National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy pre-referral remit and scope
Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	BMS	We agree that there is significant unmet need within the obstructive hypertrophic cardiomyopathy (oHCM) patient population. Current treatments only provide symptomatic relief, have varying clinical efficacy, and are associated with side-effects.[1-5] oHCM is a lifelong, progressive disease. Patients with oHCM may experience symptoms such as fatigue, angina, dyspnoea, palpitations, and syncope which negatively impact upon quality of life, and are at increased risk of sudden cardiac death (SCD) and other cardiac comorbidities such as heart failure (HF).[5-8] There is currently no disease-modifying therapy available that is indicated for the treatment of oHCM. Mavacamten is designed to target the underlying pathophysiology of oHCM; as such, an application for Promising Innovative Medicine (PIM) designation for mavacamten for the treatment of hypertrophic cardiomyopathy (HCM) has been made. Mavacamten is a novel, well tolerated and effective therapy that aims to reduce myocardial hypercontractility, thought to be one of the key pathophysiological mechanisms in oHCM.[9] Mavacamten has the potential to	Comment noted. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		slow or halt disease progression and improve patient's functional status and quality of life.[9] Therefore, this appraisal should be considered a priority.	
	Cardiomyopathy UK	-	No action needed.
Wording	BMS	The remit in the draft scope does not reflect the proposed indication submitted to the European Medicines Agency (EMA). The following text is expected to be the indication approved by the MHRA: To appraise the clinical and cost effectiveness of mavacamten within its marketing authorisation [redacted]	Comment noted. Remit in the scope has been left broad as mavacamten has not yet received its marketing authorisation. However, the population has been updated to reflect the population included in the clinical trial.
	Cardiomyopathy UK	-	No action needed.
Timing Issues	BMS	There is significant unmet medical need in this patient population due to the paucity and non-disease specific mechanism of action of current treatments. Current pharmacological treatment options for patients with symptomatic oHCM are limited to therapies that provide symptomatic control.[3,5] These therapies offer limited and variable relief of symptoms and functional status improvements for patients with oHCM, especially in patients with more advanced disease, and are often poorly tolerated due to side effects.[1-5] Clinical experts in the field of HCM with whom we have engaged, report substantial unmet need for a therapy such as mavacamten in their patients,	Comment noted. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		often citing specific examples of patients who they intend to prescribe mavacamten to as soon as reimbursed. A non-invasive therapy designed to target the underlying pathophysiological mechanism of oHCM is long-awaited by both clinicians and patients.	
	Cardiomyopathy UK	-	No action needed.
Additional comments on the draft remit	BMS	None.	No action needed.
	Cardiomyopathy UK	-	No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	BMS	BMS consider that the background information regarding the aetiology, clinical presentation and epidemiology of HCM is largely accurate and complete, however it should be clarified that most people with HCM may initially have few or no symptoms, as it is a progressive disease and symptoms may develop or worsen at any age.[6] Additionally, the description of treatment approaches is not fully consistent with BMS' understanding of current UK clinical practice. Specifically, the treatment options available when beta blockers are ineffective or contraindicated are not accurately represented. Clinical advice received suggests that the 2014 ESC guidelines[5] do not fully reflect current UK clinical practice in treating HCM patients with left ventricular outflow tract obstruction (LVOTO). In practice, Calcium Chanel Blockers (CCBs) are typically used for	The background section of the scope has been updated as follows: • A sentence had been added clarifying that most people with HCM may initially have few or no symptoms • The list of treatments for

Section	Consultee/ Commentator	Comments [sic]	Action
		patients who are refractory or intolerant to beta blockers, while disopyramide is used rarely, and mainly in patients who are non-responders to and/or contraindicated for beta blockers and CCBs. Furthermore (as addressed further in the comparators section), clinical guidelines for HCM recommend that patients with oHCM and HF receive treatment to reduce the obstruction,[5] therefore it should be clarified that, with the exception of beta blockers, the list of treatment options for heart failure (ACE inhibitors, angiotensin-receptor blockers, mineralocorticoid receptor antagonists, ivabradine, sacubitril valsartan, dapagliflozin) comprises therapies that are not used to treat oHCM patients and therefore should be considered out of scope. The background information also states "*In cases where individuals are considered to be at high risk of sudden cardiac death, implanted devices such as a pacemaker or an implantable cardioverter defibrillator (ICD) may be used (NICE technology appraisal guidance 314).*" Whereas we agree that implantable devices are a vital treatment option for those HCM patients deemed at high risk of SCD, it should be noted that implanted devices are not, per se, a treatment for symptomatic oHCM but are indicated for management of a potential complication of HCM in a specific subset of patients. These patients are not synonymous with the population for whom mavacamten would be indicated. The text should be modified to make this differentiation clear. Finally, the background information states "*If severe symptoms persist, people may have surgical myectomy. Alternatively, non-surgical reduction of the myocardial septum may be offered (NICE interventional procedures guidance 40)*." It should be clarified that these invasive options are recommended for patients who remain symptomatic despite best medical therapy,[5] and that the order of the text should be revised to reflect that SRT is generally offered downstream of beta blockers, CCBs and disopyramide.	chronic heart failure which are not used for people with oHCM has been removed • The sentences regarding invasive therapies have been updated. Consistent with the ESC guidelines and comments received from clinicians during the scoping workshop for mavacamten, disopyramide has been included in the background section as a treatment option that can be used alone in combination with beta-blockers or calcium channel blockers.

Section	Consultee/ Commentator	Comments [sic]	Action
		Taking all these points into consideration, the following revision to the background information regarding current treatment options is suggested (changes to the original text are underlined): *"…people with symptomatic disease, predominately with left ventricular outflow tract obstruction, receive beta-blockers to reduce symptoms and obstruction. If beta-blockers are ineffective or contraindicated, non-dihydropyridine calcium channel blockers (verapamil or diltiazem) are suitable alternatives. People who fail to respond to appropriate therapy with beta blockers, verapamil or diltiazem may be considered for treatment with disopyramide. Low-dose diuretics may be used to treat persistent dyspnoea, but caution must be taken to avoid hypovolaemia, and high-dose diuretics should be avoided. If severe symptoms persist on maximal tolerated guideline-recommended medical therapy, people may have surgical myectomy. Alternatively, non-surgical reduction of the myocardial septum may be offered (NICE interventional procedures guidance 40). For people with obstructive HCM who progress to heart failure, the only guideline-recommended treatment options are those recommended to manage left ventricular outflow tract obstruction. People with HCM, regardless of the presence of obstruction, should undergo clinical risk assessment for sudden cardiac death risk; known risk factors include age, family history of sudden cardiac death and unexplained syncope. In cases where individuals are considered to be at high risk of arrhythmias and sudden cardiac death, implanted devices such as a pacemaker or an implantable cardioverter defibrillator (ICD) may be used (NICE technology appraisal guidance 314)."*	
	Cardiomyopathy UK	-	No action needed.
	BMS	The intervention should be described as "mavacamten in addition to standard of care".	Comment noted. The scope has been

Section	Consultee/ Commentator	Comments [sic]	Action
The technology/ intervention		BMS consider the following description of the technology is more accurate (changes to the original text are underlined): *"Mavacamten (brand name unknown, Bristol-Myers Squibb) is a first-in-class, selective allosteric, reversible, small molecule inhibitor of cardiac myosin ATPase that reduces myosin-actin crossbridge formation and thus reduces myocardial contractility and improves diastolic relaxation. It is administered orally once a day.* *Mavacamten does not currently have a marketing authorisation in the UK for symptomatic obstructive hypertrophic cardiomyopathy. It has been studied in clinical trials compared with placebo in adults with symptomatic obstructive HCM."*	updated to clarify mavacamten has been studied as an adjunct therapy in current clinical trials and will be used with standard care. The population of the clinical trials has also been updated. Descriptions of mechanisms of action has been kept broad. No changes made.
	Cardiomyopathy UK	-	No action needed.
Population	BMS	BMS do not believe that the population is defined appropriately. The population proposed by NICE does not reflect the patient population analysed by the landmark pivotal phase III trial (EXPLORER-HCM)[9] as per the anticipated EMA license: [redacted]	Comment noted. Based on the clinical trial population and discussions at the scoping workshop for mavacamten, the population has been updated to "adults with symptomatic obstructive hypertrophic cardiomyopathy (NYHA class II-III).

Section	Consultee/ Commentator	Comments [sic]	Action
	Cardiomyopathy UK	-	No action needed.
Comparators	BMS	BMS do not consider that the proposed list of comparators is appropriate. Mavacamten is intended as an adjunctive therapy to current standard of care (SOC) for oHCM patients. This SOC reflects established medical management and should comprise: • Beta blockers; • Non-dihydropyridine calcium channel blockers (CCBs) i.e. verapamil and diltiazem; • Disopyramide. The above list of established therapeutic options for oHCM identified by BMS differs from that proposed by NICE in the draft scope, based on the following rationale: 1. The CCB diltiazem should be included in addition to verapamil. Although not as commonly used as verapamil, diltiazem forms part of guideline-directed therapy for oHCM, indicated for patients who are intolerant to or contraindicated for beta blockers or verapamil.[5] 2. ACE inhibitors, angiotensin-receptor blockers, ivabradine, dapagliflozin, mineralocorticoid receptor antagonists and sacubitril valsartan are all NICE-recommended treatments for chronic heart failure (HF), specifically HF with reduced ejection fraction (HFrEF).[10,11] Although patients with HCM can develop HF, different medical management is recommended for obstructive and non-obstructive patients. The algorithm for the treatment of HF in HCM in the 2014 ESC guidelines[5] highlight that patients with obstructive disease and HF should receive	Comment noted. Based on the consultation comment and discussions at the scoping workshop, the comparators in the scope have been updated to individually optimised standard care without mavacamten. This is defined as beta-blockers, non-dihydropyridine calcium channel blockers and disopyramide alone or in combination.

Section	Consultee/ Commentator	Comments [sic]	Action
		management of their LVOTO only. Therefore, the patient group who would be eligible for mavacamten would not be eligible for the standard HF therapies outlined by NICE (i.e. ACE inhibitors, angiotensin-receptor blockers, ivabradine, dapagliflozin, mineralocorticoid receptor antagonists and sacubitril valsartan). Furthermore, the standard HF therapies listed are only indicated for the treatment of HFrEF,[10,11] [redacted] 3. Surgical myectomy and non-surgical reduction of the myocardial septum, henceforth referred to as septal reduction therapies (SRT), are not intended to be displaced by mavacamten. Under current guidelines and clinical practice, SRT is generally considered for patients for whom maximal tolerated medical therapy is not sufficient to relieve significant symptoms i.e. consistent with NYHA class III/IV.[5] SRT carries substantial risks inherent to invasive procedures and requires expertise that is not universally available and is only conducted in a few specialist centres; notably, there is evidence that septal myectomy is associated with increased mortality when performed at low-volume centres.[12] SRT is offered to a small number of patients who are refractory to medical therapy, therefore although it does form part of the treatment pathway for oHCM, it should not be considered a direct comparator. It is not anticipated that these considerations for SRT will be changed by mavacamten, therefore it is not a relevant comparator to mavacamten in this appraisal. 4. Implanted devices (implantable cardioverter-defibrillators (ICDs) and pacemakers) are intended to treat disorders of electrical conduction in the heart, with ICDs specifically indicated for the prevention of SCD,[5] which is a potential complication of HCM. Implanted devices are not	

Section	Consultee/ Commentator	Comments [sic]	Action
		intended to be displaced by mavacamten; indeed, 22% patients in the pivotal trial, EXPLORER-HCM, had an existing ICD.[9] Mavacamten is not expected to impact implanted device use; implanted devices are expected to remain as part of standard of care within a parallel treatment pathway for those patients estimated to be at high risk of conduction abnormalities, including those resulting in SCD. Therefore, implanted devices are not a relevant comparator to mavacamten in this appraisal.	
	Cardiomyopathy UK	I would question the inclusion of ICD and pacemaker in this list of comparators as they serve a different purpose to Mavacamten	Comment noted. Implantable devices (ICDs and pacemakers) have been removed as potential comparators.
Outcomes	BMS	BMS suggest the addition of the following outcome: • Post-exercise left ventricular outflow tract (LVOT) gradient A defining feature of oHCM is obstruction of the LVOT, which may be observed at rest or provoked in response to strenuous exercise. LVOTO is responsible for a range of debilitating symptoms experienced by patients, and is associated with an increased risk of developing HF and reduced survival.[13,14] LVOTO is measured clinically as a pressure gradient across the LVOT, and a reduction in this measured gradient reflects a clinically-meaningful improvement in the underlying disease. Otherwise BMS believe the list of outcomes is generally appropriate but note that there is a degree of redundancy between some inter-related outcomes, in particular:	Comment noted. Symptom-severity has been updated to patient-reported symptom severity. Based on discussion at the scoping workshop LVOT was not seen as a key clinical outcome so has not been added to the scope. However, the list of outcomes is not exhaustive and

Section	Consultee/ Commentator	Comments [sic]	Action
		Symptom severity should be refined to 'patient-reported symptom severity' to distinguish it from NYHA class, which is physician-assessed.	clinicians noted they would be interested in seeing the data if it was available.
	Cardiomyopathy UK	-	No action needed.
Economic analysis	BMS	No comments.	No action needed.
	Cardiomyopathy UK	-	No action needed.
Equality and Diversity	BMS	No equality issues have been identified.	No action needed.
	Cardiomyopathy UK	-	No action needed.
Other considerations	BMS	The draft scope included the following consideration: *If the evidence allows the following subgroups will be considered:* • *people eligible for septal replacement therapy* In consideration of this potential subgroup, septal reduction (N.B. not replacement) therapy should not be considered a direct comparator to mavacamten, as detailed above in the section on comparators, therefore focussing on this subgroup is not relevant to the appraisal. It should be noted that there is a paucity of existing evidence comparing SRT with other current treatments for oHCM; BMS has identified no randomised	Comment noted. Subgroup has been removed from the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		controlled trials and a limited number of observational studies. Furthermore, SRT is used in only a small number of patients; this is exemplified by the EXPLORER-HCM trial.[9] Patients were eligible for enrolment in this trial if they had previously had SRT (more than 6 months before screening). Overall, 8% trial patients had previously received SRT. Thus, patient numbers in this post-SRT population were small and although it is a strength of the study that these patients were included, this does not permit robust subgroup analysis. Nevertheless, evidence from the EXPLORER-HCM trial suggests that mavacamten is equally effective across subgroups.[9] BMS understands that SRT may play an important role in the management of oHCM for a small number of patients refractory to all other therapies, and for that reason is currently conducting VALOR-HCM trial (NCT04349072).[15] VALOR-HCM is a randomised, double-blind, placebo-controlled study designed to evaluate the effect of mavacamten treatment on reducing the number of SRT procedures performed in patients with oHCM who are eligible for SRT, however the estimated completion date for this trial is December 2024, therefore this evidence will not be available at the time of submission.	
	Cardiomyopathy UK	-	No action needed.
Innovation	BMS	Mavacamten is innovative in the treatment of adults with symptomatic oHCM, due to the novel mechanism of action that is designed to target the underlying pathophysiology of HCM, in an indication that otherwise has no alternative treatments that address the molecular mechanisms of the disease.[9] Mavacamten has the potential to make a significant impact on health-related benefits in a patient population with a substantial unmet need.	Comment noted. The committee will consider the innovative nature of mavacamten during the appraisal process. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		As previously mentioned, a high unmet need exists for effective therapies for patients with oHCM. Current pharmacological treatment options offer limited and variable relief in symptoms and improvements in functional status, especially in those with more advanced disease.[3,5] Furthermore, because none target the underlying pathophysiology of the disease, they are unable to slow or halt disease progression. Increased myocardial contractility is a key factor in the pathophysiology of HCM. Phase II and III clinical trials have demonstrated that mavacamten is associated with clinically-meaningful improvements in the functional status and symptoms of patients with symptomatic oHCM.[9,16,17] Furthermore, current treatments are associated with side-effects,[5] impairing health-related quality of life (HRQoL); mavacamten was associated with few adverse events and with improvements in HRQoL.[9,18] Patients receiving mavacamten also demonstrated reduced LVOTO and reduced biomarkers of cardiac dysfunction.[9] Together, these results suggest that mavacamten has the potential to slow or halt disease progression. By targeting the underlying pathophysiology, mavacamten may lead to positive cardiac remodelling.[19] EQ-5D is the preferred measure of HRQoL. However, this is not a disease-specific instrument and, due to the nature of the limitations associated with oHCM, there may be health-related benefits that are not captured by either the physiological parameters or EQ-5D and are therefore not represented in the quality-adjusted life year (QALY) calculation. HRQoL measured in EXPLORER-HCM using the Kansas City Cardiomyopathy Questionnaire (KCCQ) instrument showed benefits associated with mavacamten in all domains, suggesting a strong cardiomyopathy-specific benefit.[18] Furthermore, these HRQoL instruments tend to capture significant lifestyle impairments. Patients with oHCM may make more modest lifestyle modifications, for example avoidance of high intensity exercise and reduction in manual work,[6]	

Section	Consultee/ Commentator	Comments [sic]	Action
		that may not be captured in the HRQoL assessment but nevertheless represent restrictions to normal life that could be improved upon. HCM is known to be associated with an increased risk of SCD. In particular, HCM is the most common cause of SCD in young people.[20] It is believed that living with awareness of this risk is associated with anxiety and avoidance.[21] The novel mechanism of action of mavacamten, which acts on cardiac hypercontractility, one of the key pathophysiological mechanisms underlying HCM, and the potential of mavacamten to slow disease progression, may eventually help to alleviate patient fear of SCD. This potential benefit of mavacamten is unlikely to be captured in the QALY calculation. BMS consider that mavacamten is innovative and represents a 'step-change' in the management of symptomatic oHCM and will result in significant benefit to patients living with this condition.	
	Cardiomyopathy UK	-	No action needed.
Questions for consultation	BMS	**Where do you consider mavacamten will fit into the existing treatment pathway?** In line with the proposed indication submitted to the regulatory authorities, use of mavacamten is considered [redacted] Therefore, BMS propose that mavacamten will be used as an adjunct to current medical SOC; beta blockers, CCBs and disopyramide. Mavacamten is suitable for use in patients with an ICD or who have previously had SRT, but these are not considered direct comparators.	Comment noted. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom mavacamten is expected to be more clinically effective and cost effective or other groups that should be examined separately? The suggested subgroup is discussed in the section on 'other considerations', above. BMS do not believe there are any other subgroups that should be examined separately. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** BMS do not consider there to be any barriers to the adoption of mavacamten into UK clinical practice	
	Cardiomyopathy UK	-	No action needed.
Additional comments on the draft scope	BMS	None.	No action needed.
	Cardiomyopathy UK	-	No action needed.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Pfizer