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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)

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- 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.

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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.

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- EAG report tables 10, 13, 16.
- Information in parts of EAG report tables 4, 8, 9, 11, 12.
- EAG report Figure 1

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.

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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.

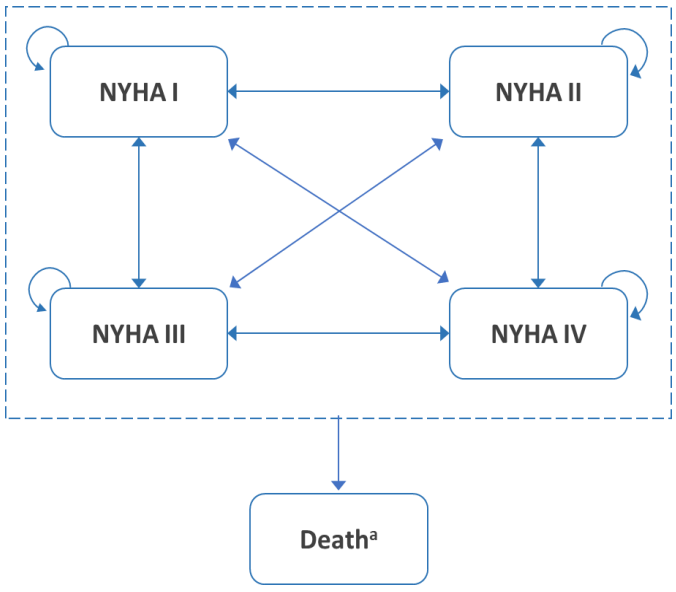

Figure 1 Illustration of the Markov model structure

[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	[redacted]	[redacted]	
	Mavacamten + BB/CCB	[redacted]	[redacted]	£29,953
+ TP estimates from trial for 30 weeks only in both arms	BB/CCB monotherapy	[redacted]	[redacted]	
	Mavacamten + BB/CCB	[redacted]	[redacted]	£45,256
+ Utilities capped at general population values for age	BB/CCB monotherapy	[redacted]	[redacted]	
	Mavacamten + BB/CCB	[redacted]	[redacted]	£49,896
+ Long-term progression rate for all treatments (4.55%)	BB/CCB monotherapy	[redacted]	[redacted]	
	Mavacamten + BB/CCB	[redacted]	[redacted]	£33,547
+ Enhanced monitoring for mavacamten ([redacted])	BB/CCB monotherapy	[redacted]	[redacted]	
	Mavacamten + BB/CCB	[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
		Cost (£)	QALYs	(£/QALY)
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