Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy [ID3928]

Slides for public: contains no confidential information

Technology appraisal committee C [12 April 2023]

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Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy

- ✓ **Background**
- ❑ Clinical evidence and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ❑ Base case assumptions
- ❑ Other considerations: Equality, innovation, severity, potential for managed access
- ❑ Summary

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Background on obstructive hypertrophic cardiomyopathy

Cardiomyopathies are chronic diseases of the heart muscle that alter the structure and impair the function of the heart

Causes

- Some obstructive HCM is caused by genetic mutations in the cardiac sarcomere (contractile unit of muscle)
- Sarcomere structure or function is altered = excessive contraction of cardiac muscle

Epidemiology

- Prevalence of HCM is estimated between 0.2% and 0.11% in the UK
- About two thirds of these are obstructive HCM
- Of these, 50-84% of these are estimated to be symptomatic

Diagnosis and classification

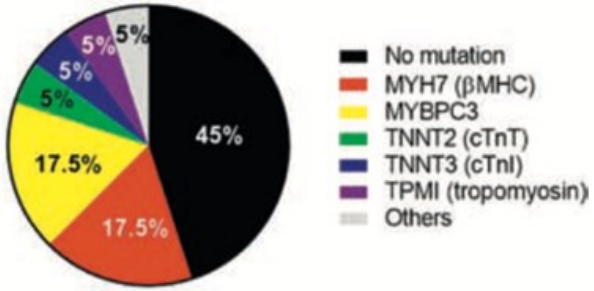
- Diagnosis is done by cardiac imaging
- Defining characteristic is left ventricular outflow tract obstruction (LVOTO), defined as peak LVOT pressure gradient is ≥ 30 mmHg

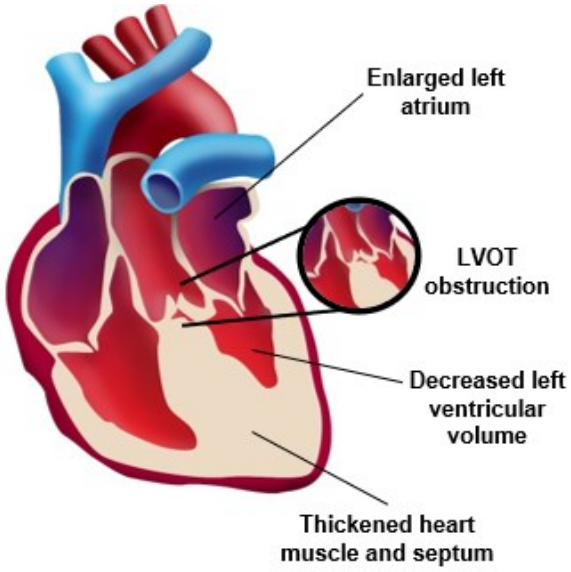
Symptoms and prognosis

- Associated with an increased risk of long-term cardiac complications and mortality. Symptoms include fatigue, dizziness, chest pains, palpitations, and breathlessness

Genetics:

- Approximately 50% of patients have mutations in one or more of >20 sarcomeric genes
- Complex genetic causation (variable penetrance and expressivity):





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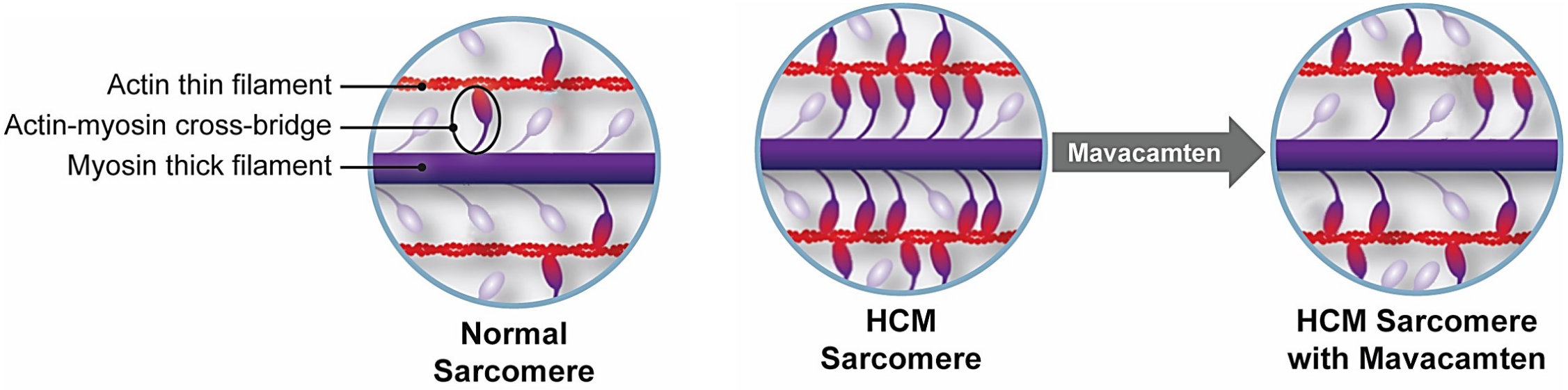
Abbreviations: HCM, hypertrophic cardiomyopathy

Mavacamten: mechanism of action

Mavacamten, a targeted inhibitor of cardiac myosin, decreases the number of myosin-actin cross-bridges and reduces excessive contractility characteristic of HCM

In obstructive hypertrophic cardiomyopathy, improves LVOT gradient, quality of life and physical functioning



Normal Sarcomere	HCM Sarcomere	HCM Sarcomere with Mavacamten
Normal contractility Effective relaxation	Hyper contractility Impaired relaxation Altered myocardial energetics	Reduces myosin-actin cross bridges To attenuate hypercontractility and improved compliance and energetics

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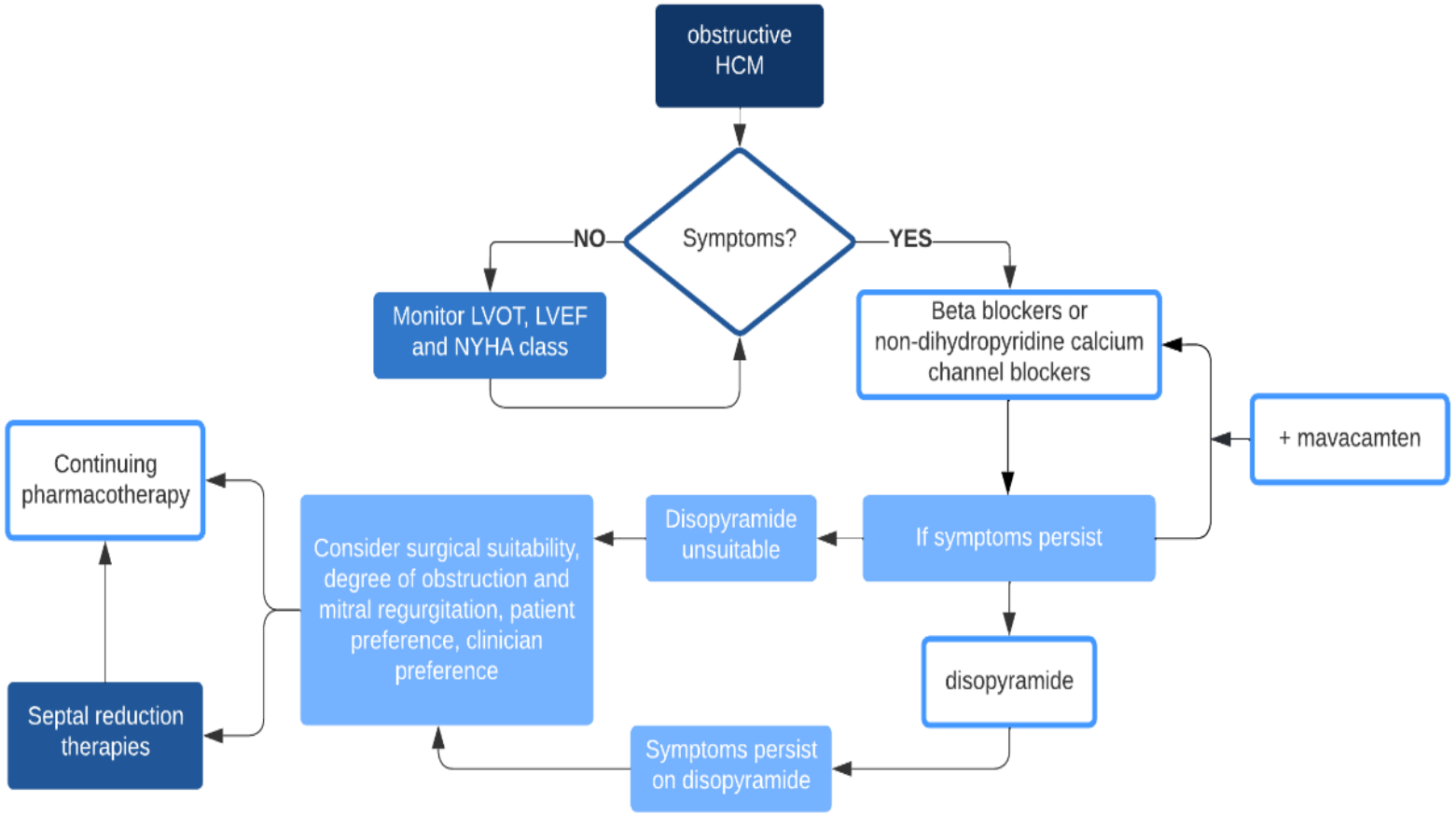
Abbreviations: LVOT, left ventricular outflow tract

Company's proposed treatment pathway

Currently no treatments that address the underlying disease mechanism



- Mavacamten positioned as adjunctive therapy for people who do not achieve sufficient symptomatic control with beta-blocker or calcium channel blocker monotherapy
- Disopyramide use is variable
- Pathway does not include combination therapy with disopyramide, or with beta blockers plus calcium channel blockers (due to safety concerns)

Abbreviations: HCM, hypertrophic cardiomyopathy

Patient perspectives

Highly impactful condition effecting individual's physical and mental health

Submission from Cardiomyopathy UK and 1 patient expert

- Most impactful physical symptoms are breathlessness, exhaustion and the inability to carry out everyday tasks
- Significant impact on mental health and ability to cope day to day. Affects relationships with family and friends
- Social isolation and loss of active lifestyle akin to a bereavement
- Considerable impact of obstructive HCM on employment and managing to cope financially
- Treatments for people who have not been helped by medication were seen as highly invasive, painful and requiring a great deal of support with the recovery process
- Not all people with obstructive HCM are suitable for myectomy or septal ablation
- Substantial need for non-invasive treatment options to improve symptoms for people who have not benefitted from current medication

"I've lost much of my mobility and have to rely on a walking stick, can't walk more than about 3 feet without having to stop due to the pain and breathlessness"

"I have always been a very active person and used to take part in a lot of sports... Not being able to take part has massively impacted my confidence and social circles."

Abbreviations: HCM, hypertrophic cardiomyopathy

Clinical perspectives

Potential to address substantial unmet clinical need

Submissions from British Cardiovascular Society, St George's University Hospitals NHS Foundation Trust, Norfolk & Norwich University Hospital

- Pathways of care for HCM are not well defined, high variability between centres and individual clinicians
- Current treatments are not disease specific, often ineffective or poorly tolerated
- If current treatment fails to improve symptoms, the next steps are invasive interventions. These require specific expertise which is not widely available, so access is limited
- Mavacamten may prevent the need for invasive procedures (currently 5-10% of people with obstructive HCM)
- Mavacamten can cause a reduction in left ventricular systolic function
- May be difficult to implement in the NHS, due to the intensive monitoring phase of drug initiation and up titration
- This will lead to increased healthcare resource use in the short term

"There are currently no disease specific medications to treat HCM and those that are currently used are often ineffective or poorly tolerated"

"Evidence suggests that mavacamten has a positive effect in improving patients' quality of life in comparison to current care"

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Abbreviations: HCM, hypertrophic cardiomyopathy

Key issues

Key issues from EAG report	Resolved?	ICER impact
Effect of treatments on mortality	No – for discussion	Large
Long-term rates of progression	Partially – for discussion	Large
Imbalance in follow up duration for transition probabilities	No – for discussion	Large
Post-authorisation safety monitoring of mavacamten	No – for discussion	Small
Exclusion of disopyramide as a comparator	No – for discussion	Unknown
Uncertain efficacy of mavacamten in patients without a sarcomere mutation	No – for discussion	Unknown

Mavacamten (CAMZYOS, Bristol-Myers Squibb)

Anticipated marketing authorisation	• Mavacamten is indicated [redacted] • [redacted]
Mechanism of action	• Mavacamten is an oral, small molecule modulator of cardiac myosin, one of the main proteins within the sarcomere • Mavacamten inhibits cardiac myosin leading to a reduction in sarcomere force production and therefore reduced hypercontractility
Administration	• Once daily, by oral administration
Price	Proposed list price (exclusive of VAT. Provisionally approved by DH, pending MA approval): £[redacted] per pack (2.5 mg capsules x28) £[redacted] per pack (5.0 mg capsules x28) £[redacted] per pack (10 mg capsules x28) £[redacted] per pack (15 mg capsules x28) Average cost of a course of treatment is: £[redacted] per patient per year
PAS	• Mavacamten has a simple discount patient access scheme (PAS)

Abbreviations: HCM, hypertrophic cardiomyopathy; DH, Department of Health; MHRA, Medicines and Healthcare products Regulatory Agency; MA, marketing authorisation

Decision problem (1)

	Final scope	Company	EAG comments
Population	Adults with symptomatic obstructive hypertrophic cardiomyopathy (NYHA class II-III)	[redacted]	None
Intervention	Mavacamten in combination with standard care	Mavacamten in combination with standard care	None
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 Company excluded disopyramide based on clinical feedback and limited use in clinical practice.	In practice, use of disopyramide is likely to vary geographically in the NHS. Further consultation may be helpful to clarify this. Use of disopyramide is highlighted as a key issue for discussion.

Abbreviations: NYHA, New York Heart Association

Decision problem (2)

	Final scope	Company	EAG comments
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 • adverse effects of treatment • health-related quality of life	Same as final scope, except for exclusion of cardiovascular events and cardiovascular related mortality. The company exclude these outcomes because the annual all-cause mortality rate in patients with HCM is <1%. This low event rate does not permit inclusion of mortality or cardiovascular (CV) mortality as trial endpoints. The same limitation applies to CV events. Mortality is modelled using NYHA class as a surrogate in the cost-effectiveness model.	Use of a surrogate for mortality in the model is reasonable given the limitations of data. But there is a lack of robust evidence to support a causal relationship between NYHA class and mortality. The assumption that improving NYHA class will improve mortality is therefore uncertain.

Abbreviations: HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association

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Key clinical trials (1)

	EXPLORER-HCM (n=251)	EXPLORER-LTE (n=231)
Design	A phase III, double-blind, randomised, placebo-controlled, multicentre study	A phase II/III open-label, single-arm, long-term safety extension study
Population	Adults diagnosed with obstructive HCM (satisfying the 2 main diagnostic criteria)	
Intervention	Mavacamten: one 2.5, 5, 10, or 15 mg capsule, once daily, by oral administration	
Comparator	Placebo once daily, by oral administration	N/A
Duration	38 weeks	5 years
Primary outcome	Clinical response at Week 30, defined as achieving one of the following: • An improvement of ≥ 1.5 mL/kg/min in pVO2 as determined by CPET and a reduction of ≥ 1 NYHA class, or • An improvement of ≥ 3.0 mL/kg/min in pVO2 with no worsening in NYHA class	Long-term safety and tolerability of mavacamten
Locations	90 clinical sites worldwide, including in Belgium, Czech Republic, Denmark, France, Germany, Israel, Italy, Netherlands, Poland, Portugal, Spain, UK, USA	Belgium, Czech Republic, Denmark, France, Germany, Israel, Italy, Netherlands, Poland, Portugal, Spain, UK, USA

Abbreviations: NYHA, New York Heart Association; HCM, hypertrophic cardiomyopathy; CPET, cardiopulmonary exercise testing; pVO2, peak oxygen uptake

Key clinical trials (2)
VALOR-HCM: study design and participant characteristics

VALOR-HCM phase III, multi-centre, randomised controlled trial	
Start/end dates	July 2020 – June 2024 (estimated completion date for non-randomised extension)
Population	People who have symptomatic obstructive HCM and additionally are eligible for SRT
Locations	20 centres in the United States (no UK patients)
Participants	Mavacamten (n=56) versus placebo (n=56) and stratified by type of SRT recommended (myectomy or alcohol septal ablation) and NYHA class
Randomisation	1:1 randomisation for 16 weeks only
Primary outcome	The primary endpoint is a composite of the following: • Decision to proceed with SRT prior to or at Week 16 • SRT guideline eligible at Week 16
Generalisability	Baseline age, sex, family history of HCM, calcium channel blocker use, resting and post-exercise LVOT gradients similar to EXPLORER-HCM trial and to patients in the UK
Disopyramide use	20% across both arms. Population is therefore not consistent with EXPLORER-HCM trial or company's current Decision Problem (which both exclude disopyramide)
Results used in economic model	No. Interim results used descriptively to support clinical effectiveness evidence reported from EXPLORER-HCM and EXPLORER-LTE studies

Abbreviations: NYHA, New York Heart Association; HCM, hypertrophic cardiomyopathy; SRT, septal reduction therapy

EXPLORER-HCM results (1)
Composite primary functional endpoint at week 30

	Mavacamten (N = 123)	Placebo (N = 128)	Mavacamten vs placebo (95% CI)
Primary endpoint			
Either ≥1.5 mL/kg per min increase in pVO_2 with ≥1 NYHA class improvement or ≥3.0 mL/kg per min increase in pVO_2 with no worsening of NYHA class, n (%)[2]	45 (37)	22 (17)	19.4 (8.7, 30.1)
Components of composite primary endpoint			
≥1.5 mL/kg per min increase in pVO_2 with ≥1 NYHA class improvement	41 (33)	18 (14)	19.3 (9.0, 29.6)
≥3.0 mL/kg per min increase in pVO_2 with no worsening of NYHA class	29 (24)	14 (11)	12.6 (3.4, 21.9)
Both ≥3 mL/kg/min in pVO_2 and an improvement of ≥1 NYHA class	25 (20)	10 (8)	12.5 (4.0, 21.0)

EAG comment on generalisability: EAG's clinical experts agreed that, with the exception of disopyramide use, the baseline characteristics of EXPLORER-HCM and EXPLORER-LTE are generally representative of patients treated for symptomatic obstructive HCM in the NHS.

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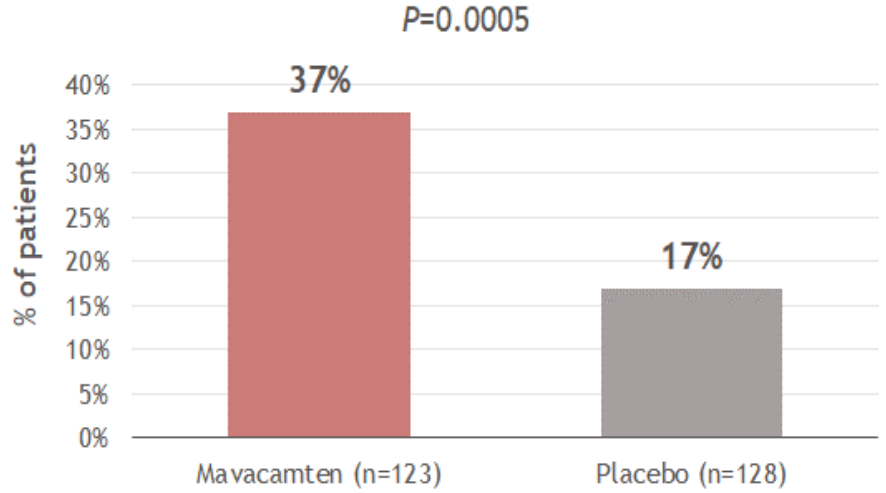
Abbreviations: NYHA, New York Heart Association; pVO2, peak oxygen uptake; CI, confidence interval

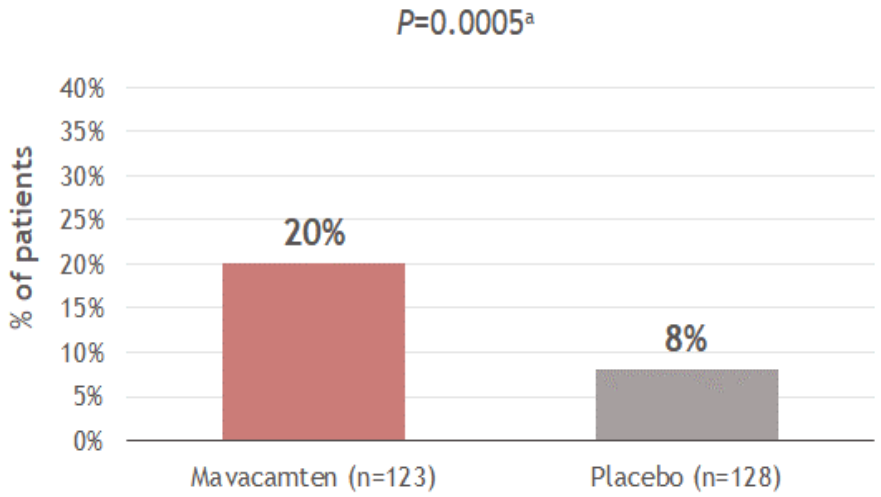
EXPLORER-HCM results (2)
Composite primary functional endpoint at week 30

Composite primary endpoint



≥1.5mL/kg per min increase in peak VO_2 with ≥1 NYHA class improvement
OR
≥3.0mL/kg per min increase in peak VO_2 with no worsening of NYHA class

Patients that achieved ≥3.0mL/kg per min increase in peak VO_2 with ≥1 NYHA class improvement



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Abbreviations: NYHA, New York Heart Association; pVO2, peak oxygen uptake; CI, confidence interval

EXPLORER-HCM results (3)

Secondary endpoints

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

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

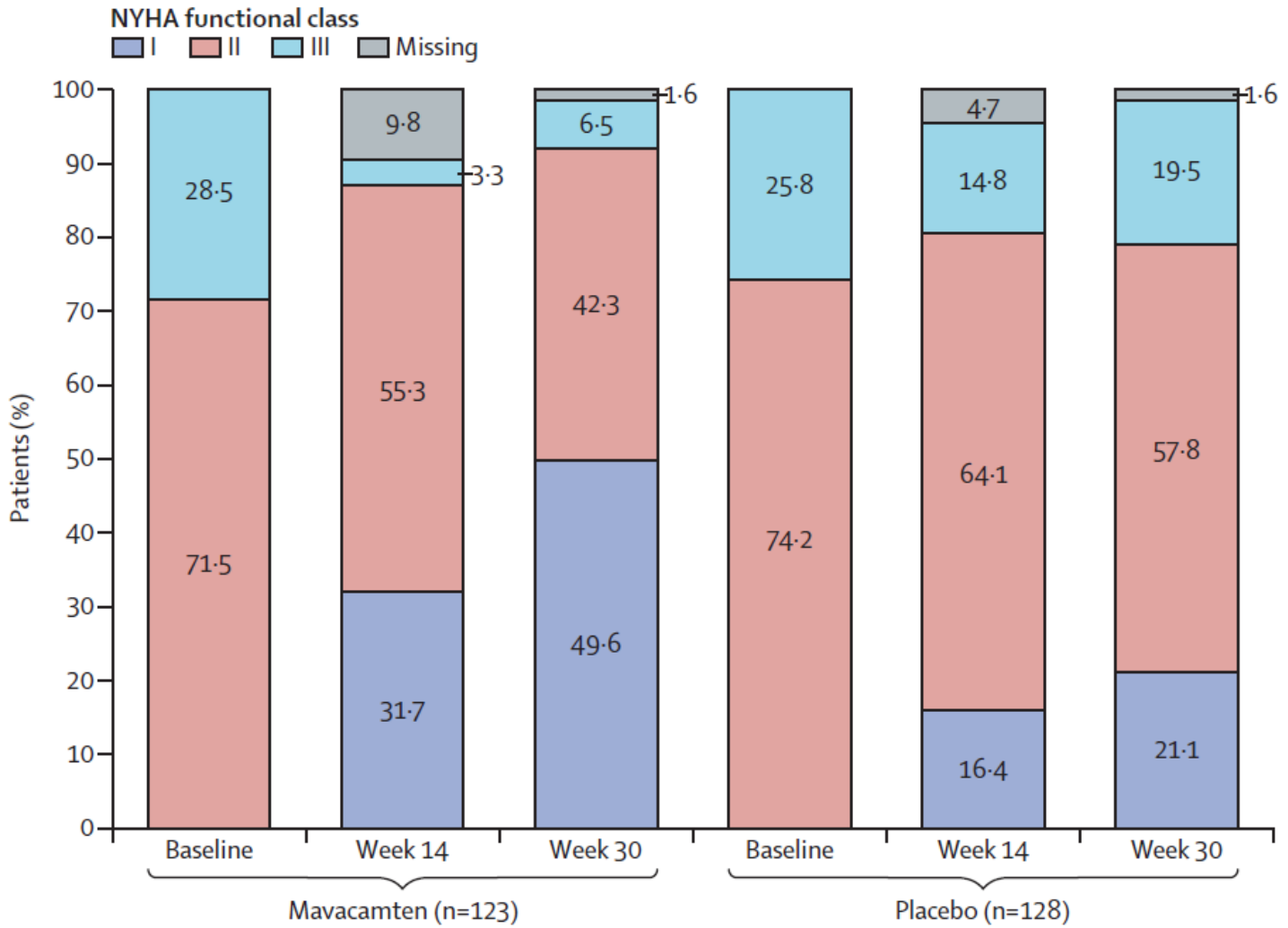
Changes from baseline to week 30 in patient-reported outcomes

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

Abbreviations: NYHA, New York Heart Association; pVO2, peak oxygen uptake; CI, confidence interval; SD, standard deviation

EXPLORER-HCM results (4)
Secondary endpoints

NYHA functional class at baseline, week 14 and week 30 for mavacamten vs placebo

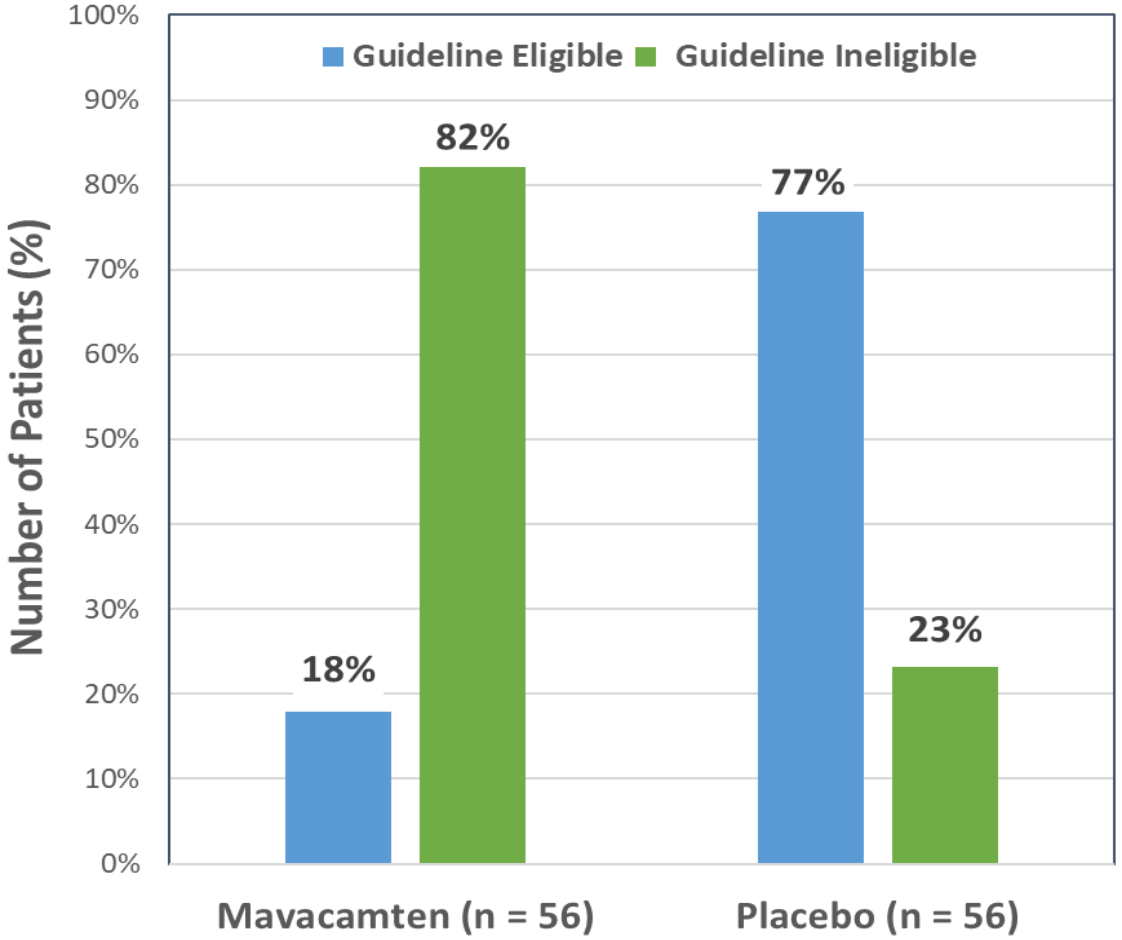


Abbreviations: NYHA, New York Heart Association

VALOR-HCM results

Primary endpoint

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



- Evidence from VALOR-HCM supports mavacamten's role in avoiding the need for SRT
- Primary analysis is based on the 16-week placebo-controlled treatment period
- A substantially smaller proportion of patients in the mavacamten arm remained guideline eligible
- Indicates that treatment with mavacamten for 16 weeks reduces LVOT gradient below the threshold of 50 mmHg, or improves patients symptoms as assessed by NYHA class, or both

Abbreviations: NYHA, New York Heart Association; SRT, septal reduction therapy; LVOT, left ventricle outflow tract

Key issue: Exclusion of disopyramide as a comparator (1)

Use of disopyramide is highly variable

Background
- Company excluded disopyramide as a comparator. Clinical experts divided on whether this is appropriate

Company
- Limited use in NHS. More commonly part of standard care in larger centres.
- But accept that use of disopyramide is highly variable. Also unreliable availability
- Delphi panel estimated xx% usage in NYHA class II, xx% in NYHA class III, and xx% in NYHA class IV
- Lack of randomised evidence on disopyramide effectiveness

EAG comments
- For some people, disopyramide is effective, well tolerated and can be used for decades
- Accept variability and more commonly used in larger specialist centres
- Comparators should reflect current NHS practice
- Agree that disopyramide studies identified are not suitable for inclusion in an ITC

Clinical expert comments
- Disopyramide is most relevant comparator: recommended in European and US guidelines
- Any difficulty in obtaining disopyramide is hard to quantify beyond anecdote

Should disopyramide be excluded as a comparator?

Abbreviations: NYHA, New York Heart Association; ITC, indirect treatment comparison

Key issue: Exclusion of disopyramide as a comparator (2)

[redacted]

- A retrospective cohort study of patients diagnosed with HCM in England has been undertaken using data from the CPRD (GOLD and Aurum datasets) and linked hospital episode statistics (HES) data.
- Between 2010 and 2020, xxxxx patients had a record of obstructive HCM. Per calendar year, the proportion of patients with obstructive HCM prescribed disopyramide averaged xx % between 2010 and 2020 (range xx to xx %)

EAG comments:

- CPRD data is uncertain due to lack of clarity in data extraction protocol
- Data from primary care use only
- NYHA class I patients were not excluded from the database (not eligible for Mavacamten)

Abbreviations: HCM, hypertrophic cardiomyopathy; CPRD, Clinical Practice Research Datalink

Key issue: Efficacy of mavacamten in people with or without a sarcomere mutation

Uncertain whether sarcomere mutations are a treatment effect modifier

Background

- Efficacy may differ between people who have a sarcomere mutation and those who do not

Company

- Mavacamten targets hyperdynamic contraction, regardless of sarcomere mutation status
- EXPLORER-HCM shows [redacted]
- Cost-effectiveness by mutation status not feasible. Genetic testing a potential barrier to access

EAG comments

- EXPLORER-HCM: there may be differences in efficacy of mavacamten between sarcomere-positive and sarcomere-negative subgroups but not consistent in direction across outcomes where differences observed
- High uncertainty due to relatively small sizes of the subgroups and lack of statistical power
- Inconsistency in treatment effect means that subgroup analysis would not be appropriate

Clinical expert comments

- Pathophysiology of obstructive HCM is complex. Possible that the mechanism of LVOTO may be less driven by hypercontractility and more related to anatomical factors in people without sarcomere mutation.
- Mavacamten should not be limited to people with sarcomere mutation unless shown to be not cost-effective

Is there sufficient evidence for sarcomere mutation status being a treatment effect modifier?

Abbreviations: HCM, hypertrophic cardiomyopathy; LVOTO, Left Ventricular Outflow Tract Obstruction

Key issue: Post-authorisation safety monitoring of mavacamten (1)

Intensive safety monitoring could be challenging to implement

Background
- Careful monitoring needed in order to manage the risk of heart failure due to systolic dysfunction

Company
- EAG assumption of indefinite [redacted] monitoring (as per draft SmPC) is unrealistic
- Frequency will become lower over time, as clinicians gain experience, most likely after [redacted]
- Prefer [redacted] for [redacted], and then standard monitoring from [redacted] onwards
- Long waiting lists for echocardiography may be overcome by [redacted]

EAG comments
- EAG preference is for cost of monitoring as per the draft SmPC, but accept this is conservative
- Uncertain whether an adequate level of safety monitoring can be applied in the NHS, given current resource pressures (e.g. staff shortages), long waiting lists and the highly skilled nature of the monitoring required

Clinical expert and NHSE comments
- Additional NHS resources will be required
- Many trusts have a 3-4 month waiting list for echo and there is a national shortage of trained echo staff
- Need to prioritise, similar to echo surveillance for oncology patients receiving cardiotoxic chemotherapy

Is an appropriate level of safety monitoring likely achievable in the NHS?

Abbreviations: SmPC, summary of product characteristics

Key issue: Post-authorisation safety monitoring of mavacamten (2)

Intensive safety monitoring could be challenging to implement

Least conservative ← → Most conservative

Original company base case	Company base case after TE	EAG scenario	EAG base case (as per SmPC)
• x outpatient visits and echo procedures in year 1 • standard monitoring subsequently	• x visits in year 1 • xxx visits (xxxxxxxxx) in year x • standard monitoring from year x onwards.	• x visits in year 1 • years 2-5 every xx xxxxxxx • standard monitoring from year 6 onwards	• x visits in year 1 • Xxxxxxxx visits for maintenance dose • xxxxxxxx visits to continue from year x

Which level of safety monitoring is most likely in the NHS?

Abbreviations: SmPC, summary of product characteristics

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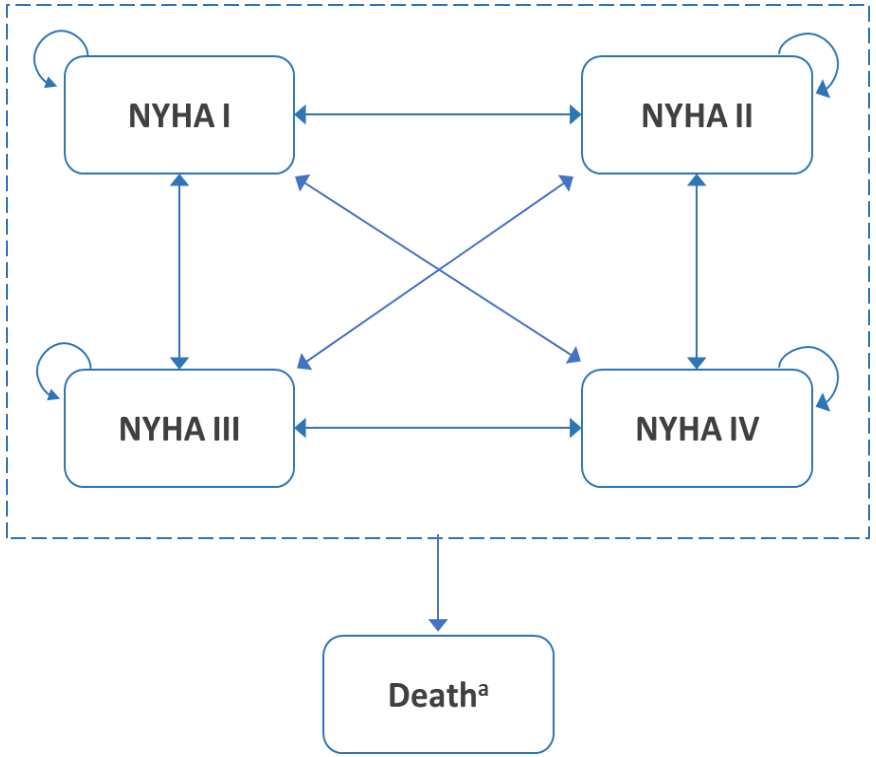
Company's model overview

Health state transition model, embedded in a treatment pathway model

- A cohort 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, people can transition between the NYHA classes, reflecting improvement or deterioration in disease severity, and deaths from HCM or other causes can occur from any NYHA state



- **Technology affects costs by:**
  - Higher costs than the comparator in EAG and company base cases
- **Technology affects QALYs by:**
  - More QALYs than comparator in company and EAG base cases
- **Assumptions with greatest ICER effect:**
  - Relative mortality rate in NYHA class II
  - Proportion of patients in NYHA class II who did not have a NYHA class improvement in first 30 weeks

[a] Death state is accessible from all non-death health states

Abbreviations: NYHA, New York Heart Association; HCM, hypertrophic cardiomyopathy

How company incorporated evidence into model

Input	Assumption and evidence source
Baseline characteristics	EXPLORER-HCM
Intervention efficacy	EXPLORER-HCM (mavacamten + BB/CCB)
Comparator efficacy	EXPLORER-HCM (placebo + BB/CCB)
Discontinuation	EXPLORER-HCM
Utilities	EXPLORER-HCM provides EQ-5D-5L data that has been mapped to EQ-5D-3L and used to derive utility inputs by NYHA class.
Costs and resource use	Per the NICE reference case, costs were sourced from NHS reference costs, BNF, PSSRU for all inputs. No reference case costs were identified for SRT, therefore these costs are informed by expert elicitation.

Abbreviations: HCM, hypertrophic cardiomyopathy; BB, beta blocker; CCB, calcium channel blocker; BNF, British National Formulary; PSSRU, Personal Social Services Research Unit; SRT, septal reduction therapy; NYHA, New York Heart Association

Key issue: Effect of treatments on mortality (1)

No evidence for causal link between NYHA class and mortality

Background
- Company model all-cause mortality using estimates of correlation between NYHA class and mortality derived from analyses of real-world data

Company
- Agree there is a lack of direct evidence for a beneficial effect of treatments on mortality, so proxy data used
- Evidence suggests higher NYHA class correlates with mortality in people with obstructive HCM
- Analysis of electronic medical records databases provides consistent evidence for this relationship

EAG comments
- Observed association between NYHA class and mortality is not necessarily causal
- Currently no evidence that treatments that reduce the symptoms of obstructive HCM have mortality benefit
- Not clear if mortality effects should be included in model – ICERs highly sensitive to this variable

Clinical expert comments
- No evidence of causal link between NYHA class and mortality, and NYHA class reporting is quite subjective
- No other treatments for LVOT obstruction have shown any mortality benefit

Is it appropriate to assume a causal association between NYHA class and mortality?

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Abbreviations: NYHA, New York Heart Association; LVOTO, Left Ventricular Outflow Tract Obstruction

Key issue: Effect of treatments on mortality (2)

Analysis suggests company base case HRs are conservative

- Electronic medical record analysis (Wang et al.) has been updated with additional data from the Market Clarity dataset, covering now a full sample of xxxxx US patients with obstructive HCM.
- This dataset gives hazard ratios for mortality by NYHA class higher than used in the Company cost-effectiveness model, which are conservative.

Mortality relationship between NYHA classes relative to NYHA class I

NYHA class	HRs from Wang et al. 2022 Humedica EMR study (original base case)	Updated HRs from Wang et al Market Clarity EMR study	Unadjusted 1-year RRs from SHaRe analysis (CS scenario)	Adjusted HRs from SHaRe analysis (CS scenario)
I	Reference class (ACM) i.e. 1.00			
II vs I	1.51	xxxxx	2.38	xxxxx
III vs I	2.77	xxxxx	9.38*	xxxxx
IV vs I	7.09	xxxxx		

*Composite III/IV HR applied to both III and IV classes separately

Is it appropriate to assume a causal association between NYHA class and mortality?

Abbreviations: HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association; ACM, all-cause mortality; HR, hazard ratio; SHaRe, Sarcomeric Human Cardiomyopathy Registry; NYHA, New York Heart Association; RR: relative risk

Key issue: Long-term rates of progression

Background
- Progressive deterioration of NYHA class is likely for people with obstructive HCM, but is complex
- Uncertainty over rate of increase in NYHA class, and whether this differs between treatments

Company
- Evidence suggests obstructive HCM is a progressive disease. Original company base case assumed no progression as a conservative approach, but did scenario using rate of 4.55% per year (Maron et al. 2016)
- Clinical experts suggest this rate is [redacted] of the rate they see in practice
- Have updated base case to reflect this rate of disease progression for both treatment arms (conservative)

EAG comments
- Agree with 4.55% rate of NYHA class progression after week 30 for all treatments
- Exploratory scenario of lower rate of progression for people on mavacamten ([redacted]%)

Clinical expert comments
- Highly problematic and simplistic to take a weighted average of a subgroup of a selected natural history study of middle-aged patients with HCM (Maron study) and extrapolate to older trial patients

Is a rate of 4.55% per year appropriate for both treatment arms?

Abbreviations: HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association

Key issue: Imbalance in trial follow up duration for calculation of transition probabilities (1)

Background
- Different methods to model transition probabilities in treatment arms may have introduced bias

Company
- This approach makes use of the longest continuous data that are available for each treatment arm
- Applying the approach for the mavacamten arm to both arms would disregard the trial data showing a diminishing effect on NYHA class in the BB/CCB monotherapy arm after week 30
- Data show [redacted] in mavacamten arm

EAG comments
- Same method should be used to estimate NYHA class transitions in both arms
- Data for weeks 30-46 is unreliable due to lack of comparative data, loss of blinding and uncertainty due to small numbers of some transition events

Clinical expert comments
- Assumption of stability of NYHA class over time requires prospective data rather than assumptions.
- Models based on NYHA class transition may be problematic: poorly quantified by physicians and patients

Is it appropriate to model transition probabilities the same in both treatment arms?

Abbreviations: NYHA, New York Heart Association; BB, beta blocker; CCB, calcium channel blocker

Key issue: Imbalance in trial follow up duration for calculation of transition probabilities (2)

[redacted]

Company:

- Analysis of the NYHA class distribution over time from the [redacted] data cut supports a [redacted] from week [redacted]

EAG comment:

- The reduced sample size at week 108 makes it difficult to interpret these data.

Is it appropriate to model transition probabilities the same in both treatment arms?

Abbreviations: NYHA, New York Heart Association

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy

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- ❑ Summary

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Summary of company and ERG base case assumptions

Assumption	Company base case	EAG base case
Health state transition probabilities	Estimates for the BB/CCB monotherapy arm between week 30 and week 46	Estimates from trial for 30 weeks only in both arms
Utilities	Utilities capped at general population values for age *	Utilities capped at general population values for age
Long term progression rate	Long-term progression rate for all treatments (4.55%) *	Long-term progression rate for all treatments (4.55%)
Safety monitoring	[redacted] visits in year [redacted] [redacted] visits ([redacted]) in year [redacted] standard monitoring from year [redacted] onwards *	Enhanced monitoring for mavacamten, in line with draft Summary of Product Characteristics

* These assumptions adopted into company base case at technical engagement stage

Abbreviations: HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association; BB, beta blocker; CCB, calcium channel blocker

Company base case results - after Technical Engagement

Model change	Incremental costs	Incremental QALYs	ICER (cost/QALY) after cumulative impact of model change
			mavacamten vs BB/CCB monotherapy
Company base case pre-technical engagement (after corrections to modelling)	£[redacted]	[redacted]	£30,139
Key Issue 3: Post-authorisation safety monitoring of mavacamten	£[redacted]	[redacted]	£30,676
Key Issue 5: Long-term rates of progression	£[redacted]	[redacted]	£17,963
Key Issue 6: Effects of treatment on mortality	£[redacted]	[redacted]	£17,597
Inclusion of EAG approach to utility values	£[redacted]	[redacted]	£19,401
Company base case post-technical engagement	-	-	£19,401

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; BB, beta blockers; CCB, calcium channel blockers

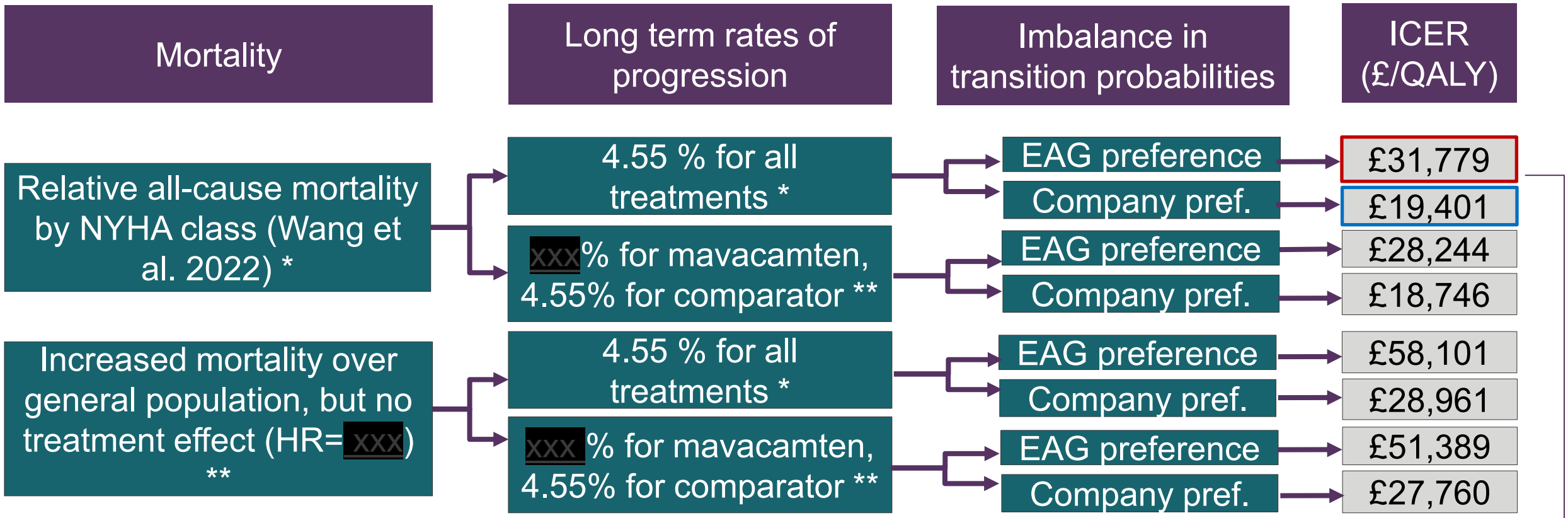
ERG base case results – after Technical Engagement

Deterministic incremental base case results

Scenario	Treatment	Total costs	Total QALYs	Increm. costs	Increm. QALYs	ICER (£/QALY)
Company's post-TE base case	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£19,401
	BB/CCB monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	
+ TP estimates for 30 weeks from both trial arms (key issue 4)	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£31,779
	BB/CCB monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	
+ Monitoring, [redacted] times in year 1, then [redacted] (key issue 3)	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£37,088
	BB/CCB monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	
EAG's post-TE base case	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£37,088
	BB/CCB monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; BB, beta blockers; CCB, calcium channel blockers

Cost effectiveness scenarios



Imbalance in transition probabilities:
EAG preference = Trial-based TPs until week 30 in both arms
Company preference = Comparator TPs from post-trial data until week 46
* = EAG and company base case assumption, ** = Clinically plausible scenario

EAG preferred
Company preferred

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Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; HR, hazard ratio; TP, transition probability

EAG scenarios for safety monitoring

Impact on EAG base case

Scenario	Treatment	Total costs	Total QALYs	Increm. costs	Increm. QALYs	ICER (£/QALY)
Year 1 [redacted] assessments; years 2 to 5 [redacted]; assessments; then standard care	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£33,623
	BB/CCB monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	
Year 1 [redacted] assessments; years 2 & 3 [redacted]; assessments; then standard care	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£32,594
	BB/CCB monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	
Year 1 [redacted] assessments; year 2 [redacted]; assessments; then standard care	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£31,983
	BB/CCB monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	
Year 1 [redacted] assessments; year 2 [redacted]; year 3: [redacted]; weeks, then standard care monitoring	Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	£31,998
	BB/CCB monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	

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Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years

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Other considerations

Equality considerations

- No equality issues were identified

Innovation

- Mavacamten considered to be a ‘step-change’ in the management of symptomatic obstructive HCM
- It is designed to modify the underlying pathophysiology in obstructive HCM
- Awarded a Promising Innovative Medicines (PIM) designation on 21 August 2021 by the Medicines and Healthcare products Regulatory Agency (MHRA)

Severity modifier

- 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
- Company did not refer to the QALY shortfall criteria for severity weighting in their submission
- NICE criteria of absolute QALY shortfall ≥ 12 or proportional QALY shortfall ≥ 85% are not met for either the company’s or the EAG’s base case analyses

Managed access (1)

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**

Managed access (2)

Suitability for a managed access recommendation

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	The IMF is targeted to the most promising medicines. NHSE recognises the high unmet meet for these patients and agrees it would be a potential candidate for the IMF.
Is it feasible to collect data that could sufficiently resolve key uncertainties?	Unclear	Further evidence collected during a period of managed access is unlikely to resolve all the uncertainties, such as long-term rates of progression, effect of treatments on mortality or imbalance in follow up duration for transition probabilities.
Can data collection be completed without undue burden on patients or the NHS system?	Yes	An ongoing extension trial (EXPLORER-LTE expected to complete 2026) could be the main source for further evidence generation.
Are there any other substantive issues (excluding price) that are a barrier to managed access?	No	Implementing safety monitoring as per SmPC may be challenging to implement in the NHS. However, this is not a barrier to managed access data collection.

Could additional data collection address the key uncertainties?

Abbreviations: SmPC, summary of product characteristics; IMF, Innovative Medicines Fund

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Key issues

Key issues from EAG report	Resolved?	ICER impact
Effect of treatments on mortality	No – for discussion	Large
Long-term rates of progression	Partially – for discussion	Large
Imbalance in follow up duration for transition probabilities	No – for discussion	Large
Post-authorisation safety monitoring of mavacamten	No – for discussion	Small
Exclusion of disopyramide as a comparator	No – for discussion	Unknown
Uncertain efficacy of mavacamten in patients without a sarcomere mutation	No – for discussion	Unknown

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Thank you