	Expert elicitation study (Appendix O)
Septal myectomy	[redacted]	

ASA: alcohol septal ablation; BB: beta-blocker; CCB: calcium channel blocker(s); SRT: septal reduction therapies.

B.3.5.2 Health-state unit costs and resource use

As described in section B.3.5, the base case HCRU, stratified by NYHA class, was informed by the expert elicitation exercise analysis excluding the interventionalists (n = 8). Prior to inclusion in the economic model, a list of data points obtained were scrutinised to ensure that they had face validity. The reasons for subsequent removal included:

- **Double counting:** When data points were obtained for an overall category and sub-categories, a decision was made to prioritise one over the other. All-cause primary care appointments were removed and GP- and nurse-led appointments were recorded separately
- **Defining the data point:** During the expert elicitation exercise, some clinicians found it difficult to provide estimates of the ambulatory 24–48-hour ECG (Holter) with any degree of certainty. This was therefore removed due to difficulties in generalising to all indirect monitoring
- **Lack of cost data:** If costs could not be obtained due to the specialist nature of the disease area and the lack of cost coding, these data points were removed.

Within the expert elicitation exercise, clinicians were asked to provide an anticipated prevalence of defibrillator and pacemaker use, unlike the annual incidence used in other

questions. These prevalence figures were adjusted based on mean survival in the model to derive annual frequency. The scenarios around mortality estimates will therefore also impact the ICD/pacemaker HCRU estimates.

Incidence rates were included in the model per annum and applied per cycle. Unit costs for each resource were collected from the NHS Schedule of Reference Costs 2019-2020 and Personal Social Services Research Unit (PSSRU) 2021 unless otherwise specified.[120,126] Table 37 presents the resources used along with unit costs.

Table 37. HCRU by NYHA class (base case)

Resource	NYHA class health state (annual frequency)				Unit cost (£)	Cost source
	I	II	III	IV		
Primary care						
Nurse consultation	[redacted]	[redacted]	[redacted]	[redacted]	14.06	PSSRU 2016 (inflated to 2021)[120]
GP consultation	[redacted]	[redacted]	[redacted]	[redacted]	39.23	PSSRU 2021[120]
Out of Hours	[redacted]	[redacted]	[redacted]	[redacted]	136.77	PSSRU 2016 (inflated to 2021) [120]
Secondary care						
Day case	[redacted]	[redacted]	[redacted]	[redacted]	840.00	PSSRU 2021[120]
Outpatient (CV) visits	[redacted]	[redacted]	[redacted]	[redacted]	137.00	PSSRU 2021[120]; assumed no difference between CV and non-CV visits
Outpatient (non-CV) visits	[redacted]	[redacted]	[redacted]	[redacted]	137.00	
Inpatient (elective) visit	[redacted]	[redacted]	[redacted]	[redacted]	4,754.00	PSSRU 2021[120]
Inpatient (non-elective) visit	[redacted]	[redacted]	[redacted]	[redacted]	3,627.00	PSSRU 2021[120]
Accident and emergency	[redacted]	[redacted]	[redacted]	[redacted]	188.28	NHS Schedule of Reference Costs 2019-2020 (AE tab), weighted average: sum of total costs/sum of attendees[126]
Coronary Care Unit	[redacted]	[redacted]	[redacted]	[redacted]	1,215.90	NHS Schedule of Reference Costs 2019-2020 (critical care, assumed based on clinical expert opinion that coronary will be cardiac with 1 organ supported)[126]
Tests/procedures						
Echocardiography procedures	[redacted]	[redacted]	[redacted]	[redacted]	191.27	NHS Schedule of Reference Costs 2019-2020 (OPROC tab); HRG- EY50Z[126]
12-lead ECG procedures	[redacted]	[redacted]	[redacted]	[redacted]	130.26	NHS Schedule of Reference Costs 2019/20 (OPROC tab); HRG- EY51Z[126]
Cardiac MRI procedures	[redacted]	[redacted]	[redacted]	[redacted]	451.49	NHS Schedule of Reference Costs 2019/20 (IMAG tab); HRG- RD10Z[126]
CPET procedures	[redacted]	[redacted]	[redacted]	[redacted]	174.60	NHS Schedule of Reference Costs 2019/20 (OPROC tab); HRG- DZ31Z[126]
BNP and NT-proBNP tests	[redacted]	[redacted]	[redacted]	[redacted]	20.00	NHS improvement[127]
Troponin T and I tests	[redacted]	[redacted]	[redacted]	[redacted]	20.00	Assumed to be equal to BNP testing[127]
Defibrillator[#]	[redacted]	[redacted]	[redacted]	[redacted]	3,191.62	NHS Schedule of Reference Costs 2019-2020 (Total HRGs: EY01* to EY02* as a weighted average)[126]

Pacemaker[#]	[redacted]	[redacted]	[redacted]	[redacted]	3,068.66	NHS Schedule of Reference Costs 2019-2020 (Total HRGs: EY03* to EY08* as a weighted average)[126]
Total cost						
Cost per cycle (£)	48.80	95.24	732.07	1,091.66	-	-
Cost per annum (£)	636.63	1,242.40	9,549.54	14,240.30	-	-

[#]Frequency of defibrillator before adjusting based on mean survival: NYHA class I: [redacted]; II: [redacted]; III: [redacted]; IV: [redacted]; frequency of pacemaker before adjusting based on mean survival: NYHA class I: [redacted]; II: [redacted]; III: [redacted]; IV: [redacted].
Asterisk (*) after HRG codes indicates the inclusion of any number of alphanumeric characters.
Costs for CV-related and non-CV-related office visits are the same
CPET: cardiopulmonary exercise testing; CV: cardiovascular; ECG: electrocardiogram; GP: general practitioner; MRI: magnetic resonance imaging; NHS: National Health Service; (NT-pro)BNP: (N-terminal pro) B-type natriuretic peptide; NYHA: New York Heart Association.

Table 38. Summary of overall HCRU costs

	Health state cost (£)			
	NYHA I	**NYHA II**	**NYHA III**	**NYHA IV**
Per 28-day cycle	48.80	95.24	732.06	1,091.64
Per annum	636.63	1,242.39	9,549.50	14,240.08
NYHA: New York Heart Association.				

The draft SmPC (Appendix C) indicates that mavacamten use requires additional monitoring in the first year. Based on the draft SmPC, monitoring for the mavacamten + BB/CCB arm in year 1 was assumed to comprise [redacted] CV-related outpatient visits with an echocardiogram performed at each visit, irrespective of NYHA class. The frequencies of CV-related outpatient visits and echocardiograms for the BB/CCB monotherapy arm are given in Table 38. From year 2 onwards, monitoring in the mavacamten arm is assumed to be equivalent to that in the BB/CCB monotherapy arm.

Note that in the event that sensitivity analysis causes the frequency of CV-related outpatient visits or echocardiograms for BB/CCB monotherapy to be greater than [redacted], mavacamten + BB/CCB monitoring in the first year is increased to equal the higher value being used for BB/CCB monotherapy i.e. mavacamten monitoring is never permitted to be lower than that of BB/CCB monotherapy.

B.3.5.3 Adverse reaction unit costs and resource use

AE management costs were informed by the NHS Schedule of Reference Costs 2019–2020 (Table 39).

Table 39. AE management costs

Adverse event	Management cost	Reference
Syncope	£985.02	NHS Schedule of Reference Costs 2019-2020 (Total HRGs-EB08*, as weighted average of total)[126]
TIA	£1,048.70	NHS Schedule of Reference Costs 2019-2020 (Total HRGs-AA29*, as weighted average of total)[126]
Cardiac failure congestive	£2,061.06	NHS Schedule of Reference Costs 2019-2020 (Total HRGs-EB03*, as weighted average of total)[126]
Viral gastroenteritis	£1,366.10	NHS Schedule of Reference Costs 2019-2020 (Total HRGs-FD01*, as weighted average of total)[126]
UTI	£1,724.59	NHS Schedule of Reference Costs 2019-2020 (Total HRGs-LA04*, as weighted average of total)[126]
AE: adverse event; HRG: healthcare resource groups; NHS: National Health Service; TIA: transient ischaemic attack; UTI: urinary tract infection.		

B.3.5.4 Miscellaneous unit costs and resource use

Healthcare costs substantially increase at the end of life due to the high number of hospital and physician visits. In TA696,[106] costs associated with terminal care were obtained from Hollingworth et al. 2016.[128] This study reported that the cost for the last 3 months of life was £8,827 per patient. This was inflated to 2021 costs (£10,147) and applied as a one-off cost for patients moving to the death state in each cycle.

B.3.6 Uncertainty

Symptomatic, obstructive HCM is a rare condition.[2,10,14,16,38,47,48] Although obstructive HCM was first described more than 60 years ago,[129] mavacamten is the first medical therapy developed to specifically target the underlying pathophysiology of the disease. Due to the historic lack of treatment options, obstructive HCM is an understudied disease, resulting in a high unmet need but also a paucity of high-quality evidence to inform certain aspects of the economic evaluation. As highlighted in the 2020 AHA/ACC clinical practice guidelines, “there have been few clinical trials, particularly RCTs, in HCM”.[7] As a result, many of the recommendations issued in the guidelines are based on observational studies or clinical consensus.

In particular, evidence gaps were identified for data to inform mortality associated with either the intervention or standard care, HCRU associated with the condition, long-term efficacy of standard care or mavacamten, and efficacy of subsequent therapies.

The evidence gap in mortality outcomes data was addressed using NYHA class as a surrogate, with the well-established relationship between NYHA class and mortality modelled using data from RWE studies. To address the paucity of evidence surrounding HCRU, a robust structured expert elicitation exercise was undertaken to quantify these parameters (Appendix O).

Data from the EXPLORER-HCM trial represents the highest-quality evidence available quantifying the efficacy of standard care in this indication, but is not sufficient to inform long-term efficacy. This uncertainty was addressed by the conservative assumption that patients’ NYHA class would not decline further in the

comparator arm after the end of the short-term period for which evidence was available. Similarly, short-term efficacy of SRT was informed by the expert elicitation study, but no data were identified to inform long-term efficacy of SRT, nor the efficacy of disopyramide, therefore patients were assumed to retain their NYHA class from the time of disopyramide initiation/entry to the post-SRT state.

Therefore, the evidence gaps identified have been substantially addressed by evidence generated by the Company and the impact of the uncertainty has been mitigated by a range of conservative assumptions employed in the modelling, along with the appropriate sensitivity analyses. Nevertheless, the rarity of obstructive HCM and the challenges of conducting RCTs and other studies in this disease area mean that evidence generation in this indication is complex and difficult, indicating that a greater degree of uncertainty should be considered acceptable within decision making for this technology.

B.3.7 Summary of base-case analysis inputs and assumptions

B.3.7.1 Summary of base-case analysis inputs

Table 40. Summary of base case variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Patient profile			
Male, %	59.4 (Table 24)	SE: 0.06 (beta)	B.3.3.1
Mean age, years	59.0 (Table 24)	SE: 0.75 (Normal)	B.3.3.1
Baseline distribution of patients with each NYHA class, %	NYHA I: 0.0 NYHA II: 72.9 NYHA III: 27.1 NYHA IV: 0.0 (Table 24)	SE assumed to be 10% of the mean (Dirichlet)	B.3.3.1
Efficacy			
Short-term transition probability	Table 25	Please see CEM Inputs sheet for each SE (Dirichlet)	B.3.3.2
Mavacamten discontinuation due to AEs	At week 30: 1.6% Annual, after week 30: 2.8% (Table 26)	SE assumed to be 10% (gamma)	B.3.3.3
Distribution of treatments following mavacamten discontinuation	100% to BB/CCB monotherapy	SE assumed to be 10% of the mean (Dirichlet)	B.3.3.3

	(Table 27)		
Proportions of patients who undergo NYHA class-dependent treatment escalation	Table 28	SE assumed to be 10% of the mean (gamma)	B.3.3.4
Transition probabilities for patients receiving SRT + BB/CCB	Table 29	Please see CEM Inputs sheet for each SE (Dirichlet)	B.3.3.4.1
Mortality relationship between NYHA classes relative to NYHA class I	NYHA II vs I HR 1.51 NYHA III vs I HR 2.77 NYHA IV vs I HR 7.09 (Table 30)	SE assumed to be 10% of the mean (lognormal)	B.3.3.5
Utility values	NYHA I: [redacted] NYHA II: [redacted] NYHA III: [redacted] (Table 33)	NYHA I SE: [redacted] (beta) NYHA II SE: [redacted] (beta) NYHA III SE: [redacted] (beta)	B.3.4.5
Costs			
Cost of mavacamten acquisition	List price: £[redacted] PPPY PAS price: £[redacted] PPPY (Table 34)	NA	B.3.5.1.1
Costs of modelled comparators and subsequent therapies	Table 35	NA	B.3.5.1.2
Market shares of comparators and subsequent therapies	Table 36	SE assumed to be 10% of the mean (Dirichlet)	B.3.5.1.2
HCRU by NYHA class	Table 37	SE assumed to be 10% of the mean (gamma)	B.3.5.2
HCRU costs	Table 38	SE: 10% assumed (gamma)	B.3.5.2
Annual monitoring costs by NYHA class	B.3.5.2	SE assumed to be 10% of the mean (gamma)	B.3.5.2
Incidence of modelled AEs	Table 32	SE: 10% assumed (gamma)	B.3.5.2
AE management costs	Syncope: £985.02 TIA: £1,048.70 Cardiac failure congestive: £2,061.06 Viral gastroenteritis: £1,366.10 UTI: £1,724.59 (Table 39)	SE assumed to be 10% of the mean (gamma)	0

AE: adverse event; BB: beta blockers; CCB: calcium channel blockers; CEM: cost-effectiveness model; HCRU: healthcare resource utilisation; NA: not applicable; NYHA: New York Heart Association; PPPY: per patient per year; SE: standard error; SRT: septal reduction therapies; TIA: transient ischaemic attack; UTI: urinary tract infection.

B.3.7.2 Assumptions

A summary of the assumptions employed in the model and the justifications for each assumption are provided in Table 41.

Table 41. List of modelling assumptions and justifications

Model Input	Assumption	Justification
Long-term transition probabilities	Patients retained the NYHA class attained at the end of short-term period and no interstate transitions among NYHA classes were modelled for both treatment arms	• This is primarily supported by the stabilisation of the NYHA class distribution observed towards the later periods of the EXPLORER-HCM trial (B.2.6.1), with a similar pattern observed in the EXPLORER-LTE cohort (B.2.6.2). • In addition, given the mavacamten mechanism of action, clinical advisors were in agreement that mavacamten is likely to slow disease progression relative to standard care and, as such, this assumption is likely to favour standard care
Discontinuation of mavacamten due to lack of response at week 30	Patients with no NYHA improvement at week 30 relative to baseline discontinue mavacamten	• The draft SmPC states that [redacted] (Appendix C). Therefore, discontinuation due to lack of response was modelled at 30 weeks (~5 months), which aligns with the EXPLORER-HCM EOT and the draft SmPC. This assumption was discussed and supported by clinicians during UK advisory meetings and deemed to be appropriate as it is unlikely that patients and clinicians will continue using mavacamten without evidence of benefit.[19,20]
Discontinuation of mavacamten due to incidence of AEs during long-term period	Discontinuation rate of mavacamten would be similar in the long term to that observed in the EXPLORER-HCM trial period (30 weeks)	• Due to paucity of long-term data, this conservative assumption has been used in the model where the discontinuation rate observed in the EXPLORER-HCM trial is carried forward throughout the lifetime horizon
Subsequent treatment post mavacamten discontinuation	All patients who discontinued mavacamten would revert to the underlying treatment (i.e., BB/CCB monotherapy) with a decision to escalate to subsequent treatments later	• It was considered likely that patients would maintain their background standard care therapies while considering subsequent treatment options. This assumption has been tested in scenario analyses
Treatment escalation in patients receiving disopyramide + BB/CCB	Patients in NYHA I would not be eligible for SRT	• Patients in NYHA class I do not experience any limitations to their physical activity and ordinary physical activity does not provoke symptoms (B.1.3.1.3.1), therefore it is unlikely that SRT would be considered clinically justified for these patients. • This assumption was strongly supported by the expert elicitation study (Appendix O)
Escalation from disopyramide to SRT	Disopyramide is used as a short-term therapy prior to SRT	• The loss of clinical efficacy of disopyramide over the short term (months) was highlighted in a UK advisory board[19] • It was therefore assumed that all patients escalate to SRT 9 months after disopyramide initiation to reflect the known tachyphylaxis effect and poor tolerability associated with disopyramide.

Efficacy of disopyramide and SRT	Patients receiving disopyramide + BB/CCB retain their NYHA class from the time of disopyramide initiation; patients receiving SRT experience an incident transition probability and retain this NYHA class thereafter	• No evidence was identified in the clinical SLR to inform the efficacy of disopyramide or long-term disease progression following SRT in the UK setting, therefore these conservative assumptions were made regarding long-term efficacy
AEs for disopyramide + BB/CCB and post-SRT (BB/CCB monotherapy)	Same as BB/CCB monotherapy	• The clinical SLR did not identify any studies to inform the safety of subsequent therapies in obstructive HCM in the UK setting (note that evidence was identified to permit modelling of mortality associated with SRT)
Utility values	Used trial-based utilities	• EXPLORER-HCM is a large, high-quality RCT evaluating HRQoL in patients directly relevant to the decision problem, therefore trial utilities were considered the best available evidence to inform the model.
Utility value for NYHA IV	Used same utility values for NYHA III and IV	• Paucity of published evidence • This assumption is likely to be an overestimate of the real utility values for NYHA class IV patients, which will potentially favour the BB/CCB monotherapy arm. However, the proportion of patients in NYHA class IV is likely to be small, so this assumption is expected to have a limited impact on model outcomes.
HCRU	Used data collected via an expert elicitation study	• Paucity of published evidence by NYHA class in this indication

AE: adverse event; BB: beta blockers; CCB: calcium channel blockers; EOT: end of treatment; HCM: hypertrophic cardiomyopathy; HRQoL: health-related quality of life; LTE: long-term extension; NYHA: New York Heart Association; RCT: randomised controlled trial; SmPC: Summary of Product Characteristics; SRT: septal reduction therapies.

B.3.8 Base-case results

B.3.8.1 Base-case incremental cost-effectiveness analysis results

Results of the base case incremental cost-effectiveness analysis are presented in Table 42. The net health benefit results provided in Table 43 show that overall population health would be increased by the use of mavacamten at an opportunity cost threshold of £30,000. Disaggregated results are presented in Appendix J. At the with-PAS price, mavacamten is cost effective at a willingness-to-pay (WTP) threshold of £30,000/QALY.

Table 42. Base-case results

Technologies	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,840.80
BB/CCB monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
ICER: incremental cost-effectiveness ratio; LY: life years; LYG: life years gained; QALY: quality-adjusted life year.							

Table 43. Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BB/CCB monotherapy	[redacted]	[redacted]	-	-	-	-
NHB: net health benefit; QALY: quality-adjusted life year.						

B.3.9 Exploring uncertainty

B.3.9.1 Probabilistic sensitivity analysis

In total, 1,000 simulations were performed, providing a distribution of incremental results and, consequently, an estimate of the overall uncertainty surrounding the cost-effectiveness results. In addition, a seed was specified to allow reproducibility of the results. The results of the probabilistic sensitivity analysis (PSA) indicate that the incremental cost-effectiveness ratio (ICER) is stable (Table 44), as the difference between the deterministic and probabilistic ICER is £[redacted]. Figure 25 presents the cost-effectiveness plane which displays that mavacamten + BB/CCB is predicted to be cost-effective in [redacted]% of the simulations at a £30,000 WTP threshold. This is supported by the cost-effectiveness acceptability frontier presented in Figure 26.

Figure 25. Cost-effectiveness plane for incremental costs and QALYs

QALY: quality-adjusted life years; WTP: willingness-to-pay

Figure 26. Cost-effectiveness acceptability frontier

BB: beta blocker; CCB: calcium channel blocker; QALY: quality-adjusted life year.

Table 44. Incremental results for the PSA

Treatment arm	Total costs	Total QALYs	Δ costs	Δ QALYs	ICER
Mavacamten + BB/CCB	[redacted]	[redacted]	-	-	-
BB/CCB monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£29,411.07

BB: beta blockers; CCB: calcium channel blockers; ICER: incremental cost-effectiveness ratio; NMB: net monetary benefit; PSA: probabilistic sensitivity analysis: QALYs: quality-adjusted life years.

B.3.9.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were conducted to identify which model parameters had the greatest influence on results, by varying one parameter at a time

between the 95% CI and assessing the impact on model outputs. Where the 95% CI were not available, the standard error was assumed to be equal to 10% of the point estimate.

The overall drivers of the ICER are the mortality rate for patients in NYHA class II and the percentage of patients in NYHA class II who did not experience a NYHA class improvement in the first 30 weeks. A tornado plot showing the impact on the ICER is presented in Figure 27.

Figure 27. DSA results (top 10) on incremental ICERs

DSA: deterministic sensitivity analysis; ICER: incremental cost-effectiveness ratio; NYHA: New York Heart Association.

B.3.9.3 Scenario analysis

Scenario analyses were conducted to explore the sensitivity of the model to a range of assumptions. Details of each scenario are presented in Table 45, and results presented in Table 46.

Table 45. Summary of scenario analyses conducted

Parameter	Base case	Description of scenarios	Cross-reference
Time horizon	Lifetime	20 years	B.3.2.2.3
		30 years	
Comparator arm transition probabilities	Trial-based transition probabilities until week 46; no NYHA class transitions beyond week 46 (unless SRT event experienced)	Trial-based transition probabilities until week 38; no NYHA class transitions beyond week 38 (unless SRT event experienced)	B.3.3.2.2
Mavacamten discontinuation at week 30 due to lack of response	All patients in NYHA III at week 30 discontinue mavacamten	Exploratory scenario where [redacted]% patients in NYHA III at week 30 discontinue mavacamten (equal to the proportion who discontinue from NYHA II)	B.3.3.3.2
Mavacamten discontinuation from week 30 onwards due to SAEs (annual %)	2.8% annually after week 30		B.3.3.3.1
		1.4% annually after week 30	
Distribution to treatments following discontinuation from mavacamten	All patients who discontinue mavacamten receive BB/CCB monotherapy in at least the first cycle after discontinuation	90% receive BB/CCB monotherapy 10% receive disopyramide + BB/CCB	B.3.3.4
		75% receive BB/CCB monotherapy 25% receive disopyramide + BB/CCB	
		For patients in NYHA I/II: 100% receive BB/CCB monotherapy For patients in NYHA III/IV: 90% receive BB/CCB monotherapy 10% receive SRT	
		For patients in NYHA I/II 100% receive BB/CCB monotherapy For patients in NYHA III/IV: 80% receive BB/CCB monotherapy 10% receive disopyramide + BB/CCB 10% receive SRT	

Parameter	Base case	Description of scenarios	Cross-reference
Distribution to treatments following mavacamten discontinuation and escalation from BB/CCB monotherapy	On escalation, all patients receive disopyramide + BB/CCB for 9 months then receive SRT	Patients who discontinue mavacamten: 100% receive BB/CCB monotherapy Patients who escalate from BB/CCB monotherapy: 100% receive SRT	B.3.3.4
		Patients who discontinue mavacamten: 90% receive BB/CCB monotherapy 10% receive disopyramide + BB/CCB Patients who escalate from BB/CCB monotherapy: 100% receive SRT	
		Patients who discontinue mavacamten: 75% receive BB/CCB monotherapy 25% receive disopyramide + BB/CCB Patients who escalate from BB/CCB monotherapy: 100% receive SRT	
		Patients who discontinue mavacamten and are in NYHA I/II: 100% receive BB/CCB monotherapy Patients who discontinue mavacamten and are in NYHA III/IV: 90% receive BB/CCB monotherapy 10% receive SRT Patients who escalate from BB/CCB monotherapy: 100% receive SRT	
		Patients who discontinue mavacamten: 100% receive BB/CCB monotherapy Patients who escalate from BB/CCB monotherapy and are in NYHA I/II: 100% receive disopyramide + BB/CCB Patients who escalate from BB/CCB monotherapy and are in NYHA III/IV: 100% receive SRT	
Efficacy of SRT (incident transition probabilities)	Expert elicitation study (Appendix O)	Knyshov *et al*. 2013[109]	B.3.3.4.1
Mortality	HRs from Wang *et al*. 2022	Adjusted HRs from SHaRe (Appendix N)	B.3.3.5
		Unadjusted RRs from ShaRe (Lakdawala *et al*. 2021[45])	
	[redacted]% ASA, [redacted]% septal myectomy	75% ASA, 25% septal myectomy	B.3.5.1.2

Parameter	Base case	Description of scenarios	Cross-reference
Market share of ASA versus septal myectomy (SRT)		25% ASA, 75% septal myectomy	
Age-adjusted utilities	Include	Exclude	B.3.4.5
HCRU	Expert elicitation study (Appendix O)	Increase all HCRU by 10%	B.3.5.2
		Decrease all HCRU by 10%	
Time on disopyramide before escalation to SRT (months)	9	6	B.3.3.4
		12	
Age at baseline (years)	59.0	52.0	B.3.2.1
		62.0	
Utilities	Trial-based utilities from EXPLORER-HCM	Utilities from Göhler *et al*, 2009[117]	B.3.4.5

ASA: alcohol septal ablation; BB: beta blockers; CCB: calcium channel blockers; HCM: hypertrophic cardiomyopathy; HCRU: healthcare resource use; HR: hazard ratio; NYHA: New York Heart Association; RR: relative risk; SAE; serious adverse event; ShaRe: Sarcomeric Human Cardiomyopathy Registry; SRT: septal reduction therapy.

Table 46 details the results of each scenario analysed, compared to the base case. The most significant impact on the ICER resulted from the scenarios that varied the time horizon. The base case assumed a lifetime horizon. Given the starting age of the population (59 years), the base case results are similar to those when assuming a 30-year time horizon, while a shorter time horizon of 20 years yielded a higher ICER. These results convey that QALY gains associated with costs incurred today are accrued further into the future. Other scenarios had limited impact on the ICER, demonstrating that mavacamten is a cost-effective use of NHS resources.

Table 46. Summary of scenario analysis results

Parameter	Scenarios	ICER
Time horizon	20 years	£36,819.98
	30 years	£30,961.32
Comparator arm transition probabilities	Trial-based transition probabilities until week 38; no NYHA class transitions beyond week 38 (unless SRT event experienced)	£31,810.03
Mavacamten discontinuation at week 30 due to lack of response	Exploratory scenario where [redacted]% patients in NYHA III at week 30 discontinue mavacamten (equal to the proportion who discontinue from NYHA II)	£31,172.20
Mavacamten discontinuation from week 30 onwards due to SAEs (annual %)	1.4% annually after week 30	£35,125.32
Distribution to treatments following discontinuation from mavacamten	90% receive BB/CCB monotherapy 10% receive disopyramide + BB/CCB	£28,851.71
	75% receive BB/CCB monotherapy 25% receive disopyramide + BB/CCB	£27,480.99
	For patients in NYHA I/II: 100% receive BB/CCB monotherapy For patients in NYHA III/IV: 90% receive BB/CCB monotherapy 10% receive SRT	£29,124.79
	For patients in NYHA I/II 100% receive BB/CCB monotherapy For patients in NYHA III/IV: 80% receive BB/CCB monotherapy 10% receive disopyramide + BB/CCB 10% receive SRT	£28,510.97
Distribution to treatments following mavacamten discontinuation and escalation from BB/CCB monotherapy	Patients who discontinue mavacamten: 100% receive BB/CCB monotherapy Patients who escalate from BB/CCB monotherapy: 100% receive SRT	£30,041.71
	Patients who discontinue mavacamten: 90% receive BB/CCB monotherapy 10% receive disopyramide + BB/CCB Patients who escalate from BB/CCB monotherapy: 100% receive SRT	£29,050.02

Parameter	Scenarios	ICER
	Patients who discontinue mavacamten: 75% receive BB/CCB monotherapy 25% receive disopyramide + BB/CCB Patients who escalate from BB/CCB monotherapy: 100% receive SRT	£27,675.58
	Patients who discontinue mavacamten and are in NYHA I/II: 100% receive BB/CCB monotherapy Patients who discontinue mavacamten and are in NYHA III/IV: 90% receive BB/CCB monotherapy 10% receive SRT Patients who escalate from BB/CCB monotherapy: 100% receive SRT	£29,327.54
	Patients who discontinue mavacamten: 100% receive BB/CCB monotherapy Patients who escalate from BB/CCB monotherapy and are in NYHA I/II: 100% receive disopyramide + BB/CCB Patients who escalate from BB/CCB monotherapy and are in NYHA III/IV: 100% receive SRT	£30,035.60
Efficacy of SRT (incident transition probabilities)	Knyshov *et al*. 2013[109]	£29,559.10
Mortality	Adjusted HRs from SHaRe (Appendix N)	£29,606.71
	Unadjusted RRs from SHaRe (Lakdawala *et al*. 2021[45])	£21,602.63
Market share of ASA versus septal myectomy (SRT)	75% ASA, 25% septal myectomy	£29,877.86
	25% ASA, 75% septal myectomy	£29,806.76
Age-adjusted utilities	Exclude	£27,178.16
HCRU	Increase all HCRU by 10%	£28,611.97
	Decrease all HCRU by 10%	£31,069.64
Time on disopyramide before escalation to SRT (months)	6	£29,906.06
	12	£29,779.32
Age at baseline (years)	52.0	£30,307.51
	62.0	£29,686.96
Utilities	Utilities from Göhler *et al*, 2009[117]	£31,901.39
ASA: alcohol septal ablation; BB: beta blockers; CCB: calcium channel blockers; HCRU: healthcare resource use; HR: hazard ratio; ICER : incremental cost-effectiveness ratio; RR: relative risk; SHaRe: Sarcomeric Human Cardiomyopathy Registry; SRT: septal reduction therapy ; WTP: willingness-to-pay.		

B.3.10 Benefits not captured in the QALY calculation

Mavacamten is a first-in-class, oral, allosteric, inhibitor of cardiac myosin ATPase, designed to target the underlying pathophysiology of HCM by inhibiting excessive myosin-actin crossbridge formation that results in hypercontractility, LV hypertrophy, and reduced compliance. Based on the innovative nature of mavacamten, a Promising Innovative Medicines designation was granted by the MHRA on 21 August

2021, indicating that mavacamten is a candidate for the treatment of a life-threatening or seriously debilitating condition with unmet need.

There are currently no disease-modifying medical therapies available for the treatment of symptomatic, obstructive HCM. Current medical treatments are not targeted to the underlying pathophysiology, and a large proportion of patients remain symptomatic despite receiving medical therapy (BB, non-dihydropyridine CCB). There are limited alternative options available for these patients, many of whom remain on BB/CCB even though their symptoms are not fully relieved and despite experiencing side effects.

Some patients may escalate to subsequent therapies, which comprise disopyramide or SRT. Disopyramide may provide symptomatic relief, however it is associated with significant side effects and tachyphylaxis commonly occurs after ~9 months; clinical expert advice indicates that, for these reasons, it is rarely used in UK clinical practice. SRT is a subsequent therapeutic option for persistent, moderate-to-severe symptoms, however, it is associated with an increased risk of complications and peri-operative mortality, and is only available through specialist, experienced centres. Many patients are reluctant to undergo SRT due to the interventional nature, preferring to remain on medical therapy despite receiving inadequate symptomatic relief. Therefore, mavacamten represents a new treatment with demonstrated safety and efficacy, for patients who have no alternative options.

As described in section B.2.6, mavacamten has significant benefits in both physician-assessed symptoms and function (NYHA class) and patient-reported quality of life, both of which are captured in the QALY calculation presented in B.3. However, mavacamten also displays significant benefits in physiological measures relevant to obstructive HCM such as pVO_2 and peak LVOT gradient. Although it is likely that the use of NYHA class and PROs to inform HRQoL indirectly capture many of the benefits associated with improvements in these additional outcomes, these measures have been demonstrated to have prognostic significance in this indication which has not necessarily been fully captured and therefore may represent significant uncaptured benefit of mavacamten.[4,5,13]

EQ-5D is the preferred measure of HRQoL and has been used in the economic analysis in accordance with the reference case. However, this is not a disease-specific instrument and, due to the nature of the limitations associated with obstructive HCM, there may be health-related benefits that are not captured by EQ-5D and are therefore not represented in the QALY calculation. HRQoL measured in EXPLORER-HCM using the KCCQ instrument showed benefits associated with mavacamten in all domains, suggesting a strong cardiomyopathy-specific benefit that may not be captured by EQ-5D.[70]

As described in section B.3.4.5, patients with symptomatic, obstructive HCM may modify their lifestyle substantially to accommodate their symptoms and, through a process of adaptation, then perceive their baseline utility as closer to population norms. This in turn may reduce the differential between NYHA classes in terms of HRQoL, given that the patients perception of their quality of life is overestimated for that particular NYHA class. Given that the differential in NYHA classes is a factor in the estimation of QALYs, if this differential is underestimated due to patient adaptation, then potential benefits for mavacamten are also underestimated in the economic model. In addition to this, the model does not capture within-NYHA class benefits, whereby a patient improves their HRQoL, however remains in the same NYHA class. This again points to benefits for mavacamten not being captured in the estimation of QALYs.

Patients receiving mavacamten also demonstrated reduced biomarkers of cardiac dysfunction.[3] Serum NT-proBNP is an important biomarker of LV wall stress used in research and clinical cardiology. In a large cohort of patients with HCM, NT-proBNP was an independent predictor of morbidity and mortality.[130] Furthermore, data from the CMR substudy show that mavacamten was associated with significant reductions in absolute intracellular myocardial mass index as well as left ventricular mass index (LVMI), maximum LV wall thickness and left atrial volume index, which are all predictors of poor prognosis in HCM[68] (Appendix M), while exploratory endpoints evaluated by TTE indicate a favourable effect of mavacamten on diastolic function.[80] Thus, by targeting the underlying pathophysiology, current evidence suggests that mavacamten may lead to positive cardiac remodelling.[68] Together, these results suggest that mavacamten has the potential to slow disease progression, a

conclusion that has also received support from clinical experts.[20] Due to the lack of long term evidence regarding mavacamten efficacy or evidence regarding the natural history of disease progression on standard care, no long-term differential efficacy between mavacamten and standard care have been modelled; patients retain the last NYHA class measured in the EXPLORER-HCM trial at week 30 (intervention arm) or the baseline assessment of the EXPLORER-LTE cohort (week 46; comparator arm). This is a conservative assumption, since it is expected based on both the data from the EXPLORER-LTE cohort and mavacamten's mechanism of action, that further benefit of mavacamten on slowing disease progression would accrue.

Therefore, mavacamten will result in significant benefit to patients living with this condition, over and above those captured within the QALY calculation. Mavacamten is considered to be innovative and represents a 'step-change' in the management of symptomatic obstructive HCM.

B.3.11 Validation

B.3.11.1 Validation of cost-effectiveness analysis

To ensure the face validity of the model as well as to make sure that it is scientifically accurate, the validity of the model was assessed by the following steps:

- Internal validation was conducted to ensure that the model outcomes were in line with what would be expected from the informing studies. For instance, the NYHA distribution generated by the model at week 30 was compared with that from the EXPLORER-HCM trial, demonstrating that the model accurately predicted the trial outcome (see Appendix J).
- No other sources of evidence were identified to permit external validation of the model outcomes, either for the intervention or the comparator arm. The absence of alternative evidence sources is expected, given that mavacamten is a first-in-class drug and the standard care medical therapies are used off-label.[2] To address this limitation in terms of validating the cost-effectiveness analysis, the model assumptions and inputs were discussed during two UK advisory board meetings and were supported by the commissioning of RWE

studies (Wang *et al*, 2022[44] and Lakdawala *et al*, 2021/Appendix N) and an expert elicitation exercise (Appendix O). Clinical and health economics experts guided the decisions and assumptions made in developing the analysis and validated that the model is appropriately structured, has clinical face validity and reflects real-world practices.[19,20,60,83]

In order to ensure the quality control of the model:

- Well-established CEM guidelines were followed and adhered throughout the model development process[103,104]
- As part of internal validation, a senior modeller not involved in the project performed a quality check to ensure that the model has been programmed appropriately and produces logical outcomes. The following tests were conducted:
    - Technical pressure testing
    - Directional input testing
    - Compliance with NICE reference case

B.3.12 Interpretation and conclusions of economic evidence

B.3.12.1 Summary of the results

The economic analysis demonstrated that mavacamten in combination with standard care (where standard care is BB/CCB monotherapy) is a cost-effective treatment for symptomatic, obstructive HCM compared to standard care alone. It was estimated that addition of mavacamten would result in gains of [redacted] QALYs and an increase in discounted incremental costs to £[redacted], resulting in an ICER of £29,840.80/QALY gained.

B.3.12.2 Relevance and generalisability

The economic evaluation is based on the patient population of EXPLORER-HCM, which evaluated mavacamten efficacy and safety in patients with symptomatic (NYHA class II or III), obstructive HCM. Therefore, the evaluation is relevant to the full population described in the decision problem. The characteristics of the population of EXPLORER-HCM are considered generalisable to England, based on best available evidence (section B.2.12.4), while the modelled treatment pathway

and inputs have been designed and selected to be fully reflective of clinical practice in England; the modelling approach and assumptions have been validated by UK clinical experts (section B.3.11).

B.3.12.3 Strengths of the economic evaluation

The key strengths of the economic analysis are:

- No cost-effectiveness studies of interventions in obstructive HCM were identified to inform the economic analysis presented in this submission (Appendix G). Therefore, a de novo economic model was developed to address the decision problem which reflects original and novel research.

- Efficacy was based on EXPLORER-HCM, a large, high-quality RCT that evaluated the intervention and relevant comparator in a population directly relevant to the decision problem.

- The efficacy for both arms was drawn from the same trial, limiting heterogeneity in the data, while the outcomes evaluated, including change in NYHA class and HRQoL based on EQ-5D, were well-suited to economic modelling and aligned with the NICE reference case.

- Treatment efficacy was captured using health states based on NYHA class, a widely-used clinical assessment of functional capacity in patients with obstructive HCM.[2,7,20] NYHA class provides a quantifiable representation of the burden of the disease, reflecting an outcome that is meaningful to patients, and was measured as part of the primary endpoint and a standalone secondary endpoint within EXPLORER-HCM.

- Due to the lack of high-quality published evidence available to inform aspects of the analysis, several evidence generation studies were commissioned to address these evidence gaps. These studies have provided a greater degree of certainty that the assumptions and inputs used are valid and applicable to the setting. Furthermore, extensive sensitivity and scenario analyses indicated that the modelling results are robust to sources of uncertainty.

B.3.12.4 Limitations of the economic evaluation

One limitation of this analysis is that there is currently no long-term data describing the efficacy of either mavacamten or the comparator. Therefore, when modelling beyond the latest time points available from the informing clinical trials, an assumption of equal efficacy was made, whereby patients remain in the same NYHA class health state over the remainder of the time horizon. This may be considered a conservative assumption, as it does not capture potential ongoing benefit of mavacamten, despite interim analysis of the long-term extension data suggesting a sustained treatment effect with the possibility of further benefit.

Another limitation of the analysis was that there is no direct evidence available to inform the effect of either intervention or comparator on mortality. Therefore, mortality was modelled as a function of NYHA class, based on a range of studies that demonstrate a clear link between NYHA class and risk of mortality both in obstructive HCM and in other heart diseases.

Finally, it is acknowledged that a limited number of modelled inputs, such as HCRU, were based on expert advice rather than published evidence, due to the paucity of alternative data sources. To mitigate the potential limitations of this type of evidence collection, these inputs were generated through a structured expert elicitation approach, where a large number of clinical experts provided quantitative estimates.

B.3.12.5 Conclusions from the economic evidence

A de novo economic model was developed in Microsoft Excel® in order to assess the cost-effectiveness of mavacamten in combination with standard care (comprising BB or CCB) versus standard care (i.e. BB or CCB monotherapy) alone, for the treatment of symptomatic, obstructive HCM. The model uses data from relevant trials studying mavacamten and standard care, as well as published sources and a structured expert elicitation exercise. Uncertainty in the model was explored through extensive deterministic, probabilistic and scenario analyses.

The economic analysis demonstrated that mavacamten in combination with standard care is a cost-effective treatment for symptomatic, obstructive HCM compared to standard care alone. It was estimated that addition of mavacamten would result in

gains of [redacted] QALYs with an incremental cost of £[redacted] compared to standard care alone, resulting in an ICER of £29,840.80/QALY gained.

As a result mavacamten reflects a cost-effective use of NHS resources and offers patients an effective and safe treatment option in a disease area with a high unmet need and limited effective treatments.

B.4 References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Addendum

October 2022

File name	Version	Contains confidential information	Date
[ID3928] Company submission addendum ACIC redacted	**1.0**	**Yes**	**18 October 2022**

Contents

Tables and figures

Abbreviations

AE	adverse event
AF	atrial fibrillation
ANCOVA	analysis of covariance
ASA	alcohol septal ablation
AV	atrioventricular
BB	beta blocker(s)
BMI	body mass index
CCB	calcium channel blocker(s)
CEM	cost-effectiveness model
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CMR	cardiac magnetic resonance
CSR	clinical study report
CV	cardiovascular
COV	coefficient of variation
DBL	database lock
ECG	electrocardiogram
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
ESC	European Society of Cardiology
HCM	hypertrophic cardiomyopathy
HF	heart failure
hs-cTnI	high sensitivity cardiac troponin I
ICD	implantable cardioverter-defibrillator
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
ITT	intention to treat
IXRS	interactive response system
KCCQ-23 CSS	Kansas City Cardiomyopathy Questionnaire clinical summary score
LA	left atrium/atrial
LAVI	left atrial volume index
LGE	late gadolinium enhancement
LTE	long-term extension
LV	left ventricle/ventricular
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
LVOTO	left ventricular outflow tract obstruction
LYG	life years gained
N	no
NA	not applicable
NHB	net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

NR	not reported
NYHA	New York Heart Association
NT-proBNP	*N*-terminal pro–B-type natriuretic peptide
PAS	patient access scheme
PRO	patient reported outcomes
pVO_2	peak oxygen consumption
QALY	quality-adjusted life year
RCT	randomised controlled trial
SAE	serious adverse event
SD	standard deviation
SmPC	Summary of Product Characteristics
SRT	septal reduction therapies
TEAE	treatment emergent adverse event
TTE	transthoracic echocardiogram
WTP	willingness to pay
Y	yes

1. Introduction and aims

This addendum provides additional clinical and cost-effectiveness evidence supporting the submission for mavacamten for the treatment of symptomatic (New York Heart Association [NYHA] class II–III) obstructive hypertrophic cardiomyopathy (HCM), which was submitted to NICE in June 2022.

The original Company submission (CS) presented clinical effectiveness evidence from two publications identified in the systematic literature review: the pivotal, phase III EXPLORER-HCM randomised controlled trial (RCT)[1] and supporting evidence from the ongoing long-term extension (i.e. the EXPLORER-LTE cohort of MAVA-LTE).[2] EXPLORER-HCM evaluated mavacamten in addition to standard care, compared to placebo plus standard care, in patients with symptomatic (NYHA class II–III) obstructive HCM, and is therefore directly relevant to the population in the decision problem and anticipated marketing authorisation.

Since the original CS, full data from an interim analysis of the VALOR-HCM trial have become available.[3] VALOR-HCM provides relevant evidence that is consistent with and complementary to the clinical efficacy and safety already demonstrated for mavacamten in the larger, pivotal phase III trial (EXPLORER-HCM).[1] These data have also been provided at Day180 regulatory responses to the EMA's request from July 22nd as supportive of the ongoing application for marketing authorisation (the latest draft SmPC can be found in the reference pack; note that it remains subject to change until final marketing authorisation is granted).[4] In light of this, this addendum has been prepared with the following aims:

1. **VALOR-HCM efficacy and safety data:** This addendum provides a comprehensive overview of the clinical effectiveness evidence from the VALOR-HCM interim analysis (section 2);
2. **VALOR-HCM as consistent and complementary evidence:** To contextualise the clinical effectiveness evidence, the population and equivalent endpoints from VALOR-HCM are compared with the main trial in the CS, showing that VALOR-HCM provides consistent and complementary evidence for the beneficial effect of mavacamten treatment to that shown in the pivotal phase III EXPLORER-HCM trial (sections 2.5–2.9);

3. **Feasibility analysis of economic modelling of VALOR-HCM:** The feasibility of including VALOR-HCM data in the economic case is explored and discussed (section 2.10).

This addendum also presents additional cost-effectiveness evidence in section 3:

4. **Minor model correction to adverse events (AE) calculation:** A minor error was identified in the calculation of the probability of AEs in the cost-effectiveness model (CEM). The correction made is described in section 3.1 and an updated version of the CEM is supplied alongside this addendum. This correction results in a small change to the incremental cost-effectiveness ratio (ICER). Therefore, sections 3.1 and Appendix A present the revised base case results and sensitivity analyses following correction of this error.
5. **Additional model scenario (disease progression)**: A scenario incorporating disease progression has been constructed in response to clinical advice received by the Company (section 3.2).

2. Clinical effectiveness evidence from VALOR-HCM

Key points

- The primary objective of VALOR-HCM was to evaluate the effect of 16 weeks of mavacamten treatment on the need for SRT in patients with obstructive HCM who met the 2011 ACCF/AHA guideline criteria for SRT and had been referred or were under active consideration for, and willing to undergo, SRT. Secondary endpoints evaluated changes in post-exercise left ventricular outflow tract (LVOT) gradient, NYHA class, symptoms (KCCQ-23 CSS) and biomarkers of cardiac left ventricular wall stress and injury (NT-proBNP, hs-cTnI).
- Patients in VALOR-HCM had comparable baseline characteristics to those in EXPLORER-HCM, including similar levels of LVOT obstruction, although the proportion of NYHA class III patients enrolled in VALOR-HCM was higher.
- After 16 weeks, 76.8% patients in the placebo group (43/56) remained guideline-eligible or chose to undergo SRT, compared with 17.9% patients in the mavacamten group (10/56) ($p < 0.001$).
- Patients receiving mavacamten demonstrated a 37 mmHg greater mean reduction in post-exercise LVOT gradient from baseline to Week 16 than patients receiving placebo ($p < 0.001$). The observed consistency in reductions between the EXPLORER-HCM and VALOR-HCM studies demonstrates the consistent impact of mavacamten on reducing LVOTO in patients with obstructive HCM.
- A larger proportion of patients receiving mavacamten (62.5%) in VALOR-HCM experienced ≥ 1 NYHA class improvement from baseline to Week 16 compared to placebo (21.4%), resulting in a treatment difference of 41.1% ($p < 0.001$). Therefore, the ability of mavacamten to improve patient symptoms and functional capacity demonstrated in EXPLORER-HCM is complemented by the VALOR-HCM data.
- Patients in the mavacamten group of VALOR-HCM reported a mean 9.4 point greater improvement in KCCQ-CSS compared to the placebo group, from baseline to Week 16 ($p < 0.001$). This is in line with the KCCQ-23 CSS improvement seen in EXPLORER-HCM, demonstrating the consistent impact of mavacamten on patient-reported quality of life.
- In VALOR-HCM, a significantly greater reduction in both NT-proBNP and hs-cTnI was seen from baseline to Week 16 in the mavacamten group compared to the placebo group ($p < 0.001$). Although cardiac biomarkers were exploratory endpoints in EXPLORER-HCM, consistent results were seen between the two trials.
- Overall, mavacamten was well-tolerated in VALOR-HCM, with no new safety signals observed compared to EXPLORER-HCM and the EXPLORER-LTE cohort of MAVA-LTE. Two of 56 participants had LVEF < 50% resulting in temporary discontinuation, however, both participants recovered LVEF > 50% and resumed treatment without further adverse events. No participant had a reduction of LVEF < 30% necessitating permanent drug discontinuation.
- The evidence from VALOR-HCM continues to demonstrate the clinical benefit of mavacamten in patients with symptomatic (NYHA class II–III) obstructive HCM.

2.1. Rationale for the VALOR-HCM trial

VALOR-HCM (NCT04349072) is a multicentre, phase III, randomised, double-blind, placebo-controlled study of mavacamten versus placebo in adult patients with symptomatic obstructive HCM who met the 2011 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline criteria for septal reduction therapy (SRT),[5] were referred or under active consideration for SRT within the previous 12 months, and were willing to undergo the procedure.[3,6] VALOR-HCM provides consistent and complementary evidence of the clinical efficacy and safety of mavacamten already demonstrated in the pivotal phase III trial EXPLORER-HCM for patients with symptomatic (NYHA class II–III) obstructive HCM.

As described in the CS (B.1.3.2.4), SRT procedures are associated with a range of peri- and post-operative risks including surgical mortality, atrioventricular (AV) block, ventricular septal defect and aortic regurgitation.[7,8] Furthermore, due to the specialised nature of SRT, availability of procedures is often restricted to a limited number of experienced centres.[3,7,8] Therefore, this study also provides important evidence regarding the ability of mavacamten to improve symptoms and haemodynamic parameters sufficiently that patients no longer meet the requirements to be eligible for SRT.

2.2. Summary of methodology of VALOR-HCM

Patients were included if they had symptomatic obstructive HCM treated with maximally-tolerated medical therapy and had been referred or under active consideration within the past 12 months for SRT procedure, were willing to have the SRT procedure, and met the 2011 ACCF/AHA guideline criteria for SRT procedure (detailed in Table 1).[5,6,9] A summary of the trial design and methodology for VALOR-HCM is presented in Table 1 and described below, with full details available in the trial protocol.[6,10]

Table 1. Summary of VALOR-HCM trial methodology

Trial acronym	VALOR-HCM[6,10]
Trial design	A phase III, double-blind, randomised, placebo-controlled, multicentre, parallel-group study to evaluate mavacamten in adults with symptomatic obstructive HCM who are eligible for septal reduction therapy
Inclusion criteria	**Key inclusion criteria:** • Adults aged at least 18 years

Trial acronym	VALOR-HCM[6,10]
	• Body weight ≥ 45 kg • Diagnosed with obstructive HCM (maximal septal wall thickness ≥ 15 mm at time of initial diagnosis or ≥ 13 mm with a positive family history of HCM) consistent with ACCF/AHA 2011 and/or ESC 2014 guidelines and met guideline recommendations for invasive SRT: o Clinical criteria: Despite maximally tolerated drug therapy, severe dyspnoea or chest pain (NYHA class III or IV) or NYHA class II with exertion-induced syncope or near syncope. o Hemodynamic criteria: dynamic LVOT gradient at rest or with provocation (i.e., Valsalva or exercise) ≥ 50 mmHg associated with septal hypertrophy. o Anatomic criteria: targeted anterior septal thickness sufficient to perform the procedure safely and effectively in the judgment of the individual operator. • Referred or under active consideration within the past 12 months for SRT procedure and willing to have SRT procedure • LVEF ≥ 60% at screening • Resting oxygen saturation ≥ 90% • Adequate acoustic windows to enable accurate TTE
Exclusion criteria	**Key exclusion criteria:** • Known infiltrative or storage disorder causing cardiac hypertrophy that mimics obstructive HCM, such as Fabry disease, amyloidosis, or Noonan syndrome with LV hypertrophy • Moderate to severe aortic stenosis • Planned invasive procedure during first 32 weeks of study • Papillary muscle or mitral valve in need of repair or any other intracardiac procedure planned • Paroxysmal, intermittent AF with AF at screening • Persistent or permanent AF and not on anticoagulation for ≥ 4 weeks prior to screening and/or not adequately rate controlled ≤ 6 months prior to screening • Previous invasive septal reduction • Planned ICD placement or pulse generator change during the first 32 weeks • Dose adjustment of BB, CCB or disopyramide < 14 days prior to screening or anticipated change during the first 16 weeks of the study • Any medical condition that precludes upright exercise stress testing • Acute or serious comorbid condition
Settings and locations where the data were collected	19 sites in the United States
Intervention	Mavacamten 2.5, 5, 10 or 15 mg capsule, once daily, by oral administration.
Comparator	Placebo to match mavacamten capsule, once daily, by oral administration.
Permitted and disallowed concomitant medications	Prior or concomitant treatment with cardiotoxic agents, such as doxorubicin or similar, was not permitted. Drugs metabolized by CYP2C19 pathway (moderate and potent inhibitors) and by the CYP3A4 pathway (potent inhibitors) were not permitted. Use of St. John's Wort or biotin supplements was not permitted from 14 days prior to screening through the end of the study. Multivitamins which contain biotin were to be taken > 24 hours prior to clinical visits.
Randomisation and blinding	Eligible patients were randomised via an interactive response technology (IXRS) in a ratio of 1:1 to receive either once daily mavacamten or matching placebo. Randomisation was double-blinded. The 16-week randomised controlled portion of the study was unblinded to the sponsor in February 2022. The investigators and subjects remain blinded and also dose-blinded in the active and LTE periods.
Primary outcome	The primary endpoint was a composite of the following: • Decision to proceed with SRT prior to or at Week 16

Trial acronym	VALOR-HCM[6,10]
	• SRT guideline eligible at Week 16
Other outcomes	Secondary outcomes include change from baseline to Week 16 in: • NYHA functional class • Kansas City Cardiomyopathy Questionnaire 23-item Clinical Summary Score (KCCQ-23 CSS) • cardiac biomarkers • post-exercise LVOT gradient Additional exploratory and safety outcomes can be found in the CSR.

AF: atrial fibrillation; BB: beta blockers; BMI: body mass index; CCB: calcium channel blocker; HCM: hypertrophic cardiomyopathy; ICD: implantable cardioverter defibrillator; KCCQ-23 CSS: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LTE: long-term extension; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; NYHA: New York Heart Association; SRT: septal reduction therapies; TTE: transthoracic echocardiogram.

2.2.1. Trial design and methodology

The study design is outlined in Figure 1 and a summary of the design and methodology is presented in Table 1. The study duration will be up to 136 weeks:[6]

1. **Two week screening period (Week -2 to Day 1)**
2. **Placebo-controlled, randomised (Day 1 to Week 16):** patients received either mavacamten or placebo (double-blind) for 16 weeks, with possible down-titration from Week 4 or up-titration at Weeks 8 and 12 based on left ventricular ejection fraction (LVEF) and Valsalva LVOT gradient.
3. **Active-controlled, non-randomised (Week 16 to 32):** Patients on placebo cross over to the mavacamten arm, that is, all those who received placebo in the first 16 weeks began mavacamten 5 mg at Week 16; while patients who received mavacamten in the first 16 weeks continued on their dose at Week 16. Dose and dose-adjustment remain blinded in all treatment arms and determined by core laboratory results.
4. **Long-term extension (LTE) (Week 32 to Week 128):** all patients receive mavacamten once daily. Possible up-titration to a maximum of 15 mg/day based on the site read echocardiogram of LVEF and Valsalva LVOT gradient.
5. **Eight week post-treatment period (Week 128 to 136)**

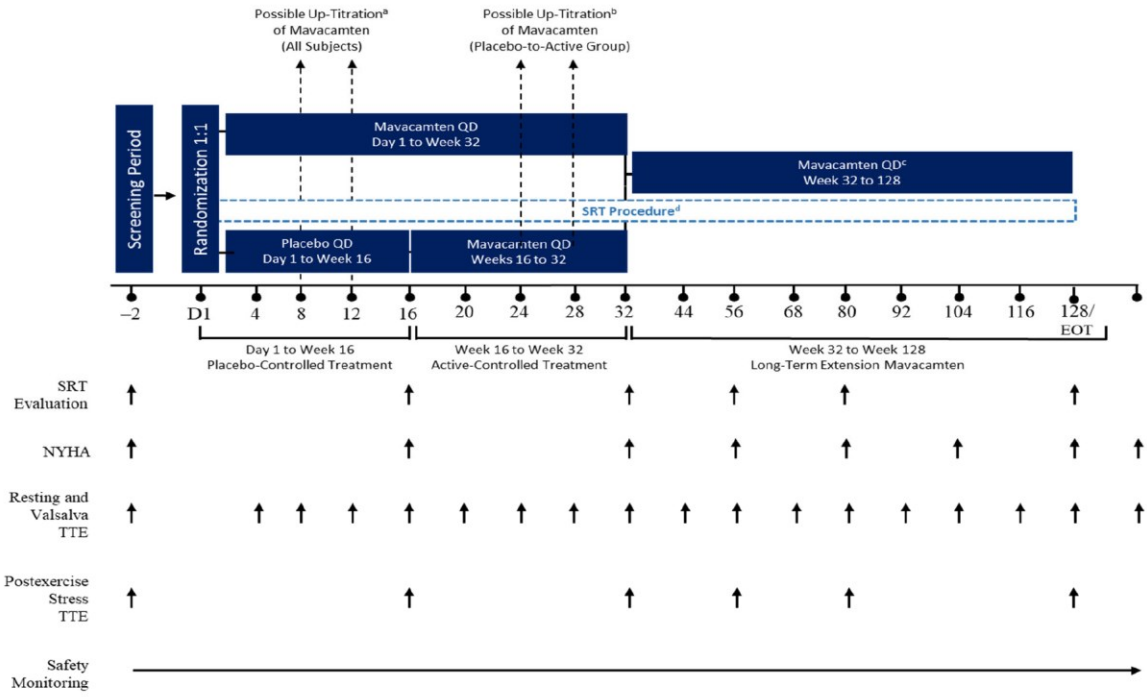

Figure 1. VALOR-HCM study schematic

Source: VALOR-HCM CSR.[9]
EOT, end of treatment; NYHA, New York Heart Association; QD, once a day; SRT, septal reduction therapy; TTE, transthoracic echocardiogram.

Eligible patients were randomised in a ratio of 1:1 to receive either once daily mavacamten (5 mg) or matching placebo. Randomisation was stratified by type of SRT recommended (surgical myectomy or alcohol ablation), and by NYHA functional class. During the study, LVEF and LVOT gradient were evaluated every 4 weeks by transthoracic echocardiography (TTE), and used as the basis for possible down-titration at Week 4 (based on Valsalva LVOT < 30 mmHg), or up-titration at Weeks 8 and 12 based on LVEF ≥ 50% and Valsalva LVOT ≥ 30 mmHg; possible doses were 2.5, 5, 10, or 15 mg, once daily. Patients in the placebo-to-active group begin mavacamten at Week 16 and are therefore evaluated for down-titration at Week 20 and up-titration at Weeks 24 and 28. Note that doses may be down-titrated for safety at any time. The pre-specified criteria for treatment interruption or discontinuation of study drug included resting LVEF < 50%, with dosing resumed at one lower dose strength if LVEF ≥ 50% at a 2–4 week follow-up.

The primary objective of the study was to evaluate the effect of mavacamten on the need for SRT in guideline-eligible patients with obstructive HCM who are referred for

SRT. The primary endpoint in VALOR-HCM was the composite of the proportion of patients proceeding with SRT or who remained guideline-eligible after 16 weeks' treatment (Table 2). Secondary endpoints evaluated the effect of 16 weeks of mavacamten treatment on post-exercise LVOT gradient, patient-reported outcomes and symptom severity, including NYHA class, and cardiac biomarkers (Table 2). Exploratory objectives aim to evaluate the effect of mavacamten on the need for SRT in a long-term follow-up period and the effect of mavacamten on symptoms, haemodynamic parameters, cardiac biomarkers, patient activity level and quality of life through to Week 128, with selected exploratory endpoints evaluated at Week 16.

Table 2. Study endpoints for VALOR-HCM

VALOR-HCM trial outcomes[6,10]	
Primary endpoint	The primary endpoint is a composite of the following: • Decision to proceed with SRT prior to or at Week 16 • SRT guideline eligible at Week 16 based on the 2011 ACCF/AHA HCM guidelines
Secondary endpoints	Change from baseline to Week 16 in the mavacamten group compared with the placebo group (in order of hierarchy): • Post-exercise LVOT gradient • NYHA functional class • Kansas City Cardiomyopathy Questionnaire-23 (KCCQ-23) Clinical Summary Score (CSS) • NT-proBNP and cardiac troponin I
Exploratory endpoints	Change from baseline to Week 16 in: LVOT gradient at rest and induced by Valsalva; LVEF; LV filling pressures; left atrium size; cardiac biomarkers; accelerometry; EQ-5D-5L questionnaire In a long-term follow-up period (assessments at Weeks 32, 56, 80, and 128), a composite of: • Decision to proceed with SRT • SRT guideline eligible based on the 2011 ACCF/AHA HCM guidelines In a long-term follow-up period (assessments at Weeks 16, 32, 56, 80, and 128), a composite of: • Decision to proceed with SRT • SRT eligible based on the investigator determination as recorded on the SRT evaluation CRF Analysis of NYHA functional class, KCCQ-23 (Overall Summary Score [OSS], Total Summary Score [TSS], and individual domains), LVOT gradients, LVEF, LV filling pressures, left atrium size, cardiac biomarkers, accelerometry, and EQ- 5D-5L, throughout to Week 128 Change from baseline to Week 16, Week 16 to 32, and Week 32 to 128 in HCM standard of care cardiac medications
Safety endpoints	Incidence and severity of TEAEs, treatment-emergent SAEs, and laboratory abnormalities Incidence of: LVEF < 50% determined by TTE; SAEs before and after SRT among patients who undergo SRT; major adverse cardiac events (MACE:

VALOR-HCM trial outcomes[6,10]	
	death, stroke, acute myocardial infarction, heart failure hospitalisation); hospitalizations (due to CV and non-CV causes); HF events (including hospitalisations and urgent emergency room/outpatient visits for HF and escalation in HF treatment); atrial fibrillation/flutter (new from screening and recurrent); ICD therapy and resuscitated cardiac arrest; ventricular tachyarrhythmias (includes VT, VF and TdP); adverse events of special interest (AESIs; symptomatic overdose, outcomes of pregnancy, LVEF ≤ 30%)
Pharmacokinetics	Summarise mavacamten plasma concentrations from on-treatment sample collection

AESI: adverse events of special interest; CRF: case report form; HCM: hypertrophic cardiomyopathy; HF: heart failure; ICD: implantable cardioverter defibrillator; KCCQ-23: Kansas City Cardiomyopathy Questionnaire; LVEF: left ventricular ejection fraction; LV: left ventricular; LVOT: left ventricular outflow tract; NYHA: New York Heart Association; SAE: serious adverse event; SRT: septal reduction therapy; TdP: torsades de pointes; TEAE: treatment emergent adverse event; VF: ventricular fibrillation; VT: ventricular tachyarrhythmias.

2.2.2. Study populations

The data presented from VALOR-HCM are from the randomised placebo-controlled period (Day 1 to Week 16), based on the interim analysis of the [redacted] database lock (DBL), which had a clinical data cut-off of [redacted].[3,9] By the clinical data cut-off, 152 potential patients had been screened and 112 patients randomised (56 patients in mavacamten group, 56 patients in placebo group), forming the intention to treat (ITT) population of the placebo-controlled (Day 1 to Week 16) period. A total of 111 patients out of 112 received at least one dose of study drug, forming the safety population. At the time of data cut-off, all randomised patients had completed the 16-week double-blind period follow-up, except for 2 patients in the placebo arm who discontinued the study (1 patient withdrew as they met exclusion criterion, and 1 withdrew consent after randomisation but before the first dose). Additionally, 2 patients in each of the mavacamten and placebo arms discontinued and chose to proceed with SRT.[3] Full details of patient disposition can be found in the VALOR-HCM clinical study report (CSR).[9]

2.3. Statistical analysis and definition of study groups

A summary of the statistical methodology for the VALOR-HCM trial is provided in Table 3. Further details can be found in the VALOR-HCM clinical study protocol and the VALOR-HCM CSR.[9,10]

Table 3. Statistical analysis summary for VALOR-HCM

	VALOR-HCM[9,10]
Analysis populations	The analysis populations defined for this interim analysis were:

	VALOR-HCM[9,10]
	• ITT population: all randomised participants regardless of whether they received study drug, with analyses conducted according to the randomised treatment assignment • Safety analysis population: all randomised participants who receive at least 1 dose of study drug with analyses conducted by actual treatment received. • LTE population: all participants who receive at least 1 dose of mavacamten. This population will be used for all long-term follow up analysis • PK analysis population: all randomised participants who received at least 1 dose of study drug and had at least 1 evaluable mavacamten plasma drug concentration
General considerations	All efficacy analyses were based on the ITT population. Descriptive statistics for efficacy parameters by time point and change from baseline were provided. The estimates of treatment group differences and the 95% CIs were provided for the placebo-controlled period. All efficacy analysis comparing the mavacamten and placebo treatment groups using CMH method were stratified by type of SRT recommended (myectomy vs alcohol septal).
Interim analysis	A formal interim analysis was conducted to assess efficacy and safety of mavacamten by the independent Statistical Data Analysis Center and reviewed by the iDMC after 50 patients completed the Week 16 visit or terminated early. A fixed p value of <0.001 for the primary endpoint was required to recommend stopping the trial early, leaving an alpha of 0.049 at the final analysis. On August 24, 2021, the iDMC communicated to a small sponsor group not involved in the trial that the stopping boundary for overwhelming efficacy had been crossed. As specified in the iDMC Charter, the sponsor conferred with the study chair and they jointly decided that continuing the trial would best serve the interests of patients by ensuring that the final results would be sufficiently robust to define mavacamten's role in avoiding the need for SRT. All study personnel remained blinded to treatment assignment until final DBL.[3]
Statistical analysis of primary endpoint	The primary analysis is based on the 16-week placebo-controlled treatment period. Data collected through the clinical cut-off date of [redacted] was cleaned and locked prior to conducting the primary analysis. The comparison of the proportions of patients meeting the primary endpoint between the mavacamten and placebo treatment groups stratified by the type of SRT procedure recommended and NYHA class was performed using the CMH test. The point estimate and the 95% CIs for the treatment difference was provided. Baseline maximum LVOT gradient was included in the CMH test as a sensitivity analysis to estimate the treatment effect. A tipping point analysis was performed to assess the impact of the missing data and the robustness of the primary endpoint result.
Statistical analysis of key secondary endpoints	Secondary endpoints were tested in a pre-specified sequential order. Secondary endpoints were summarised for each treatment group at each visit using descriptive statistics. Change from baseline to Week 16 in post-exercise LVOT gradient was analysed using an ANCOVA model. Proportion of participants who had at least 1 class of improvement from baseline in NYHA class at Week 16 was analysed using the same method as for the primary endpoint. Change from baseline to Week 16 in NT-proBNP, cardiac troponin I, and KCCQ-23 CSS was analysed using a MMRM. Sensitivity analyses were conducted using MAR mechanism.
Statistical analysis of safety endpoints	All safety analyses were performed using the safety analysis population. Safety endpoints were summarized descriptively using safety analysis population. All AEs were coded to SOCs and PTs using the MedDRA version 24.1 or higher. Overall summary of TEAEs, TEAEs by SOC and PT, drug related and serious drug-related TEAEs, AESI, TEAEs with fatal outcome and resulting in permanent treatment discontinuation were tabulated.

	VALOR-HCM[9,10]
Pre-planned subgroups	Primary and secondary efficacy endpoints were analysed for subgroups of subjects with the following characteristics at baseline: • Type of SRT procedure recommended (myectomy vs ASA) • NYHA class (II vs higher) • LVOT resting peak gradient (≤ 50 mmHg vs > 50 mmHg) • LVOT resting peak gradient (≤ 30 mmHg vs > 30 mmHg) • Sex (male vs female) • Age (≤ 49 years, 50 to 64 years, ≥ 65 years) • BMI (< 30 kg/m^2 vs ≥ 30 kg/m^2) • Race (white vs non-white) • Presence of HCM pathogenic mutation (pathogenic vs variant of uncertain significance (VUS) • vs not pathogenic) • Time from diagnosis of obstructive HCM (≤ 5 years vs > 5 years) • Beta-blocker use (yes vs no) • Calcium channel blocker use (yes vs no) • Disopyramide use (yes vs no) • Use of multiple of background HCM medications (2 or more medication vs 1 medication vs • none) • Resting LVEF (< 75% vs ≥ 75%) • Left atrial volume index (≤ median vs > median based on ITT population) • NT-proBNP (≤ median vs > median based on ITT population) • hs-Cardiac troponin-I (≤ upper limit of normal [ULN] vs > ULN)

AE: adverse event; AF: atrial fibrillation; ASA: alcohol septal ablation; BB: beta blockers; BMI: body mass index; CCB: calcium channel blocker; CMH: Cochran-Mantel-Haenszel; CMR: cardiac magnetic resonance; cTnI: cardiac troponin I; ECG: electrocardiogram; HCM: hypertrophic cardiomyopathy; hs-cTnI: high sensitivity cardiac troponin I; ITT: intention to treat; LGE: late gadolinium enhancement; KCCQ-23 CSS: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; NT-proBNP: N-terminal pro–B-type natriuretic peptide; NYHA: New York Heart Association; pVO_2: peak oxygen consumption; SOC: standard of care; SRT: septal reduction therapies; TEAEs: treatment emergent adverse events; TTE: transthoracic echocardiogram; ULN: upper limit of normal.

2.4. Critical appraisal of VALOR-HCM

The quality assessment of VALOR-HCM (Table 4) indicated that this study represents a high-quality randomised controlled trial (RCT) with low risk of bias. Minor differences observed between the two arms is considered within the stochastic variation expected as a result of randomisation. Overall, this is a strong and well-balanced study.

Table 4. Quality assessment of the VALOR-HCM trial

Study questions	VALOR-HCM[3] Grade (yes/no/not clear/NA)
Was randomisation carried out appropriately?	Yes (interactive voice web response system)
Was the concealment of treatment allocation adequate?	Yes (interactive voice response system with matching placebo)
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes (minor differences between groups in background therapy)
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes

Study questions	VALOR-HCM[3] Grade (yes/no/not clear/NA)
Were there any unexpected imbalances in dropouts between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

University of York Centre for Reviews and Dissemination.[11]
ITT: intention-to-treat; NA: not applicable.

2.5. Baseline characteristics

In VALOR-HCM, all 112 patients enrolled were symptomatic, with the majority of patients (93%) experiencing NYHA class III symptoms or higher (n = ▌ with NYHA class IV symptoms). The mean age of patients was 60 ± 12 years, and 51% were male.[3] At baseline, the majority of patients were using beta blocker (BB) monotherapy (45.5%), with 15.2% of patients using calcium channel blocker (CCB) monotherapy, and 32% of patients were on combination therapy. A total of 6 patients were on no HCM medications and did not tolerate standard care medications.[3,9] Baseline characteristics of patients in the VALOR-HCM trial are shown in Table 5.

The study population of VALOR-HCM had comparable baseline characteristics to patients enrolled in EXPLORER-HCM (Table 5), including similar levels of LVOT obstruction, although the proportion of patients enrolled in VALOR-HCM in NYHA class III was higher than in EXPLORER-HCM. A similar proportion of patients were using BB as background therapy, however patients in VALOR-HCM were permitted a broader range of combinations of background HCM therapy.[1,3]

Table 5. Baseline characteristics of patients in VALOR-HCM and EXPLORER-HCM

Characteristic	VALOR-HCM[3,9]		EXPLORER-HCM[1,12]	
	Mavacamten (N = 56)	Placebo (N = 56)	Mavacamten (N = 123)	Placebo (N = 128)
Age, years	59.8 ± 14.2	60.9 ± 10.5	58.5 ± 12.2	58.5 ± 11.8
Female (%)	27 (48.2)	28 (50.0)	57 (46)	45 (35)
Race[*]				
White	48 (85.7)	52 (92.9)	115 (93)	114 (89)
Black	3 (5.4)	0 (0.0)	1 (1)[†]	5 (4)[†]
Asian	2 (3.6)	0 (0.0)	4 (3)	2 (2)
Unspecified or other	3 (5.4)	4 (7.1)	3 (2)[‡]	6 (5)[‡]
Body mass index, kg/m^2	29.3 ± 4.8	31.9 ± 6.2	29.7 ± 4.9	29.2 ± 5.6
Systolic blood pressure, mmHg	130.4 ± 16.5	131.2 ± 16.6	128 ± 16.2	128 ± 14.6
Diastolic blood pressure, mmHg	74.0 ± 10.5	74.2 ± 8.9	75 ± 10.8	76 ± 9.9
Duration of obstructive HCM disease, years	7.5 ± 9.4	6.7 ± 7.4	NR	NR
Family history of HCM	17 (30.4)	15 (26.8)	33 (27)	36 (28)
Medical history				
History of atrial fibrillation	11 (19.6)	8 (14.3)	12 (10)	23 (18)
History of hypertension	36 (64.3)	34 (60.7)	57 (46)	53 (41)
History of syncope or presyncope	29 (51.8)	30 (53.6)	NA[††]	NA[††]
Internal cardioverter defibrillator	9 (16.1)	10 (17.9)	27 (22)	29 (23)
NYHA class II (with exertional syncope in VALOR-HCM)	4 (7.1)	4 (7.1)	88 (72)	95 (74)
NYHA class III	NA	NA	35 (28)	33 (26)
NYHA class III or higher	52 (92.9)	52 (92.9)	NA[††]	NA[††]
Type of septal reduction therapy recommended				
Alcohol septal ablation	8 (14.3)	7 (12.5)	NA[††]	NA[††]
Myectomy	48 (85.7)	49 (87.5)	NA[††]	NA[††]
Background HCM therapy				
BB monotherapy	26 (46.4)	25 (44.6)	94 (76)	95 (74)
Non-dihydropyridine CCB monotherapy	7 (12.5)	10 (17.9)	25 (20)	17 (13)
Disopyramide monotherapy	0 (0.0)	2 (3.6)	NA[††]	NA[††]
BB and CCB	6 (10.7)	10 (17.9)	NA[††]	NA[††]
BB and disopyramide	11 (19.6)	3 (5.4)	NA[††]	NA[††]
CCB and disopyramide	1 (1.8)	2 (3.6)	NA[††]	NA[††]
BB, CCB, and disopyramide	2 (3.6)	1 (1.8)	NA[††]	NA[††]
None, medication intolerance	3 (5.4)	3 (5.4)	4 (3.3)	16 (12.5)

Characteristic	VALOR-HCM[3,9]		EXPLORER-HCM[1,12]	
	Mavacamten (N = 56)	Placebo (N = 56)	Mavacamten (N = 123)	Placebo (N = 128)
Echocardiographic parameters				
LVOT gradient, mmHg				
Resting	51.2 ± 31.4	46.3 ± 30.5	52 ± 29	51 ± 32
Valsalva	75.3 ± 30.8	76.2 ± 29.9	72 ± 32	74 ± 32
Post-exercise	82.5 ± 34.7	85.2 ± 37.0	86 ± 34§	84 ± 36§
LVEF, %	67.9 ± 3.7	68.3 ± 3.2	74 ± 6	74 ± 6
LAVI, mL/m^2	41.3 ± 16.5	40.9 ± 15.2	40 ± 12¶	41 ± 14¶
KCCQ-23 CSS, points	69.5 ± 16.3	65.6 ± 19.9	NR	NR
NT-proBNP, ng/L	724 (291-1913)	743 (275-1,196)	777 (136)‖	616 (108)‖
Cardiac troponin I, ng/L	17.3 (7.0-31.6)	12.9 (6.1-26.0)	12.5 (208)**	12.5 (373)**
Cardiac troponin T, mg/L	0.014 (0.01-0.02)	0.011 (0.008-0.02)	NR	NR

Values are mean ± SD, n (%), or median (IQR).
* Race was self-reported in VALOR-HCM.
† Black and African American
‡ Race unknown
§ Data missing for one patient in the mavacamten group and one patient in the placebo group.
¶ Data missing for one patient in the mavacamten group.
|| Data missing for three patients in the mavacamten group and two patients in the placebo group. Data shown as geometric mean (COV%). The variation number (COV%) is the coefficient of variation, which is defined as the ratio of the SD to the mean
** Data missing for three patients in the mavacamten group and nine patients in the placebo group. Data shown as geometric mean (COV%). The variation number (COV%) is the coefficient of variation, which is defined as the ratio of the SD to the mean
†† NA values due to differences in eligibility criteria between the two trials
CCB: calcium channel blockers; COV: coefficient of variation; HCM: hypertrophic cardiomyopathy; KCCQ-23 CSS: Kansas City Cardiomyopathy Questionnaire 23-item Clinical Summary Score; LAVI: left atrial volume index; LV: left ventricular; LVOT: left ventricular outflow tract; NA: not applicable; NR: not reported; NT-pro BNP: N-terminal pro brain natriuretic peptide; NYHA: New York Heart Association.

2.6. Clinical effectiveness evidence

2.6.1. VALOR-HCM primary efficacy endpoint

After 16 weeks, 76.8% patients in the placebo group (43/56) remained guideline-eligible or chose to undergo SRT, compared with 17.9% patients in the mavacamten group (10/56) ($p < 0.001$; Figure 2, Table 6). As two patients in each arm decided to proceed with SRT at Week 16 (Table 6), the primary endpoint was driven by the proportion of patients who continued to meet the guideline criteria at Week 16.[3,9] The substantially smaller proportion of patients in the mavacamten arm who remained guideline eligible indicates that treatment with mavacamten for 16 weeks reduces LVOT gradient below the threshold of 50 mmHg, or improves patients symptoms as assessed by NYHA class, or both.

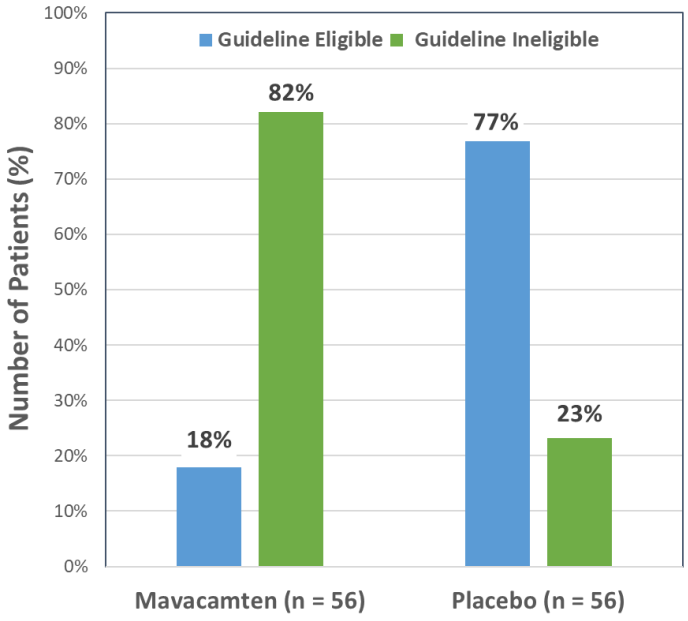

Figure 2. Proportion of patients who remained guideline eligible for SRT or chose to undergo SRT at 16 weeks

Figure adapted from Desai et al. 2022.[3] SRT: septal reduction therapy.

Table 6. Proportion of patients meeting the primary endpoint at Week 16 - ITT population

Parameters	Mavacamten (N = 56)	Placebo (N = 56)	Treatment Diff. (95% CI)[a]
Primary efficacy composite endpoint[b], n (%)	10 (17.9)	43 (76.8)	58.9 (44.0–73.9) p <0.001
Patient decision to proceed with SRT, n (%)	2 (3.6)	2 (3.6)	NA
SRT-eligible based on guideline criteria[c], n (%)	8 (14.3)	39 (69.6)	NA
SRT status not evaluable, imputed as meeting criteria[d], n (%)	0	2 (3.6)	NA

[a]Treatment difference and 95% CI were generated in analysis of covariance model including baseline variable as a covariate and baseline stratification factors for type of SRT recommended (alcohol septal ablation or myectomy) and NYHA functional class (class II or class III/IV).
[b]Cochran-Mantel-Haenszel method stratified by baseline NYHA criteria (II vs higher) and type of SRT recommended (myectomy vs alcohol septal ablation). Difference in proportions estimated as placebo rate minus mavacamten rate, where a positive value indicates a beneficial treatment effect.
[c]The guideline criteria are based of the 2011 ACCF/AHA HCM clinical and hemodynamic criteria. Patients with maximum LVOT ≥50 mmHg gradient (from rest, Valsalva, or post-exercise) and no improvement in NYHA functional class at Week 16 are considered eligible for SRT.
[d]If assumed that both patients in the placebo group did not meet the primary endpoint, the result shows treatment difference of similar magnitude to the primary analysis with same level of significance. Treatment difference 55.36 (95% CI: 40.02-70.69); P < 0.0001.
Source: Desai et al. 2022,[3] VALOR-HCM CSR[9]
CI: confidence interval; LVOT: left ventricular ejection fraction; NA; not applicable; NYHA: New York Heart Association; SRT, septal reduction therapy.

2.6.2. VALOR-HCM secondary efficacy endpoints

The secondary endpoints in VALOR-HCM represent changes in LVOT obstruction, functional capacity (NYHA class), symptoms (Kansas City Cardiomyopathy Questionnaire clinical summary score [KCCQ-23 CSS]) and cardiac biomarkers (N-terminal pro–B-type natriuretic peptide [NT-proBNP], high sensitivity cardiac troponin I [hs-cTnI]) associated with symptomatic obstructive HCM. Mavacamten showed significant improvement in all secondary endpoints compared with placebo (Table 7, Figure 3–Figure 5).[3,9]

The results from the VALOR-HCM secondary endpoints were consistent with the findings from the larger pivotal phase III trial EXPLORER-HCM, as detailed below (Table 7), although it should be noted that due to the differences in baseline characteristics, assessment periods and baseline values between the two trials, direct numerical comparison between each endpoint should be treated with caution.[1,3]

Table 7. Secondary efficacy endpoints from baseline to Week 16 in VALOR-HCM compared to EXPLORER-HCM endpoints

Endpoints	VALOR-HCM Changes from baseline to Week 16			EXPLORER-HCM Changes from baseline to Week 30		
	Mavacamten (N = 55)	Placebo (N = 53)	Treatment difference (95% CI)	Mavacamten (N = 123)	Placebo (N = 128)	Treatment difference (95% CI)
Secondary endpoints in VALOR-HCM and EXPLORER-HCM						
Post-exercise LVOT peak gradient, mmHg, mean (SD)	-39.1 (36.5)	-1.8 (28.8)	**-37.2 (-48.1, -26.2) p < 0.001**	-47 (40)	-10 (30)	**-35.6 (-43.2, -28.1) p < 0.0001**
NYHA improved ≥ 1 class, n (%)	35 (62.5)	12 (21.4)	**41.1 (24.5, 57.7) p < 0.001**	80 (65)	40 (31)	**34 (22, 45) < 0.0001**
KCCQ-23 CSS, mean (SD) change from baseline	10.4 (16.1)	1.9 (12.0)	**9.4 (4.9, 14.0) p < 0.001**	13.6 (14.4)	4.2 (13.7)	**9.1 (5.5, 12.7) p < 0.0001**
Secondary endpoints in VALOR-HCM; exploratory endpoints in EXPLORER-HCM						
NT-proBNP (ng/L), geometric mean ratio to baseline (% CV)	0.35 (83.677)	1.13 (57.809)	**0.33 (0.26, 0.42)[b] < 0.001**	0.20 (266.91)	1.02 (55.80)	**0.20 (0.17, 0.24) p < 0.0001**
hs-cTnI (ng/L), geometric mean ratio to baseline (% CV)	0.50 (100.992)	1.03 (85.716)	**0.53 (0.41, 0.70)[b] p < 0.001**	0.58 (49.17)	0.99 (143.34)	**0.59 (0.5, 0.69) p < 0.0001**

Sources: Desai et al. 2022,[3] VALOR-HCM CSR,[9] Olivotto et al 2020[1], EXPLORER-HCM CSR[12]
aTreatment difference and 95% CI were generated in analysis of covariance model including baseline variable as a covariate and baseline stratification factors for type of SRT recommended (alcohol septal ablation or myectomy) and NYHA functional class (class II or class III/IV).
bGeometric mean ratios <1.0 represent an x-fold decrease for mavacamten compared with placebo
CI: confidence interval; KCCQ-23 CSS, Kansas City Cardiomyopathy Questionnaire 23-item Clinical Summary Score; LVOT, left ventricular outflow tract; NT-pro BNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; SRT, septal reduction therapy.

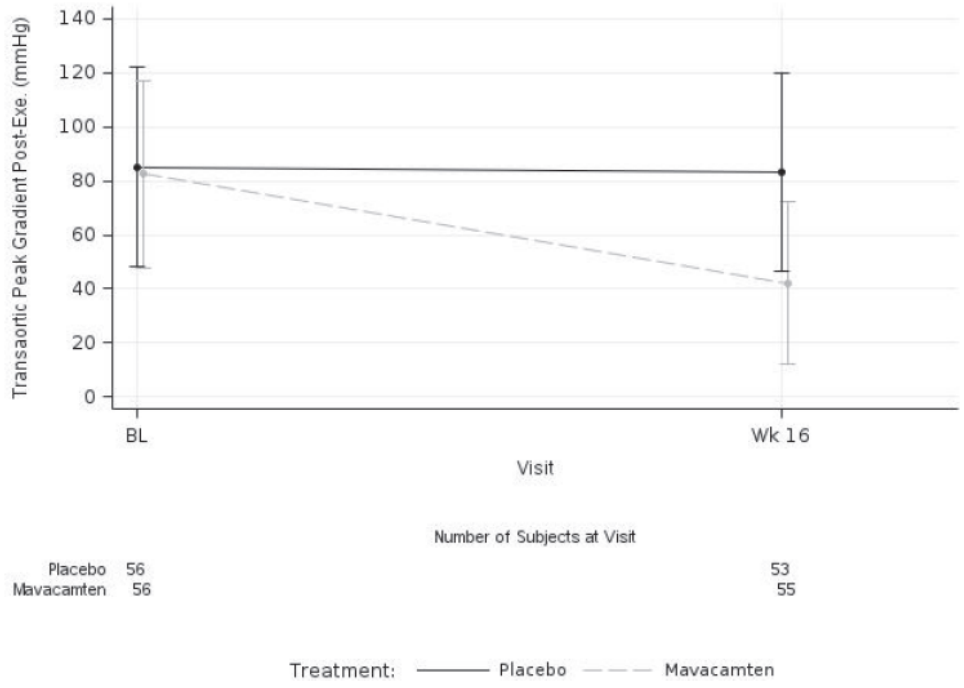

Figure 3. Change in post-exercise LVOT gradient from baseline to Week 16, ITT population

Data are mean±SD. Source: VALOR-HCM CSR[9]

Post-exercise LVOT gradient is a physiological measure of the severity of outflow tract obstruction; obstruction is defined as a gradient ≥ 30 mmHg, while ≥ 50 mmHg forms part of the eligibility criteria for SRT.[8] Patients receiving mavacamten demonstrated a 37 mmHg greater mean reduction in post-exercise LVOT gradient from baseline to Week 16 than patients receiving placebo ($p < 0.001$); the mean gradient after 16 weeks of mavacamten treatment was < 50 mmHg (Figure 3).[3,9] This is consistent with the 35.6 mmHg greater mean reduction in post-exercise LVOT gradient seen between baseline and Week 30 in EXPLORER-HCM for mavacamten compared to placebo (Table 7 and CS B.2.6.1.2).[1] The observed consistency in reductions in post-exercise LVOT gradients between the EXPLORER-HCM and VALOR-HCM studies demonstrates the consistent impact of mavacamten on reducing outflow tract obstruction in patients with obstructive HCM.

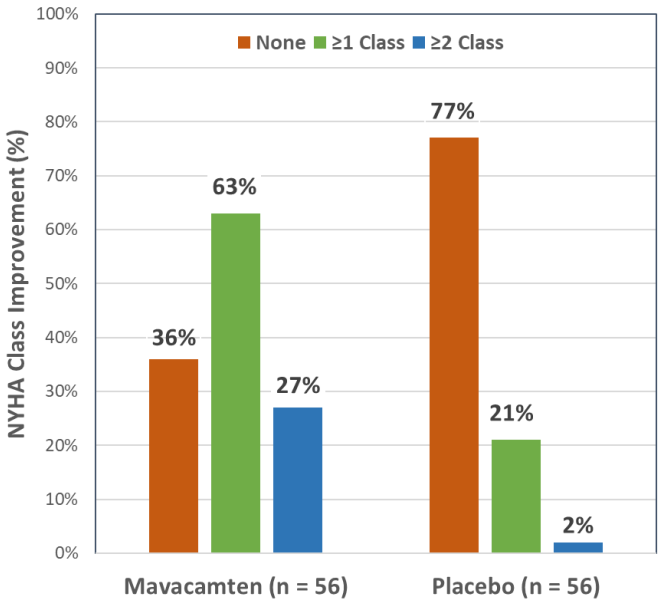

Figure 4. Proportion of patients who improved by 0, ≥ 1 or ≥ 2 NYHA classes from baseline to Week 16, ITT population

Figure adapted from Desai et al. 2022.[3] ITT: intention to treat; NYHA: New York Heart Association

NYHA class is a physician-assessed measure of functional capacity (CS B.1.3.1.3.1). A larger proportion of patients receiving mavacamten (63%) in VALOR-HCM experienced ≥ 1 NYHA class improvement from baseline to Week 16 compared to placebo (21%), resulting in a treatment difference of 41% ($p < 0.001$) (Figure 4).[3,9] Although the baseline distribution of NYHA class was different between the EXPLORER-HCM and VALOR-HCM studies, the proportion of patients demonstrating symptomatic improvement, as assessed by NYHA class, in VALOR-HCM was consistent with that seen in EXPLORER-HCM, where 34% more patients experienced ≥ 1 NYHA class improvement in the mavacamten arm compared to the placebo arm after 30 weeks of treatment (Table 7; CS B.2.6.1.2).[1] Therefore, the ability of mavacamten to improve patient symptoms and functional capacity demonstrated in EXPLORER-HCM is consistently shown in VALOR-HCM.

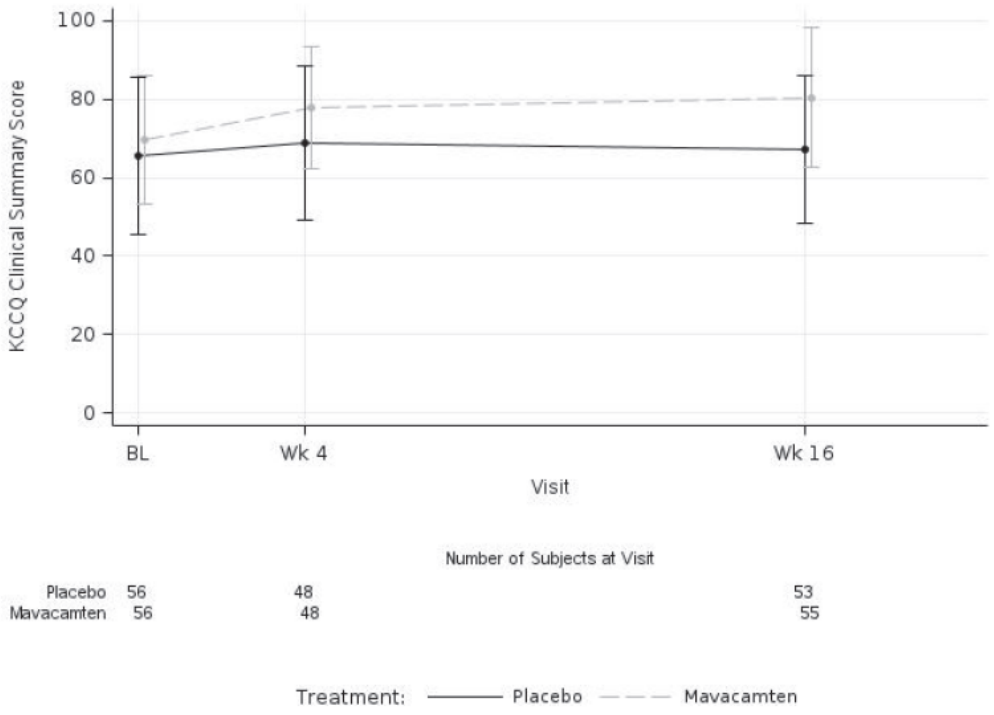

Figure 5. Change in KCCQ-23 CSS from baseline to Week 16, ITT population

Data are mean±SD. Source: VALOR-HCM CSR[9]
KCCQ-23 CSS: Kansas City Cardiomyopathy Questionnaire clinical summary score; ITT: intention to treat

KCCQ-23 is a cardiomyopathy-specific patient reported outcome (PRO) instrument that has been validated for use in patients with symptomatic obstructive HCM.[13] The KCCQ-23 CSS represents a combination of the total symptom score and physical limitation domains, providing a patient-reported parallel to the physician-assessed NYHA class.[14] Patients in the mavacamten group of VALOR-HCM reported a 9.4 point greater mean improvement in KCCQ-23 CSS compared to the placebo group, from baseline to Week 16 ($p < 0.001$, Figure 5).[3,9] This is in line with the 9.1 point greater mean improvement in KCCQ-23 CSS reported by patients in the mavacamten arm of EXPLORER-HCM compared to placebo, from baseline to Week 30 (Table 7; CS B.2.6.1.2),[1,14] demonstrating the consistent impact of mavacamten on patient-reported quality of life.

The secondary endpoints of VALOR-HCM also included biomarkers of heart left ventricular (LV) wall stress (NT-proBNP) and cardiac injury (hs-cTnI). A significantly greater reduction in both biomarkers was seen from baseline to Week 16 in the mavacamten group compared to the placebo group ($p < 0.001$, Table 7).[3] Although these were exploratory endpoints in EXPLORER-HCM, consistent results were seen

between the two trials (Table 7),[1] indicating that VALOR-HCM complements the efficacy demonstrated in the pivotal phase III trial.

2.6.3. VALOR-HCM exploratory endpoints

Key exploratory endpoints specified in the NICE decision problem (CS B.1.1) are presented here; details of other exploratory endpoints can be found in Desai *et al*., 2022 and the CSR.[3,9]

A small increase in EQ-5D-5L index score was seen at Week 16 compared to baseline in both arms, which was numerically greater in the mavacamten arm and similar in magnitude to the difference seen in EXPLORER-HCM (Table 8).[9,15]

In line with results from EXPLORER-HCM and consistent with the mechanism of action of mavacamten, patients treated with mavacamten showed a small decrease in LVEF compared to placebo (-3.4% versus 0.3%, respectively; Table 8).[1,3] Although statistically significantly different, these changes to LVEF are not expected to be clinically meaningful.

Table 8. Selected exploratory endpoints from VALOR-HCM and EXPLORER-HCM

Selected exploratory endpoints	VALOR-HCM Changes from baseline to Week 16			EXPLORER-HCM Changes from baseline to Week 30		
	Mavacamten (N = 55)	Placebo (N = 53)	Treatment difference (95% CI)	Mavacamten (N = 123)	Placebo (N = 128)	Treatment difference (95% CI)
EQ-5D-5L index score	[redacted]	[redacted]	[redacted]	0.084	0.009	0.075 (0.028, 0.122) p = 0.002
LVEF %, mean (SD)	-3.4 (6.23)	0.3 (4.19)	-4.0 (-5.5, -2.5) p < 0.0001	-3.9 (7.7)	-0.01 (6.8)	-4.0 (-5.5, -2.5)

Sources: Desai et al. 2022,[3] VALOR-HCM CSR,[9] Olivotto et al 2020,[1] Xie et al. 2022,[15] EXPLORER-HCM CSR.[12] CI: confidence interval; LVEF: left ventricular ejection fraction

2.7. Subgroup analysis

Primary and secondary efficacy endpoints were analysed for a subgroup of patients who met a pre-specified set of characteristics at baseline, outlined in Table 3. Due to low sample size in the subgroups, analyses were not stratified. For the primary endpoint from baseline to Week 16, the results were consistent across all subgroups, favouring the mavacamten group relative to the placebo group.[3,9] Comprehensive

data from the subgroup analysis of each of the primary and secondary endpoints can be found in the VALOR-HCM CSR.[9]

2.8. Adverse reactions

All safety data were reported in the safety analysis population for the double-blind period, and interim analyses in the long-term follow-up period up to the clinical data cut-off date. Two of 56 participants had LVEF < 50% resulting in temporary discontinuation, however, both participants recovered LVEF > 50% and resumed treatment without further adverse events, remaining in the VALOR LTE study.[3,9] No participant had a reduction of LVEF < 30% necessitating permanent drug discontinuation. Investigator-reported on-treatment adverse events were more common in the mavacamten group (n = 123 events in 41 patients) than the placebo group (n = 93 events in 34 patients), but none resulted in withdrawal from the trial. In each arm, [redacted] events were deemed related to study drug. A summary of the AEs that occurred during the double-blind period are presented in Table 9Table 9. Overall, mavacamten was well-tolerated, with no new safety signals observed compared to EXPLORER-HCM and the EXPLORER-LTE cohort (CS B.2.10).

Table 9. Safety endpoints and adverse events summary

	Mavacamten (N = 56) n (%)	**Placebo (N = 55) n (%)**
Safety endpoints		
LVEF < 50%	2 (3.6)	0 (0.0)
Permanent discontinuation for LVEF	0 (0.0)	0 (0.0)
Death, myocardial infarction or stroke	0 (0.0)	0 (0.0)
On-treatment AEs		
Total number of on-treatment AEs	123	93
Number of patients with		
≥ 1 on-treatment AE	41 (73.2)	34 (61.8)
≥ 1 AE leading to death	0	0
≥ 1 treatment-related AE	[redacted]	[redacted]
≥ 1 AE leading to study discontinuation	0	0
≥ 1 AE leading to permanent treatment discontinuation	0	0
≥ 1 AE leading to drug interruptions	[redacted]	[redacted]
Serious on-treatment adverse events		
Number of serious on-treatment adverse events	4	1
Number of patients with serious adverse events	3 (5.4)	1 (1.8)
Atrial fibrillation	2 (3.6)	0 (0.0)
Coronavirus disease-2019	1 (1.8)	0 (0.0)
Alcohol poisoning	0 (0.0)	1 (1.8)

	Mavacamten (N = 56) n (%)	Placebo (N = 55) n (%)
Nonserious on-treatment adverse events		
Number of nonserious on-treatment adverse events	119	92
Cardiovascular, number of patients		
Chest pain	2 (3.6)	3 (5.5)
Palpitations	2 (3.6)	2 (3.6)
Presyncope	1 (1.8)	0 (0.0)
Syncope	1 (1.8)	0 (0.0)
Atrial fibrillation	2 (3.6)	0 (0.0)
Non-sustained ventricular tachycardia	0 (0.0)	5 (9.1)
Bradycardia	2 (3.6)	0 (0.0)
Atrioventricular block second degree	1 (1.8)	0 (0.0)
Other adverse events of interest		
Fatigue	5 (8.9)	2 (3.6)
Headache	2 (3.6)	5 (9.1)
Dyspnoea	4 (7.1)	3 (5.5)
Dizziness	4 (7.1)	3 (5.5)
Nausea	4 (7.1)	1 (1.8)
Rash	4 (7.1)	0 (0.0)
Coronavirus disease-2019	1 (1.8)	2 (3.6)

Source: Desai et al. 2022[3] and VALOR-HCM CSR[9]
AE: adverse event; CSR: clinical study report; LVEF: left ventricular ejection fraction.

2.9. Interpretation of clinical effectiveness evidence

2.9.1. Principal findings from VALOR-HCM

The additional evidence presented in support of the clinical efficacy and safety of mavacamten is from interim analyses of the VALOR-HCM ([redacted] DBL).[3,9] VALOR-HCM is an ongoing phase III, randomised, double-blind, placebo-controlled study of adult patients with symptomatic obstructive HCM, who met the 2011 ACCF/AHA guideline criteria for SRT,[5] were referred or under active consideration for an SRT procedure in the previous 12 months, and were willing to undergo the procedure.

Results from analysis of the primary endpoint demonstrate that myosin inhibition with mavacamten reduces the number of patients who choose to proceed with, or are guideline-eligible for, SRT following a 16-week treatment period (section 2.6.1). Results from secondary and exploratory endpoints provide consistent and complementary evidence for the beneficial effect of mavacamten in patients with symptomatic obstructive HCM (section 2.6.2 and 2.6.3), consistent with the results of the pivotal phase III EXPLORER-HCM trial.

The principal findings from the interim analysis of VALOR-HCM were:

- A significantly lower proportion of mavacamten-treated patients met the primary endpoint compared to placebo (17.9% versus 76.8%, $p < 0.001$), demonstrating that, following a 16-week treatment period, mavacamten significantly reduces the number of patients proceeding to SRT or remaining SRT guideline-eligible at Week 16.[3,9]
- Mavacamten was associated with statistically significant improvements in all secondary outcomes ($p < 0.001$), including:[3,9]
    - A significantly greater reduction in post-exercise LVOT gradient was seen in mavacamten-treated patients compared to placebo (-39.1 versus -1.8 mmHg, $p < 0.001$).
    - Improvement in symptoms assessed by physicians, where a significantly greater number of patients in the mavacamten group improved by ≥ 1 NYHA class (35 [62.5%]), compared to placebo (12 [21.4%], $p <0.001$). Additionally, 15 of 56 patients in the mavacamten group, compared to 1 of 56 in the placebo group, improved by ≥ 2 NYHA classes.
    - Clinically meaningful improvements in KCCQ-23 CSS, significantly greater in the mavacamten group compared to placebo ($p < 0.001$).
    - Compared to placebo, mavacamten-treated patients showed a significantly greater improvement in each of the cardiac biomarkers NT-proBNP ($p < 0.001$) and hs-cTnI ($p < 0.001$).

The results of these secondary efficacy endpoint analyses were consistent with the equivalent secondary and exploratory endpoints from EXPLORER-HCM. Note that no comparison between the primary endpoint of VALOR-HCM and EXPLORER-HCM is possible, because EXPLORER-HCM did not assess any comparable endpoint.

Interim analysis of the VALOR-HCM safety cohort shows that, consistent with results from EXPLORER-HCM and the EXPLORER-LTE cohort (October 2020 and August 2021 DBL), mavacamten presented with an acceptable safety profile and was well tolerated.[3,9] Evaluation of the safety of mavacamten will continue for the duration of the ongoing VALOR-HCM trial.

2.9.2. External validity of VALOR-HCM to patients in routine clinical practice

In VALOR-HCM, the mean patient age was 60 years, 49% of patients were female, and [redacted]% of patients were white.[3,9] This is comparable to the HCM cohort of a large cohort study of electronic health records in England from 1997–2010 (mean age 55.8 years, 41% female, 91.3% white) and to the EXPLORER-HCM cohort (mean age 58.5 years, 41% female, 91% white).[16] Thus, the VALOR-HCM population is demographically similar to HCM patients in English practice.

Eligibility for VALOR-HCM was based on the 2011 ACCF/AHA guidelines on SRT eligibility: severe dyspnoea or chest pain (usually NYHA functional classes III or IV) or occasionally other exertional symptoms (such as syncope or near syncope) that interfere with everyday activity or quality of life despite optimal medical therapy and resting or provoked LVOT gradient ≥ 50 mmHg and suitable anatomy.[5] These criteria align with the European Society of Cardiology (ESC) guidelines on diagnosis and management of hypertrophic cardiomyopathy (2014), which recommend SRT for patients with LVOTO gradient ≥ 50 mmHg, and moderate-to-severe symptoms (NYHA class III–IV) and/or recurrent exertional syncope in spite of maximal tolerated drug therapy.[8] Therefore, the VALOR-HCM trial eligibility has relevance to UK clinical practice.

2.9.3. Strengths and limitations of VALOR-HCM

The main strength of VALOR-HCM is that it provides further randomised, placebo-controlled evidence consistent with the efficacy results already demonstrated in the pivotal phase III trial, EXPLORER-HCM. In particular, the secondary endpoint results from VALOR-HCM are consistent with the results for the equivalent endpoints from the EXPLORER-HCM study and complement the positive and clinically-meaningful efficacy results of EXPLORER-HCM (section 2.6.2). Both studies demonstrated improvements in clinically-relevant aspects of obstructive HCM, including reduced LVOT gradient, improved symptoms (NYHA class), improved health status (KCCQ-23 CSS) and reductions in cardiac biomarkers of LV wall stress (NT-proBNP) and myocardial injury (cTn-I), in largely overlapping populations.

The VALOR-HCM trial also provides compelling evidence that mavacamten compared to placebo is effective at improving symptoms and/or haemodynamic

parameters sufficiently that patients no longer meet the requirements for SRT or choose not to undergo it.[3] This is particularly meaningful for patients, who may be reluctant to undergo the procedure, or may have contraindications that prevent them undergoing SRT despite clinical need. As described in the CS (B.1.3.2.4), clinical advice is that over half of SRT-eligible patients typically undergo the intervention, indicating that a substantial proportion of eligible patients choose not to. This is due to SRT-associated risks, as well as contraindications and the limited availability of specialist centres (B.1.3.2.4).[3,7,8]

There are several limitations to the VALOR-HCM trial evidence:

1. The VALOR-HCM data currently represents a relatively short 16-week treatment period, and long-term maintenance of the observed clinical efficacy and safety of mavacamten can not yet be evidenced from this trial.

2. VALOR-HCM is a relatively small trial and recruited only in the US. Although it is expected that the results are generalisable to the UK population (section 2.9.2).

3. The VALOR-HCM evidence relates specifically to adult patients with symptomatic (NYHA class III/IV, or NYHA class II with history of exertion-induced syncope or presyncope), obstructive HCM who are guideline-eligible for and willing to undergo an SRT procedure and have been referred for an SRT procedure in the previous 12 months. This differs from the full anticipated marketing authorisation and includes patients who would not be included in the marketing authorisation.

These limitations of VALOR-HCM are fully addressed by the pivotal phase III EXPLORER-HCM trial described in the original CS. EXPLORER-HCM evaluated patients over 30 weeks in the double-blind period, and is supported by the ongoing long-term extension cohort, which now has published data to 84 weeks, and ad hoc analysis up to 108 weeks. Furthermore, EXPLORER-HCM recruited a large, multinational cohort, including patients from the UK. Finally, the population in EXPLORER-HCM is directly relevant to the decision problem, comprising patients with symptomatic, obstructive HCM in NYHA classes II or III. Due to these strengths,

EXPLORER-HCM is considered the primary, pivotal evidence for the clinical benefits of mavacamten in this submission, with support from the EXPLORER-LTE cohort and VALOR-HCM.

2.10. Feasibility of including VALOR-HCM in the CEM

As VALOR-HCM provides supportive, relevant clinical evidence regarding the benefit of mavacamten, the feasibility of incorporating data from VALOR-HCM within the current CEM was explored.

To incorporate VALOR-HCM data into the submitted Markov model with health states defined by NYHA class (CS B.3.2.2), the secondary endpoint in VALOR-HCM "Change in NYHA class" (Addendum section 2.6.2) was considered. The feasibility of replacing the base case NYHA class transition probabilities specifically for patients who are potentially eligible to SRT in EXPLORER-HCM with transition probabilities calculated from VALOR-HCM data was also assessed.

During this process, however, several limitations were identified:

1. The CEM is structured with cycle lengths reflecting the assessment periods of EXPLORER-HCM, with cycle lengths of two or four weeks in the first 30 weeks of the model. However, in VALOR-HCM, NYHA class is only assessed at Day 1 and Week 16. Therefore, applying VALOR-HCM transition probabilities within the current model would require imposing assumptions on the transition probabilities between these two assessment timepoints. Furthermore, in EXPLORER-HCM there were assessments at Weeks 14 and 18 but not Week 16, therefore further assumptions would be needed to derive transition probabilities from VALOR-HCM that align with the modelled cycles.

2. It would also be necessary to assume that NYHA class III patients from VALOR-HCM follow the same trajectory as EXPLORER-HCM patients once they move out of NYHA class III. This is due to the short duration of data available from VALOR-HCM (i.e. 16 weeks) and the small number of patients starting in VALOR-HCM in NYHA classes II or IV, which would not permit calculation of reliable transition probabilities for VALOR-HCM patients starting in NYHA classes other than class III.

Furthermore, to incorporate these transition probabilities, the overlapping population between VALOR-HCM and EXPLORER-HCM would need to be quantitatively identified within the EXPLORER-HCM Individual Patient Data and quantitatively pooled with or replaced by VALOR-HCM data. Although populations across both trials are broadly similar, to enable consistent and complimentary support to the main pivotal trial, there are slight differences that need to be taken into account for quantitative analyses e.g. the proportion enrolled in NYHA class III was higher in VALOR-HCM, described in Addendum Section 2.5. Therefore this approach would add considerable uncertainty to the analysis.

In conclusion, the combined limitations described above would add substantial uncertainty into the CEM, which would not further aid decision making. Therefore, it was not considered appropriate to include data from VALOR-HCM in the CEM.

2.11. Conclusion

Overall, VALOR-HCM provides consistent and complementary evidence for efficacy measures assessed in EXPLORER-HCM. Both the VALOR-HCM and EXPLORER-HCM studies show that treatment with mavacamten results in improvement of clinically-relevant aspects of obstructive HCM, including reduced LVOT gradient, improved symptoms and function in patients in NYHA classes II and III, as well as health status and reductions in cardiac biomarkers. By targeting the underlying disease pathophysiology, mavacamten can improve multiple aspects of the disease (including reducing the need for SRT) better than standard care alone. This emerging evidence on treatment benefit and safety further supports the main clinical evidence base of this appraisal.

3. Updated cost-effectiveness evidence

Key points

- The Company base case ICER has been updated. The new base case ('Addendum base case') corrects a minor error in the calculation of the annual probability of serious adverse events, and demonstrated that mavacamten in combination with standard care (where standard care is BB/CCB monotherapy) remains a cost-effective treatment for symptomatic, obstructive HCM compared to standard care alone.
- It was estimated that addition of mavacamten would result in gains of [redacted] QALYs and an increase in discounted incremental costs to £[redacted], resulting in an ICER of £29,952.29/QALY gained.
- Two scenarios are also presented, modelling long-term disease progression; one where the same rate of disease progression is applied regardless of treatment (ICER: £17,889.62/QALY), the other where a benefit of mavacamten on disease progression is applied, informed by EXPLORER-HCM (ICER: £17,341.05/QALY). This further demonstrates that mavacamten is likely to represent a cost-effective use of NHS resources.

The cost-effectiveness evidence submitted as part of this addendum to the original CS contains two additional updates:

1. A correction to a minor error identified in the calculation of annual serious adverse event (SAE) probabilities. This represents a change to the base case and has a small impact on the ICER (section 3.1), with the uncertainty around the ICER explored in updated sensitivity and scenario analyses (Appendix A);
2. Introduction of a new scenario that models long-term natural disease progression (section 3.2).

Note that the changes to the CEM described in sections 3.1 and 3.2 have been incorporated into the most recent version of the Company CEM, which had been updated in response to clarification questions (CQs) and was shared with NICE and the EAG on 4 August 2022 (filename: "(ID3928) Company submission CEM post CQs").

3.1. Updated base case with corrected adverse event probabilities

An error was identified in the formula used to convert the 30-week probabilities of SAEs to annual probabilities, which informs the probability of discontinuation of mavacamten due to SAEs in the post-trial period, as described in CS B.3.3.3.

The formula in the original Company CEM treated the SAEs as a rate, rather than as a probability. Altering the formula to correctly reflect SAEs as a probability changes the annual probability of SAEs from 2.799% to 2.766%. This correction can be found in 'mainboard'!D86. The impact on the ICER of this correction is minimal; the updated Company base case results are in section 3.1.1, with updated scenario and sensitivity analysis in Appendix A.

3.1.1. Base-case incremental cost-effectiveness analysis results

The base case results updated with the correction to the calculation of the annual rate of serious AEs resulted in only a minor change in the ICER (an increase of £111.49) and the net health benefit (NHB). At the with-patient access scheme (PAS) price, mavacamten remains cost-effective at a willingness-to-pay (WTP) threshold of £30,000/quality-adjusted life year (QALY) (Table 10). The NHB results presented in show that overall population health would be increased by the use of mavacamten at an opportunity cost threshold of £30,000 (Table 11). Updated disaggregated costs are presented in Table 12 and Table 13; clinical outcomes and disaggregated QALYs remain unchanged by the update (CS Appendix J).

Table 10. Post-clarification questions base case and addendum base case results

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Base case post-CQs	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	29,840.80
	BB/CCB monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Addendum base case (new Company base case)	**Mavacamten + BB/CCB**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**29,952.29**
	BB/CCB monotherapy	[redacted]	[redacted]	[redacted]	**-**	**-**	**-**	**-**

BB: beta blockers; CCB: calcium channel blockers; CQs: clarification questions; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 11. Net health benefit (updated)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BB/CCB monotherapy	[redacted]	[redacted]				

BB: beta blockers; CCB: calcium channel blockers; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; NHB: net health benefit

Table 12. Summary of costs by health state (updated)

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	% absolute increment
NYHA I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NYHA: New York Heart Association.

Table 13. Summary of predicted resource use by category of cost (updated)

Item	Cost intervention	Cost comparator	Increment	Absolute increment	% absolute increment
Treatment acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug monitoring cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health care resource utilisation cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE: adverse event; NYHA: New York Heart Association.

3.2. Scenario incorporating disease progression

Disease progression in obstructive HCM is described in the literature in broad terms, such as ongoing cardiac remodelling leading to progressive dysfunction and cumulative burden of adverse clinical outcomes (CS B.1.3.1.3).[17-20] The original CS base case assumed no disease progression, with no NYHA class transitions in the long term (unless a patient escalated to SRT). This assumption was made due to the sparsity of quantitative evidence suitable for modelling a rate of disease progression in patients with obstructive HCM, and identifying suitable inputs and developing the methodology was still ongoing at the time of the original CS.

However, since the CS, data have been identified and methodology developed to allow an exploratory scenario incorporating disease progression. Furthermore, feedback has been provided to the Company from clinicians in the Netherlands stating that patients' underlying natural disease progression should be incorporated into the CEM, to portray the symptomatic burden more accurately in the long term.[21]

Therefore, two scenarios are presented; one in which all patients experienced the same annual progression regardless of treatment (Table 14 and section 3.2.1), and another in which patients receiving mavacamten experienced a slower rate of disease progression compared to all other therapies (Table 14 and section 3.2.2).

Table 14. Annual disease progression rates

NYHA class progression	Mavacamten + BB/CCB		BB/CCB monotherapy	Disopyramide + BB/CCB	SRT + BB/CCB
	Scenario 1	Scenario 2			
I to II	4.55%	[redacted]	4.55%	4.55%	4.55%
II to III	4.55%	[redacted]	4.55%	4.55%	4.55%
III to IV	4.55%	[redacted]	4.55%	4.55%	4.55%
Source	Maron *et al*., 2016[19]	EXPLORER-HCM[1]	Maron *et al*., 2016[19]		

BB: beta blockers; CCB: calcium channel blockers; NYHA: New York Heart Association; SRT: septal reduction therapy

Note that when disease progression is implemented in the model, an assumption is made that patients whose NYHA class worsens compared to the previous cycle while on mavacamten treatment will discontinue mavacamten and follow the base case distribution of subsequent treatments outlined in CS B.3.3.3.

3.2.1. Modelling the natural history of obstructive HCM (scenario 1)

Although disease progression has been broadly described in the literature,[17-20] there is no single consensus measure representing disease progression in obstructive HCM; however, the AHA 2020 guidelines state that "*The decrease in sudden death rates [due to ICD use] in HCM appears now to have shifted focus to heart failure as the predominant cause of disease-related morbidity and mortality and, therefore, greatest unmet treatment need in adults.*"[22] Therefore, development and progression of heart failure (HF) symptoms, as characterised by the NYHA classification system, represents a reasonable approach to defining disease progression.

Maron *et al*., 2016 was the only source identified that quantified the natural history of HCM in terms of NYHA classification. In this study, 573 patients with HCM in NYHA class I and II were prospectively evaluated over a median follow-up of 6.8 years. Of this cohort, 104 had resting LVOTO and 220 had exercise-induced LVOTO; 7.4% and 3.2% of patients progressed from NYHA class I/II to class III/IV per year for the resting and exercise-induced LVOTO groups, respectively.[19] Note that this study also included patients with non-obstructive HCM; data from these patients have not been considered.

An annual weighted average of 4.55% for progression from NYHA class I/II to III/IV was calculated using the annual progression rates for patients with resting and exercise-induced LVOTO. As no data were identified to inform the progression from NYHA class I to II, or from NYHA class III to IV, this annual average was assumed to apply to each transition to the next NYHA class (Table 14).

3.2.2. Modelling treatment effects on disease progression (scenario 2)

In a UK advisory board, three clinicians specialising in the treatment of obstructive HCM patients reached a consensus that they expected mavacamten to have a positive impact on underlying natural disease progression, based on the mechanism of action of mavacamten, with an agreement that disease progression in patients receiving mavacamten would be expected to be slower relative to standard care.[23] While no medical therapy for obstructive HCM modifies disease progression or outcomes, the effect of mavacamten on cardiac function and structure were explored in a cardiac magnetic resonance (CMR) imaging substudy of the EXPLORER-HCM

study. The findings below suggest that mavacamten treatment had a favourable effect on cardiac structure in patients with obstructive HCM, even in the short term. The results of the CMR substudy primary endpoint showed mavacamten reduced mean LV mass index compared to placebo (mean between-group difference, −15.8 g/m^2 [95% CI, −22.6 to −9.0]; p < 0.0001), as well as reduction in maximum LV wall thickness (mean between-group difference, −2.4 mm [95% CI, −3.9 to −0.9]; p = 0.0079) and maximum left atrial volume index (LAVI; mean between-group difference, −10.3 mL/m^2 [95% CI, −16.0 to −4.6]; p = 0.0004) – all predictors of poor prognosis in obstructive HCM.[24] It was not possible to implement this in the base case due to the assumption of no disease progression in the long term, however this disease progression scenario allows the potential impact of treatment effects to be explored.

The long-term effect of mavacamten on disease progression was extrapolated using data from EXPLORER-HCM.[1] After the first 30 weeks of EXPLORER-HCM, [redacted]% of patients on placebo and [redacted]% of those on mavacamten saw no NYHA class improvement; a relative difference of [redacted]% (mavacamten vs placebo arm). No data were identified to inform the effect of either the comparator (BB/CCB monotherapy) or subsequent therapies (i.e. disopyramide, SRT) on disease progression, therefore the second scenario assumed patients on comparator and subsequent therapies would experience the annual rate of progression derived from Maron *et al*., (4.55%; section 3.2.1), and the relative difference of [redacted]% was applied to this to obtain a [redacted]% annual rate of progression for patients receiving mavacamten + BB/CCB (Table 14).[1]

3.2.3. Disease progression scenario results

The results of the two scenarios incorporating long-term disease progression (Table 15) indicate that mavacamten remains cost-effective in both scenarios, and the decision is not changed from the base case analysis.

Table 15. Scenario analysis results: disease progression

Parameter	Scenarios	ICER (£/QALY)
Natural disease progression modelled	Same annual natural disease progression rate (4.55%) applied to intervention, comparator and subsequent therapies	17,889.62
	[redacted]% annual rate of disease progression in mavacamten arm; 4.55% otherwise	17,341.05

ICER : incremental cost-effectiveness ratio; QALY: quality-adjusted life year

3.3. Interpretation and conclusions of economic evidence

The Addendum base case (updated to correct the calculation of annual SAEs) demonstrated that mavacamten in combination with standard care (where standard care is BB/CCB monotherapy) remains a cost-effective treatment for symptomatic, obstructive HCM compared to standard care alone. It was estimated that addition of mavacamten would result in gains of [redacted] QALYs and an increase in discounted incremental costs to £[redacted], resulting in an ICER of £29,952.29/QALY gained. The scenarios presented in Appendix A are the same as those presented in the CS but updated to reflect the correction of the AE probabilities, which had a minor effect on the final ICER (increase by ~£100).

In addition, a new scenario is presented, reflecting clinical advice regarding disease progression and the anticipated effect of mavacamten. The study used to inform the rate of natural disease progression analysed a large, prospectively-enrolled, multicentre (US and Italy) cohort and had an extensive follow-up period. However, it should be noted that the number of patients in the cohort who progressed to NYHA class III/IV was comparatively small (n = 24), and no data were available to specifically inform the progression from NYHA class I to II, or III to IV. However, given that no alternative data sources were identified, the current approach was considered appropriate to address the uncertainty around the impact of disease progression, through a scenario analyses. The new scenarios modelling disease progression both substantially reduce the ICER, further demonstrating that mavacamten is likely to represent a cost-effective use of NHS resources. Due to the paucity of data describing disease progression, the Company considers these best suited to scenario analyses. However, the conservative nature of the base case ICER should be noted with regard to decision making, in light of the uncertainties

inherent in this rare disease context and the substantial unmet need in patients with symptomatic obstructive HCM.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Summary of Information for Patients (SIP)

June 2022

File name	Version	Contains confidential information	Date
		No	21 June 2022

Summary of Information for Patients (SIP):

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Mavacamten (CAMZYOS®).

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Mavacamten is intended to treat adult patients with symptomatic, obstructive hypertrophic cardiomyopathy (HCM). Patients eligible for mavacamten will have symptoms consistent with class II or III according to the New York Heart Association (NYHA) classification system. NYHA classification is a common system used by clinicians to classify the severity of symptoms in people with obstructive (HCM). Patients who fall within NYHA class II or III will have either a slight (class II) or marked (class III) limitation of activity due to symptoms.[1]

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

A marketing authorisation application has been filed with the European Medicines Agency (EMA) for mavacamten for treatment of symptomatic obstructive HCM in adult patients. This has not yet been approved, and the exact wording of the authorisation will be confirmed at approval.

1d) Disclosures,. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

• BMS supported a request from the Arrhythmia Alliance for £5,000 for printed materials in 2021. • BMS contracted the Atrial Fibrillation Association for £700 for professional advisory services in 2021. • BMS contracted Atrial Fibrillation Association for £2,100 for consultancy services associated with NHS Artificial Intelligence Awards for stroke prevention in 2021. • BMS supported a request from the Atrial Fibrillation Association for £25,000 to support the production of the Finger on the Pulse Educational Videos in 2021.

- BMS contracted Atrial Fibrillation Association for £1,820 for consultancy services associated with NHS Artificial Intelligence Awards for stroke prevention in 2021.
- BMS supported the Atrial Fibrillation Association with £25,000 for the Detect Protect Correct Atrial Fibrillation (AF) programme in 2022. This is multi-sponsored programme and the total requested amount from BMS is 20% of the overall budget of £125,000.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

HCM is a chronic, progressive disease of the heart muscle that causes changes to the structure of the heart, which may reduce heart function and lead to other complications. HCM causes the heart muscle to become abnormally thick and stiff, reducing the amount of blood that can enter and leave the heart. Approximately two out of every three patients with HCM have the obstructive form of the disease. This occurs when thickening of the dividing wall (septum) between the two bottom chambers (ventricles) of the heart causes an obstruction to the blood leaving the heart to circulate around the body.[2] This is called left ventricular outflow tract (LVOT) obstruction, and when present, the condition is referred to as obstructive HCM.

HCM can be an inherited genetic disease, that may be passed from parents to offspring. Most identified genetic mutations associated with HCM are located in genes that code for proteins involved in the contraction and relaxation of heart muscle. Although HCM is the most common inherited heart condition in the UK,[3] symptomatic obstructive HCM is a rare disease. Screening studies have estimated a prevalence of HCM of 0.11% in the UK,[4] while around two thirds of patients with HCM are thought to have the obstructive form of the disease,[5] while 50–84% patients are reported to experience symptoms.[6-9]

The effects of obstructive HCM are varied. Some patients have few or no symptoms, while others experience significant or debilitating symptoms including shortness of breath, chest pain, fatigue, feeling faint or fainting.[2] The daily symptoms experienced by patients with obstructive HCM can impair quality of life, affect the mental well-being of patients, and have a significant impact on their family life, ability to work, or carry out daily tasks such as self-care and housework.[6,7] In addition to the ongoing impact of symptomatic burden, as HCM can be an inherited genetic disease, patients further suffer from the psychological impact of the risk that the condition will be passed to their offspring.[6]

Patients with obstructive HCM are also at increased risk of a range of serious adverse outcomes, including heart failure, irregular heartbeat (atrial fibrillation and ventricular arrhythmias), stroke and death, including sudden cardiac death.[5] In particular, having LVOT obstruction (i.e. obstructive HCM) is associated with a worse prognosis (the likely course of a medical condition) than the non-obstructive form of the disease, including an increased risk of disease progression and a higher risk of complications.[5,10-13] One study demonstrated that the risk of progression to NYHA class III or IV (moderate to severe limitation of activity due to symptoms) or death from heart failure or stroke, was 4.4 times higher in HCM patients with LVOT obstruction than those without.[10]

Mortality associated with HCM has improved in recent years due to more widespread use of implantable cardioverter-defibrillators (ICDs) in patients at high risk of sudden cardiac death. An ICD is an implanted device that monitors the heart rhythm and gives an electrical shock to restore normal rhythm if a dangerous, abnormal rhythm is detected. Despite this, recent studies indicate that patients with HCM still experience higher rates of mortality, with one European study suggesting mortality in HCM patients is twice as high across all ages compared with the general population.[14] Although most studies focus on a general HCM patient population rather than obstructive HCM specifically, several studies indicate that the presence of LVOT obstruction in patients with HCM is significantly associated with increased mortality. For example, in combined analysis of multiple studies totalling 12,146 patients with HCM, obstruction was a significant predictor of mortality,[11] while in an English study of 917 adult patients with HCM, survival from all-cause mortality or heart transplantation over five years was lower in the 288 patients with LVOT obstruction compared to patients without.[12]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Generally, obstructive HCM is diagnosed based on a combination of medical history, family history, physical examination and diagnostic test results. Diagnosis rests on detecting increased thickening of the wall of the left ventricle, which is measured using imaging techniques, typically echocardiography. An echocardiogram uses sound waves (ultrasound) to measure the thickness of the heart muscle, and to check blood flow from the heart. If thickening is detected, and it cannot be explained by other common conditions such as coronary artery disease, further investigations to confirm or rule out HCM should be carried out.

In some cases, another method of imaging the heart known as cardiovascular magnetic resonance imaging (CMR) may be performed, while other diagnostic tests typically include an electrocardiogram (ECG) to assess the electrical activity of the heart, and blood tests for proteins that could indicate damage to the heart. In some cases, obstructive HCM is an inherited disorder caused by genetic mutations, therefore may be diagnosed by genetic testing of family members.[5,13] Diagnosis of the obstructive form of HCM requires assessing the pressure gradient across the LVOT, which is also measured using echocardiography. An abnormally high gradient indicates obstruction, and may be present only when provoked by activity (standing, exercise, the Valsalva manoeuvre) or may also be present when the patient is resting.

Due to the non-specific nature of obstructive HCM symptoms, such as shortness of breath, the journey to a diagnosis is often prolonged and only occurs after other causes have been ruled out. It is reported that patients are frequently misdiagnosed with asthma, mitral valve prolapse, anxiety or depression.[6,15] This delayed diagnosis and misdiagnosis limits patient access to disease specialists and can have a significant long-term impact on patients' physical and emotional health. In a Voice of the Patient report published by the Hypertrophic Cardiomyopathy Association (HCMA), patients frequently reported misdiagnosis or a lag in diagnosis, with many patients being diagnosed at middle age or in their 70s despite experiencing symptoms much earlier in life. A key theme of the report stated that "The path to diagnosis is often long and difficult; many people remain undiagnosed or misdiagnosed, leading to lengthy disability and early death".[6] Similarly, the Cardiomyopathy UK Change Agenda published in 2021 reported that "many cardiomyopathy patients have struggled to receive an appropriate diagnosis, spending too long in primary care being treated inappropriately".[16]

No additional diagnostic tests are required with the new treatment, however, patients will require tests including echocardiography to assess their suitability for mavacamten before starting treatment.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

There are currently no UK-specific clinical guidelines for the overall management of obstructive HCM. Relevant international guidelines are the European Society of Cardiology (ESC) 2014 guidelines[5] and the American Heart Association/American College of Cardiology (AHA/ACC) 2020 guidelines.[13]

These guidelines recommend medical management of symptoms using drugs known as beta blockers, non-dihydropyridine calcium channel blockers (specifically, verapamil or diltiazem), or, if symptoms persist, disopyramide, which are mainly used 'off label' for obstructive HCM. Some patients who have moderate or severe symptoms that are not relieved by any of the existing drugs may be referred for an interventional procedure known as septal reduction therapy (SRT). The treatment pathway, including the likely place for mavacamten, is outlined in Figure 1 and described in more detail below.

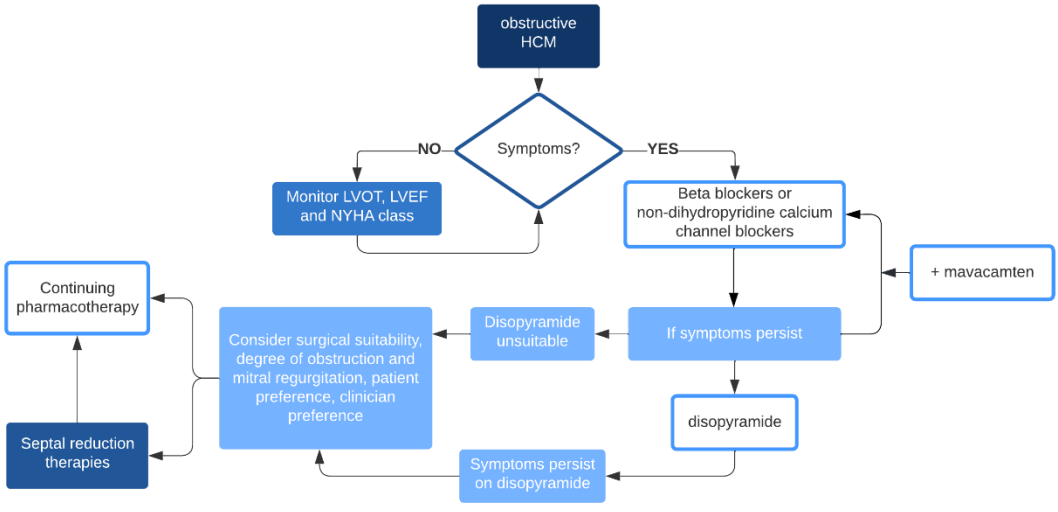

Figure 1. Overview of the management of obstructive HCM. Mavacamten is likely to be used in addition to beta blockers or calcium channel blockers if symptoms are not relieved by those treatments alone.

Beta blockers are currently used as the initial treatment for patients with symptomatic, obstructive HCM. Beta blockers are effective at relieving symptoms in some patients, however, not all patients find their symptoms are adequately managed with beta blockers. Beta blockers can also be associated with side effects such as fatigue, reduced exercise capacity, asthma,

depression and low blood pressure. Calcium channel blockers are recommended as alternatives to beta blockers when beta blockers are not effectively reducing symptoms or are not tolerated or contraindicated. Calcium channel blockers are also not effective at managing symptoms in all patients and can be associated with side effects including ankle oedema (swelling), fatigue, constipation and electrical changes in the heart (decreased atrioventricular conduction).

Disopyramide is considered a second-line therapy that may be prescribed in combination with beta blocker or calcium channel blocker therapy in patients who still have symptoms despite maximum-tolerated doses of these therapies. Disopyramide can be associated with significant side effects such as dry eyes and mouth, difficulty urinating, constipation and electrical changes in the heart (QTc prolongation). Disopyramide can be effective in managing symptoms, however the effectiveness can reduce after several months, and many patients are reported to stop using the drug due to the side effects.

SRTs are non-pharmacological, interventional therapies for obstructive HCM that aim to reduce the thickness of the septum and therefore reduce the obstruction of blood flow from the heart. The two approaches used are septal myectomy and alcohol septal ablation (ASA). Septal myectomy is an open-heart surgical procedure, in which excess heart muscle is surgically removed from the septum. In ASA, a thin tube is thread through a blood vessel to the septum, where alcohol is injected. The alcohol causes heart muscle cells to die, reducing the thickness of the septum. SRT can be effective in reducing obstruction and therefore reducing symptoms, however, these techniques are not a cure and patients often continue to require treatment and repeated SRTs. These procedures can also cause serious complications including surgical mortality,[5] and patients are often reluctant to undergo invasive surgery. SRTs are typically considered for patients with moderate or severe symptoms that are not relieved by any of the existing drugs. Clinical experts have advised that a small number of patients in England are eligible for and willing to undergo SRT each year, but this is not a widely-used therapy and should only be performed in specialist, experienced centres.

Current pharmaceutical and interventional therapies address only the symptoms of obstructive HCM, and do not target the underlying cause of the disease, or disease progression.[5,13] In addition to inadequate symptom relief, these treatments are often poorly tolerated.[17] There is no curative treatment for obstructive HCM. SRTs to reduce the septal hypertrophy may be considered, however, these procedures are associated with potentially severe complications, including the potential need for pacemaker implantation[18] and further high risk treatment following SRT.[5]

Mavacamten is the first in its class of drugs and the first therapy designed to target the underlying cause of obstructive HCM. It has been shown to improve quality of life, symptoms and cardiac function in symptomatic (NYHA class II/III) patients for whom standard care is not adequate or well tolerated.[19] Mavacamten is intended to be used in addition to standard therapies (beta blockers or calcium channel blockers) for patients whose symptoms are not adequately controlled.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

In addition to the risk of serious complications, the symptoms of obstructive HCM can impair quality of life, affect the mental well-being of patients, and have a negative impact on their social life and ability to work.[7] Furthermore, disturbance to their working life can have a devastating impact on a patients finances, adding to the burden of living with the disease. Patients require lifelong follow-up to detect changes in symptoms, risk of adverse events including sudden cardiac death, LVOT obstruction, and heart rhythm disturbances.[5]

A survey of 444 adult patients with HCM, 58% of whom had obstructive disease, found that fatigue (74%), shortness of breath upon exertion (73%), and light-headedness (70%) were the symptoms most commonly experienced, while only 21% patients reported no limitation of physical activity. In patients with obstructive disease, 84% reported four or more HCM symptoms, with 43% reporting symptoms consistent with NYHA class III or IV, representing moderate to severe disease.[7] Interviews conducted as part of the same study reported the most common impacts on patients' lives as limitations to physical activities (78%), emotional impacts (78%), feeling anxious or depressed (78%), and impacts on work (63%).[7]

In 2017, Cardiomyopathy UK (CMUK) published a guide to emotional health and mental wellbeing, put together using insights shared by those affected by cardiomyopathy, through an online survey, focus group and reader panel. Of those who completed the online survey, most people felt that cardiomyopathy had an impact on their mental health and emotional wellbeing, either some or most of the time.[20] In 2020, the Hypertrophic Cardiomyopathy Association (HCMA) held an externally led patient-focused drug development meeting to hear patient and caregiver perspectives on living with or caring for those with HCM.[6] The report included the following key themes and accounts of the burden of disease and impact on daily living:

Key theme: Patients report the most burdensome symptom of HCM is living with shortness of breath, followed by fatigue, exercise intolerance, palpitations, and fainting. While this can cause patients to limit many forms of exercise…it can also impact simple activities of daily living such as ironing, house cleaning, and getting dressed.

Key theme: HCM patients make lifestyle changes including diet changes, adjustments in work schedules, and most often, changes in exercise and social interactions to accommodate for burdensome symptoms and fatigue. Symptoms can occur due to HCM itself or as a side effect of medications.

Key theme: Regardless of age, the overall impact of living with HCM is reflected in the emotional and psychological toll patients experience…This can lead to chronic anxiety, depression, isolation, failed relationships, and lost job opportunities.

Patients spoke eloquently about their frustrations and disappointments at not being able to hold a job, tend to their children, or complete simple tasks such as bathing, cooking, and dressing. Along with the uncertainty is the angst of not knowing whether the immediate change in function is short-lived or a serious digression that will require additional testing, medications, and treatments.

"I never know what my day will hold! Activities just shopping can completely do me in. I used to be such an active person. Now I am so limited. My husband and I used to dirt bike and motorcycle together and I can no longer join him. I can feel fine and then just like a flash I can have a horrible day." – Lisa

Many patients spoke to the difficulties in finding the right "combination" of treatment options. Patients varied on whether treatments and lifestyle changes had had any impact on them, if at all.

"The current treatments just aren't enough. As patients, we've become accustomed to the thought of only ever being able to get treatment for symptoms . . . but we're tired of that. We want more than just symptom relief." – Wendy

"We really need better medications with side effects that are at least tolerable and medications that are not cumulatively toxic. People diagnosed with HCM can lead relatively normal lives for over 50 years so it is not acceptable to rely on medications that will poison us quickly." – Sara [6]

Additionally, as HCM can be an inherited genetic disease, patients are often concerned about the familial aspect and the likelihood of passing on the condition to their offspring, particularly with the current lack of effective therapies. In the HCMA Voice of the Patient report, patients voiced concerns about starting a family, about the guilt of unknowingly passing the gene to offspring, and other emotional challenges they and their families face.[6] One patient commented the following:

"I have a heavy heart (pardon the pun) regarding our children's future and the potentially bumpy life they may face. While genetics are just a part of who we are, there is a lingering guilt that I am technically responsible for passing on this mutation to them." – Brad [6]

These patient accounts highlight the significant impact that obstructive HCM symptoms have on their daily life, and in particular, the lifestyle modifications made to accommodate the impact of these symptoms.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Evidence suggests that heart muscle cells in patients with obstructive HCM may contract too much each time the heart pumps and then not relax enough before the next heartbeat. Over time, this causes thickening (hypertrophy) of the heart muscle, making it progressively harder for the heart to pump blood around the body. This leads to the potential symptoms and complications associated with obstructive HCM. Current pharmacological agents available for obstructive HCM may provide relief of symptoms by reducing the rate and force of heart contraction, but there is no evidence that they can change the progression or prognosis of the disease, they can cause troublesome side-effects, and are not always effective. They are also used 'off-label', meaning they are not specifically designed to treat HCM. There is therefore a great unmet need for new drugs that are targeted for obstructive HCM, and are effective in treating the underlying condition.

Mavacamten is a small molecule that works by binding to a specific component of heart muscle called cardiac myosin, which is part of the molecular machinery that makes the muscle cells contract and relax. Mavacamten is designed to target the underlying mechanism of HCM by reducing the activity of cardiac myosin. This reduces the excess contraction and enables relaxation of the heart muscle, improving heart function. Mavacamten is taken once a day as an oral (by mouth) tablet.

Mavacamten is the first treatment designed to target not just the symptoms, but the underlying cause of the disease, providing patients with a safe and effective treatment option that relieves symptoms and improves function, leading to increased quality of life. Owing to its mechanism of action, mavacamten has the potential to slow down disease progression.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? • Yes / No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
Mavacamten is intended to be used when standard medical therapies are not able to adequately control symptoms, are not tolerated or are contraindicated. Mavacamten is not a combination therapy but will be used in addition to standard medical care (beta blockers or calcium channel blockers or, if both beta blockers and calcium channel blockers are unsuitable, mavacamten may be used on its own). This is directly supported by clinical trial evidence from the EXPLORER-HCM trial, which showed improvements in symptoms and function in patients receiving mavacamten in addition to their standard therapy (beta blockers, calcium channel blockers or neither) compared to patients receiving only their standard therapy.[19]

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Mavacamten is taken as an oral (by mouth) tablet and can be self-administered at home. The recommended starting dose is 5 mg once a day. Dosing is reviewed regularly in the first year to ensure each patient is receiving the lowest effective dose of 2.5 mg, 5 mg, 10 mg or 15 mg. The maximum dose is 15 mg once daily. Mavacamten treatment is a chronic therapy, because obstructive HCM is a chronic disease. Mavacamten treatment should be initiated under the supervision of a physician knowledgeable in the management of patients with obstructive HCM. It is not anticipated that this administration method will affect patients or their caregivers. Mavacamten has a similar method of administration (oral) to existing medical therapies for obstructive HCM.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.
Completed trials in adult patients with obstructive HCM: • PIONEER-HCM. This was a phase II study in 21 patients with symptomatic, obstructive HCM. This trial evaluated the efficacy, pharmacokinetics, pharmacodynamics, safety and tolerability of mavacamten (also known as MYK-461) in patients aged 18-70 years with symptomatic HCM and LVOT obstruction. This trial was completed in November 2017 and is published in Heitner et al 2019.[21] Further information can also be found at ClinicalTrials.gov (trial identifier: NCT02842242).

- EXPLORER-HCM. This was the pivotal phase III, multicentre, international, randomised, double-blind, placebo-controlled study of mavacamten in patients with symptomatic, obstructive HCM. 251 participants were randomised to receive placebo or mavacamten and the safety and efficacy of mavacamten compared to placebo was evaluated over 30 weeks of treatment with an additional 8-week washout period off therapy. This trial was completed in May 2020 and is published in Olivotto et al 2020.[19] Further information can also be found at ClinicalTrials.gov (identifier: NCT03470545).

Completed trials in adult patients with non-obstructive HCM:

- MAVERICK-HCM. This was a phase II multicentre, randomised, double-blind, placebo-controlled exploratory study in 59 patients with symptomatic, non-obstructive HCM and preserved left ventricular ejection fraction (ejection fraction is a measurement of how much blood the left ventricle (chamber) of the heart pumps out with each contraction). Patients were randomised to receive a 16-week course of mavacamten doses titrated to achieve one of two target drug concentrations. This trial was completed in January 2020 and is published in Ho et al 2020.[22] Further information can also be found at ClinicalTrials.gov (identifier: NCT03442764).

Ongoing trials in adult patients include:

- PIONEER-OLE. This is an open-label extension study in 12 patients with symptomatic, obstructive HCM who completed the PIONEER-HCM trial. The estimated completion date is November 2023. Further information can be found at ClinicalTrials.gov (identifier: NCT03496168).
- MAVA-LTE. This is a long-term extension study evaluating the safety of mavacamten in patients who completed either the EXPLORER-HCM trial for patients with symptomatic, obstructive HCM (224 patients) or the MAVERICK-HCM trial for patients with symptomatic, non-obstructive HCM (86 patients). The estimated completion date is November 2025, however interim results have been presented at the American College of Cardiology 2021 conference[23] and 2022 conference.[24] Further information can also be found at ClinicalTrials.gov (identifier: NCT03723655).
- VALOR-HCM. This is a randomised, double-blind, placebo-controlled, multicentre phase III study in 100 patients with symptomatic, obstructive HCM who are eligible for SRT. This study is designed to evaluate the effect of mavacamten treatment on reducing the number of SRT procedures performed in patients with symptomatic obstructive HCM who are eligible for SRT based on ACCF/AHA 2011 and/or ESC 2014 guidelines. The estimated completion is June 2024, however, interim results have been presented at the American College of Cardiology 2022 conference, showing that fewer patients on mavacamten treatment were eligible for or chose to undergo SRT procedures at week 16 compared to those on placebo, and no new safety signals were identified.[25,26] Further information can be found at ClinicalTrials.gov (identifier: NCT04349072).
- EMBARK-HFpEF, an exploratory, open-label, proof-of-concept phase IIa study to assess the safety, tolerability and preliminary efficacy of mavacamten in 35 patients with heart failure with preserved ejection fraction (HFpEF) and chronic elevation of cardiac biomarkers. Data from this study will inform future study designs of mavacamten in patients with HFpEF. The estimated completion date is March 2023. Further information can be found at ClinicalTrials.gov (identifier: NCT04766892).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with

current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The data used to demonstrate how effective mavacamten is combination with standard care compared to current standard care in patients with symptomatic, obstructive HCM are from the EXPLORER-HCM clinical trial.[19] As outlined in section 3d), this trial compared 123 patients receiving mavacamten with 128 patients receiving placebo, over 30 weeks. The trial specifically enrolled patients who had symptoms classified as NYHA II or III. Across the two groups (mavacamten group and placebo group), 75% of patients were taking beta blockers, 17% were taking calcium channel blockers and 8% were taking neither beta blockers nor calcium channel blockers.[19]

The primary outcome used to measure efficacy assessed a combination of change in NYHA class and change in exercise capacity (specifically, peak oxygen consumption) from day 0 to week 30. This combined outcome, known as a 'composite endpoint', was chosen to reflect the most relevant treatment benefits i.e. improvements to symptoms and to function, and was designed based on consultation with HCM experts, patients and regulatory authorities. Significantly more patients in the mavacamten group achieved this combined outcome (36.6%) compared with the placebo group (17.2%; $p = 0.0005$).[19]

Other measures used to assess efficacy of mavacamten included change from day 0 to week 30 in LVOT gradient after exercise, peak oxygen consumption, proportion of patients who improved by one or more NYHA classes and the outcomes of questionnaires designed to understand patient quality of life (see section 3f).[19] For all these measures, mavacamten showed significantly greater benefit than placebo.[19]

Furthermore, a greater proportion of patients in the mavacamten group also achieved a combination of NYHA class I and LVOT peak gradient < 30 mmHg at rest, during Valsalva, and after exercise, compared with the placebo group (27% vs 1%; $p < 0.0001$). NYHA class I represents no limitation of physical activity, while an LVOT peak gradient < 30 mmHg is below the diagnostic threshold for LVOT obstruction.

Overall, treatment with mavacamten was well tolerated and demonstrated superior efficacy compared to placebo for all primary and secondary endpoints.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In addition to the risk of serious complications, the daily symptoms experienced by patients with symptomatic obstructive HCM – fatigue, shortness of breath, chest pain, dizziness and fainting – can cause a significant burden and impact on quality of life.

Quality of life was assessed in the EXPLORER-HCM trial using assessment questionnaires designed to understand how patients with heart conditions consider their quality of life to be affected by their condition. The disease-specific assessments used in the EXPLORER-HCM trial included the

Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath (HCMSQ). The HCMSQ is a new questionnaire specifically designed to evaluate symptomatic burden in patients with HCM, including shortness of breath, chest pain, dizziness and fainting, while the KCCQ is widely used for patients with heart failure and has been validated for use in patients with obstructive HCM.[27,28] In addition to these disease-specific questionnaires, a generic quality-of-life assessment known as the EQ-5D-5L was used, which represents patient-reported outcomes relating to mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

Mavacamten led to statistically significant improvements in patient quality of life, demonstrated by patient-reported outcomes from the KCCQ, HCMSQ and EQ-5D:[19,29-31]

KCCQ

Increased KCCQ scores represent improved quality of life. Rapid and sustained improvements in two KCCQ scores (the overall score and the clinical summary score) were observed with mavacamten, and they were greater than those observed in patients receiving placebo ($p < 0.001$). An increase from baseline of 10 points or more in KCCQ-CSS represents a moderate to very large clinical improvement. After 30 weeks of treatment, 52% of patients in the mavacamten group achieved an improvement of 10 or more points from baseline in KCCQ-CSS compared with 31% in the placebo group.[29]

HCMSQ

Decreases in the shortness-of-breath score of the HCMSQ represent improvements to quality of life and a decrease of 2.5 points or more in the 'shortness of breath' score was considered clinically meaningful. After 30 weeks on treatment, 50% of patients in the mavacamten group had achieved a clinically-meaningful improvement in the shortness of breath score compared with 21% in the placebo group.[31]

EQ-5D

An EQ-5D index score is calculated where an increased score represents improved quality of life. At week 30, patients who had been treated with mavacamten had a statistically significant improvement from the baseline EQ-5D index score compared with patients who had received placebo (0.084 versus 0.009; $p < 0.05$).
The EQ-VAS score is a self-rating that records the patient's own assessment of their health status. A significantly greater improvement was also observed for the change in EQ-VAS score from baseline to week 30 among patients in the mavacamten versus the placebo arm (8.5 versus 0.7; $p < 0.05$).[30]

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The safety and side effects of mavacamten in patients with obstructive HCM were assessed in the EXPLORER-HCM trial and are continuing to be assessed in the MAVA-LTE and VALOR-HCM trials. In the EXPLORER-HCM trial the side effects (adverse events) were similar in number and type in the group of patients receiving mavacamten compared to the group of patients receiving placebo.[19]

The most commonly-reported adverse events were dizziness (21.1% mavacamten group, 13.3% placebo group), breathlessness (14.6% mavacamten group, 10.2% placebo group), headache (12.2% mavacamten group, < 10% placebo group) and nasopharyngitis (inflammation of the nose and throat: 12.2% mavacamten group, 14.8% placebo group).

Interim results from the MAVA-LTE trial have not identified any new side effects and provide support for the longer-term safety of mavacamten.[23] Interim results from VALOR-HCM have also not identified any new side effects.[26]

Based on the available evidence, the safety profile of mavacamten can be considered manageable and acceptable in the context of the benefit to symptom relief, improved function and improved quality of life experienced by patients compared to the placebo arm in the EXPLORER-HCM trial.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Symptomatic, obstructive HCM is a chronic, progressive disease in which the heart muscle becomes thickened and blood flow leaving the heart is obstructed, leading to reduced heart function, symptoms such as shortness of breath, dizziness and palpitations, and increased risk of serious complications.

There are no current pharmacological therapeutic options specifically indicated for symptomatic obstructive HCM, highlighting the unmet need for targeted, effective therapies in these patients. Current pharmacological agents available for obstructive HCM aim to relieve symptoms only, can cause troublesome side effects, and are not always effective. A significant number of patients continue to live long-term with symptoms that impair their quality of life when treated with currently available therapies.

Mavacamten is the first treatment designed to target the molecular mechanism underlying the disease with demonstrated efficacy in a phase III clinical trial. It is a first-in-class, oral, selective inhibitor of cardiac myosin. Mavacamten has demonstrated efficacy and safety in patients with symptomatic obstructive HCM in a large, randomised, placebo-controlled trial. Mavacamten has been shown to significantly reduce symptoms and improve function, leading to a meaningful impact on patient quality of life.[7,19]

The highly innovative nature of mavacamten has been recognised with the award of a Promising Innovative Medicines (PIM) designation by the Medicines and Healthcare products Regulatory Agency (MHRA). This indicates that mavacamten is a promising candidate likely to offer a major advantage over methods currently used for the treatment of a life-threatening or seriously debilitating condition with high unmet need owing to the lack or serious limitations of existing treatments.[32] Mavacamten provides patients with a non-invasive treatment option to add to current standard care.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Compared to available therapies there are no notable disadvantages anticipated relating to the mode of action, effectiveness, or mode of administration.

As mavacamten may be used in combination with standard therapies (beta blockers, calcium channel blockers), patients may experience additional side effects. However, clinical trial data shows that in patients receiving mavacamten combined with standard care, side effects were mild and comparable to placebo.[23]

Mavacamten treatment initially requires additional monitoring in the first year of treatment in order to achieve and maintain the most appropriate dose for each patient. Patients may consider these additional visits to be a disadvantage, however, HCM is a life-long disease and initial monitoring is anticipated to be only temporary. Mavacamten may be discontinued if ejection fraction, a measurement of how much blood the left ventricle (chamber) pumps out at each contraction, falls too low (below 50%). It is anticipated that the additional monitoring associated with starting mavacamten therapy will be over the first year; from the second year onwards it is expected that monitoring will return to the previous level associated with current standard care.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How does the model reflect obstructive HCM

The cost-effectiveness of mavacamten was demonstrated using a health economic model which compared mavacamten in combination with standard care against standard care alone. The model uses NYHA class to define the different levels of disease severity experienced by patients, which is appropriate as NYHA class is routinely used in clinical practice and has been widely used in previous models of cardiovascular disease. Therefore, patients in the model exist in one of five 'health states': NYHA classes I, II, III, IV and a death state representing patients who have died.

In line with the patient population of the EXPLORER-HCM trial and the anticipated marketing authorisation for mavacamten, patients with symptomatic obstructive HCM enter the model in either NYHA class II or III health states. Patients can then move to any other health state or stay in the same health state, based on the effect that treatments (either mavacamten in combination with standard care, or standard care alone), has on their NYHA class. Patients who experience death move to the death health state in the economic model. In the model, standard care is considered to be beta blockers or calcium channel blockers.

Each health state is associated with a cost (i.e. the cost of being in a particular health state) and an assessment of health-related quality of life (HRQoL), for that health state. The assessment of HRQoL is based on the EQ-5D questionnaire, which is the measure preferred by NICE. Individuals in the model are followed through their entire remaining lifetime (up to a maximum age of 100 years).

Modelling how much the treatment extends life
There is no direct evidence from the clinical trials about the effect of mavacamten on the risk of dying. However, it is known from other studies that patients with obstructive HCM who are in a higher NYHA class have a higher risk of dying. Therefore, the data linking NYHA class to risk of dying is included in the model. As more patients receiving mavacamten in combination with standard improve their NYHA class compared to patients receiving standard care only, the model predicts that patients receiving mavacamten in combination with standard care live, on average, 1 year longer than those receiving standard care alone.

Modelling how much the treatment improves quality of life
As noted above, HRQoL in the model is measured using the EQ-5D questionnaire and these data are taken from the EXPLORER-HCM trial, as trial-based data reflects the actual experience of patients in different NYHA classes being treated with mavacamten (section 3f).

Modelling how the costs of treatment differ with the new treatment
The model predicts that the introduction of mavacamten will result in increased overall costs to the health service. This is due to the cost of buying mavacamten and any associated additional monitoring. However there is no difference in the way mavacamten is administered compared with standard therapies, as they are oral formulations.

Uncertainty
Obstructive HCM is a rare disease, which means that there is a lack of high-quality evidence to inform some aspects of the economic model. Therefore, as with most economic models, a range of assumptions were made in the modelling. These assumptions were tested through 'sensitivity analysis', where alternative assumptions or values are included in the model to determine the impact of these changes on the overall results. The sensitivity analysis showed that the model input that had the greatest impact on cost-effectiveness was the percentage of patients in NYHA class II who did not show improvement in NYHA class during the first 30 weeks. In addition to sensitivity analysis, to reduce the uncertainty in the model, the model assumptions were validated by clinical experts, including the use of a structured expert elicitation exercise, to make sure the model reflects real-world practices.

Cost effectiveness results
The economic model reports outcomes for patients as quality-adjusted life years (QALYs), which is a routinely used measure, reflecting the impact of a treatment on both the quantity and quality of life. The analysis found that treatment with mavacamten in combination with standard care resulted in a gain in total life years and QALYs compared to standard care alone.

When the gain in QALYs associated with mavacamten in addition to standard care are combined with the increase in costs compared to standard care alone, the model shows that mavacamten is cost-effective at a willingness-to-pay threshold of £30,000 per QALY. Further details can be found in section B.3.8 of the Company evidence submission.

Benefits not captured in the modelling

As described above, the economic model uses NYHA class and patient-reported quality of life based on EQ-5D to quantify the benefits associated with mavacamten. However, mavacamten also displays significant benefits in other relevant measures such as exercise capacity and peak LVOT gradient. Although it is likely that the model indirectly captures these benefits within the NYHA class and EQ-5D, these other measures have been demonstrated to link to prognosis in patients with obstruction HCM.[10,11,33] This has not necessarily been fully captured in the model and therefore may represent significant uncaptured benefit of mavacamten. Furthermore, the EQ-5D questionnaire used to understand quality of life was not designed to be specifically used in obstructive HCM patients, therefore there may be health-related benefits that are specific to the disease that were not captured and are subsequently not represented in the cost-effectiveness calculations, such as those measured using the KCCQ or HCMSQ (section 3f).[29]

Mavacamten has also demonstrated beneficial effects compared to placebo on reductions in markers of cardiac dysfunction and improvements in cardiac structure.[19,34] These results suggest that mavacamten has the potential to slow disease progression. However, due to the current lack of long-term evidence regarding mavacamten efficacy, no long-term difference in efficacy between mavacamten and standard care have been modelled, therefore any potential benefits associated with mavacamten in addition to standard care in the longer term compared to standard care are not reflected in the cost-effectiveness results.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Mavacamten in addition to standard care has been shown to significantly improve a range of measures and outcomes directly relevant to patients with obstructive HCM compared to placebo with standard care. These include improvements in NYHA class, exercise capacity (represented by peak oxygen consumption), LVOT gradient (i.e. reduced LVOT obstruction) and quality of life.[19] When used in addition to standard care (beta blockers and calcium channel blockers), mavacamten had a similar side effect profile compared to standard care alone.[19]

The economic modelling predicts that using mavacamten in addition to standard care would be a cost-effective use of NHS resources at a threshold of £30,000 per QALY, compared to standard care alone. However, as described in section 3j, mavacamten is also expected to result in significant benefit to patients living with this condition, over and above those captured in the economic model.

Mavacamten is a first-in-class, oral inhibitor of cardiac myosin ATPase, and is the first treatment designed to target the underlying pathophysiology of HCM with demonstrated efficacy in a phase III clinical trial. The highly innovative nature of mavacamten has been recognised with the award of a PIM designation by the MHRA, indicating that mavacamten is a promising treatment likely to offer a major advantage over methods currently used for the treatment of a life-threatening or

seriously debilitating condition with high unmet need owing to the lack or serious limitations of existing treatments.[32]

Based on the demonstrated efficacy and safety and the innovative mechanism of action, which address a significant unmet need for patients with symptomatic obstructive HCM, the Company considers mavacamten to represent a 'step-change' in the management of symptomatic obstructive HCM.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
There are no equality issues that have been identified relating to mavacamten treatment.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Further information on key clinical trials showing the safety and efficacy of mavacamten: • The EXPLORER-HCM clinical trial is registered on ClinicalTrials.gov: Clinical Study to Evaluate Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy - Full Text View - ClinicalTrials.gov • The following publication provides a plain language summary of the EXPLORER-HCM trial: Waldman CB and Owens A 2021. DOI 10.2217/fca-2021-0044[35] • The following publications relate to EXPLORER-HCM: Olivotto et al. 2020. DOI: https://doi.org/10.1016/S0140-6736(20)31792-X[19] Xie J, et al. 2021. DOI: [30] Naidu 2021. Available at: https://esc365.escardio.org/presentation/233059[31] • The MAVA-LTE clinical trial is registered on ClinicalTrials.gov: A Long-Term Safety Extension Study of Mavacamten in Adults Who Have Completed MAVERICK-HCM or EXPLORER-HCM – Full Text View – ClinicalTrials.gov • MAVA-LTE interim results presented at the American College of Cardiology 2021 and 2022 conferences can be found in the following publications: Rader et al 2021. DOI: 10.1016/S0735-1097(21)01891-X[23] Rader et al 2022. https://www.acc.org/Latest-in-Cardiology/Articles/2022/04/02/13/22/Sun-945am-Treatment-Mavacamten-acc-2022[24] Further information on hypertrophic cardiomyopathy: • Cardiomyopathy UK: Cardiomyopathy | Cardiomyopathy UK

- British Heart Foundation information on hypertrophic cardiomyopathy: Hypertrophic cardiomyopathy | British Heart Foundation (bhf.org.uk)

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Cardiac myosin: a molecule found in heart muscle cells; part of the machinery that causes the heart muscle to contract and relax to pump blood. Mavacamten reduces the activity of cardiac myosin to normalise contraction and relaxation of the heart.
Composite endpoint: several measurable outcomes in a clinical trial that are combined into one.
Double-blind: clinicians, researchers and patients did not know whether a patient was receiving mavacamten or placebo.
Efficacy: how well a drug or treatment works, evaluated by a clinical trial.
Ejection fraction: a measurement of how much blood the left ventricle (chamber) of the heart pumps out with each contraction.
Left ventricular outflow tract (LVOT) obstruction: when the heart beats, blood pumped out of the left ventricle (chamber) passes through the LVOT into the aorta and around the body. Thickening of the wall dividing the left and right sides of the heart (septum) can lead to obstruction of the blood leaving the heart and causes a large pressure gradient in the LVOT. This feature characterises obstructive HCM.
New York Heart Association (NYHA) class: a classification system used by clinicians to assess the severity of heart-related symptoms based on how limited the patient is in physical activity.
Open-label: a type of study where both the health providers and the patients are aware of the drug or treatment being given.
Peak oxygen consumption: the maximum rate of oxygen used during exercise, which is a measure of exercise capacity. The higher the peak oxygen consumption, the greater the exercise capacity.
Placebo-controlled: a trial where one group of patients receives the active treatment under investigation (i.e. mavacamten) and another group receives a placebo, in order to control for the placebo effect.
Randomised: patients were randomly assigned to either mavacamten or placebo in order to balance any differences in background factors that could affect the progression of the disease, such as age or sex.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. American Heart Association. Classes of heart failure. 2021.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Clarification questions

July 2022

File name	Version	Contains confidential information	Date
ID3928 mavacamten clarification questions to PM response ACIC redacted	1.0	Yes	04.08.22

Section A: Clarification on effectiveness data

A1. The reported screening process in Appendix D sections 2.3.1 and 2.3.2 refers to application of PICOS selection criteria from Table 1 which are broader than the scope of the current appraisal. However, it is not clear whether the PICOS selection criteria from Table 2 were applied as an extra step or applied independently to the original set of results, and how many reviewers were involved and their roles. Please explain how the PICOS criteria listed in Table 2 were implemented during eligibility screening for this appraisal.

Abstract screening and full text inclusion/exclusion was first performed by applying the broad global systematic literature review (SLR) PICOS criteria (Table 1 in Company Submission [CS] Appendix D). The refined set of PICOS criteria specific to the NICE decision problem (summarised in Table 2 in CS Appendix D) were then applied in a second round of screening to the set of full text studies that met the global SLR inclusion criteria. Two reviewers independently assessed all studies at each stage and any discrepancies were resolved by a third reviewer.

A2. The list of excluded studies in Appendix G within Appendix D does not include the studies that were "excluded from the NICE decision problem." Please provide a list of these excluded studies.

The four studies that were excluded following the application of the refined set of PICOS criteria specific to the NICE decision problem are as follows:

Hamada, Mareomi, et al. "Impact of chronic use of cibenzoline on left ventricular pressure gradient and left ventricular remodeling in patients with hypertrophic obstructive cardiomyopathy." *Journal of Cardiology* 67:3 (2016) 279-286.

Hamada, Mareomi, et al. "Class Ia antiarrhythmic drug cibenzoline: a new approach to the medical treatment of hypertrophic obstructive cardiomyopathy." *Circulation* 96.5 (1997) 1520-1524.

Hamada, Mareomi, et al. "Impact of cibenzoline treatment on left ventricular remodelling and prognosis in hypertrophic obstructive cardiomyopathy." *ESC Heart Failure* 8:6 (2021) 4832-4842.

Ogimoto, Akiyoshi, et al. "Pharmacogenetic interactions between angiotensin-converting enzyme insertion/deletion polymorphism and response to cibenzoline in patients with hypertrophic obstructive cardiomyopathy." *Journal of Cardiovascular Pharmacology* 55:5 (2010): 506-510.

A3. PRIORITY QUESTION The risk of bias assessment for the EXPLORER-LTE study (Appendix D) is difficult to interpret because some key information required for the ROBINS-I assessment is missing. The conclusion from the assessment, that EXPLORER-LTE is at low risk of bias, implies that EXPLORER-LTE is equivalent in design to a well-conducted randomised controlled trial (RCT) in mitigating all sources of bias. This seems implausible given that EXPLORER-LTE is a single cohort study.

a. **Please define what the intervention and comparator groups are in EXPLORER-LTE for the ROBINS-I assessment. If all participants in the EXPLORER LTE cohort received mavacamten then what is the comparator? Is ROBINS-I the most appropriate assessment tool to use for this study design?**

EXPLORER-LTE is a non-comparative cohort extension study enrolling patients from EXPLORER-HCM. The ROBINS-I tool is one option designed to assess risk of bias in non-randomised controlled trials and is recommended in the Cochrane Methods for assessing risk of bias in non-randomised studies, although it is acknowledged that there are limitations in the relevance to non-comparative follow-up (cohort) studies.[1] Cochrane recommend the Newcastle-Ottawa Scale (NOS) as an alternative[1], therefore an additional risk of bias assessment is provided using the NOS[2] (Appendix A). The total score for the NOS risk of bias assessment was 7, indicating that the study is of good quality.[3]

b. **Please specify all confounding variables that could be relevant to each of the reported outcomes for EXPLORER-LTE, as per the detailed instructions for conducting a ROBINS-I assessment (https://www.bristol.ac.uk/media-library/sites/social-community-medicine/images/centres/cresyda/ROBINS-I_detailed_guidance.pdf).**

Please see the response to part a.

c. **Please provide a clear rationale for your risk of bias judgements. We appreciate your answers to the ROBINS-I signalling questions (Table at the end of Appendix D) but we have no explanation for how these judgements were reached.**

Please see the response to part a.

d. **Please explain what "dose-blinded" means (CS section B.2.3.1.2) and how this was implemented.**

All participants in MAVA-LTE (which includes the EXPLORER-LTE cohort) are receiving mavacamten 2.5, 5, 10 or 15 mg once a day in a double-blind manner, for a duration of up to 5 years (252 weeks). Study drug administration is double-blinded via the interactive response system, such that the investigator, site staff, the pharmacist, and the participant do not know which dose strength is being administered. MAVA-LTE is enrolling in parallel from two parent studies; MAVERICK-HCM and EXPLORER-HCM. In order to preserve the treatment assignment blinding of the parent study, the protocol specified that the dose of mavacamten in MAVA-LTE should be blinded. Additionally, all participants undergo the same assessments and visit schedule (per cohort) to preserve the blind of assignments in the parent study.

A4. The evidence assessment group (EAG) will provide a validity assessment of the VALOR-HCM and two real world evidence (RWE) studies in our report to NICE. We would welcome risk of bias assessments for these studies for us to consider if the company can provide them.

Risk of bias assessments are provided for VALOR-HCM (Desai *et al*., 2022[4]; Table 1), and the two real-world evidence (RWE) studies (Wang *et al*., 2022[5] and Lakdawala *et al*., 2022[6]; Appendix A)**.**

The quality assessment of VALOR-HCM (Table 1) indicated that this study represents a high-quality randomised controlled trial (RCT) with low risk of bias. It was noted that there were minor differences between the two arms in the use of beta blocker+disopyramide combination therapy. This difference is within the stochastic variation expected as a result of randomisation and represents a small proportion of trial participants; the difference between the two arms in that subgroup is eight

patients (~7% of the study cohort), therefore the imbalance is four patients (~3.6% of the study cohort). Overall, this is a strong and well-balanced study.

The risk of bias assessments of the two RWE studies was conducted using the NOS and gave scores of 8 for Wang *et al*.[5] and 7 for Lakdawala *et al*.[6], indicating that these studies can be considered of good quality.[3]

Table 1. Quality assessment checklist for VALOR-HCM

Study questions	VALOR-HCM (Desai *et al*., 2022) Grade (yes/no/not clear/NA)
Was randomisation carried out appropriately?	Yes (interactive voice web response system)
Was the concealment of treatment allocation adequate?	Yes (interactive voice response system with matching placebo)
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes (minor differences between groups in background therapy)
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in dropouts between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

University of York Centre for Reviews and Dissemination[7].
ITT: intention-to-treat; NA: not applicable.

A5. PRIORITY QUESTION Company submission (CS) sections B.1.3.2.3.3 and B.2.12.4 refer to an analysis of the Clinical Practice Research Datalink (CPRD) Gold database for [redacted] patients with obstructive hypertrophic cardiomyopathy (HCM) in England, but do not provide a reference citation. Please provide a copy of this reference and any other relevant information on this database.

This study is an ongoing retrospective cohort study of patients diagnosed with hypertrophic cardiomyopathy (HCM) in England. The data have been obtained from the Clinical Practice Research Datalink (CPRD) using both the GOLD and Aurum datasets (with de-duplication due to any overlap between the datasets performed by CPRD) and linked hospital episode statistics (HES) data.[8] Although CPRD is UK-wide, HES only collect data for England, therefore the data used for this study are restricted to England by the HES linkage.

The protocol for this study was approved by the Independent Scientific Advisory Committee (ISAC) on 8 April 2021 (ISAC application reference 21_000342), however

there were COVID-19–related delays in accessing the data from CPRD and associated HES linkage. Therefore, the full analysis of the data is currently ongoing and publication of the full results for both GOLD and Aurum is currently anticipated to be complete at the end of 2022.

However, some of the planned analyses of the GOLD dataset were complete at the time of evidence submission, and these are the data quoted in the CS, in support of expert clinical opinion regarding the limited use of disopyramide in England, and to provide demographic data relevant to the population in the decision problem. As noted in the CS, there is a paucity of published data that can be used to inform aspects of the evidence submission, therefore, while it is acknowledged that the CPRD data analysis is not yet complete, we have provided interim results as evidence within the context of the limited available alternatives.

A6. PRIORITY QUESTION Appendix N: SHaRe RWE Study. Please explain the process for identifying and selecting relevant patient records from the SHaRe registry: how many people conducted the record selection? Was a process for checking data validity applied?

As outlined in Ho *et al*., 2018,[9] the Sarcomeric Human Cardiomyopathy Registry (SHaRe) is a longitudinal database originally established by eight high-volume, experienced HCM centres, and includes both retrospective and prospectively-collected data. Definitions for key demographic, historical, clinical, phenotypic and genetic parameters were harmonised to ensure standardisation across centres. Historical events that occurred before SHaRe entry are carefully ascertained and vetted for accuracy through systematic, detailed review of medical history and medical records, both at the initial visit and at subsequent visits, while prospective data are captured via quarterly uploads from site databases.

Since Ho *et al*.[9] was published, additional centres have been added to the database and new data cuts have become available. The analysis presented in the ShaRe RWE mortality study used in the CS (Wang *et al*. 2022[5] and Appendix N) uses the same data cut as that presented by Canepa *et al*., 2020,[10] which represents data from over 7,000 patients from 11 centres. Once the inclusion criteria were applied, the study cited in the CS included patients from 10 centres.

Record selection was therefore performed on data that have already been extensively reviewed for quality, and was based on the following criteria:[6]

1. At least one record of left ventricular outflow tract (LVOT) peak gradient > 30 mmHg OR at least one record of septal reduction therapy AND

2. At least one record of definite New York Heart Association (NYHA) functional class, defined as NYHA functional class I, II, III or IV, at the age of 18 years or older. Visits with missing NYHA functional class or indefinite functional classes (e.g. NYHA I–II) were discounted.

A7. PRIORITY QUESTION Appendix N: SHaRe RWE study. The analysis did not adjust for centre or country. How variable were the results between centres/countries? Were any UK centres included? Please provide results for each of the 12 centres if possible, or evidence that the global data are representative of the UK and European data.

The SHaRe investigators have received funding from the Company through unrestricted research grants. Although MyoKardia employees were co-investigators on the SHaRe mortality analysis and were able to provide input into the protocol and analysis plan, the ultimate prioritisation and decision making of the analysis and subsequent requests were directed by the SHaRe investigators. Consequently, the Company is not able to supply results by centre.

As described in the response to A6, the data used in the mortality study came from 10 of the centres that contribute to the SHaRe database, and included the [redacted] and [redacted], which together contributed [redacted]% of the patients included in the study, therefore it can be considered reasonably representative of European populations. A comparison of the US- and non-US cohorts presented in Canepa *et al*., 2020,[10] which used the same datacut, showed similar age at diagnosis and trend over time between cohorts.

Furthermore, a comparison of the published demographics from the SHaRe analysis with available UK demographic data for patients with HCM (and, where data are available, the obstructive subgroup) indicate that the populations appear to be comparable (Table 2). Data from four UK-based studies indicate that HCM patients

in England have a comparable sex distribution and age at diagnosis, and the distribution of racial demographics is also similar, albeit the UK populations report ~5% patients are Asian, which is not precisely reflected in the SHaRe cohort, although may be captured within the 6% 'other' category reported by Lakdawala *et al*.[6,11-13] Maximal left ventricular wall thickness was also comparable between the SHaRe cohort and two UK studies.[11,13] Only one publication was identified that reported family history of HCM, which was higher than in the SHaRe study (34.6% versus 29%).[13] This publication dates from 2006, therefore this observation is consistent with longitudinal data presented by Canepa *et al*. showing a decrease in proportion of patients with family history of HCM over time, from 38.8% in patients diagnosed before 2000 to 32.7% in patients diagnosed after 2010.[10] Although a family history of HCM is thought to associate with an increased risk of adverse outcomes compared to no family history, there is no evidence that family history would affect the relationship between NYHA class and mortality, which is seen in multiple studies in HCM.[5,13-15] Overall, the best available evidence suggests that the SHaRe RWE study is likely to be representative of UK and European patients with HCM.

Table 2. Baseline characteristics of SHaRe RWE study population compared to UK studies reporting demographic data in HCM

	Lakdawala* et al.*, 2021 (SHaRe)*[6]	**Pujades-Rodriguez *et al*., 2018[12]**	**Lorenzini *et al*., 2020[11]**	**Elliott *et al*., 2006[13]**	**CPRD GOLD analysis (provisional, unpublished; see response to A5)**
Study and cohort type	*Registry, 10 centres including [redacted] European; obstructive HCM*	EHR, England; all HCM	Retrospective European cohort, UK subgroup; all HCM	Cohort, England (single-centre); patients with LVOTO ≥ 30 mmHg	EHR, England; obstructive HCM
Female sex, %	*42*	41	36	39	[redacted]
Race/ethnicity, %			NR	NR	**
White	*89*	91	-	-	[redacted]
Black	*4*	2.3 (Afro-Caribbean)	-	-	[redacted]
Hispanic	*1*	NR	-	-	NR
Other	*6*	1.2 (Other) 5.2 (Asian)	-	-	[redacted] (Asian)
Missing/unknown	*1*	NR	-	-	[redacted]
Family history of HCM, %	*29*	NR	(28% family history of sudden death)	34.6	-
Age at HCM diagnosis, mean (SD) years	*48 (17)*	NR	45 (16)	41 (17)	-
Maximal LVWT, mean (SD) mm	*20 (5)*	NR	19 (6)	21.9 (5.2)	-

* Note that two baseline characteristics reported by Lakdawala *et al.*[6] were not reported in any of the UK studies identified and have therefore been omitted from this table: left ventricular ejection fraction and left ventricular outflow tract peak gradient at rest.
** It was stated in the CS that the data on race in the CPRD GOLD analysis were subject to a high proportion of missingness and were therefore not reported (CS document B, section 2.12.4, page 87). Since submitting that evidence, further analysis has been undertaken on the HES data linked to the patients in GOLD, which has addressed the issue of missingness.
CPRD: Clinical Practice Research Datalink; CS: company submission; EHR: electronic health record; HCM: hypertrophic cardiomyopathy; HES: Hospital Episode Statistics; LVOTO: left ventricular outflow tract obstruction; LVWT: left ventricular wall thickness; NR: not reported; SD: standard deviation; SHaRe: Sarcomeric Human Cardiomyopathy Registry

A8. The rationale for pooling of NYHA Class III/IV in the SHARE study is unclear.

a. **CS section B.3.3.5 states that "NYHA classes III and IV could not be disaggregated in the SHaRe data" but no explanation is given. Could a subset of the overall SHaRe dataset be made available in which NYHA Class III and Class IV could be analysed separately?**

The SHaRe investigators have communicated to the Company that initial exploratory analysis on the dataset used for the SHaRe mortality study indicated that NYHA class IV at index represented only [redacted] of all included patients. As such, the sample size of NYHA class IV patients was too small to be analysed as a separate category, and the decision taken by the investigators was to combine those patients in NYHA class IV at index with the NYHA class III patients. As described in the response to A7, the prioritisation and decision making of the analysis and subsequent requests are directed by the SHaRe investigators, therefore it is not possible to provide the requested subset analysis. It is worth noting that all SHaRe publications to date that include data on NYHA class do not report analysis for NYHA classes III and IV separately (except as baseline characteristics in Canepa *et al*., 2020), due to this limitation.[9,10,16-18]

b. **Appendix N states for the SHaRe study that "Visits with missing NYHA assessments or multiple NYHA functional classes (e.g., NYHA class I-II, NYHA class II-III, and NYHA class III-IV) were excluded." This contradicts the inclusion of pooled NYHA Class III/IV in the CS. Please explain this discrepancy.**

It is a limitation of real-world medical record-based evidence that individual clinicians may have recorded a patient's NYHA class in the form of a range, although this is not considered best practice. As it is not possible to unambiguously assign a NYHA class to a patient when a range has been recorded, these visits are therefore excluded from the analysis. This does not contradict the pooling of NYHA class III and IV, which was performed for the reasons outlined in the response to question A8a i.e., that NYHA class IV patients represented only [redacted]% of all included patients.

A9. PRIORITY QUESTION Appendix O refers to "the BMS observational study (CV027-042 – epidemiology, treatment patterns and burden of illness

associated with obstructive HCM in England)" but does not provide a reference citation. Please provide a copy of this reference and any other relevant information on this study.

This is the ongoing study using data from the CPRD database, which is clarified in response to question A5.

Section B: Clarification on cost-effectiveness data

B1. PRIORITY QUESTION The short-term transition probabilities used in the model are reported in CS Table 25. The company state that these figures were calculated with missing data imputed by the last observation carried forward method. Please provide numbers of observations for Table 25, including numbers in each cell as well as row totals, with and without imputation.

In the CS, short-term transition probabilities were computed using the last observation carried forward imputation procedure for any missed NYHA assessments prior to a patient's last observed assessment (which could have been earlier than the end of the study in case of discontinuation from the study). For the NYHA class component of the primary endpoint, and the NYHA class secondary endpoint, if the NYHA class assessment was missing at week 30, it was imputed with data from week 26, where available.[19] Patients whose NYHA class response status was still missing at week 30 after imputation were classified as nonresponders.[19] This approach to imputation was specified in the EXPLORER-HCM statistical analysis plan (SAP).[20] Therefore, the observed final distribution in Olivotto *et al*. at week 30 included the full intention-to-treat (ITT) population. Olivotto *et al*. only calculated the difference between baseline and week 30, therefore imputation at the other timepoints was not performed in that publication. However, in order to ensure that the full ITT population was represented in the modelling at week 30, it was necessary to perform a similar imputation to that specified in the SAP for missing values at each study visit. This approach allowed reproducibility between the modelled NYHA distribution at week 30 and the data published by Olivotto *et al.* Without imputation, a single missing observation at a timepoint would exclude a patient from being represented in the transition matrix to and from that timepoint;

with multiple missing observations at different timepoints resulting in a cumulative effect.

As requested by the EAG, Table 3 shows the number of observations used to calculate each transition probability, including imputed observations, with the short-term transition probabilities (as given in CS Table 25) in brackets. Table 4 shows the same information, but without imputation for missing values at each time point.

Table 3. Transition probabilities with imputations for missing values

Week		Mavacamten + BB/CCB, N (%)					BB/CCB monotherapy, N (%)				
	To / From	NYHA I	NYHA II	NYHA III	NYHA IV	N	NYHA I	NYHA II	NYHA III	NYHA IV	N
Baseline to week 4	NYHA I*	[redacted]									
	NYHA II	[redacted]									
	NYHA III	[redacted]									
	NYHA IV*	[redacted]									
Week 4 to 6	NYHA I	[redacted]									
	NYHA II	[redacted]									
	NYHA III	[redacted]									
	NYHA IV	[redacted]									
Week 6 to 8	NYHA I	[redacted]									
	NYHA II	[redacted]									
	NYHA III	[redacted]									
	NYHA IV	[redacted]									
Week 8 to 12	NYHA I	[redacted]									
	NYHA II	[redacted]									
	NYHA III	[redacted]									
	NYHA IV	[redacted]									
Week 12 to 14	NYHA I	[redacted]									
	NYHA II	[redacted]									
	NYHA III	[redacted]									
	NYHA IV	[redacted]									

Week 14 to 18	NYHA I	[redacted]									
	NYHA II	[redacted]									
	NYHA III	[redacted]									
	NYHA IV	[redacted]									
Week 18 to 22	NYHA I	[redacted]									
	NYHA II	[redacted]									
	NYHA III	[redacted]									
	NYHA IV	[redacted]									
Week 22 to 26	NYHA I	[redacted]									
	NYHA II	[redacted]									
	NYHA III	[redacted]									
	NYHA IV	[redacted]									
Week 26 to 30	NYHA I	[redacted]									
	NYHA II	[redacted]									
	NYHA III	[redacted]									
	NYHA IV	[redacted]									
Week 30 to 38	NYHA I						[redacted]				
	NYHA II						[redacted]				
	NYHA III						[redacted]				
	NYHA IV						[redacted]				
Week 38 to 46#	NYHA I						[redacted]				
	NYHA II						[redacted]				
	NYHA III						[redacted]				
	NYHA IV						[redacted]				

*No transition probability data for NYHA I and IV were available from EXPLORER-HCM for week 0 (i.e., baseline) to week 4 since the trial included only patients who were NYHA class II or III at baseline.

Week 46 refers to day 0 of EXPLORER-LTE cohort NYHA distribution.

NA represents a time point within the trial in which no patients were assessed to be within the defined NYHA class.

BB: beta-blocker; CCB: calcium channel blocker; HCM: hypertrophic cardiomyopathy; LTE: long-term extension; NYHA: New York Heart Association.

Table 4. Transition probabilities without imputations for missing values

Week		Mavacamten + BB/CCB, N (%)					BB/CCB monotherapy, N (%)				
	To / From	NYHA I	NYHA II	NYHA III	NYHA IV	N	NYHA I	NYHA II	NYHA III	NYHA IV	N
Baseline to week 4	NYHA I*	[redacted]									
	NYHA II	[redacted]									
	NYHA III	[redacted]									
	NYHA IV*	[redacted]									
Week 4 to 6	NYHA I	[redacted]									
	NYHA II	[redacted]									
	NYHA III	[redacted]									
	NYHA IV	[redacted]									
Week 6 to 8	NYHA I	[redacted]									
	NYHA II	[redacted]									
	NYHA III	[redacted]									
	NYHA IV	[redacted]									
Week 8 to 12	NYHA I	[redacted]									
	NYHA II	[redacted]									
	NYHA III	[redacted]									
	NYHA IV	[redacted]									
Week 12 to 14	NYHA I	[redacted]									
	NYHA II	[redacted]									
	NYHA III	[redacted]									
	NYHA IV	[redacted]									
Week 14 to 18	NYHA I	[redacted]									
	NYHA II	[redacted]									
	NYHA III	[redacted]									
	NYHA IV	[redacted]									
Week 18 to 22	NYHA I	[redacted]									
	NYHA II	[redacted]									

	NYHA III	[redacted]									
	NYHA IV	[redacted]									
Week 22 to 26	NYHA I	[redacted]									
	NYHA II	[redacted]									
	NYHA III	[redacted]									
	NYHA IV	[redacted]									
Week 26 to 30	NYHA I	[redacted]									
	NYHA II	[redacted]									
	NYHA III	[redacted]									
	NYHA IV	[redacted]									
Week 30 to 38	NYHA I						[redacted]				
	NYHA II						[redacted]				
	NYHA III						[redacted]				
	NYHA IV						[redacted]				
Week 38 to 46#	NYHA I						[redacted]				
	NYHA II						[redacted]				
	NYHA III						[redacted]				
	NYHA IV						[redacted]				

*No transition probability data for NYHA I and IV were available from EXPLORER-HCM for week 0 (i.e., baseline) to week 4 since the trial included only patients who were NYHA class II or III at baseline.

Week 46 refers to day 0 of EXPLORER-LTE cohort NYHA distribution.

NA represents a time point within the trial in which no patients were assessed to be within the defined NYHA class.

BB: beta-blocker; CCB: calcium channel blocker; HCM: hypertrophic cardiomyopathy; LTE: long-term extension; NYHA: New York Heart Association.

To validate the approach, NYHA class distribution at week 30 from EXPLORER-HCM was compared to the NYHA health state occupancy at week 30 predicted by the model using imputed and non-imputed transition probabilities (Table 5). Health state occupancy estimated by the model using imputed transition probabilities was closer to the trial data than the estimates using the non-imputed transition probabilities (Table 5).

Table 5. EXPLORER-HCM trial data compared to model predictions for NYHA class distribution at week 30

NYHA class	Intervention arm			Comparator arm		
	EXPLORER-HCM, %[19]	Model transition probabilities with imputation, %	Model transition probabilities without imputation, %	EXPLORER-HCM, %[19]	Model transition probabilities with imputation, %	Model transition probabilities without imputation, %
NYHA I	49.60	[redacted]	[redacted]	21.10	[redacted]	[redacted]
NYHA II	42.30	[redacted]	[redacted]	57.80	[redacted]	[redacted]
NYHA III	6.50	[redacted]	[redacted]	19.50	[redacted]	[redacted]
NYHA IV	0.00	[redacted]	[redacted]	0.00	[redacted]	[redacted]

CS uses imputed transition probabilities. Values in parenthesis represent the absolute difference between the NYHA class health state occupancy predicted by the model and the trial data observed at week 30

B2. PRIORITY QUESTION Please explain how the percentages of discontinuation due to lack of response reported in CS Table 26 were calculated. We cannot replicate the [redacted] value for the NYHA II subgroup or the 100% value for the NYHA III subgroup. Based on the results reported in Clinical Study Report (CSR) section 9.5 and Table 27 (pages 109 and 111), we estimate the percentages with no NYHA class improvement at week 30 compared to baseline were [redacted] for NYHA class II and [redacted] for NYHA class III.

The EAG are correct that in EXPLORER-HCM, of those patients who were in NYHA class II at baseline, [redacted]% had not improved NYHA class by week 30; similarly for those patients in NYHA class III at baseline, [redacted]% had not improved NYHA class at week 30. However, the percentages in CS Table 26 do not represent the percentage of patients in each NYHA class at baseline who did not improve (i.e. the figures cited above), but instead denote the percentage of patients within each NYHA class health state at week 30 who had not experienced a NYHA class improvement and therefore discontinue due to lack of response. In detail:

- As all patients start in the model in NYHA class II or III (aligning with the EXPLORER-HCM eligibility criteria and the anticipated marketing authorisation), all patients who are in the NYHA class III health state at week 30 have arrived there either from NYHA class II at baseline (i.e. a worsening from baseline) or from NYHA class III at baseline (i.e. no improvement from baseline). Therefore, by definition, 100% patients in the NYHA class III health state at week 30 discontinue due to lack of response.

- Of those patients in the NYHA class II health state at week 30 in EXPLORER-HCM, [redacted]% ([redacted]) arrived there from NYHA class III (i.e. an improvement from baseline) while [redacted]% ([redacted]) arrived there from NYHA class II (i.e. no improvement from baseline) NB. these figures can be found in the CSR Table 27. Therefore, in the model, [redacted]% patients in NYHA class II at week 30 discontinue due to lack of response.

- For clarity, no patients in the NYHA class I health state at week 30 discontinue due to lack of response in the model, because all have improved from either NYHA class II or NYHA class III at baseline.

B3. PRIORITY QUESTION The acquisition cost of mavacamten in the model is adjusted for missing doses or protocol-driven temporary discontinuation (adherence rate of [redacted] (CS section B.3.5.1.1). Please cite a source for this figure, we could not find it in the CSR for EXPLORER-HCM or the Olivotto et al. 2020 paper.

The rate used to adjust for missing doses, including protocol-driven temporary discontinuation, was derived directly from the patient-level data of EXPLORER-HCM; specifically, the Study Drug Exposure Analysis Dataset (ADEX) in ADaM format. This dataset contains a variable describing treatment compliance during the trial, measured as % pills for each patient, according to treatment arm allocation. This variable was computed by dividing the cumulative number of dose capsules administered by the duration of exposure, i.e. the variable was adjusted for time on treatment for those patients who discontinued treatment prior to 30 weeks, resulting in a single time-adjusted value per patient at week 30. Average treatment compliance was then calculated as mean % doses taken for each treatment arm, resulting in [redacted]% for patients in the mavacamten arm.

B4. PRIORITY QUESTION The modelled dose of propranolol (10 mg per day) appears to be inconsistent from the information in the current version of the British National Formulary (BNF) (accessed 12 July 2022). This appears to be low compared with the recommended dose for the HCM indication stated in the BNF (10-40 mg 3-4 times a day). Please confirm the correct daily dose of propranolol 10mg tablets, correct the per cycle costs and revise the model as required.

This issue was also highlighted to the Company in correspondence with NICE and an updated version of the model and updated CS documents were sent to NICE on 20th July 2022. For clarity, the doses of propranolol, verapamil, diltiazem and disopyramide were updated to reflect the most recent British National Formulary (BNF) update and the costs of these drugs were updated to use electronic market information tool (eMIT) costs rather than BNF costs (Table 6). These updates are

also included in the version of the model that accompanies this response ((ID3928) Company submission CEM post CQs).

Table 6. Updated costs of modelled comparators and subsequent therapies

Treatment	Form	Pack size	Dosing	Cost	Source
Propranolol (BB)	10 mg tablet	28	10 mg, three times daily	£0.25 per pack	Costs: eMIT[21] Posology: BNF, June 2022[22]
Verapamil (CCB)	80 mg tablet	84	80 mg, three times daily	£1.51 per pack	Costs: eMIT[21] Posology: BNF, June 2022[23]
Diltiazem (CCB)	60 mg modified release tablet	84	60 mg, three times daily	£9.03 per pack	Costs: eMIT[21] Posology: BNF, June 2022[24]
Disopyramide	100 mg capsule	100	300 mg, daily	£12.95 per pack	Costs: eMIT[21] Posology: BNF, June 2022[25]

BB: beta-blocker; BNF: British National Formulary; CCB: calcium channel blocker; eMIT: electronic market information tool.

B5. The method used to derive the treatment escalation rates in CS Table 28 is outlined on page 108 of the CS. Please explain the process that was used to dynamically adjust the escalation rates and report how successful the approach was at meeting calibration targets (the estimated annual SRT rates by NYHA class from expert elicitation).

Inputs related to treatment escalation rates (by NYHA class) over a lifetime were collected via the UK expert elicitation study (CS Appendix O), giving lifetime proportions of NYHA I: [redacted]%, II: [redacted]%; III: [redacted]%; IV: [redacted]%. These lifetime proportions were used to derive annual proportions (CS Table 28), which were implemented in the model using the following expression:

$$\%\ patients\ escalating\ per\ year = \frac{\%\ patients\ escalating\ over\ lifetime}{mean\ overall\ survival\ by\ NYHA\ class}$$

Mean overall survival specific for each NYHA class was estimated as follows:

1. Proportion of patients who survived at each age (by NYHA class) was estimated as a complement of the probability of patients dying at each age i.e., calculated as a product of age- and sex-adjusted lifetable-based general

mortality rate[26] and NYHA class-specific mortality. In the base case, the NYHA class-specific mortality was based on the HRs from Wang *et al*.[5] but note that mean overall survival will depend on the inputs used for mortality.

2. The percentage of patients alive was summed for each NYHA class to obtain mean overall survival for each NYHA class. In the base case, NYHA I: [redacted] years; II: [redacted] years; III: [redacted] years; IV: [redacted] years but as noted above, these figures will depend on the inputs used to derive mortality.

As an example, using the base case mortality assumptions, % patients escalating to septal reduction therapy (SRT) from NYHA IV = [redacted] = [redacted]% of the population per year.

Internal validation of the escalation rates predicted by the model (under base case assumptions) using the above approach compared to the escalation rates from the expert elicitation study is presented in Table 7. The model prediction is comparable to the rates estimated by the expert elicitation, although as no modelled patients were in NYHA class IV after week 30 and escalation is modelled to only occur after week 30, no escalation from NYHA IV to SRT was possible.

Table 7. Comparison of expert elicitation study data with model prediction for lifetime escalation to SRT

	NYHA I	NYHA II	NYHA III	NYHA IV
Lifetime escalation rates to SRT: expert elicitation study	[redacted]	[redacted]	[redacted]	[redacted]
Lifetime escalation rates to SRT: model prediction	[redacted]	[redacted]	[redacted]	[redacted]

B6. Please provide results for the company scenario with 0% mavacamten discontinuation due to serious adverse events (SAEs) from week 30 onwards. This scenario is specified in CS Table 45, but the results are not reported in in CS Table 46.

This scenario was a typographical error in the CS. Although trial data indicate that mavacamten is associated with a tolerable adverse event profile, it is not considered clinically plausible that 0% patients would discontinue any medication over a long time horizon, as evidenced by the 1.6% discontinuation over 30 weeks reported in the EXPLORER-HCM trial. The NICE processes and methods guide states that *“In*

general, all model parameter values used in base-case, sensitivity, scenario and subgroup analyses should be both clinically plausible and should use methods that are consistent with the data. Results from analyses that do not meet these criteria will not usually be suitable for decision making."[27] Consistent with this advice, the Company do not believe this implausible scenario would aid decision making.

B7. There appears to be an error in the calculation of transition probabilities after SRT from Knyshov et al. 2013 (used in scenario analysis). Figure 1 in the Knyshov paper reports that of the 2 NYHA class IV patients who had SRT (myectomy or septal ablation), 1 remained at NYHA IV and 1 improved to NYHA III. However, CS Table 29 and the model indicate that 66.7% remained in NYHA IV and 33.3% improved to NYHA III. Please can you check this.

Upon review of the data, the Company agrees that there was an error in the calculations of the transition probabilities for this scenario. The transition probabilities (Table 8) have been updated in the version of the model that accompanies this response ((ID3928) Company submission CEM post CQs), however it should be noted that the scenario incremental cost-effectiveness ratio (ICER) is unchanged because no modelled patients were in NYHA class IV after 30 weeks.

Table 8. Transition probability matrix based on Knyshov et al. 2013

	NYHA I	NYHA II	NYHA III	NYHA IV
NYHA I	100.0%	0.0%	0.0%	0.0%
NYHA II	33.3%	66.7%	0.0%	0.0%
NYHA III	0.0%	85.7%	14.3%	0.0%
NYHA IV	0.0%	0.0%	50.0%	50.0%

B8. Please explain the rationale for the selection of adverse events (AEs) that are included in the model (CS Table 32). It is not apparent why some AEs reported in Olivotto et al. 2020 Table 4 (such as the cases of atrial fibrillation and stress cardiomyopathy) are not included in the model.

A more detailed rationale for the exclusion of treatment-emergent serious adverse events (SAEs) reported in Olivotto *et al*., 2020[19] is given in Table 9.

Table 9. Serious adverse events excluded in the base case

Serious TEAE[19]	Reason for exclusion from model
AF	In general, AF in patients with HCM is a prevalent condition as opposed to an event. [redacted]
Stress cardiomyopathy	Literature searching did not identify any plausible cost inputs, however, [redacted]
Diverticulitis	Not CV based. [redacted]
Infection	Not CV based; [redacted]
Rheumatoid arthritis	Not CV based
Contusion	Physical event ([redacted])
Forearm fracture	Physical event ([redacted])
Dehydration	Not CV based
Vocal cord polyp	Not CV based
Cholesteatoma	Not CV based
Prostate cancer	Not CV based

AF: atrial fibrillation; CV: cardiovascular; HCM: hypertrophic cardiomyopathy; TEAE: treatment-emergent adverse event

In order to further explore the impact of the selection of AEs on the economic model, several alternative scenarios are presented:

1. All SAEs with a frequency of > 1% in either arm i.e. atrial fibrillation (AF), syncope, stress cardiomyopathy, urinary tract infection (UTI)

2. All cardiovascular (CV)-related SAEs i.e. AF, syncope, stress cardiomyopathy, transient ischaemic attack (TIA) and cardiac failure congestive.

3. All SAEs with a frequency of > 1% in either arm OR CV-related SAEs i.e. AF, syncope, stress cardiomyopathy, TIA, cardiac failure congestive and UTI.

As noted in Table 9, no plausible costs were identified in literature searches for stress cardiomyopathy, therefore the cost has been assumed to be £0 in the scenarios. The cost applied for AF was a weighted average of the NHS reference costs for EB07, which were used in TA197[28] (in the scenarios, the 2019/2020 reference costs were used: £1,007.12). The results presented for the three scenarios

(Table 10) demonstrate that the ICER is insensitive to the selection of adverse events.

Table 10. Adverse events scenarios

Scenario	ICER (£/QALY)
Base case	*29,840.80*
All SAEs > 1% in either arm	30,013.62
All CV-related SAEs	30,035.45
All SAEs > 1% in either arm OR CV-related SAEs	29,813.61
CV: cardiovascular; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SAE: serious adverse event	

Section C: Textual clarification and additional points

The EAG have no additional clarification questions.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Clarification questions

Appendix A: Risk of bias assessments

July 2022

File name	Version	Contains confidential information	Date
ID3928 mavacamten clarification questions response Appendix A	1.0	No	04.08.22

Appendix A: Risk of bias assessments

This appendix contains the requested risk of bias assessments (Table 1) in response to questions A3 (EXPLORER-LTE cohort of MAVA-LTE study[1]) and A4 (Wang *et al*., 2022[2] and Lakdawala *et al*., 2022[3]). Note that the requested quality assessment of VALOR-HCM in response to question A4 is included in the main response document.

Table 1. Risk of bias assessments using the Newcastle-Ottawa Scale

	EXPLORER-LTE cohort of MAVA-LTE[1]	Wang *et al.*, 2022[2]	Lakdawala *et al.*, 2022[3]
Selection (maximum 4 points)			
1) Representativeness of the exposed cohort			
a) truly representative of the average *obstructive HCM* patients in the community *	0	1	1
b) somewhat representative of the average *obstructive HCM patients* in the community *	1 (patients given the option to enter the study following participation in the pivotal EXPLORER-HCM RCT	0	0
c) selected group of users eg nurses, volunteers	0	0	0
d) no description of the derivation of the cohort	0	0	0
2) Selection of the non exposed cohort			
a) drawn from the same community as the exposed cohort *	0	0	0
b) drawn from a different source	0	0	0
c) no description of the derivation of the non exposed cohort	0	0	0
3) Ascertainment of exposure			
a) secure record (eg surgical records) *	1	1	1
b) structured interview *	0	0	0
c) written self report	0	0	0
d) no description	0	0	0
4) Demonstration that outcome of interest was not present at start of study			
a) yes *	1	1	1
b) no	0	0	0
Total for selection domain	*3*	*3*	*3*
Rating	*Good*	*Good*	*Good*
Comparability (maximum 2 points)			
1) Comparability of cohorts on the basis of the design or analysis			

a) study controls for NYHA class *	1	1	1
b) study controls for any additional factor (adjusting for age at diagnosis, gender, and race) *	0	1	0
Total for comparability domain	*1*	*2*	*1*
Rating	*Fair*	*Good*	*Fair*
Outcome (maximum 3 points)			
1) Assessment of outcome			
a) independent blind assessment *	1	0	0
b) record linkage *	0	1	1
c) self report	0	0	0
d) no description	0	0	0
2) Was follow-up long enough for outcomes to occur			
a) yes (at least 16 weeks for LVOT, LVEF, NYHA class) *	1	1	1
b) no	0	0	0
3) Adequacy of follow up of cohorts			
a) complete follow up - all subjects accounted for *	1	1	1
b) subjects lost to follow up unlikely to introduce bias - small number lost - > 5% follow up, or description provided of those lost	0	0	0
c) follow up rate < 95% and no description of those lost	0	0	0
d) no statement	0	0	0
Total for outcome domain	*3*	*3*	*3*
Rating	*Good*	*Good*	*Good*
Total	**7**	**8**	**7**

Risk of bias assessment performed using the Newcastle-Ottawa Quality Assessment Scale[4]
Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Clarification questions

November 2022

File name	Version	Contains confidential information	Date
ID3928 mavacamten clarification questions to PM for company response ACIC marked	1.0	Yes	24.11.22

Section A: Clarification on effectiveness data

Decision problem

A1. Population: section 2.9.3 of the company Addendum states that VALOR-HCM includes patients who would not be included in the marketing authorisation. Please explain how many patients this applies to in each trial arm and the specific reason(s) why they would be outside of the marketing authorisation.

The inclusion criteria for VALOR-HCM permitted enrolment of patients who were in New York Heart Association (NYHA) class IV at baseline,[1] who would therefore not be included in the proposed marketing authorisation, which is for patients in NYHA class II or III. In total, [redacted]/112 ([redacted]%) patients enrolled in the study were in NYHA class IV at baseline (assigned to the mavacamten arm).[2]

Clinical effectiveness

A2. For the outcome NYHA improvement (%) at 30 weeks by beta-blocker subgroup use reported in Table 16 of the original company submission please provide the numerators and denominators for these percentages:

Source	+ BB use		No BB use	
	Mavacamten	Placebo	Mavacamten	Placebo
CS Table 16	65%	35%	66%	21%

The abstract published by Jacoby *et al*., 2021,[3] from which these data are sourced, reports the denominators for each group. These were inadvertently omitted from the original Company submission (CS), and are reproduced below in the table header. Jacoby *et al*. did not report the numerators for each outcome analysed, including the % NYHA improvement, but these data have been included in the table extract below.[4] Note that the reference pack for the original CS contained the Jacoby *et al*. abstract; the Company is now able to supply the poster presented, which can be found in the reference pack for this response document.[5]

Source	+ BB use		No BB use	
	Mavacamten (N = 94)	Placebo (N = 95)	Mavacamten (N = 29)	Placebo (N = 33)
CS Table 16	65% (n = 61)	35% (n = 33)	66% (n = 19)	21% (n = 7)

A3. The original company submission (CS section B.2.7.1) refers to subgroup analyses of baseline beta-blocker use in EXPLORER-HCM. However, the EXPLORER-HCM clinical study report (CSR Figure 7) and paper by Jacoby et al. 2021 refer to patients "using" or "receiving" beta-blockers, implying concomitant on-trial beta-blocker therapy rather than baseline beta-blocker therapy is being referred to. Please clarify whether the subgroup analyses refer to beta-blocker use at baseline or on study.

All pre-specified subgroup analyses, including beta blocker use, were based on stratification factors, demographics and other characteristics assessed at baseline (EXPLORER-HCM clinical study report [CSR] section 9.4 p 106).[6] As a note, and as described in Olivotto *et al*., 2020, "*Patients were allowed to continue standard hypertrophic cardiomyopathy medical therapy except disopyramide (for safety reasons), including monotherapy with β blockers or calcium channel blockers, if dosing remained stable for at least 2 weeks before screening and no changes were anticipated during the study.*"[7] It was also specified in the EXPLORER-HCM CSR (section 7.4.7, page 44) that patients *"…who were receiving standard cardiomyopathy therapy (eg, beta-blocker, verapamil, or diltiazem) were to continue on a stable dose from at least 14 days prior to screening to the Week 38/end of study visit, as long as it was well tolerated."*[6] Therefore, while the stratification was performed on baseline beta blocker status, it was expected that patients who were on beta blockers at baseline would remain on a stable dose of beta blockers concomitantly throughout the study.

A4. For the VALOR-HCM trial, Desai et al. 2022 report subgroup analyses by beta-blocker use in Supplementary Appendix Figure 1. Please clarify whether this refers to beta-blocker use at baseline or on study.

The subgroup analysis reported by Desai *et al*., 2022 was performed by beta blocker use at baseline.[1,8] However, as patients were expected to remain on stable

background therapy, beta blocker use at baseline was considered representative of use during the study; as described in the supplementary material, one study exclusion criterion was "*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.*"[1]

Furthermore, the VALOR-HCM clinical trial protocol specifies that "*Background HCM medications (eg, beta blocker, verapamil, diltiazem, or disopyramide) are allowed during the study. Subjects should be on optimal tolerated HCM medication as determined by the investigator and informed by HCM treatment guidelines (Elliott et al. 2014; Gersh et al. 2011). The treatment should be well tolerated for at least 2 weeks prior to screening and should be maintained through Week 32. Investigators are encouraged not to change background HCM medications from Day 1 to Week 32; however, investigators should manage subjects appropriately using their clinical judgment. After Week 32, investigators should manage background HCM medications as clinically appropriate. Background cardiomyopathy therapy (eg, beta blocker, verapamil, or diltiazem) may be adjusted or stopped after Week 32 as determined by the investigator in conjunction with the MyoKardia Medical Monitor. Any change in HCM medications must be entered into the eCRF with the rationale for the change.*"[9]

Therefore, patients who were on beta blockers at baseline were expected to remain on beta blockers as a concomitant medication at least to Week 32, unless clinically indicated otherwise. Data from the interim analysis show that for the safety population during the double-blind period (i.e. up to Week 16), only ▌ patient in the mavacamten arm and ▌ patients in the placebo arm discontinued their existing beta blocker concomitant medication (CSR Table 14.1.4.3.1).[10]

A5. The original company submission reports in several places (e.g. CS Tables 9, 13, 14, 15) that statistical analyses were stratified by beta-blocker use. Does this refer to baseline or on-study beta-blocker use?

All analyses reported as stratified by beta blocker use refer to baseline beta blocker status, however, as described in detail in response to question A3, patients were

expected to remain on their baseline beta blocker or calcium channel blocker (CCB) dosage as a concomitant medication for the duration of the trial.

Section B: Clarification on cost-effectiveness data

B1. The addendum states that, since the original company submission, 'data have been identified and methodology developed' to enable the disease progression scenarios, and that Maron et al. 2016 'was the only source identified that quantified the natural history of HCM in terms of NYHA classification'.

(a) Was a systematic review or other search conducted to identify other data sources potentially relevant for these scenarios? If so, please report the methods of the review, studies identified and reasons for exclusion. If not, please explain why no search was conducted.

In alignment with the NICE Process and methods guide,[11] a clinical SLR was conducted by the Company (CS Appendix D), designed to identify studies evaluating the efficacy and safety of specific treatments (i.e. mavacamten) and relevant comparator therapies. Prognostic factors were a pre-specified exclusion criterion of the review. From the studies identified it was not possible to quantify disease progression in a general obstructive HCM population to inform the natural history of the disease. There is a need for good quality long-term clinical studies with a placebo arm in this patient population, however neither the SLR nor the targeted searches described below have identified such evidence.

In order to address this evidence gap, a supplementary prognostic SLR has been initiated (results expected early 2023). Pending results, a targeted literature review identified Liu *et al*. 2017,[12] a systematic review and meta-analysis of survival and prognostic factors in hypertrophic cardiomyopathy which included studies up to September 2015. However, the inclusion criteria included all patients with HCM, rather than just the obstructive sub-type, therefore further assessment of suitability was required.

Nineteen studies were included in Liu *et al*., representing 12,146 patients with HCM. Of these 19 studies, 15 included a NYHA class III/IV outcome. The majority reported

the proportion of patients in NYHA class III/IV at baseline, with only some reporting the proportion of patients in NYHA class III/IV also at the end of follow-up.[12] However, of those studies that reported NYHA class III/IV at baseline, this was in a subset of patients specific to a different outcome (i.e. those who had a mortality event). Other issues included the lack of data relating to the obstructive sub-type and generalisability to the target population as well as the variability in follow-up. Therefore, none of the studies identified by Liu *et al.* were deemed appropriate to inform this model scenario.

Additional targeted searches were undertaken (key terms included obstructive/obstruction, HCM and disease progression), which identified Maron *et al*. 2016,[13] a study published after the search period of Liu *et al.* (September 2015). This study was considered suitable to inform the modelling based on the following conditions: (1) reported patients with obstructive HCM or obstructive HCM as a pre-defined subgroup; (2) reported NYHA class at baseline and over time; (3) was rate adjusted to allow for a yearly rate to be obtained or calculated. Although there are limitations with this paper which are clearly articulated in the addendum to the CS, the Company believes this to be the most appropriate source identified for use for this model input.

(b) Were any studies identified that reported long-term NYHA progression data for adults with obstructive HCM being treated with disopyramide or following septal reduction therapy?

The clinical SLR (CS Appendix D) included 143 studies evaluating septal reduction therapy (SRT) and 4 studies evaluating disopyramide that also reported NYHA class as an outcome. These studies varied in their reporting of NYHA class, including NYHA class at baseline, NYHA class at follow-up, pre-intervention NYHA class, post-intervention NYHA class and mean NYHA class at follow-up.

Studies evaluating disopyramide

Of the 4 studies evaluating disopyramide,[14-17] Sherrid *et al*., 2013, had the longest follow-up, with a median of 4.5 (range, 2.2–7.6) years.[15] This study evaluated management of patients enrolled in a prospectively-registered referral cohort of HCM patients initially evaluated from 1985 to June 30, 2011 at a single US centre. Of 737

patients in the registry, 299 had obstructive HCM and were classified as “advanced care” (symptoms unresponsive to beta blockers and/or verapamil (a CCB) and left ventricular outflow tract gradient ≥ 50 mmHg). Of these, 221 received disopyramide therapy 80 went on to receive SRT, while 141 continued on disopyramide.

These 141 patients had a NYHA class at initial evaluation of 2.7±0.6, and at last visit of 1.9±0.5.[15] However, this subgroup of disopyramide-treated patients who achieved a “favourable response” is, by design, a responder population, as patients who failed disopyramide were then eligible for SRT. This issue affects the other studies, including Sherrid *et al*. 2005.[14] Therefore, the effectiveness observed in studies of a responder population is not representative of all patients receiving disopyramide as it doesn’t include patients who failed disopyramide therapy. The obstructed, advanced care group (n = 299) does quantify longer-term disease progression for the whole advanced care therapies pathway, however it is not suitable to inform the model as it is not possible to identify and remove the impact of SRT from disease progression.

As described in the CS, clinical advice received by the Company regarding disopyramide use in the UK suggested that disopyramide is rarely used for treatment of symptomatic obstructive HCM in clinical practice in England and Wales due to side-effects that many patients find difficult to tolerate, the phenomenon of tachyphylaxis (a loss of clinical benefit over time), and difficulty in accessing the drug. Although the management outlined by Sherrid *et al*., 2013[15] contrasts with this, disopyramide data from the US setting may not be generalisable to current UK clinical practice. The advice from UK clinicians was reflected in the structure of the cost-effectiveness model, with a small proportion of patients receiving disopyramide as a downstream therapy, who then escalate to SRT after 9 months.

Studies evaluating SRT

Of the included studies evaluating SRT identified (n = 143), ten provided ≥ 5 years follow-up for NYHA class outcomes. The longest (Stassano *et al*., 2004[18]) had mean follow-up of the ‘alive in good condition’ subgroup (n = 14/18) of 21.9 ± 1.7 years. All patients in this small study underwent limited left ventricular myotomy-myectomy and mitral valve replacement (note that, therefore, this study does not represent patients receiving alcohol septal ablation, who are expected to form ~50% SRT patients in

the UK). For the 'alive' sub-group, the pre-op, post-op and end of follow-up NYHA classes were 3.2 ± 0.8, 1.8 ± 1.0 and 2.1 ± 0.9, respectively. All six patients who received biological valves had a subsequent surgical intervention within 6.3–9.3 years after the initial operation, but no information was provided on pharmacological therapy or re-initiation of myectomy.[18]

The nine other SRT studies reporting a NYHA class outcome over ≥ 5 years of follow-up were:

- Burghardt *et al*., 2018[19] – Mean (±SD) follow-up: 64.5 (53.2) months
- De la Torre Hernandez *et al*., 2014[20] – Mean (IQR) follow-up: 12.3 (11–13.5) years
- Faber *et al*., 2008[21] – Mean (±SD) follow-up: 6 (4) years
- Fortunato de Cano *et al*., 2016[22] – Mean (±SD) follow-up: 8 (4) years
- Javidgonbadi *et al*., 2017[23] – Mean (IQR) follow-up: 11.8 (9.1) years
- Jensen *et al*., 2013[24] – Mean (±SD) follow-up: 8.4 (3.9) years
- Lapenna *et al*., 2020[25] – Mean (IQR) follow-up: 6.5 (2.7–9)
- Ommen *et al*., 2005[26] – Mean (±SD) follow-up: 6.2 (6) years
- Veselka *et al*., 2014[27] – Mean (IQR) follow-up: 5.1 (0.1–15.4) years

These studies were excluded from consideration in the model because, despite the long follow-up, transition matrices were unable to be calculated. This was due to a combination of factors including a lack of reporting of disease progression for all NYHA classes and lack of patient distribution across NHYA classes at both baseline and follow-up. Small sample size was an additional limitation. Therefore, estimating a quantitative figure for disease progression from Maron *et al.* was considered the most suitable approach.

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Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Cardiomyopathy UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Cardiomyopathy UK is the national charity for people affected by cardiomyopathy. The charity provides a range of support and information services, provides clinical education opportunities, raises awareness of the condition among the general public, facilitates research and advocates for improved access to quality treatment. The charity's database contains 18,000 individuals and there are around 150 active volunteers who facilitate support groups, provide peers support, advocate for improvements in health services, undertake fundraising activities and take on a range of other roles. The charity's trustees, the majority of whom have personal experience of the condition, are ultimately responsible for the charity and are supported by a professional staff team. The charity is funded by community fundraising (33%), donations and legacies (24%) charitable trusts and companies (29%) and the pharmaceutical industry (14%). Total income from the year January 2021-December 2021 was £945K
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	The charity received £60,000 from Bristol Myers Squibb in 2021. This income constituted 6.3% of total income in that year. Funding was for the charity's online national conference, website development, social media, and awareness activity. In 2021, the charity also received funding from; Novartis, £23,800 towards a national awareness campaign for cardiomyopathy Pfizer, £21,100 towards regional advocacy project Sanofi, £5,000 towards online medical education AstraZeneca, £10,000 towards online medical education Alnylam, £10,000 towards online medical education

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	1) The charity ran a focus group with 7 people with personal experience of obstructive hypertrophic cardiomyopathy. This group contained 3 male and 4 female participants. 2) The charity ran a national survey for people with all forms of cardiomyopathy **(n.507)** and the partners, carers and loved ones of people with cardiomyopathy **(n.62)** 3) As part of the national survey additional questions were put to individuals with obstructive hypertrophic cardiomyopathy **(n.63)** and people who support individuals with obstructive hypertrophic cardiomyopathy **(n 7)**. These questions directly reflected those asked in this consultation. 4) The charity shared a draft of this submission with our focus group and with individuals with obstructive hypertrophic cardiomyopathy who had completed our national survey **(n.33)** to ensure that statements made in this submission reflect their personal experiences. 5) Additional feedback was provided by the charity's team of helpline nurses who have direct daily contact with people with cardiomyopathy. These nurses have logged **(n.53)** calls relating to obstructive hypertrophic cardiomyopathy over the last year.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	81% of survey respondents said that their obstructive hypertrophic cardiomyopathy impacted their lives day to day. 27% described this impact as severe. Focus group and survey respondents indicated that the most impactful physical symptoms of the condition were breathlessness, exhaustion and the inability to carry out day to day tasks. Respondent told us; *"I would say that the grinding daily fatigue is the hardest of all the symptoms to cope with as it takes away much of the enjoyment of life"* *"I'm existing, not living, I've lost much of my mobility and have to rely on a walking stick, can't walk more than about 3 feet without having to stop due to the pain and breathlessness and sheer exhaustion, have had to have a wet room fitted as can't use a bath, can't lay down at all so have to sleep on my recliner sofa sitting bolt upright… I barely leave the house anymore except for appointments mainly. I want a life back"* Survey and focus group participants agreed that it was important to recognise that obstructive hypertrophic cardiomyopathy has a significant impact not just on physical health but also on an individual's mental health and their ability to cope day to day including their ability to maintain employment. Over 60% of survey respondents with obstructive hypertrophic cardiomyopathy said that over the last six months they have found it hard to cope with the mental health impact of their condition. They noted that the impact of obstructive hypertrophic cardiomyopathy on their sense of isolation and loneliness was especially hard to manage. Respondents highlighted that they struggled with the impact of the condition on their ability to exercise and undertake even light physical activity. Focus group respondents had, prior to the onset of symptoms, lived an active lifestyle and the loss of this lifestyle was seen as akin to a bereavement.

	"I have always been a very active person and used to take part in a lot of sports (running, swimming, cycling, rugby & football). Not being able to take part has massively impacted my confidence and social circles." *"The feeling of loss, being unable to do activities that were once easy is depressing and also some of the symptoms create feelings of fear and anxiety."* Survey respondents also noted the impact of obstructive hypertrophic cardiomyopathy on employment and managing to cope financially. 88% of respondents told us that they have sought advice on the benefits available to them. We also saw the impact of the condition from the partners perspective. One person described how obstructive hypertrophic cardiomyopathy impacted their partner; *"Her life has got smaller as the symptoms have worsened, now she can become breathless just getting up in the mornings, needing rests between showering and dressing. She remains fairly independent, I pick up the tasks she can't do, like making the bed and bending down, but her life is increasingly restricted by the condition"*
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	In our survey of people with obstructive hypertrophic cardiomyopathy, 28% had had a septal ablation, 15% a myectomy, 55% and ICD or pacemaker and 86% were on some form of medication. Our focus group participants also had experiences of myectomy and septal ablation. While individual reported negative experience of septal ablations, finding it to be a painful procedure and not always effective, feedback from people who had had a myectomy was especially negative. They told us about the pain experienced, the huge impact on their daily lives, and the support needed for recovery; *"It was two weeks in hospital. For the first week I was hallucinating really badly it was so painful to move or do anything. It has been a long slow road, it knocked the stuffing out of me but I am starting to recover*

	although I still have no energy on some days. I was told to expect a long and slow recovery … I am still struggling. One morning my sternum was hurting so badly I could not move, sneezing was unbelievably painful. If that could be prevented it would be a good thing." *"It was a ten-hour operation and I woke up two stone heavier as there were some complications. After two days I was thinking "why on earth did I do this" but a couple of weeks later I was feeling better. It was a lot of pain and a very bad few weeks…not something you would ever want to do if you did not have to."* *"Very painful, I remember the agony of opening a packet of crisps… It was six weeks of quite a lot of pain and a year to get back to normal"* Some respondents discussed the fact that they struggled with the decision-making process. They felt ill equipped to make such a significant decision and balance the potential risks and rewards. Participant felt that it was important that this additional burden was recognised. Overall, the current treatments for people who have not been helped by medication were seen as highly invasive, painful and requiring a great deal of support with the recovery process.
8. Is there an unmet need for patients with this condition?	Not all individuals with obstructive cardiomyopathy are suitable for myectomy or septal ablation either due to co-morbidities or unsuitability of the position of their obstruction for surgery. The most significant need identified by people with this condition was for non-invasive treatment options that would improve symptoms for individuals who have not benefitted from current medication.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	When we spoke to our focus group about this new technology all felt that the main advantage would be its potential to improve breathlessness and exhaustion without the need for myectomy or a septal ablation. This was seen as being hugely significant given the fear that people had of these procedures. It is important to note that in our national survey of people with cardiomyopathy respondents with obstructive hypertrophic cardiomyopathy had a younger age profile that respondents with other forms of cardiomyopathy including those with non-obstructive hypertrophic cardiomyopathy. We believe that this is because symptom onset for obstructive hypertrophic cardiomyopathy occurs earlier and is more impactful. Our respondents and focus group participants told us that prior to symptom onset they were living full and active lives and now faced a severely restricted life for a longer time. They saw this technology as a way to return to previous levels of activity and have more quality of life for a longer period.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Focus group participants were realistic about the treatment and recognise that it would not necessary solve all their issues. There was some reluctance to adding to burden of medication but all participants felt that this was vastly outweighed by the potential of avoiding surgical interventions.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	No
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None

Other issues	
13. Are there any other issues that you would like the committee to consider?	If approved, Mavacamten will be the first treatment designed specifically for people with cardiomyopathy. As such it is important that NICE considers the impact of the treatment not just in terms of an individual's quality of life but also the impact a new treatment would have on the wider cardiomyopathy community. We believe that approval is likely to increase recognition of the condition among the clinical community and the importance of providing a detailed diagnosis rather than just treating the symptoms as heart failure without considering aetiology. We also believe that approval will lead to an increased understanding of inherited cardiac conditions and the importance of taking a family history and considering genetic testing.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- This is a highly impactful condition effecting individual's physical and mental health and their ability to cope day to day
- Current medication does not provide symptom relief for all and myectomy and septal ablation are not suitable for all individuals
- Myectomy and septal ablation are invasive, painful and require a great deal of support with recovery
- Mavacamten is seen by the community as a major breakthrough as it presents an opportunity for non-invasive treatment
- Approval would also have a positive impact on the wider cardiomyopathy community

Thank you for your time.

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Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Cardiovascular Society**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence-base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**Professional body/learned society representing UK cardiologists and allied professionals involved in the delivery of cardiovascular healthcare. It is a UK-registered charity and according to accounts on the BCS website, derives the bulk of its income from membership fees, receipts from educational courses, publications, fellowships, conference fees, and grants.**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	BCS has received funding from Bristol Myers Squibb in the last 12 months. Not sure what the Principal Partners (PP) Sponsorship covers. November 2021: PP Sponsorship for 21/22 - £18,000.00 June 2022: BCS Conference Stand sale - £19,200.00 June 2022: BCS Conference 2022 Sponsored Symposia – £20,160.00 July 2002: PP Sponsorship for 22/23 - £12,000.00

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The primary aim is to relieve or ameliorate symptoms due to dynamic left ventricular outflow tract obstruction (LVOTO) in the setting of hypertrophic cardiomyopathy (which may manifest as exertional breathlessness, chest pain, pre-syncope, and reduced exercise tolerance), and thereby improve quality of life.

7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvement in functional status: change in New York Heart Association (NYHA) functional class by at least one unit. The NYHA scale is in principle easy to use in clinical practice but is not always accurately quantified,[1] so its use in heart failure clinical trials is gradually being superseded by the Kansas City Cardiomyopathy Questionnaire (KCCQ). For the latter, the overall score examines symptom frequency; symptom burden; symptom stability; physical limitations; social limitations; quality of life; and self-efficacy. The clinical summary score (KCCQ-CSS) focusses on symptom and physical/social functional scales. A change in score of 5 would denote a small but significant change; 10 would represent a moderate-to-large change; and 20 would represent a large-to-very large change in functional status.[2] I would consider an improvement of 10 or above relative to a comparator/placebo to be clinically relevant in this context. However, it is also important to consider the proportions of patients achieving each category of change relative to cost.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. About ~1/3 patients with hypertrophic cardiomyopathy have LVOTO at rest rising to ~2/3 if provocation testing is used to identify exertional gradients. In concert with lifestyle measures (weight loss where relevant, avoiding dehydration and excess alcohol) and avoidance/discontinuation of afterload reducing drugs, such patients if symptomatic with gradients >50mmHg can often be effectively managed with non-vasodilating beta blockade or for those with contraindications to this, a non-dihydropyridine calcium channel antagonists (verapamil/diltiazem). For those who remain symptomatic, disopyramide is usually introduced. For those who continue to have significant symptoms despite optimisation of medical therapy (NYHA class III+), septal reduction therapy is considered usually surgical, or in those who are not fit for surgery or express preference for this, alcohol septal ablation. However, a small number of patients who are NYHA III or worse despite medical therapy are either not fit for surgery or have anatomy that is not favourable for either invasive approach. In addition, many patients experience side effects with beta blockers or verapamil, limiting their up-titration and/or long-term use. For those on disopyramide, particularly at higher doses, anticholinergic side effects can be problematic (~7% of patients).[3] In addition, the latter can cause QT prolongation which can albeit rarely require discontinuation. Disopyramide is also contraindicated in patients with significant comorbid coronary disease. There is thus a subgroup of patients who might benefit from an alternative to existing therapies where the latter are either contraindicated, not tolerated, or prove ineffective. Furthermore, a large subset of patients are NYHA Class II and so are symptomatic but insufficiently so to warrant invasive therapy according to current guidelines in most settings.

What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	See Box 8 above. Patients with significant gradients should be managed in dedicated inherited cardiac conditions (ICC)/cardiomyopathy clinics with access to a high volume surgical gradient reduction therapy programme/alcohol septal ablation and associated multidisciplinary team or in concert with such services as part of an ICC Network.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	2014 ESC Guidelines on diagnosis and management of hypertrophic Cardiomyopathy.[4] 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients with Hypertrophic Cardiomyopathy.[5]
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes. There is reasonable accord and overlap in authorship for the above international treatment guidelines with respect to left ventricular outflow tract obstruction. Patients with a new diagnosis of hypertrophic cardiomyopathy should be referred to a dedicated ICC service (usually based in a tertiary care setting) where the diagnosis is confirmed; the need for family screening considered and initiated; genetic testing is considered/offered; risk stratification for sudden death is undertaken; and patients are evaluated for outflow tract obstruction. Follow up may continue in the tertiary centre or where the patient is stable and symptoms are controlled, this may continue in secondary care centres with referral back for those who develop complications. Patients with significant symptomatic outflow tract obstruction should continue follow up or be seen in a tertiary centre with experience in managing this condition pharmacologically, access to advanced imaging required to evaluate this further, and a programme of invasive/surgical reduction therapy. There is reasonable access to such a pathway throughout England but with some inevitable geographical variations in ease/speed of access.
• What impact would the technology have on the current pathway of care?	Patients previously living with NYHA Class II symptoms or worse or with side effects or tolerability issues with existing therapies may request re-referral back to a tertiary centre for consideration of mavacamten as an alternative approach to their current therapy but otherwise would not envisage much further change in current

	care pathways. If effective at ameliorating class III+ symptoms in patients who have failed other medical therapy, it could conceivably reduce the number of patients needing to proceed to surgery/invasive therapy.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Likely to be useful in patients who remain symptomatic despite maximum tolerated doses of beta blocker/non-dihydropyridine calcium channel antagonists *and* disopyramide (where this is not contraindicated and is tolerated) who have resting or provocable gradients >50mmHg and NYHA II or III symptoms.
• How does healthcare resource use differ between the technology and current care?	Mavacamten can cause a reduction in LV systolic function (as measured by ejection fraction). Its introduction and titration will therefore require serial echocardiography to guard against significant drops in LV function. To achieve efficient titration, additional outpatient appointments are likely to be required to optimise therapy and possibly biochemical assays/therapeutic drug monitoring (likely 3-4 visits based on MAVA-LTE protocol). This would likely lead to increased healthcare resource use in the short term.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist inherited cardiac conditions clinics with access to a regular multidisciplinary team meeting and invasive options for gradient reduction therapy.
• What investment is needed to introduce the technology? (For example, for	Likely to require dedicated initiation and up-titration clinics with access to frequent echocardiography, analogous to monitoring of LV function in breast cancer patients receiving trastuzumab, until a stable effective dose is reached. Patients who are NYHA Class II and managed in secondary care may request referral to a tertiary centre. Most secondary care centres are unlikely to have the volume of patients required to sustain a dedicated LVOT obstruction clinic nor the supporting imaging and specialist expertise needed. If therapeutic

facilities, equipment, or training.)	drug monitoring is needed for dose titration, then appropriate investment in laboratory assays and pharmacy support might also be needed.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Possibly – for patients who are symptomatic (NYHA Class II+) despite conventional therapy with beta blockade/calcium channel antagonists who cannot take or tolerate disopyramide. For those who are NYHA Class III, it is possible that treatment might avoid the need for surgery. It is important to note that the results of the VALOR-HCM study which examined this have only been published in abstract form at the American College of Cardiology 2022 meeting and that only a minority of the patients included in that study (20%) were on disopyramide (an existing effective and generic treatment) which might otherwise have been similarly effective.
• Do you expect the technology to increase length of life more than current care?	No. There is no evidence that either the novel therapy or existing pharmacotherapy prolongs life. Patients undergoing gradient reduction surgery for severe symptomatic LVOT obstruction appear to have improved survival compared to those treated medically in observational registry series, but it is important to note that this is non-randomised data and may simply reflect lower survival in those not eligible for surgery due to other comorbidities. Treatment is therefore directed at relief of symptoms rather than length of life.
• Do you expect the technology to increase health-related quality of life more than current care?	Not necessarily. The only fully published blinded randomised controlled trial data for mavacamten (EXPLORER-HCM)[6] compared the drug with placebo in patients treated with beta blockers or calcium channel antagonists (~96% in both arms). The mean heart rate in both groups was 63 beats per minute so the baseline therapy may not have been fully up-titrated but assuming all patients were on maximum tolerated therapy, there was a significant improvement in functional status as evaluated by NYHA class and KCCQ-CSS, although 25% of patients did not complete the latter questionnaire at both baseline and study end. However, patients were not allowed to be disopyramide (ostensibly owing to potential safety concerns at the time), which is an effective second line agent in current clinical use. It is therefore difficult to assess whether mavacamten would have been as effective as disopyramide or whether the magnitude of benefit seen would have been realised if patients had received disopyramide. In VALOR-HCM, 27% of patients on mavacamten had a 2-class improvement in NYHA class from III to I. The comparable data for surgery is often >70%. Of note, while ~3/4 patients did not need to proceed to surgery, in earlier studies of disopyramide, ~2/3 patients did not need to proceed to surgery,[3] in other words, the effect of

	mavacamten mirrors outcomes with an existing drug that has been used for decades. Ideally a head-to-head comparison is therefore needed to judge the added value of mavacamten over disopyramide (only 20% of patients in VALOR-HCM were on disopyramide).
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with advanced or "burned-out" hypertrophic cardiomyopathy who have LV impairment at baseline (given that mavacamten can cause LV dysfunction and LVEF<50% was a discontinuation criterion for the latter in EXPLORER-HCM).[6] ~90% of patients in EXPLORER-HCM were white so it is impossible to know whether there may be any differences in efficacy in different ethnic groups, particularly Afro-Caribbean populations where there is a high prevalence of comorbid hypertension which can contribute to hypertrophy. Patients with NYHA Class IV symptoms were excluded from EXPLORER-HCM but were studied in VALOR-HCM although the latter is yet to be published other than in abstract form. Only a proportion of patients with HCM have sarcomere mutations. Genetic data were collected in EXPLORER-HCM but are not reported. It may be that only those with truly sarcomeric HCM respond to mavacamten and those with non-sarcomeric disease may not (where speculatively the mechanism of LVOTO may be less driven by hypercontractility and more related to anatomical factors). This requires clarification.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed,	Slightly more difficult owing to the likely need for serial echocardiography during titration for safety monitoring as well as potential need for therapeutic drug monitoring assays and the additional clinic appointments needed for timely up-titration. This might be an issue for patients in terms of the time and expense and travel requirement to attend tertiary clinics. However, in my experience with other treatments including surgery, most patients are willing to accept this for the longer-term potential gain in functional status.

additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It is likely that a significant drop in LVEF to below 50% would be a discontinuation/down-titration criterion as per clinical trials along with QTc>500ms if induced by the drug. I would also envisage that patients who remain NYHA III or see no clinical improvement might have the drug discontinued in favour of invasive options if appropriate or feasible. Dose titration may need to be informed by therapeutic drug monitoring with drug assays as well as echocardiography to follow LV ejection fraction.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-	No - should be captured by appropriate QALY calculation. However, the RCT data thus far involves a relatively small number of patients and there is no longer-term follow up data to attest to sustained efficacy (and safety) over time, although there is also no reason to suspect diminution of efficacy over time and initial data from MAVA-LTE appear promising (reported in abstract form).

adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Mavacamten may offer a therapeutic option to severely symptomatic patients not eligible for invasive gradient reduction therapy (by surgical myectomy or alcohol septal ablation) either through comorbidities or unsuitable anatomy or those who express a preference for a non-invasive approach. It would also provide an option for the reasonable number of patients who experience limiting side effects with existing pharmacotherapy or who experience an incomplete symptomatic response to existing treatment. However, there really need to be trials of mavacamten in addition to dual therapy with a beta-blocker/calcium channel antagonist *and* disopyramide with a substantial number of patients on the latter. If mavacamten is to supplant the latter due to perhaps better tolerability and/or efficacy, there need to be head-to-head comparative trials to substantiate this.
• Is the technology a 'step-change' in the management of the condition?	It is a first-in-class therapy specifically designed to address LVOT obstruction in HCM as opposed to repurposing of existing drugs. In EXPLORER-HCM, the number needed to treat to achieve a large or very large change in KCCQ-CS score was ~5,[6,7] however, whether a similar magnitude of benefit would have been seen among responders had they been on disopyramide (a more cogent comparator) is unclear.
• Does the use of the technology address any particular unmet need of the patient population?	It potentially offers a genuinely new therapeutic option for patients who are ineligible for invasive therapy or who cannot tolerate existing medical therapy or achieve satisfactory quality of life with the latter due to side effects or incomplete efficacy.

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The long-term safety profile remains unclear but initial data from MAVA-LTE are encouraging. Patients with HCM are at increased risk of sudden death but thankfully this is an uncommon complication of the condition. There were no worrying signals of an increased risk of sudden death in clinical trials, but these had small sample sizes which would have been inadequately powered to detect any change in incidence. Careful pharmacovigilance will be essential as will all new agents. The only worrying safety signal from EXPLORER-HCM was the occurrence of two cases of stress cardiomyopathy in the active treatment arm (versus zero in the placebo arm), but this may have occurred by chance. Some patients did experience falls in left ventricular ejection fraction but almost all of these reversed with discontinuation, emphasising the need for careful monitoring with serial echocardiography. The long-term clinical significance of this is unclear but LV dysfunction is associated with increased sudden death risk in HCM, although the latter is likely to reflect advanced disease status and fibrosis burden rather than necessarily being related to reduced cardiac output *per se*. The main impact on quality of life would have been the need for additional echocardiography and visits to stop/down-titrate/reinitiate the drug.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	No. Most patients in the UK would be offered disopyramide if still symptomatic despite either a beta blocker or calcium channel antagonist. EXPLORER-HCM specifically excluded patients who were on disopyramide. In VALOR-HCM (published in abstract form), only ~20% of patients were on disopyramide.
• If not, how could the results be extrapolated to the UK setting?	The data would be relevant in patients who either have a contraindication to the use of disopyramide, who have not responded to the latter, or who experience intolerable side effects requiring discontinuation. While patients in EXPLORER-HCM were not offered disopyramide or did not enter the study after a run-in period on disopyramide (to demonstrate intolerance), for example, it might be reasonable to offer patients not eligible for it or who have had to discontinue it, mavacamten as an alternative based on the evidence from EXPLORER-HCM. VALOR-HCM included ~20% of patients on disopyramide but prospective randomised data are required to specifically look at the additive value of mavacamten over and above the latter (as opposed to exploratory subgroup analysis). There is no evidence mavacamten is more (or less) efficacious than disopyramide: a head-

	to-head RCT would be required to provide this and allow recommendation of the former in favour of the latter based on efficacy alone.
• What, in your view, are the most important outcomes, and were they measured in the trials?	As the purpose of treatment is to improve symptoms, functional status, and thereby quality of life, these outcome measures are the most meaningful. The primary endpoint in EXPLORER-HCM was a composite of improvement in NYHA class and/or peak VO_2 of 1.5ml/kg/min or if no change in NYHA class, 3.0 ml/kg/min (NB: 1 Metabolic Equivalent or MET, *i.e.*, energy used just while resting is: ~3.5ml/kg/min). The latter while more objective is more abstract from a patient perspective. KCCQ-CS score was also used but as a secondary endpoint but is arguably more relevant. Other relevant secondary endpoints included complete response to therapy defined as all gradients <30mmHg and NYHA class I status. These measures were assessed in the trials but not against disopyramide which would have been the most relevant comparator, particularly for a cohort of patients who were minimally symptomatic (>70% NYHA II).
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The relevance of change in peak VO_2 of the small magnitude described is unclear for this disease group. In the RESET-HCM study,[8] an improvement in peak VO_2 of 1.4ml/kg/min was achieved in HCM patients with just a moderate intensity exercise training programme (and with unclear long-term clinical significance).
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not as far as I am aware from the published or available literature.
19. Are you aware of any relevant evidence that	No.

might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA314]?	No.
21. How do data on real-world experience compare with the trial data?	N/A
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Nothing specific to mavacamten, however, I would note the lack of diversity in the study population enrolled in EXPLORER-HCM, and the relatively older age (mean age 58) of the study cohort relative to the patients we often encounter in clinical practice.

22b. Consider whether these issues are different from issues with current care and why.	This is sadly not different from current care. Much of the limited evidence-base in this area has been derived from studies in which trial participants were not necessarily representative of the diversity seen among those affected by hypertrophic cardiomyopathy.
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Mavacamten produces modest improvements in objective measures of exercise capacity (peak VO_2).
- Clinical trials have not compared mavacamten with disopyramide which would represent the most cogent comparator treatment. The magnitude of benefit or added value relative to the latter agent, which is the current standard of care, is therefore unclear.
- The number needed to treat to see a large or very large improvement in quality of life with mavacamten versus placebo was only ~5 (based on KCCQ scores) but magnitude of benefit that might have been seen relative to disopyramide unclear.
- Mavacamten may represent a valuable option for treating symptomatic patients with LVOT obstruction who cannot take, tolerate, or do not respond to existing pharmacotherapy (including disopyramide), particularly those who are NYHA class II and so usually not symptomatic enough to warrant surgery.
- Adoption of mavacamten would require additional resource/investment in echocardiography (for surveillance of LV ejection fraction during therapy) and possibly investment in therapeutic drug monitoring if assays of drug levels are required for effective titration. There would also need to be additional resource/clinic slots available to assess suitability and to initiate/up-titrate therapy. The expertise required for this, volume of patients, imaging support, and supporting MDTs are likely to be found in tertiary inherited cardiac conditions clinics.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

NHS organisation submission (CCG and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**On behalf of NHS England**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? ☐ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☑ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are consensus guidelines available from both the ESC (2014) and the ACC/AHA (latest version 2020) to guide the treatment of all patients with hypertrophic cardiomyopathy (HCM). Within these documents are separate sections specific to the management of patients with obstructive HCM.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Although HCM is a relatively common condition affecting approximately 1 in 500 of the adult population, not all UK patients with this condition are diagnosed and/or under regular follow up in centres with expertise in inherited cardiac conditions / heart muscle disease. There is broad agreement that assessing these patients is complex and requires a comprehensive and detailed work up including a number of specialised investigations (including but not limited to resting and exercise echocardiography, cardiac MRI, cardiac biomarkers and cardiopulmonary exercise testing). A focused history is important; it is noteworthy that patient symptoms are often *not* proportional to the degree of obstruction (as defined by the peak left ventricular outflow tract gradient). There are relatively few experienced centres in the UK currently offering alcohol septal ablation and even fewer with expertise in surgical septal myectomy. Septal reduction therapies, SRT (i.e. surgical septal myectomy and alcohol septal ablation), when performed by experienced HCM teams at dedicated centres have been shown to improve symptoms and functional status but there are still no RCT data to support improved mortality. Indeed, it is important to stress to patients that the primary goal of treatment with SRT is to improve symptoms; there is insufficient evidence to recommend SRT to improve patient survival. This is not always widely appreciated by clinicians and as a result, their patients. Patients with symptomatic obstructive HCM might benefit from the development of wider UK networks to facilitate MDT discussion which may improve access to specialised treatments such as mavacamten and SRT.
8. What impact would the technology have on the current pathway of care?	Mavacamten is an important drug. There are limited pharmacotherapies (beta-blockers, calcium channel blockers and disopyramide) for HCM patients with obstructive symptoms and a substantial proportion of

	patients cannot tolerate therapeutic doses of these agents. In particular, disopyramide is difficult to access due to supply issues and often tends to be poorly tolerated. Based on the EXPLORER-LTE data presented at ACC (3/4/2022) mavacamten will no doubt reduce the number of patients requiring or indeed, wanting to pursue SRT. This medicine should in my opinion be offered as a second-line agent (i.e. after either a beta-blocker / calcium channel blocker) if the patient remains symptomatic (as per the entry criteria in the trial). Many patients are reluctant to travel long distances for assessment in expert centres with experience in surgical myectomy. There is a potential risk that widespread use of mavacamten could lead to less timely referrals to such centres with dedicated expertise in SRT. All patients who could benefit from mavacamten +/- SRT merit an early discussion in an MDT setting, ideally via the development of a UK HCM network.
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	Mavacamten is not currently available.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, the same criteria which used for study inclusion in the EXPLORER-HCM trial should be applied to patients with obstructive HCM in NHS clinical practice.
• How does healthcare resource use differ	

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist ICC/HCM clinics or in secondary care following input from a dedicated tertiary ICC / HCM service (potentially via remote MDT through establishment of a UK network).
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Although not a specific requirement for the introduction of this drug, to ensure improved access to expert care in ICC, there needs to be an increase in appointments of dedicated ICC Consultants, IT and admin support to develop a UK network/registry, increase in echo and physiology provision as well as ICC nursing support.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	Data from a long-term extension study with follow up out to a median 62 weeks suggests the drug is well tolerated, with no signal for significant treatment-related adverse events. Starting rules should follow study entry criteria (>=18 yr age, LVOT gradient >=50mmHg, LVEF >=55%, NYHA II-III).
11. What is the outcome of any evaluations or audits of the use of the technology?	The EXPLORER-HCM study has been published at ACC 2022 (Florian Rader); Spertus et al. Lancet 2021; 397:2467-75; Olivotto et al Lancet 2020; 396:759-69. Compared with placebo, this medicine improves functional capacity and health status and was well tolerated by trial participants with a sustained improvement in biomarkers and LVOT gradient to 48 weeks.
Equality	

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	ICC services are not evenly spread across the country, with fewer centres in the North which might impact patients' ability to access this important non-invasive therapy for symptomatic obstructive HCM.
12b. Consider whether these issues are different from issues with current care and why.	The above issue is not specific to mavacamten but broadly applies to all ICC care in the UK.

Thank you for your time.

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Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Professional organisation submission

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You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Norfolk & Norwich University Hospital**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	√ an employee or representative of a healthcare professional organisation that represents clinicians? √ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**Norfolk & Norwich University Hospital NHS Trust** NHS England Department of Health
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The product Mavacamten is a first in class inhibitor of cardiac myosin ATPase. It aims to reduce actin – myosin cross bridge formation and thereby reduce cardiac hyper contractility and improves myocardial energetics in Hypertrophic Cardiomyopathy – an inherited cardiac condition, characterised by left ventricular hypertrophy, and with features of hyper contractility and dynamic left ventricular outflow tract obstruction. The aim of this treatment is to reduce symptoms, by decreasing the left ventricular outflow tract obstruction and to improve NYHA classification.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Improvement of 1 NYHA class. Reduction of LVOTO by 30mmhg. Significant improvement in patient symptom classification / questionnaire.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Most definitely. There are currently no disease specific medications to treat HCM and those that are currently used are often ineffective or poorly tolerated. Mavacamten is a first in class, disease specific, medical therapy. Currently, if medical therapy fails to improve symptoms, the next steps are invasive interventions, which require specific expertise which is not widely available and many patient do not have access to.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Patients are usually managed under a local or regional ICC centre. Patients with symptomatic LVOTO will usually receive monotherapy with a Beta blocker or Calcium channel blocker or one of these is combined with Disopyramide. If patients fail to improve with medical therapy, then they are assessed and considered for septal reduction techniques, with either percutaneous alcohol septal ablation or by surgical myomectomy. Both of these procedures are undertaken in a limited number of units in the UK, so access can be limited and waiting times prolonged.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	ESC guidelines on the diagnosis and management of HCM 2014
• Is the pathway of care well defined? Does it vary or are there differences of opinion	There is likely to be differences in the pathway of care, dependent on the ICC centre, the individual expert and their views and whether specific interventions and treatments are readily available at the centre, or whether patients have to be referred out to another unit. Compared to a number of cardiovascular conditions, the pathways of care for HCM are not so well defined.

between professionals across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	This new treatment, would be a further option for maximising medical management of symptomatic LVOTO in HCM. It would be a step prior to consideration of SRT (septal reduction techniques) and for some patients, if effective, may prevent the need for them to have invasive treatments.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This is the first disease specific treatment for HCM, so will be a new option for disease management. Patient assessment for this treatment, will involve standard care and investigations, to determine if there is significant symptomatic LVOTO at rest, or post exercise. Conventionally, these patients may be treated with beta blockers, calcium channel blockers or a combination of one of these groups with Disopyramide. Mavacamten may be used in combination with beta blockers or calcium channel blockers and in the Explorer-HCM trial, patients on a Mavacamten combination demonstrated significant symptomatic benefits.
• How does healthcare resource use differ between the technology and current care?	Potentially with this new treatment, some patients may avoid the need for invasive / surgical management to reduce symptoms
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist ICC clinics.
• What investment is needed to introduce the technology? (For	During the Explorer HCM trial patients were followed up every 2-4 weeks over a 30 week period with ECGs, Echos and Mavacamten plasma concentration. Additionally, at screening and week 30 a CPET and exercise echo were performed. If clinical use in the real world required the same protocol then this would be really challenging to deliver in the current NHS model. Particularly the need for frequent transthoracic

example, for facilities, equipment, or training.)	echos would be really problematic, with many trusts having a 3-4 month waiting list for echo and there is a national shortage of trained echo physiologists, which is an area of concern.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	I think mortality benefits are as yet uncertain.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The use will be specifically for a subgroup of patients with HCM who have symptomatic LVOTO, with obstructive gradients meeting a predefined level of severity.

The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	More difficult to use than the current medical treatments, however the current medical treatments are not disease specific and are often ineffective or poorly tolerated. During the Explorer HCM trial patients were followed up every 2-4 weeks over a 30 week period with ECGs, Echos and Mavacamten plasma concentration. Additionally at screening and week 30 a CPET and exercise echo were performed. If clinical use in the real world required the same protocol then this would be really challenging to deliver in the current NHS model. Particularly the need for frequent transthoracic echos would be really problematic, with many trusts having a 3-4 month waiting list for echo and there is a national shortage of trained echo physiologists, which is an area of concern.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I suspect, that NICE will recommend continuing Mavacamten only if certain parameters are met, like in the Explorer trial, such as a decrease in LVOT gradients by 30mmhg, or an increase in VO2 max, by a certain proportion.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Mavacamten offers a disease specific treatment for symptomatic LVOTO. In the trials, it demonstrated significant quantitative and qualitative benefits. It may decrease the need for invasive septal reduction techniques, which have long waiting lists, as a result of the expertise required and a limited number of centres performing these niche procedures.
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any	Improved medical management of symptoms.

particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Overall serious cardiac side effect rates were low in the trials, though by its mode of action Mavacamten can cause a transient decrease in LVEF, hence the need for echocardiographic surveillance.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, I believe so.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Yes. Important to measure improvements in LVOT gradients, symptomatic class, functional performance and health status, all of which the Explorer HCM trial did.
• If surrogate outcome measures were used, do they adequately predict	

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA314]?	No
21. How do data on real-world experience compare with the trial data?	

Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	
23. In up to 5 bullet points, please summarise the key messages of your submission. • First disease specific therapy for symptomatic LVOTO in HCM. • Significant quantitative and qualitative benefits, above current medical therapy. • May reduce the need for invasive and difficult to access interventional and surgical therapies. • Low risk of side effects. • May be difficult to implement in the NHS, due to the intensive investigations required during the monitoring phase of drug initiation and up titration.	

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**St George's University Hospitals NHS Foundation Trust, Blackshaw Road, Tooting, London, SW17 0QT, United Kingdom**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**St George's Hospital is a major acute hospital that offers very specialist care for the most complex of injuries and illnesses, including specialist cardiac care. The Inherited Cardiovascular Condition service (ICC) at St George's is one of the largest in the country and offers specialised care for the diagnosis, symptoms evaluation and management of patients and families affected with inherited cardiovascular conditions. We are a multidisciplinary team working across South-West London receiving supra-regional referrals from Surrey and the UK. The Trust is funded by the Government and charitable funds.**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No, the Trust has not received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months.**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve symptoms and functional capacity relating to dynamic left ventricular outflow tract obstruction.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Reduction in symptoms relating to left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy. Response to therapy is usually determined by echocardiographic assessment of outflow tract gradient in conjunction with assessment of patient symptoms.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, existing pharmacological methods are limited by intolerance to beta-blockers and calcium channel antagonists (e.g. symptomatic bradycardia), and QTc prolongation in patients managed with disopyramide. These drugs are not effective in reducing left ventricular outflow tract obstruction in a significant number of patients, many of whom may not be suitable for a surgical procedure.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Pharmacological management with beta-blockers, calcium channel antagonists, disopyramide, transcoronary septal ablation or surgical myectomy, where indicated.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, European Society of Cardiology guidelines for management of patients with Hypertrophic Cardiomyopathy.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	Existing international guidelines are followed with physician discretion according to individual patient characteristics.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Reduced the need for invasive procedures. Alternative treatment option to improve health status of patients.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This technology will be new to the NHS clinical practice and will be used as a clinical trial drug on eligible patients.
• How does healthcare resource use differ between the technology and current care?	Patients currently do not have access to innovative treatments including this technology.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This will be used in a secondary care setting.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Staff training in using this technology and also the Trust needs to be reimbursed for the use of the technology and assessment of its efficacy in reducing left ventricular outflow obstruction and improving functional capacity.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, this technology is expected to have clinically significant benefits in treating patients with obstructive hypertrophic cardiomyopathy.
• Do you expect the technology to increase length of life more than current care?	There is an expectancy that mavacamten will contribute to increasing length of life as it targets the underlying pathophysiology of obstructive hypertrophic cardiomyopathy and may reduce the incidence of atrial fibrillation and heart failure.
• Do you expect the technology to increase health-related quality of life more than current care?	Recent research publications have provided supporting evidence that mavacamten has had a positive effect in improving patients' quality of life in comparison to the current care.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology will be most effective in treating patients diagnosed with obstructive cardiomyopathy.
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	This treatment can be easily integrated into the current patients' care pathway, however additional close monitoring will be required by the treating cardiologist as this a trial drug.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
15. Do you consider that the use of the technology will result in any substantial health-	No

related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. It may provide a non-invasive method of ameliorating left ventricular outflow obstruction in patients who are refractory to current medical therapies such as beta blockers, calcium channel antagonists and disopyramide.
• Is the technology a 'step-change' in the management of the condition?	Yes, currently the pharmacological treatment available for hypertrophic cardiomyopathy is inadequate and some drugs are poorly tolerated by patients hence their condition is not managed appropriately.
• Does the use of the technology address any particular unmet need of the patient population?	Up to 10% of patients with HCM have dynamic left ventricular outflow obstruction that is not easily treated with pharmacological agents.

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The current side effects are no different from the current treatment available.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	No, not currently available in the UK, has FDA approval.
• If not, how could the results be extrapolated to the UK setting?	The results could be utilised to form best treatment options.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes will improvement to current treatment available.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable.

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA314]?	No
21. How do data on real-world experience compare with the trial data?	Still currently under investigations.
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No will be offered to all patients suitable for this treatment.
22b. Consider whether these issues are different from issues with current care and why.	No equality issues identified.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Left ventricular outflow obstruction affects 30-50% patients with HCM.
- Current pharmacological therapies cannot ameliorate obstruction sufficiently to alleviate symptoms and are not always tolerated well due to fatigue, low blood pressure or anti-cholinergic effects of disopyramide.
- 5- 10% patients require surgical intervention which may be preventable with mavacamten.
- Mavacamten has the potential of improving functional capacity and quality of life in a significant proportion of patients with HCM.

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External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy (ID3928)

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
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We thank the following for providing expert clinical advice to the project team and for reading and commenting on a draft of the report:

- Professor Robert Cooper, Consultant Cardiologist, Liverpool Heart and Chest Hospital NHS Foundation Trust.
- Dr John Rawlins, Consultant Interventional Cardiologist, Southampton University Hospitals NHS Foundation Trust.

- Professor Hugh Watkins, Radcliffe Professor of Medicine, Radcliffe Department of Medicine, University of Oxford.

We also thank

- Lorna Hazell, Southampton Health Technology Assessments Centre (SHTAC), for reading and commenting on a draft of this report for quality assurance.

Declared competing interests of the authors and advisors

The authors declare none.

Professor Cooper has received funding to take part in independent virtual expert panels in the past year organised by Bristol-Myers Squibb (BMS; manufacturer of mavacamten) and one face to face panel meeting organised by a third party on behalf of BMS. Professor Cooper was not informed of the results of these panels nor whether BMS would use any information from these panels in their submission to NICE; he confirms that he did not work on any aspects of the company submission to NICE. Professor Cooper is the national principal investigator for the SEQUOIA trial which started in the UK in July 2022. This is a randomised controlled trial of aficamten, a myosin inhibitor, not manufactured by BMS, with very similar properties to mavacamten. This trial is due to run until late 2023 with results anticipated to be available late 2024.

Dr Rawlins received funding to participate in two independent expert panels during the past 6 months that were organised by a third-party company on behalf of BMS. He was not informed of the results of these panels nor whether BMS would use any information from these panels in their submission to NICE. One panel (approximately 20 experts in hypertrophic cardiomyopathy) used the Delphi method to explore current best practice for patients with hypertrophic cardiomyopathy. The other panel was an independent advisory board that commented on the accuracy of information in materials relating to the licence application for mavacamten. Dr Rawlins confirms that he did not work on any aspects of the company submission to NICE.

Professor Watkins declares no financial relationships with BMS or the companies marketing the comparator therapies listed in the NICE scope. He has a paid consultancy contract with Cytokinetics Inc, a company which is in early-stage trials with aficamten. He also leads a research team, called CureHeart, which has been awarded the British Heart Foundation ‘Big Beat Challenge’ award (a grand challenge award) and this team includes patient charities (including Cardiomyopathy UK) which will have an interest in the outcome of the appraisal.

The CureHeart team worked with BMS in the preparation of the bid, but BMS are not participants in the award or signatories to the research agreement. The goal of this programme is to create curative genetic therapies for hypertrophic cardiomyopathy. Professor Watkins will be co-supervisor of a research fellow recently funded on the BMS-Oxford Fellowship Programme.

Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Lord J, Woods LE, Takahashi MT, Frampton G. Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy: A Single Technology Appraisal. Southampton Health Technology Assessments Centre, 2022.

Contributions of authors

Joanne Lord critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Lois Woods critically appraised the company searches and the clinical effectiveness systematic review, and drafted the report; Marcia Tomie Takahashi critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Geoff Frampton critically appraised the clinical effectiveness systematic review, drafted the report and is the project co-ordinator and guarantor.

[redacted]

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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
AHA	American Heart Association
ASA	Alcohol septal ablation
BB	Beta blocker
BMS	Bristol-Myers Squibb
BNF	British National Formulary
CCB	Calcium channel blocker
CI	Confidence interval
CMR	Cardiovascular Magnetic Resonance
CPET	Cardiopulmonary exercise testing
CPRD	Clinical Practice Research Datalink
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CTAF	California Technology Assessment Forum
DSA	Deterministic sensitivity analysis
EAG	Evidence Assessment Group
Echo	Echocardiogram
EHR	Electronic healthcare record
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
ESC	European Society of Cardiology
FDA	US Food and Drug Administration
HCM	Hypertrophic cardiomyopathy
HCMSQ(-SoB)	Hypertrophic Cardiomyopathy Symptom Questionnaire (-Shortness of Breath)
HCRU	Healthcare resource use
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ISS	Integrated safety summary

ITT	Intent to treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LOCF	Last observation carried forward
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
LVOTO	Left ventricular outflow tract obstruction
LVWT	Left ventricular wall thickness
MCT	Meaningful change threshold
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NOS	Newcastle-Ottawa Scale
NYHA	New York Heart Association
PH	Proportional hazards
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
REMS	Risk evaluation and mitigation strategy
ROBINS-I	Risk Of Bias In Non-randomised Studies of Interventions
RR	Relative risk
RWE	Real-world evidence
SAE	Serious adverse event
SD	Standard deviation
SHaRe	Sarcomeric Human Cardiomyopathy Registry
SLR	Systematic literature review
SmPC	Summary of product characteristics
SRT	Septal reduction therapy
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TP	Transition probability
UK	United Kingdom
US	United States

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues

Issue number	Headline description	EAG report sections
1	Exclusion of disopyramide as a comparator	2.3.2
2	Uncertain efficacy of mavacamten in patients without a sarcomere mutation	2.3.4
3	Post-authorisation safety monitoring of mavacamten	3.7
4	Imbalance in follow up duration for transition probabilities	4.2.3.1
5	Long-term rates of progression	4.2.3.2
6	Effect of treatments on mortality	4.2.8
NYHA: New York Heart Association		

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An incremental cost effectiveness ratio (ICER) is the ratio of the extra cost for every QALY gained.

Table 2 Base case results with Patient Access Scheme (PAS) price discount for mavacamten

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/ QALY)
BB/CCB monotherapy	[redacted]	[redacted]	[redacted]			
Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,953
ICER: incremental cost-effectiveness ratio; Inc: incremental; LYG: life years gained; PAS Patient access scheme; QALY: quality-adjusted life year						

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Exclusion of disopyramide as a comparator

Report section	EAG rationale
Description of issue and why the EAG has identified it as important	Disopyramide (alone or in combination with either beta-blockers or non-dihydropyridine calcium blockers) is a comparator (as part of standard care) in the NICE scope. However, the company argue that disopyramide is not relevant as it is rarely used in clinical practice, for several reasons (Table 4 below). Two of the EAG's three clinical experts agreed that it is reasonable to exclude disopyramide as a comparator due to its limited use in practice; however, one expert stated that disopyramide is used as standard care, particularly in large centres. Furthermore, the Consultee Submission from the British Cardiovascular Society (BCS) states that "most patients in the UK would be offered disopyramide if still symptomatic despite either a beta blocker or calcium channel antagonist" and emphasises its relevance as a cogent comparator to mavacamten. In an expert elicitation exercise conducted by the company it was noted that "patients are generally given disopyramide in addition to calcium channel blockers and beta blockers ahead of septal reduction therapy" (although as noted in CS section B.1.3.2.4 the majority of obstructive HCM patients do not receive SRT) and "all patients will be on combination therapy (such as disopyramide) by New York Heart Association (NYHA) class III and IV" (CS Appendix O). In contrast, the NHS England Consultee Submission states that disopyramide is difficult to access due to supply issues. It is important that the economic model reflects standard clinical practice as accurately as possible.
What alternative approach has the EAG suggested?	Further clarification on the extent to which disopyramide is used to treat obstructive hypertrophic cardiomyopathy (HCM) in the NHS would be helpful.

What is the expected effect on the cost-effectiveness estimates?	The company's model includes disopyramide as a subsequent treatment option, only used for escalation of treatment after standard monotherapy with a beta-blocker or calcium channel blocker. The impact of including disopyramide as a comparator is difficult to assess due to the lack of comparative effectiveness evidence.
What additional evidence or analyses might help to resolve this key issue?	We are not aware of any data (e.g. audits) that would clarify this issue other than interim data cited by the company from the Clinical Practice Research Datalink (CPRD) GOLD and Aurum datasets (which collected data from clinical practices and electronic patient records respectively) in support of the extent of use of disopyramide in patients with obstructive HCM in England (CS sections B.1.3.2.3.3 and B.2.12.4 and CS clarification response A5). Full publication of these datasets is expected at the end of 2022 and might provide more up-to-date information on disopyramide use (subject to any limitations in the format of the collected data). Consultation with additional clinical experts may also be helpful.

Issue 2 Efficacy of mavacamten in patients with or without a sarcomere mutation

Report section	EAG rationale
Description of issue and why the EAG has identified it as important	Although the NICE scope does not specify any subgroups, the efficacy of mavacamten could plausibly differ between patients who have a sarcomere mutation and those who do not. The British Cardiovascular Society Consultee Submission states that "It may be that only those with truly sarcomeric HCM respond to mavacamten and those with non-sarcomeric disease may not (where speculatively the mechanism of LVOTO may be less driven by hypercontractility and more related to anatomical factors). This requires clarification." This may be relevant to interpreting the efficacy results of the EXPLORER-HCM trial where we note that 63% of patients receiving mavacamten did not achieve the primary outcome (section 3.6.1 below) and we also note that the majority of patients in EXPLORER-HCM did not have a sarcomere mutation (pathogenic or likely pathogenic genetic mutation) (CS Table 8).
What alternative approach has the EAG suggested?	According to CS Table 8, genetic mutations were analysed in EXPLORER-HCM, with the subgroup sizes for pathogenic mutations being n=28 for the mavacamten group and n=22 for the placebo group. Analysis of the pathogenic mutation subgroups for the primary outcome is reported in CS Figure 19 with wide confidence intervals due to the small sample sizes.
What is the expected effect on the cost-	If there is evidence of a greater clinical benefit if mavacamten use is limited to the subgroup with a sarcomere mutation, this is

effectiveness estimates?	likely to translate to a lower ICER in that subgroup (and higher ICER in the subgroup without a mutation).
What additional evidence or analyses might help to resolve this key issue?	We request that the company conduct a cost-effectiveness analysis to explore the relationship between HCM genetic test results and cost effectiveness. See section 4.2.3.1 for a suggestion on how transition probabilities for the model could be estimated for the small subgroup samples.

Issue 3 Post-authorisation safety monitoring of mavacamten

Report section	EAG rationale
Description of issue and why the EAG has identified it as important	Post-authorisation safety monitoring of patients with obstructive HCM was identified as a critical issue by the US Food and Drug Administration (FDA) in their appraisal of mavacamten. The EAG and our clinical experts are uncertain whether an adequate level of safety monitoring can be applied in the NHS, given current resource pressures (e.g. staff shortages) and the highly skilled nature of the monitoring required. For example, the Norfolk and Norwich NHS Consultee Submission notes "many trusts having a 3-4 month waiting list for echo and there is a national shortage of trained echo physiologists, which is an area of concern".
What alternative approach has the EAG suggested?	The EAG preferred assumption includes estimates of the cost of monitoring as per the revised draft Summary of Product Characteristics (SmPC), and we test uncertainty around the costs of monitoring in scenario analysis. But this does still leave the question of whether the required degree of monitoring is feasible for the NHS.
What is the expected effect on the cost-effectiveness estimates?	This would have a cost impact if more intense monitoring would be expected for longer. The company assume at least [redacted] outpatient visits with an echocardiogram at each visit in the first year after initiation of mavacamten, with no additional monitoring from year 2 onwards. [redacted] EAG analysis indicates that with enhanced monitoring, the ICER increases from £29,953 in the company's revised base case to £36,840 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Further clinical expert opinion may help to clarify whether the required intensity of monitoring to ensure safe use of mavacamten can be achieved in the NHS.

1.4 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 4 Imbalance in trial follow up duration for calculation of transition probabilities

Report section	EAG rationale
Description of issue and why the EAG has identified it as important	In their base case analysis, the company use post-trial data to estimate transition probabilities between NYHA classes from week 30 up to week 46 in the comparator arm; but assume no change in NYHA class over this period in the intervention arm. We consider that the use of different methods to model transition probabilities between weeks 30 and 46 in the mavacamten and BB/CCB monotherapy arms is likely to have introduced bias. This analysis uses control arm data from the 30-week end of trial and 38-week end of study assessments of the EXPLORER-HCM randomised controlled trial, and the baseline assessment from the EXPLORER-LTE open label follow on study (referred to as week 46). Over this period, there was a deterioration in NYHA class in patients randomised to the control arm in the trial, which was then held constant over the remaining time horizon in the company's base case. In contrast, NYHA class was assumed to hold constant from 30 weeks in the mavacamten arm. Given the lack of comparative data, loss of blinding and uncertainty due to small numbers of some transition events, we consider the data for weeks 30-46 to be unreliable.
What alternative approach has the EAG suggested?	We suggest that the same method should be used to estimate NYHA class transitions in both arms: with transition probabilities prior to 30 weeks estimated from EXPLORER-HCM data, followed by assumptions regarding long-term progression.
What is the expected effect on the cost-effectiveness estimates?	The EAG estimated that using 30-week trial data for both arms increased the ICER for the company's revised base case from £29,953 to £45,256 per QALY gained
What additional evidence or analyses might help to resolve this key issue?	We do not think that further evidence or analysis is necessary.

Issue 5 Long-term rates of progression

Report section	EAG rationale
Description of issue and why the EAG has identified it as important	We agree with the argument in the Company Addendum that gradual progressive deterioration of NYHA class is likely, on average, for people with obstructive HCM. Although, independent clinical experts advising the EAG have noted that progression in obstructive HCM is complex, changes over time and varies with age and between patient subgroups. There is uncertainty over the average rate of increase in NYHA class, and over whether and how this is likely to differ between treatments. These parameters are required to model the long-term outcomes and treatment effects. The company based their scenario analyses on an estimated rate of NYHA progression (4.55% per year) from a prospective cohort study by Maron et al. 2016 (Company Addendum 3.2.1).[1] This study was identified from targeted searches, so it is not known if there are other sources of evidence on this issue. The company report that a systematic literature review to address this evidence gap has been initiated, and that results are expected in early 2023 (Company Addendum clarification response B1).
What alternative approach has the EAG suggested?	We agree with use the company's base case assumption of an equal rate of NYHA class progression after week 30 with all treatments. However, further evidence regarding the rate of progression could help to reduce uncertainty.
What is the expected effect on the cost-effectiveness estimates?	The model results are highly sensitive to a scenario based on the 4.55% progression rate estimated from the Maron et al. study: the company's ICER reduced from the base case value of £29,953 to less than £20,000 per QALY gained in both of their scenarios including NYHA class progression.
What additional evidence or analyses might help to resolve this key issue?	Evidence from the company's new prognostic systematic literature review and from other stakeholders regarding the long-term rate of progression of NYHA class for people with obstructive HCM, and whether this differs between treatments.

Issue 6 Effect of treatments on mortality

Report section	EAG rationale
Description of issue and why the EAG has identified it as important	The company model all-cause mortality using estimates of an association between NYHA class and mortality derived from analyses of real-world data (US electronic health record data, SHaRe registry).[2 3] However, this approach has been criticised on the basis that the observed association between NYHA class and mortality is not necessarily causal, and that there is currently no evidence that treatments that reduce the symptoms of obstructive HCM have any mortality benefit. In the absence of causal evidence, mortality benefits have not traditionally been ascribed to other treatments for obstructive HCM. Given the lack of direct evidence for a beneficial effect of treatment on mortality, and the lack of evidence that the observed association between NYHA class and mortality is causal, it is not clear whether mortality effects should be included in the model.
What alternative approach has the EAG suggested?	We report two scenarios which remove the assumption that the observed association between NYHA class and mortality is causal and that treatments for obstructive HCM, including mavacamten, have an effect on survival.
What is the expected effect on the cost-effectiveness estimates?	The model is highly sensitive to uncertainties in the magnitude and nature of the relationship between NYHA class and mortality. In particular, the EAG scenarios that removed the assumption of treatment effects on survival increased the company's base case ICER from £29,953 to £49,022 and £52,282 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Further expert opinion and evidence regarding the plausibility of the assumption that treatments for obstructive HCM have an impact on survival. Evidence regarding life expectancy for people with obstructive HCM, which could be used to validate the model outcomes, including survival.

1.5 Summary of EAG's preferred assumptions and resulting ICERs

Based on the EAG critique of the company's model (discussed in section 4), we have identified four key aspects of the company base case with which we disagree. Our preferred model assumptions are the following:

1 No use of post-trial data to inform NYHA transitions for the comparator arm

2 Utilities should be capped at UK general population norms for age

3 Long-term progression rate for all treatments (4.55%)

4 Enhanced monitoring for mavacamten which results in higher costs

The ICER obtained using the EAG's preferred assumptions (Table 3) increases from £29,953 to £41,328 per QALY.

Table 3 Cumulative cost-effectiveness results for EAG's preferred model assumptions (discounted, PAS price for mavacamten)

Scenario	Incremental cost	Incremental QALYs	ICER (£/QALY)
Company's revised base case	[redacted]	[redacted]	£29,953
+ NYHA transition estimates from trial for 30 weeks only in both arms	[redacted]	[redacted]	£45,256
+ Utilities capped at UK population norms	[redacted]	[redacted]	£49,896
+ Long-term NYHA class progression (4.55% per year)	[redacted]	[redacted]	£33,547
+ Enhanced monitoring for mavacamten	[redacted]	[redacted]	£41,328
EAG's preferred base case	[redacted]	[redacted]	£41,328

Modelling errors identified and corrected by the company and EAG are described in section 5.2. For further details of the exploratory and sensitivity analyses done by the EAG, see section 6.1 and 6.3.

Brief overview of EAG conclusions and uncertainties, see section 6.4.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Bristol-Myers Squibb on the clinical effectiveness and cost effectiveness of mavacamten [CAMZYOS®] for treating adult patients with symptomatic obstructive hypertrophic cardiomyopathy (New York Heart Association [NYHA] classes II-III). It identifies the strengths and weaknesses of the CS. Clinical experts were consulted to advise the evidence assessment group (EAG) and to help inform this report.

The CS was received by the EAG from the company on 30th June 2022. Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 14th July 2022. Responses from the company via NICE were received by the EAG on 5th August 2022 and can be seen in the NICE committee papers for this appraisal.

An Addendum was received by the EAG from the company on 19th October 2022. Clarification on some aspects of the Company Addendum was requested from the company by the EAG via NICE on 9th November 2022. Responses from the company via NICE were received by the EAG on 28th November 2022 and can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on symptomatic obstructive hypertrophic cardiomyopathy

The CS (section B.1.3.1) provides a clear and accurate overview of symptomatic obstructive hypertrophic cardiomyopathy, including a description of the condition, its genetic causes, prevalence, diagnosis, morbidity and mortality, symptoms and effects on health-related quality of life (HRQoL). We summarise the key facts of relevance from the CS together with supplemental information, where appropriate, below.

CS section B.1.3.1 gives an accurate overview of hypertrophic cardiomyopathy (HCM), a cardiac disease that is often genetically inherited, where the muscles of the heart's walls thicken due to an increased number of cross-bridges between actin and myosin filaments. HCM impairs the function of the heart through hypercontractility, driving ventricular hypertrophy and impaired ventricular relaxation. Obstructive HCM has the additional defining feature of left ventricular outflow tract obstruction (LVOTO), a thickening of the walls of the

left ventricle of the heart in a way that reduces the amount of blood flowing out of the heart to the rest of the body.[4-6]

In the majority of people with HCM the disease is a complex, polygenic trait, whilst a minority have HCM caused by a specific pathogenetic mutation in a sarcomere gene (a gene that encodes proteins influencing heart muscle contractility), referred to as a sarcomere mutation (CS section B.1.3.1.2).[7-9] These groups can be described as having "sarcomere negative" and "sarcomere positive" HCM respectively.[9]

The European Society of Cardiology (ESC) and the American Heart Association/American College of Cardiology (AHA/ACC) guidelines state that from ~30% and up to 60% of patients with HCM have an identifiable or likely pathogenic genetic variant (i.e. sarcomere mutation).[4] [5] The company's pivotal trial, EXPLORER-HCM, reflects a proportion of patients who had a pathogenic or likely pathogenic HCM gene variant at the lower end of this range (CS section B.2.3.3 and Appendix 9.2 of this report). A recent meta-analysis of 7675 HCM patients from 51 studies assessed genotype-phenotype associations with clinical outcomes and found that sarcomere mutations may be associated with differences in age of onset (earlier onset) and prognosis of HCM,[10] and clinical experts to the EAG agree. Early findings from the Sarcomeric Human Cardiomyopathy Registry (SHaRe) concluded that the presence of a sarcomere mutation predicted adverse outcomes.[7]

Global prevalence of HCM is thought to be about 1 in 500[11] and the EAG's clinical experts commented that this prevalence is likely to apply to England. However, this overestimates the prevalence of symptomatic obstructive HCM in England to an uncertain extent, since around one third of diagnosed HCM patients have non-obstructive HCM and not all patients who have obstructive HCM are symptomatic; and many people with obstructive HCM remain undiagnosed (CS section B.1.3.1.4). HCM can manifest at any age (and not all sarcomere mutation carriers may develop clinical HCM).[13] Symptoms of HCM include breathlessness, palpitations, chest pain, syncope, and a reduced capacity for exercise and/or ability to carry out daily activities.[4] [5] The CS discusses the clinical impact of LVOTO, explaining that the increased left ventricular systolic pressure exacerbates the ongoing progression of hypertrophy, myocardial stiffening and fibrosis, leading to increased morbidity and mortality risks (CS section B.1.3.1.3.4).

2.2.2 Diagnosis and disease staging

Diagnosis of HCM involves evaluation of family history, non-cardiac symptoms and signs, electrocardiogram abnormalities, laboratory tests and cardiac imaging. These tests assess the structure and thickness of the heart wall and the performance of the heart muscle.[4 5] The EAG's clinical experts confirmed genetic testing is routine practice as part of diagnosing HCM in the NHS, in instances where HCM is diagnosed in patients under 50 years or is seen to be familial, although uptake can be variable. Additionally, to diagnose obstructive HCM, the left ventricular outflow tract (LVOT) is measured for obstruction which is indicated when the peak pressure gradient (LVOT gradient), measured by echocardiogram, is $\geq$ 30 mmHg.[5] The LVOT gradient may be assessed at three different points: when a person is at rest, immediately post-exercise, and/or on performing the Valsalva manoeuvre.[5]

The severity of HCM is assessed by the treating physician using the New York Heart Association scale of classes I-IV (CS Table 3).[14] The EAG's clinical experts confirmed that the NYHA class system is used universally across the NHS, with one expert noting it is mandatory to record NYHA class at every patient interaction. Symptomatic obstructive HCM corresponds to NYHA classes II-IV. Cardiopulmonary exercise testing (CPET) and LVOT peak gradient measure the impact of LVOTO on cardiopulmonary function and exercise capacity.

2.2.3 Clinical management of symptomatic obstructive hypertrophic cardiomyopathy

All cardiomyopathy guidelines that are relevant to HCM are listed and discussed in the CS (section B.1.3.2.2).[4 5 15-17] No guidelines exist specifically for obstructive HCM, and the only related UK guidance is for surgical reduction of the myocardial septum or management of chronic heart failure (IPG40 and NG106 respectively).[16 17]

The EAG's clinical experts agreed that the overview of the management of obstructive HCM outlined in the CS and illustrated in CS Figure 5 is appropriate, being informed by a survey of UK cardiac clinicians. However, we note there is heterogeneity in the care pathway in England: for example, not all the EAG's clinical experts clinical experts prescribe disopyramide; and they noted that there can be barriers to referral to specialist centres for septal reduction therapy (SRT) due to regional variation in referral patterns and patient reluctance to travel.

Care for patients involves symptom management using lifestyle modification, drug therapy, and/or surgery, but currently no therapies treat the underlying cause of hypertrophy. The

EAG's clinical experts noted that patients make lifestyle changes either to improve their health, or out of fear of experiencing exercise induced symptoms of obstructive HCM.

First-line pharmacological management of obstructive HCM consists of beta blockers and/or calcium channel blockers, and if a patient is non-responsive to these then disopyramide may be used. The EAG agree with the company that the availability of disopyramide fluctuates and varies across the UK (CS section B.1.3.2.3.3). An EAG clinical expert who prescribes disopyramide according to the current HCM guidelines,[4 5] commented that: disopyramide is more likely to be used in specialist centres; not all patients have side effects and for some it is "transformative"; when it is tolerated it is an effective and cheap option; and for some patients it can be used for decades. In an expert elicitation study involving a Delphi panel the company estimated the proportion of patients in the UK diagnosed with obstructive HCM who receive disopyramide to be approximately [redacted] in NYHA class II, [redacted] in NYHA class III, and [redacted] in NYHA class IV (Table 12 in CS Appendix O). According to feedback from our clinical experts and the British Society for Cardiology Consultee Submission, the EAG believe that while not all UK cardiologists prescribe disopyramide, others regard it as an effective second-line agent in current clinical use (albeit with inconsistent availability).[18] The relevance of disopyramide as a comparator for this appraisal is discussed further in section 2.3.2 below.

Patients who do not tolerate or respond to the drug therapies may be considered for septal reduction therapy (SRT) if they have access to a specialist centre.[4 5] Options for SRT are septal myectomy in which some of the muscle from the ventricular septum is surgically removed, or alcohol septal ablation in which alcohol is injected into the hypertrophic area of heart muscle causing it to shrink and die. Each method has its own risks and uncertain benefits.[19-23] Whilst SRT can improve symptoms in some patients, the EAG are not aware of any evidence that SRT influences disease progression or disease-associated mortality. However, there is a range of peri- and post-procedural complications associated with each SRT approach, including surgical mortality, atrioventricular block, ventricular septal defect and aortic regurgitation (CS section B 1.3.2.4).

2.2.4 Background information on mavacamten

Mavacamten, brand name CAMZYOS®, is an oral medicine in capsule form which targets the underlying sarcomere dysfunction of obstructive HCM. Mavacamten is a first in class myosin inhibitor that specifically binds to cardiac myosin. It stabilises myosin in the super-relaxed state, thereby reducing the number of cross-bridges (myosin heads bound to actin)

in the heart muscle, reducing hypercontractility and enabling diastolic relaxation. Descriptions of mavacamten are provided in CS section B.1.2 and in the revised draft Summary of Product Characteristics (SmPC).[24] (NB the SmPC in CS Appendix C is superseded by the revised draft SmPC which was provided with the Company Addendum and includes efficacy and safety results from the interim analysis of the VALOR-HCM trial).

The revised draft SmPC states that mavacamten is indicated [redacted]. This is in line with the scope of this appraisal and the patients included in the EXPLORER-HCM pivotal trial (the trial is discussed in section 3.2.1 below).

Because the mechanism of action reduces cardiac contractility it is important to identify the correct dose so that mavacamten does not cause hypocontractility which in turn can cause systolic dysfunction with the potential for heart failure. There are four available doses: 2.5 mg, 5.0 mg, 10.0 mg, and 15.0 mg, and the recommended starting dose is 5.0 mg daily. The revised draft SmPC states that the [redacted]. This monitoring is used to manage dose escalation, down-titration, and/or treatment interruption. Implications of the frequency of monitoring are discussed in relation to resource use and costs in section 4.2.9.2 of this report.

Marketing authorisation is in progress: the earliest anticipated times for a Committee for Medicinal Products for Human Use (CHMP) opinion and a European Commission (EC) decision were [redacted] and [redacted] respectively (CS Table 2). The [redacted]. Mavacamten was approved by the US Food and Drug Administration (FDA) in April 2022 subject to an FDA approved risk evaluation and mitigation strategy (REMS) to mitigate the risk of heart failure due to systolic dysfunction.[25]

2.2.5 The position of mavacamten in the treatment pathway

CS section B.1.3.3 ('Role of mavacamten in the care pathway') mainly justifies the use of mavacamten rather than explaining its position in the care pathway. However, CS section

B.1.3.3.2 suggests that "*mavacamten used in combination with standard care provides functional and symptomatic improvement to patients whose symptoms are inadequately controlled by BB or CCB*" thus placing it either alongside or after beta blockers and/or calcium channel blockers. The company clarified in their Factual Accuracy Check that mavacamten is positioned as an adjunctive therapy for patients who do not achieve sufficient symptomatic control with beta-blocker or calcium channel blocker monotherapy. CS section A.2 ('Clinical pathway of care') specifies its use alongside other treatments in standard care: Figure 1 in CS section A.2 positions mavacamten use alongside beta blockers and/or calcium channel blockers. Additionally, if mavacamten is positioned corresponding to the way it is used in the company's pivotal EXPLORER-HCM trial it can be used either alongside or instead of treatments such as beta blockers and calcium channel blockers. Whilst mavacamten can be used in combination with disopyramide, or beta-blockers in combination with calcium channel blockers, the revised draft SmPC recommends [redacted]. The company clarified in their Factual Accuracy Response that for this reason the proposed position for mavacamten does not include combination therapy with disopyramide, or concomitantly with both beta blockers and calcium channel blockers.

The EAG's clinical experts suggested that, if recommended by NICE, mavacamten would likely be used after beta blockers and possibly after calcium channel blockers as well, but prior to any septal reduction therapy. Two experts suggested those who normally prescribe disopyramide would position mavacamten after disopyramide for the majority of patients, whilst the third expert suggested some clinicians may prefer to position mavacamten ahead of disopyramide (but after beta blockers) due to the safety profile of disopyramide.

Treatment with mavacamten needs to be continuous as the effects of mavacamten are reversible (as demonstrated in the pivotal EXPLORER-HCM trial where effects of mavacamten on left ventricular ejection fraction (LVEF) and patient-reported outcomes attenuated after treatment discontinuation (CS sections B.2.6.1.3 and B.2.6.1.4)).

2.3 Critique of the company's definition of the decision problem

Table 4 compares the company's decision problem to the final scope for this appraisal issued by NICE. The EAG consider that the decision problem adheres to the NICE scope but with the following caveats:

2.3.1 Population

No concerns from the EAG.

2.3.2 Comparators

The company argue that disopyramide should not be considered part of standard care. However, whilst two of the EAG's clinical experts supported this view, the third expert did not (Table 4). In practice, use of disopyramide is likely to vary geographically in the NHS. We suggest that further consultation may be helpful to clarify this. Accordingly, we have listed the use of disopyramide as a key issue (see Table 1 and section 1.1 above).

2.3.3 Outcomes

The company argue that the low incidence of mortality and cardiovascular events precludes these being included as clinical outcomes that can inform the economic model. As an alternative the company applied NYHA class as a proxy for mortality for their economic analysis. The EAG's clinical experts agreed that mortality and cardiovascular event rates could not be used directly in the economic model so the use of a proxy is not unreasonable. However, the experts cautioned that there is a lack of robust evidence to support a causal relationship between NYHA class and mortality. It is therefore uncertain whether the supposition that improving NYHA class will improve mortality is appropriate. The EAG also have concerns around the accuracy of the relationship between NHYA class and mortality which the company deduced from two retrospective "real world evidence" studies (Table 4).

2.3.4 Subgroups to be considered

The NICE scope and company Decision Problem do not specify any subgroups. However, the EXPLORER-HCM trial had predefined subgroup analyses for the primary outcome according to randomisation stratification factors, patient demographics and other baseline characteristics including beta-blocker use (CS section 2.7), as well as post-hoc subgroup analyses of several other outcomes by beta blocker use reported in CS section 2.7.1 (see section 3.5.4 below).

The EAG are uncertain whether the benefit/risk profile for mavacamten would be the same in patients with or without a sarcomere mutation. The efficacy of mavacamten might plausibly differ between these subgroups as its mode of action targets sarcomere dysfunction. Results of subgroup analyses in EXPLORER-HCM (section 3.6.10 below) suggest that mavacamten efficacy may differ between sarcomere mutation positive and negative patients, although the

small group analyses lack statistical significance. We have therefore raised this as a key issue to allow further consideration (see Table 1 and section 1.1 above).

Table 4 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem (CS Table 1)	Differences between scope and Decision problem
Population	Adults with symptomatic obstructive hypertrophic cardiomyopathy (NYHA class II-III)	Adults with symptomatic obstructive hypertrophic cardiomyopathy (NYHA class II-III)	No concerns
Intervention	Mavacamten in combination with standard care	Mavacamten in combination with standard care	No concerns
Comparators	Individually optimised standard care without mavacamten. Standard care is defined as: • Beta-blockers • Non-dihydropyridine calcium channel blockers • Disopyramide, alone or in combination with either beta-blockers or non-dihydropyridine calcium channel blockers	Individually optimised standard care without mavacamten. Standard care is defined as: • Beta-blockers • Non-dihydropyridine calcium channel blockers	The company argue (CS Table 1) that disopyramide is not a relevant comparator, as it is not a part of standard care due to: • Side effects which patients find hard to tolerate • Tachyphylaxis (loss of clinical benefit over time) • Difficulty in obtaining disopyramide, limiting its use Two of the EAG's clinical experts concurred with the company. However, the third expert disagreed, noting that: • Disopyramide is standard care in some centres, particularly larger specialist centres with more patients. • Whilst many patients do not tolerate disopyramide, some tolerate it well and have been on disopyramide for 1-2 decades. • Access to disopyramide is currently difficult and has worsened, but patients previously receiving

			disopyramide who can no longer obtain it have reported worsening of their symptoms. We note also that the BCS consultee submission [18] and results of a company expert elicitation Delphi panel indicate that disopyramide is used in clinical practice (NYHA class II: range [redacted]% to [redacted]%, median [redacted]%; NYHA class III: range [redacted]% to [redacted]%, median [redacted]%) (Tables 12 and 13 in CS Appendix O). The EAG believe there is uncertainty in the extent to which disopyramide is used in clinical practice. Given the mixed opinions of our clinical experts, we have noted this as a key issue that would benefit from further clarification).
Outcomes	The outcome measures to be considered include: • response rates • mortality • cardiovascular events • cardiovascular related mortality • exercise capacity • oxygen consumption • patient-reported symptom severity • change in NYHA class • change in left ventricular ejection fraction	The outcome measures to be considered include: • response rates, given as proportion of patients with complete response (CS section B.2.6.1.4) • mortality (modelled) • exercise capacity, given by cardiopulmonary exercise test (CPET) parameters, particularly peak oxygen consumption (pVO_2), which forms part of the composite primary outcome and a separate secondary endpoint in	The company's decision problem matches the NICE scope except that the company have excluded mortality, cardiovascular events and cardiovascular-related mortality as outcomes. The company's rationale for excluding these outcomes is that the event rates in patients with obstructive HCM are too low (<1%) to assess reliably unless a prohibitively long-duration trial is conducted. The company addressed the lack of trial mortality data by using NYHA class as a surrogate for mortality in the cost-effectiveness model, deriving hazard ratios for all-cause mortality by NYHA class from real-world data from patients with obstructive

	• adverse effects of treatment • health-related quality of life	the pivotal trial (CS sections B.2.6.1.1 and 2.6.1.2) • oxygen consumption; pVO_2 measured by CPET), which forms part of the composite primary outcome and a separate secondary endpoint in the pivotal trial (CS sections B.2.6.1.1 and 2.6.1.2) • patient-reported symptom severity, assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ)-23, HCM Symptom Questionnaire Shortness-of-Breath (HCMSQ-SoB) and EQ-5D (CS section 2.6.1.3) • change in NYHA class, which forms part of the composite primary outcome and a separate secondary endpoint in the pivotal trial (CS sections B.2.6.1.1 and 2.6.1.2) • change in left ventricular ejection fraction (CS section B.2.6.1.4) • adverse effects of treatment (CS section B.2.10)	HCM (see section B.3.3.5). No such data have been identified to permit an analysis of CV mortality or CV events, therefore evidence is not provided in this submission for these outcome measures. We note that while the real-world evidence studies are suggestive of higher mortality rates with higher NYHA class, the data selection process in the retrospective real world evidence studies is not reported, so selection bias cannot be ruled out (see section 3.3.4). EAG clinical experts acknowledged that while a relationship between mortality and NYHA class is plausible, such a correlation is not supported by robust evidence; and correlation can only identify an association, not causality. The experts also expressed concerns that the definitions of NYHA classes, especially class III, are variable and subjective, so any correlation with mortality will have uncertainty. We discuss the approach to modelling mortality for the economic evaluation in section 4.2.8 below.

		• health-related quality of life (CS section B.2.6.1.3).	
Subgroups	None specified	None specified	The EXPLORER-HCM trial had predefined subgroup analyses for the primary outcome according to randomisation stratification factors, patient demographics and other baseline characteristics including beta-blocker use, as well as post-hoc subgroup analysis of other outcomes by beta blocker use (see section 3.5.4 below). The EAG are uncertain whether the cost effectiveness of mavacamten would differ between subgroups of patients with and without a sarcomere mutation. This is discussed as a key issue in Table 1 above.
Source: partly reproduced from CS Table 1 BCS: British Cardiovascular Society; CPET: cardiopulmonary exercise testing; CV cardiovascular; HCMSQ-SoB: HCM Symptom Questionnaire Shortness-of-Breath; KCCQ: Kansas City Cardiomyopathy Questionnaire; NYHA: New York Heart Association; pVO_2: peak oxygen consumption.			

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review

The EAG have critiqued the company's systematic literature review (SLR) of clinical efficacy studies, as described in Appendix 9.1 of this report. After updating the company's literature searches and risk of bias assessments to address some limitations in the evidence review, we agree that the company's review is at low risk of bias and no relevant studies are likely to have been missed.

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation

The company identified several relevant studies and carried out expert elicitation to address evidence gaps, as summarised in Table 5. Further details of the included studies are provided in sections 3.2.1 to 3.2.5 below.

Table 5 Summary of studies identified by the company

Study name / identifier	Brief details	Included/excluded	EAG report section
EXPLORER-HCM; [26-30] NCT03470545	Company pivotal trial; phase III RCT of mavacamten (plus standard care) versus placebo (standard care) in symptomatic obstructive HCM patients.	Included	3.2.1
EXPLORER-LTE; [31] (cohort of MAVA-LTE; NCT03723655)	Long-term extension of company pivotal trial; cohort study for participants previously enrolled in EXPLORER-HCM who continued into the long-term extension study MAVA-LTE.	Included	3.2.2
Masini et al. 1981[32]	Randomised cross-over trial comparing the beta blocker pindolol and the calcium channel blocker verapamil.	Excluded appropriately (the placebo arm of the more recent RCT, EXPLORER-HCM, contains evidence for BBs and CCBs in direct comparison with mavacamten).	Not applicable
PIONEER-HCM; NCT02842242	Phase II open-label RCT and open-label extension cohort study	Excluded appropriately (inferior evidence to	Not applicable

PIONEER-OLE; NCT03496168	of mavacamten in symptomatic obstructive HCM patients.	pivotal trials: small sample size, and concomitant use of BBs was not allowed therefore the population is inconsistent with the pivotal trial).	
VALOR-HCM;[33] NCT04349072	RCT of symptomatic obstructive HCM patients eligible for SRT receiving mavacamten (plus standard care) or placebo (standard care).	Included as supportive clinical effectiveness in the CS. Interim analysis results provided in the Company Addendum.	3.2.4
'EHR study'; [2] analysis of data from the Cardiac Cohort of the Optum Electronic Health Records database **'SHaRe study'**; [34] analysis of data from the SHaRe registry	Company-commissioned real-world evidence studies to explore the relationship between NYHA class and all-cause mortality. Reported in two conference abstracts and CS Appendix N.	Included to inform the economic model only.	3.2.5
Expert elicitation	Company-run modified Delphi panel reported in CS Appendix O.	Included to fill gaps in data about the care pathway and resource use in the UK.	3.2.6
Advisory boards[35-38]	Four company advisory boards reported as data on file.	Included to fill gaps in data about the care pathway and resource use in the UK and to guide design of the economic model.	3.2.7
BBs: beta blockers; CCBs: calcium channel blockers; NYHA: New York Heart Association; RCT: randomised controlled trial; SHaRe: Sarcomeric Human Cardiomyopathy Registry; SRT: septal reduction therapy.			

3.2.1 EXPLORER-HCM: study design

EXPLORER-HCM (NCT03470545) is a company-sponsored phase III, multi-centre, international, randomised controlled trial evaluating mavacamten (plus standard care) (n=123) versus placebo (standard care) (n=128). The study design is reported in CS Tables 4, 5 and 6 and section B.2.3.1.1.

- The population consisted of people with symptomatic (NYHA class II-III) obstructive HCM who were randomised in a ratio of 1:1 to the two arms.
- Randomisation was carried out using an interactive response technology and stratified by NYHA class, current treatment with beta-blocker, planned type of ergonometer to be used, and consent for participating in a cardiovascular magnetic resonance (CMR) sub-study.

- EXPLORER-HCM was double-blinded.
- As standard care, participants received beta blockers or calcium channel blockers but not both; therefore, mavacamten could be used with either beta-blockers or calcium channel blockers but not both.
- Dual therapy combinations of mavacamten plus disopyramide or mavacamten plus ranolazine were not permitted.
- After a 30-day screening period, participants received either mavacamten or placebo for 30 weeks. An eight-week (blinded) post-treatment follow-up period followed, with the end of study being at 38 weeks.
- Pre-planned sub-group analyses for the primary outcome were specified for most of the participant characteristics, including beta-blocker use, at baseline (CS Table 5). Additionally, a post-hoc subgroup analysis was conducted for other outcomes for participants with and without beta-blocker use at baseline (CS section B.2.7 and discussed further below in section 3.5.4).
- Two centres were in the UK, but it is not clear how many UK participants were enrolled. A note in CS Table 8 lists the UK last in a list of other regions ordered by number of patients.
- Data presented in the clinical effectiveness evidence are from journal publications [26] [28] [29] [39] and the clinical study report (CSR).[40]
- The study is complete.

EXPLORER-HCM included a CMR sub-study of participants who gave consent for CMR scans and had scans at week 1 and week 30.[41] Mavacamten arm, n=17 and placebo arm, n=18. The EAG do not consider this sub-study further as the outcomes (exploratory outcomes including measures of cardiac morphology, ventricular function and myocardial tissue characteristics[41]) are outside the scope of this appraisal.
Participant characteristics of EXPLORER-HCM are discussed in section 3.2.3 below.

3.2.2 EXPLORER-LTE: study design

EXPLORER-LTE refers to a cohort of participants previously enrolled in the EXPLORER-HCM trial who continued into a long-term safety extension study called MAVA-LTE (NCT03723655). Note that the MAVA-LTE study recruited patients both from EXPLORER-HCM and from a trial focusing on non-obstructive HCM (MAVERICK-HCM). Only the patients who came from the EXPLORER-HCM trial are included in the EXPLORER-LTE cohort. The study design of MAVA-LTE is reported in CS Tables 4 and 5 and CS section B.2.3.1.2.

- EXPLORER-LTE is an ongoing single-arm study.
- Efficacy results reported in the CS are from an interim analysis based on the most recent database lock in August 2021.[31] CS Appendix M presents data from an earlier database lock in October 2020.
- There are 67 study centres (CS Appendix M), but it is unknown how many UK patients are enrolled.
- At the most recent database lock 231 participants were enrolled, with 217 remaining on treatment. The safety analysis population is reported for the full population (N=231) (see section 3.7 below).
- Site, care provider and patients were blinded to the mavacamten dose by using the interactive response system (clarification question A3.d). Only the sponsor was unblinded to the dose although it is unclear for what purpose.
- After a 28-day screening period, participants receive mavacamten 5.0 mg daily irrespective of the dose they received in the EXPLORER-HCM trial. Dose adjustments are made in weeks 4, 8 and 12 according LVEF and Valsalva LVOT gradient; dose adjustments were also possible at 24 weeks based on post-exercise LVOT gradient (CS section B.2.3.1.2).
- Participants continue in the study for five years: results from the interim analysis (August 2021) are reported for up to 84 weeks in the study.

3.2.3 Participant characteristics for EXPLORER-HCM and EXPLORER-LTE

Baseline characteristics for participants in the EXPLORER-HCM trial and the EXPLORER-LTE cohort are reported in CS Table 8 and CS section B.2.3.3.

The EAG agree that baseline characteristics are similar between the mavacamten and placebo arms of EXPLORER-HCM, and the EAG's clinical experts noted that there were no obvious clinically important differences that would clearly favour either arm.

Of those patients who received genetic testing in the EXPLORER-HCM trial 31% and 22%, in the mavacamten and placebo arms respectively had a pathogenic or likely pathogenic HCM gene variant (CS Table 8). The ESC and AHA/ACC guidelines state that from ~30% and up to 60% of patients with HCM have an identifiable or likely pathogenic genetic variant,[4 5] so the EXPLORER-HCM trial population represents the lower end of this range

The CS argues that the trial population is similar to the overall HCM population in England based on a large cohort study of English health records and the EAG agree.[42] The company

also argue that the trial population is similar to the obstructive HCM population in England based on age and sex characteristics from an unpublished, ongoing, company study using data from the UK Clinical Practice Research Datalink in combination with English data from Hospital Episode Statistics (n=320) (CS section B.2.12.4). The EAG are unable to verify any aspect of this study as no study documentation was provided with the submission nor in response to clarification questions A5 and A9.

The EAG's clinical experts agreed that, with the exception of disopyramide use (discussed further below) the baseline characteristics of EXPLORER-HCM and EXPLORER-LTE are generally representative of patients treated for symptomatic obstructive HCM in the NHS. The experts noted some minor differences from an NHS population which they would not expect to affect the outcomes in a meaningful way: the trial populations are mainly White, whereas there would be slightly more Black patients (it can be difficult to diagnose HCM in Black people, hence they are under-represented) and slightly fewer Asian patients (Asian patients with HCM tend to have nonobstructive disease) in the NHS population; and slightly less than 40% of patients in the UK would have hypertension (compared to 41% to 46% in EXPLORER-HCM). According to our clinical experts these differences in baseline characteristics are unlikely to have major consequences for the trial outcomes.

There is uncertainty in how well the EXPLORER-HCM and EXPLORER-LTE populations reflect the use of disopyramide in NHS practice. These studies excluded patients who received disopyramide, whilst the EAG's clinical experts differed in their opinions about the extent to which disopyramide is used in clinical practice (see section 2.3.2 and Table 4 above). The EAG believe this is an area of uncertainty that may benefit from further clarification (see section 1.3 above).

3.2.4 VALOR-HCM: study design and participant characteristics

VALOR-HCM is an ongoing RCT evaluating the efficacy of mavacamten in patients who have symptomatic obstructive HCM and additionally are eligible for SRT.

The VALOR-HCM trial (NCT04349072) is not mentioned in CS section B.2.2 in relation to relevant clinical trial evidence. However, results from an interim analysis are cited by the company in CS sections B.2.11, B.2.12.1 and B.12.2 and used descriptively to support the clinical effectiveness evidence reported from the EXPLORER-HCM and EXPLORER-LTE studies.[43 44] Further results from the same interim analysis are reported in the Company Addendum and full study publication.[33] Evidence from VALOR-HCM supports mavacamten's role in avoiding the need for SRT (Company Addendum Table 3).

Data from VALOR-HCM are not used in the economic model, mainly because the timing of the assessments of NYHA class differ from and cannot be pooled with data from the EXPLORER studies to model transition probabilities. Full justification is given in Company Addendum section 2.10 and the EAG agree that this is appropriate (section 4.2.3.1 below).

- VALOR-HCM is a company-sponsored phase III, multi-centre, randomised controlled trial comparing mavacamten (plus standard care) versus placebo (standard care).
- Country: 20 centres in the United States, i.e. no UK patients.
- Randomisation: 1:1 ratio for mavacamten (n=56) versus placebo (n=56) and stratified by type of SRT recommended (myectomy or alcohol septal ablation) and NYHA class. This is a smaller sample size than in the EXPLORER-HCM trial and EXPLORER-LTE study.
- The randomised comparison (weeks 0 to 16) was followed by a period during weeks 16 to 32 in which patients in the placebo arm crossed over to mavacamten, while patients in the mavacamten arm continued on their mavacamten dose. This was followed by a long-term extension (LTE) study during weeks 32 to 128 in which all patients received mavacamten. The 16-week randomised comparison is shorter than in the EXPLORER-HCM trial. The LTE study is ongoing (no results are reported).
- Blinding: double-blind. The 16-week randomised placebo-controlled portion of the study was unblinded to the sponsor in February 2022, with the investigators and participants remaining blinded for the rest of the study.
- The primary outcome is a composite of the decision to proceed with SRT prior to or at week 16 or remaining guideline eligible for SRT at week 16. This endpoint has been met and data from the interim analysis are reported in CS section B.2.11, the Company Addendum, and the study publications.[33 44]
- The study duration of the randomised placebo-controlled period is short: baseline to 16 weeks and matches the timing of the primary outcome. This is a shorter comparative period than in the EXPLORER-HCM trial.

Baseline characteristics of participants in VALOR-HCM are reported in Table 5 of the Company Addendum (presented alongside those of participants in the EXPLORER-HCM trial) and the study publications.[33 44] See also Appendix 9.2 of this report to view them alongside the patient baseline characteristics of both EXPLORER-HCM and EXPLORER-LTE.

There were some slight differences in the trial baseline characteristics between the mavacamten and placebo arms of VALOR-HCM but the EAG's three clinical experts agreed that these would be unlikely to affect trial outcomes (i.e. low risk of selection bias; see section 3.3.2).

The EAG's clinical experts agreed that baseline age, sex, family history of HCM, calcium channel blocker use, and resting and post-exercise LVOT gradients in VALOR-HCM are similar to those in the pivotal EXPLORER-HCM trial and to patients in the UK. The trial authors acknowledge that the population was predominantly White patients treated in high-volume centres.[33] NYHA class is higher than in the EXPLORER-HCM trial as 92.9% of participants are NYHA class III or higher which is to be expected considering that these are people eligible for SRT. However, [redacted] patients in the trial would be included in the proposed marketing authorisation (i.e. NYHA class II or III) because only [redacted]/112 patients were in NYHA class IV at baseline (Company Addendum clarification response A1). Beta blocker use is much lower in the VALOR-HCM population: 46.43% and 44.64% in the mavacamten and placebo arms respectively compared to 76% and 74% in the mavacamten and placebo arms of EXPLORER-HCM (Appendix 9.2). Disopyramide use was 20% across both arms of the VALOR-HCM trial, and therefore the population is not consistent with the EXPLORER-HCM trial or the company's current Decision Problem which both exclude disopyramide (Table 4).

3.2.5 Real-world evidence studies: study design and participant characteristics

Two real-world evidence studies investigating the association between NYHA class and mortality are included in the CS to provide mortality data for the economic model (CS section B.3.3.5; discussed in section 4.2.8 of this report). These are a company analysis of the Sarcomeric Human Cardiomyopathy Registry (SHaRe)[34] (CS Appendix N) and an electronic health record registry study ("EHR study") reported by Wang et al. 2022.[2]. The SHaRe registry was set up to obtain data on clinical and genetic information, longitudinal outcomes, and disease burden for HCM internationally.[7] Table 6 summarises the key characteristics of these studies.

Table 6 Key characteristics of the real-world evidence studies

Study characteristic	SHaRe study[34] (CS Appendix N)	EHR study[2]
Study design	Company sponsored retrospective analysis of registry data	Company sponsored retrospective analysis of electronic healthcare records
Country	International (10 centres: 2 European; 0 United Kingdom)	United States
Timeframe	First visit with NYHA assessment 2019 Q1 (up to March 2019) to end	Patient records with obstructive HCM between 1/1/2007 and

	of follow-up in SHaRe or SRT, whichever occurred first. Follow up not explicitly clear, appears to be 1 year for the unadjusted analysis (CS Appendix N Figure 2) but longer for the analysis in CS Appendix N Figure 3 and Table 2 – we assume this was used for the adjusted analysis in CS Appendix N Table 3 which supports a scenario analysis in the economic evaluation.	30/6/2020 and with ≥1 NYHA class assessment after diagnosis Length of follow-up not reported but CS Figure 4 which is attributed to the Wang et al. study (data source unclear) suggests good follow-up
Population	Adults with obstructive HCM selected from the SHaRe registry N=2495	Adults with obstructive HCM selected from the Cardiac Cohort of the Optum Electronic Health Records database N=3322
Intervention(s) or comparator(s) included in the study	None reported	None reported
Outcome	Association of NYHA class with a) the risk of all-cause mortality and b) a composite endpoint of death and heart transplant	Association of NYHA class over time with risk of mortality
Measures of association	Hazard ratios with 95% confidence intervals and log-rank tests comparing mortality risk across baseline NYHA functional classes, adjusted for age, sex, race, family history of HCM, LVOT at rest, LVEF, and maximal LVWT	Hazard ratios from Cox models with confidence intervals comparing risk of mortality between NYHA classes, and comparing change in NYHA class from baseline, adjusted for age, sex, and race
Use in the model (CS section B.3.9.3)	Company scenario analysis: Adjusted hazard ratios from CS Appendix N; unadjusted risk ratios calculated from Lakdawala 2021	Company base case: Hazard ratios from Wang 2022
Participant characteristics		
NYHA class (n/N)	I 951/2495 II 1031/2495 III/IV 513/2495	I 572/3322 II 1265/3322 III 1280/3322 IV 205/3322
Age at diagnosis, years, mean	47.6	61
Sex, female (%)	42	51
Race, n (%) White Black Hispanic Other Missing	 2192 (89) 98 (4) 32 (1) 136 (6) 37 (2)	 2658[a] (80) Not reported Not reported Not reported Not reported
[a] n calculated by EAG LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; LVWT: left ventricular wall thickness; NYHA: New York Heart Association; SHaRe: Sarcomeric Human Cardiomyopathy Registry; SRT: septal reduction therapy.		

Limited participant characteristics were reported that would determine similarity to the obstructive HCM pivotal trial populations in terms of age, sex, race, and NYHA class; for

example, the EHR study did not report the proportions of Black or Asian participants included in the study. The SHaRe study reports baseline characteristics for family history of HCM, resting LVOT peak gradient, maximum left ventricular wall thickness and LVEF, for which age, LVEF and resting LVOT gradient are slightly lower than in the EXPLORER-HCM trial (CS Appendix N). Compared to EXPLORER-HCM, the SHaRe cohort were [redacted] (mean age NYHA classes I to III/IV respectively [redacted], [redacted] and [redacted] compared to 58.5 years for NYHA classes II-III in EXPLORER-HCM. There were no UK centres in either study. However, the company's response to clarification question A7 confirms that two European centres contributed [redacted] of patients in the SHaRe study. Additionally, it is unclear what length of time the studies covered and whether sufficient time had passed to allow for mortality events (Table 6).

Table 2 in clarification response A7 compares five SHaRe study baseline characteristics (sex, race/ethnicity, family history of HCM, age at diagnosis and left ventricular wall thickness) against the population characteristics of four UK cohorts with either HCM or obstructive HCM.[34 42 45 46] It is difficult to draw any clear conclusions about the similarity of the SHaRe population to these UK cohorts since limited data are available: for two of the studies only sex and race/ethnicity can be compared, although the limited available characteristics are broadly similar between the cohorts.

Company and EAG critical appraisal and risk of bias assessments for the SHaRe and EHR studies are provided in Appendices 9.3.4 and 9.3.5 of this report.

3.2.6 Expert elicitation

The company carried out a modified Delphi panel expert elicitation study to help address knowledge gaps concerning the care pathway and resource use (CS sections B.2.2.2 and B.2.3.4). The methods and results of the modified Delphi panel study on healthcare resource use in the UK are reported in CS Appendix O and are summarised in Table 7 below.

Table 7 Summary of the modified Delphi panel study

Method characteristics	Understanding the healthcare resource use of adults with obstructive HCM (CS Appendix O)
Date	Not reported for the study itself; report dated March/July 2022
Topics covered	Primary and secondary care consultations, tests / procedures and prevalence of devices / procedures; care of obstructive HCM in the UK
Participants	10 clinicians selected from 24 UK specialist centres. 2/10 were interventionalists specialising in SRT – results are presented including and excluding their responses.

Elicitation methods	Modified Delphi panel approach modified to enable quantification of results; pilot questionnaire with internal company clinicians; panel discussion facilitated independently; no pre-read material reported.
Results	Reported in CS Appendix O
Financial reward	Not reported
Parts of economic model informed	Frequency and efficacy of SRT (CS section B.3.4.4); costs of SRT procedures and market share of SRT (CS Table 23); proportions of patients who undergo NYHA class-dependent treatment escalation (CS Table 28); use and efficacy of subsequent therapies (CS section B.3.3.4); estimates of HCRU by NYHA class and prevalence of defibrillator and pacemaker use (CS section B.3.5).
HCM: hypertrophic cardiomyopathy; HCRU: healthcare resource use; NYHA: New York Heart Association; SRT: septal reduction therapy.	

The EAG critically appraised the expert elicitation, following criteria provided by Nasa et al. 2021.[47] Our appraisal indicates that the elicitation was generally well-conducted without obvious risks of bias (neutrally worded questions, independent discussion facilitation, anonymity of experts), although the modified approach meant that consensus criteria were not pre-specified but consensus was established on a case-by-case basis and agreed on in panel discussion. However, ranges estimated by experts were converted to middle values for analysis and therefore do not appear to have informed the final ranges and 95% confidence intervals presented in the Results section of CS Appendix O which may therefore underestimate uncertainty. Some items, e.g. cost of SRT, were noted narratively as highly uncertain (e.g. Tables 73 and 74 in CS Appendix O) but are presented as point estimate prices in the main Results section. (NB The EAG probabilistic sensitivity analysis (PSA) results for the economic analysis (Table 23) assume standard errors of 10% around the means for the elicited parameters rather than being based on variation between the experts' estimates).

3.2.7 Advisory boards

The company provided a brief report for each of four advisory boards which were convened to address further knowledge gaps and uncertainties as follows:

- UK HTA validation advisory board. Covering: the model structure, inputs, and utilities; healthcare resource use; and longer term modelling and assumptions[38]
- Clinical and health economic UK advisory board. Covering: the access proposition for mavacamten; modelling submission strategy; and the value of mavacamten[37]
- Global HTA advisory board. Covering: the mavacamten evidence base; treatment positioning; the SLR and indirect treatment comparison; and the cost-effectiveness model[36]

- SRT advisory board. Covering: the role of SRT in the treatment pathway; the efficacy of SRT; and the role of mavacamten and SRT[37]

The results of the advisory board discussions are not reported. Due to the limited information provided, the EAG are unable to corroborate any findings from these advisory boards as discussed in the CS, e.g. relating to model health states (CS section B.3.2.2.2), model transition probabilities (CS section B.3.3.2.3), treatment with SRT (CS section B.3.3.4), efficacy of disopyramide (CS Table 41) and assumptions around mavacamten discontinuation (CS Table 41).

EAG conclusion on the included studies

The CS includes all studies relevant to the clinical effectiveness and safety of mavacamten, assuming (per the company's decision problem) that disopyramide is not a relevant comparator. The company did not search systematically for studies of disopyramide, but the EAG and our clinical experts are not aware of any further RCTs that would be included if disopyramide is considered as a relevant comparator (cohort studies on disopyramide exist[48 49] but it is unclear whether it would be appropriate or feasible to include these in an indirect comparison against mavacamten). A company expert elicitation (Delphi panel) and four advisory boards inform economic analysis parameters but due to limitations in reporting may underestimate uncertainty in these.

3.3 Risk of bias assessment

This section provides the EAG's critical appraisal of:

- EXPLORER-HCM and VALOR-HCM RCTs,
- EXPLORER-LTE observational cohort,
- Two "real world" retrospective observational cohorts.

3.3.1 EXPLORER-HCM

The company assessed risk of bias in the EXPLORER-HCM trial using the Centre for Reviews and Dissemination (CRD) checklist (CS Table 11). The company answered questions in the checklist but do not state how their answers translate into risks of bias. We agree with most of the company's answers as reported in CS Table 11 and have provided an interpretation of these in terms of risks of bias in Appendix 9.3.1 below.

There were substantial missing data for the KCCQ-23 CSS and HCMSQ-SoB score[50]). However, detailed sensitivity analyses by the study authors[29] and the FDA[50] concluded that the missing data appeared to be unrelated to treatment, and the conclusion of treatment benefit for mavacamten remained unchanged after applying worst-case missing data assumptions.

Overall, we conclude that the risk of bias for the main analyses in the EXPLORER-HCM trial is low, except for the EQ-5D change from baseline to week 30 which has a high risk of bias due to unaccounted for missing data (Appendix 9.3.1 below).

For the subgroup analyses in EXPLORER-HCM the risk of bias is unclear since the CS reports that 24 subgroup comparisons were pre-specified in EXPLORER-HCM (CS Table 5), but results are presented for only nine of these analyses in CS Figure 19, the trial publication,[26] and Figure 6 in the CSR.

3.3.2 VALOR-HCM

As with the EXPLORER-HCM trial, the company assessed risk of bias in the VALOR-HCM trial using the CRD checklist (Clarification Response Table 1). The EAG's interpretation of the risk of bias in VALOR-HCM is provided in Appendix 9.3.2 below. Note that the Company Addendum includes a risk of bias assessment for VALOR-HCM but this does not differ from the assessment already provided by the company in the CS and in Clarification Response Table 1.

Overall we consider the VALOR-HCM trial to be at low risk of bias (Appendix 9.3.2). There are some slight baseline imbalances in population characteristics between the mavacamten and placebo groups (Appendix 9.2) but the EAG's three clinical experts considered these unlikely to introduce systematic error in the trial outcomes, i.e. the risk of selection bias would be low.

3.3.3 EXPLORER-LTE

The company critically appraised the EXPLORER-LTE study using the ROBINS-I tool (Part B of CS Appendix D). ROBINS-I requires that the comparator(s) should be specified.[51] It is not clear how the tool can be used to assess the single-cohort EXPLORER-LTE study which comprises only mavacamten-treated patients, without an obvious comparator. The company did not specify the following aspects of information required by the ROBINS-I tool:[51] (i) the comparator(s) of interest; (ii) the "target" trial design for the assessment; (iii) the list of

relevant confounders; and (iv) the rationale for the company's answers to the signalling questions. In response to Clarification Response A3(a), the company provided an alternative assessment of EXPLORER-HCM using the Newcastle-Ottawa Scale (NOS) (Clarification Response Appendix A).

The EAG note that the NOS does not provide an explicit assessment of the risk of bias. Key limitations of the NOS as applied to EXPLORER-LTE are:

- The output is an overall quality rating that incorporates some aspects of internal validity (risk of bias), external validity and precision, summarised in descriptive statements (e.g. "fair") and numeric scores which do not directly reflect the degree of systematic error.
- The version of the NOS provided by the company for cohort studies requires that exposed and unexposed cohorts and confounders are defined but these were not specified by the company. It is therefore unclear whether the NOS is appropriate for appraising EXPLORER-LTE given that this is a mavacamten-only single prospective cohort study.

The EAG checked the company's NOS assessment, commented on which NOS questions relate to risk of bias, and provided additional information for sources of bias not adequately covered by the NOS (Appendix 9.3.3 below).

The EAG conclude that the EXPLORER-LTE study has a high risk of bias for the following reasons (Appendix 9.3.3) (these do not influence the economic analysis):

- Extensive missing data for several of the outcomes. Notably, at week 84 there were 69-70% of the data missing, without imputation, for changes in resting LVOT gradient, Valsalva LVOT gradient and LVEF. (NB the company clarified in their Factual Accuracy Check that the data were missing because the majority of patients in this interim analysis had not reached week 84.)
- In addition to the sources of bias assessed by the NOS, the protocol for EXPLORER-LTE[52] states that the Hypertrophic Cardiomyopathy Symptom Questionnaire - Shortness of Breath (HCMSQ-SoB) and the EQ-5D were assessed at week 48, week 72 and subsequent timepoints but no results for these outcomes are reported, suggestive of a high risk of selective outcome reporting bias (Appendix 9.3.3).
- A key feature of EXPLORER-LTE is that there is no comparator group. As such, the results for all efficacy outcomes are illustrative rather than definitive.

3.3.4 Real-world evidence studies

The company provided NOS assessments of the studies by Lakdawala et al. 2021[3] ('SHaRe analysis') and Wang et al. 2022[2] ('EHR study') in Clarification Response Appendix A. The EAG's comments on the company assessments using the NOS are provided in Appendix 9.3.4 below for the SHaRe analysis (Lakdawala et al. 2021 study) and in Appendix 9.3.5 below for the Wang et al. 2022 study.

Pre-specified criteria were used in both the real-world evidence studies to select an appropriate obstructive HCM population from electronic records. However, the data collection was retrospective, and no details are provided on how the data were selected and extracted from the electronic records or checked for their accuracy. In the SHaRe analysis it is unclear how baseline data were identified and obtained (this information was not provided in clarification response A6). All data in the Wang et al. 2022 analysis are from a conference abstract giving very limited methodological information.[2] Due to the lack of information on study methods the EAG regard the results of these studies as uncertain with an unclear risk of bias (Appendices 9.3.4 and 9.3.5).

Further limitations of the real-world evidence studies, not captured in the NOS, are that the NYHA classification is inherently subjective; and the single-cohort retrospective designs of the studies are unable to demonstrate a causal relationship between NYHA class and mortality.

EAG conclusion on risk of bias

Overall, the EXPLORER-HCM and VALOR-HCM trials have a low risk of bias, except that EXPLORER-HCM has a high risk of bias in the EQ-5D change from baseline and an unclear risk of bias in the subgroup analyses. EXPLORER-LTE, being a single cohort, has an inherently high risk of bias (so results are illustrative rather than confirmatory of long-term changes in outcomes). Additionally, EXPLORER-LTE has missing data or results for several outcomes. The two real-world evidence studies are only able to establish an association, not a causal link, between NHYA class and mortality and their results are uncertain due to limited reporting of the methods.

3.4 Outcomes assessment

Comparative efficacy results from the EXPLORER-HCM and VALOR-HCM trials and supporting results from the EXPLORER-LTE cohort are presented in section 3.6 of this report for the outcomes specified in the NICE scope. The relevance and interpretation of the

reported efficacy outcomes are discussed in sections 3.4.1 (efficacy outcomes) and 3.4.2 (HRQoL outcomes) below.

Safety results from the clinical trials are presented in section 3.7 of this report. The relevance and interpretation of the safety outcomes are discussed in section 3.4.3 below.

Outcomes used in the economic model are change in NYHA class, EQ-5D-5L, and adverse effects of treatment from both EXPLORER-HCM and EXPLORER-LTE. Outcomes from VALOR-HCM do not inform the economic analysis.

The clinical studies reported several secondary and exploratory outcomes which are not included in the CS as they are out of scope. These include echocardiogram measurements of cardiac structure, systolic and diastolic function, biomarkers, pharmacokinetics, and cardiographic magnetic resonance imaging measurements (CS Table 4). The EAG agree that exclusion of these outcomes from the CS is reasonable. The company's justification of the trial outcomes included in the CS is given in CS section B.2.3.1.1.1.

3.4.1 Efficacy outcomes

The EXPLORER-HCM primary outcome was a composite outcome designed specifically for use in the EXPLORER-HCM trial. It combined two physician-assessed outcomes, peak oxygen consumption (pVO_2) and change in NYHA class, that were also assessed separately as secondary outcomes. The definition was:

- either ≥1.5 mL/kg per min increase in pVO_2 with ≥1 NYHA class improvement; or
- ≥3.0 mL/kg per min increase in pVO_2 with no worsening of NYHA class, at week 30.

The CS additionally reports a more stringent version of this outcome that is not in the study protocol combining the greater increase in peak oxygen consumption (≥3 mL/kg/min) and the increase of ≥1 NYHA class (as opposed to 'no worsening').

The VALOR-HCM primary outcome was the proportion of patients who remained guideline eligible for SRT or chose to undergo SRT at 16 weeks. Guideline eligibility for SRT was defined as a composite of NYHA class and LVOT gradient: NYHA class III or IV, or NYHA class II with exertion-induced syncope or near syncope, and a dynamic LVOT gradient of ≥50 mmHg whether at rest or induced by Valsalva or exercise. Table 7.2.1-1 in the CSR defines SRT eligibility according to 2011 ACCF/AHA HCM guidelines,[53] but we note that this is consistent with the more recent ESC and AHA/ACC guidelines.[4 5]

pVO_2 was assessed onsite and at a central laboratory (as were all other cardiopulmonary exercise testing (CPET) measures). It provides an objective measure of functional exercise capacity. The company consider an improvement of ≥1 mL/kg/min in pVO_2 as clinically meaningful based on a retrospective study of CPET and prognosis in HCM.[54] Two of the EAG's clinical experts agree that this amount is probably clinically meaningful and said there is no validated alternative, therefore this value is pragmatic and objective; another expert thought this might be too small an improvement to be clinically meaningful. One of the EAG's clinical expert advisors noted that pVO_2 is useful to indicate response in a clinical trial but that it is not used for assessing response in clinical practice.

Change in NYHA class is a physician assessed outcome. It provides a broader (albeit somewhat subjective) assessment of symptoms and functional capacity. A change of ≥1 class was considered clinically meaningful, possibly according to expert elicitation via the company UK validation advisory board or the company clinical and health economic UK advisory board, although results were not included in the advisory board reports.[35 38] The EAG's clinical experts noted that these are broad classes with most patients assigned to class II or III and that patients may have symptomatic improvement within a class; allocation of patients to NYHA classes II and III (slight versus marked limitation of physical activity) can be subjective. This suggests the outcome should not be used on its own to demonstrate response; however, it is the only measure of clinical response entered into the economic model.

LVOT peak gradient is assessed by echocardiogram (all echocardiographic data were assessed on-site and at a central laboratory). It measures haemodynamic pressure in the left ventricular outflow tract whereby a pressure gradient of ≥30 mm/Hg defines left ventricular outflow tract obstruction (LVOTO), and a gradient of ≥50 mm/Hg can indicate surgery (septal reduction therapy) if patients do not respond to drugs.[4 5] LVOT peak gradient is measured either at rest, during the Valsalva manoeuvre, or immediately post-exercise. For diagnostic purposes, any type of LVOT gradient showing a peak of ≥30 mm/Hg is sufficient to indicate obstruction.[5]. LVOT peak gradient is not used in the economic model.

Change in LVEF is assessed by echocardiogram (all echocardiographic data were assessed on-site and at a central laboratory). An ejection fraction of ≤50% in HCM patients indicates impaired systolic function (reduced volume of blood being pumped out of the heart) and the potential for heart failure. A reduced left ventricular ejection fraction can indicate hypocontractility of the heart muscle and the potential for dose modification. The revised draft SmPC uses the LVEF <50% threshold to indicate

[redacted]. [24] According to the study protocols, LVEF ≤30% is [redacted] and thus is critical to safety as well as relevant to clinical effectiveness.[52 55]

Cardiopulmonary exercise testing (CPET) outcomes. A range of CPET parameters are reported (CS Table 15) which are appropriate for providing objective information about the severity of functional limitation.[4] One of the EAG's clinical experts noted that although these parameters are important in clinical research they do not translate easily to clinical practice for resource reasons; the most useful markers are pVO_2 and VE/VCO_2, but symptom assessment and echocardiograms are more important.

Complete response is a stringent composite outcome which requires an achievement of NYHA class I (i.e., no symptoms) and LVOT peak gradient <30 mm/Hg at rest, during Valsalva, and post exercise (i.e., below the threshold for diagnosing left ventricular outflow obstruction) thereby describing HCM that is no longer symptomatic nor obstructive.[2 5 34 56]

3.4.2 HRQoL outcomes

The Kansas City Cardiomyopathy Questionnaire (KCCQ-23) is a 23-item patient-reported outcome measure[57] qualified by the FDA in April 2020 for use in clinical investigations in heart failure.[58] The clinical summary score (KCCQ-23 CSS) combines responses on symptom frequency, symptom burden and physical limitations.[57] The FDA review concluded that the measure detects meaningful changes in HRQoL in patients with obstructive HCM[50] and a company study has validated its use in patients with obstructive HCM using data from the EXPLORER-HCM trial.[59] There is some evidence that meaningful thresholds of change are in 5 point increments: changes of 5, 10 and 20 points represent small, moderate-to-large and large-to-very-large clinical changes, but they have yet to be validated.[57] The CS states that an increase of ≥10 points indicates a moderate to very large clinical improvement (CS section B.2.6.1.3).

The HCM symptom questionnaire (HCMSQ) is a patient-reported symptom measurement instrument developed specifically for patients with HCM. It was found to be fit-for-purpose in assessing treatment benefit by a company funded analysis of its use in the EXPLORER-HCM and MAVERICK-HCM clinical trials.[60 61] The CS only reports the shortness of breath

subscale (HCMSQ-SoB) which demonstrated the strongest content validity and psychometric performance,[60] and the EAG agree that this is appropriate. A change of one to two points for shortness of breath and the total symptom scores is considered a within-patient meaningful change.[60]

EQ-5D-5L assessments are used to inform the economic model which is appropriate for a NICE Technology Appraisal.

Other patient-reported outcomes: According to the CSR, participants in the EXPLORER-HCM trial additionally completed self-reported assessments for the Patient Global Impression of Change (PGIC) scale, the Patient Global Impression of Severity (PGIS) scale and the Work Productivity and Activity Impairment-Specific Health Problem (WPAI:SHP) questionnaire. These are exploratory outcomes and not reported in the CS. The EAG agree that it is appropriate to focus on the disease-specific measures (i.e. KCCQ-23 and HCMSQ-SoB).

3.4.3 Safety outcomes

EXPLORER-HCM, VALOR-HCM and EXPLORER-LTE recorded adverse events, with assessment of the safety and tolerability of mavacamten being the primary objective of the EXPLORER-LTE study. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 (CS Table 9) which the EAG agree is appropriate. The EAG's clinical experts agreed that the safety analysis approach is appropriate and that all relevant adverse events have been considered.

EAG conclusion on the outcomes assessment

All outcomes reported for efficacy, including those for patient-reported severity and HRQoL, and for safety are relevant and clinically meaningful. Although there are many further per-protocol outcomes reported in the CSR, not the CS, they are exploratory and/or record pharmacokinetics or biomarkers of HCM, therefore the EAG do not consider selective reporting to be an issue. Echocardiography data and CPET data were sent to a central lab for assessment, providing independent verification of any site-read assessments. Outcomes informing the economic model (change in NYHA class, EQ-5D-5L, and adverse effects of treatment) are relevant and appropriate.

3.5 Statistical methods of the included studies

3.5.1 Statistical methods in EXPLORER-HCM

The EAG consider the statistical analysis approach for EXPLORER-HCM (CS Table 9) to be appropriate. We note that the US FDA[50] conducted a detailed review of the EXPLORER-HCM trial and identified no concerns relating to the sample size and statistical power, efficacy and safety analysis populations, or the choice of statistical tests applied. The FDA review did, however, raise concerns around missing data for secondary outcomes and how these were accounted for in analyses. A substantial proportion of data for the HRQoL outcomes KCCQ-23 CSS and HCMSQ-SoB (around 30%) were missing. The company clarified to the FDA that baseline data were missing due to "operational challenges" which included staff learning about the electronic clinical assessment procedure, participants forgetting to bring their clinical outcome assessment device on their first visit, and completion of the HCMSQ-SoB questionnaire daily was found to be burdensome. The company[29] and FDA review[50] conducted a range of sensitivity analyses to investigate the impact on outcomes of the missing data.

The extent of missing data for each of the efficacy outcomes are considered in the risk of bias assessment (section 3.3.1), with the sensitivity analyses suggesting that the KCCQ-23 CSS and HCMSQ-SoB outcomes were robust to the missing data, although missing data are a concern for the change in EQ-5D from baseline to week 30 (i.e. high risk of attrition bias for this outcome; Appendix 9.3.1).

3.5.2 Statistical methods in EXPLORER-LTE

EXPLORER-LTE is an ongoing observational study. The results reported in the CS are taken from an August 2021 data cut. However, the length of follow up for this data cut is not reported in the CS. The company have presented outcomes data up to 84 weeks from baseline.

CS Table 10 states that the clinical efficacy outcome analysis population defined for the interim analysis in EXPLORER-LTE was the ITT population, i.e. "all randomised participants regardless of whether they received study drug, with analyses conducted according to the randomised treatment assignment". We assume that this is a typographic error, since EXPLORER-LTE is a single intervention cohort study with no comparator (the Statistical Analysis Plan[62] does not refer to an ITT analysis).

The outcomes in EXPLORER-LTE were analysed with descriptive statistics to summarise changes from baseline (CS Table 10 and the Statistical Analysis Plan [62]), which the EAG agree is appropriate.

3.5.3 Statistical methods in VALOR-HCM

VALOR-HCM is an ongoing study that has met its primary outcome, a composite of the decision to proceed with SRT prior to or at week 16 or remaining guideline-eligible for SRT at week 16. All efficacy analyses during the randomised comparison (i.e. up to week 16) were based on the ITT population, defined as all randomised patients regardless of whether they received the study drug, with analyses stratified by type of SRT recommended (myectomy versus alcohol ablation) and NYHA class. Statistical test methods are summarised in Company Addendum Table 3, the CSR and the trial publication[33] and appear broadly appropriate.

Secondary outcomes were tested in a pre-specified sequential order to account for multiple testing. The order of outcomes and rationale for the sequence is not explained in the Company Addendum, although the order, but not the rationale, is reported in the trial publication[33] All outcomes in the sequence were ultimately declared statistically significant.

Sensitivity analyses to assess the impact of missing data were conducted using a tipping point analysis for the primary outcome and “using MAR mechanism” for secondary outcomes (Company Addendum Table 3) which is not explained but the EAG assume that MAR means data were assumed to be missing at random. Results of these sensitivity analyses on missing data are not reported in the Company Addendum. However, the proportion of data missing appears to be low (≤2% of participants’ data in the mavacamten arm and ≤5% in the placebo arm were missing at week 16 across all outcomes according to Company Addendum Figures 2 to 5), suggestive of a low risk of attrition bias for the primary and secondary outcomes (Appendix 9.3.2).

3.5.4 Subgroup analyses

EXPLORER-HCM

The company conducted pre-specified subgroup analyses in EXPLORER-HCM for the primary outcome (CS Table 5; results summarised in section 3.6.10 below) and for post-exercise LVOT gradient (reported in the trial publication).[26] Beta-blocker use at baseline was the only subgroup that had a statistically significant effect (on the primary outcome only). To

explore the effect of beta-blocker use further the company conducted post-hoc subgroup analyses by beta-blocker use for a range of outcomes as reported in CS Table 16.

The CS does not state whether the pre-specified subgroup analyses were powered statistically to detect specific differences in the outcomes tested. The EAG assume that neither the pre-specified nor post-hoc subgroup analyses were powered statistically. Conversely, the CS does not mention any adjustment for multiple statistical testing in the subgroup analyses. There is therefore uncertainty around the extent to which the subgroup analyses would be subject to type I and type II errors, i.e. false negative and false positive subgroup effects. We note that whilst most of the reported subgroup analyses had moderate sample sizes (50 to 100 participants per group), analyses of age (for the class ≤49 years) and the proportion with an HCM pathogenic mutation had small sample sizes (<30 per group) (CS Figure 19), meaning that results of these analyses are less certain.

VALOR-HCM

In VALOR-HCM, 20 pre-planned subgroup analyses were specified covering a range of baseline covariates (Company Addendum Table 3). The Company Addendum refers the reader to CSR for the results of these (the trial publication presents results for 10 subgroup analyses[33]). However, these subgroup results are difficult to interpret since there appear to be unbalanced missing data without explanation (only a maximum of 10 mavacamten patients contributed to each subgroup analysis whilst 43 contributed from the placebo group (Appendix Figure 1 in Desai et al. 2022[33]).

> **EAG conclusion on study statistical methods.** The EXPLORER-HCM and VALOR-HCM trials and the EXPLORER-LTE study appear to have followed appropriate statistical methods. The analysis stratification/adjustment factors differed between the trials (e.g. EXPLORER-HCM did not adjust for SRT) and it is unclear how sensitive the analyses would be to varying the covariates adjusted for. The main statistical concern relates to missing data which were not imputed or adjusted for, for the EQ-5D outcome in EXPLORER-HCM, and for resting and Valsalva LVOT gradients and LVEF in EXPLORER-LTE. Subgroup analyses in VALOR-HCM have small and unbalanced sample sizes, limiting interpretation.

3.6 Efficacy results of the intervention studies

Results are presented here for the pivotal EXPLORER-HCM and supporting VALOR-HCM RCTs as well as illustrative results from the non-comparative EXPLORER-LTE study. For interpretation of the following efficacy outcomes please refer to section 3.4 above.

3.6.1 EXPLORER-HCM composite primary outcome

The composite primary outcome and also its individual components (i.e. changes in NYHA class and changes in pVO_2) were achieved at 30 weeks in EXPLORER-HCM by just over twice as many patients in the mavacamten group as in the placebo group, with the differences being statistically significant (95% confidence intervals for the differences between mavacamten and placebo groups exclude zero) (Table 8). The CS notes that the most stringent combination of the composite endpoint (both ≥3 mL/kg/min in pVO_2 and an improvement of ≥1 NYHA class) was met by 20% of patients on mavacamten plus standard care and 8% of patients on placebo, also being statistically significant.

The EXPLORER-HCM primary outcome was not assessed in the EXPLORER-LTE cohort (the objective of which was primarily safety monitoring).

Table 8 Composite primary outcome in EXPLORER-HCM at week 30

	Mavacamten (N = 123)	Placebo (N = 128)	Mavacamten vs placebo (95% CI) [a]
Primary outcome			
Either ≥1.5 mL/kg per min increase in pVO_2 with ≥1 NYHA class improvement or ≥3.0 mL/kg per min increase in pVO_2 with no worsening of NYHA class, n (%) [b]	45 (37)	22 (17)	19.4 (8.7 to 30.1)
Components of composite primary outcome			
≥1.5 mL/kg per min increase in pVO_2 with ≥1 NYHA class improvement, n (%) [b]	41 (33)	18 (14)	19.3 (9.0 to 29.6)
≥3.0 mL/kg per min increase in pVO_2 with no worsening of NYHA class, n (%) [b]	29 (24)	14 (11)	12.6 (3.4 to 21.9)
Both ≥3 mL/kg/min in pVO_2 and an improvement of ≥1 NYHA class, n (%) [c]	25 (20)	10 (8)	12.5 (4.0 to 21.0)

Source: Reproduction of CS Table 12 with minor modifications.
[a] Adjusted difference in proportions; the analysis was stratified on NYHA class, BB use, and exercise type.
[b] Missing NYHA class at Week 30 was imputed using available NYHA class at Week 26. After the imputation, the participants whose response status at Week 30 was still missing were classified as non-responders. Low proportion of missing data: 2.4% for pVO_2 and 1.6% for NYHA class (proportion missing and imputed not reported for the composite outcome but presumed by the EAG to be low).
[c] These are the most stringent pVO_2 and NYHA class components of the composite functional outcome.

The EAG note that the majority of patients in the mavacamten group (63%) did not achieve the primary outcome. The EAG's clinical experts suggested several potential explanations for this:

- Results might reflect heterogeneous subgroups, e.g. differences in mavacamten efficacy in relation to sarcomere positive and negative groups (for further discussion of this issue see section 1.3 above).
- The symptomatic improvement noted (see section 3.6.9 below) suggests wider efficacy benefits of mavacamten than captured by the primary outcome alone.
- pVO_2 may have been assessed too early, as change in pVO_2 may be expected to occur after the other changes e.g. in myocyte function, LVOT gradient and symptoms (12 or 24 month assessments may be more appropriate).

3.6.2 Primary outcome in VALOR-HCM

In **VALOR-HCM**, the primary outcome was the proportion of patients who remained guideline eligible for SRT or chose to undergo SRT at 16 weeks. After 16 weeks, a statistically significant greater proportion of patients in the placebo group remained guideline eligible or chose to undergo SRT (43/56; 76.8%) compared with the mavacamten group (10/56; 17.9%), p<0.001 (Company Addendum section 2.6.1). The adjusted treatment difference is reported as 58.9% (95% CI 44.0% to 73.9%).[33] The study authors note that a limitation of the primary outcome is that it was driven by a reduction in guideline eligibility for SRT rather than by patients' decisions not to undergo SRT.

3.6.2.1 Change in NYHA class

The change in NYHA class was specified as a secondary outcome in EXPLORER-HCM and VALOR-HCM and as an "efficacy" outcome in EXPLORER-LTE.

In **EXPLORER-HCM** 80/123 of the mavacamten group (65%) and 40/128 of the placebo group (31%) improved by ≥ 1 NYHA class from baseline to week 30. The unadjusted difference between mavacamten plus standard care and placebo was 34% (95% CI 22.0% to 45.0%; p<0.0001) (CS Table 13). The EAG have no concerns about the handling of missing data as only 1.6% of data for this outcome were missing and those with missing data were classified as non-responders.

In **EXPLORER-LTE** 139/206 patients (67.5%) who received mavacamten improved by ≥ 1 NYHA class from baseline to week 48 (CS section B.2.6.2.1). At week 48, 31.1% remained in the same class and 1.5% worsened by one or more NYHA classes at Week 48[31] (CS

Figure 15). Missing data were not imputed, although the proportion of missing data for the week 48 assessment (11/217) was relatively low (5%). According to the protocol,[52] NYHA class was not assessed at week 84, whilst the next protocol-specified assessment, at 108 weeks, had not been reached at the data cut.

In **VALOR-HCM** 35/56 patients (62.5%) who received mavacamten and 12/56 (21.4%) who received placebo improved by ≥1 NYHA class from baseline to week 16; the adjusted treatment difference between mavacamten and placebo is reported as 41.1% (95% CI 24.5% to 57.7%; p<0.001) (Company Addendum Table 7).

3.6.3 Post-exercise LVOT gradient

The change in post-exercise LVOT gradient was specified as a secondary outcome in the EXPLORER-HCM and VALOR-HCM trials. In EXPLORER-LTE, according to the protocol,[52] the post-exercise LVOT gradient was measured only at week 24 (to support dose-adjustment decisions) and is not reported in the CS or publications.[31 63]

In **EXPLORER-HCM** the mean (95% CI) change from baseline to 30 weeks in post-exercise LVOT gradient was -47.0 mmHg (-54.6 to -39.9 mmHg) in the mavacamten group and -10.4 mmHg (-15.7 to -5.1 mmHg) in the placebo group. The adjusted mean difference between groups (controlling for treatment group, baseline value of the outcome and the 3 stratification factors: BB use, NYHA class, ergometer type) was -35.6 (-43.2 to -28.1) mmHg (CS Table 13 and CSR Table 22). The CSR states that missing data were not imputed; however, the proportion missing was relatively low (6/123 in the mavacamten group and 6/128 in the placebo group, i.e. 5% in each group).

In **VALOR-HCM** the mean (SD) change from baseline to week 16 in post-exercise LVOT gradient was -39.1 mmHg (36.5 mmHg) in the mavacamten group compared to -1.8 mmHg (28.8 mmHg) in the placebo group; the adjusted treatment difference was -37.2% (CI -48.1% to -26.2%; p<0.001) (Company Addendum Table 7).

3.6.4 Resting LVOT gradient

The change in resting LVOT gradient was specified as an “exploratory” outcome in EXPLORER-HCM and VALOR-HCM, and an “efficacy” outcome in EXPLORER LTE.

In **EXPLORER-HCM** the mean (95% CI) change from baseline to 30 weeks in resting LVOT gradient was -39.0 mmHg (-44.0 to -33.2 mmHg) in the mavacamten group and -6.0 mmHg

(-10.5 to -0.5 mmHg) in the placebo group. This outcome is not reported in the CS; data are sourced from Table 22 in the CSR.[40] The CSR states that missing data were not imputed; however the proportion missing was relatively low (6/123 in the mavacamten group and 7/128 in the placebo group, i.e. 5% in each group).

In **EXPLORER-LTE** the mean (SD) change from baseline in resting LVOT gradient for patients who received mavacamten was -35.6 (32.6) mmHg at week 48 and -32.8 (30.8) mmHg at week 84 (confidence intervals are not reported) (CS Figure 17). The sample sizes for these assessments, n=206 and n=66 respectively, represent 95% and 30% of the 217 patients on treatment in EXPLORER-LTE at the August 2021 data cut. It is unknown whether patients with missing LVOT gradient data (i.e. 5% and 70% respectively at these timepoints) would have had similar outcomes.

In **VALOR-HCM** the mean (SD) change in resting LVOT gradient from baseline to week 16 was -36.0 (28.8) for the mavacamten group compared to -1.5 (26.5) in the placebo group; the adjusted treatment difference was -33.4% (95% CI -42.3% to -24.5%).[33]

3.6.5 Valsalva LVOT gradient

The change in Valsalva LVOT gradient was specified as an “exploratory” outcome in EXPLORER-HCM and VALOR-HCM, and an “efficacy” outcome in EXPLORER LTE.

In **EXPLORER-HCM** the mean (95% CI) change from baseline to 30 weeks in Valsalva LVOT gradient was -49.0 mmHg (-55.4 to -43.0 mmHg) in the mavacamten group and -12.0 mmHg (-17.6 to -6.6 mmHg) in the placebo group. The CSR states that missing data were not imputed; however the proportion missing was relatively low (6/123 in the mavacamten plus standard care group and 4/128 in the placebo group, i.e. 5% and 3% respectively). This outcome is not reported in the CS; data are sourced from Table 22 in the CSR.[40]

In **EXPLORER-LTE** the Mean (SD) change from baseline in Valsalva LVOT gradient was -45.3 (35.9) mmHg at week 48 and -46.4 (35.8) mmHg at week 84 (CS Figure 17). The sample sizes for these assessments, n=206 and n=67 respectively, represent 95% and 31% of the 217 patients on treatment in EXPLORER-LTE at the August 2021 data cut. It is unknown whether patients with missing LVOT gradient data (i.e. 5% and 69% respectively at these timepoints) would have had similar outcomes.

In **VALOR-HCM** the mean (SD) change in Valsalva LVOT gradient from baseline to week 16 was -45.2 (28.5) mmHg for the mavacamten group compared to 0.4 (29.7) mmHg in the placebo group; the adjusted treatment difference was -47.6% (95% CI -58.2% to -37.0%) mmHg.[33]

3.6.6 Resting LVEF

The change in LVEF was specified as an "exploratory" outcome in EXPLORER-HCM and VALOR-HCM and an "efficacy" outcome in EXPLORER LTE.

In **EXPLORER-HCM** the mean (SD) change from baseline to week 30 in LVEF was -3.9% (7.7%) in the mavacamten group and -0.01% (6.8%) in the placebo group (difference -4.0%; 95% CI -5.5% to -2.5%) (study publication,[26] CS section B.2.6.1.4 and Table 22 in the CSR). [redacted] (CS section B.2.6.1.4). The CSR states that missing data were not imputed. The proportion missing was 9/123 in the mavacamten group and 9/128 in the placebo group (i.e. 7% in each group). It is unclear whether the change in LVEF would have been similar for patients with missing data.

In **EXPLORER-LTE** the mean (SD) change from baseline in LVEF was -7.0% (8.3%) at week 48 and -9.0% (8.1%) at week 84 (CS Figure 18). The sample sizes for these assessments, n=197 and n=66 respectively, represent 91% and 30% of the 217 patients on treatment in EXPLORER-LTE at the August 2021 data cut. It is unknown whether patients with missing LVEF data (i.e. 9% and 70% respectively at these timepoints) would have had similar outcomes.

In **VALOR-HCM** the mean (SD) change in LVEF from baseline to week 16 was -3.4 (6.23) mmHg in the mavacamten group compared to 0.3 (4.19) mmHg in the placebo group which the company describe as statistically significant (treatment difference -4.0, 95% CI -5.5 to -2.5) mmHg ($p<0.0001$) but not expected to be clinically meaningful (Company Addendum section 2.6.3 and Table 8).

The decrease in resting LVEF in each study is consistent with the mode of action of mavacamten, but in all studies the baseline LVEF exceeded 60% and the relative decrease was small. Centrally-read LVEF measurements were higher (i.e. more favourable) than those of site-read measurements in EXPLORER-LTE, notably at the start of the study (CS Figure 18) but the reason for this difference is unclear.

3.6.7 Other CPET and echocardiogram outcomes

Changes from baseline in several exploratory CPET outcomes are reported in the CS from the EXPLORER-HCM trial (CS Table 15), but were not assessed in EXPLORER-LTE or VALOR-HCM. These outcomes are summarised briefly here for completeness but are not key outcomes in the company's submission.

In EXPLORER-HCM, relative to placebo, mavacamten resulted in statistically significant improvements in the peak oxygen consumption (pVO_2), peak and slope of the ventilation/CO_2 production relationship (VE/VCO_2), peak circulatory power, peak metabolic equivalents of task (MET), peak partial pressure of exhaled CO_2 ($PETCO_2$) and ventilatory power at 30 weeks (CS Table 15). The EAG's clinical experts agreed that collectively these outcomes indicate improved exercise performance with mavacamten compared to placebo.

3.6.8 Complete response

A complete response (defined as NYHA class I and all resting, post-exercise and Valsalva LVOT peak gradients less than 30mmHg), assessed only in EXPLORER-HCM at 30 weeks, was observed in 32/117 patients (27%) in the mavacamten group and 1/126 patients (1%) in the placebo group. The difference between groups was 26.6% (95% CI 18.3 to 34.8%; p<0.0001) (CS section 2.6.1.4). Relatively few data were missing for the mavacamten group (6/123; 5%) and placebo group (2/128; 2%) and those with missing data were assumed to be non-responders which is a conservative assumption.

3.6.9 HRQoL outcomes

For interpretation of the HRQoL outcomes please refer to section 3.4.2 above.

KCCQ-23 CSS (a secondary outcome in both RCTs) demonstrated a statistically significant and clinically meaningful effect of mavacamten in reducing patients' symptoms in both EXPLORER-HCM (Table 9) and VALOR-HCM (Table 10). In EXPLORER-HCM the effect attenuated to the baseline level after treatment had stopped at 30 weeks (CS Figure 11).

A clinically meaningful improvement of ≥10 points was experienced by 52% of patients receiving mavacamten and 31% of patients receiving placebo at 30 weeks. As noted above (section 3.3.1) there were substantial missing data for this outcome in EXPLORER-HCM but sensitivity analyses indicated that the conclusion of treatment benefit for mavacamten remained unchanged after applying worst-case missing data assumptions.

HCMSQ-SoB score (a secondary outcome) was assessed only in EXPLORER-HCM and demonstrated a statistically significant and clinically meaningful effect of mavacamten in reducing patients' shortness of breath (Table 9). A clinically meaningful decrease of ≥2.5 points was experienced by 50% of patients receiving mavacamten and 21% of patients receiving placebo at 30 weeks. As noted above (section 3.3.1) there were substantial missing data for this outcome but sensitivity analyses indicated that the conclusion of treatment benefit for mavacamten remained unchanged after applying worst-case missing data assumptions.

EQ-5D index and VAS scores were exploratory outcomes assessed in a post-hoc analysis for patients who had both a baseline and a week 30 measurement (EXPLORER-HCM) or a week 16 measurement (VALOR-HCM). In EXPLORER-HCM the change from baseline in both EQ-5D measures was statistically significantly greater in the mavacamten group than the placebo group (Table 9). However, data are missing for 27/123 participants (22%) in the mavacamten group and 39/128 patients (30%) in the placebo group. It is unknown whether patients with missing data would have had similar EQ-5D scores to those who provided data, meaning that the EQ-5D results from EXPLORER-HCM are uncertain.

In VALOR-HCM there was only a small change in EQ-5D-5L index score, from baseline to week 16, in both groups, and the difference between mavacamten and placebo groups was not statistically significant (Table 10). The EQ-5D VAS score was not assessed in VALOR-HCM.

Table 9 Changes from baseline to week 30 in symptom and HRQoL outcomes in EXPLORER-HCM

Change from baseline to week 30 in:	Mavacamten		Placebo		Mavacamten vs placebo (95% CI)	p value
	N	mean (SD) [a]	N	mean (SD)[a]		
KCCQ-23 CSS	92	13.6 (14.4)	88	4.2 (13.7)	9.1 (5.5 to 12.7) [b]	< 0.0001
KCCQ-23 OS	92	14.9 (15.8)	88	5.4 (13.7)	9.1 (5.5 to 12.8) [b]	< 0.0001
HCMSQ-SoB subscore	85	-2.8 (2.7)	86	-0.9 (2.4)	-1.8 (-2.4 to -1.2) [b]	< 0.0001
EQ-5D-5L index score	96	0.084	89	0.009	0.075 (0.028 to 0.122) [b] 0.073 (0.027 to 0.118) [c]	0.002 [b] 0.002 [c]
EQ-VAS score	96	8.5	89	0.7	7.8 (2.0 to 13.6) [b] 7.5 (1.8 to 13.2) [c]	0.009 [b] 0.010 [c]

Source: Reproduction of CS Table 14 with minor adjustments.
[a] Missing NYHA class at Week 30 was imputed using available NYHA at Week 26. After imputation, patients whose response status at Week 30 was still missing were classified as non-responders.
[b] Unadjusted analysis.
[c] Adjusted analysis (adjusted for NYHA class, II or III; beta-blocker use, yes or no; ergometer type, treadmill or exercise bike) from Xie et al. 2022.[64]

Table 10 Changes from baseline to week 16 in symptom and HRQoL outcomes in VALOR-HCM

Change from baseline to week 16 in:	Mavacamten		Placebo		Mavacamten vs placebo (95% CI)	p value
	N	mean (SD)	N	mean (SD)		
KCCQ-23 CSS	55	10.4 (16.1)	53	1.9 (12.0)	9.4 (4.9 to 14.0)	<0.001
EQ-5D-5L index score	55	[redacted]	53	[redacted]	[redacted]	[redacted]
Source: CS Addendum Tables 7 and 8						

The CS reports that in EXPLORER-HCM the mean EQ-5D index scores over 30 weeks decreased with higher NYHA class (Table 11), with the differences between classes being statistically significant.[64] However, the EQ-5D index scores within each NHYA class did not differ statistically significantly between the mavacamten and placebo groups. There were few missing data for this analysis (mavacamten n=4, placebo n=3) but the distribution of patients between each NYHA class in Table 11 is not reported.

Table 11 Mean EQ-5D index scores for each NYHA class in EXPLORER-HCM

NYHA class	Mavacamten (N=119)	Placebo (N=125)
I	0.950	0.952
II	0.866	0.850
III/IV	0.708	0.704
Sources: CS section 2.6.1.3; Xie et al. 2022[64] All patients with at least one post-baseline EQ-5D assessment at weeks 6, 12, 18 and/or 30 and a NYHA functional class assessment at these timepoints were included in the analysis.		

3.6.10 Subgroup analyses

No subgroup analyses are specified in the NICE scope. However, the EXPLORER-HCM trial had predefined subgroup analyses for the primary outcome according to randomisation stratification factors, patient demographics, beta-blocker use and other baseline characteristics as well as post-hoc subgroup analysis for other outcomes by beta blocker use (see section 3.5.4 above). The EAG assume that the subgroup analyses were not powered statistically to detect specified effects on outcomes and were not adjusted for

multiple testing; we also note that sample sizes were relatively small, particularly for the age and HCM pathogenic mutation subgroup comparisons (section 3.5.4). Results of the subgroup analyses are therefore uncertain.

EXPLORER-HCM

The company's pre-specified subgroup analyses found no statistically significant difference across subgroups in the relative efficacy of mavacamten for the primary outcome (CS Figure 19) or for post-exercise LVOT gradient[26] compared to placebo, except for the beta-blocker subgroup analysis of the primary outcome. Mavacamten showed a greater magnitude of improvement in the primary outcome for those who were not on beta-blockers at baseline (53%; 95% CI 39.2 to 72.2) than those who were on beta-blockers (9%; 95% CI -3.6 to 21.1) (CS section B.2.7.1). Such an effect of beta-blocker use was not evident for post-exercise LVOT gradient.[26]

The subgroup analysis in EXPLORER-HCM suggests that the benefit of mavacamten may have been larger in patients with a sarcomere mutation (i.e. a pathogenic or likely pathogenic mutation) than those who were sarcomere mutation negative, although the effect was statistically significant for the sarcomere mutation positive group only, with overlapping confidence intervals for the subgroups (CS Figure 19). If mavacamten efficacy differs between these subgroups this would have implications for cost-effectiveness (discussed as a key issue in section 1.3 above). Subgroup analysis according to sarcomere mutation presence/absence was also conducted in VALOR-HCM but results are only presented for the sarcomere mutation negative subgroup (CSR section 7.2.4), which we assume reflects an inadequate sample size for the sarcomere mutation positive subgroup.

To further explore the potential effect of beta-blocker use on mavacamten efficacy the company conducted beta-blocker subgroup analyses post-hoc for the secondary and exploratory outcomes of EXPLORER-HCM (Table 12).

Table 12 Outcomes reported for subgroup comparisons: mavacamten ± beta-blockers in EXPLORER-HCM, change from baseline to week 30

Outcome (mean & SD unless stated)	**With beta-blocker**		**Without beta-blocker**		**Source**
	Mavacamten N=94	**Placebo** N=95	**Mavacamten** N=29	**Placebo** N=33	
Heart function outcomes assessed on cardiopulmonary exercise testing					
pVO_2, mL/kg/min	1.1 (3.1)	0.1 (3.2)	2.2 (3.0)	-0.5 (2.4)	CS Table 16; Jacoby et al. 2021[39]
Resting LVOT gradient, mmHg	-37.5 (30.1)	-5.1 (27.5)	-42.2 (27.9)	-6.8 (29.7)	CS Table 16; Jacoby et al. 2021[39]

Valsalva LVOT gradient, mmHg	-50.0 (36.8)	-10.4 (30.3)	-46.3 (25.6)	-17.3 (32.8)	CS Table 16; Jacoby et al. 2021[39]
LVEF, %	-3.6 (7.7)	0.4 (7.1)	-5.0 (7.6)	-1.3 (5.8)	Jacoby et al. 2021[39]
NYHA ≥1 class improvement % of patients	65	35	66	21	CS Table 16; Jacoby et al. 2021[39]
KCCQ-23 CSS score	14.2 (14.3)	3.3 (13.7)	11.0 (15.0)	6.3 (13.8)	CS Table 16; Jacoby et al. 2021[39]
KCCQ CSS: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; NYHA: New York Heart Association class; pVO_2: peak oxygen consumption; RER: respiratory exchange ratio; SD: standard deviation					

The change in peak oxygen consumption (pVO_2), a component of the composite primary functional outcome, was smaller for patients using beta-blockers compared with those who were not using beta-blockers (Table 12). This difference between beta-blocker use subgroups was also evident for the baseline values of pVO_2. The company note that beta-blockers have a known effect reducing heart rate (mean 119 versus 138 beats/minute in EXPLORER-HCM[26]) and they argue that the effect of beta-blockers on pVO_2 is consistent with this (CS section B.2.7.1).

As shown in Table 12 the symptom outcomes (NYHA class improvement and change in KCCQ-23 CSS score) do not appear to have been strongly influenced by beta-blocker use, although the sample sizes for the no beta-blocker group are relatively small (N=29 and N=33 for mavacamten and placebo respectively). The company did not present any subgroup analyses for the KCCQ-23 OS, HCMSQ-SoB or EQ-5D outcomes.

Based on nine outcomes submitted for FDA review (Table 12), the FDA concluded that clinical improvements associated with mavacamten treatment were generally preserved in participants receiving beta blockers despite the subgroup findings for the primary efficacy outcome.[50]

EXPLORER-LTE

The company provide beta-blocker subgroup analysis results for three outcomes in the EXPLORER-LTE cohort: resting and Valsalva LVOT gradients and % of patients with NYHA class improvement (CS Table 16). It is unclear why other outcomes (labelled as "not determined" in CS Table 16) were not assessed in the EXPLORER-LTE cohort. Sample sizes for the EXPLORER-LTE subgroups are presumably relatively small but are not reported in CS Table 16. Due to these uncertainties, and the lack of a placebo comparator, it is difficult to draw firm conclusions about the robustness of subgroup findings in the LTE cohort. However, the non-comparative data in CS Table 16 suggest that temporal

improvements in the three measured outcomes among patients receiving mavacamten were not influenced substantially by concomitant beta-blocker use up to 48 weeks of follow up in EXPLORER-LTE.

VALOR-HCM

Subgroup analyses are reported for the VALOR-HCM trial in the trial publication Appendix [33] and section 7.2.4 of the CSR but sample sizes are small and appear unbalanced between the mavacamten and placebo groups (see section 3.5.4 above). The subgroups in VALOR-HCM appear to be too small to draw any conclusions on effects of beta-blocker use.

> **EAG conclusion on beta-blocker use subgroup analyses:** The EAG concur with the conclusions of the company, FDA and Jacoby et al.[39] that, based on the results of the EXPLORER-HCM trial, mavacamten demonstrated a clinically meaningful efficacy benefit compared to placebo both among patients who received beta-blockers and those who did not.

3.7 Safety results

3.7.1 EXPLORER-HCM and EXPLORER-LTE

Safety results are reported in CS section B.2.10 for EXPLORER-HCM and EXPLORER-LTE. Table 13 below gives an overview of the results.

Table 13 Summary of safety outcomes in EXPLORER-HCM and EXPLORER-LTE

Safety outcome	EXPLORER-HCM		EXPLORER-LTE August 2021
	Mavacamten N=123	Placebo N=128	Mavacamten N=231
Exposure in weeks, mean (median)	[redacted]	[redacted]	Unclear [b]
Any TEAE, n (%) [a]	[redacted]	[redacted]	201 (87.0)
At least one study drug related TEAE, n (%)	[redacted]	[redacted]	40 (17.3)
Any SAE, n (%) [c]	10 (8)	11 (9)	34 (14.7)
Drug-related SAE, n (%) [c]	0	1 (1) [d]	5 (2.2)
Treatment interruption due to TEAE, n (%)	[redacted]	[redacted]	26 (11)
Treatment discontinuation due to TEAEs, n (%)	[redacted] [e]	NR	10 (4.3)

Sources: CS section B.2.10; CS Tables 17, 19, 20, 21 and 22.
NR: not reported; TEAE: treatment-emergent adverse event; SAE: serious adverse event
[a] Reported for weeks 1-38, i.e., includes washout period.
[b] Not reported [mean (median) duration of exposure at the October 2020 data cut was 31.8 (32.3) weeks].
[c] Reported for weeks 1-30, i.e., on-treatment period only.
[d] Sudden death
[e] [redacted]

The CS reports dizziness, dyspnoea, headache, and nasopharyngitis as the most common TEAEs experienced in 10% or more participants in the EXPLORER-HCM trial (CS Table 18), and dizziness, fatigue, and hypertension are reported for 10% or more participants in the EXPLORER-LTE trial (CS Table 21 footnote).

The CS does not report results for the protocol-defined adverse events of special interest (AESIs). The study CSRs report [redacted] (MAVA-LTE CSR section 12.3.1.2.2.1 Table 50). No participants experienced LVEF ≤30% in [redacted], and both study CSRs report [redacted]. (EXPLORER-HCM CSR section 11.6; MAVA-LTE CSR section 12.3.1.2.2.1 Table 50). There was one fatality in the EXPLORER-HCM placebo arm from sudden death, which was the only SAE in the study (CS section B.2.10.4).

3.7.2 VALOR-HCM

Selected adverse events are reported for VALOR-HCM in CS section B.2.11, the study publication,[44] and in Company Addendum section 2.8. They indicate no new safety signals compared to the EXPLORER-HCM trial and the EXPLORER-LTE cohort study. No participants experienced LVEF ≤30% based on echocardiographic measurements during scheduled site visits,[65] and the two participants who experienced LVEF ≤50% did not discontinue treatment permanently (Company Addendum 2.8). There were [redacted] adverse events leading to drug interruptions in the mavacamten arm ([redacted] ([redacted]%)) compared to the placebo arm ([redacted] ([redacted]%)) (Company Addendum Table 9). No participants experienced SAEs of congestive heart failure, syncope, or sudden cardiac death.[44]

3.7.3 FDA review

The EAG note that the FDA review of mavacamten included an integrated safety summary (ISS) that pooled safety data from EXPLORER-HCM, PIONEER-HCM, MAVERICK-HCM, MAVA-LTE and PIONEER-OLE.[50] This maximised the number of mavacamten-treated participants (n=263, including n=54 non-obstructive HCM participants from the MAVERICK-HCM and MAVA-LTE studies) and the duration of exposure for analysis (median 8.3 months). Overall results for treatment-emergent adverse events and serious adverse events were similar to those reported in EXPLORER-HCM alone. However, the ISS showed a slight

increase of occasions (3.4% of participants) where LVEF levels were lowered enough to meet permanent discontinuation of study drug criteria although the FDA reviewer comment noted that effects on LVEF were generally reversed once participants had discontinued treatment.[50] The ISS also described the outcomes of two further symptomatic overdoses. The EAG note that there were some differences in dosing strategies for the MAVERICK-HCM trial included in the ISS which influenced these results, thus highlighting the importance of the dosing strategy for ensuring the safety of mavacamten.

The FDA conducted a risk evaluation and mitigation strategy (REMS) review,[66] and consequently mavacamten is only available in the US via the restricted Camzyos® REMS program.[67] The program ensures regular monitoring with echocardiograms to manage the risk of heart failure due to systolic dysfunction (LVEF <50%) and avoidance of certain prescription and over-the-counter medicines that interfere with the metabolism of mavacamten. The EAG is uncertain whether this level of post-authorisation safety monitoring would also apply in the NHS. The revised draft SmPC describes the recommended assessments and frequency of monitoring required (as enforced in the US in the Camzyos® REMS program) because there is a clear risk of heart failure when LVEF levels fall below 50% and serial echocardiograms are important to detect falling LVEF levels.[24]

EAG conclusion on safety outcomes

Mavacamten appears to be well-tolerated. If dosage and effects on participant LVEF levels are monitored and where protocol-specified treatment interruption or discontinuation is adhered to the adverse effects on LVEF appear to be generally reversible. The EAG believe careful monitoring of patients should be carried out in order to manage the risk of heart failure due to systolic dysfunction (LVEF <50%).

3.8 Meta-analysis of intervention studies

No meta-analysis or indirect treatment comparison was conducted by the company for the current technology appraisal. We agree that this is appropriate since the relevant evidence (RCTs with different study designs and a single-cohort long-term extension study) are not in a format suitable for meta-analysis.

3.9 Additional work on clinical effectiveness undertaken by the EAG

The clinical effectiveness SLR was seven months old at the time of submission so the EAG ran targeted searches in MEDLINE, Embase and ClinicalTrials.gov for the period December 2021 to July 2022. The search identified the full paper reporting the results of VALOR-HCM[33]

but no further studies relevant to this appraisal were identified. Three new ongoing studies relevant to mavacamten in obstructive HCM patients (cohort, registry, and RCT) in non-UK populations were identified; all ongoing studies are listed in Appendix 9.4 of this report.

3.10 Conclusions on the clinical effectiveness evidence

3.10.1 Clinical efficacy

Overall, the evidence submitted by the company demonstrates clinical efficacy of mavacamten in improving patients' cardiac functioning and symptoms, to an extent which appears to be clinically meaningful to patients.

The comparative evidence available is for mavacamten plus standard care compared to standard care alone. The CS excludes disopyramide (a comparator in the NICE scope) but there is some uncertainty whether disopyramide should be included in standard care to reflect NHS practice (which appears to be heterogeneous). We have questioned the relevance of disopyramide in the current appraisal as a key issue for further consideration (section 1.3 above).

The majority of people receiving mavacamten did not achieve the primary composite outcome in EXPLORER-HCM, but it is unclear whether this reflects a limitation of the outcome rather than lack of efficacy of mavacamten. The possibility that patients' genetic background (whether they are positive or negative for a sarcomere mutation) might explain heterogeneity in the efficacy of mavacamten warrants consideration. If the genetic mutation influences mavacamten efficacy this would have implications for the cost-effectiveness of mavacamten so we have raised this as a key issue for further consideration (section 1.3 above).

3.10.2 Safety

Mavacamten appears to be well tolerated. However, it does have the potential to reduce patients' resting LVEF which could in extreme cases lead to heart failure. The clinical evidence suggests that this is unlikely (reductions in LVEF were small relative to starting values that exceeded 65% in the trials), but it is possible that a reduction of LVEF could be exacerbated if mavacamten is administered with other therapies. The FDA recommended routine post-authorisation monitoring of LVEF to address this risk (section 3.7) and the latest draft version of the mavacamten SmPC sets out minimum levels of monitoring. The EAG are

unclear whether the requisite levels of monitoring are achievable in the NHS so we have raised this as a key issue for consideration (section 1.3 above).

3.10.3 Uncertainties and limitations

As noted above, the EAG have identified the following three key clinical efficacy issues for further consideration (section 1.3 above) to potentially reduce uncertainty in the clinical effectiveness of mavacamten:

Issue 1: Exclusion of disopyramide as a comparator. Discussed in section 2.3.2 above.
Issue 2: Potential influence of genetic mutation on mavacamten efficacy. Discussed in section 2.3.4 above.
Issue 3: Feasibility of post-authorisation safety monitoring of mavacamten in the NHS. Discussed in section 3.7 above.

As noted in section 1.3 above these key issues also have implications for the cost-effectiveness analysis. Other limitations in the clinical efficacy evidence primarily relate to unexplained missing data or analyses, as summarised in section 3.3 above. The limitations of key relevance to the economic analysis concern the real-world evidence studies used to estimate an association between NYHA class and all-cause mortality (section 3.3.4).

4 COST EFFECTIVENESS METHODS

4.1 Critique of the company's cost-effectiveness review

The company conducted a systematic literature review to identify evidence on the cost-effectiveness, quality of life, resource use and costs of treatments for obstructive HCM (see CS B.3.1 and Appendix G). Thirty-five studies were included in the company's review, but none of these reported on cost-effectiveness. The EAG ran an update search on 8 July 2022 (Embase and MEDLINE databases only), which identified seven additional publications [68-74], including two relevant modelling studies which we summarise below.[68 69] See sections 4.2.6 and 4.2.7 below for discussion of published studies relating to health-related quality of life and healthcare resource use/ costs, respectively.

Beinfeld et al. (2022) reported a cost-effectiveness analysis of mavacamten for obstructive HCM conducted for the California Technology Assessment Forum (CTAF).[68] The assessment and panel discussion is described in more detail in a report by Wasfy et al. (2021).[75] There are similarities between the CTAF economic model and the company's

submitted model for the current appraisal: both used a Markov structure with health states based on NYHA class, and transition probabilities and utilities for mavacamten and standard care (BB/CCB) derived from EXPLORER-HCM. However, the CTAF model included disopyramide, septal ablation and myectomy as comparators, rather than as subsequent treatments as in the company's model. In the CTAF model, the effect on NYHA class was derived from a retrospective study by Sherrid et al. (2005)[48] for disopyramide, and from a systematic review of cohort studies by Liebregts et al. (2015)[76] for septal ablation and myectomy. The CTAF model results used a 'placeholder' price for mavacamten because a US price was not available at the time of analysis. The cost-effectiveness results are not generalisable to a UK context.

Desai et al. (2022) reported a company-funded analysis to estimate long-term health benefits (life year and QALY gains) for mavacamten compared with standard care alone (BB or CCB monotherapy) for treatment of obstructive HCM in a US context.[69] The model structure, assumptions and parameter sources in this paper are similar to those in the company's submitted model for the current appraisal, but with some differences. The Desai et al. model used a pooled health state for NYHA class III and IV, whereas the current company model uses four separate NYHA health states. The life-year and QALY results reported by Desai et al. were discounted at a 3% annual rate, so are not directly comparable with those reported in the CS.

EAG conclusion on review of cost-effectiveness evidence

The company did not identify any published cost-effectiveness studies relevant to the decision problem. The EAG updated the company's search and found reports of two economic models: a US HTA review and analysis;[68 75] and long-term health outcome projections based on EXPLORER-HCM and EXPLORER-LTE data.[69] Neither study is directly relevant to the current decision problem.

4.2 Critique of the company's submitted economic evaluation

4.2.1 NICE reference case

Table 14 shows the EAG's assessment of the company's economic evaluation against the NICE reference case criteria.[77] We consider that the analysis is consistent with the NICE reference case, with the possible exception that disopyramide is modelled as a subsequent treatment to mavacamten and the standard care comparator (BB or CCB monotherapy),

rather than as part of the standard care comparator as indicated in the NICE scope. We raise this as a key issue for further discussion (see section 4.2.2.3 below).

Table 14 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment
Defining the decision problem	The scope developed by NICE	Analysis is consistent with the scope, except disopyramide is modelled as a subsequent treatment rather than as part of the standard care comparator
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	Meets reference case
Perspective on costs	NHS and personal social services (PSS)	Meets reference case
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Meets reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Meets reference case Maximum age 100 years
Synthesis of evidence on health effects	Based on systematic review	Meets reference case
Measuring and valuing health effects	Health effects should be expressed in quality-adjusted life years (QALYs). The EQ-5D is the preferred measure of health-related quality of life in adults	Meets reference case
Source of data for measurement of health-related quality of life	Reported directly by patients or carers, or both	Meets reference case EQ-5D-5L data from EXPLORER-HCM trial used to estimate health state utilities
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Meets reference case EQ-5D-5L data mapped to the UK 3L value set with the Hernández-Alava et al. 2020 method [78]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances	Meets reference case The NICE decision modifier for severity is not applied (see section 7 below)

Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Meets reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Meets reference case
Source: developed by the EAG based on information in the CS		

4.2.2 Model structure

4.2.2.1 Overview of the model structure

The company's model is described in CS B.3.2.2. It is implemented in Excel and comprises a health state transition (Markov) model, embedded in a treatment pathway model.

The Markov model is illustrated in CS Figure 20. It includes five mutually exclusive health states representing the NYHA functional classes I to IV, and death. A cohort of patients with obstructive HCM is initially distributed between NYHA classes II and III, in accordance with the baseline characteristics of the EXPLORER-HCM trial population. In successive model cycles, members of the cohort can transition between the NYHA classes, reflecting improvement or deterioration in disease severity, and deaths from HCM related or other causes can occur from any NYHA state.

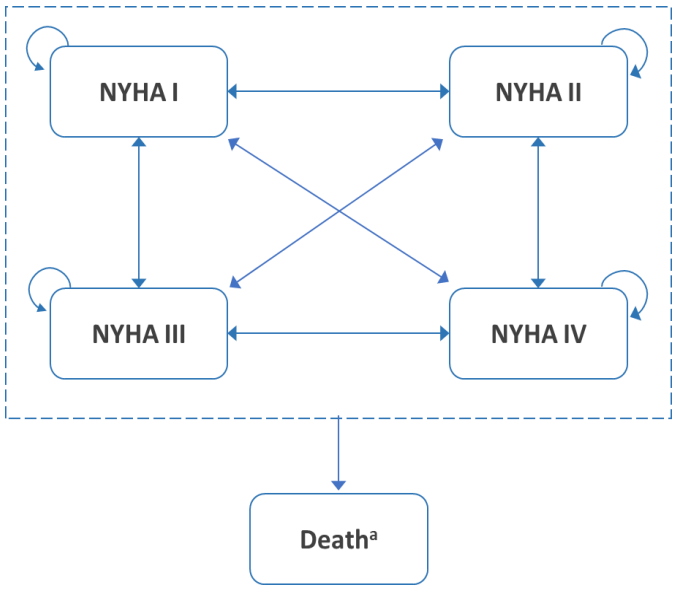

Figure 1 Illustration of the Markov model structure

[a] Death state is accessible from all non-death health states

Source: reproduced from CS Figure 20

The company explain their reasons for basing the health states on NYHA class in CS B.3.2.2, including precedent from NICE appraisals of treatments for heart disease (TA314 and TA696), and other published economic evaluations for heart failure.[79-81] However, in TA696, despite accepting an NYHA class-based model structure as the best available option, the committee expressed concerns over this approach (TA696 Tafamidis, paragraphs 3.6 and 3.12). In other NICE appraisals of treatments for chronic heart failure with reduced ejection fraction, health states based on quartiles of KCCQ scales rather than NYHA class have been accepted as suitable for decision making (TA679 paragraph 3.15, and TA773 paragraph 3.7).

The treatment sequencing model is illustrated in CS Figure 24. The mavacamten arm starts with a 30-week period for treatment initiation, dose adjustment and monitoring of response. In this period, the cycle length varies to match the timing of assessments in the EXPLORER-HCM trial, with three two-week cycles and six four-week cycles (see CS Figure 7). At the end of 30 weeks, a proportion of patients stop mavacamten because of adverse events or lack of response (no improvement of NYHA class from baseline) and continue with BB/CCB monotherapy alone. After 30 weeks, a fixed cycle length of four weeks is used. During this long-term phase, patients who initially continued on mavacamten may stop and switch to BB/CCB monotherapy, and subsequently they may escalate to disopyramide and then to SRT. The process is similar for the control arm, with patients assumed to remain on BB/CCB monotherapy alone in the first 30 weeks, after which they may escalate to disopyramide and SRT. See section 4.2.5 below for discussion of assumptions on treatment sequencing.

The company summarises key features of their economic analysis in CS Table 23, base case input parameters in CS Table 40, and model assumptions in CS Table 41.

EAG conclusion on the model structure

- The EAG considers that the structure of the Markov model is appropriate.
- There is some uncertainty over the use of NYHA class to define the model health states. Independent clinical experts advising the EAG noted that this system has limitations, as most people with obstructive HCM are in NYHA class II or III and the distinction between these classes is subjective. However, NYHA class is routinely assessed in NHS practice and the experts agreed that improvement in NYHA class is a meaningful outcome for assessment of symptomatic effect in obstructive HCM.

- A possible alternative would have been to define the model health states by quartiles of KCCQ scores, as in some previous NICE appraisals (TA679 and TA713). However, the robustness of transition probabilities derived from the EXPLORER-HCM KCCQ-23 CSS would be questionable, because of the extent of missing data for this outcome (section 3.6.9 above).
- We agree with the use of an explicit treatment sequencing model to incorporate subsequent treatment costs and outcomes after discontinuation of mavacamten and escalation from BB/CCB monotherapy, although it is not clear that the company's assumptions and data used to model subsequent treatments reflect NHS practice. See section 4.2.5 below for further discussion.

4.2.2.2 Modelled population

The population in the company's cost-effectiveness analysis is adults with symptomatic (NYHA II–III) obstructive HCM (CS B.3.2.1). The baseline demographics and NYHA distribution for the modelled cohort are based the population in the EXPLORER-HCM trial (CS Table 24), which provides clinical effectiveness and utility data for the model. As noted in section 3.2.3 above, independent clinical experts advising the EAG agreed that the EXPLORER-HCM trial population is generally representative of patients treated for symptomatic obstructive HCM in the NHS.

The company did not model results for any subgroups. As noted in section 2.3.4 above, sarcomere mutations are prognostic for adverse outcomes, and due to its mechanism of action, the efficacy of mavacamten might plausibly differ between subgroups with and without such a mutation. If so, it is likely that the cost-effectiveness of mavacamten would differ between these subgroups. We have raised this as a key issue and request that the company conduct subgroup analysis to explore the relationship between HMC genetic test results and cost-effectiveness. See section 4.2.3.1 below for discussion of a method that could be used to estimate transition probabilities for the small subgroups.

EAG conclusion on the modelled population

- The modelled population is appropriate, as it is consistent with the NICE scope, the anticipated marketing authorisation and the population in the EXPLORER-HCM trial, which provides effectiveness and utility data for the model.
- The EAG has raised potential differences in the effectiveness of mavacamten for subgroups

4.2.2.3 Modelled intervention and comparators

The model compares 'mavacamten with standard care' and 'standard care alone', with standard care assumed to comprise BB or CCB monotherapy (CS B.3.2.3). This broadly reflects 'background' therapy in EXPLORER-HCM, as current or planned treatment with disopyramide or with combination BB+CCB treatment were exclusion criteria (CS Table 5). For costing purposes, the company assumed that propranolol is representative of BBs and that CCB therapy comprises verapamil or diltiazem.

Disopyramide is not included in the model as part of the standard care comparator, although the company do include it as a subsequent treatment after discontinuation of mavacamten and BB/CCB monotherapy, and prior to SRT. The company state that they based this approach on expert clinical advice that disopyramide is not typically used as long-term therapy due to tolerability and adverse effects. See section 4.2.5 below for discussion of the company's approach to modelling subsequent treatments.

There does not appear to be consensus amongst clinical experts over the question of whether disopyramide should be considered as a comparator for mavacamten. The independent clinical experts advising the EAG gave a range of opinions on the current extent of use of disopyramide, the proportion of patients who cannot tolerate disopyramide, the proportion who remain on long-term treatment with disopyramide, and the likely position of mavacamten in relation to disopyramide in the treatment pathway (see section 2.2.5). The British Cardiovascular Society stated that "most patients in the UK would be offered disopyramide if still symptomatic despite either a beta blocker or calcium channel antagonist" and argued that it should be considered as a comparator to mavacamten. The NHS England Consultee Submission states that disopyramide is difficult to access due to supply issues and that it tends to be poorly tolerated.

EAG conclusion on the modelled intervention and comparator

As noted in section 2.3.2 above, it is not clear whether the exclusion of disopyramide as a comparator alongside mavacamten appropriately reflects current clinical practice in the NHS. We raise this as a key issue for further discussion and engagement.

4.2.3 Transition probabilities between NYHA classes

The main measure of clinical effectiveness that drives the model is change in NYHA class over time. Transitions between the four NYHA class health states are governed by transition

probabilities (TPs); with short-term TPs defined for the first 30 weeks and long-term TPs thereafter.

4.2.3.1 Short-term transition probabilities

The company describe their approach to estimation of short-term TPs in CS sections B.3.3.2.1 and B.3.3.2.2 for mavacamten and BB/CCB monotherapy, respectively. For both arms, patient-level data on NYHA class from the EXPLORER-HCM trial was used to estimate a series of TP matrices covering the trial period from baseline to 30 weeks (see CS Figure 7). Separate TP matrices were estimated between successive trial assessments (from baseline to week 4, from week 4 to week 6, etc.). Thus the first 30 weeks in the Markov model consists of 9 model cycles of either 2 or 4 weeks duration. See CS Table 25 for the short-term TP matrices used in the model.

The company used a last observation carried forward (LOCF) approach to impute missing NYHA data from the trial. They provided further information about missing data and the impact of LOCF imputation in response to clarification question B1. Data completeness was generally good, with data available to calculate a minimum of [redacted] NYHA transitions between consecutive assessments within the 30-week trial period for mavacamten and placebo respectively (calculated by the EAG from Table 4 of the company's clarification response). Completeness dropped to [redacted] at week 46 (baseline assessment for EXPLORER-LTE) for patients who had been randomised to placebo. Model predictions of the NYHA class distribution at week 30 with and without imputation were similar, and both sets of model predictions were similar to the EXPLORER-HCM data (Table 5 of the company's clarification response).

There are some large fluctuations in TP estimates for successive 2 to 4 week model cycles due to small numbers of observed transitions and null events. The model made appropriate use of Dirichlet distributions to integrate uncertainty on transitions in the probabilistic analysis, but this does not account for uncertainty related to null events. An alternative approach would have been to estimate the TP matrices over the whole 30-week trial period and to assume a constant rate of NYHA change within this time. This would increase the numbers of observed transitions and produce more stable TP estimates. Numerical methods could be used to adjust the Markov chain TP matrices for shorter model cycles,[82] but this is not necessary because the input parameters required to calculate costs and QALYs are all constant in the first year, and treatment discontinuation and escalation are assumed not to

occur before week 30. Therefore we believe that mean costs and QALYs could be calculated based on initial and 30-week NYHA class.

The company did not make use of data from the VALOR-HCM trial for estimation of TPs. They explain that pooling of data from EXPLORER-HCM and VALOR-HCM would have been hampered by different timing of assessments and duration of follow up and argue that differences in the trial populations would have added to uncertainty (Company Addendum 2.10).

EAG conclusion on estimation of short term transition probabilities

- The methods used to estimate short-term TPs from EXPLORER-HCM NYHA class data are reasonable. Data completeness was good, and the modelled projections with LOCF imputation produced a similar distribution of NYHA class at 30 weeks as was observed in the trial.
- The TP estimates vary considerably between successive model cycles because of the low numbers of observed transition events in these 2-4 week periods. We do not expect that this would affect the deterministic cost-effectiveness results, because of the similarity of the modelled and observed NYHA class distributions at 30 weeks.
- The EAG has requested that the company conduct an exploratory subgroup analysis to investigate whether the cost-effectiveness of mavacamten differs by HCM genetic test results. To facilitate this analysis in the small subgroups, we suggest that TP matrices are estimated for the whole 30-week trial period, rather than for separate 2-4 week model cycles. Mean costs and QALYs over the first 30 weeks can be calculated directly with an assumption of a constant rate of NYHA class change over this period.
- We agree with the decision not to use VALOR-HCM trial data in the model.

4.2.3.2 Long-term transition probabilities

After week 30, the model uses a fixed 4-week cycle length over the remaining time horizon. In the base case analysis, the company assume no further transitions between NYHA classes in the mavacamten arm after week 30, except in the cycle immediately following an escalation to SRT (CS B.3.3.2.3). See section 4.2.5 below for assumptions regarding the effects of subsequent treatments including SRT.

The base case assumption of no change in NYHA class was also applied to the BB/CCB monotherapy arm, but only after week 46. In the period between week 30 and week 46, NYHA transition probabilities for BB/CCB were estimated from the EXPLORER-HCM end of trial (week 30) and end of study (week 38) assessments, and from the EXPLORER-LTE baseline assessment at week 46. The week 30-38 and week 38-46 probabilities were each adjusted to 4-week probabilities and used in the first four cycles of the long-term Markov model for BB/CCB. The company reported a scenario with NYHA class on BB/CCB monotherapy assumed to be constant after week 38, except after SRT. They did not report a scenario with NYHA class held constant from week 30 for BB/CCB monotherapy, as for the mavacamten arm.

The same set of long-term transition probabilities was used for the BB/CCB monotherapy comparator arm and following discontinuation of mavacamten. Desai et al. (2022) commented that this is a conservative assumption, as it assumes no persistence of treatment benefit after discontinuation.[69]

The Company Addendum included two additional scenarios that modelled long-term 'natural' disease progression. The first scenario assumes that 4.55% of patients in NYHA classes I, II and III would deteriorate by one NYHA class per year, applied across all treatments (Company Addendum Table 14). This rate was estimated from a prospective cohort study by Maron et al. 2016 (Company Addendum 3.2.1). [1]

The second progression scenario assumed a reduced rate of progression while patients were receiving mavacamten (Company Addendum 3.2.2). The company argue that this assumption is appropriate based on opinion from clinical experts and findings from the CMR substudy of EXPLORER-HCM. They do not consider reduced rates of progression for other treatments, as no data were identified to estimate such effects. The company state that the reduced long-term rate of NYHA class progression on mavacamten ([redacted] per year) was extrapolated based on a 'relative difference' of [redacted]. It appears that this latter figure is a relative risk, calculated as the ratio of the proportions of people with no class improvement during 30 weeks of follow up in EXPLORER-HCM: [redacted] ([redacted]) of patients on placebo and [redacted] ([redacted]) of those on mavacamten ([redacted]). However, it is not clear that this is the correct estimate of the relative effect for preventing deterioration (progression) of NYHA class.

Results for the two disease progression scenarios are reported in Table 15 of the Company Addendum. In both progression scenarios, the company assume that patients who

experience a deterioration in NYHA class while on mavacamten discontinue treatment in the same model cycle and transfer to alternative treatments (BB/CCB, disopyramide or SRT). The impact of the progression scenarios on cost-effectiveness are complex, as they affect the costs of treatment, monitoring and follow up, as well as quality of life and mortality.

Independent clinical experts advising the EAG noted that progression in obstructive HCM is complex, changes over time and will vary with age and between patient subgroups. Patients with the genetic form of HCM are usually on a plateau by the time of diagnosis and relatively stable. LVOT gradient may decrease in older patients due to heart remodelling and increased background risks of AF, heart failure and cardiovascular disease with age.

EAG conclusion on estimation of long term transition probabilities

- We consider that the use of different methods to model transition probabilities between weeks 30 and 46 in the mavacamten and BB/CCB monotherapy arms is likely to have introduced bias. The use of 38-week data from EXPLORER-HCM and 46-week data from EXPLORER-LTE to model NYHA class transitions between 30 and 46 weeks for BB/CCB led to a deterioration in this arm, which was then held constant over the remaining time horizon in the company's base case. In contrast, NYHA class was assumed to hold constant from 30 weeks in the mavacamten arm. Given the lack of comparative data, loss of blinding and uncertainty due to small numbers of some transition events, we consider the data for weeks 30-46 to be unreliable. For EAG analysis, we therefore prefer to use the same method to estimate NYHA class transitions in both arms: with transition probabilities prior to 30 weeks estimated from EXPLORER-HCM data, followed by assumptions regarding long-term progression.
- We agree with the argument in the Company Addendum that gradual progressive deterioration of NYHA class is likely over the long-term, as the incidence and symptoms of heart failure increase with age. This reflects advice to the EAG from independent clinical experts, and available evidence (e.g. from Maron et al. 2016). However, there is uncertainty over the average rate of increase in NYHA class, and over whether and how this is likely to differ between treatments. The company identified the Maron et al. 2016 study from targeted searches, so it is not known if there are other sources of evidence on this issue. The company state that results from a systematic literature review to address this evidence gap are expected in early 2023 (Company response to clarification questions 24/11/22, question B1).

- For EAG analysis, we use the company's progression scenario of an equal rate of NYHA class progression after week 30 (4.55% per year) with all treatments. However, we also report results for scenarios with the assumption of: no long-term progression; a lower rate of progression on mavacamten ([redacted]); and a lower rate of progression on mavacamten, disopyramide and following SRT.

4.2.4 Discontinuation of mavacamten

The model includes discontinuation of mavacamten due to adverse events and due to lack of response (see CS Table 26). The rate of discontinuation due to SAEs during the EXPLORER-HCM trial (1.6%) was applied as a one-off event at week 30. The same rate (2.8% per year) was then applied on an ongoing basis while patients remained on mavacamten.

The revised draft of the SmPC submitted with the Company Addendum states that [redacted]

In the base case model, with the assumption of no long-term disease progression, discontinuation of mavacamten due to lack of response only occurred at week 30, based on the observed proportion with no NYHA class improvement in the mavacamten arm in EXPLORER-HCM ([redacted] in NYHA class II and 100% in class III or IV at week 30). See also the company's response to clarification question B2. In the progression scenarios reported in the Company Addendum, discontinuation of mavacamten can also occur due to deterioration of NYHA class after week 30.

Independent clinical experts advising the EAG noted that the company's assumptions about discontinuation of mavacamten due to lack of effect may not be applied in practice, as assessment of NYHA class is subjective, and patients and clinicians may want to continue treatment if there is a symptomatic improvement within a class. If so, this would be likely to reduce the cost-effectiveness of mavacamten in practice. It is also possible that delays in seeking or obtaining NHS appointments when symptoms get worse could cause a lag in discontinuation of mavacamten, which would also have a negative impact on cost-effectiveness.

EAG conclusion on mavacamten discontinuation

There is uncertainty over the long-term rates of treatment discontinuation due to adverse effects, intolerance and lack of effect. We broaden the range of scenario analysis around discontinuation rates to explore the impact of this uncertainty.

4.2.5 Subsequent treatments

The company's base case assumptions about subsequent treatment after discontinuation of mavacamten are illustrated in CS Figure 24 (CS section B.3.3.4). The approach was informed by discussions with clinical advisors. The company present a range of scenario analyses to investigate the impact of assumptions about use of subsequent treatments.

No change in treatment is considered within the first 30 weeks. After week 30, patients who discontinue mavacamten due to lack of effect or adverse events are assumed to continue initially on BB or CCB monotherapy. Subsequently, patients may escalate from BB/CCB to disopyramide or SRT. Rates of escalation were derived from the company's expert elicitation (CS Appendix O) and were assumed to increase with NYHA class (CS Table 28). See section 3.2.6 above for EAG critique of the expert elicitation. In the base case, the company assume that patients who escalate from BB/CCB monotherapy have combination therapy with the addition of disopyramide for a fixed period of 9 months, after which they undergo SRT. The annual rate of escalation to disopyramide was then estimated within the model by working backwards from expert estimates of the proportions of the lifetime incidence of SRT by NYHA class: [redacted], [redacted], [redacted] and [redacted] respectively for class I to IV (CS Appendix O). The company explain this process in their response to clarification question B5, and report concordance of the modelled and expert estimates of SRT use (Clarification Response Table 7). The company assumes no change of NYHA class while patients are being treated with disopyramide, due to a paucity of evidence.

As discussed in section 4.2.2.3 above, there are differing opinions about the level of use of disopyramide in NHS practice, over how well it is tolerated and its effectiveness for long-term symptomatic management. Discussion with independent clinical experts advising the EAG indicates that use of disopyramide is variable. They agreed that it may be used as a stop gap prior to SRT, but that a proportion of those who start disopyramide do continue to take it for a longer period; estimates of this proportion ranged from around 30% to 50%, although not all of these would be thought to have clear symptomatic benefit. There is a lack of randomised evidence for the effectiveness of disopyramide. Observational evidence suggests that a proportion of patients can tolerate continued use of disopyramide and with reduced LVOT gradient and improved NYHA functional status.[48 49]

Assumptions about the effectiveness of SRT are shown in CS Table 29. For the base case, SRT effectiveness was based on results from the company's expert elicitation exercise, excluding the two experts regarded as experts in structural intervention. The company also present a scenario with the effects of SRT on NYHA class based on a study by Knyshov et al. 2013.[83] In response to clarification question B7, the company note that there was an error in the calculation of transition probabilities for this scenario. The correct values are shown in Table 8 of the company response to clarification questions. The Knyshov scenario results were corrected in an updated version of the company's model (see section 5.3.3 below).

EAG conclusion on subsequent treatment assumptions

There is uncertainty over the company's assumptions in the treatment sequencing model (CS Figure 24). In particular, it is not clear that disopyramide would only be considered in current practice as a short-term bridging therapy prior to SRT, as expert advice and observational evidence does suggest that some patients are maintained on disopyramide as a medium to long-term treatment option.[48 49]

4.2.6 Health state utilities

The utility values by NYHA class used in the company's base case analysis are shown in CS Table 33. These values were derived from EQ-5D-5L data collected in the EXPLORER-HCM trial and mapped to UK 3L values using the Hernandez-Alava and Pudney crosswalk method with the EEPRU dataset, as recommended in the NICE 2022 methods update.[77 78 84] The trial data was analysed using a linear mixed effect model to account for repeated measures, see CS B.3.4.2 and B.3.4.5 and CS Appendix P sections 4.5 and 4.6 for further detail on the utility analysis model. Results were merged for NYHA class III and IV, due to the small number of EQ-5D assessments for class IV.

Utility is adjusted for age within the model, using UK utility estimates reported by Ara et al. 2010.[85] The company note that the utility for NYHA I estimated from the trial results ([redacted]) is higher than would be expected in the UK general population with the age and gender mix of the modelled cohort (0.833). The company argue that this could be related to two factors: lifestyle modifications made by people with symptomatic obstructed OCM; and/or a short term 'feel good' effect from symptom improvement while in the trial. Independent clinical experts advising the EAG did not think it likely that the high utility values in the trial could be

explained by lifestyle factors, but they agreed that it might be related to a ‘feel good’ factor due to trial participation.

The company also cite similarities between the NYHA I utility estimates from EXPLORER-HCM, and values reported from a Danish study of asymptomatic patients with congenital heart disease and EQ-5D-5L preferences of patients with heart disease in Singapore. Neither study is consistent with the NICE reference case.

EAG conclusion on health state utilities

The company use appropriate methods to estimate and value utilities associated with NYHA class using EQ-5D data from the EXPLORER-HCM trial. However, we do not consider that it is realistic to assume that people with obstructive HCM NYHA class I would have better utility than people in the general population of the same age and gender. For EAG preferred analysis we therefore assume that the NYHA class I utility is equal to that expected in the general population, with utilities for class II and III/IV adjusted proportionately. We use the company’s base case and scenarios in EAG scenario analysis.

4.2.7 Adverse events

Incidence rates for adverse events included in the model are reported in CS Table 32. The event rates used in the model were derived from observed rates for the mavacamten and placebo arms in the EXPLORER-HCM trial. The company used the placebo arm rates for patients treated with disopyramide and after SRT, noting that these are likely to be conservative assumptions.

In response to clarification question B8, the company explained the reasons for exclusion of some serious adverse events from the model and reported additional scenario analyses with different criteria for SAE inclusion (company response to clarification questions Table 10).

The model included adverse event treatment costs (CS Table 39). However, loss of utility associated with the adverse events was not modelled, as the company argued this would be double-counting utility effects that should have been captured in the health state utilities. We agree with this approach

4.2.8 Mortality

The company describe their approach to modelling mortality in CS B.3.3.5. They assume that all-cause mortality rates in NYHA class I are the same as for people of the same age and sex in the general population (ONS 2018-2020).[86]. Mortality rates in NYHA class II to IV are then adjusted relative to NYHA class I (CS Table 30). For the base case, relative mortality by NYHA class is based on an analysis of US electronic health record (EHR) data for obstructive HCM (n=3322) by Wang et al. 2022.[2]. Two scenarios are also reported based on analyses of international SHaRe registry data (n=2495): an unadjusted analysis reported by Lakdawala et al. 2021,[3] and adjusted estimates from an analysis reported in CS Appendix N. The company justify the decision to use the Wang et al. estimates for the base case, because this provided separate HRs for NYHA class III and IV, whereas the SHaRe analyses only report pooled estimates for these classes. See section 3.2.5 above for the EAG assessment of these real-world cohort studies.

The model also includes a one-off 1.2% mortality risk associated with SRT procedures: calculated as a simple mean of the rates of 1.12% for alcohol-ablation therapy and 1.27% for myectomy reported by Bytyçi et al. 2020.[19] This is applied as a one-off event at the time of the procedure.

Some clinical experts have emphasised that the observed association between NYHA class and mortality is not necessarily causal, and that there is currently no evidence that treatments that reduce the symptoms of obstructive HCM have any mortality benefit. This point was made in the BCS submission for this appraisal and by an expert consulted by the EAG, who noted that in the absence of randomised evidence, mortality benefits have not traditionally been ascribed to other treatments for obstructive HCM, including BB, CCB, disopyramide or SRT. Beinfeld et al. did not include mortality effects in their economic analysis of mavacamten for the California Technology Assessment Forum (CTAF) (referred to in section 4.1 above).[68 75] Desai et al. 2022 did include mortality effects in their outcome modelling study, but they noted in the discussion that “currently no direct evidence indicates the benefit of mavacamten in reducing mortality because it requires long-term follow-up of patients.” [69]

EAG conclusion on mortality

Given the lack of direct evidence for a beneficial effect of treatment on mortality, and the lack of evidence that the observed association between NYHA class and mortality is causal, it is not clear whether mortality effects should be included in the model. Independent clinical experts advising the EAG had different opinions on

this question. We have therefore raised this as a key issue for further discussion, and report results for the EAG preferred analysis with two additional scenarios which assume that mortality within the modelled cohort does not change with changing NYHA class (see section 6.1 below).

4.2.9 Resource use and costs

4.2.9.1 Drug acquisition

Drug acquisition costs for mavacamten at list price and with the proposed simple price discount are reported in CS Table 2. At the proposed list price (provisionally approved by DH, pending MA approval), the estimated cost of an average course of treatment is [redacted] per patient per year. With the proposed simple discount PAS the net price is [redacted] per patient per year. In the model, these costs are adjusted for adherence, the mean percentage of mavacamten doses taken in the EXPLORER-HCM trial ([redacted]) (see company response to clarification question B3). The cost per pack [redacted].

Unit costs for comparator and subsequent treatments are listed in CS Table 35, including revisions made in the company's response to clarification question B4. The assumed proportions of patients using BB (propranolol) or CCB (diltiazem or verapamil) are shown in CS Table 36. These estimates result in an average cost per year of £20.51 for BB/CCB monotherapy and £162.41 for disopyramide and BB/CCB.

4.2.9.2 Drug administration and monitoring

No administration costs were included because all drugs are oral formulations.

The company based assumptions about monitoring for patients on mavacamten on a draft SmPC (CS Appendix C), which required additional monitoring in the first year. The company assume a minimum of [redacted] cardiovascular outpatient visits and echocardiogram procedures during the first year of mavacamten treatment, and no additional monitoring subsequently. Thus, from year two onwards, monitoring costs are assumed to be the same for mavacamten and BB/CCB monotherapy.

A revised version of the draft SmPC was submitted with the Company Addendum. This remains subject to change until final marketing authorisation is granted.

[redacted]

[redacted]

Monitoring arrangements with standard care, stratified by NYHA class, were estimated from the expert elicitation exercise (CS B.3.5.2). The estimated frequency of cardiovascular outpatient visits ranged from [redacted] per year in NYHA class I to [redacted] per year in NYHA class IV (CS Table 37). The estimated number of echocardiography procedures per year ranged from [redacted] in NYHA class I to [redacted] in NYHA IV.

Independent clinical experts advising the EAG commented that current monitoring of people with obstructive HCM is variable, reflecting heterogeneity of the severity of the disease. All patients would start with intensive monitoring in the first 6 months to assess risk of serious LVEF reduction. Thereafter approximately 10-20% of patients would have one appointment per month, around 50% would have one appointment per year, and the rest would be monitored at 2-3 yearly intervals. The experts also noted that in practice assessments are dependent on operational constraints and staff availability. In particular, there is a notable shortage of sonographers.

EAG conclusions on mavacamten monitoring

- [redacted]
- We understand that in current practice, the availability of sonographers can affect the frequency of assessments for people with obstructive HCM. This and other NHS resource limitations may present a constraint on the implementation of appropriate monitoring for mavacamten. We have raised this as a key issue.

4.2.9.3 Health state costs

The company's systematic review of economic evidence did not identify any studies that reported on healthcare resource use of costs related to obstructive HCM in the UK. The EAG update of the economic searches identified two papers (Owens et al. 2021 and 2022)[72 73] that reported on resource use and costs based on a company-funded analysis of US claims data. These are not relevant to a UK context.

The mean quantities of resource use with standard care by NYHA class were estimated from the expert elicitation exercise (CS Appendix O and section 3.2.6 above). For the base case, responses from the two specialists in structural interventions were excluded, with the justification that the patients seen by these specialists would not be representative of the overall population with obstructive HCM (CS B.3.5.2). The mean annual frequency of use and unit costs for a range of primary and secondary care consultations, and related tests and procedures are reported in CS Table 37. Total annual health state costs are reported in CS Table 38.

The clinical experts consulted by the EAG agreed that the estimates of the numbers of primary care consultations looked reasonable. However, they noted that the use of secondary resources would generally be higher for NYHA class III than for IV, as 'there are more things to try', with attempts at treatment with reassessment of haemodynamics. In particular, they indicated that echocardiograms are not much used in class IV. One expert commented that more echocardiograms would be performed in class II and IV.

The model also included a palliative care cost of £8,827 in the last three months of life (Hollingworth et al. 2016).[87] This cost was applied in the model as a one-off cost at the time of death time.

4.2.9.4 Subsequent treatment costs

The cost of subsequent treatments are summarised in CS Table 35. We have commented on the total annual costs for the drug treatments in section 4.2.9.2 above. The average cost per SRT procedure was estimated at £11,306, based on the relative use and unit costs of alcohol ablation therapy and myectomy procedures, estimated from the expert elicitation exercise.

5 COST EFFECTIVENESS RESULTS

5.1 The company's original base case

CS B.3.8.1 reports the deterministic results for the company's base case analysis (reproduced in Table 15 below). They include a confidential PAS discount price for mavacamten and list prices for all other treatments. The company made corrections to their base case analysis in the Company Addendum (Table 10), which we report in section 5.3 below.

Table 15 Company's original base case results (deterministic with PAS discount for mavacamten and list price for all other treatments)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
BB/CCB monotherapy	[redacted]	[redacted]	[redacted]				
Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,841

Source CS Table 42 (company model version dated 14 July 2022)
BB: beta blockers; CCB: calcium channel blockers; ICER: incremental cost-effectiveness ratio; ICER: incremental cost effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years;

5.1.1 Probabilistic sensitivity analysis

Results of the probabilistic sensitivity analysis (PSA) for the company's base case analysis are presented in CS section B 3.9.1. The company reported that the probabilistic results for their base case are stable and consistent with the deterministic results, with a mean probabilistic ICER of £29,411 per QALY gained (Table 44), which is close to the deterministic estimate. Uncertainty around this mean estimate is illustrated in the scatterplot and cost effectiveness acceptability curve in CS Figures 25 and 26 respectively. The company report that at a willingness-to-pay threshold of £30,000 per QALY, mavacamten + BB/CCB has a [redacted]% probability of being cost-effective compared to BB/CCB monotherapy.

5.1.2 Deterministic sensitivity analysis

CS section B.3.9.2 reports one-way deterministic sensitivity analyses (DSA) for the company's base case. The ten parameters with the greatest impact on the ICER are shown in the tornado diagram in CS Figure 27. The relative mortality rate in NYHA class II and the proportion of patients in NYHA class II who did not have a NYHA class improvement in the first 30 weeks (discontinuation rate for mavacamten due to lack of effect) are the key drivers of the model results. The annual discontinuation rate due to adverse events beyond 30 weeks, health state utility values for NYHA classes I and III, mortality in NYHA class III and

the rates and costs of inpatient admissions also impact the model results, but to a lesser extent.

5.1.3 Scenario analysis

The company explored a range of scenarios to test structural and methodological uncertainty (CS section 3.9.3). The scenarios are described in CS Table 45 and the results are presented in CS Table 46. The company report that the scenario with a time horizon of 20 years had the biggest impact on the ICER (increase to £36,820 per QALY), and that other scenarios had limited impact. However, we note that the ICER increased to £35,125 per QALY with a reduced rate of mavacamten discontinuation after week 30 (1.4% per year compared with 2.8% per year in the base case). The largest reduction in the ICER was produced by the scenario with higher relative risks for mortality in NYHA classes II to IV, as estimated in the unadjusted analysis of ShaRe data by Lakdawala et al. 2021 (ICER £21,603 per QALY).[3]

5.2 Model validation and face validity checks

5.2.1 Company model validation checks

The company describe their approach to model validation in CS section B.3.11.1. This included:

- Quality checks by a senior modeller not involved in the project to verify that the model had been programmed correctly and produced logical outcomes.
- Advisory board meetings with clinical and economic experts to assess the face validity and relevance to real-world practice of the model structure, inputs, assumptions and results, see section 3.2.7 above.[35-38]
- Commissioning of real-world evidence studies [2] [3] and an expert elicitation exercise (detailed in CS Appendix O). See sections 3.2.5 and 3.2.6 above for EAG critique of these evidence sources.
- Assessment of internal validity: comparison of NYHA distribution at 30 weeks from the model and observed EXPLORER-HCM trial (CS Appendix J).

The company did not identify any sources of evidence for assessment of the external validity of the model outcomes.

5.2.2 EAG model validation checks

The EAG conducted a range of tests to verify model inputs, calculations and outputs:

- Cross-checking all parameter inputs against values reported in the CS and the cited sources;
- Checking all model outputs against results cited in the CS, including the base case, deterministic sensitivity analyses, scenario analyses and probabilistic sensitivity analyses;
- Manually running scenarios and checking model outputs against results reported in the CS for the deterministic sensitivity analyses and scenario analyses;
- Checking the individual equations within the model ('white box' checks);
- Applying a range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed ('black box' checks).

We noted one additional error in the Company Addendum version of the model. The pack size for disopyramide was stated as 100 for the June 2021 eMIT price of £12.95 (CS Table 35), which differs from the for the June 2021. However, the Company Addendum model assumed a pack size of 84. This has a negligible impact on the revised base case results.

We also checked the stability of the probabilistic results. The company reported results with 1,000 PSA iterations. Table 16 below shows that increasing the number of iterations above 1,000 has little impact on the ICER result. Therefore, the EAG agree that 1,000 iterations is sufficient.

Table 16 EAG check for stability of PSA results (revised company base case)

Iterations	Mean ICER (£/QALY)	Difference (probabilistic - deterministic ICER)	Percentage of iterations with ICER < £30,000 per QALY
Deterministic	£29,952		
Probabilistic 100	£30,121	[redacted]	[redacted]
500	£29,524	[redacted]	[redacted]
1000	£29,720	[redacted]	[redacted]
2000	£29,628	[redacted]	[redacted]
3000	£29,714	[redacted]	[redacted]
4000	£29,743	[redacted]	[redacted]
5000	£29,696	[redacted]	[redacted]
Source: produced by the EAG from the Company Addendum model			

There is a paucity of external evidence for assessment of external validity. We show baseline demographics, overall survival and mean NYHA class estimated from the model compared with results reported for a single-centre cohort of patients with symptomatic obstructed HCM reported by Sherrid et al. 2013.[49] The results are shown in Table 17Table 17 below.

Table 17 Comparison of baseline characteristics and modelled outcomes compared with reported results from Sherrid et al 2013[49] populations

	Sherrid et al. 2013	Modelled estimates for standard care
Baseline age (years)	53.8	59.0
Baseline sex (males, %)	57.0	59.4
Overall survival after 10 years (%)	86.6	82.1
NYHA class mean - initial evaluation	2.7	2.3
NYHA class mean – last visit (follow up 4.8 years median)	1.8	1.9
Sources: Sherrid et. al, 2013[49] Tables 1 and 3 and company submission model considering standard care treatment NYHA: New York Heart Association		

5.3 The company's revised base case

In the response to clarification questions, the company made some corrections:

- The doses of propranolol, verapamil, diltiazem and disopyramide were updated to reflect the most recent British National Formulary (BNF) update and the costs were updated to use electronic market information tool (eMIT) costs rather than BNF costs (clarification question B4)
- The transition probabilities matrix based on Knyshov et al. in CS Table 29 were amended (see clarification question B7, Table 8)

The company made an additional correction in the Company Addendum of 18 October 2022:

1) The formula used to convert 30-week probabilities of discontinuation of mavacamten due to SAEs in the post-trial period to an annual probability was corrected (Company Addendum section 3.1).

In addition, the EAG has corrected the pack size used for costing disopyramide from 84 to 100 in the Company Addendum model.

The revised base case results with the above corrections are shown in Table 18 below. The above changes result in a small increase in the ICER, from £29,841 per QALY in the original company submission to £29,953 per QALY gained.

Table 18 Revised base case (corrected), deterministic analysis with PAS discount for mavacamten and list price for all other treatments

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. Costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
BB/CCB monotherapy	[redacted]	[redacted]	[redacted]				
Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,953

Source: Produced by the EAG from the Company Addendum model
ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; BB: beta blockers; CCB: calcium channel blockers

5.3.1 Probabilistic sensitivity analysis

Probabilistic results for the revised base case analysis are shown in Table 1 of the appendix to the Company Addendum. This reports a mean probabilistic ICER of £29,714 per QALY gained, close to the deterministic value. Uncertainty around this mean is illustrated in Figures 1 and 2 of the appendix, and the company report a [redacted]% probability of mavacamten being cost-effective compared to BB/CCB monotherapy at a threshold of £30,000 per QALY gained. The EAG confirm that we obtained similar results based on 5,000 PSA iterations.

5.3.2 Deterministic sensitivity analysis

Results for the one-way DSA for the revised base case are illustrated in the Tornado graph in Figure 3 of the appendix to the Company's Addendum. We show results for the parameters with the largest impact on the ICER in Table 19 below.

Table 19 DSA results for revised base case (corrected): largest impacts on ICER

Parameter	Parameter value			ICER (£ per QALY)	
	Base case	Lower limit	Upper limit	Lower limit	Upper limit
Relative mortality in NYHA II	1.51	1.23	1.83	[redacted]	[redacted]
% discontinuation, lack of effect NYHA II	64%	51%	75%	[redacted]	[redacted]
Annual discontinuation after week 30	0.028	0.023	0.033	[redacted]	[redacted]
Health state utility in NYHA I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state utility in NYHA III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unit cost for elective inpatient stay (£)	4,754	3,868	5,730	[redacted]	[redacted]
Relative mortality in NYHA III	2.77	2.27	3.35	[redacted]	[redacted]
Unit cost, non-elective inpatient stay (£)	3,627	2,951	4,372	[redacted]	[redacted]
Non-elective inpatient stays pa NYHA III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Elective inpatient stays per year NYHA III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Health state utility in NYHA II	[redacted]	[redacted]	[redacted]	xxxxxxx	xxxxxxx
Source: Produced by the EAG from the company's revised base case model					

5.3.3 Scenario analysis

The company report scenario analysis results for their revised base case in Table 2 of the appendix to the Company Addendum. Two additional scenarios regarding long-term disease progression are reported in Table 15 of the Company Addendum. We report results for all of these company scenarios, with the EAG correction for the cost of disopyramide in Table 20 below. The results are very similar to those reported by the company.

Table 20 Scenario analysis on revised base case (corrected)

Revised base case assumptions	Company scenarios	ICER (£/QALY)
Revised base case (EAG correction)		£29,953
Age of cohort at baseline		
59 years	52 years	£30,445
	62 years	£29,788
Time horizon		
Lifetime	20 years	£36,934
	30 years	£31,075
Comparator arm transition probabilities after week 30		
Trial-based TPs to week 46, then no NYHA change (except for SRT)	Trial-based TPs until Week 38	£31,927
Mavacamten discontinuation		
All NYHA class III at week 30	[redacted]% in NYHA class III at week 30 (same proportion as in class II)	£31,288
2.8% per year after week 30	1.4% per year after Week 30	£35,126
Treatment after mavacamten discontinuation		
All patients receive BB/CCB monotherapy in at least the first cycle after discontinuation	90% BB/CCB; 10% disopyramide + BB/CCB	£28,956
	75% BB/CCB; 25% disopyramide + BB/CCB	£27,575
	NYHA I/II: 100% BB/CCB NYHA III/IV: 90% BB/CCB; 10% SRT	£29,235
	NYHA I/II: 100% BB/CCB NYHA III/IV: 80% BB/CCB; 10% disopyramide + BB/CCB; 10% SRT	£28,620
Treatment after mavacamten discontinuation and escalation from BB/CCB		
100% disopyramide + BB/CCB for 9 months then SRT	After mavacamten: 100% BB/CCB After BB/CCB escalation: 100% SRT	£30,154
	After mavacamten: 90% BB/CCB; 10% disopyramide + BB/CCB After BB/CCB escalation: 100% SRT	£29,154

Revised base case assumptions	Company scenarios	ICER (£/QALY)
	After mavacamten: 75% BB/CCB; 25% disopyramide + BB/CCB After BB/CCB escalation: 100% SRT	£27,770
	After mavacamten: NYHA I/II 100% BB/CCB NYHA III/IV 90% BB/CCB; 10% SRT After BB/CCB escalation: 100% SRT	£29,438
	After mavacamten: 100% BB/CCB After BB/CCB escalation NYHA I/II: 100% disopyramide + BB/CCB NYHA III/IV: 100% SRT	£30,148
Time on disopyramide before escalation to SRT 9 months	6 months	£30,018
	12 months	£29,891
Efficacy of SRT: one-off NYHA class transitions		
CS Table 29 (expert elicitation)	Knyshov *et al*. 2013[83]	£29,670
Mortality		
Relative all-cause mortality by NYHA class from US EHR data (Wang et al. 2022)	Adjusted HRs from SHaRe (CS Appendix N)	£29,716
	Unadjusted one-year RR from SHaRe (Lakdawala *et al*. 2021)[3]	£21,671
Long-term natural progression of NYHA class		
No change in NYHA class	Scenario 1: 4.55% per year, all treatments	£17,890
	Scenario 2: 2.31% per year on mavacamten; 4.55% on all other treatments	£17,341
Health state utilities		
EXPLORER-HCM EQ-5D analysis by NYHA class, with age-adjustment	Exclude age adjustment	£27,280
	Utilities from Göhler *et al*, 2009[88]	£32,021
Health care resource use and costs		
SRT procedures: [redacted] ASA, [redacted] septal myectomy (expert elicitation)	75% ASA, 25% septal myectomy	£29,990
	25% ASA, 75% septal myectomy	£29,919
Health care resource use by NYHA class (CS Table 37, expert elicitation)	Increase all HCRU by 10%	£28,724
	Decrease all HCRU by 10%	£31,182
Adverse event rates		
Treatment emergent SAEs (CS Table 32 and company response to clarification question B8).	All SAEs > 1% in either arm	£30,126
	All CV-related SAEs	£30,148
	All SAEs > 1% in either arm OR CV-related	£29,925
Source: Produced by the EAG from the company's revised base case model		

6 EAG ADDITIONAL ANALYSES

6.1 Additional EAG scenario analysis

We show the results for 12 additional scenarios applied to the company's revised base case in Table 21 below. These scenarios were chosen to explore key areas of uncertainty that are not included in the company's scenario analyses, or to expand the range of assumptions for some of the company's analyses:

- **EAG scenario 1**: In their base case, the company use post-trial data to estimate transition probabilities for the BB/CCB monotherapy arm between week 30 and week 46, whereas for mavacamten no change in NYHA class was assumed in this period (see section 4.2.3.1 above). In EAG scenario 1, we use 30-week trial data in both arms, followed by the same assumptions about long-term transitions after this time.

- **EAG scenarios 2-3**: extend the company's scenario on treatment discontinuation for patients without an improvement in NYHA class at week 30. These exploratory scenarios were motivated by comments from independent clinical experts advising the EAG that in practice, treatment might sometimes be continued in such cases (section 4.2.4).

- **EAG scenario 4-5**: As discussed in section 4.2.8 above, there is a lack of evidence that the observed association between NYHA class and mortality is causal and that treatments for obstructive HCM, including mavacamten, have an effect on survival.

    - EAG scenario 4, which was coded in the company's model, assumes no increased mortality risk associated with NYHA class. This is likely to overestimate survival, as the general population life tables are applied across the cohort.

    - EAG scenario 5 therefore applies a pooled HR (1.85) all across NYHA classes to reflect the increased baseline mortality risk in the modelled cohort, relative to the general population. This pooled HR is calculated as an average of the Wang et al. 2022 HRs (CS Table 30) weighted for the initial distribution of NYHA class (CS Table 24) and does not change as NYHA changes within the model.

- **EAG scenarios 6-8**: The Company Addendum reports two scenarios on long-term progression of NYHA: one in which the same annual rate of progression (4.55%) is applied regardless of treatment; and a second with a reduced rate of progression

during treatment with mavacamten. EAG scenarios 6-8 illustrate the effect of extending the latter assumption to subsequent treatments in the model (disopyramide and/or SRT).

- **EAG scenario 9**: The utility for NYHA class I estimated from the analysis of EQ-5D data from the EXPLORER-HCM trial was higher than for people of the same age in the general population (see 4.2.6 above). EAG scenario 9 assumes that people in NYHA class I have the same utility as the UK general population (adjusted for age and gender), and utilities for NYHA class II, III and IV are estimated using multipliers relative to class I calculated from the trial results.

- **EAG scenarios 10-12:** These test the impact of different assumptions about additional monitoring that will be required for patients being treated with mavacamten (see section 4.2.9.2).

Table 21 Additional EAG scenarios on the revised base case (with EAG correction)

Base case assumptions	EAG scenarios	ICER (£/QALY)
Revised base case (EAG correction)		£29,953
Comparator arm transition probabilities		
Trial-based TPs to week 46, then no NYHA change (except for SRT)	1) Trial-based TPs until week 30 (same as for mavacamten arm)	£45,256
Mavacamten discontinuation		
All without NYHA class improvement at week 30 stop treatment (0% NYHA class I, [redacted]% NYHA class II, and 100% NYHA class III/IV)	2) 90% of those in NYHA class II and III with no improvement at week 30 discontinue ([redacted] in class II and 90% in class III)	£31,830
	3) 80% of those in NYHA class II and III with no improvement at week 30 discontinue ([redacted] in class II and 80% in class III)	£33,712
Mortality		
Relative all-cause mortality by NYHA class from Wang et al. 2022,[2] which changes with NYHA in model	4) No increased risk by NYHA class (general population mortality)	£49,022
	5) HR of 1.85 used across all NYHA classes (estimated from Wang et al. 2022 HRs and the baseline NYHA distribution)	£52,282
Long-term natural progression of NYHA class		
No change in NYHA class	6) [redacted] per year on mavacamten and disopyramide; 4.55% on all other treatments	£17,355
	7) [redacted] per year on mavacamten and after SRT; 4.55% on all other treatments	£17,482

Base case assumptions	EAG scenarios	ICER (£/QALY)
	8) [redacted] per year on mavacamten, disopyramide and after SRT; 4.55% on BB/CCB monotherapy	£17,496
Health state utilities		
EXPLORER-HCM EQ-5D analysis by NYHA class, with age-adjustment	9) General population utility for NYHA class I, with proportional adjustments for NYHA classes II-IV and for age	£33,024
Monitoring costs for mavacamten		
Monitoring for mavacamten: additional outpatient visits and echocardiography in first year, no additional monitoring from year 2	10) [redacted]	£36,840
	11) [redacted]	£32,089
	12) [redacted]	£30,545
Source: Produced by the EAG from the company's revised base case model		

6.2 EAG's preferred assumptions

Our preferred assumptions are:

- **EAG scenario 1**: Use of transition probability estimates from the trial period of 30 weeks only, in both arms. We believe that the imbalance in the use of post-trial data in the company's base case is a source of bias.
- **EAG scenario 9**: Utilities should be capped at general population values for age. Clinical experts consulted by the EAG did not consider it likely that mean utility for people with obstructive HCM in NYHA class I would be better than for people of the same age in the general population outside of the trial context. We match the utility for NYHA class I to that in the general population and adjust utilities for NYHA class II to IV using relative estimates from the EXPLORER-HCM trial (utility multipliers). As in the company base case, we agree that utilities should also be adjusted for declining age through the modelled time horizon.
- **Company progression scenario 1**: We consider that the scenario with a progressive increase in NYHA class with age is likely to be more realistic than the base case assumption of no change. As there is currently a lack of evidence to support the assumption that mavacamten, or other treatments obstructive HCM, will reduce the long-term natural rate of progression, we prefer the more conservative scenario in which the same rate of progression is assumed regardless of treatment.

- **EAG scenario 10**: We prefer this scenario with enhanced monitoring arrangements for patients being treated with mavacamten.

[redacted]

Table 22 shows the cumulative results of these EAG-preferred assumptions, applied to the company's revised base case analysis. The ICER with all of the assumptions is £41,328 per QALY gained.

Probabilistic results for the EAG preferred analysis were estimated for 1,000 simulations, see Table 23 below. The probabilistic ICER is £38,690, £2,638 lower than the deterministic ICER. At a willingness-to-pay threshold of £30,000 per QALY, mavacamten + BB/CCB has an estimated [redacted]% probability of being cost-effective compared to BB/CCB monotherapy.

Table 22 Cumulative change from the company's revised base case with the EAG preferred assumptions (deterministic, proposed PAS discount for mavacamten)

Assumption	Treatments	Total costs	Total QALYs	ICER (£/QALY)
Revised company base-case (with EAG correction)	BB/CCB monotherapy Mavacamten + BB/CCB	[redacted] [redacted]	[redacted] [redacted]	£29,953
+ TP estimates from trial for 30 weeks only in both arms	BB/CCB monotherapy Mavacamten + BB/CCB	[redacted] [redacted]	[redacted] [redacted]	£45,256
+ Utilities capped at general population values for age	BB/CCB monotherapy Mavacamten + BB/CCB	[redacted] [redacted]	[redacted] [redacted]	£49,896
+ Long-term progression rate for all treatments (4.55%)	BB/CCB monotherapy Mavacamten + BB/CCB	[redacted] [redacted]	[redacted] [redacted]	£33,547
+ Enhanced monitoring for mavacamten ([redacted])	BB/CCB monotherapy Mavacamten + BB/CCB	[redacted] [redacted]	[redacted] [redacted]	£41,328

Source: produced by the EAG from the company's model
BB: beta blockers, CCB: calcium channel blockers, ICER incremental cost effectiveness ratio; QALY: quality adjusted life year

Table 23 Probabilistic results for the EAG preferred analysis (with PAS discount for mavacamten and list price for all other treatments)

Technologies	Total costs (£)	Total QALYs	Incremental		ICER (£/QALY)
			Costs (£)	QALYs	

BB/CCB monotherapy	[redacted]	[redacted]			
Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£38,690
ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; BB: beta blockers; CCB: calcium channel blockers					

6.3 Scenario analyses conducted on the EAG's preferred assumptions

We report selected scenario analysis conducted on the EAG preferred analysis in Table 24 below. These include company and EAG scenarios relating to key uncertainties and where there differences between the company's and EAG's assumptions which have an impact on the ICER. See Appendix 9.5 below for a full list of results for all of the company's and EAG scenarios reported above.

Table 24 Selected scenario analyses conducted on the EAG's preferred analysis (deterministic, PAS price for mavacamten)

EAG assumptions	Scenarios	Incremental		ICER (£/QALY)
		Cost (£)	QALYs	
EAG preferred analysis		[redacted]	[redacted]	£41,328
Comparator arm transition probabilities (TP) after week 30				
Trial-based TPs until week 30 in both arms	Comparator TPs from post-trial data until week 46	[redacted]	[redacted]	£25,294
	Comparator TPs from post-trial data until week 38	[redacted]	[redacted]	£27,262
Mavacamten discontinuation				
All with no NYHA class improvement at 30 weeks	[redacted] patients in NYHA class III (same proportion as in class II)	[redacted]	[redacted]	£43,181
	80% in NYHA class II and III with lack of effect at week 30 (EAG scenario 3)	[redacted]	[redacted]	£46,648
2.77% per year due to SAEs after week 30	1.4% per year after week 30	[redacted]	[redacted]	£46,718
Mortality				
Relative all-cause mortality by NYHA class from US EHR data (Wang et al. 2022)[2]	Adjusted HRs from SHaRe registry (CS Appendix N)	[redacted]	[redacted]	£42,195
	Unadjusted one-year RR from SHaRe (Lakdawala et al. 2021)[3]	[redacted]	[redacted]	£33,757
	No increased risk, general population mortality (EAG scenario 4)	[redacted]	[redacted]	£61,994
	Pooled HR for baseline NYHA (1.85), no change within model (EAG scenario 5)	[redacted]	[redacted]	£70,481
Long-term natural progression of NYHA class				
	No change after week 30	[redacted]	[redacted]	£60,393

EAG assumptions	Scenarios	Incremental		ICER (£/QALY)
		Cost (£)	QALYs	
Annual rate of NYHA progression: 4.55% regardless of treatment	[redacted] per year on mavacamten; 4.55% otherwise	[redacted]	[redacted]	£37,114
	[redacted] per year on mavacamten and disopyramide; 4.55% other treatments	[redacted]	[redacted]	£37,138
	[redacted] per year on mavacamten and after SRT; 4.55% other treatments	[redacted]	[redacted]	£37,363
	[redacted] per year on mavacamten, disopyramide and after SRT; 4.55% on BB/CCB monotherapy	[redacted]	[redacted]	£37,388
Health state utilities				
EXPLORER-HCM utilities adjusted to not exceed UK population norms for age and sex	EXPLORER-HCM adjusted for change with age but not for UK norms	[redacted]	[redacted]	£37,485
	No age adjustment of utilities	[redacted]	[redacted]	£38,043
	Utilities from Gohler et al, 2009[88]	[redacted]	[redacted]	£39,205
Monitoring costs for mavacamten				
Enhanced monitoring ([redacted])	Additional monitoring in year 1	[redacted]	[redacted]	£33,547
	[redacted]	[redacted]	[redacted]	£34,479
	[redacted]	[redacted]	[redacted]	£36,705

Source: Produced by ERG from Company Addendum model
ASA: alcohol septal ablation, BB: beta blocker, CCB: calcium channel blocker, EHR: electronic health records, HR: hazard ratio, ICER: incremental cost effectiveness ratio, RR: relative risk, NYHA: New York Heart Association, TP transition probability

6.4 Conclusions on the cost effectiveness evidence

The company developed a model to estimate the cost-effectiveness of mavacamten with BB/CCB monotherapy compared with BB/CCB monotherapy alone for adults with symptomatic (NYHA class II or III) obstructive HCM. The EAG consider that the structure of the disease model (based on NYHA class) is reasonable, although it is not clear if their assumptions about the treatment pathway reflect current practice, and the likely position of mavacamten if recommended.

No serious errors in the model were identified. The company have made some minor corrections in their response to clarification questions and in their Addendum of October 2022. The EAG has identified one further very minor inconsistency related to the costing of

disopyramide, which has a negligible impact on the cost-effectiveness results (see section 5.2).

The model uses clinical effectiveness and utility data from the EXPLORER-HCM trial, and the company make a reasonable case that it is not appropriate to incorporate data from the VALOR-HCM trial due to differences in the trial populations and timing of assessments. The trial data is supplemented with observational evidence used to estimate long-term progression of NYHA class and the relationship between NYHA class and mortality, and other model parameters and assumptions are informed by advisory board meetings and an expert elicitation exercise. We consider that the model generally makes appropriate use of the available data, although we have concerns about some key assumptions and uncertainties which we discuss below.

The Company Addendum reports a revised base case with an ICER of £29,952 per QALY gained, and two new scenarios with assumptions about long-term progression of NYHA class (ICERs £17,890 and £17,341 per QALY gained). ICERs for other company scenarios are similar to the base case, with the exception of the use of a shorter time horizon (£36,933 per QALY over 20 years) and a lower rate of discontinuation after the trial period (£35,125). See section 5.3 above.

We report results for additional EAG scenario analysis and discuss the rationale and results of our preferred assumptions in sections 6.1 and 6.2 above. Our preferred analysis includes four changes to the company's revised base case:

- No use of post-trial data to inform NYHA transitions for the comparator arm
- Utilities capped at UK general population norms for age
- Long-term progression rate for all treatments (4.55%)
- Enhanced monitoring for mavacamten which results in higher costs

Collectively these assumptions result in an increase in the ICER: £41,328 per QALY gained for the deterministic analysis; £38,690 per QALY for the probabilistic analysis (Table 22 and Table 23 respectively). The inclusion of one of the company's assumptions about long-term NYHA disease progression causes a sizeable reduction in the ICER, but this is offset by our correction to the use of post-trial data for the comparator arm (which we consider a source of bias), the capping of utilities at UK population norms and our more conservative assumptions about the cost of monitoring.

The scenario analysis on the EAG preferred analysis in Table 24 highlights some other key uncertainties:

- The model is sensitive to uncertainties over the magnitude and nature of the relationship between NYHA class and mortality. In particular, the ICER is highly sensitive to assumptions about whether a reduction in NYHA class due to treatment will improve survival. We test two scenarios in which the assumption of a causal relationship between NYHA class and mortality is removed from the model. Given the lack of evidence for survival benefits of any treatment for obstructive HCM, we believe that these scenarios should be considered as plausible.
- The scenario analysis indicates that ICERs increase with reductions in rates of discontinuation of mavacamten after the trial period. This suggests that the cost-effectiveness of mavacamten in practice would be reduced if treatment is not discontinued in a timely fashion when it is not providing a clear benefit. Constraints on NHS resources, and delays in patients seeking or obtaining appointments for assessment could reduce the cost-effectiveness of treatment.
- We have not assumed a difference between treatments in rates of long-term progression of NYHA class. If mavacamten is associated with a reduction in progression, this would improve its cost-effectiveness.
- The ICER is very sensitive to different assumptions about the costs of monitoring for patients on mavacamten. Adding the company's assumptions about the cost of monitoring to other EAG preferred assumptions, the ICER falls to £33,547 per QALY gained. We are conscious that our assumption on monitoring costs is conservative, and in practice the costs might be lower than we have anticipated.

Finally, we note key structural uncertainties that we have not been able to address in scenario analyses:

- There is not a consensus on the position of disopyramide in clinical practice, the extent to which is tolerated, its effectiveness, and whether it should be considered as a comparator for mavacamten. These are key uncertainties, and very difficult to address given the lack of robust comparative evidence.
- Given the mechanism of action of mavacamten, there is a question of whether its effectiveness, and hence cost-effectiveness might differ between patients with and without a pathogenic (i.e. sarcomere) mutation. The company report results from the EXPLORER-HCM trial for subgroups with different HCM genetic test results (section 3.6.10 above). The use of these results in a cost-effectiveness subgroup analysis is

challenging because of the small numbers of patients in the genetic subgroups. However, we believe that an exploratory analysis is possible and have made suggestions for how transition probability matrices might be obtained by pooling data over the whole trial period (see section 4.2.3.1 above).

- There are challenges in modelling given the paucity of epidemiological evidence for obstructive HCM. The company have made good attempts to analyse routinely collected data on the relationship between NYHA class and mortality, but uncertainty remains over whether treatments that improve symptoms have survival benefits. Observational data on long-term progression of symptomatic disease is also weak. There is uncertainty over the estimated rate of NYHA class progression (4.55% per year) from the Maron et al. 2016 cohort study, so we welcome the supplementary systematic literature review for prognostic evidence referred to in the response to clarification questions on the Company Addendum.

7 SEVERITY MODIFERS

The 2022 NICE Health Technology Evaluations Manual specifies criteria for QALY weightings for severity based on the proportional and absolute QALY shortfall for the population with the condition, in comparison with the general population with the same age and sex distribution.[89] The company do not refer to the QALY shortfall criteria for severity weighting in their submission. We report the absolute and proportional QALY shortfalls for the company's base case analysis and EAG preferred analysis in Table 25 below. The NICE criteria of absolute QALY shortfall ≥ 12 or proportional QALY shortfall ≥ 85% are not met for either analysis.

Table 25 QALY shortfall analysis

Analysis	Modelled population		Expected total QALYs [a]		QALY shortfall	
	Mean age (years)	% male	General population [b]	Model	Absolute	Proportional
Company base case	59.0	59.4	12.66	10.58	2.08	16.43%
EAG preferred	59.0	59.4	12.66	8.96	3.70	29.22%

Source: Calculated by the EAG from the online QALY Shortfall Calculator, Schneider et al. 2021 (https://shiny.york.ac.uk/shortfall).[90]

[a] Discounted at 3.5% per year

[b] General population expected QALYs based on national life tables for England (2017-2019 pooled)[86] and utilities from 2017 and 2018 Health Survey for England data mapped from EQ-5D-5L health states to the EQ-5D-3L UK value set using the Hernández-Alava et al. 2020[78] crosswalk procedure.

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9 APPENDICES

9.1 EAG appraisal of the company's methods for the systematic review of clinical effectiveness

Systematic review components and processes	EAG response	EAG comments
Was the review question clearly defined using the PICOD framework or an alternative?	Yes	The eligibility criteria relevant to this submission (CS Appendix D Table 2) are an amended version of the company's original 'global SLR' PICOS criteria (CS Appendix D Table 1).
Were appropriate sources of literature searched?	Yes	The company searched Embase, MEDLINE, MEDLINE In-Process, Cochrane CENTRAL and CDSR, and several relevant cardiology and heart failure conferences (CS section B.2.1.1 and CS Appendix D sections 2.2.1 and 2.2.2).
Was the time period of the searches appropriate?	Yes	Databases were searched from inception to 3rd December 2021; conferences were hand searched for 2019 to 2021 (CS section B.2.1.1 and CS Appendix D sections 2.2.1 and 2.2.2). The database searches were seven months out of date at time of the submission therefore the EAG re-ran the company searches in MEDLINE and MEDLINE In-Process, Embase, and ClinicalTrials.gov. We identified two new ongoing studies in symptomatic obstructive HCM populations, see section 3.9 of this report.[91 92] There were no new studies for inclusion (NB the full paper reporting interim results for an already included trial (VALOR-HCM) was identified).[33]
Were appropriate search terms used and combined correctly?	Yes	Relevant index terms and relevant free-text terms were both used. Published search filters for RCTs and observational studies were used. (Appendix I within CS Appendix D)

Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and relevant to the decision problem?	Yes	Inclusion and exclusion criteria for this submission are specified in the PICOS criteria table (CS Appendix D Table 2). The amended PICOS criteria reflect the company decision problem outlined in CS section B.1.1 by removing disopyramide as a comparator from the clinical effectiveness evidence screening (NB the company's decision problem for comparators does not reflect the NICE scope, as discussed in section 2.3.2 of this report).
Were study selection criteria applied by two or more reviewers independently?	Yes	The reported screening process in CS Appendix D sections 2.3.1 to 2.3.2 refers to application of the initial PICOS criteria (CS Appendix D Table 1). This screening was performed in parallel and independently by two reviewers with discrepancies resolved by a third reviewer. The selection criteria from the amended PICOS criteria (CS Appendix D Table 2) were applied independently by two reviewers to the set of full-text papers identified using the initial PICOS criteria, with a third reviewer resolving any discrepancies (confirmed in response to clarification question A1). The studies excluded during the application of the amended PICOS criteria are listed in the response to clarification question A2.
Was data extraction performed by two or more reviewers independently?	No	One researcher extracted the data. A second researcher reviewed the extracted data and checked for accuracy and completeness (CS Appendix D section 2.3.3). The EAG agree that this approach is acceptable.
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used and was it appropriate?	Partly	The company assessed the RCTs (EXPLORER-HCM and VALOR-HCM) using an appropriate tool (CRD checklist[93]). However, the company inappropriately used the ROBINS-I tool to assess the EXPLORER-LTE cohort. [94] In response to EAG clarification questions the company subsequently provided assessments for EXPLORER-LTE and the two real world evidence studies using the Newcastle

		Ottawa Scale (NOS). [95] The NOS does not fully capture all risks of bias but the EAG have provided additional interpretation to address this limitation. See Appendix 9.3 below for full details of the company and EAG risk of bias assessments.
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	No	One reviewer conducted the quality assessment of included articles; a second reviewer checked the quality assessment for accuracy (CS Appendix D section 2.4). The EAG agree this approach is acceptable.
Is sufficient detail on the individual studies presented?	Yes	All relevant documents including SAPs, CSRs and published papers were supplied for EXPLORER-HCM, MAVA-LTE (for the EXPLORER-LTE cohort), PIONEER-HCM, PIONEER-OLE, and VALOR-HCM.
If statistical evidence synthesis (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Not applicable	No meta-analysis was performed. The EAG agree that this is appropriate.
CDSR Cochrane Database of Systematic Reviews; CENTRAL Cochrane Central Register of Controlled Trials; CRD Centre for Reviews and Dissemination, University of York; CSR Clinical study report; N/A Not applicable; PICOS: Population, Intervention, Comparator, Study design; RCTs Randomised controlled trials; ROBINS-I Risk of Bias in Non-Randomized Studies of Interventions; RWE: Real-world evidence; SAP: Statistical analysis plan.		

9 Appendices - continued

9.2 Baseline characteristics of the included studies

Characteristic	EXPLORER-HCM[26 40]		EXPLORER-LTE cohort (N = 231)[31]	VALOR-HCM	
	Mavacamten (N = 123)	Placebo (N = 128)		Mavacamten (N = 56)	Placebo (N = 56)
Age, mean years (SD)	58.5 (12.2)	58.5 (11.8)	60.0 (11.9)	59.8 (14.2)	60.9 (10.5)
Female sex, n (%)	57 (46)	45 (35)	91 (39.4)	27 (48.2)	28 (50.0)
Race, n (%)					
White	115 (93)	114 (89)	NR**	48 (85.7)	52 (92.9)
Black or African American	1 (1)	5 (4)		3 (5.4)	0 (0.0)
Native American or Alaskan Native	0	1 (1)		NR	NR
Asian	4 (3)	2 (2)		2 (3.6)	0 (0.0)
Unknown / unspecified or other	3 (2)	6 (5)		3 (5.4)	4 (7.1)
Region, n (%)				-	
USA	53 (43)	55 (43)	NR**	56 (100)	56 (100)
Spain	17 (14)	16 (13)		-	-
Poland	16 (13)	16 (13)		-	-
Other	37 (30)*	41 (32)*		-	-
Ex-USA sites	-	-		-	-
NYHA					
Class I	-	-	14 (6.1)	-	-
Class II (with exertional syncope in VALOR-HCM)	88 (72)	95 (74)	152 (65.8)	4 (7.1)	4 (7.1)
Class III	35 (28)	33 (26)	65 (28.1)	-	-
Class ≥ III	-	-	-	52 (92.9)	52 (92.9)
Class IV	-	-	-	[redacted]	[redacted]
Medical history, n (%)			NR††		
Family history of HCM	33 (27)	36 (28)		17 (30.4)	15 (26.8)
AF	12 (10)	23 (18)		11 (19.6)	8 (14.3)
SRT	11 (9)	8 (6)		-	-
Hypertension	57 (46)	53 (41)		36 (64.3)	34 (60.7)
Hyperlipidaemia	27 (22)	39 (30)		-	-
Coronary artery disease	12 (10)	6 (5)		-	-
Obesity	15 (12)	14 (11)		-	-
Type 2 diabetes	6 (5)	7 (6)		-	-
Asthma	17 (14)	11 (9)		-	-
Chronic obstructive pulmonary disease	2 (2)	3 (2)		-	-
pVO_2, mL/kg/min, mean (SD)	18.9 (4.9)	19.9 (4.9)	NR††	-	-

Characteristic	EXPLORER-HCM[26 40]		EXPLORER-LTE cohort (N = 231)[31]	VALOR-HCM	
	Mavacamten (N = 123)	Placebo (N = 128)		Mavacamten (N = 56)	Placebo (N = 56)
NT-proBNP, ng/L, geometric mean (CV%)	777 (136)*	616 (108)*	NR**	-	-
NT-proBNP, ng/L, median (IQR)	NR	NR	783 (326, 1593) [n = 230]	724 (291-1913)	743 (275-1,196)
Background therapy, n (%)					
BB	94 (76)	95 (74)	175 (75.8)	26 (46.4)	25 (44.6)
CCB	25 (20)	17 (13)	38 (16.5)	7 (12.5)	10 (17.9)
Neither BB nor CCB	4 (3.3)	16 (12.5)	NR	3 (5.4)	3 (5.4)
Combination (any, including disopyramide)	-	-	-	20 (35.7)	16 (28.5)
BB and CCB	-	-	-	6 (10.7)	10 (17.9)
Implantable cardioverter-defibrillator, n (%)	27 (22%)	29 (23%)	NR††	-	-
HCM genetic testing performed, n (%)	90 (73)	100 (78)	NR††	-	-
Pathogenic/likely pathogenic HCM gene variant, n/N tested (%)	28/90 (31)	22/100 (22)			
BMI, kg/m^2, mean (SD)	29.7 (4.9)	29.2 (5.6)	NR**	29.3 (4.8)	31.9 (6.2)
Heart rate, beats per minute, mean (SD)	63 (10.1)	62 (10.6)	NR**	-	-
Systolic blood pressure, mmHg, mean (SD)	128 (16.2)	128 (14.6)	NR††	130.4 (16.5)	131.2 (16.6)
Diastolic blood pressure, mmHg, mean (SD)	75 (10.8)	76 (9.9)	NR††	74.0 (10.5)	74.2 (8.9)
pVO_2, mL/kg/minute, mean (SD)	18.9 (4.9)	19.9 (4.9)	NR††	-	-
High-sensitivity cardiac troponin I, geometric mean, ng/L, (COV%)	12.5 (208)‡	12.5 (373)‡	NR††	17.3 (7.0-31.6)[b]	12.9 (6.1-26.0)[b]
Echocardiographic parameters, mean (SD)					
LVEF, %	74 (6)	74 (6)	74.0 (5.9) [n = 230]	67.9 (3.7)	68.3 (3.2)
Maximum LV wall thickness, mm	20 (4)	20 (3)	NR††	-	-
LVOT gradient, rest, mmHg	52 (29)	51 (32)	48.3 (31.9)	51.2 (31.4)	46.3 (30.5)
LVOT gradient, Valsalva, mmHg	72 (32)	74 (32)	69.5 (33.3) [n = 228]	75.3 (30.8)	76.2 (29.9)
LVOT gradient, post-exercise, mmHg	86 (34)§	84 (36)§	NR††	82.5 (34.7)	85.2 (37.0)
Left atrial volume index, mL/m^2	40 (12)¶	41 (14)¶	NR††	41.3 (16.5)	40.9 (15.2)
Left atrial diameter, mm	42 (5)‖	42 (6)‖	NR††	-	-

Characteristic	EXPLORER-HCM[26 40]		EXPLORER-LTE cohort (N = 231)[31]	VALOR-HCM	
	Mavacamten (N = 123)	Placebo (N = 128)		Mavacamten (N = 56)	Placebo (N = 56)

Sources: reproduced from CS Table 8, Company Addendum Table 5 and Desai 2022.[44]
[a] percentage calculated by reviewer from Company Addendum clarification response A1: [redacted]/112 ([redacted]%) assigned to the mavacamten arm.
[b] median (IQR)
*Other comprised Israel, Germany, France, Czech Republic, Denmark, Netherlands, Portugal, Italy, Belgium, and the UK (ordered by number of patients).
†Data missing for three patients in the mavacamten group and two patients in the placebo group. The variation number (COV%) is the coefficient of variation, which is defined as the ratio of the SD to the mean.
‡Data missing for three patients in the mavacamten group and nine patients in the placebo group.
§Data missing for one patient in the mavacamten group and one patient in the placebo group.
¶Data missing for one patient in the mavacamten group.
||Data missing for five patients in each group.
**Reported for October 2020 DBL; see Appendix M
††Baseline characteristics not currently available for the EXPLORER-LTE cohort.[31 96]
AF: atrial fibrillation; BMI: body mass index; CCB: calcium channel blocker; COV: coefficient of variation; HCM: hypertrophic cardiomyopathy; IQR: interquartile range; LV: left ventricular; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; NR: not reported; NT-proBNP: N-terminal pro B-type natriuretic peptide; NYHA: New York Heart Association; pVO_2: peak oxygen consumption; SD: standard deviation; SRT: septal reduction therapies.

9.3 Company and EAG critical appraisal of the included studies

9.3.1 Company and EAG critical appraisal of the EXPLORER-HCM trial

Study questions	Company response	EAG response	Risk of bias (EAG interpretation)
Was randomisation carried out appropriately?	Yes	Yes	Low
Was the concealment of treatment allocation adequate?	Yes	Yes	Low
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes (stated No in CS Appendix D Table 28)	Probably yes. Some differences, but likely to be inconsequential (not systematically favouring either arm)	Probably low
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes. Stated all study participants were blinded (CS Appendix D Table 28)	Low
Were there any unexpected imbalances in dropouts between groups?	No	No. Dropout rate small (n=4 and n=3) and reasons similar between groups (CS Appendix D Figure 2)	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	Low
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	● ITT analysis for primary outcome. ● Few missing data (≤5%) for change in NHYA class, change in resting and Valsalva LVOT gradients, NT-proBNP and complete response. Moderate missing data (7%) for change in LVEF. ● Extensive (~30%) missing data for KCCQ-23 CSS and HCMSQ-SoB but treatment effect robust to missing data in sensitivity analyses. ● Extensive (mavacamten 22%, placebo 30%) missing data for EQ-5D change from baseline to week 30 (CS Table 14). NB this does not apply to the estimation of EQ-5D by NYHA class which had few missing data (Table 11).	● Low risk of bias for primary outcome, KCCQ-23 CSS and HCMSQ-SoB. ● Probably low risk of bias for change in NHYA class, change in resting and Valsalva LVOT gradients and complete response. ● Uncertain risk of bias for change in LVEF. ● High risk of bias for change in EQ-5D from baseline to week 30. ● Low risk of bias for estimation of mean EQ-5D score per NYHA class.

Source: CS Table 11 with EAG additions
HCMSQ-SoB: Hypertrophic Cardiomyopathy Symptom Questionnaire – Shortness of Breath; ITT: intention to treat; KCCQ-23 CSS: Kansas City Cardiomyopathy Questionnaire Complete Symptom Score; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; NT-proBNP: N-terminal pro B-type natriuretic peptide: NYHA: New York Heart Association.

9.3.2 Company and EAG critical appraisal of the VALOR-HCM trial

Study questions	Company response	EAG response	Risk of bias (EAG interpretation)
Was randomisation carried out appropriately?	Yes (interactive voice web response system)	Agree with company	Low
Was the concealment of treatment allocation adequate?	Yes (interactive voice response system with matching placebo)	Agree with company	Low
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes (minor differences between groups in background therapy)	Minor differences, considered by the three clinical experts advising the EAG to be likely inconsequential	Low
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes, stated all study personnel were blinded	Low
Were there any unexpected imbalances in dropouts between groups?	No	No, difference in dropouts between arms ≤5% for all outcomes	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	Low
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Probably yes. Handling of missing data in ITT analysis not fully explained but number missing low (n=2 and n=4)	Probably low

Source: Clarification Response Table 1 with EAG additions
ITT: intention to treat.

9.3.3 Company and EAG critical appraisal of the EXPLORER-LTE study using the Newcastle-Ottawa Scale

From Table 1 in Clarification Response Appendix A		Company response	EAG response
Representative-ness of the exposed cohort	a) truly representative of the average *obstructive HCM* patients in the community *	0	Question assesses external validity (not risk of bias). External validity would be the same as for EXPLORER-HCM, discussed in section 3.2.3 above.
	b) somewhat representative of the average *obstructive HCM patients* in the community *	1 (patients given the option to enter the study following participation in the pivotal EXPLORER-HCM RCT	

	c) selected group of users eg nurses, volunteers	0	
	d) no description of the derivation of the cohort	0	
Selection of the non-exposed cohort	a) drawn from the same community as the exposed cohort *	0	*Not applicable, single-cohort intervention-only study.*
	b) drawn from a different source	0	
	c) no description of the derivation of the non exposed cohort	0	
Ascertainment of exposure	a) secure record (eg surgical records) *	1	Stated in protocol section 12.4.5. **Low risk of bias.**
	b) structured interview *	0	
	c) written self report	0	
	d) no description	0	
Demonstration that outcome of interest was not present at start of study	a) yes *	1	Changes from baseline assessed, so outcome at baseline is not a source of bias in this study.
	b) no	0	
	Total for selection domain	*3*	*Not interpretable as the risk of bias*
	Rating	*Good*	
Comparability of cohorts on the basis of the design or analysis	a) study controls for NYHA class *	1	*Not applicable, single-cohort intervention-only study.*
	b) study controls for any additional factor (adjusting for age at diagnosis, gender, and race) *	0	
	Total for comparability domain	*1*	*Not interpretable as the risk of bias*
	Rating	*Fair*	
Assessment of outcome	a) independent blind assessment *	1	Triple blinded to EXPLORER-HCM study arm and to mavacamten dose & dose changes (Table 1 in CS Appendix M). Sponsor unblinded (role of sponsor not stated). **Probably low risk of bias.** But note **high risk of outcome reporting bias** for the HCMSQ-SoB and EQ-5D (see section 3.3.3) – outcome reporting bias is not explicitly assessed in this instrument.
	b) record linkage *	0	
	c) self report	0	
	d) no description	0	
Was follow up long enough for outcomes to occur?	a) yes (at least 16 weeks for LVOT, LVEF, NYHA class) *	1	Yes, 48-week and/or 84-week outcomes reported. **Low risk of bias.**
	b) no	0	
Adequacy of follow up of cohorts	a) complete follow up - all subjects accounted for *	1	
	b) subjects lost to follow up unlikely to introduce bias - small number lost - > 5% follow up, or description provided of those lost	0	

	c) follow up rate < 95% and no description of those lost	0	● Few missing data for change in NYHA class (5%) (assessed at week 48 only). **Probably low risk of bias for this outcome.** ● Extensive week 84 missing data (69%-70%) for: resting and Valsalva LVOT gradients, LVEF and NT-proBNP outcomes. **High risk of bias for these outcomes.**
	d) no statement	0	
	Total for outcome domain	*3*	*Not interpretable as the risk of bias*
	Rating	*Good*	
	Total	**7**	

9.3.4 Company and EAG critical appraisal of the SHaRe analysis (Lakdawala et al. 2021; CS Appendix N) using the Newcastle-Ottawa Scale

From Table 1 in Clarification Response Appendix A		**Company response**	**EAG response**
Representative-ness of the exposed cohort	a) truly representative of the average *obstructive HCM* patients in the community *	1	Question assesses external validity (not risk of bias). Population slightly younger than in EXPLORER-HCM but appears broadly reflective of UK HCM population (Table 2 in clarification response A7).
	b) somewhat representative of the average *obstructive HCM patients* in the community *	0	
	c) selected group of users eg nurses, volunteers	0	
	d) no description of the derivation of the cohort	0	
Selection of the non-exposed cohort	a) drawn from the same community as the exposed cohort *	0	Exposed and non-exposed cohorts are not defined by the company but the EAG assume they refer to the different NYHA classes. Mortality would likely be underestimated in all NYHA classes as patients dying outside of hospital (e.g. in hospice or care home were presumably excluded). Unclear whether such underestimation would be similar across NYHA classes. **Unclear risk of bias**.
	b) drawn from a different source	0	
	c) no description of the derivation of the non exposed cohort	0	
Ascertainment of exposure	a) secure record (eg surgical records) *	1	Retrospective review of electronic records but no details of the process used to extract, check and verify accuracy of the data. Sources and verification of baseline
	b) structured interview *	0	
	c) written self report	0	
	d) no description	0	

			data not described (clarification response A6). **Unclear risk of bias.**
Demonstration that outcome of interest was not present at start of study	a) yes *	1	All-cause mortality was the outcome of interest; non-events were censored. **Low risk of bias.**
	b) no	0	
	Total for selection domain	*3*	*Not interpretable as the risk of bias*
	Rating	*Good*	
Comparability of cohorts on the basis of the design or analysis	a) study controls for NYHA class *	1	Where there were differences between NYHA classes (age, sex, race, family HCM history) these were adjusted for in the analysis. **Low risk of bias.**
	b) study controls for any additional factor (adjusting for age at diagnosis, gender, and race) *	1	
	Total for comparability domain	*2*	*Not interpretable as the risk of bias*
	Rating	*Good*	
Assessment of outcome	a) independent blind assessment *	0	Not reported whether records were assessed independently or whether methods were in place to ensure rigour in the outcome assessment. **Unclear risk of bias.**
	b) record linkage *	1	
	c) self report	0	
	d) no description	0	
Was follow up long enough for outcomes to occur?	a) yes (at least 16 weeks for LVOT, LVEF, NYHA class) *	1	Follow up appears adequate (Table 6 above) **Low risk of bias.**
	b) no	0	
Adequacy of follow up of cohorts	a) complete follow up - all subjects accounted for *	1	Pre-specified index date and end of study for all participants. **Low risk of bias.**
	b) subjects lost to follow up unlikely to introduce bias - small number lost - > 5% follow up, or description provided of those lost	0	
	c) follow up rate < 95% and no description of those lost	0	
	d) no statement	0	
	Total for outcome domain	*3*	*Not interpretable as the risk of bias*
	Rating	*Good*	
	Total	**8**	

9.3.5 Company and EAG critical appraisal of the Wang et al. 2022 (EHR) study using the Newcastle-Ottawa Scale

From Table 1 in Clarification Response Appendix A		Company response	EAG response
	a) truly representative of the average *obstructive HCM* patients in the community *	1	Question assesses external validity (not risk

Representative-ness of the exposed cohort	b) somewhat representative of the average *obstructive HCM patients* in the community *	0	of bias). A US-only population with a slightly higher proportion female (51%) and lower proportion white ethnicity (80%) than in EXPLORER-HCM but no other comparable baseline characteristics are reported.
	c) selected group of users eg nurses, volunteers	0	
	d) no description of the derivation of the cohort	0	
Selection of the non-exposed cohort	a) drawn from the same community as the exposed cohort *	0	Exposed and non-exposed cohorts are not defined by the company but the EAG assume they refer to the different NYHA classes. Mortality would likely be underestimated in all NYHA classes as patients dying outside of hospital (e.g. in hospice or care home were presumably excluded). Unclear whether such underestimation would be similar across NYHA classes. **Unclear risk of bias**.
	b) drawn from a different source	0	
	c) no description of the derivation of the non exposed cohort	0	
Ascertainment of exposure	a) secure record (eg surgical records) *	1	Retrospective review of electronic records but no details of the process used to extract, check and verify accuracy of the data. Conference abstract only with limited information. **Unclear risk of bias.**
	b) structured interview *	0	
	c) written self report	0	
	d) no description	0	
Demonstration that outcome of interest was not present at start of study	a) yes *	1	All-cause mortality was the outcome of interest. **Low risk of bias.**
	b) no	0	
	Total for selection domain	*3*	*Not interpretable as the risk of bias*
	Rating	*Good*	
Comparability of cohorts on the basis of the design or analysis	a) study controls for NYHA class *	1	No baseline characteristics reported for the NYHA classes. Not reported whether the analyses adjusted for any confounding variables. **Unclear risk of bias**.
	b) study controls for any additional factor (adjusting for age at diagnosis, gender, and race) *	0	
	Total for comparability domain	*1*	*Not interpretable as the risk of bias*
	Rating	*Fair*	
Assessment of outcome	a) independent blind assessment *	0	Not reported whether records were assessed independently or whether methods were in place to ensure rigour in the outcome
	b) record linkage *	1	
	c) self report	0	
	d) no description	0	

			assessment. **Unclear risk of bias.**
Was follow up long enough for outcomes to occur?	a) yes (at least 16 weeks for LVOT, LVEF, NYHA class) *	1	Follow up appears adequate (Table 6 above) **Low risk of bias.**
	b) no	0	
Adequacy of follow up of cohorts	a) complete follow up - all subjects accounted for *	1	Pre-specified retrospective cohort but no information on data censoring. **Unclear risk of bias.**
	b) subjects lost to follow up unlikely to introduce bias - small number lost - > 5% follow up, or description provided of those lost	0	
	c) follow up rate < 95% and no description of those lost	0	
	d) no statement	0	
	Total for outcome domain	*3*	*Not interpretable as the risk of bias*
	Rating	*Good*	
	Total	**7**	

9.4 Ongoing studies

Study name / identifier	Summary	Estimated study completion date
EXPLORER-LTE; (cohort of MAVA-LTE; NCT03723655)	Cohort study for participants previously enrolled in EXPLORER-HCM who continued into the long-term extension study MAVA-LTE.	September 2025. Further interim analyses expected in the 12 months following submission (CS section B.2.11).
VALOR-HCM; NCT04349072	After Week 16 the study enters the active-controlled period and subsequently the long-term extension study where all participants receive mavacamten	June 2024.
CV027-042	Epidemiology, treatment patterns and burden of illness associated with obstructive HCM in England – unpublished, incomplete company observational study using UK CPRD data (GOLD and Aurum) in combination with HES data. (CS sections B.1.3.2.3.3 and B.2.12.4, Appendix O, clarification responses A5 and A9)	End of 2022.
HORIZON-HCM; NCT05414175	Company cohort study of mavacamten in Japanese adults with symptomatic obstructive HCM	Primary completion date December 2023; completion date January 2027.
NCT05174416	Lian Bio LLC-sponsored RCT with long term extension for Chinese adults with symptomatic OHCM; mavacamten:placebo ratio is 2:1	Primary completion date November 2022; completion date May 2024.
DISCOVER-HCM; NCT05489705	Company prospective registry study to assess real-world patient characteristics, treatment patterns, and longitudinal outcomes in patients in the United States receiving mavacamten and other treatments for symptomatic obstructive hypertrophic cardiomyopathy; primary outcome is incidence of heart failure; comparators include disopyramide.	July 2029.

PIONEER-OLE; NCT03496168	Company phase II study; exclusion agreed as appropriate by EAG (Table 5).	November 2023.
CPRD: Clinical Practice Research Datalink; HCM: hypertrophic cardiomyopathy; HES: Hospital Episode Statistics; OHCM: obstructive hypertrophic cardiomyopathy; RCT: randomised controlled trial.		

9.5 Scenario analysis conducted on model with EAG preferred assumptions

EAG assumptions	Company's base case	Scenarios	Incremental		ICER
			Cost (£)	QALYs	(£/QALY)
EAG preferred analysis			[redacted]	[redacted]	**£41,328**
Age of cohort at baseline					
59 years	59 years	52 years	[redacted]	[redacted]	£37,944
		62 years	[redacted]	[redacted]	£42,951
Time horizon					
Lifetime horizon	Lifetime horizon	20-year time horizon	[redacted]	[redacted]	£49,651
		30-year time horizon	[redacted]	[redacted]	£42,052
Comparator arm transition probabilities (TP) after week 30					
Trial-based TPs until week 30 in both arms	Comparator TPs from post-trial data until week 46	Comparator TPs from post-trial data until week 46	[redacted]	[redacted]	£25,294
		Comparator TPs from post-trial data until week 38	[redacted]	[redacted]	£27,262
Mavacamten discontinuation					
All with no NYHA class improvement at 30 weeks	All with no NYHA class improvement at 30 weeks	[redacted] patients in NYHA class III (same proportion as in class II)	[redacted]	[redacted]	£43,181
		90% in NYHA class II and III with lack of effect at week 30 (EAG scenario 2)	[redacted]	[redacted]	£43,981
		80% in NYHA class II and III with lack of effect at week 30 (EAG scenario 3)	[redacted]	[redacted]	£46,648
2.77% per year due to SAEs after week 30	2.77% per year due to SAEs after week 30	1.4% per year after week 30	[redacted]	[redacted]	£46,718
Treatment after mavacamten discontinuation					
100% BB/CCB monotherapy	100% BB/CCB monotherapy	90% BB/CCB monotherapy 10% disopyramide + BB/CCB	[redacted]	[redacted]	£37,928
		75% BB/CCB monotherapy 25% disopyramide + BB/CCB	[redacted]	[redacted]	£33,660

EAG assumptions	Company's base case	Scenarios	Incremental		ICER (£/QALY)
			Cost (£)	QALYs	
		NYHA I/II: 100% BB/CCB NYHA III/IV: 90% BB/CCB; 10% SRT	[redacted]	[redacted]	£39,470
		NYHA I/II: 100% BB/CCB monotherapy NYHA III/IV: 80% BB/CCB; 10% disopyramide + BB/CCB; 10% SRT	[redacted]	[redacted]	£37,930
Treatment after mavacamten discontinuation and escalation from BB/CCB					
100% disopyramide + BB/CCB for 9 months then SRT	100% disopyramide + BB/CCB for 9 months then SRT	After mavacamten: 100% BB/CCB After BB/CCB: 100% SRT	[redacted]	[redacted]	£41,566
		After mavacamten: 90% BB/CCB; 10% disopyramide + BB/CCB After BB/CCB: 100% SRT	[redacted]	[redacted]	£38,171
		After mavacamten: 75% BB/CCB; 25% disopyramide + BB/CCB After BB/CCB: 100% SRT	[redacted]	[redacted]	£33,908
		After mavacamten: NYHA I/II: 100% BB/CCB; NYHA III/IV: 90% BB/CCB, 10% SRT After BB/CCB: 100% SRT	[redacted]	[redacted]	£39,710
		After mavacamten: 100% BB/CCB After BB/CCB NYHA I/II: 100% disopyramide + BB/CCB NYHA III/IV: 100% SRT	[redacted]	[redacted]	£41,568
Time on disopyramide before escalation to SRT: 9 months	Time on disopyramide before escalation to SRT: 9 months	6 months	[redacted]	[redacted]	£41,406
		12 months	[redacted]	[redacted]	£41,254
Efficacy of SRT: one-off NYHA class transitions					
From expert elicitation (CS Table 29)	From expert elicitation (CS Table 29)	Knyshov et al. 2013[83]	[redacted]	[redacted]	£40,768

EAG assumptions	Company's base case	Scenarios	Incremental		ICER (£/QALY)
			Cost (£)	QALYs	
Mortality					
Relative all-cause mortality by NYHA class from US EHR data (Wang et al. 2022)[2]	Relative all-cause mortality by NYHA class from US EHR data (Wang et al. 2022)[2]	Adjusted HRs from SHaRe registry (CS Appendix N)	[redacted]	[redacted]	£42,195
		Unadjusted one-year RR from SHaRe (Lakdawala et al. 2021)[3]	[redacted]	[redacted]	£33,757
		No increased risk, general population mortality (EAG scenario 4)	[redacted]	[redacted]	£61,994
		Pooled HR for baseline NYHA (1.85), no change within model (EAG scenario 5)	[redacted]	[redacted]	£70,481
Long-term natural progression of NYHA class					
Annual rate of NYHA progression: 4.55% regardless of treatment	No change in NYHA class after week 30	No change after week 30	[redacted]	[redacted]	£60,393
		[redacted] per year on mavacamten; 4.55% otherwise	[redacted]	[redacted]	£37,114
		[redacted] per year on mavacamten and disopyramide; 4.55% other treatments	[redacted]	[redacted]	£37,138
		[redacted] per year on mavacamten and after SRT; 4.55% other treatments	[redacted]	[redacted]	£37,363
		[redacted] per year on mavacamten, disopyramide and after SRT; 4.55% on BB/CCB monotherapy	[redacted]	[redacted]	£37,388
Health state utilities					
EXPLORER-HCM utilities adjusted to not exceed UK population norms for age and sex	EXPLORER-HCM utilities adjusted for change with age but not for UK norms	EXPLORER-HCM adjusted for change with age but not for UK norms	[redacted]	[redacted]	£37,485
		No age adjustment of utilities	[redacted]	[redacted]	£38,043
		Utilities from Gohler et al, 2009[88]	[redacted]	[redacted]	£39,205

EAG assumptions	Company's base case	Scenarios	Incremental		ICER (£/QALY)
			Cost (£)	QALYs	
Monitoring costs for mavacamten					
Enhanced monitoring ([redacted])	Additional monitoring in first year, no additional monitoring from year 2	Additional monitoring in year 1	[redacted]	[redacted]	£33,547
		[redacted]	[redacted]	[redacted]	£34,479
		[redacted]	[redacted]	[redacted]	£36,705
Health care resource use (HCRU) and costs					
SRT procedures: [redacted] ASA, [redacted] septal myectomy	SRT procedures: [redacted] ASA, [redacted] septal myectomy	75% ASA, 25% septal myectomy	[redacted]	[redacted]	£41,367
		25% ASA, 75% septal myectomy	[redacted]	[redacted]	£41,292
HCRU by NYHA class (CS Table 37, expert elicitation)	HCRU by NYHA class (CS Table 37, expert elicitation)	HCRU increased by 10%: 1.1	[redacted]	[redacted]	£39,518
		HCRU decreased by 10 %: 0.9	[redacted]	[redacted]	£43,139
Adverse event rates					
Treatment emergent SAEs (CS Table 32)	Treatment emergent SAEs (CS Table 32)	All SAEs > 1% in either arm	[redacted]	[redacted]	£41,533
		All cardiovascular-related SAEs	[redacted]	[redacted]	£41,559
		All SAEs > 1% in either arm OR cardiovascular-related	[redacted]	[redacted]	£41,297

Source: Produced by ERG from Company Addendum model
ASA: alcohol septal ablation, BB: beta blocker, CCB: calcium channel blocker, EHR: electronic health records, HCRU: healthcare resource use, HR: hazard ratio, ICER: incremental cost effectiveness ratio, RR: relative risk; SAE: serious adverse event, SRT: septal reduction therapy, NYHA: New York Heart Association

Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 16 January 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Page numbers cited by the EAG refer to the tracked changes version of the EAG report

Issue 1 Attribution of aficamten

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 2. "This [SEQUOIA] is a randomised controlled trial of aficamten, a myosin inhibitor with very similar properties to mavacamten."	Please clarify that aficamten is not a BMS product/SEQUOIA is not a BMS-sponsored trial.	The comparison of aficamten and mavacamten could be erroneously interpreted that aficamten is a BMS product or that SEQUOIA is a BMS-sponsored trial.	Not a factual inaccuracy. However, to avoid any doubt we have stated on page 2 that aficamten is not manufactured by BMS.

Issue 2 Descriptions of the evidence surrounding disopyramide usage

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 12, Issue 1 table. "The EAG's clinical experts did not fully agree with the company, with one expert suggesting that disopyramide is used, particularly in large centres."	The following text is proposed: "Two of the EAG's clinical experts agreed that disopyramide should not be considered part of standard care, however one expert suggested that disopyramide is used, particularly in large centres".	The Company's interpretation is that two of the EAG's clinical experts agreed with the Company's understanding that disopyramide is rarely used in clinical practice for the majority of patients relevant to this indication, and should therefore not form part of standard care (supported by	Thank you for highlighting the potential for misinterpretation. We have amended the text on page 13 to clarify the number of experts who expressed each view.

		the statement on page 25 that “The company argue that disopyramide should not be considered part of standard care. However, whilst two of the EAG’s clinical experts supported this view, the third expert did not”). However, the phrasing on page 12 could be interpreted that none of the experts fully agreed.	
Page 12, Issue 1 table. “In an expert elicitation exercise conducted by the company it was noted that “patients are generally given disopyramide in addition to calcium channel blockers and beta blockers ahead of septal reduction therapy””	The following text is proposed: “In an expert elicitation exercise conducted by the company it was noted that “patients are generally given disopyramide in addition to calcium channel blockers and beta blockers ahead of septal reduction therapy”, however it should be noted that septal reduction therapy (SRT) is only performed in a small proportion of patients.”	The Company considers that this quotation, taken out of context, could be misinterpreted unless additional clarification is added. The Company agrees that the clinical experts have indicated that disopyramide forms a necessary part of the care pathway prior to SRT. However, usage of disopyramide cannot be inferred from its positioning before SRT, because SRT itself is only performed in a small proportion of patients,	Not a factual inaccuracy. However, to improve the accuracy of interpretation we have added a statement on page 13 to clarify that the majority of obstructive HCM patients do not receive SRT.

		due to the range of reasons outlined in the Company submission (CS) B.1.3.2.4.	
Page 13, Issue 1 table. "We are not aware of any data (e.g. audits) that would clarify this issue…"	The Company proposes the following amendment to the text: "The only data we are aware of is the interim analysis that the company provided…"	The Company considers this to be inaccurate, as interim data from analysis of the clinical practice research datalink (CPRD) GOLD database have been provided, pending analysis of the larger dataset that combines CPRD Aurum data with GOLD.	Not a factual inaccuracy. The EAG report Table for Issue 1 does mention the company's citation of interim data from the GOLD and AURUM datasets. However, we have reworded the text on page 14 to emphasise that we are aware of these data.
Page 22. "In an expert elicitation study involving a Delphi panel the company estimated the proportion of patients in the UK diagnosed with obstructive HCM who receive disopyramide to be approximately [redacted]% in NYHA class II, [redacted]% in NYHA class III, and [redacted]% in NYHA class IV (Table 12 in CS Appendix O)."	The following text is proposed: "In an expert elicitation study involving a Delphi panel the company estimated the median proportion of patients in the UK diagnosed with obstructive HCM who receive disopyramide to be approximately [redacted]% in NYHA class II, [redacted]% in NYHA class III, and [redacted]% in NYHA class IV (Table 12 in CS Appendix O). This Delphi panel included two clinicians who specialise in structural interventions and who see patients with more	The estimates cited by the EAG are medians, drawn from the dataset including the two clinicians who specialise in structural interventions, i.e. SRT (n = 10).	Not a factual inaccuracy. The specified experts represent only two of ten experts consulted. Patients receiving SRT are within the scope of the appraisal, albeit not the majority, so the minority representation of interventionists on the Delphi panel appears appropriate. The results are described as approximate, indicating that they are subject to uncertainty. No

	severe disease, therefore may overestimate disopyramide usage."		change made.

Issue 3 Description of EXPLORER-HCM and EXPLORER-LTE data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15, Issue 4 table. "This analysis uses control arm data from the 30-week end of trial and 38-week end of study assessments of the EXPLORER-HCM randomised controlled trial, and 46-week data from the EXPLORER-LTE open label follow on study."	The following text is proposed: "This analysis uses control arm data from the 30-week end of trial and 38-week end of study assessments of the EXPLORER-HCM randomised controlled trial, and the baseline assessment from the EXPLORER-LTE open label follow on study (referred to as Week 46)."	This could be interpreted as Week 46 data from EXPLORER-LTE, which is not correct. "Week 46" refers to the start of EXPLORER-LTE, representing the average time elapsed between the start of the EXPLORER-HCM study (Week 0) and the baseline assessment of the EXPLORER-LTE study (CS B.3.3.2.2).	Thank you for highlighting the potential for misinterpretation. We have amended the text as suggested on page 16.

Issue 4 Aetiology and pathophysiology of obstructive HCM and the relationship to mavacamten's mechanism of action

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 19.	The following text is proposed:	No causal genetic link has been identified for all cases of HCM (as discussed on	Thank you for highlighting this inconsistency within the report. We have amended

“CS section B.1.3.1 gives an accurate overview of hypertrophic cardiomyopathy (HCM), an inherited cardiac disease…”	“CS section B.1.3.1 gives an accurate overview of hypertrophic cardiomyopathy (HCM), a cardiac disease that is often genetically inherited, where the muscles of the heart’s walls…”	p.20 of the EAG report) therefore it is not accurate to describe it as an ‘inherited cardiac disease’ without qualification.	the text as suggested on page 20.
Page 19. “HCM impairs the function of the heart, causing hypertrophy and sometimes hypercontractility of the heart muscle, ventricular hypertrophy and impaired ventricular relaxation.”	The following text is proposed: “HCM impairs the function of the heart through hypercontractility, driving ventricular hypertrophy and impaired ventricular relaxation.”	This does not accurately reflect the sequence of pathophysiological events in HCM. The biochemical hypercontractility is thought to drive the development of hypertrophy and impair relaxation in diastole. Ventricular contraction in HCM is typically described as ‘hyperdynamic’, characterised by supra-normal left ventricular ejection fraction (LVEF), as can be seen, for example, in EXPLORER-HCM, where mean baseline LVEF was 74% (SD 6%).[1] The American College of Cardiology (ACC) classify	Thank you for highlighting this inaccuracy. We have amended the text as suggested on page 20.

		LVEF > 70% as hyperdynamic.[2]	
Page 22. "Mavacamten, brand name CAMZYOS®, is an oral medicine in capsule form which targets the underlying sarcomere dysfunction of obstructive HCM. Patients with sarcomere mutations experience excessive cross-links between the actin and myosin filaments within the cardiac muscle sarcomeres, causing cardiac muscle hypercontractility."	The Company suggests removing "Patients with sarcomere mutations experience excessive cross-links between the actin and myosin filaments within the cardiac muscle sarcomeres, causing cardiac muscle hypercontractility."	This does not accurately represent the relationship between mavacamten's mechanism of action and the pathophysiology of obstructive HCM. While the Company agrees that mavacamten is targeting the underlying dysfunction in obstructive HCM, this paragraph could be interpreted as suggesting that mavacamten specifically targets sarcomere-positive HCM, which is not accurate.	Thank you for highlighting the potential for inappropriate interpretation here. We have deleted the sentence on page 24 as suggested to address this.
Page 22. "Mavacamten It is a first in class myosin inhibitor that specifically bonds to cardiac myosin. It stabilises and reduces the number of filaments in the walls of the heart muscle thereby reducing	The following text is proposed: "Mavacamten is a first in class myosin inhibitor that specifically binds to cardiac myosin. It stabilises myosin in the super-relaxed state, thereby reducing the number of cross-bridges (myosin heads bound to actin),	This is not an accurate description of the mechanism of action. Mavacamten reduces the number of cross-bridges that form between myosin and actin filaments, but does not alter filament number.[5]	Thank you for highlighting this descriptive error. We have amended the text on page 24 as suggested to address this.

hypercontractility and enabling diastolic relaxation.”	normalising the hypercontractility and enabling diastolic relaxation.”		

Issue 5 Prevalence estimates are not reflective of the indication

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 20. The EAG’s description of the prevalence accurately reflects some of the evidence regarding prevalence of HCM overall, however, this does not reflect the prevalence of the population in the decision problem.	The Company requests that the section on prevalence be modified to include the imaging-based estimate of overall HCM prevalence from Lopes et al of 0.11%, and that text is added to explain that the prevalence of patients relevant to the decision problem i.e. those with symptomatic, obstructive HCM, can be reasonably assumed to be considerably lower.	The population specified in the decision problem is for adults with symptomatic (NYHA class II-III) obstructive HCM. An account of the prevalence should endeavour to reflect the population under consideration. The EAG cited one UK Biobank study, which considered prevalence of pathogenic and likely pathogenic mutations. However, as highlighted by one of the EAG’s clinical experts, estimates based on the presence of mutations does not indicate clinical disease, therefore	Thank you for highlighting this mismatch between the stated prevalence of HCM and the prevalence of asymptomatic obstructive HCM relevant to the population in the NICE scope. We have amended the text on page 21 to address this. NB to keep the text concise when making this amendment we have removed the citation of reference 12 and deleted this reference from the bibliography (page 103).

		alternative approaches to estimating prevalence should be given weight. An alternative UK Biobank study (Lopes *et al*., 2021) looked at cardiac imaging evidence for unexplained maximal left ventricular wall thickness ≥ 15 mm (the clinical definition of HCM), estimated the prevalence of HCM in England as 0.11%.[6] This was a similar approach to that taken by Maron *et al*. (1995),[7] from which the original 1/500 estimate derives, but in a larger, more contemporary, UK-based population. The figure from Lopes *et al*. is also likely to represent an overestimate of clinically-apparent HCM, due to the variability in HCM presentation; one population based cohort study of 3,290,455 eligible people in the CALIBER cohort in England found a diagnosis	

		of HCM in 4 in 10,000 people.[8] Furthermore, approximately two thirds of diagnosed patients are expected to have obstructive (as opposed to non-obstructive) HCM, and of those, a proportion are expected to be asymptomatic.[9] Therefore, the prevalence of the population relevant to the indication is expected to be considerably lower than the figures cited by the EAG.	

Issue 6 Mortality associated with SRT

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 22 section 2.2.1. "Whilst SRT can improve symptoms in some patients, the EAG are not aware of any evidence that SRT influences mortality."	The Company proposes the sentence be amended to read "Whilst SRT can improve symptoms in some patients, the EAG are not aware of any evidence that SRT influences disease progression, including disease-associated mortality, and there is	There is evidence that SRT is associated with peri-operative risks, which include peri-operative mortality; this should be reflected.	Thank you for highlighting that our statement about mortality was incomplete. We have added text on page 23 as suggested to distinguish disease-related

	evidence of a range of peri- and post-procedural complications associated with each approach, including surgical mortality, AV block, ventricular septal defect and aortic regurgitation".[9-12]		and procedure-related mortality.

Issue 7 The positioning of mavacamten

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 23, section 2.2.3. "However, CS section B.1.3.3.2 suggests that *"mavacamten used in combination with standard care provides functional and symptomatic improvement to patients whose symptoms are inadequately controlled by BB or CCB"* thus placing it ambiguously either alongside or after beta blockers and/or calcium channel blockers."	The following text is proposed: "However, CS section B.1.3.3.2 suggests that *"mavacamten used in combination with standard care provides functional and symptomatic improvement to patients whose symptoms are inadequately controlled by BB or CCB"* i.e. mavacamten is positioned as an adjunctive therapy for patients who do not achieve sufficient symptomatic control with BB or CCB monotherapy".	The Company does not believe the positioning of mavacamten to be ambiguous. The intended positioning for mavacamten is, as stated, for patients whose symptoms are inadequately controlled by beta blockers (BB) or calcium channel blockers (CCB). Clinical advice received by the Company has suggested that clinicians are unlikely to discontinue BB or CCB, even if they are not producing adequate symptom control, except in	Not a factual inaccuracy, as the wording of CS section B.1.3.3.2 does not explicitly exclude the potential use of mavacamten after BB or CCB therapy. We have amended the text on page 25 to clarify the intended positioning of mavacamten as confirmed in this Factual Accuracy Check.

		cases where the patient is contraindicated for or intolerant to both classes. Therefore, mavacamten is most likely to be used as an adjunctive therapy, in combination with either BB or CCB.	
Page 24, section 2.2.3. However, mavacamten cannot be used alongside all therapies: the revised draft SmPC recommends [redacted].	The following text is proposed: "Mavacamten can be used in combination with disopyramide, or beta blockers in combination with calcium channel blockers, however the revised draft SmPC recommends [redacted]. Therefore, the proposed position for mavacamten does not include combination therapy with disopyramide, or concomitantly with beta blockers and calcium channel blockers."	Mavacamten can, in principle, be used in combination with disopyramide, or with BB and CCB. In VALOR-HCM, 25% patients in the mavacamten arm were taking disopyramide background therapy, while 10.7% were taking both BB and CCB.[13] Although as a US study, VALOR-HCM may not be representative of UK prescribing practices (disopyramide usage is anticipated to be higher in the US, while clinical advice received by the Company is that concomitant therapy with BB and CCB is not clinical practice in the UK), it	Thank you for clarifying this discrepancy. However, this use of mavacamten is not referred to in CS section B.1.3.3.2. We have amended the text on page 25 to address this issue.

		provides evidence that mavacamten can be used in these combinations. However, as stated in the draft SmPC, close monitoring is required and consequently, the Company is not currently seeking to position mavacamten in combination with disopyramide or with BB+CCB in England and Wales.	

Issue 8 Description of beta blocker subgroup analysis as 'post hoc'

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pages 25, 29, 32, 49, 58, 59. Description of the subgroup analysis by beta blocker usage as 'post-hoc'.	The following text is proposed: "the EXPLORER-HCM trial had predefined subgroups according to randomisation stratification factors, patient demographics and other baseline characteristics, which are reported in CS section 2.7 (see section 3.5.4 below)."	Beta blocker usage at baseline was a post hoc analysis in MAVA-LTE, but was a prespecified subgroup analysis in EXPLORER-HCM.[1415]	Not a factual inaccuracy. However, to avoid misinterpretation we have amended the text on pages 26-27, 31, 34 and 60 to clarify that the pre-specified subgroup analysis refers to the primary outcome and that post-hoc subgroup analyses by beta-blocker

			use were conducted for other outcomes.

Issue 9 NYHA 'subjectivity'

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 28, 43, 45, 68, 75. NYHA class described as 'subjective'.	Add a clarification that 'the NYHA classification is a subjective assessment made by clinicians that routinely perform symptomatic assessment of the patient'.	Although the Company recognises that the clinical experts consulted by the EAG described NYHA class as 'subjective', we would like to clarify that it is the subjective assessment of expert clinicians, who are experienced in its use and application.	Not a factual inaccuracy. We consider that the suggested amendment would not influence interpretation. No changes made (pages 30, 45, 47, 71).

Issue 10 Evidence for tachyphylaxis

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 27, Table 4. "It is unclear where the evidence for tachyphylaxis comes from – no	The statement should be removed.	The CS (B.1.3.2.3.3) gives the following references in support of this statement: • Ammirati *et al*., Eur J Heart Fail (2016), 18,	Thank you for clarifying the sources of evidence for tachyphylaxis. We have amended the text as suggested on page 28 to

references cited by the company provide any.”		1106-1118. In the section titled ‘Treatment of dynamic left ventricular outflow tract obstruction’, the manuscript reads: ‘Moreover, disopyramide tends to lose its efficacy over time’.[16] • Spoladore *et al*., Eur. Heart J., (2012), 33, 1724-1733. In the section titled ‘Pharmacological control of left ventricular outflow tract obstruction’, the manuscript reads: ‘Disopyramide has been proven safe and effective, but can be problematic in the long-term due to its anticholinergic side-effects and, in a significant percentage of patients, to a loss of clinical benefits decrease over time.’[17]	address this.

		• Maron, N Engl J Med (2018), 379, 655-668.[18] This was erroneously cited, and should have been Maron *et al*., J Am Coll Cardiol: Heart Fail (2018), 6, 353-363.[19] In the section titled 'HF treatment in HCM', the manuscript reads: '…although parasympathetic side effects and limited long-term efficacy can decrease its [disopyramide's] use'.	

Issue 11 Incomplete description of VALOR-HCM study design

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 35. "The randomised comparison (weeks 0 to 32) was followed by a long-term extension (LTE) study during weeks 32 to	The following text is proposed: "The randomised, placebo-controlled comparison (weeks 0 to 16) was followed by an active-controlled period (weeks 16 to 32) in which patients in the placebo arm crossed over to mavacamten, while patients in	Day 1 to Week 16 placebo-controlled dosing period i.e. patients randomised to mavacamten or placebo Week 16 to Week 32 active-controlled dosing period i.e. placebo arm patients	Thank you for highlighting this discrepancy. We have amended the text on page 37 as suggested to address this.

128 in which all patients received mavacamten.”	the mavacamten arm continued on their mavacamten dose. This was followed by a long-term extension (LTE) study during weeks 32 to 128 in which all patients received mavacamten.”	crossed over to mavacamten (blinded dose) while patients in mavacamten arm continue on mavacamten dose Week 32 to Week 128 LTE dosing period. All patients continue on blinded dose of mavacamten.[20]	

Issue 12 Clarification of missing data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 42 and Appendix 9.3.3. “Extensive missing data for several of the outcomes. Notably, at week 84 there were 69-70% of the data missing, without imputation, for changes in resting LVOT gradient, Valsalva LVOT gradient and LVEF.”	The following text is proposed: “Extensive missing data for several of the outcomes, due to this being an interim analysis of an ongoing study. Notably, at week 84 there were 69-70% of the data missing, without imputation, for changes in resting LVOT gradient, Valsalva LVOT gradient and LVEF”	While the Company does not disagree with the interpretation of this in terms of risk of bias, it should be noted that these data were missing because the majority of patients at this interim analysis had not yet reached Week 84.	Not a factual inaccuracy; the CS does not state reasons for the data being missing. However, for completeness we have noted on page 44 the reason for the data being missing.

Issue 13 Incorrect attribution of KCCQ

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 46, section 3.2.3.2. "The Kansas City Cardiomyopathy Questionnaire (KCCQ-23) is a 23-item patient-reported outcome measure that was developed by the company[57]"	Please remove the text "that was developed by the company".	To clarify, KCCQ-23 was not developed by the Company, it was originally developed and validated for use in patients with heart failure (HF) by Professor John Spertus and team.[21] Professor Spertus owns the copyright of the KCCQ instrument and his affiliation is Saint Luke's Mid America Heart Institute.[22] MyoKardia, Inc, a wholly owned subsidiary of BMS, funded the validation of KCCQ in symptomatic obstructive HCM, which was performed in collaboration with Professor Spertus and team.[23]	Thank you for highlighting this error. We have amended the text on page 48 as suggested to address this.

Issue 14 Transcription inaccuracies in ICERs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 88, Table 20. Incremental cost effectiveness ratio (ICER) in the 4th row of Treatment after mavacamten discontinuation reads £29,320. This is incorrect when checked against the EAG model and should read £29,235.	Please change the ICER in the table from £29,320 to £29,235.	Inaccurate ICERs.	Thank you for noting this error. We have made the correction as requested (Table 20 page 91).
Page 89, Table 20. ICER in the 4th row of Treatment after mavacamten discontinuation and escalation from BB/CCB reads £29,523. This is incorrect when checked against the EAG model and should read £29,438.	Please change the ICER in the table from £29,523 to £29,438.		Thank you for noting this error. We have made the correction as requested (Table 20 page 92).
Page 93.	Please change the ICER from £39,690 to £38,690, and the		Thank you for noting this error. We have made the

The probabilistic ICER given of £39,690 is incorrect, this should read £38,690. This means that the next figure of "£1,638 lower than the deterministic ICER" is also incorrect and should read £2,638". This error is repeated in Table 23 on page 93 and in the conclusions on page 96.	difference between the probabilistic and deterministic ICERs to £2,638. Please also change the ICER in Table 23 and the conclusions section on page 96, from £39,690 to £38,690.		correction as requested (Table 23 page 97). We have also corrected the related values in the preceding paragraph (page 96) and in the conclusions in section 6.4 (page 99).
Page 122. ICER for the scenario concerning treatment after mavacamten discontinuation, which currently reads as £39,689, is incorrect and should read £39,470.	Please change the ICER from £39,689 to £39,470.		Thank you for noting this error. We have made the correction as requested (Appendix section 9.5 page 126).
Page 122. ICER for the scenario concerning treatment after mavacamten discontinuation and	Please change the ICER from £39,931 to £39,710.		Thank you for noting this error. We have made the correction as requested (Appendix section 9.5 page 126).

escalation from BB/CCB, which currently reads as £39,931, is incorrect and should read £39,710.			

Issue 15 Description of discontinuation scenario

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 90 bullet "EAG scenarios 2-3" and page 91, Table 21. The description of scenario 3 (mavacamten discontinuation) is misleading, "80% in NYHA class II and III with no improvement at week 30 discontinue" is not actually 80%, rather it is a reduction of the base-case figures of 20%.	Please relabel this scenario as "a 20% reduction in the base-case discontinuation due to no improvement at week 30 ([redacted]% in class II and 80% in class III)"	To add clarity to aid understanding of the scenario.	Not a factual inaccuracy. However, we agree that clarity could be improved. We have reworded the description of EAG scenarios 2 and 3 in Table 21 (page 94) to address this.

Issue 16 Description of mortality scenario

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 91, Table 21, scenario 5. "Pooled HR for baseline NYHA distribution (1.85), no change within model".	"HR of 1.85 used across all NYHA classes, generated from the baseline NYHA distribution and the EMR data".	Stating “no change within the model” could be interpreted as this being the Company’s base case, which is not accurate.	Thank you for highlighting this potential for incorrect interpretation. We have reworded the description of EAG scenario 5 in Table 21 (page 95) to address this.

Issue 17 Description of utilities scenario

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 92, Table 21, scenario 9. “EXPLORER-HCM utilities adjusted to not exceed UK population norms for age and sex”	Add clarification that utilities for NYHA classes II-IV are adjusted proportionately.	The Company’s understanding is that this scenario also includes the relative adjustment by NYHA class.	Thank you for highlighting this discrepancy. We have reworded the description of EAG scenario 9 to improve clarity in Table 21 (page 95).

Issue 18 Typographical errors that may affect interpretation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pages 16, 68, 74, 75, 79, 80, 90. Comments from “EAG experts."	Please clarify whether these were the external clinical experts consulted or experts within the EAG.	To clarify the source of the advice.	The experts referred to were independent of the EAG. We have amended the text on pages 17, 71, 72, 73, 76, 77, 78, 79, 80, 82, 83, 93 and 118 to clarify this.
Page 21, section 2.2.1.1. Echocardiogram is abbreviated to ECG, however, in the table of abbreviations (p. 10), ECG is given as ‘electrocardiogram’.	Echocardiogram should be shortened to ‘echo’ or ‘ECHO’, reflecting common clinical usage. If electrocardiogram is being referred to, ECG should be used.	Echocardiogram is not typically abbreviated to ECG, which more typically is taken to mean ‘electrocardiogram’ in the literature and in clinical practice. The Company suggest that for echocardiogram, the more commonly used abbreviation ‘echo’ should be used, to avoid confusion with electrocardiogram.	Thank you for highlighting this anomaly. We have updated the table of abbreviations (page 10) and restricted the “echo” abbreviation to where it is quoted directly from a consultee submission (page 15). Elsewhere we have spelt echocardiogram/graph in full (changes made on pages 15, 22, 85).
Page 38, Table 7. Table row ‘participants’ states that “2/10 were interventionalists.”	The following text is proposed: “2/10 were interventionalists, specialising in SRT”	Clinical experts to the Company indicate that ‘interventional cardiology’ is broader than the specific	Thank you for suggesting this clarification. We have amended the text on page 41 as suggested.

		specialism in SRT that is relevant here, therefore for clarity would request that this specialism is specified.	
Page 67, Section 4.2.2.1. Figure 1 is not complete as the footnote "[a]" has been omitted.	Add to footnote "[a] Death state is accessible from all non-death health states".	The addition to the footnote of Figure 1 should be added to reflect the figure as in the CS, to provide clarity to the reader on the structure of the Markov model.	Thank you for highlighting this omission. We have added the missing footnote on page 70.
Page 74, last bullet. "For EAG analysis, we use the company's base case assumption of an equal rate of NYHA class progression after week 30 (4.55% per year)"	The following text is proposed: "For EAG analysis, we use the company's base case assumption of an equal rate of NYHA class progression after week 30, implementing the rate of progression used in the company's scenario analysis (4.55% per year)"	The Company base case assumes equal rate of NYHA class progression after Week 30, but in the base case this rate of progression is 0%, not 4.55%, which was submitted as a scenario.	Thank you for highlighting this dscrepancy, we agree that this is misleading. We have replaced "the company's base case assumption" with "the company's progression scenario" on page 77.
Page 76, Section 4.2.5 "clarification question B6"	Correct to B5.	Typographical error; incorrect clarification question is referenced.	Thank you for highlighting this error which we have corrected on page 79.
Page 87, Table 19.	Remove the last item from the table; Health state utility in NYHA II.	Typographical error; the table is labelled as top 10 impacts on ICER. It is also described as such in the	Thank you for highlighting this discrepancy. We have deliberately included the 11th parameter in this table,

		paragraph above. However, there are 11 items in the table.	because the range of variation is similar to that in the previous row. We have deleted 'top 10' from the heading of Table 19 and the text above on page 90.

ACIC check

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
EAG report, page 27, Table 4, row 3, column 4.	Results from the Delphi panel should be marked AIC.	NYHA class II: range [redacted]% to [redacted]%, median [redacted]%; NYHA class III: range [redacted]% to [redacted]%, median [redacted]%	We have highlighted the Delphi panel results as AIC on page 29.
EAG report, page 61, section 3.2.6.2.	[redacted] participants experienced LVEF ≤30% based on echocardiographic measurements during scheduled site visits. This was presented at ACC2022 and is therefore not AIC.	No participants experienced LVEF ≤30% based on echocardiographic measurements during scheduled site visits.	We have removed this AIC highlight on page 64.
EAG report, page 79, section 4.2.9.1.	Company pricing strategy is CIC.	[redacted]	We have highlighted this statement as CIC on page 83.

References

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (Section 1.1).

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **23 February 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	Teresa Lemmer
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Bristol-Myers Squibb
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Exclusion of disopyramide as a comparator	Yes	The Evidence Assessment Group (EAG) have requested further clarification on the extent to which disopyramide is used to treat obstructive hypertrophic cardiomyopathy (HCM) in the NHS, to clarify the exclusion of disopyramide as a comparator with particular interest in the Clinical Practice Research Datalink (CPRD) updated information on disopyramide use. The Company is submitting updated evidence from this CPRD analysis showing that, on average, the use of disopyramide in clinical practice has been minimal over the last decade and therefore exclusion of disopyramide is appropriate. Furthermore, this is aligned with the clear trend in other countries across the globe where disopyramide use is low, where the low usage is further limited by global supply problems, or where reimbursement has been delisted.[1-4] Finally, although the company acknowledges that there is likely to be some heterogeneity in the use of disopyramide in clinical practice, as reflected in the uncertainty highlighted by the EAG, the overall expert consensus aligns with the CPRD data. Each of these points is discussed in detail in the following paragraphs. As described in the Company Submission (CS) B.1.3.2.3.3 and in the Company response to EAG clarification question A5 (July 2022), a retrospective cohort study of patients diagnosed with HCM in England has been undertaken using data from the CPRD (GOLD and Aurum datasets) and linked hospital episode statistics (HES) data. Due to COVID-19–related delays in accessing the data from CPRD the full analyses were not complete at the time of

		the original CS. Therefore, limited interim data on disopyramide based on CPRD GOLD only could be included in the CS. Analysis of disopyramide prescription patterns in the combined, de-duplicated GOLD and Aurum cohorts of patients with a record of obstructive HCM has now been completed. Between 2010 and 2020, [redacted] patients had a record of obstructive HCM. Per calendar year, the proportion of patients with obstructive HCM prescribed disopyramide averaged [redacted]% between 2010 and 2020 (range [redacted] to [redacted]%) (Table 1). [redacted]Table 1. Proportion of patients with a record of obstructive HCM or HCM in CPRD GOLD/Aurum with at least one disopyramide prescription per calendar year. Details of this CPRD study are presented more fully in Appendix 1. A short communication that includes these data is currently in preparation, in which disopyramide use in both England is presented alongside data from France (French National Heath Data Information System 2012-2019) and Germany (WIG2 Benchmark database 2011-2019). Among [redacted] patients with obstructive HCM identified in France, use ranged from [redacted], while in Germany, no disopyramide use was identified from 2011 to 2019.[4] The Company has not been able to identify new data regarding tolerability of disopyramide, beyond the consensus in the literature and from clinical experts consulted that the parasympathetic side-effects result in poor tolerability (CS B.1.3.2.3.3), but would like to highlight the insight from the expert elicitation panel discussion that disopyramide is only tolerated by [redacted]% patients in New York Heart Association (NYHA) class II, and is also only used in NYHA class III if tolerated (CS Appendix O). It is worth noting that the supply issues affecting disopyramide are a global concern. In Australia, disopyramide was discontinued in December 2022 due to the manufacturing issues,[3] while an assessment of managed care considerations for mavacamten in the US concluded that it was not necessarily clinically reasonable to require the use of disopyramide when developing coverage criteria, due both to the lack of high-quality randomised controlled trials (RCTs) for the use of disopyramide in patients with obstructive HCM and to the substantial long-term supply chain issue.[5] This is substantiated by two US claims database analyses. In one, 85% of 4,883 patients with symptomatic obstructive HCM received pharmacotherapies, of which disopyramide represented 2.4%,[2] while in the other,

		disopyramide was used by 2.1% patients with obstructive HCM in 0–6 months after index date and remained low, at 3.3% patients in 30–36 months after the index date.[1] Although the Company acknowledges that there is likely to be some heterogeneity in the use of disopyramide in clinical practice in England and Wales, as reflected in the uncertainty highlighted by the EAG, the overall expert consensus aligns with the CPRD data, as summarised below: • Two of the three independent clinical experts advising the EAG agreed that it is reasonable to exclude disopyramide as a comparator due to its limited use in practice. • While the third expert stated that disopyramide is used in standard care, particularly in larger centres, they also agreed that many patients do not tolerate disopyramide, and that access to disopyramide is currently difficult and has worsened (EAG report Table 4). • Similarly, while the Consultee Submission from the British Cardiovascular Society (BCS) states that *"most patients in the UK would be offered disopyramide if still symptomatic despite either a beta blocker or calcium channel antagonist"*, the NHS England Consultee Submission states that disopyramide is difficult to access due to supply issues and that it tends to be poorly tolerated. • Clinical experts consulted by the Company agreed that disopyramide is associated with many side-effects, has safety and tolerability issues, has variable efficacy including displaying tachyphylaxis, and that access is a major concern due to supply issues (CS B.1.3.2.3.3).[6,7] This aligns with published evidence regarding parasympathetic side-effects, the potential for QTc prolongation and the loss of efficacy over time.[8-11] Furthermore, the Company agrees with the EAG that there is lack of randomised evidence on disopyramide effectiveness (EAG report page 79) which, in contrast to mavacamten, has not been studied in any high-quality RCTs. The study cited in this statement, Sherrid *et al*., 2005,[12] was a retrospective study and subject to risk of bias, including from treatment selection bias.[13] Therefore, the Company would like to highlight issues with the submission

		from the BCS, which states that " …*while ~3/4 patients [in VALOR-HCM] did not need to proceed to surgery, in earlier studies of disopyramide, ~2/3 patients did not need to proceed to surgery, in other words, the effect of mavacamten mirrors outcomes with an existing drug that has been used for decades*." It should not be considered appropriate to draw any conclusions on relative treatment efficacy between mavacamten and disopyramide based on a naïve comparison between the observational study by Sherrid *et al*. and the RCT VALOR-HCM. The EAG report notes that *"The company did not search systematically for studies of disopyramide, but the EAG and our clinical experts are not aware of any further RCTs that would be included if disopyramide is considered as a relevant comparator (cohort studies on disopyramide exist[12,14] but it is unclear whether it would be appropriate or feasible to include these in an indirect comparison against mavacamten)."* A systematic literature review (SLR) that included disopyramide as a comparator has now been undertaken (Appendix 2). This has been used to inform a feasibility analysis of conducting an indirect treatment comparison (ITC) between mavacamten and disopyramide (Appendix 3). Applying a set of PICO (Population, Interventions, Comparators, Outcomes) criteria developed for the feasibility analysis to the records identified in the SLR identified: • 6 records reporting on 4 studies in adults with obstructive HCM, which included mavacamten as an intervention/comparator and NYHA class as an outcome; one additional record identified after the search date was also added • 10 records reporting on 10 studies in adults with obstructive HCM that included disopyramide as an intervention/comparator or background therapy used entirely within a reported group or sub-group Of these 10 studies, only one (Sherrid *et al*., 2013),[14] reported change in NYHA class at a specified timepoint. The patient group reported in this study was, by definition, a responder population (i.e., includes only patients who have adequately responded to disopyramide therapy) as non-responders became eligible for septal reduction therapy (SRT) and were removed from the disopyramide group. Therefore, the estimates of effectiveness cannot be generalised to a patient population receiving disopyramide in the real world which also includes non-responders. Hence, the appropriateness of this study to inform an indirect

		treatment comparison is questionable. As discussed in detail in Appendix 3, the VALOR-HCM trial included disopyramide as a background therapy, therefore the feasibility of a direct comparison using VALOR-HCM data was also explored; however, was considered unfeasible due to small patient numbers (14 and 8 patients in the mavacamten and placebo arms, respectively), the absence of randomisation on background therapy, the short time period of assessment (16 weeks) and the issue of generalisability of the SRT-eligible population of VALOR-HCM to the broader population encompassed within the decision problem. Therefore, neither a direct nor an indirect treatment comparison between mavacamten and disopyramide is considered feasible based on available evidence. In conclusion, the overall weight of data and clinical opinion suggests that disopyramide represents a second-line therapy that is not widely used in this patient population and does not represent part of the 'standard care' comparator for mavacamten.
2. Uncertain efficacy of mavacamten in patients without a sarcomere mutation	Yes	Mavacamten is expected to benefit patients with obstructive HCM regardless of sarcomere mutation status. From a mechanistic perspective, HCM patients with and without sarcomere mutations exhibit hyperdynamic contraction, which is targeted by mavacamten's mechanism of action. Furthermore, data from two RCTs (EXPLORER-HCM and VALOR-HCM) has demonstrated a strong benefit of mavacamten on left ventricular outflow tract obstruction (LVOTO), the key pathophysiological feature of obstructive HCM, providing evidence that the mechanism of action of mavacamten is relevant to all patients with obstructive disease. This is further supported by additional EXPLORER-HCM data showing [redacted], and EXPLORER-LTE cohort data showing [redacted]. Nevertheless, as requested by the EAG, the Company explored the feasibility of a cost-effectiveness analysis by mutation subgroup, however, this scenario was found to be infeasible. Additionally, requiring genetic testing for sarcomere mutations would represent a barrier to access and potentially raise equality issues. Each of these points is discussed in detail in the following paragraphs. <u>HCM pathophysiology and mavacamten mechanism of action</u> In patients with HCM, biochemical hypercontractility is thought to drive the development of hypertrophy and impair relaxation in diastole. Studies of myocardial samples from HCM patients with and without sarcomere mutations have demonstrated that HCM patients have

		'systolic hyperactivity and diastolic dysfunction' regardless of aetiology.[15] Clinically, this is observed as 'hyperdynamic' ventricular contraction, characterised by supra-normal left ventricular ejection fraction (LVEF > 70%).[16] In EXPLORER-HCM, mean baseline LVEF was 74% (SD 6%).[17] Therefore, patients at baseline exhibited hyperdynamic contraction, despite the majority of those tested not having a pathogenic or likely pathogenic gene variant identified, providing further indication that hypercontractility is not unique to patients with sarcomere mutations. Mavacamten's mechanism of action normalises hypercontractility and enables diastolic relaxation,[18-20] thus directly addressing the underlying pathophysiology outlined above, regardless of mutation status. Clinical data: EXPLORER-HCM As previously described (CS B.2.6.1.2), the EXPLORER-HCM trial demonstrated strong benefit of mavacamten on LVOTO, with a greater mean reduction of post-exercise LVOT gradient from baseline to week 30 compared to placebo (35.6 mmHg; 95% CI −43·2 to −28·1; p <0·0001). At baseline, patients in both arms had a mean post-exercise LVOT gradient above the guideline-based threshold for invasive SRT (> 50 mmHg), whereas at week 30, only patients in the mavacamten arm had a mean gradient below this threshold.[17] Furthermore, at week 30, the mean resting LVOT gradient in patients receiving mavacamten was 14.1 mmHg, which is below the diagnostic threshold for LVOT obstruction (30 mmHg), while patients receiving placebo had a mean resting LVOT gradient at week 30 of 45.9 mmHg.[17] LVOTO is an established prognostic factor in obstructive HCM, and the presence of outflow tract obstruction has been found to be more characteristic of sarcomere-negative disease than sarcomere-positive disease.[21] If, as described in the literature,[21] LVOTO is more characteristic of sarcomere-negative patients, then the strong benefit of mavacamten on LVOTO should be expected to translate to a benefit in sarcomere-negative obstructive HCM. Clinical data: subgroup analyses in EXPLORER-HCM, EXPLORER-LTE cohort and VALOR-HCM

		The clinical benefit of mavacamten can also be explored in subgroup analyses. As described in the response to additional issue 5 (Table 3, this document), EXPLORER-HCM was neither designed nor statistically powered to detect significant differences in subgroups. Interpretation of subgroup results should therefore be made with caution, particularly on a composite primary endpoint as this further limits interpretation. Nevertheless, subgroup analysis was performed on those patients who had been tested for HCM gene variants (190/251), and suggests that mavacamten had a [redacted] (Figure 1).[22] [redacted]Figure 1. Differences in change from baseline to week 30 between treatment groups across HCM mutation subgroups for a) resting LVOT gradient b) Valsalva LVOT and c) post-exercise LVOT peak gradient. Vertical dotted line represents the overall estimate. HCM genotype and the number of patients with pathogenic/likely pathogenic variants and VUSs were based on current genotype testing using the 60-gene Invitae panel and clinically-based testing was collected from medical records where available. Data source: EXPLORER-HCM CSR[22]. CSR: clinical study report; HCM: hypertrophic cardiomyopathy; LVOT: left ventricular outflow tract; VUS: variant of unknown significance In the description of issue 2, the EAG cite the consultee submission from the BCS that: *"It may be that only those with truly sarcomeric HCM respond to mavacamten and those with non-sarcomeric disease may not (where speculatively the mechanism of LVOTO may be less driven by hypercontractility and more related to anatomical factors)."* However the evidence presented here from EXPLORER-HCM does not support this speculation, instead showing a [redacted] regardless of the presence of [redacted]. Subgroup analysis by mutation status on the other secondary endpoints also suggested a [redacted] (Figure 2).[22] [redacted]Figure 2. Differences in change from baseline to week 30 between treatment groups across HCM mutation subgroups for percentage of patients with improvement in NYHA class. Vertical dotted line represents the overall estimate. Data source: EXPLORER-HCM CSR[22]. CSR: clinical study report; HCM: hypertrophic cardiomyopathy; NYHA: New York Heart Association; VUS: variant of unknown significance Subgroup results for the difference between treatment groups in change from baseline to week 30 in pVO_2 (Figure 3) and Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS; Figure 4) [redacted]. For pVO_2, the

		pathogenic/likely pathogenic and mutation negative subgroups had [redacted], while for KCCQ-CSS [redacted] was in the pathogenic/likely pathogenic and variant of unknown significance (VUS) subgroups.[22] [redacted]Figure 3. Differences in change from baseline to week 30 between treatment groups across HCM mutation subgroups for change in pVO_2. Vertical dotted line represents the overall estimate. Data source: EXPLORER-HCM CSR[22]. CSR: clinical study report; HCM: hypertrophic cardiomyopathy; pVO_2: peak oxygen consumption; VUS: variant of unknown significance [redacted]Figure 4. Differences in change from baseline to week 30 between treatment groups across HCM mutation subgroups for change in KCCQ-CSS. Vertical dotted line represents the overall estimate. Data source: EXPLORER-HCM CSR[22]. CSR: clinical study report; HCM: hypertrophic cardiomyopathy; KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; VUS: variant of unknown significance Overall, it is worth noting that the subgroup analyses [redacted], but instead suggest that patients have the [redacted]. Subgroup analyses have also been explored using data from the ongoing EXPLORER-LTE cohort of MAVA-LTE. Interpretation of these analyses should be performed with caution due to small numbers in each group, particularly at the week 108 timepoint (as EXPLORER-LTE is ongoing, a proportion of patients had not reached the week 108 visit at the time of the [redacted] database lock [DBL]; NB. further information on this new DBL can be found in the response to issue 4); furthermore, these are ad hoc analyses, not pre-specified. Nevertheless, subgroup analysis by sarcomere mutation status suggests [redacted] (Figure 5) and [redacted] (Figure 6). [redacted]Figure 5. NYHA class over time in the EXPLORER-LTE cohort of MAVA-LTE in patients with a) pathogenic or likely pathogenic HCM mutations; b) variants of unknown significance; c) negative for HCM pathogenic mutations. [redacted] DBL. NYHA: New York Heart Association. [redacted]Figure 6. Resting LVOT gradient over time by HCM genotype. Bars indicate standard deviation. [redacted] DBL. LVOT: left ventricular outflow tract; VUS: variant of unknown significance In the VALOR-HCM trial, 45.5% patients did not have a pathogenic mutation identified, but [redacted]

		[redacted][23]. Cost-effectiveness and access considerations In summary, the available evidence supports the benefit of mavacamten for patients with symptomatic obstructive HCM, irrespective of sarcomere mutation status. Nevertheless, as requested by the EAG, the Company explored the possibility of conducting a cost-effectiveness analysis to explore the relationship between HCM genetic test results and cost effectiveness. The EAG suggested that *"…we believe that an exploratory analysis is possible and have made suggestions for how transition probability matrices might be obtained by pooling data over the whole trial period"*. However, as described in the response to additional issue 2 (Table 3, this document), the EAG's suggested method for calculating the transition probabilities for this scenario (EAG report section 4.2.3.1) did not provide a good fit to the clinical data and produced clinically implausible results, therefore this method was considered generally unsuitable to inform the modelling. The errors underlying the poor fit to the clinical data are more likely to occur when the transition probabilities are small, and are therefore likely to have a greater impact on subgroup analyses due to the smaller number in each group, leading to the introduction of additional uncertainty and unsuitability for informing decision-making. Therefore, the suggested scenario could not be explored further. Furthermore, requiring genetic testing for sarcomere mutations would represent a barrier to access and potentially raise equality issues. A ten-patient virtual roundtable conducted by the Company in December 2002 emphasises the unmet need impacting patients with obstructive HCM.[24] Patients discussed the impact that HCM has on their lives in terms of mental and physical health, as well as the challenges associated with the current standard of care to treat the condition. During the roundtable, patients emphasised the detrimental impact on their quality of life as a result of living with HCM. From a physical perspective, patients describe how they are no longer able to live their lives as they previously had, despite some having been extremely active. Multiple patients described how HCM impacts their mobility, leading to patients struggling to exercise owing to the fatigue caused by HCM and its treatments. Patients have also detailed the effect of being diagnosed with HCM on their mental wellbeing. Anxiety, depression and guilt were commonplace for those living with

		HCM as a result of the symptoms associated with the disease, with specific fear of imminent death and guilt of passing this disease on to offspring. Finally, patients outline how the impact of the existing interventions had a significant detrimental impact their lives as a result of the side effects of medication and the invasive nature of the surgery. One patient described their experience as "existing, not living". Patients highlighted the negative impact of current standard of care; one patient stated that "for 2 years I was a zombie" with a sense of constant fatigue because of the medication, and the impact of side effects was described by one patient as "the drugs make me feel like there is an alien in my body". Equitable access to effective treatments is vital in this disease area where there are limited options. Although the EAG's experts suggest genetic testing is a routine part of diagnosis in the NHS for patients diagnosed aged < 50 years or with indications of familial disease, UK clinical experts consulted by the Company in a series of 1-to-1 interviews have indicated that, in practice, genetic testing may not be routinely offered (Appendix 4). Furthermore, in addition to [redacted], some clinical experts felt that patients in [redacted] were less likely to be offered or accept genetic testing, particularly [redacted] (Appendix 4). Therefore, it seems likely that any requirements around genetic testing would lead to access difficulties for some patients with protected characteristics, which should be considered in light of the evidence supporting the benefit of mavacamten irrespective of sarcomere mutation status.
3. Post-authorisation safety monitoring of mavacamten	Yes	The EAG base case assumed echo monitoring every [redacted] during maintenance for patients receiving mavacamten, for the duration of their time on treatment. An error in the implementation of this was identified; the Company base case assumption of [redacted] monitoring visits in the first year was implemented in every subsequent year on mavacamten, however, visits every [redacted] is equivalent to [redacted] visits per year. Implementing [redacted] visits in year 1, as in the Company's original base case, then [redacted] visits annually while on treatment thereafter (equivalent to every 12 weeks), changes the EAG's base case with-PAS (patient access scheme) incremental cost effectiveness ratio (ICER) from £41,328 to £40,150. The EAG requested further clinical expert opinion to clarify whether the required intensity of monitoring to ensure safe use of mavacamten can be achieved in the NHS. There are two

		areas of uncertainty encompassed in this issue: what intensity of monitoring is required, and how this is achievable in the real world. The Company has consulted with five UK clinical experts to provide additional insight into both these areas, which is detailed below and in Appendix 4. The Company considers the EAGs assumption of a [redacted] monitoring holding on for indefinite time to be unrealistic, due to the burden on both clinicians and patients. A more realistic assumption is that the frequency will become lower over time, possibly even following a declining curve as clinicians gain experience in the use of mavacamten, resulting in patients who are clinically stable on a maintenance dose moving to a reduced frequency of visits, in line with current standard care. To gain further insights from clinicians experienced in the care of patients with obstructive HCM, a survey was used in a series of 1-to-1 interviews conducted by the Company (Appendix 4), to generate specific estimates. Of the five clinicians who responded, two clinicians considered that additional monitoring would be required for [redacted], one said for [redacted], with monitoring expected to return to the current standard care thereafter, one stated additional monitoring for [redacted], and one estimated that monitoring would return to the level of standard care [redacted] The weight of responses in the survey was that clinicians expect to feel confident to reduce monitoring frequency after the [redacted]. To account for some residual uncertainty, the Company has adopted a more conservative approach in the updated base case. The new base case assumes [redacted] monitoring visits in [redacted], in alignment with the draft SmPC, then [redacted] over [redacted], which is modelled as monitoring visits every [redacted], with standard care monitoring frequency resuming in [redacted]. This has a minimal impact on the cost-effectiveness estimate, changing the original Company base case ICER from £29,826 to £30,364 (Table 4 and Appendix 5). The uncertainty has also been explored in scenario analyses, demonstrating minimal impact on the ICER (Appendix 5). The Company acknowledges that increased monitoring requirements have the potential to generate challenges within the current capacity constraints, and for the purpose of this submission reached out with a list of questions to three expert centres and received responses from two around the scale of the challenge and solutions these might explore (Appendix 6). These questions are also being explored in a series of workshops with an

		expert clinical committee.[25] Centres have advised that although there are substantial waiting lists, solutions such as [redacted] are already being explored and implemented by those centres. Other potential solutions that those centres would consider exploring include [redacted] Although one specialist centre felt they would [redacted], another specialist centre consulted underlined that as the [redacted] (Appendix 6).[25] In conclusion, the Company agrees that the base case should be updated to reflect a longer period of additional monitoring; however, although additional monitoring is likely, the assumption made by the EAG is considered a substantial overestimate. The updated Company base case aligns with likely clinical practice, as informed by clinical experts.
4. Imbalance in follow up duration for transition probabilities	Yes	The data available up to week 30 for the mavacamten+BB/CCB (beta blockers/calcium channel blockers) arm and week 46 in the BB/CCB monotherapy arm were used to inform the model transition probabilities because at the time of submission they represented the longest continuous data available for each treatment arm, respectively. The EAG suggests that the approach used for the mavacamten+BB/CCB arm should be applied to both arms, however, this approach would disregard the trial data showing a diminishing effect on NYHA class in the BB/CCB monotherapy arm after week 30 (CS B.3.3.2.1). Longer-term data from the most recent EXPLORER-LTE DBL ([redacted])[26] support the base case assumption that there is [redacted] in the mavacamten+BB/CCB arm and, furthermore, demonstrates [redacted] on NYHA class transition [redacted] (Figure 7). Note that neither published data nor a full clinical study report for the [redacted] DBL are yet available, but for transparency the Company is supplying a set of analyses as part of this technical engagement response, ahead of results publication (which is anticipated for [redacted]).[26] [redacted] Figure 7. NYHA class over time in the EXPLORER-LTE cohort of MAVA-LTE ([redacted] DBL)

		Analysis of the NYHA class distribution over time from the [redacted] DBL supports a [redacted] from [redacted] (Figure 8). Using a two-sided Dunn's test between each pair of assessment timepoints, adjusting for multiple comparisons, shows that after [redacted]. [redacted]Figure 8. Evolution of observed NYHA class distribution over time in the EXPLORER-LTE cohort of MAVA-LTE ([redacted] DBL) Note that baseline/week 0 in Figure 7 and Figure 8 are equivalent to week 46 in the model, indicating that substantial uncaptured benefit extends beyond this point in the modelled time horizon. Therefore, the available data support the appropriateness of the Company's approach to modelling transition probabilities.
5. Long-term rates of progression	Yes	The EAG agrees that gradual progressive deterioration of NYHA class is likely, on average, for people with obstructive HCM. There are substantial data supporting, in general, the concept that obstructive HCM is a progressive disease; for example, Sarcomeric Human Cardiomyopathy registry (SHaRe) data examining > 24,000 patient-years from 4,591 patients with HCM showed a substantial lifetime cumulative morbidity dominated by heart failure and atrial fibrillation.[27] The original Company base case did not include disease progression as a conservative assumption, as no appropriate quantification of disease progression had been identified to inform the model at that point in time. However, following identification of suitable data to inform the modelling (Company Addendum, section 3.2), the Company base case has now been updated to include disease progression in line with the EAG base case. Implementing this change in the model reduces the original Company base case ICER from £29,826 to £17,826 (Table 4 and Appendix 5). The EAG has requested additional evidence regarding the long-term rate of progression of NYHA class for people with obstructive HCM, and whether this differs between treatments. Although the prognostic SLR remains ongoing, we are able to supply two new lines of evidence in support of the new base case: 1. Expert clinical opinion; 2. Imaging data from VALOR-HCM, which supplements the cardiac magnetic resonance (CMR) imaging data from EXPLORER-HCM described in the CS (CS Appendix M). Expert clinical opinion

		Clinical opinion collected through a structured survey showed that the five respondents were overall supportive of the disease progression approach currently applied (Appendix 4). Specifically, three of the five clinical experts considered that the annual NYHA class progression rate derived from Maron *et al*., 2016 was [redacted] of the rate they see in practice. One clinician elaborated that it was [redacted] for transitions from NYHA I to II and II to III, but that [redacted]. The fifth clinician responded that the rate published by Maron *et al*. [redacted], while the rate published [redacted]. The model does not distinguish between resting and exercise-induced LVOTO therefore this cannot be explored explicitly, however it seems likely that the effect is averaged out when the weighted average is applied in the model. The overall consensus, therefore, supports the rate of progression used in the EAG's base case, which is now incorporated into the Company's base case. Furthermore, all five clinicians agreed that they [redacted]. Imaging data from EXPLORER-HCM and VALOR-HCM As described in brief in CS Appendix M, an exploratory CMR substudy was conducted as part of EXPLORER-HCM.[28] CMR was used to explore the effect of mavacamten on cardiac function and structure, with participants undergoing CMR on day 1 and at week 30. Data from the CMR substudy show that mavacamten was associated with significant reductions in absolute intracellular myocardial mass index as well as left ventricular mass index (LVMI), maximum LV wall thickness and left atrial volume index, which are all predictors of poor prognosis in obstructive HCM.[28] Echocardiographic imaging was also performed as part of VALOR-HCM, with data up to week 32 showing improvements in parameters including left ventricular mass index and left atrial volume, attributable to favourable changes in cardiac function.[29] An exploratory substudy was also conducted with participants from the VALOR-HCM trial, examining the effects of mavacamten treatment on diastolic function.[30] Diastolic dysfunction is a typical component of HCM pathophysiology, contributes to disease symptoms and has been associated with poor prognosis in obstructive HCM.[30] Diastolic function grade is a composite of diastolic function parameters assessed by echo. From baseline to week 16, 15 of 51

		patients (29.4%) treated with mavacamten had at least a one-grade improvement in diastolic function, compared with 6 of 47 patients (12.8%) who received placebo (p = 0.05).[30] The imaging data from EXPLORER-HCM and VALOR-HCM suggest that by targeting the underlying pathophysiology mavacamten may lead to positive cardiac remodelling. Together, these results suggest that mavacamten has the potential to slow disease progression, a view that was supported by clinical experts consulted by the Company (Appendix 4). This was explored in a scenario in the Company Addendum section 3.2, but does not form part of the Company's base case. In conclusion, the new evidence presented shows that considering disease progression as part of the new base case is plausible; furthermore this approach can still be considered conservative as there may be significant uncaptured benefit associated with mavacamten under the current assumption that disease progression does not differ between treatment arms.
6. Effect of treatments on mortality	Yes	The Company acknowledges that there is currently a lack of direct evidence for a beneficial effect of treatments on mortality, which is expected given the practical limitations of attempting to power a trial on mortality in this disease area. Absence of trial mortality data and the use of a suitable surrogate can be acceptable in health technology assessment, as for example in many oncology indications, where disease-free survival can be a surrogate for overall survival. Nevertheless, current literature is clear that mortality in obstructive HCM is higher than in the general population[27,31,32] and there is evidence that higher NYHA class correlates with mortality in patients with obstructive HCM.[33,34] Firstly, there is consistent evidence from the UK, Spain, Italy, Denmark and the US that mortality is higher in patients with HCM compared to the general population,[27,31,32] For example, in a recent Danish registry study of 1,197 patients with HCM, after adjustment for relevant co-morbidities and medications, HCM was associated with a significantly increased rate of all-cause mortality compared with age- and sex-matched controls (hazard ratio [HR] 1.48 [95% CI 1.18–1.84, p = 0.001]), across all age groups.[31] Similarly, a retrospective cohort study in 4,893 HCM patients across 7 European referral centres reported significant excess mortality associated with HCM compared to the general European population across all age groups.[32] A retrospective cohort study in 161 HCM patients that died between 2000–

2020 further analysed the underlying causes of mortality and found that 64% deaths were from HCM-related causes.[35]

Furthermore, the literature also demonstrates that, consistent with studies in other cardiac pathologies,[36,37] higher NYHA class is statistically significantly associated with greater risk of all-cause mortality in obstructive HCM, as described in CS B.1.3.1.3.4 and B.3.3.5, with data from SHaRey (Lakdawala *et al*., 2020[38] and CS Appendix N) and the Humedica electronic medical records (EMR) database (Wang *et al*., 2022[34]) providing consistent evidence for this relationship. It should be noted that in the original CS, only the abstract for Wang *et al*. (2022) was provided, in error; this has now been rectified with the inclusion of the conference poster in the reference pack, which provides the additional information required for assessing the methodology of the study (EAG report section 3.3.4 and EAG report appendix 9.3.5). This EMR analysis has now been updated with additional data from the Market Clarity dataset, covering now a full sample of [redacted] US patients with obstructive HCM.[33] Using a time-varying Cox regression model adjusted for age at diagnosis, sex and race gives hazard ratios for mortality by NYHA class higher than used in the Company CEM (Table 2).

NYHA class	HRs from Wang *et al.* 2022 Humedica EMR study[34] (Company base case)	Updated HRs from Wang *et al* Market Clarity EMR study[33]	Unadjusted 1-year RRs from SHaRe analysis[38] (CS scenario)	Adjusted HRs from SHaRe analysis (CS Appendix N) (CS scenario)
I	Reference class (ACM) i.e. 1.00			
II vs I	1.51	[redacted]	2.38	[redacted]
III vs I	2.77	[redacted]	9.38*	[redacted]
IV vs I	7.09	[redacted]		

*Composite III/IV HR applied to both III and IV classes separately.
ACM: all-cause mortality; HR: hazard ratio; SHaRe: Sarcomeric Human Cardiomyopathy Registry; NYHA: New York Heart Association; RR: relative risk

Table 2. Mortality relationship between NYHA classes relative to NYHA class I

This new analysis was performed based on the limitations of the Humedica database, which represented a cohort of patients with a diagnosis of acute myocardial infarction, unstable

		angina or heart failure. The new analyses (i.e. Market Clarity, which encompasses Humedica) is a more representative population. This wider population means that the patients in NYHA class I are more representative of obstructive HCM patients, as those from the Humedica dataset were, by definition, a comorbid asymptomatic patient and therefore likely to experience higher event rates than NYHA class I obstructive HCM patients without comorbidities. This accounts for the higher HRs for mortality seen in the Market Clarity analysis. Due to the limitations of the Humedica database, the HRs using the Market Clarity data are considered more suitable to inform the model, and have been included in the Company's updated base case (Table 4 and Appendix 5). Implementing this change to the model changes the original Company base case ICER from £29,826 to £26,000. In conclusion, it is reasonable to conclude that not only is all-cause mortality higher in patients with obstructive HCM than in the general population,[27,31,32] but also that the existing observational evidence supports consistent association between the NYHA class endpoint and final mortality outcome in obstructive HCM.[33,34,38] As such, the EAG scenario that assumes equal mortality in patients regardless of NYHA class is implausible in light of the available evidence and lacks clinical face validity. Although it is not feasible to evaluate the direct effect on mortality in an RCT due to the low event rate, there is clear link between NYHA class and mortality, and clinical trial evidence of a sustained benefit of mavacamten on NYHA class in patients with obstructive HCM (see response to issue 4).

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Calculation of utilities	1.5 4.2.6	No	The EAG's preferred analysis caps utilities at general population norms for age, because they consider that it is not realistic to assume that people with obstructive HCM NYHA class I would have better utility than people in the general population of the same age and sex. However, the Company considers that it is plausible that patients who move into NYHA class I following treatment, having previously had symptoms consistent with NYHA class II or III, feel better quality of life than the general population. Patients in NYHA class I by definition are not experiencing limiting symptoms, therefore it should not be considered implausible that they are reporting a higher utility than the general population, which will include people with a range of undiagnosed conditions and consequent reduction in utility. Utilities higher than general population have been reported for the fittest patients in other cardiac indications and this issue was raised in TA679 (Dapagliflozin for treating heart failure with reduced ejection fraction), where the health state utility values for the fittest patients were above general population norms, which was accepted in the committee's preferred ICER.[39] However, the Company also acknowledges that in TA773 (Empagliflozin for treating chronic heart failure with reduced ejection fraction),[40] which also had trial utilities higher than general population, a general population cap was proposed by the EAG and accepted by the manufacturer. In light of the uncertainty around this parameter, the Company accepts the EAG's preferred approach to utilities and has included this in the revised Company base case (Table 4 and Appendix 5). The incorporation of

<table>
<tr><td></td><td></td><td></td><td>the EAG’s preferred utility values results in an increase in the original Company base case ICER from £29,826 to £32,825</td></tr>
<tr><td>Additional issue 2:
Alternative approach to calculating transition probabilities</td><td>4.2.3.1 p. 74</td><td>Yes</td><td>The Company has explored the EAG’s suggested alternative method for calculating transition probability matrices i.e. to estimate them over the whole 30-week trial period and assume a constant rate of NYHA change within this time. A single transition matrix was created from baseline until week 30, which included all transition probabilities for this time period. These were then converted into rates in order to rescale the transition probabilities to fit the 2- and 4-week cycles in the model, which were designed to reflect the assessment timepoints in EXPLORER-HCM. To validate this approach, the estimated NYHA classes per arm at week 30 were compared with those observed in the EXPLORER-HCM trial (Table 2).
<table>
<tr><th></th><th>NYHA I</th><th>NYHA II</th><th>NYHA III</th></tr>
<tr><td>Mavacamten arm</td><td></td><td></td><td></td></tr>
<tr><td>Observed, week 30</td><td>61</td><td>52</td><td>8</td></tr>
<tr><td>Estimated, week 30</td><td>65</td><td>44</td><td>12</td></tr>
<tr><td>Placebo arm</td><td></td><td></td><td></td></tr>
<tr><td>Observed, week 30</td><td>27</td><td>74</td><td>25</td></tr>
<tr><td>Estimated, week 30</td><td>27</td><td>75</td><td>24</td></tr>
</table>
Table 2. Comparison between observed NYHA class distribution at week 30 in EXPLORER-HCM with model predictions using the EAG’s suggested method for calculating transition probabilities
For the placebo arm, the EAG’s method seems to be a reasonable approximation to the observed data. However, the EAG’s method does not validate well against the mavacamten arm. The process required to convert the transition probabilities into the model cycle lengths is known to result in errors in cases when it is possible to transition to more than two health states (including remaining in the current health state). Where one transition probability is small, the higher the</td></tr>
</table>

			likelihood of error.[41] As there were only 8 patients observed in NYHA class III in the mavacamten arm at week 30, the transition probabilities for these patients to either remain within NYHA class III or transition from NYHA class I or II to class III are therefore small. These errors are responsible for the difference between the observed and estimated numbers in Table 2. The Company's base case approach provided a closer fit to the observed data (CS Appendix J). An additional concern about the EAG's suggested method is that the approach implies that once patients reach NYHA class I they cannot transition out, which does not align with trial data and lacks face validity in the context of a progressive disease. The EXPLORER-HCM trial provides highly granular data on patients' NYHA class, and the original approach to calculating transition probabilities, utilising this granular data, should be considered the most appropriate approach. In conclusion, the EAG's suggested approach is considered less suitable to inform the model than the Company's base case approach, therefore the Company has retained their original approach in their revised base case.
Additional issue 3: Time on treatment for non-responders	EAG scenarios 2 and 3		In the original Company base case, patients who do not experience an improvement in NYHA class after 30 weeks of mavacamten treatment discontinue the treatment, which is in line with the draft SmPC. The EAG modelled two scenarios around this discontinuation, in which a proportion of patients who did not experience any symptomatic improvement continued on mavacamten treatment indefinitely. This was justified on the basis that "constraints on NHS resources, and delays in patients seeking or obtaining appointments for assessment" could affect when patients discontinue. Although the Company recognises that there is some uncertainty around the potential impact of appointment timing on timing of discontinuation, modelling patients to receive mavacamten treatment indefinitely despite deriving no symptomatic benefit lacks face validity.

			In these EAG scenarios, a proportion of patients in the model progress to NYHA class IV and remain on mavacamten, which is both clinically implausible and outside of the anticipated indication. In 1-to-1 interviews with five clinical experts, the Company asked whether they believed it was likely that NHS capacity concerns could cause delays in discontinuing mavacamten for patients not receiving symptomatic benefit. One clinician [redacted], but four of the five answered [redacted] i.e. they [redacted] (Appendix 4). Nevertheless, the Company has explored this uncertainty in a more clinically plausible scenario, where 20% patients who do not experience symptomatic improvement at week 30 experience a delay in discontinuation to week 38. The minimal impact of this scenario on the ICER indicates this uncertainty is unlikely to alter the cost-effectiveness (Appendix 5).
Additional issue 4: Clinically meaningful changes in pVO_2	3.4.1	No	An improvement in $pVO_2 \geq 1$ mL/kg/min is considered clinically meaningful based on an observational cohort study of 53 patients with HCM who underwent cardiopulmonary exercise testing and were then followed up for a median of 5.6 years, which showed that the risk (95% confidence interval) of death or transplant was reduced by 21% (11% to 26%) for each 1 mL/kg/min increase in pVO_2.[42]
Additional issue 5: Clarification on statistical analysis in EXPLORER-HCM	Section 3.5.4, page 52	No	To clarify, EXPLORER-HCM was neither designed nor statistically powered to detect significant differences in subgroups, and the results were not adjusted for multiple statistical testing. Although all subgroup analyses were pre-planned and stated a priori in the protocol, they are part of secondary questions and should be considered as exploratory. Interpretation of subgroup results should therefore happen with caution, especially for subgroups with small sample sizes.
Additional issue 6:	N/A	No	A minor error was identified in the original Company base case model, in the implementation of age-adjusted utilities. The formulae in the relevant cells considered the percentage of males alive at each age interval, instead of the overall male proportion; this has been corrected

Correction to minor error in utilities calculation			in “Life tables!AF13 to AF113” in the updated Company base case model. Correcting this error has a minimal impact on the ICER (reduced updated Company base case ICER by ~£70). All ICERs reported in this TE response incorporate this correction, with the exception of the EAG base case ICER and related correction to monitoring calculation described in issue 4.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Original company base case analysis (post corrections made 1. in response to clarification questions, 2. including EAG's update to the pack size of disopyramide, 3. correction to utilities calculation described in additional issue 6)	Not applicable	Not applicable	£29,826
Key issue 3. Post-authorisation safety monitoring of mavacamten.	The original Company base case analysis applied [redacted] outpatient visits and echos in year 1. In year 2 onwards, the NYHA-class based monitoring frequency employed in the BB/CCB arm was used.	[redacted] monitoring has been adjusted to include [redacted] outpatient visits and echos. Additional monitoring in [redacted] has been added to the base case to include outpatient visits and echos every [redacted]. In [redacted] patients then move to the NYHA class-based monitoring rates used in the BB/CCB arm.	£30,364

Key issue 5. Long-term rates of progression.	The original Company base case analysis assumed no disease progression in the long term, post-trial period.	The base case has been updated to include disease progression as modelled in the Company addendum scenario, in line with the EAG base case. This applies the disease progression rates informed by Maron *et al*., 2016 for all treatments.	£17,826
Key issue 6. Effect of treatments on mortality	The original Company base case used hazard ratios for mortality derived from analysis of data from the Humedica EMR database.	The base case has been updated to use hazard ratios for mortality derived from analysis of data from the Market Clarity EMR database.	£26,000
Additional issue 1: Calculation of utilities	The original Company base case used utility values directly from EXPLORER-HCM.	The base case has been updated to use the approach to utility values from the EAG base case i.e. capped at age- and sex-adjusted general population norms (NYHA class I = general population; NYHA classes II, III, IV estimated using multipliers relative to class I, calculated from EXPLORER-HCM data)	£32,885
Company's base case following technical engagement Note: this includes the following amendments:	**Incremental QALYs:** [redacted]	**Incremental costs:** £[redacted]	**ICER:** £19,725

• Changes to year 1 and year 2 monitoring for mavacamten. • Disease progression included for all treatments. • Use of Market Clarity EMR hazard ratios for mortality. • EAG approach to utility values adopted.			

Sensitivity analyses around revised base case

See Appendix 5 for details of sensitivity analyses.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Clinical expert statement and technical engagement response form

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- resolve any uncertainty that has been identified OR
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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

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Thank you for your time.

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NICE National Institute for Health and Care Excellence

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NICE National Institute for Health and Care Excellence

Part 1: Treating symptomatic obstructive HCM and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Juan Pablo Kaski
2. Name of organisation	University College London and Great Ormond Street Hospital
3. Job title or position	Associate Professor and Consultant Paediatric Cardiologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with HCM? ☐ A specialist in the clinical evidence base for HCM or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
8. What is the main aim of treatment for symptomatic obstructive HCM? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To reduce symptoms and improve quality of life in symptomatic patients with obstructive HCM

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Reduction in patient-reported symptoms, improvement in activities of daily living. Reduction in NYHA functional class or other symptoms scores (e.g. KCCQ) Reduction in LVOT gradient (as measured by echocardiography) – ideally to below 30-50mmHg Additional measures of treatment response may include increased objective exercise capacity, reduction of NT-proBNP (or BNP) levels
10. In your view, is there an unmet need for patients and healthcare professionals in symptomatic obstructive HCM?	Yes
11. How is symptomatic obstructive HCM currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Current approach broadly follows 2014 ESC guidelines on HCM and 2020 AHA/ACC guidelines on HCM (Please note, there are new ESC guidelines due to be released in August 2023). 1st line treatment beta-blockers or calcium channel blockers (verapamil or, occasionally, diltiazem). If still symptomatic, disopyramide can be added. If still symptomatic, septal reduction therapy is indicated (alcohol septal ablation or myectomy, depending on mechanism of obstruction, degree of LVH, age of patient, comorbidities, local expertise). Beta blockers are often not effective and calcium channel blockers are limited by side effects. There are often problems with supply of disopyramide, such that this is often not easily available. In addition, there can be significant tachyphylaxis that develops with disopyramide, so symptomatic benefit is not always long-lasting. Mavacamten would play a major role as a second line treatment, most likely in addition to beta blockers or calcium channel blockers, with a likely significant reduction in the need for invasive septal reduction therapies. There will also likely be an increasing role for Mavacamten as a single agent treatment.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	The use of mavacamten will require additional clinical monitoring (including with more frequent echocardiography, as in the EXPLORER trial), due to the risk of impaired systolic function. This will need to be performed in specialist centres and resources will need to be increased to allow this.

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes – based on the results of the clinical trials, and on the imperfect response to current treatments. Main benefits will be in relation to symptom reduction, improvement in quality of life and reduction in need for more invasive procedures. Effect on mortality is not yet known.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	At present, the data are only available for adult patients with symptomatic obstructive HCM. Data are emerging on the use of mavacamten (and the next in class aficamten) in atients with non-obstructive HCM; data on the paediatric population are not available.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Currently, more difficult due to the requirement for additional clinical monitoring. However, with increasing clinical experience and with adequate resourcing, I would anticipate, longer-term, the use of mavacamten to become embedded within standard clinical practice.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes – indication for starting treatment will be as in the clinical trials (symptomatic despite treatment with beta blockers or calcium channel blockers, EF>55%, LVOT gradient >50mmHg, age>18 years…). Discontinuation criteria will evolve, but will include reduction in EF below 50%, lack of response or intolerable side effects. Monitoring during initiation, titration and follow up will be required.

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Main benefits will be on symptom status, quality of life and reduction in the need for invasive septal reduction therapies
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, this is the first disease-specific drug developed for HCM, targeting the underlying pathophysiology. Based on the results of the clinical trials, the drug is well tolerated and likely to result in a significant improvement in symptoms and quality of life, as well as a likely reduction in the need for invasive therapies.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Clinical trial results suggest mavacamten is very well tolerated. Monitoring for reduction in EF is required.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes. A possible difference may be the lack of a comparison with disopyramide, but given the issues outlined above in relation to side effects, tachyphylaxis and availability, this is not a major concern. Data on the use of cardiac myosin inhibitors and disopyramide are likely to emerge very soon. Outcome measures are appropriate and reflect current UK clinical practice.

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	No real world data available yet
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	Difference in availability of clinical expertise around the UK may be a consideration, but the new NHSE ICC service specification should hopefully help to address this.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

1. Exclusion of disopyramide as a comparator	While I agree that the lack of data comparing mavacamten with disopyramide is a consideration, I would not consider this a major issue. Disopyramide can be associated with significant side effects and tachyphylaxis, and, crucially, is not easily available (there have been several occasions in the last few years where the drug has not been available in the UK and clinicians/Trusts/patients have been forced to source alternatives). It is likely that data on disopyramide and myosin inhibitors will be available soon, but in my opinion, the exclusion of disopyramide as a comparator should not prevent the introduction of mavacamten into NHS clinical practice.
2. Uncertain efficacy of mavacamten in patients without a sarcomere mutation	There are currently insufficient data to determine whether the efficacy differs in patients with and without sarcomeric variants, and the numbers in the EXPLORER trial are too small to draw conclusions on the subgroup analysis. Larger datasets will be required to robustly test this, but this will take time and may introduce additional uncertainties that will be almost impossible to address (e.g. are there differences between different sarcomeric genes, variant location etc.). Of note, most patients in the EXPLORER trial did not have a sarcomeric variant. In the absence of additional information, I would consider that the use

	of mavacamten should not be limited to patients with sarcomeric variants only from a medical perspective, but of course financial considerations will also be important.
3. Post-authorisation safety monitoring of mavacamten	This is a significant issue that will require additional resourcing. While mavacamten appears to be very well tolerated, there will be a requirement for closer clinical monitoring (including with echocardiography) than with current clinical care. This will need to be carried out in expert centres, which will need to be adequately resourced. There is no doubt in my mind that this can be achieved within the NHS (and it is important that it is), but clearly will require a commitment from commissioning groups to ensure adequate staffing and resources. Again, the NHSE service specification for ICC should feed into this.
4. Imbalance in follow up duration for transition probabilities	
5. Long-term rates of progression	
6. Effect of treatments on mortality	Currently, there is limited evidence to suggest that the treatment of LVOTO in HCM results in improvements in mortality. Retrospective historical data have suggested improved survival in patients who have undergone myectomy, for instance, but this has not necessarily been borne out by other studies, and more contemporary data are lacking. It is possible that there may be some survival benefit in treating LVOTO with mavacamten (which would more likely be done at an earlier stage in the disease process than invasive therapies), but there is no evidence to confirm this at present.
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

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Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

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Part 1: Treating symptomatic obstructive HCM and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Sunil Nair
2. Name of organisation	Norfolk & Norwich University Hospital
3. Job title or position	Consultant Cardiologist, Lead for heart muscle disease
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with HCM? ☐ A specialist in the clinical evidence base for HCM or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
8. What is the main aim of treatment for symptomatic obstructive HCM? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	
10. In your view, is there an unmet need for patients and healthcare professionals in symptomatic obstructive HCM?	
11. How is symptomatic obstructive HCM currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	

• Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. How do data on real-world experience compare with the trial data?	
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this	

treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

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Table 2 Issues arising from technical engagement

1. Exclusion of disopyramide as a comparator	I personally use Disopyramide as a second line agent for my symptomatic LVOTO HCM patients to add onto beta blocker or calcium channel blocker therapy. It can be limited by side effects and tolerability, but some patient get a good response. One of the main challenges relates to uncertainty over availability and in recent years there have been at least 2 occasions where there has suddenly been no availability across the country and this causes major difficulties. My experience of working in other HCM centres and of discussions at MDT with centres that perform septal reduction techniques, is that these centres also use Disopyramide as an add on to beta blockers or calcium channel blockers. I think it would be more realistic, to compare Mavacamten to beta blocker or calcium channel blocker plus Disopyramide, rather than a beta blocker or calcium blocker alone.
2. Uncertain efficacy of mavacamten in	This is a very interesting question, and may well help to explain why some patients had a very good response versus others with little response. It would be helpful to have further date on the responders as to whether they were patients with a relevant sarcomere mutation, given the mode of action of

patients without a sarcomere mutation	Mavacamten. If further evidence pointed towards responders being those with a sarcomere mutation, then this would help from a marketing and guidelines perspective, to enable the most targeted and cost effective use of the product.
3. Post-authorisation safety monitoring of mavacamten	This I see as being a potential problem for the NHS. Whilst the overall numbers of patient accessing Mavacamten will not be large across the whole country, the safety monitoring schedule is intensive in terms of frequent follow up appointments and perhaps more importantly and difficult to achieve, the need for multiple echocardiogram evaluations over the first year. Most NHS trusts, including the larger tertiary centres looking after the HCM patients, have long echo waiting lists. The echo surveillance follow up will need to be prioritised in a way similar to the need for frequent echo surveillance in some oncology patients receiving cardiotoxic chemotherapy agents. With the numbers being small, it is not impossible to get round these hurdles, but there will be challenges.
4. Imbalance in follow up duration for transition probabilities	
5. Long-term rates of progression	
6. Effect of treatments on mortality	I agree, it is difficult to draw confident conclusions over mortality benefits. The causal link to changes in NYHA status is not widely accepted and NYHA status can be quite a subjective measure in any case. I don't believe that mortality effects shoud be included in the model, particularly given the uncertain link and the effect if has on the ICER estimates.
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

• First disease specific therapy for symptomatic LVOTO in HCM.
• Significant quantitative and qualitative benefits, above current medical therapy, though not compared with commonly given combination therapy.
• May reduce the need for invasive and difficult to access interventional and surgical therapies.
• Low risk of side effects.
• May be difficult to implement in the NHS, due to the intensive investigations required during the monitoring phase of drug initiation and up titration.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (Section 1.1).

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

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Technical engagement response form

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Cardiomyopathy UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Exclusion of disopyramide as a comparator	Yes	Cardiomyopathy UK's specialist helpline nurses make detailed notes relating to all calls taken on the charity's helpline. A review of call notes relating to calls taken from January 2021 to December 2022 (1,457 calls) shows 7 instances where disopyramide had been discussed. The charity's database of calls is not designed to be a clinical registry and cannot give accurate data on the number of people with cardiomyopathy taking disopyramide in the UK. We do believe however that the very low number of calls mentioning this medication, in comparison to other medications and interventions, does indicate a very low level of disopyramide usage among helpline callers. A review of discussions posted on the charity's closed Facebook group (2,264 active members) shows that only 38 posts (less than 1.2%) mentioned disopyramide in 2022. The majority of discussions about this medication related to ongoing problems with supply. We believe that the charity's Facebook group is another accurate barometer of the cardiomyopathy community and therefore the low number of discussions in the

		group about disopyramide, in comparison to other medications and interventions, does indicate a very low level of disopyramide usage among group members. It should be noted that our understanding is that mavacamten would be offered to patients if disopyramide was deemed to be inappropriate or infective. This, along with the known supply issues and low usage, supports the argument that disopyramide should be excluded as a comparator.
2. Uncertain efficacy of mavacamten in patients without a sarcomere mutation	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
3. Post-authorisation safety monitoring of mavacamten	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
4. Imbalance in follow up duration for transition probabilities	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
5. Long-term rates of progression	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
6. Effect of treatments on mortality	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (Section 1.1).

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

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Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Association of Inherited Cardiac Conditions
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Exclusion of disopyramide as a comparator	No	Disopyramide is an established treatment for symptomatic LVOTO. Robust observational data demonstrate safety and effectiveness (Sherrid M et al. Circ HF 2013) and it is part of standard, guideline recommended treatment in both Europe and US. I agree with the BCS comments that disopyramide would be offered in the UK as standard treatment of symptomatic LVOTO and ideally included in the economic model. The company's model includes disopyramide as a subsequent treatment option, only used for escalation of treatment after standard monotherapy with a beta-blocker or calcium channel blocker which does not reflect UK or international practice. In my experience the supply issues are intermittent, temporary and have resolved. There are no UK data to my knowledge describing the use of disopyramide in the UK (a study using the CALIBRE platform reported on BB and CCB but not disopyramide - Pujades-Rodriguez et at PLoSOne 2018). Single UK centre experience (Collis et at EHJ FH 2017) described the treatment of 347 patients prior to surgical treatment: 55.4% of patients were managed with β-blockers, 24.6% with non-dihydropyridine calcium channel blocker therapy and 39.5% with disopyramide therapy. Sherrid et al 2013 (US single centre) showed that approximately half of symptomatic patients are effectively treated with BB/CCB

		monotherapy. 50% of patients with refractory symptoms on BB/CCB monotherapy respond positively to the addition of disopyramide. Can these (imperfect) data be constructively used in the modelling?
2. Uncertain efficacy of mavacamten in patients without a sarcomere mutation	No	The numbers involved in the trial are probably too small to assess this and any results of subgroup analysis would be fraught with uncertainty. Most patients with HCM in the UK do not have genetic testing unless they are referred to a tertiary referral centre.
3. Post-authorisation safety monitoring of mavacamten	No	As mavacamten is a new drug, monitoring for safety as SmPC is a reasonable course of action. Cost savings from a reduction in the number of invasive septal reduction procedures can be used to fund monitoring. I expect that monitoring clinics can be set up akin valve disease clinics.
4. Imbalance in follow up duration for transition probabilities	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
5. Long-term rates of progression	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
6. Effect of treatments on mortality	No	Even though HCM patients have a higher relative risk of mortality than the general population, the absolute risk is small. The available studies examining mavacamten are too small and of short duration to assess a meaningful impact on mortality. In my view this is a futile exercise. Other treatment of LVOT have been conclusively been associated with improved survival.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

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NICE National Institute for Health and Care Excellence

About you

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Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	**British Cardiovascular Society**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**n/a**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Exclusion of disopyramide as a comparator	Yes ([redacted]) No ([redacted])	I was surprised at the suggestion that disopyramide is not a valid comparator. It has been used to treat left ventricular outflow tract obstruction since 1982.[1] It is the recommended agent of choice as a second line to treat obstruction if patients remain symptomatic despite a trial or either a beta blocker or verapamil in both European (European Society for Cardiology)[2] and US (American College of Cardiology/American Heart Association)[3] guidelines for the management of hypertrophic cardiomyopathy. It is widely used in the UK for this indication and available as a generic for a typical monthly cost of £32.08. It has also been used in children for this indication for at least 30 years.[4] Both sets of international guidelines regard the use of disopyramide as a second-line agent to treat LVOT obstruction in HCM as a class 1 indication.[2,3] While there have been some intermittent supply shortages in the UK, none of my own patients have been left without a treatment supply and we have always managed to source medication for all patients who needed it. There have been similar shortages of lots of other commonly prescribed medications such as hormone replacement therapy and at times even penicillin. This should not in my view mean that we should abandon prescribing HRT or penicillin, or in the case of disopyramide, not use it as a comparator to a novel agent seeking to supplant its place in current authoritative international treatment guidelines. It may be true that it is underutilised in the UK,

		but this reflects the fact that many patients are likely underdiagnosed, undertreated, or lack access to care in specialist centres familiar with prescribing the agent or managing LVOT obstruction in general. Again, these do not seem valid reasons for excluding it as a comparator given the same can be said for other cardiovascular diseases: *e.g.*, hypertension is frequently underdiagnosed and undertreated. The results of the VALOR-HCM study have now been published in full (they were previously only available in abstract form).[5] As previously noted, only 27% of patients in the mavacamten treatment arm had a 2-class improvement in NYHA functional class whereas comparable data for surgery is >70%.[6] Data for disopyramide date back to 2005 (and included patients from the UK).[7] When added to first line therapy with a beta blocker or calcium channel antagonist, 66% of patients treated with disopyramide avoided the need for surgery.[7] Although direct comparisons are difficult, this effect is similar to the 58.9% absolute treatment difference with mavacamten versus placebo in the VALOR-HCM study for patients who were judged as not having ongoing indications for surgery.[5] In VALOR-HCM, only 22 out of the 112 patients studied was on disopyramide.[5] This is despite the fact that all the patients enrolled were being considered for surgical myectomy. The design of EXPLORER-HCM where mavacamten was added to a beta blocker or calcium antagonist (but not disopyramide) implies that the proposed role for this agent is as a second-line therapy to these agents. This is the current role of disopyramide. It is therefore inexplicable why mavacamten was not trialled head-to-head against disopyramide (the current standard of care), rather than placebo. The potential issue of tachyphylaxis was also raised as a reason why disopyramide should not be used as a comparator, citing as evidence, opinions of un-named experts on an industry-funded advisory board. It should be noted that the observational data attesting to the efficacy of disopyramide involved a mean follow up duration of 3.1 years,[7] suggesting that this is unlikely to be a major practical problem in clinical practice in most patients, something that chimes with my own experience using the agent. Anticholinergic side effects can be an issue at higher doses, but these are often not needed and while they may be a problem for

		some patients (only ~7% of patients in one seminal case series),[7] they are not an issue for the overwhelming majority of patients. For those who do experience a reduction in efficacy over time, it's unclear how much is due to true pharmacological tachyphylaxis and how much is related to disease progression or acquisition of confounding comorbidities over time. Whether a similar issue, *i.e.*, tachyphylaxis, pertains to mavacamten also is not presently known: the VALOR-HCM study involved follow up of patients only out to 16 weeks (~3-4 months), and EXPLORER-HCM out to 30 weeks (~6 months), although there is now an open-label extension phase to EXPLORER-HCM (MAVA-LTE) which may shed light on this. The interim data has only been published in abstract form but appears encouraging thus far. Loss of efficacy for disopyramide may be more of an issue in paediatric cohorts, where disease is often more severe by definition (due to onset in childhood rather than adulthood),[4,8] and where the myocardium/heart may be subject to more growth and underlying disease progression. For these reasons, paediatric data cannot therefore be readily extrapolated to adult practice. Feedback from experts from BCS in different parts of the country is that disopyramide is a valid comparator for treatment with mavacamten. Any difficulty in obtaining disopyramide is hard to quantify beyond anecdote. Disopyramide may still not lead to adequate symptom improvement and is often poorly tolerated. Therefore mavacamten is still likely to have a role even when compared to additional use of disopyramide.
2. Uncertain efficacy of mavacamten in patients without a sarcomere mutation	Yes	The pathophysiology of left ventricular outflow tract obstruction is complex and involves to varying degrees an interplay between functional myocardial abnormalities and morphological/anatomical factors pertaining not just to the myocardium but the mitral valve and sub-valvular apparatus. Mavacamten (a cardiac myosin-ATPase inhibitor) was ostensibly specifically developed to address hypercontractility seen in hypertrophic cardiomyopathy patients with thick filament sarcomere mutations. Its application in these patients therefore seems cogent, particularly where there is associated LVOT obstruction to which a hypercontractile state may contribute. An equivalent mechanism of action for example cannot be

		assumed for patients with some thin filament mutations, where the underlying pathophysiology may be entirely different, resulting in gene/mutation specific effects some of which may nonetheless be beneficially modified.[9] However, whether the impact on cardiac myosin or salutary benefits on cellular calcium handling are relevant to the pool of patients (the majority of patients with HCM in many series) without thick or thin filament sarcomere mutations – so-called sarcomere negative HCM is unclear. Paradoxically, the presence of left ventricular outflow tract obstruction appears to be a good predictor of a sarcomere gene mutation negative status.[10] Given how heterogenous HCM is and that the majority of patients with LVOT obstruction are sarcomere gene mutation negative, unless polygenic factors result in comparable effects on cardiac contractility, a therapy targeted at cardiac myosin may not prove efficacious in all patients. If such a therapy were safe, cheap, and efficacious in the majority, then the most facile way to address this is a therapeutic trial in a given patient. This is arguably what happens with current therapy for LVOT obstruction where the drugs used are cheap, safe, and often very effective. However, such a strategy may not prove cost effective if the intervention is expensive and requires serial echocardiography/monitoring. Of note, 64% of patients in EXPLORER-HCM on mavacamten did not experience a large improvement in Kansas City Cardiomyopathy Questionnaire – Overall Summary score.[11] The failure of such a large proportion of patients to improve substantially may be due to: (1) symptoms being related to factors other than LVOT obstruction such as microvascular ischaemia or diastolic dysfunction or comorbidities; (2) the drug targeting hypercontractility in individuals where morphological abnormalities or other relevant mechanisms may have predominated. For example, elongation of the anterior leaflet of the mitral valve is an important feature in many patients with HCM and contributes to the propensity of the anterior leaflet to move anteriorly and cause obstruction. Patients with very long anterior leaflets (typically 33 mm or more), particularly if the associated papillary muscles are anteriorly and medially displaced, do not respond well to disopyramide (which like mavacamten is also a negative inotrope).[12]

		This issue is worthy of further study but we would consider post hoc sub-group analysis as hypothesis generating. There is preclinical data of potential varying efficacy with/without mutation ((https://cinc.org/2021/Program/accepted/235_Preprint.pdf). Larger trials with adequate power to fully address this question would be beneficial. Until further trial evidence is available we do not think it would be possible to differentiate based on sarcomeric mutation or not.
3. Post-authorisation safety monitoring of mavacamten	Yes	On the basis of the trials to date, it is likely that mavacamten will need monitoring with serial echocardiography, particularly during the up-titration phase to ensure there are no significant falls in left ventricular ejection fraction which may have safety implications. Once a stable dose is achieved, it's feasible that the frequency of such monitoring could be reduced. This is nevertheless likely to pose a major challenge to many echocardiography/imaging departments where there may be competing priorities (*e.g.*, need to provide prompt access to echo to enable rapid diagnosis and treatment of heart failure with reduced ejection fraction). Centres with large oncology services are already committed to doing frequent serial echocardiography for recipients of potentially cardiotoxic chemotherapy, *e.g.*, Herceptin/traztuzumab for common cancers such as breast cancer. I note the REMS (Risk Evaluation and Mitigation Strategy) programme required by US regulators which in effect mandates 7 echocardiograms in the first year and 4 per year thereafter, or more if any dose changes are needed.[13] This is unlikely to be feasible outside of large tertiary centres and assuming the pool of patients being considered for therapy is small owing to capacity issues, competing demands, and ongoing workforce issues (please see: https://committees.parliament.uk/writtenevidence/108668/pdf/). There would of course also need to be physician oversight of such monitoring with related implications for clinic capacity and competing clinical priorities. Echocardiographic services around the country play a key role in monitoring the heart during a wide variety of treatments, notably for example, during chemotherapy such as trastuzumab (Herceptin). We do not think that treatment should be withheld due to concerns regarding echocardiographic capacity. Costs of surveillance should be included in the assessment.

4. Imbalance in follow up duration for transition probabilities	Yes ([redacted]) No ([redacted])	I would regard any models based solely on NYHA class transition with a degree of scepticism given how poorly quantified it is by both physicians and patients.[14] Importantly, most patients in EXPLORER-HCM where in NYHA Class II (70%).[11,15] It is unfortunate that 28% of patients were missing baseline and/or follow up KCCQ data,[11] particularly as this was an important secondary study endpoint and arguably provides more reliable/granular understanding of changes in symptoms. The assumption of stability of NYHA class over time requires prospective data rather than assumptions, particularly given the older age of the cohorts studied in EXPLORER-HCM and VALOR-HCM.[11,15] Agree with NICE EAG.
5. Long-term rates of progression	Yes ([redacted]) No ([redacted])	It is highly problematic to make inferences on the progression of NYHA class using observational registry data from a selected series of supraregional tertiary centres (Maron *et al*),[16] given the intrinsic heterogeneity of hypertrophic cardiomyopathy and important and significant differences between the patients enrolled in EXPLORER-HCM/VALOR-HCM.[11,15] Breathlessness in HCM is often multifactorial and as well as being related to outflow tract obstruction, may be due to microvascular ischaemia, diastolic dysfunction, atrial fibrillation, deconditioning, and other comorbidities. These factors may make differing contributions at different ages. For example, atrial fibrillation is more common in older rather than younger patients and so the rate of new onset AF may be higher in the older trial participants of EXPLORER-HCM (mean age 58.5 years)[15] and VALOR-HCM (mean age 60)[5] than in the younger registry cohort reported by Maron *et al* (mean age ~44 years).[16] Diastolic dysfunction is also more relevant in older than younger patients. The data from Maron *et al* included only 573 patients in total despite representing the cohorts of 3 large tertiary HCM centres (implying likely significant selection bias). Only ~1 in 3 patients were offered genetic testing and only those eligible for exercise testing were included. Overall, 10% of patients without obstructive HCM progressed to NYHA class III/IV heart failure at a rate of 1.6%/year. Of those with overt obstruction, 7.4%/year progressed to NYHA III/IV

		heart failure whereas for those with latent (provocable) obstruction, the rate was 3.2%/year, illustrating the heterogeneity of natural history based on resting LVOT status alone. I also do not believe it is rationale to assume that the probability of transition from class I to class II symptoms is the same as that for transition from class II to III symptoms. It is plausible that rates will be higher in those who are class II and that this might occur faster in older than younger patients. In the interests of balance, equally, it is feasible that the rate of progression may even be higher in those who are NYHA class II at a younger age with the younger age of onset of Class II symptoms perhaps implying a more severe and aggressive (and therefore progressive) disease phenotype, particularly in light of data from the SHARE registry regarding age at diagnosis.[17] In either scenario, it is highly problematic and simplistic to take a weighted average of a subgroup of a selected natural history study of middle-aged patients with HCM and extrapolate outcomes to more senior trial patients who were on average 15 years older and with other important differences in characteristics that may portend a different natural history trajectory (older age at onset being associated with better outcomes as a general rule for HCM). Agree with NICE EAG.
6. Effect of treatments on mortality	Yes ([redacted]) No ([redacted])	I do not believe it is plausible to argue that mavacamten will have a significant impact on mortality (nor is there any evidence as yet that it would have a deleterious effect). It is simply not credible to argue that a change in NYHA class can be extrapolated into a change in mortality or outcome. We know from the inotrope literature in heart failure that inotropes improve symptoms/functional status in clinical trials but that this actually translates into increased mortality.[18,19] It is therefore fallacious to assume that there is a causal link between the two or to exclude unanticipated deleterious effects that small trials are not powered to detect. None of the existing pharmacological treatments for LVOT obstruction have shown any mortality benefit (or otherwise). There is therefore no cogent reason to assume otherwise for mavacamten. It has been posited that as mavacamten has been designed specifically to target the pathophysiology of HCM, it may therefore

		be different somehow. However, only a minority of patients with LVOT obstruction actually have thick filament sarcomere mutations with the defect that mavacamten seeks to target. Its use and therefore potential benefit in reducing symptoms in the majority of patients with a polygenic HCM or other variants stem are likely to stem from its negative inotropic properties rather than being mechanism specific. Beta blockers, non-dihydropyridine calcium antagonists, and disopyramide also all have negative inotropic effects by different underlying mechanisms, again, without any positive or negative impact on survival. There is data from surgical series showing that treatment of obstruction by surgical gradient reduction therapy results in improved survival relative to those managed conservatively.[6] However, these data must be interpreted with caution as they are non-randomised and it is plausible that those who were managed conservatively (in a non-randomised fashion) had worse outcomes as they had comorbidities that precluded fitness for surgery among other possible confounders. Similarly, comparisons with actuarial data from healthy adults is again no substitute for randomised data. Also, in the age groups studied in EXPLORER-HCM (mean age 58.5 years),[15] competing risks start to become more relevant. We also know that HCM is not one disease and that outcomes for patients with sarcomere mutations are very different from those with polygenic/non-sarcomeric HCM, with the latter generally experiencing a more favourable outcome.[10,17] We also know that age of disease onset is an important driver of both outcome and the nature of that outcome.[17] Sudden arrhythmic cardiac death is an important complication seen in younger patients with HCM but is less of an issue in older cohorts. We also know that while patients with HCM presenting at age 60 years or older have higher all-cause mortality than age-matched population controls, this is driven by non-HCM related diseases or outcomes.[20] Mortality and adverse cardiac events in HCM in much younger patients are more likely to be driven by HCM itself (rather than comorbidities) and so potentially more amenable to disease modification. The age of onset of HCM in the patients enrolled in EXPLORER-HCM is not published but the average age of participants at enrolment was 58.5 years.[15] The absence of any positive data for any intervention (other than ICDs to prevent sudden arrhythmic death) also likely reflects the relatively low event rates seen with this disease when appropriately

		managed. It is therefore likely that if mavacamten does have a mortality benefit (or increases mortality somehow), a very large study would be required to detect an impact due to the small size of any effect. In any scenario, it is not tenable to make speculative assumptions about based on change in NYHA class alone. The effect of reduction in left ventricular outflow tract obstruction on mortality remains debated. Currently BCS consider the best evidence is for improvement in symptoms and quality of life. This may allow some patients to avoid going on to septal reduction surgery, reducing the operative risks associated.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (Section 1.1).

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **23 February 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	NHSE
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Speaker and/or advisory board fees from Bristol-Myers Squibb (manufacturer of mavacamten), Pfizer, Alnylam, Akcea, Ionis.**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
1. Exclusion of disopyramide as a comparator	Personal view / own data	Disopyramide is commonly trialled in patients with symptoms related to LVOT obstruction which persist after maximal beta-blockade. The issue with this drug is its tolerability and safety. From experience (tertiary referral centre for HCM with >1200 patients with HCM under on-going follow up of which only circa. 50 are on disopyramide long-term) only about a third of patients gain long-term symptomatic benefit from this drug. Many have to stop the drug early on because of anticholinergic side effects (blurred vision, urinary retention), many cannot reach a therapeutic dose because of QT prolongation and many develop tachyphylaxis. There has also been an issue with supply in the UK particularly during 2021/2022 but this situation appears to have improved of late. The reality is that if mavacamten becomes available, it would be more appropriate to replicate the RCT protocol and to prescribe it as the second-line agent after beta-blockers. For that reason, and due to its limited use, NHSE agrees with 2 of the 3 experts consulted that it is reasonable to exclude the drug as a comparator. The perception among cardiologists with expertise in this area is that mavacamten is a more efficacious than disopyramide and that it will be better tolerated (although clinicians have no good evidence to support this view). It is worth noting that there are no clinical data (as known at this stage) on use of disopyramide in combination with mavacamten. Therefore, NHSE does not support prescribing mavacamten to

		be taken alongside disopyramide. A need to use disopyramide ahead of mavacamten could result in unnecessary delays in treating patients with obstructive HCM with optimal therapy.
2. Uncertain efficacy of mavacamten in patients without a sarcomere mutation	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
3. Post-authorisation safety monitoring of mavacamten	Personal view	NHSE shares concerns about the impact this drug will have on echo departments (assuming access is limited to tertiary ICC/heart muscle units until more safety data is available this will not be a widespread issue).NHSE does not, however, see this as a good reason not to offer the drug to symptomatic patients. This is akin to not providing Herceptin to patients with ER positive breast cancer because of a lack of diagnostic imaging resources. This issue is not unique to mavacamten. How echo is delivered without patients having to travel long distances also needs to be thought about carefully from a commissioning perspective.
4. Imbalance in follow up duration for transition probabilities	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
5. Long-term rates of progression	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
6. Effect of treatments on mortality	Yes (further review of ref 41 in ERG report)	NHSE agrees with the EAG report that ascribing mortality benefits to treatments for obstructive HCM is very difficult. However NHSE disagress that EAG do not consider the CMR Explore sub-study because of “exploratory outcomes”. LV mass is a very robust, prognostic marker and has been independently associated with CV outcomes across a breath of large scale population studies not just in HCM but also wider populations. It may be possible to predict improvements in hard outcomes based on the level of reduction in LV mass. The CMR sub-study in EXPLORER (albeit in small numbers) showed mavacamten was associated with significant reductions LV mass index, maximum LV wall thickness, and left atrial volume index—all predictors of poor prognosis in obstructive hypertrophic cardiomyopathy. https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.052359

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Evidence Review Group Report commissioned by the
NIHR Evidence Synthesis Programme on behalf of NICE

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy (ID3928)

Evidence Review Group's summary and critique of the company's response to technical engagement: including company correction of 30/03/23

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
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Date completed	31 March 2023

[redacted]

[redacted]

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List of abbreviations

BB	Beta-blocker
CCB	Calcium channel blocker
CPRD	Clinical Practice Research Datalink
CSR	Clinical study report
EAG	External Assessment Group
Echo	Echocardiogram
FDA	Food and Drug Administration
HCM	Hypertrophic cardiomyopathy
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
LVOT	Left ventricular outflow tract
NYHA	New York Heart Association
pVO_2	Peak oxygen consumption
QALY	Quality-adjusted life year
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SRT	Septal reduction therapy
TE	Technical engagement
TP	Transition probability

1 Introduction

This document is the External Assessment Group (EAG)'s summary and critique of the response by the company, Bristol-Myers Squibb, to the key issues for technical engagement (TE) proposed in the EAG report for this appraisal (submitted to NICE on 6th January 2023). The EAG received the company's response on 28th February 2023.

The company's TE response form contains the following information:

- A written response to each of the 6 key issues, all of which include new evidence and/or analyses (see Table 1).
- Responses to 6 additional issues related to comments in the EAG Report, EAG scenarios and an error in the company's base case model see (Table 1).
- A set of updated cost-effectiveness results, incorporating changes to the company's base case analysis in response to some of the key issues for TE and additional issues considered by the company.
- An Appendix reporting sensitivity analysis for the company's revised base case.
- An updated version of the company's economic model accompanied the response form.
- The company submitted a correction to the post-TE cost-effectiveness results on 30 March 2023. This included revisions to the results in section 3 and Appendix 5 of their TE response, and a corrected version of the economic model.

In this report we present the following:

- Our critique of the company's response to each of the key issues for TE and additional issues raised in the company's company response to TE (Section 2)
- A validation of the results of the company's corrected post-TE cost-effectiveness analysis, and the results of an updated EAG base case and scenario analyses (Section 3)

Table 1 Summary of key issues for technical engagement

Issue number	Summary of issue	Does this response contain new evidence, data or analyses?
1	**Exclusion of disopyramide as a comparator** Disopyramide (alone or in combination with either beta-blockers or non-dihydropyridine calcium blockers) is a comparator (as part of standard care) in the NICE scope. However, the company argue that disopyramide is not relevant as it is rarely used in clinical practice.	Yes
2	**Efficacy of mavacamten in patients with or without a sarcomere mutation** Although the NICE scope does not specify any subgroups, the efficacy of mavacamten could plausibly differ between patients who have a sarcomere mutation and those who do not. The company argue that mavacamten efficacy does not differ between these subgroups.	Yes
3	**Post-authorisation safety monitoring of mavacamten** Post-authorisation safety monitoring of patients with obstructive HCM was identified as a critical issue by the US Food and Drug Administration (FDA) in their appraisal of mavacamten. The EAG and our clinical experts are uncertain whether an adequate level of safety monitoring can be applied in the NHS.	Yes
4	**Imbalance in trial follow up duration for calculation of transition probabilities** The EAG consider that the company's use of different methods to model transition probabilities between weeks 30 and 46 in the mavacamten and BB/CCB monotherapy arms is likely to have introduced bias.	Yes
5	**Long-term rates of progression** The EAG noted that there is uncertainty over the average rate of increase in NYHA class, and over whether and how this is likely to differ between treatments. This has a large impact on estimates of cost-effectiveness.	Yes
6	**Effect of treatments on mortality** The company model all-cause mortality using estimates of an association between NYHA class and mortality derived from analyses of real-world data. However, this approach has been criticised on the basis that the observed association between NYHA class and mortality is not necessarily causal, and that there is currently no evidence that treatments that reduce the symptoms of obstructive HCM have any mortality benefit.	Yes

Issue number	Summary of issue	Does this response contain new evidence, data or analyses?
Additional issue 1	**Calculation of utilities** The EAG's preferred analysis caps utilities at general population norms for age, because they consider that it is not realistic to assume that people with obstructive HCM NYHA class I would have better utility than people in the general population of the same age and sex. However, the company consider it plausible that patients who move into NYHA class I, having previously had symptoms consistent with NYHA class II or III, feel better quality of life than the general population.	No
Additional issue 2	**Alternative approach for calculating transition probabilities** The company have explored the EAG's suggested alternative method for calculating transition probability matrices i.e. to estimate them over the whole 30-week trial period and assume a constant rate of NYHA change within this time.	Yes
Additional issue 3	**Time on treatment for non-responders** In the original company base case, patients not experiencing an improvement in NYHA class after 30 weeks of mavacamten treatment discontinue the treatment, consistent with the draft Summary of Product Characteristics (SmPC). The EAG modelled two scenarios around this discontinuation, in which a proportion of patients who did not experience any symptomatic improvement continued on mavacamten treatment indefinitely. The company consider this approach to lack face validity.	Yes
Additional issue 4	Clinically meaningful changes in pVO_2	No
Additional issue 5	Clarification on statistical analyses in EXPLORER-HCM	No
Additional issue 6	Correction to minor error in utilities calculation	Yes (minor)

2 Critique of the company's response to key issues for technical engagement

2.1 Key Issue 1 – Exclusion of disopyramide as a comparator

Frequency of disopyramide use

The company estimated the annual frequency of disopyramide prescriptions during 2010 to 2020 among patients with obstructive HCM in England based on the latest available data from the CPRD database (company response Appendix 1). Overall, the annual mean proportion of patients with obstructive HCM who received at least one disopyramide prescription was [redacted]% (range [redacted]% to [redacted]%, over the period 2010 to 2020).

However, the EAG believe these data are uncertain because:

- The CPRD cohort does not reflect the number of patients eligible for mavacamten since NYHA class I patients, who would not be eligible for mavacamten and would be unlikely to receive disopyramide, were not excluded from the database. The proportion of patients who received disopyramide prescriptions may therefore be an underestimate for the population of relevance to this technology appraisal.
- According to the data sources that inform the CPRD cohort, only prescriptions issued in primary care would have been captured. The company do not discuss the implications of this, i.e. whether any disopyramide prescriptions issued in secondary or tertiary care would have been missed.
- No information is provided on the reliability of the data extraction process; the company do not report the number of people who extracted data, their affiliations, and whether any data checking was done.
- The company state that the analysis was protocol-based but the protocol was not provided with the company's response. It is unclear whether protocol-approved methods were followed.

We note that whilst the CPRD data suggest that the annual rate of disopyramide prescriptions appears to have been relatively stable over time (Table 5 in company Appendix 1), the six consultee submissions that comment on the company's response to TE disagree about the extent of disopyramide availability in recent years. The EAG are unclear whether the heterogeneity of consultee responses reflects variation in clinicians' procurement routes for disopyramide (which might mean that some clinicians or centres were more easily able to access disopyramide, or were more aware of drug availability issues, than others).

Systematic literature review to identify disopyramide studies potentially relevant to an indirect treatment comparison (ITC) with mavacamten

The company's response to TE provides a systematic literature review (SLR) of clinical effectiveness studies that included disopyramide as an intervention or comparator (company Appendix 2). The SLR was conducted in May 2022, shortly prior to the EAG's updated searches (July 2022). The SLR appears comprehensive with appropriate methods, although the review is large (described as a "Global SLR") and includes a range of therapies for obstructive HCM besides disopyramide. The disopyramide studies identified are listed in company Appendix 3. However, of the 10 listed disopyramide studies [1-10] it is unclear why a study by Hamada et al. 2016[10] has been included since the study was on cibenzoline, not disopyramide (NB this study is incorrectly labelled Hamada 1997 in company Appendix 3). The disopyramide studies have various limitations, including being retrospective, having small sample sizes, having short duration, being relatively old and/or being conducted outside the UK. The company conducted a systematic feasibility assessment to ascertain which if any of the included disopyramide studies could inform an ITC comparing disopyramide to mavacamten for the outcome change in NYHA class (company Appendix 3). Only one study, by Sherrid et al. 2013,[4] reports NYHA class at a specified timepoint, but the population is limited to responders to disopyramide (i.e. patients not eligible for septal reduction therapy) so has uncertain generalisability to the full population of patients who would receive disopyramide in clinical practice. The EAG agree with the company that the identified disopyramide studies are unsuitable for inclusion in an ITC and we are not aware of any alternative studies that would reduce uncertainty in the relative clinical effectiveness of mavacamten versus disopyramide.

Comparison with model assumptions about use of disopyramide

In their economic model, the company assume that disopyramide is used after escalation from BB or CCB monotherapy, for a fixed period prior to septal reduction therapy (SRT), see Table 2 below. Based on the initial distribution of NYHA class used in the model, the estimated proportion of patients who escalate from BB/CCB monotherapy to disopyramide + BB/CCB per year would be approximately [redacted]. This is broadly consistent with the company's CPRD estimate of approximately [redacted] of patients with obstructive HCM having at least one prescription for disopyramide per year, but likely to be an underestimate for the population who would be eligible and for mavacamten: patients who remain symptomatic (NYHA class II to IV) despite treatment with BB, and possibly also CCB (EAG report section 2.2.5).

Table 2 Assumptions about use of disopyramide in the company's model

	NYHA I	NYHA II	NYHA III	NYHA IV	Total
Initial distribution by NYHA class [a]	0%	72.9%	27.1%	0%	100%
Assumed proportion on BB/CCB escalating to disopyramide per year [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assumed mean duration of disopyramide treatment prior to SRT (months) [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Produced by the EAG from data in the company's model

[a] Baseline distribution of NYHA class from EXPLORER-HCM

[b] Estimated from company expert elicitation (CS Appendix O)

2.2 Key Issue 2 – Uncertain efficacy of mavacamten in patients without a sarcomere mutation

Clinical evidence

The company provide a plausible argument why the mode of action of mavacamten would not be expected to differ between sarcomere-positive patients and those without a sarcomere mutation. However, as noted by the company, there is evidence that cardiac pathology differs between sarcomere-positive and sarcomere-negative patients.[11 12] Such pathological differences might influence responses to pharmacotherapies.

The company present evidence from EXPLORER-HCM which suggests there was [redacted] in the efficacy of mavacamten between sarcomere-positive and sarcomere-negative subgroups for reduction in LVOT gradients (company response Figure 1), improvements NYHA class (company response Figure 2), and change in pVO_2 (company response Figure 3). However, results for the KCCQ-CSS outcome suggest that whilst [redacted] (company response Figure 4).

The company's response to TE does not mention the impact of mavacamten on sarcomere-positive and sarcomere-negative patients for the primary outcome of EXPLORER-HCM (a combination of peak oxygen consumption [pVO_2] and NYHA class improvement). However, the EXPLORER-HCM clinical study report (CSR) (section 8.3.1.1) states "[redacted]

[redacted]."

In addition to the results from EXLORER-HCM the company present data from EXPLORER-LTE which suggest that the effect of mavacamten on improvement in NYHA class (company response Figure 5) and on resting LVOT gradient (company response Figure 6) [redacted]. The company briefly also discuss data from VALOR-HCM, citing the VALOR-HCM CSR. However, the sarcomere mutation subgroup data reported in Figures 7.2.4.1-1 to 7.2.4.2-3 of the VALOR-HCM CSR do not provide effect estimates for all the subgroups.

Overall, the results from EXPLORER-HCM suggest that there may be differences in the efficacy of mavacamten between sarcomere-positive patients and sarcomere-negative patients but these may not be consistent in direction across all outcomes, or applicable to all outcomes. Due to the relatively small sizes of the subgroups and lack of statistical power (see Additional Issue 5 below) there is uncertainty around these findings and it is difficult to draw firm conclusions about whether there would be implications for the cost-effectiveness of mavacamten in these subgroups.

Three of the six consultee responses to TE commented on whether the efficacy of mavacamten would be expected to differ between sarcomere-positive and sarcomere-negative patients. These consultees concurred that data are currently insufficient to draw firm conclusions, due to the relatively small subgroup sizes in the clinical trials.

Cost-effectiveness subgroup analysis

As the subgroup analyses of EXPLORER-HCM trial data do not provide evidence of a consistent difference in the treatment effect of mavacamten by sarcomere mutation status, cost-effectiveness subgroup analysis would not be appropriate. In particular, we note the lack of evidence for a subgroup effect for the outcome of change in NYHA class (company TE response Figure 2), which is the outcome that drives the health economic model.

2.3 Key Issue 3 – Post-authorisation safety monitoring of mavacamten

Clinical opinion on resource availability for post-authorisation monitoring

It is unclear whether the intensity of post-authorisation safety monitoring of mavacamten as specified in the draft SmPC would be feasible in the NHS given current shortages of sonographers and lengthy echocardiography waiting lists. The company contacted three expert centres to obtain clinical opinion on the feasibility of the monitoring that would be required if mavacamten were to be recommended by NICE. Two centres responded and the company held telephone interviews with them (company response Appendix 6). The company have not identified these two centres or the staff they interviewed and do not state whether the responses received are the personal opinions of individuals or reflect a consensus in each centre. The feedback received differed between the two centres, suggesting that consultation with a wider number of cardiomyopathy centres may be advisable to obtain a more complete picture of the resource implications of post-authorisation mavacamten monitoring in the NHS.

Of the six consultee responses to TE received by NICE, five commented on the resource availability in the NHS for echo monitoring if mavacamten were to be recommended by NICE. The consultees concurred that additional resources would be required. One consultee suggested additional echo monitoring might be funded by cost savings from a reduction in the need for septal reduction therapies. Another consultee suggested a need to prioritise echo surveillance for obstructive HCM patients in a similar way to how oncology clinics prioritise cardiac screening of patients who receive cardiotoxic chemotherapy. The remaining three consultees commented only that resourcing of mavacamten monitoring would need to be considered from a commissioning perspective.

Monitoring assumptions in the health economic model

The draft SmPC for mavacamten submitted with the company's Addendum of 19 October 2022 specifies that [redacted] assessments should be conducted for patients on a maintenance dose:

[redacted]

[redacted]

In their Addendum base case, the company assumed an average of [redacted] assessments in year 1 for patients on mavacamten, each assessment comprising an echocardiogram and a cardiovascular outpatient visit. From year 2 onwards, the company assumed that monitoring for patients on mavacamten would be the same as for standard treatment: [redacted] echocardiograms per year for NYHA classes I to IV respectively; and [redacted] cardiovascular outpatient visits per year for NYHA classes I to IV. For the EAG analysis, we preferred to assume that the [redacted] assessments per year would continue until mavacamten was discontinued because the draft SmPC does not specify if or when additional monitoring should be stepped down.

In their TE response, the company note that a more correct interpretation of the draft SmPC monitoring requirements is [redacted] assessments in the first year (which includes additional tests for treatment initiation and dose adjustment), and then [redacted] assessments per year ([redacted]) for patients on a maintenance dose. The company report results from interviews with five clinical experts (company response Appendix 4): four of whom stated that they would expect additional monitoring for a patient on a maintenance dose of mavacamten to continue for [redacted], and one expert stated that they would expect additional monitoring to continue for [redacted]. In their post-TE base case, the company assume [redacted] assessments [redacted], [redacted] assessments ([redacted]) in [redacted], and standard monitoring from [redacted] onwards. The generalisability of the clinicians' opinions reported in company response Appendix 4 is somewhat uncertain, as there is no indication of the type and location of the centres or any potential conflicts of the experts consulted.

The EAG agree that the draft SmPC indicates [redacted] assessments in the first year and [redacted] assessments per year ([redacted]) for patients on a maintenance dose. Based on the wording in the current draft SmPC, we prefer to maintain our assumption for the purposes of costing that the [redacted] assessments would continue from year 2 onwards. We accept that this is a conservative assumption, and that the frequency of monitoring in practice may be reduced over time for some or all patients. However, this is uncertain and additional monitoring for mavacamten could have a high impact given existing pressures on NHS capacity and waiting times for echocardiography and cardiovascular outpatient services. We report scenario analyses for a range of assumptions about the duration of enhanced monitoring (see sections 3.2 and 3.4).

2.4 Key Issue 4 – Imbalance in follow up duration for transition probabilities

The company maintain their view that transition probabilities for the initial stage of the economic model should be based on EXPLORER-HCM data up to the end of trial assessment (week 30) for the mavacamten arm, and up to week 46 for the comparator arm including data from the end of study assessment (week 38) and from the baseline assessment for the long-term safety extension study EXPLORER-LTE (week 46). The study designs and assessment timepoints for the EXPLORER-HCM and EXPLORER-LTE studies are shown in CS Figures 7 and 8, and the distribution of NYHA class in these studies is illustrated in CS Figure 23. The study drugs were withdrawn at week 30, and the treatment groups were unblinded at week 38.

In the model, the first 30 weeks of data in both arms are used to estimate NYHA class transitions up to the point of assessment for response, prior to entry to the long-term Markov model. The remaining 16 weeks of data for the comparator arm are used to model NYHA transitions in the first four model cycles in the long-term model, while the mavacamten arm uses assumptions about long-term progression (see section 2.5 below). The company argue that this approach makes use of the longest continuous data that are available for each treatment arm.

The EAG have concerns about the potential for bias in the decision to use different durations of follow up for the treatment arms. There is potential for informative censoring as patients move from the randomised trial into the LTE study. Completion rates for NYHA data were good during the trial: [redacted] out of 123 patients in the mavacamten arm provided NYHA data at week 30, and [redacted] out of 128 patients in the comparator arm (unimputed data from company clarification response Table 4). The proportions of patients continuing to LTE study enrolment were also good: 115 from the mavacamten arm and 116 from the comparator arm. However, the numbers of transition events that govern changes in NYHA class are low, and the changes that occurred between week 30 and 46 in the comparator arm are carried forward through remaining time horizon.

The company provide an update of results from the EXPLORER-LTE trial in their TE response, Figures 7 and 8. They report that this supports an assumption of [redacted]. The reduced sample size at [redacted] makes it difficult to interpret these data.

2.5 Key Issue 5 – Long-term rates of progression

The company's original base case assumed that NYHA class would remain constant after an initial period of 30 weeks for the mavacamten arm, or 48 weeks for the comparator arm (CS section B.3.3.2.3). The CS Addendum retained the base case assumption of no long-term progression of NYHA class, but reported two alternative scenarios (CS Addendum section 3.2):

1) A natural background rate of progression of 4.55% per year for all treatments, estimated from a prospective cohort study by Maron et al. 2016[13]; and
2) A lower annual rate of progression during treatment with mavacamten ([redacted]) than with BB/CCB monotherapy, disopyramide or after SRT (4.55%).

We incorporated the company's first progression scenario (4.55% per year for all treatments) in EAG the base case. This decision was based on feedback from clinical experts that progression in NYHA class is plausible, and the available evidence from the Maron et al. 2016 study (EAG report section 4.2.3.2). Following technical engagement, the company have also revised their base case to include this assumption.

In response to an EAG clarification question, the company reported that they had initiated a SLR on long-term progression of NYHA class in obstructive HCM, with results expected in early 2023. This is important to determine whether there is any other data to inform assumptions about progression. The SLR is still in ongoing, but the company have provided some new evidence in the form of clinical opinion from interviews with five clinical experts (company TE response Appendix 1) and results of a sub-study of VALOR-HCM trial data on the effect of mavacamten on diastolic function (Cremer et al. 2022).[14] The interviews with clinicians are generally supportive of the 4.55% progression rate from the Maron et al. 2016 study as being [redacted] of the rate they see in practice, although one respondent considered that [redacted].

The cardiac magnetic resonance imaging (CMR) sub-study of EXPLORER-HCM (CS Appendix M and Saberi et al. 2021)[15] and the VALOR-HCM sub-study investigating the effect of mavacamten on diastolic function (Cremer et al. 2022)[14] are described by their authors as exploratory and 'hypothesis-generating'. These studies are suggestive of a positive effect of mavacamten on cardiac structure and function, but the samples were small (n=35 in the EXPLORER-HCM CMR study; and n=98 in the VALOR-HCM sub-study); and the results may be susceptible to confounding, as multivariate analysis was limited.[14]

For the EAG base case, we retain the assumption of long-term progression of NYHA, based on the Maron et al. 2016 study (4.55% per year), applied equally across all treatments in the model (mavacamten, BB/CCB monotherapy, disopyramide and SRT). However, we note that uncertainty remains over the background rate of progression and over whether mavacamten or other treatments might slow progression relative to standard care. We therefore report a range of EAG scenario analyses, including no long-term progression in NYHA class and differential rates of progression between treatments (see Table 7 below).

2.6 Key Issue 6 – Effect of treatments on mortality

We agree that there is strong evidence that mortality is higher for people with obstructive HCM than in the general population, and that there is an association between NYHA class and mortality. However, there is a lack of direct evidence of a beneficial effect of treatment on mortality: it has not been demonstrated that a treatment-related improvement in NYHA class causes a reduction in mortality.

The company, consultees responding to technical engagement and clinical experts advising the EAG agree on this lack of direct evidence for a mortality benefit from mavacamten or other treatments for obstructive HCM. But there is a difference of opinion on whether a mortality benefit can be inferred and should be included in the economic model. The company argues that use of a suitable surrogate can be acceptable in health technology assessment and the respondent for NHS England argues that the CMR sub-study of EXPLORER-HCM data provides such data, because left ventricular mass is a robust prognostic marker and could potentially be used for modelling. Other commentators argue that there is insufficient evidence to infer a causal link from changes in NYHA status to mortality and that estimates of cost-effectiveness should not assume a mortality benefit.

The company assume that treatment-related changes in NYHA status impact on mortality in their base case analyses. Mortality in NYHA class I is assumed to be the same as for the general population (adjusted for age and sex). Hazard ratios (HRs) for NYHA class II to IV are then defined relative to NYHA class I. In their previous base case, the company used HRs for mortality by NYHA class estimated from the Humedica Electronic Medical Records (EMR) database, as reported in an abstract by Wang et al. 2022 (CS Table 30).[16] The post-TE company base case uses mortality HRs from a new analysis that uses additional EMR data from the Market Clarity dataset (company TE response Table 2). The company state that the Market Clarity data are more representative of the population with obstructive HCM

than the previous Humedica dataset, as the latter was restricted to a population with a diagnosis of acute myocardial infarction, unstable angina or heart failure. We are unable to verify the details of the Market Clarity analysis because the unpublished manuscript in preparation by Wang et al. 2023 (reference 33 in the company's TE response), was not included with reference pack that we received from the company.

Uncertainty over the inclusion of treatment effects on mortality in the economic analysis has not been resolved. We therefore maintain our previous stance on this issue, following the company's base case in the EAG preferred analysis (section 3.3), but reporting two additional scenarios that do not assume a treatment effect on mortality (EAG scenarios 4 and 5 as described in section 6.1 of the EAG report):

- The first scenario, which was coded in the company's model, assumes no increased mortality risk in the obstructive HCM population (HR = 1 for all NYHA classes, so general population life tables are applied). This is not a plausible scenario but was included to illustrate the overall impact of mortality on model outcomes.
- The second scenario uses a pooled mortality HR across all NYHA classes to reflect the overall mortality risk for the cohort with obstructive HCM relative to the general population, but without assuming a causal link between changes in NYHA class and mortality. The pooled HR in our previous base case (HR = 1.85) was calculated as an average of the Wang et al. 2022 HRs (CS Table 30) weighted by the initial distribution of NYHA class (CS Table 24). We update the pooled HR for this scenario using the Market Clarity estimates (HR = [redacted]), see section 3.4.

2.7 Additional issues

2.7.1 Additional issue 1 - Calculation of utilities

The EAG agree with the change in the company's base case to include a general population cap on utilities, as in our preferred analysis. Although people may sometimes report health-related quality of life better than general population norms after a health improvement, this 'feel-good factor' is likely to be temporary.

2.7.2 Additional issue 2 - Alternative approach to calculating transition probabilities

As noted in section 4.2.3.1 of the EAG report, the input parameters required to calculate costs and QALYs are all constant in the first year, and treatment discontinuation and escalation are assumed not to occur before week 30. Thus our suggestion was to model the 30-week short-term segment of the model as a decision tree, rather than as a series of

Markov cycles. However, in the absence of evidence of a difference in change in NYHA class for sarcomere mutation subgroups (Key Issue 2), there is no real need for this change.

2.7.3 Additional issue 3 - Time on treatment for non-responders

We agree that the company's new discontinuation scenario provides a better way of testing the impact of delay in assessment of lack of response at 30 weeks than the EAG scenario. However, our comment that "delays in seeking or obtaining NHS appointments when symptoms get worse could cause a lag in discontinuation of mavacamten" was not intended to apply to discontinuation at the 30 week assessment (EAG report section 4.2.4). If a 'stopping rule' to discontinue treatment due to lack of response at a fixed timepoint of 30 weeks, it would be feasible to schedule an appointment to assess response at this time. Uncertainties over the impact of appointment delays relate more to unexpected changes after 30 weeks, such as a worsening of symptoms with NYHA class progression or the onset of an adverse event. Neither the EAG nor company discontinuation scenarios are sufficiently flexible to capture the impact of such effects.

2.7.4 Additional issue 4 - Clinically meaningful changes in pVO2

The EAG are unclear why the company have included Additional Issue 4 in their TE response. The company's interpretation that an improvement in $pVO_2 \geq 1$ mL/kg/min is considered clinically meaningful, citing Coats et al. 2015 [17] as the source, has already been stated in CS section B.2.3.1.1.1 and in EAG Report section 3.4.1.

2.7.5 Additional issue 5 - Clarification on statistical analysis in EXPLORER-HCM

In EAG report section 3.5.4 (page 52) the EAG commented that "The CS does not state whether the pre-specified subgroup analyses were powered statistically to detect specific differences in the outcomes tested." The company have clarified that "EXPLORER-HCM was neither designed nor statistically powered to detect significant differences in subgroups, and the results were not adjusted for multiple statistical testing."

2.7.6 Additional issue 6 - Correction to minor error in utilities calculation

The company noted an error in the calculation of age-adjustments in the company model. We agree with the company's correction of this error and incorporate the revision in EAG analyses reported below. This has a small impact on the ICERs.

3 Updated cost-effectiveness results

The following sections summarise and critique results based on three versions of the company's economic model:

- The model received on 19th October 2022, submitted with the company's CS Addendum (henceforth, referred to as the 'company addendum model')
- The model received on 27th February 2023, submitted with the company's response to TE (henceforth, referred to as the 'company post-TE economic model')
- The model received on 30th March 2023, submitted with a correction to the company post-TE model (referred to as the 'company post-TE corrected model')

3.1 Company's post technical engagement base case analysis

The company define changes to their base case in Table 4 of their response to TE. These include:

- *Key issue 3*: Changes to the monitoring schedule for mavacamten
- *Key issue 5*: Inclusion of long-term progression of NYHA class
- *Key issue 6*: Effects of treatment on mortality from Market Clarity EMR analysis
- *Additional issue 1*: Capping of utility at general population values
- *Additional issue 6*: Correction to age adjustment of utilities

The cumulative impact of changes to the company's revised base case, including the additional correction to the life table for women, is shown in Table 3 below (company TE response correction Table 2). The post-TE base case results in a reduction in the ICER from £29,953 to £19,401. The change that has the biggest impact on the ICER is the inclusion of an ongoing rate of NYHA class progression (4.55% per year for all treatments). This reduces total QALYs in both arms and the difference in QALYs between the arms. However, the lower QALY gain with mavacamten is more than offset by an increase in healthcare costs in the standard care arm, as the cohort spends more time in NYHA classes III and IV (see Figure 3 and Figure 4 in the Appendix below).

The company report sensitivity and scenario analyses for their post-TE base case in the correction to their TE response. They report a probabilistic ICER of £19,292 (with 1,000 iterations), similar to the deterministic ICER. The EAG replicated this finding. The tornado plot for the deterministic sensitivity analyses shows that the new base-case analysis is most sensitive to the annual rate of progression in NYHA class II, the annual rate of mavacamten discontinuation after week 30, and rates and unit costs for inpatient stays. Tables 9 and 10 in

the company's TE response correction show results for a range of scenarios applied to the company's post-TE base case, all of which have a modest impact on the ICER.

Table 3 Cumulative effect of changes to the company's base case

Scenario	Treatment	Total costs	Total QALYs	Increm. costs	Increm. QALYs	ICER (£/QALY)
Company addendum base case (19/10/2022)	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£29,953
	BB/CCB monotherapy	[redacted]	[redacted]			
+ Correction to age adjustment of utilities (additional issue 6)	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£29,826
	BB/CCB monotherapy	[redacted]	[redacted]			
+ Correction to the life data table for women (corrected model 30/03/2023)	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£30,139
	BB/CCB monotherapy	[redacted]	[redacted]			
+ Changes to the monitoring schedule for mavacamten (key issue 3)	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£30,676
	BB/CCB monotherapy	[redacted]	[redacted]			
+ Inclusion of long-term progression (key issue 5)	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£17,963
	BB/CCB monotherapy	[redacted]	[redacted]			
+ Effects on mortality from Market Clarity database (key issue 6)	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£17,597
	BB/CCB monotherapy	[redacted]	[redacted]			
+ Capping of utility at general population values (additional issue 1)	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£19,401
	BB/CCB monotherapy	[redacted]	[redacted]			
Company's post-TE base case	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£19,401
	BB/CCB monotherapy	[redacted]	[redacted]			

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; BB, beta blockers; CCB, calcium channel blockers
Source: Company TE response correction Table 1 (30/03/23), results checked by the EAG

3.2 Additional EAG scenario analysis on the company's post-TE base case

We report results from some additional scenario analyses applied to the company's revised base case in Table 4 below. One of these scenarios increases the ICER above £30,000 per QALY gained; the use of transition probabilities for the comparator arm from the EXPLORER-HCM trial only up to week 30 (as in the mavacamten arm). The EAG scenario with a fixed HR for mortality in the obstructive HCM population relative to the general population applied equally across all NYHA classes increases the ICER to £28,961 (HR = [redacted], estimated from the Market Clarity results reported in Table 2 of the company's TE response, weighted for the baseline distribution of NYHA class).

Table 4 EAG additional scenario analysis on the company's post-TE base case

Scenario	Treatment	Total costs	Total QALYs	Increm. costs	Increm. QALYs	ICER (£/QALY)
Company's post-TE base case	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£19,401
	BB/CCB monotherapy	[redacted]	[redacted]			
Transition probabilities for comparator arm						
Trial-based TPs until week 30 (same as for mavacamten arm)	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£31,779
	BB/CCB monotherapy	[redacted]	[redacted]			
Mavacamten discontinuation						
80% of those in NYHA class II and III with no improvement at week 30 discontinue ([redacted] in class II and [redacted] in class III)	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£22,195
	BB/CCB monotherapy	[redacted]	[redacted]			
Mortality						
No increased risk by NYHA class (general population mortality)	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£19,328
	BB/CCB monotherapy	[redacted]	[redacted]			
No treatment effect on mortality: fixed HR for population [redacted] (Market Clarity) [a]	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£28,961
	BB/CCB monotherapy	[redacted]	[redacted]			
Long-term natural progression of NYHA class						
2% annual progression for all treatments (reduced from 4.55%)	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£23,713
	BB/CCB monotherapy	[redacted]	[redacted]			

Frequency of monitoring for mavacamten (ECHO and CV outpatient visit)						
[redacted] visits in year 1; standard care from year 2	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£19,057
	BB/CCB monotherapy	[redacted]	[redacted]			
[redacted] visits in year 1; years 2-5 every [redacted]; then standard care	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£20,719
	BB/CCB monotherapy	[redacted]	[redacted]			
[redacted] visits in year 1; every [redacted] from year 2	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£23,197
	BB/CCB monotherapy	[redacted]	[redacted]			
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; BB, beta blockers; CCB, calcium channel blockers; ECHO echocardiogram; HR hazard ratio; TP transition probability [a] Weighted mean based on baseline distribution of NYHA class and HRs from Market Clarity study Source: produced by the EAG from the company's post-TE corrected model (30/03/23)						

3.3 EAG's preferred assumptions after technical engagement

We agree with the following changes to the company's base case introduced in their response to TE:

- *Additional issue 6*: Correction to age adjustment of utilities
- *Additional issue 1*: Capping of utility at general population values
- *Key issue 5*: Long-term progression (4.55% per year for all treatments)
- *Key issue 6*: Revised estimates of mortality risks by NYHA class (Market Clarity)
- *The correction to the life table for women, as applied in the company's post-TE correction of 30 March 2023.*

However, we include two different assumptions in our preferred analysis:

- *Key issue 4*: Transition probabilities based on equal duration of follow-up of randomised patients in the EXPLORER-HCM arms: 30 weeks for both BB/CCB and mavacamten + BB/CCB. See section 2.4 above.
- *Key issue 3*: Monitoring schedule for mavacamten. As explained in section 2.3 above, we prefer to assume [redacted] assessments in the first year and [redacted] assessments ([redacted] assessments per year) from year 2 onwards.

Results for the EAG's preferred analysis are shown in Table 5 below. The changes to the company's base case increase the ICER to £37,088 per QALY gained.

Table 5 Cumulative results for the EAG's preferred model assumptions

Scenario	Treatment	Total costs	Total QALYs	Increm. costs	Increm. QALYs	ICER (£/QALY)
Company's post-TE base case	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£19,401
	BB/CCB monotherapy	[redacted]	[redacted]			
+ TP estimates for 30 weeks from both trial arms (key issue 4)	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£31,779
	BB/CCB monotherapy	[redacted]	[redacted]			
+ Monitoring, [redacted] times in year 1, then [redacted] (key issue 3)	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£37,088
	BB/CCB monotherapy	[redacted]	[redacted]			
EAG's post-TE base case	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£37,088
	BB/CCB monotherapy	[redacted]	[redacted]			
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; BB, beta blockers; CCB, calcium channel blockers						

The EAG ran the PSA with the EAG's post-TE base case (Table 6 below). The difference between the deterministic and probabilistic ICER is [redacted], with a marginal difference in QALYs. Considering the EAG post-TE base case, mavacamten + BB/CCB treatment is predicted to be cost-effective in [redacted] of the simulations at a £30,000 WTP threshold, as we can observe in Figure 1 and Figure 2.

Table 6 EAG post-TE PSA results

PSA	Incremental costs	Incremental QALYs	ICER (£/QALY)
EAG post-TE base case	[redacted]	[redacted]	£37,088
EAG post-TE PSA results	[redacted]	[redacted]	£34,693
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years			

Figure 1 Cost-effectiveness plane for incremental costs and QALYs (EAG base case)

Figure 2 . Cost-effectiveness acceptability frontier (EAG base case)

3.4 Scenario analyses with the EAG's preferred assumptions

Table 7 below presents results for selected scenario analyses applied to the EAG's post-TE base case analysis. We include the EAG additional scenarios from Table 4 above, all of the company's scenarios defined in Tables 1 and 9 of the company's TE response correction, as well as selected scenarios from Table 10 which are subject to uncertainty and have an impact on the results. Considering the post-trial data to estimate transition probabilities for the BB/CCB monotherapy arm produced the largest reduction in the ICER, from £37,088 to £24,900 (until week 38) and £23,197 (until week 46). All other scenarios resulted in ICERs greater than £30,000 per QALY gained. The scenarios with the largest impact on the ICER were associated with mortality, with the ICER between £33,118 and £70,547.

Table 7 Scenario analysis on the EAG revised base case

Scenario	Treatment	Total costs	Total QALYs	Increm. costs	Increm. QALYs	ICER (£/QALY)
EAG's post-TE base case	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£37,088
	BB/CCB monotherapy	[redacted]	[redacted]			
Transition probabilities for comparator arm						
Trial-based TPs until week 38	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£24,900
	BB/CCB monotherapy	[redacted]	[redacted]			
Trial-based TPs until to week 46	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£23,197
	BB/CCB monotherapy	[redacted]	[redacted]			
Frequency of monitoring for mavacamten (echocardiography and CV outpatient visit)						
Year 1 [redacted] assessments; years 2 to 5 [redacted]; assessments; then standard care	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£33,623
	BB/CCB monotherapy	[redacted]	[redacted]			
Year 1 [redacted] assessments; years 2 & 3 [redacted]; assessments; then standard care	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£32,594
	BB/CCB monotherapy	[redacted]	[redacted]			
Year 1 [redacted] assessments; year 2 [redacted]; assessments; then standard care	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£31,983
	BB/CCB monotherapy	[redacted]	[redacted]			
Year 1 [redacted] assessments; year 2 [redacted]; year 3: [redacted]; weeks, then standard care monitoring	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£31,998
	BB/CCB monotherapy	[redacted]	[redacted]			
Mavacamten discontinuation						
[redacted] in NYHA II/III with no response at week 30 ([redacted] class II and [redacted] class III), [redacted] delay to week 38	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£37,168
	BB/CCB monotherapy	[redacted]	[redacted]			
[redacted]% discontinue due to lack of response in NYHA III at week 30 (same as in class II)	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£38,593
	BB/CCB monotherapy	[redacted]	[redacted]			
1.4% per year discontinue due to SAEs after week 30	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£41,776
	BB/CCB monotherapy	[redacted]	[redacted]			

Scenario	Treatment	Total costs	Total QALYs	Increm. costs	Increm. QALYs	ICER (£/QALY)
Mortality						
No increased mortality risk HR = 1 NYHA classes I to IV	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£58,431
	BB/CCB monotherapy	[redacted]	[redacted]			
Increased mortality but no treatment effect: HR = [redacted] for NYHA classes I to IV [a]	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£70,547
	BB/CCB monotherapy	[redacted]	[redacted]			
Increasing mortality risk by NYHA class (Humedica EMR, Wang et al. 2022) [b]	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£40,110
	BB/CCB monotherapy	[redacted]	[redacted]			
Increasing mortality risk by NYHA class (unadjusted RRs from SHaRe analysis [18]) [b]	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£33,118
	BB/CCB monotherapy	[redacted]	[redacted]			
Increasing mortality risk by NYHA class (adjusted HRs from SHaRe. CS Appendix N) [b]	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£41,000
	BB/CCB monotherapy	[redacted]	[redacted]			
Long-term natural progression of NYHA class						
No progression	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£51,247
	BB/CCB monotherapy	[redacted]	[redacted]			
2.5% annual progression for all treatments	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£41,688
	BB/CCB monotherapy	[redacted]	[redacted]			
[redacted] per year on mavacamten; 4.55% on all other treatments	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£33,248
	BB/CCB monotherapy	[redacted]	[redacted]			
Health state utilities						
EXPLORER-HCM utilities with no general population utility cap	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£33,638
	BB/CCB monotherapy	[redacted]	[redacted]			
Exclude age adjustment	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£34,214
	BB/CCB monotherapy	[redacted]	[redacted]			
Utilities from Göhler *et al*, 2009 [19]	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£35,488
	BB/CCB monotherapy	[redacted]	[redacted]			

Scenario	Treatment	Total costs	Total QALYs	Increm. costs	Increm. QALYs	ICER (£/QALY)
Source: EAG analyses using the company's post-TE economic model ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; BB, beta blockers; CCB, calcium channel blockers; ECHO echocardiogram; HR hazard ratio; RR relative risks; TP transition probability [a] Weighted mean based on baseline distribution of NYHA class and HRs from Market Clarity study [b] Mortality for NYHA classes II to IV adjusted relative to NYHA class I using HRs/RRs from sources cited in Table 2 of the company's TE response						

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Appendix - Breakdown of costs and outcomes from the economic model

Figure 3 Health state occupancy, company's post-TE base case without progression (left); with progression (right)

Figure 4 Disaggregated costs and outcomes, company's post-TE base case without progression (left); with progression (right)

Figure 5 Health state occupancy: company's post-TE base case (left); and EAG post-TE base case progression (right)

Figure 6 Disaggregated costs and outcomes: company's post-TE base case (left); and EAG post-TE base case progression (right)

Overview

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Centre (EAC) report. Further detail for each consideration is available within the separate tabs.

Whilst a rationale is provided, in general the ratings for each area:
Green - No key issues identified
Amber - Either outstanding issues that the Managed Access team are working to resolve, or subjective judgements are required from committee / stakeholders (see key questions)
Red - The managed access team does not consider this topic suitable for a managed access recommendation.

The Managed Access Team may not assess other areas where its work has indicated that topic is not suitable for a managed access recommendation

The feasibility assessment indicates whether the Managed Access team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access team.

Topic name: **Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy**
Topic ID: **3928**
Managed Access Lead: **Milena Wobbe**
Date of assessment(s): **23/02/2023**

Is Managed Access appropriate - Overall rating	Comments / Rationale
Committee judgement required	Further evidence collected during a period of managed access would not resolve all the uncertainties that have a high impact on the cost-effectiveness estimates. Longer-term clinical evidence of mavacamten from the EXPLORER-LTE trial would provide further evidence on long-term rates of progression, but would not provide any evidence to support any relative differences between treatments. The EXPLORER-LTE trial is expected to report in 2026.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	The IMF is targeted to the most promising medicines. The company consider that mavacamten is suitable as it addresses a high unmet need and is a first-in-class therapy that has demonstrated efficacy and safety in a large randomised controlled trial for obstructive HCM. NHSE recognises the high unmet meet for these patients and agrees it would be a potential candidate for the IMF.
Is it feasible to collect data that could sufficiently resolve key uncertainties?	Unclear	Further evidence collected during a period of managed access would not resolve all the uncertainties that have a high impact on the cost-effectiveness estimates. Longer-term clinical evidence of mavacamten from the EXPLORER-LTE trial would provide further evidence on long-term rates of progression, but would not provide any evidence to support any relative differences between treatments. The EXPLORER-LTE trial is expected to report in 2026.
Can data collection be completed without undue burden on patients or the NHS system	Yes	An ongoing extension trial could be the main source for further evidence generation.
Are there any other substantive issues (excluding price) that are a barrier to a MAA	No	Implementing the echocardiograms as per SmPC may be challenging to implement in the NHS currently. However, this relates to safety monitoring and is not a barrier to managed access data collection. Furthermore, as the technology is expected to be prescribed in specialist centres, it is thought that monitoring would occur there. Patient numbers are expected to be small and therefore the additional burden on specialist centres is expected to be manageable on top of the regular monitoring already happening.

Further managed access activity	Rating	Comments / Rationale
pre-committee feasibility assessment update	Unclear	The managed access team will continue to explore the suitability of managed access with the company prior to ACM1, and if applicable update the document.
pre-committee data collection working group	Unclear	
pre-committee patient involvement meeting	No	

Key questions for committee if Managed Access is considered	
1	Would longer-term clinical evidence of mavacamten from the EXPLORER-LTE trial sufficiently resolve uncertainty on long-term rates of progression?
2	Are the remaining uncertainties that would not expected to be resolved during a period of managed access be a barrier to decision-making at the guidance update at the currently agreed price?

Early Identification for Managed Access

Explanation on criteria
These criteria should be met before a technology can be recommended into managed access through the CDF or IMF. To give a 'high' rating, the Managed Access Team should be satisfied that it can be argued that the technology meets the criteria. Companies interested in managed access must engage early with NICE and demonstrate that their technology is suitable for the managed access.

Date agreed with NHSE	17/02/2022

Is the technology a potential candidate for managed access?	
Rating	**Rationale**
Yes	The technology addresses a high unmet need. However, it is an adjuvant treatment to standard care and that the majority of participants in the pivotal trial did not reach the primary outcome. It is expected that this technology is going to be NHSE commissioned, and prescribed in specialist centres.

IMF prioritisation criteria	Supporting Evidence
Potential to address a high unmet need	No pharmacological treatment options for obstructive hypertrophic cardiomyopathy (oHCM) is currently available. However, symptomatic relief is available, e.g. to control blood pressure, prevent blood clots,… The clinical pathway according to the CS does not alter significantly with the presence of mavacamten and mavacamten would not be first line but adjuvant therapy to standard care. Neither the company or EAG consider the topic meets the criteria for severity weighting.
Potential to provide significant clinical benefits to patients	Mavacamten is expected to reduce symptoms and improve function in people with symptomatic oHCM, increasing quality of life. Although a significant proportion of EXPLORER-HCM participants did not meet the primary outcome (see uncertainty EAG2), the patients who would benefit could see a significant health improvement.
represents a step-change in medicine for patients and clinicians	While it would be beneficial to patients whose symptoms are not adequately controlled with standard care or who are contraindicated, mavacamten is expected to be an adjuvant therapy to standard care, to aid symptom management. Due to the high unmet need, it could be seen as a step-change.
new evidence could be generated that is meaningful and would sufficiently reduce uncertainty	See uncertainties tab

Uncertainties

Explanation

This page details the Managed Access Team's assessment on whether data collection could sufficiently resolve key uncertainties through further data collection within managed access. The overall assessment is the key judgement from the Managed Access Team.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether the further data collection could lead to a positive NICE decision at the point the technology exits managed access. For this reason individual uncertainties that have a higher impact on the ICER have a greater impact on the overall rating.

Further detail is available on each uncertainty identified primarily informed from a company's managed access proposal, the External Assessment Group (EAG) report, judgements from the NICE Managed Access Team, and where available directly from NICE committee deliberations. The likelihood that data could sufficiently resolve each specific outcome is informed both by the expected primary data source in general (as detailed in the separate tab) and specifically whether the data collected is expected to sufficiently resolve that uncertainty.

Likelihood data collection could sufficiently resolve key uncertainties?	
Rating	**Rationale**
Medium	The company has suggested data collection in the IMF to enable longer-term evidence of clinical effectiveness, although the impact on the ICER is unclear. Data collection could be possible through RWE datasets to collect data on the use of a comparator, although this data is already available without the use of managed access. Other uncertainties, including those with a known significant impact on the ICER cannot be resolved through further data collection.

Key Uncertainties

Issue	Key uncertainty	Company preferred assumption	ERG preferred assumption	Impact on ICER	Data that could sufficiently resolve uncertainty	Proposed primary data source	Likelihood data collection could sufficiently resolve uncertainty	Rationale / Notes
EAG1	Exclusion of disopyramide as a comparator	Disopyramide (alone or in combination with either beta-blockers or non-dihydropyridine calcium blockers) is a comparator (as part of standard care) in the NICE scope. However, the company argue that disopyramide is not relevant as it is rarely used in clinical practice.	Further clarification on the extent to which disopyramide is used to treat obstructive hypertrophic cardiomyopathy (HCM) in the NHS needed.	Unquantified	RWE and consultation with additional clinical experts	Clinical Practice Research Datalink (CPRD) GOLD and Aurum datasets (which collected data from clinical practices and electronic patient records respectively)	No further data collection possible / proposed	Full publication of these datasets is expected at the end of 2022.

EAG2	Efficacy of mavacamten in patients with or without a sarcomere mutation	The efficacy of mavacamten could plausibly differ between patients who have a sarcomere mutation and those who do not, highlighted by the British Cardiovascular Society Consultee Submission.	Genetic mutations were analysed in EXPLORER-HCM, with the subgroup sizes for pathogenic mutations being n=28 for the mavacamten group and n=22 for the placebo group.	Unquantified	Request that the company conduct a cost-effectiveness analysis to explore the relationship between HCM genetic test results and cost effectiveness.	Further evidence provision before ACM	No further data collection possible / proposed	This may be relevant to interpreting the efficacy results of the EXPLORER-HCM trial where we note that 63% of patients receiving mavacamten did not achieve the primary outcome and we also note that the majority of patients in EXPLORER-HCM did not have a sarcomere mutation. If there is evidence of a greater clinical benefit if mavacamten use is limited to the subgroup with a sarcomere mutation, this is likely to translate to a lower ICER in that subgroup (and higher ICER in the subgroup without a mutation).
EAG3	Post-authorisation safety monitoring of mavacamten	The company based their base case model on a certain number of echocardiograms in their first year and none thereafter, which is not in line with the Summary of Product Characteristics (SmPC)	The EAG preferred assumption includes estimates of the cost of monitoring as per the revised draft SmPC, and we test uncertainty around the costs of monitoring in scenario analysis. But this does still leave the question of whether the required degree of monitoring is feasible for the NHS.	Medium	Further clinical expert opinion may help to clarify whether the required intensity of monitoring to ensure safe use of mavacamten can be achieved in the NHS.	Further evidence provision before ACM	No further data collection possible / proposed	The SmPC recommends more frequent echocardiograms than currently modelled. The company's ICER would increase if echocardiograms were performed as according to SmPC, instead of the specified number of visits in the first year and then none thereafter. NHSE consider the intensity of monitoring is expected to be manageable as this technology is expected to be commissioned in specialist centres, where regular monitoring already takes place.
EAG4	Imbalance in trial follow up duration for calculation of transition probabilities	In their base case analysis, the company use post-trial data to estimate transition probabilities between NYHA classes from week 30 up to week 46 in the comparator arm; but assume no change in NYHA class over this period in the intervention arm.	EAG suggest that the same method should be used to estimate NYHA class transitions in both arms: with transition probabilities prior to 30 weeks estimated from EXPLORER-HCM data, followed by assumptions regarding long-term progression.	High	Transition probabilities prior to 30 weeks estimated from EXPLORER-HCM data, followed by assumptions regarding long-term progression.	Balanced comparative data	No further data collection possible / proposed	Data collection to resolve this uncertainty would require a new randomised controlled trial that could provide comparative data.
EAG5	Long-term rates of progression	The company based their scenario analyses on an estimated rate of NYHA progression from a prospective cohort study by Maron et al. 2016. This study was identified from targeted searches, so it is not known if there are other sources of evidence on this issue.	EAG agree with use the company's base case assumption of an equal rate of NYHA class progression after week 30 with all treatments. However, further evidence regarding the rate of progression could help to reduce uncertainty.	High	Evidence from the company's new prognostic systematic literature review and from other stakeholders regarding the long-term rate of progression of NYHA class for people with obstructive HCM, and whether this differs between treatments.	Further evidence provision before ACM EXPLORER-LTE	Medium	The company report that a systematic literature review to address this evidence gap has been initiated, and that results are expected in early 2023. Given the enrolment in EXPLORER-LTE (n=282) further data from this study may provide further information on long-term rates of progression for mavacamten, but would not provide any evidence to support relative differences between treatments.

EAG6	Effect of treatments on mortality	The company model all-cause mortality using estimates of an association between NYHA class and mortality derived from analyses of real-world data. However, this approach has been criticised on the basis that the observed association between NYHA class and mortality is not necessarily causal.	EAG report two scenarios which remove the assumption that the observed association between NYHA class and mortality is causal and that treatments for obstructive HCM, including mavacamten, have an effect on survival.	High	Further expert opinion and evidence regarding the plausibility of the assumption that treatments for obstructive HCM have an impact on survival. Evidence regarding life expectancy for people with obstructive HCM, which could be used to validate the model outcomes, including survival.	Discussion at ACM in addition to further evidence provision ahead of ACM	No further data collection possible / proposed	ICER increases substantially when the causal assumption between symptom reduction and mortality is removed. A period of managed access will not long enough to resolve this uncertainty, nor could it provide data on mortality for the other treatments.
MAT1	Long-term clinical effectiveness of Mavacamten	The submission currently uses data from the full trial EXPLORER-HCM; however, at point of submission data from the EXPLORER-HCM cohort that was followed up within the long-term extension trial MAVA-LTE was still immature and therefore unable to be included in the cost-effectiveness model.	N/A	High	More mature data from the LTE cohort when available	EXPLORER-LTE	Medium	This is an uncertainty highlighted by the company in their managed access proposal, and highlighted by the EAG as a key issue (EAG5) The company considers that the uncertainty they could obtain more data on is a long-term clinical effectiveness. However, the trial is a long-term follow-on study designed to collect data safety data. No new comparative data will be available. The company and EAG assume an equal rate of NYHA class progression after week 30 with all treatments. The scenarios where the company consider a reduced progression on mavacamten has a minimal impact on the ICER, however the ICER is sensitive to the overall rate. Given the enrolment in EXPLORER-LTE (n=282) further data from the study will provide further information on long-term rates of progression for people taking mavacamten, but would not provide any evidence to support relative differences between treatments. Other sources of evidence, such as a the targeted literature search (EAG5) may provide further data on long-term progression in general.

Trial Data

Are there further relevant trial data that will become available after the NICE evaluation?	
Rating	**Rationale/comments**
Medium	The long term safety extension study of EXPLORER-HCM, EXPLORER-LTE, is still ongoing. It is unclear whether the outcome measure and data collection of EXPLORER-LTE is adequate to resolve uncertainties.

EXPLORER-HCM Clinical trial data	
Anticipated completion date	May-20
Link to clinicaltrial.gov	https://clinicaltrials.gov/ct2/show/NCT03470545
Start date	May-18
Data cut presented to committee	N/A
Link(s) to published data	https://pubmed.ncbi.nlm.nih.gov/32498620/ https://pubmed.ncbi.nlm.nih.gov/32871100/ https://pubmed.ncbi.nlm.nih.gov/34004177/ https://pubmed.ncbi.nlm.nih.gov/34018809/ https://pubmed.ncbi.nlm.nih.gov/34907813/ https://pubmed.ncbi.nlm.nih.gov/34915982/ https://pubmed.ncbi.nlm.nih.gov/35718845/ https://pubmed.ncbi.nlm.nih.gov/35902155/
Description of trial	Phase III international multicentre, placebo-controlled RCT studying clinical effectiveness of mavacamten in adults with symptomatic obstructive hypertrophic cardiomyopathy. Primary outcome was the percentage of participants achieving a clinical response. N=251.

EXPLORER-LTE Clinical trial data	
Anticipated completion date	Apr-26
Link to clinicaltrial.gov	https://clinicaltrials.gov/ct2/show/NCT03723655
Start date	Oct-18
Data cut presented to committee	Aug-21
Link(s) to published data	N/A
Description of trial	A phase III long-Term Safety Extension Study of Mavacamten (MYK-461) in Adults With Hypertrophic Cardiomyopathy Who Have Completed the MAVERICK-HCM (MYK-461-006) or EXPLORER-HCM (MYK-461-005) Trials (MAVA-LTE) - for clarification the MAVERICK trial is for people with non-obstructive hypertrophic cardiomyopathy, whereas the EXPLORER trial looks at obstructive hypertrophic cardiopathy. n=282 affecting both non-obstructive and obstructive hypertrophic cardiomyopathy. The primary outcome measures are the frequency and severity of treatment-emergent adverse events and serious adverse events (other outcome measures are not mentioned).

Data collected in clinical practice

Is RWE data collection within managed access feasible?	
Overall Rating	**Rationale/comments**
Medium	The EAG highlighted the CPRD Gold and Aurum datasets, both routinely collected datasets. These could provide further data on comparative data. However it is not expected that data collection through these datasets would be relevant to resolve any key uncertainties during a period of managed access.

Data Source		
Relevance to managed access		
Existing, adapted, or new data collection	Existing	
Prior experience with managed access	Low	Primary care datasets (CPRD Gold and Aurum). Potential problem with primary care data and managed access and managing all data, e.g. echocardiogram outcomes?
Relevance of existing data items	Low	Drug exposure is monitored but does not give any indication on whether there may be adherence problems. Unclear whether specialist/secondary care data items would be captured. The company proposes that the ongoing EXPLORE-LTE trial be used to collect data within managed access. It is unlikely that any RWE through existing datasets would resolve any key uncertainties (see uncertainties tab)
If required, ease that new data items can be created / modified	Not applicable	
How quickly could the data collection be implemented	Normal timelines	
Data quality		
Population coverage	High	
Data completeness	Medium	Unclear about secondary care data and its completeness
Data accuracy	Medium	These datasets have not been created with data collection for research purposes, which means that the data might not be as reliable and the data entry might be difficult to read (e.g. free text)
Data timeliness	Medium	Unclear
Quality assurance processes	Unclear	
Data availability lag	Low	
Data sharing / linkage		
New data sharing arrangements required?		
New data linkages required?		
If yes, has the governance of data sharing been established		
Analyses		
How easily could collected data be incorporated into an economic model	Low	Company has based its managed access proposal on trial study only. The EAG would like to use RWE to check the validity of comparator use.

Existing methodology to analyse data	Unclear	
If no, is there a clear process to develop the statistical analysis plan	No	
Existing analytical capacity	Low	
Governance		
Lawful basis for data collection		
Privacy notice & data subject rights		
Territory of processing		
Data protection registration		
Security assurance		
Existing relevant ethics/research approvals		
Patient consent		
Funding		
Existing funding		
Additional funding required for MA		
If yes, has additional funding been agreed in principle		
Service evaluation checklist - registry specific questions		
HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
Does data collection through registry require any change from normal treatment or service standards?		
Are any of the clinical assessments not validated for use or accepted clinical practice		
HRA question 3. Is the study designed to produce generalisable or transferable findings?		
Would the data generated for the purpose of managed access be expected to be used to make decisions for a wider patient population than covered by the marketing authorisation / NICE recommendation		
Additional considerations for managed access		
Are the clinical assessments and data collection comparable to current clinical practice data collection?		
Burden		

Additional patient burden		
Additional clinical burden		
Other additional burden		

Other issues

Explanation

This page details the Managed Access Team's assessment on whether there are any potential barriers to agreeing a managed access agreement and that any potential managed access agreement operates according to the policy framework developed for the Cancer Drugs Fund and Innovative Medicines Fund.

The items included are informed by the relevant policy documentation, expert input from stakeholders including the Health Research Authority, and the Managed Access team's experience with developing, agreeing and operating managed access agreements. Additions or amendments may be made to these considerations as further experience is gained from Managed Access.

The Managed Access Team will justify it decision, but broadly it is a matter of judgement on whether any issues identified, taken as a whole, are likely to lead to a barrier to a Managed Access Agreement being agreed, or operationalised in the NHS. No assessment is made whether a Commercial Access Agreement is likely to be reached between the company and NHS England, which could be a substantive barrier to managed access.

Are there any substantive issues (excluding price) that are a barrier to a MAA	
Overall rating	**Rationale/comments**
Yes - Minor	This is an orally administered medicine, used as an adjuvant treatment to standard care. A potential barrier to managed access is implementation of the echocardiograms required to monitor patients, However feedback from NHSE is that this monitoring would be routinely available in specialist centres, where it expected this would be commissioned.

		Rating	Rationale / comments
Burden	Expected overall additional patient burden from data collection?	Low	Data sources are clinical trial EXPLORE-LTE and Clinical Practice Research Datalink (CPRD) GOLD and Aurum datasets
	Expected overall additional system burden from data collection?	Low	Data sources are clinical trial EXPLORE-LTE and Clinical Practice Research Datalink (CPRD) GOLD and Aurum datasets
	Do stakeholders consider any additional burden to be acceptable	Not applicable	Data sources are clinical trial EXPLORE-LTE and Clinical Practice Research Datalink (CPRD) GOLD and Aurum datasets
	Would additional burden need to be formally assessed, and any mitigation actions agreed, as part of a recommendation with managed access	No	

		Rating	Rationale / comments
Patient Safety	Have patient safety concerns been identified during the evaluation?	No	
	Is there a clear plan to monitor patient safety within a MA?	Yes	
	Are additional patient safety monitoring processes required	No	

		Rating	Rationale / comments
Patient access after MAA	Are there are any potential barriers to the agreed exit strategy for managed access, that in the event of negative NICE guidance update people already having treatment may continue at the company's cost	Yes	
	If yes, have NHS England and the company agreed in principle to the exit strategy	Yes	

		Rating	Rationale / comments
Service implementation	Is the technology disruptive to the service	Yes	Implementation of the technology adds burden to patients, healthcare providers and clinicians. However, it is expected that the patients are seen in specialist centres, where added patient monitoring is unlikely to cause significant additional burden.
	Will implementation subject the NHS to irrecoverable costs?	No	

	Is there an existing service specification which will cover the new treatment?	No	

		Rating	Rationale / comments
Patient eligibility	Are there specific eligibility criteria proposed to manage clinical uncertainty	No	
	If yes, are these different to what would be used if the technology had been recommended for routine use?	Not applicable	

		Rating	Rationale / comments
Service evaluation checklist	HRA question 1. Are the participants in your study randomised to different groups?		
	Will the technology be available to the whole recommended population that meet the eligibility criteria?	Yes	
	HRA question 2. Does the study protocol demand changing treatment/care/services from accepted standards for any of the patients/service users involved?		
	Will the technology be used differently to how it would be if it had been recommended for use?	No	
	Any issues from registry specific questions	No	
	HRA question 3. Is the study designed to produce generalisable or transferable findings?		
	Any issues from registry specific questions	No	
	Additional considerations for managed access		
	Is it likely that this technology would be recommended for routine commissioning disregarding the cost of the technology?	Yes	
	Any issues from registry specific questions	No	

		Rating	Rationale / comments
Equality	Are there any equality issues with a recommendation with managed access	No	

		Rating	Rationale / comments
Timings	Likelihood that a Data Collection Agreement can be agreed within normal FAD development timelines	Yes	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Correction to post-technical engagement cost-effectiveness results

March 2023

File name	Version	Contains confidential information	Date
[ID3928] Post-TE corrected CE results ACIC redacted	**1.0**	**Yes**	**30 March 2023**

Contents

Tables and figures

Abbreviations

AE	adverse events
ASA	alcohol septal ablation
BB	beta blocker(s)
CCB	calcium channel blocker(s)
CEM	cost-effectiveness model
DSA	deterministic sensitivity analysis
EAG	External Assessment Group
EAR	external assessment report
EMR	electronic medical records
HCM	hypertrophic cardiomyopathy
HCRU	healthcare resource use
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
LYG	life years gained
NHB	net health benefit
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
PAS	patient access scheme
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
RR	relative risk
SHaRe	Sarcomeric Human Cardiomyopathy Registry
SRT	septal reduction therapy
TE	technical engagement
WTP	willingness to pay

1. Introduction

This document provides updated cost-effectiveness evidence supporting the submission for mavacamten for the treatment of symptomatic (New York Heart Association [NYHA] class II–III) obstructive hypertrophic cardiomyopathy (HCM), which was submitted to NICE in June 2022. After submission of the Company response to technical engagement (TE; 27 February 2023), an error was identified in the application of life tables in the cost-effectiveness model (CEM)(ID3928 Company submission CEM Technical engagement ACIC Marked). In cells K15–K113 of the Life tables sheet, the annual probability that women would die was incorrectly calculated using the life table data for men. This has now been corrected to use the life table data for women. For example, the formula previously included in cell K15 was "=IF(I15>100, 0, K14*(1-VLOOKUP($I14, life_table, **2**, FALSE)))". This has been changed to "=IF(I15>100, 0, K14*(1-VLOOKUP($I14, life_table, **3**, FALSE)))" (corrected values in **bold;** equivalent correction made to cells K16–K113).

An updated version of the CEM is supplied alongside this document. The correction results in a small change to the incremental cost-effectiveness ratio (ICER). Therefore, updated results for the Company post-TE base case, sensitivity and scenario analyses following correction of this error are summarised in Section 2. These results supersede those supplied in the Company response to technical engagement.

2. Updated cost-effectiveness evidence

Key points

- The Company base case ICER has been updated. The new base case corrects a minor error in the calculation of general population mortality for women, and demonstrates that mavacamten in combination with standard care (where standard care is BB/CCB monotherapy) remains a cost-effective treatment for symptomatic, obstructive HCM compared to standard care alone.
- The previous Company post-TE base case estimated that the addition of mavacamten would result in gains of [redacted] QALYs and an increase in discounted incremental costs to £[redacted], resulting in an ICER of £19,725/QALY gained.
- After correcting the error in the model, the updated Company post-TE base case estimates that addition of mavacamten would result in gains of [redacted] QALYs and an increase in discounted incremental costs to £[redacted], resulting in an ICER of £19,401/QALY gained. Therefore, the impact of the error on the ICER is minor.

1.1. Summary of changes to the Company's cost-effectiveness estimate at technical engagement

Having applied the correction described above, the results in Table 1 below are intended to replace the results presented in the Company TE response Table 4.

Table 1 . Changes to the Company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Original company base case analysis (post corrections made 1. in response to clarification questions, 2. including EAG's update to the pack size of disopyramide, 3. correction to utilities calculation described in additional issue 6)	Not applicable	Not applicable	£30,139
Key issue 3. Post-authorisation safety monitoring of mavacamten.	The original Company base case analysis applied [redacted] outpatient visits and echos in year 1. In year 2 onwards, the NYHA-class based monitoring frequency employed in	[redacted] monitoring has been adjusted to include [redacted] outpatient visits and echos. Additional monitoring in [redacted] has been added to the base case to include outpatient visits and	£30,676

	the BB/CCB arm was used.	echos every [redacted]. In [redacted] patients then move to the NYHA class-based monitoring rates used in the BB/CCB arm.	
Key issue 5. Long-term rates of progression.	The original Company base case analysis assumed no disease progression in the long term, post-trial period.	The base case has been updated to include disease progression as modelled in the Company addendum scenario, in line with the EAG base case. This applies the disease progression rates informed by Maron *et al*., 2016 for all treatments.	£17,408
Key issue 6. Effect of treatments on mortality	The original Company base case used hazard ratios for mortality derived from analysis of data from the Humedica EMR database.	The base case has been updated to use hazard ratios for mortality derived from analysis of data from the Market Clarity EMR database.	£26,349
Additional issue 1: Calculation of utilities	The original Company base case used utility values directly from EXPLORER-HCM.	The base case has been updated to use the approach to utility values from the EAG base case i.e. capped at age- and sex-adjusted general population norms (NYHA class I = general population; NYHA classes II, III, IV estimated using multipliers relative to class I, calculated from EXPLORER-HCM data)	£33,230
Company's base case following technical engagement Note: this includes the following amendments: • Changes to year 1 and year 2 monitoring for mavacamten. • Disease progression included for all treatments. • Use of Market Clarity EMR	**Incremental QALYs:** [redacted]	**Incremental costs:** £[redacted]	**ICER:** £19,401

hazard ratios for mortality. • EAG approach to utility values adopted.			

BB: beta blockers; CCB: calcium channel blockers; EAG: External Assessment Group; EMR: electronic medical records; ICER: incremental cost-effectiveness ratio; NYHA: New York Heart Association; QALY: quality-adjusted life year

1.2. Corrected cost-effectiveness results, sensitivity analyses and scenarios following technical engagement

This section describes in detail the cost-effectiveness results, sensitivity analyses and scenarios post-TE, following correction of the error. Having applied the correction described above, the tables and figures in sections 1.2.1, 1.2.2 and 1.2.3 are intended to replace the results presented in the Company TE response appendix 5.

1.2.1. Cost-effectiveness results

Table 2 presents the summary of cost-effectiveness outcomes. Each row represents the cumulative impact of the additional assumption and it runs from the NICE submission Company base case down to the updated Company base case.

The updated base case resulted in a change in the ICER to £19,401 (Table 3) and the net health benefit (NHB) to 0.501 (Table 4). At the with-patient access scheme (PAS) price, mavacamten is cost-effective at a willingness-to-pay (WTP) threshold of £20,000/quality-adjusted life year (QALY). The NHB results presented show that overall population health would be increased by the use of mavacamten at an opportunity cost threshold of £20,000 (Table 4). Updated disaggregated costs are presented in Table 5 and Table 6.

Table 2. Summary of changes to cost-effectiveness outcomes when applying cumulative changes to model assumptions

Model change	Incremental costs	Incremental QALYs	ICER (cost/QALY) after cumulative impact of model
			mavacamten vs BB/CCB monotherapy

Company base case (following corrections in response to clarification questions, EAG report and utility calculation as described in additional issue 6)	£[redacted]	[redacted]	**£30,139**
Key Issue 3: Post-authorisation safety monitoring of mavacamten	£[redacted]	[redacted]	£30,676
Key Issue 5: Long-term rates of progression	£[redacted]	[redacted]	£17,963
Key Issue 6: Effects of treatment on mortality	£[redacted]	[redacted]	£17,597
Inclusion of EAG approach to utility values	£[redacted]	[redacted]	£19,401
Company base case post-technical engagement – thereafter "base case"			
-			**£19,401**

BB: beta blockers; CCB: calcium channel blockers; EAG: External Assessment Group; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year

Table 3. Base case analysis results

	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Base case (Addendum with correction to disopyramide pack size)	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,139.15
	BB/CCB monotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Base case (Post TE base case)	**Mavacamten + BB/CCB**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**19,400.96**
	BB/CCB monotherapy	[redacted]	[redacted]	[redacted]	**-**	**-**	**-**	**-**

BB: beta blockers; CCB: calcium channel blockers; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; TE: technical engagement

Table 4. Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BB/CCB monotherapy	[redacted]	[redacted]				

BB: beta blockers; CCB: calcium channel blockers; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; NHB: net health benefit

Table 5. Summary of costs by health state

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	% absolute increment
NYHA I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	% absolute increment
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NYHA: New York Heart Association.

Table 6. Summary of predicted resource use by category of cost

Item	Cost intervention	Cost comparator	Increment	Absolute increment	% absolute increment
Treatment acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug monitoring cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health care resource utilisation cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE: adverse event.

1.2.2. Sensitivity analyses

The results of the probabilistic sensitivity analysis (PSA) indicate that the ICER is stable (Table 7Table 7), as the difference between the deterministic and probabilistic ICER is £[redacted].

Figure 1 presents the cost-effectiveness plane which displays that mavacamten + BB/CCB is predicted to be cost-effective in [redacted]% of the simulations at a £30,000 WTP threshold. This is supported by the cost-effectiveness acceptability frontier presented in Figure 2.

In the deterministic sensitivity analysis (DSA) the overall drivers of the ICER are annual disease progression for all patients in NYHA II and the annual discontinuation rate beyond week 30. A tornado plot showing the impact on the ICER is presented in Figure 3.

Table 7. Incremental results for the PSA

Treatment arm	Total costs	Total QALYs	Δ costs	Δ QALYs	ICER
Mavacamten + BB/CCB	[redacted]	[redacted]	-	-	-
BB/CCB monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BB: beta blockers; CCB: calcium channel blockers; ICER: incremental cost-effectiveness ratio; PSA: probabilistic sensitivity analysis: QALYs: quality-adjusted life years

Figure 1. Cost-effectiveness plane for incremental costs and QALYs

[redacted]

QALY: quality-adjusted life years; WTP: willingness-to-pay

Figure 2. Cost-effectiveness acceptability frontier

BB: beta blocker; CCB: calcium channel blocker; QALY: quality-adjusted life year.

Figure 3. DSA results (top 10) on incremental ICERs

DSA: deterministic sensitivity analysis; ICER: incremental cost-effectiveness ratio; NYHA: New York Heart Association.

1.2.3. Scenario analysis

Details of the new scenarios presented by the Company in response to technical engagement are given in Table 8, with corrected ICERs presented in Table 9. Corrected ICERs for the scenarios presented in the original Company submission are given in Table 10.

Table 8. Summary of new scenario analyses conducted

Parameter	Base case	Description of scenarios
Mavacamten discontinuation at week 30 due to lack of response	All without NYHA class improvement at week 30 stop treatment ([redacted]% NYHA class I, [redacted]% NYHA class II, and [redacted]% NYHA class III/IV)	[redacted]% in NYHA class II and III with no improvement at week 30 discontinue ([redacted]% in class II and [redacted]% in class III). The remaining [redacted]% of patients without NYHA class improvement discontinue at week 38.
Monitoring	Patients receiving mavacamten attend [redacted] outpatient visits and echos in [redacted] then every [redacted] in [redacted].	[redacted] visits in [redacted] then every [redacted] in [redacted], then standard care monitoring thereafter.
		[redacted] visits in [redacted] then every [redacted] in [redacted], then standard care monitoring thereafter.
		[redacted] visits in [redacted] then every [redacted] in [redacted] and every [redacted] in [redacted], then standard care monitoring thereafter.

Table 9. Summary of new scenario analysis results

Parameter	Scenarios	ICER
Mavacamten discontinuation at week 30 due to lack of response	[redacted]% in NYHA class II and III with no improvement at week 30 discontinue ([redacted]% in class II and [redacted]% in class III). The remaining [redacted]% of patients without NYHA class improvement discontinue at week 38.	£19,447.85
Monitoring	[redacted] visits in [redacted] then every [redacted] in [redacted], then standard care monitoring thereafter.	£19,983.65
	[redacted] visits in [redacted] then every [redacted] in [redacted], then standard care monitoring thereafter.	£19,546.82
	[redacted] visits in [redacted] then every [redacted] in [redacted] and every [redacted] in [redacted], then standard care monitoring thereafter.	£19,557.69

ICER: incremental cost-effectiveness ratio; HR: hazard ratio

Table 10. Updated results of previous scenario analysis

Parameter	Scenarios	ICER
Time horizon	20 years	£22,749.05
	30 years	£19,659.02
Comparator arm transition probabilities	Trial-based transition probabilities until week 38; no NYHA class transitions beyond week 38 (unless SRT event experienced)	£20,924.16
Mavacamten discontinuation at week 30 due to lack of response	Exploratory scenario where [redacted]% patients in NYHA III at week 30 discontinue mavacamten (equal to the proportion who discontinue from NYHA II)	£20,337.80
Mavacamten discontinuation from week 30 onwards due to SAEs (annual %)	1.4% annually after week 30	£22,300.54
Distribution to treatments following discontinuation from mavacamten	90% receive BB/CCB monotherapy 10% receive disopyramide + BB/CCB	£18,184.39
	75% receive BB/CCB monotherapy 25% receive disopyramide + BB/CCB	£16,587.29
	For patients in NYHA I/II: 100% receive BB/CCB monotherapy For patients in NYHA III/IV: 90% receive BB/CCB monotherapy 10% receive SRT	£18,650.64
	For patients in NYHA I/II 100% receive BB/CCB monotherapy For patients in NYHA III/IV: 80% receive BB/CCB monotherapy 10% receive disopyramide + BB/CCB 10% receive SRT	£18,037.97
Distribution to treatments following mavacamten discontinuation and escalation from BB/CCB monotherapy	Patients who discontinue mavacamten: 100% receive BB/CCB monotherapy Patients who escalate from BB/CCB monotherapy: 100% receive SRT	£19,551.43
	Patients who discontinue mavacamten: 90% receive BB/CCB monotherapy 10% receive disopyramide + BB/CCB Patients who escalate from BB/CCB monotherapy: 100% receive SRT	£18,338.34
	Patients who discontinue mavacamten: 75% receive BB/CCB monotherapy 25% receive disopyramide + BB/CCB Patients who escalate from BB/CCB monotherapy: 100% receive SRT	£16,744.68
	Patients who discontinue mavacamten and are in NYHA I/II: 100% receive BB/CCB monotherapy Patients who discontinue mavacamten and are in NYHA III/IV: 90% receive BB/CCB monotherapy 10% receive SRT Patients who escalate from BB/CCB monotherapy:	£18,802.34

Parameter	Scenarios	ICER
	100% receive SRT	
	Patients who discontinue mavacamten: 100% receive BB/CCB monotherapy Patients who escalate from BB/CCB monotherapy and are in NYHA I/II: 100% receive disopyramide + BB/CCB Patients who escalate from BB/CCB monotherapy and are in NYHA III/IV: 100% receive SRT	£19,552.69
Efficacy of SRT (incident transition probabilities)	Knyshov *et al*. 2013	£19,103.30
Mortality	Adjusted HRs from SHaRe (Appendix N)	£19,367.13
	Unadjusted RRs from SHaRe (Lakdawala *et al*. 2021)	£18,424.02
	Humedica EMR	£19,805.08
Market share of ASA versus septal myectomy (SRT)	75% ASA, 25% septal myectomy	£19,433.53
	25% ASA, 75% septal myectomy	£19,371.03
Age-adjusted utilities	Exclude	£17,877.52
HCRU	Increase all HCRU by 10%	£18,138.34
	Decrease all HCRU by 10%	£20,663.58
Time on disopyramide before escalation to SRT (months)	6	£19,449.63
	12	£19,355.32
Age at baseline (years)	52.0	£16,735.61
	62.0	£20,586.77
Utilities	Utilities from Göhler *et al*, 2009	£18,548.95
	Utilities from EXPLORER-HCM	£17,596.64
Natural disease progression	[redacted]% annual rate of disease progression in mavacamten arm; 4.55% otherwise	£18,746.30

ASA: alcohol septal ablation; BB: beta blockers; CCB: calcium channel blockers; HCRU: healthcare resource use; HR: hazard ratio; ICER : incremental cost-effectiveness ratio; RR: relative risk; SHaRe: Sarcomeric Human Cardiomyopathy Registry; SRT: septal reduction therapy; WTP: willingness-to-pay

Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

Information on completing this form

In part 1 we are asking you about living with symptomatic obstructive HCM or caring for a patient with symptomatic obstructive HCM. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with symptomatic obstructive HCM

Table 1 About you, symptomatic obstructive HCM, current treatments and equality

1. Your name	Laura Kelly
2. Are you (please tick all that apply)	A patient with symptomatic obstructive HCM? A patient with experience of the treatment being evaluated? A carer of a patient with symptomatic obstructive HCM? A patient organisation employee or volunteer? Other (please specify):

3. Name of your nominating organisation	Cardiomyopathy UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	No (please review all the questions and provide answers when possible) Yes, my nominating organisation has provided a submission I agree with it and **do not wish to** complete a patient expert statement Yes, I authored / was a contributor to my nominating organisations submission I agree with it and **do not wish to** complete this statement I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	I am drawing from personal experience I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: I have completed part 2 of the statement **after attending** the expert engagement teleconference I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference I have not completed part 2 of the statement
6. What is your experience of living with symptomatic obstructive HCM? **If you are a carer (for someone with symptomatic obstructive HCM) please share your experience of caring for them**	Before I started having symptoms, I lived a full and active life. I was very sociable, loved seeing friends and family and going on holidays. I especially liked taking part in sport and played badminton, volleyball and hockey. I also took part in fundraising walks and even did a skydive. I was fit, active and having fun. Around winter 2019 I started to feel bad. I thought it was just asthma but could also feel my heart beating irregularly and was very tight chested. It got so bad one night that I had to go straight to A&E. I was admitted and after a week or so of tests and a cardioversion, I was diagnosed with cardiomyopathy. It helped that I could share with them my auntie's records as she has the same problem. My cardiomyopathy impacts me in a number of ways. The biggest physical impact is being out of breath and exhausted. I struggle walking and am constantly getting out of breath. I

	even pretend to be texting on my phone as looks silly having to keep stopping all the time. On a good day I can walk for a couple of minutes if I am going downhill or maybe about 25 meters if it is flat. Going up any sort of incline is impossible. I also get chest pains and even holding a conversation can be completely exhausting. As I am not getting any exercise it feels like I am wasting away and loosing muscle tone. As well as the physical impact it has had a massive impact on me mentally and on my relationships with my partner, friends and family. I hardly going out and get cabin fever stuck in all the time. I miss seeing friends, I try to keep in contact but miss out all the big occasions and being part of their lives. My family live in Northampton and getting there on a train from Brighton where I live is just too much to manage. All this also impacts on my partner and my stepson who is autistic and struggles to understand why I can't do anything with him even simple things like going out for a coffee. It has also had a big impact on work. I used to be very hard working and enjoyed work but now working is a real challenge. My employer is understanding but I can only work for about three weeks then I need three weeks to recover. I work with machinery so it's not safe being at work when I am exhausted. The statutory sick pay is limited and can run out. I have also been turned down for benefits because some days I can cope with basic tasks. Because I am not earning I am now getting into debt. I am worried about needing to take three months off if I have an operation and have to time this in a way that I can take sick pay otherwise I don't know how I can cover costs and will be in more debt.

7a. What do you think of the current treatments and care available for symptomatic obstructive HCM on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	A) I was given amiodarone but had to stop this after I had an ablation and went into AF. I have had 4 cardioversions in all and I also had an ICD fitted last September. The ICD has gone of twice since then. I now take 600 mg of disopyramide and 10mg of bisoprolol. I have not had any noticeable side effects. After the ablation, 4 cardioversions and pills I have some days that are better than others but ultimately they have not helped much and I am still in the same boat. My doctor has put me down for surgery. It is scary but it feels like it is the only way of getting my life back, I don't want to spend rest of my time doing nothing and stuck in the flat. I had pre-op assessment last September and was told the operation would be in November but I have not heard anything and don't have a new date. It is very hard not knowing when it will be as I have to plan taking 3 months off and sorting out care and not getting into more debt. I have to say though that overall I feel I have been treated well by people and could not fault the NHS. My doctor in Brighton sent me to Guys and St Thomas' in London as they have the experts there and they know what they are doing. B) My Aunty has the same condition but not as bad as me. My mum and brother also have it but they are coping better for now. When we knew it was in our family my cousin did not want to know if he had it and did not want to go through the tests. He thought that there was nothing you could do anyway, and he would rather not know. Sadly he died last year when he had a cardiac arrest in his sleep.
8. If there are disadvantages for patients of current NHS treatments for symptomatic obstructive HCM (for example, how they are given or taken, side effects of treatment, and	The have not worked for me

any others) please describe these	
9a. If there are advantages of mavacamten over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does mavacamten help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	A) It would be great to have another option and especially when I have tried everything else and it has not worked. I want to put off or stop needing surgery and I want to get some kind of life back. I thought there would be more things to try and more time between being diagnosed and needing surgery. I want more time to adapt. B) Something to manage my symptoms would be the biggest advantage.
10. If there are disadvantages of mavacamten over current treatments on the NHS please describe these. For example, are there any risks with mavacamten? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I don't know side effects, compared to treatments or Disopyramide but I am used to taking pills and not worried about this. If it is going to give some form of life back I want to try it.
11. Are there any groups of patients who might benefit more from mavacamten or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	My brother is 34 and has the condition but is in the early stages. I am thinking about him in the future and how he could have a new treatment that could save him going through all this pain and the impact it has on your life.
12. Are there any potential equality issues that should be taken into account when considering symptomatic obstructive HCM and mavacamten? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership,	Where you live could make a difference. I now see my doctor in London and my mum goes from Northampton to Oxford. Travelling can be really hard.

pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- The impact on my quality of life has been awful
- I have had lots of treatments and drugs but these have not really helped
- I want to avoid needing surgery if I can
- I want to try something else as surgery is a last resort
- I just want to get some of my life back

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please tick this box if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Innovative Medicines Fund clinical lead input on managed access feasibility

IMF lead responses in blue

Burden of safety monitoring requirements

- There is substantial heterogeneity in clinical expert opinion on the practicality of implementing the safety monitoring requirements as stipulated in the draft SmPC (see relevant extract below – note this is currently confidential), but all experts are in agreement that some additional monitoring will be required.
- Does NHSE have any further input regarding the ability of the NHS to provide this additional monitoring, or whether it is likely that a lesser degree of monitoring (than stipulated in the SmPC) will be implemented in practice? If so, what level of monitoring above the current standard for oHCM is most likely?

NHSE agree that additional monitoring will be required and a there will be a significant challenge to already strained Echo services to provide this. There will inevitably be centre to centre variation. NHSE do not recommend any lesser degree of monitoring and would not deviate from the SMPC recommendations. At this stage it is not possible to quantify what the increase in monitoring will be above the current standard for oHCM as practice does vary

Is disopyramide is a relevant comparator?

- The company consider that disopyramide is not a relevant comparator because it is not widely used. The company have cited estimates of the annual frequency of disopyramide prescriptions during 2010 to 2020 from the CPRD database.
- But the EAG are not sure of the robustness of these estimates because they consider that its possible this database only captures prescriptions from primary care. Clinical experts suggest that usage is highly variable according to individual clinician preference and experience, and that larger centres are much more likely to use disopyramide. The EAG are unclear whether the heterogeneity of consultee responses reflects variation in clinicians' procurement routes for disopyramide (which might mean that some clinicians or centres were more easily able to access disopyramide, or were more aware of drug availability issues, than others).
- Does NHSE have anything to add to these considerations?

Disopyramide currently is routinely in the NHS in a small proportion of

patients. It is not possible to give a national estimate but one large centre states that about 4-5% of their patients take this drug.

Assessing symptom severity in people with obstructive HCM

- Is the NYHA the most commonly used measure in clinical practice to assess symptom severity in people with obstructive HCM? It has been suggested by a clinical expert that it is being phased out (in clinical trials at least) in favour of the Kansas City Cardiomyopathy Questionnaire (KCCQ). This is due to concerns over its accuracy and robustness, with the suggestion that it is quite subjective and that results can depend on how it is implemented.
- To what extent should these potential limitations of the NYHA be a cause for concern in this appraisal?

The NYHA classification is routinely used in the NHS so should not be discounted

Bristol Myers Squibb™

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May 15th, 2023

Updated PAS for Mavacamten (Camzyos®) (ID3928)

Dear Linda Landells,

We are writing to confirm a change in the [redacted] for Mavacamten (Camzyos®), following the appraisal committee meeting held on 12th April 2023.

The current provisional list price is [redacted].
The updated PAS price is [redacted]

The Committee-preferred assumptions for decision making are listed below:

- Correction to age adjustment of utilities
- Capping of utility at general population values
- Updated life table for women, as applied in the company's post-TE correction
- Long-term progression (4.55% per year for all treatments)
- Revised estimates of mortality risks increasing by NYHA class
- Transition probabilities based on equal duration of follow-up for both arms
- Monitoring schedule for mavacamten assuming [redacted] assessments in the first year and [redacted] assessments ([redacted] assessments per year) from year 2 onwards

The PAS and accepted assumptions result in an ICER of £19,997 per QALY gained.

Yours sincerely,

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