Health Technology Briefing
September 2024

Mavacamten for treating non-obstructive hypertrophic cardiomyopathy

Company/Developer	Bristol-Myers Squibb Pharmaceuticals Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30415	NICE ID: Not available	UKPS ID: 674933

Licensing and Market Availability Plans

In phase III clinical development for non-obstructive hypertrophic cardiomyopathy (nHCM).

Summary

Mavacamten is in clinical development for treatment of non-obstructive hypertrophic cardiomyopathy (HCM). HCM is often an inherited disease, where the heart muscle cells enlarge, and the walls of the heart thicken. If there is no significant blocking of blood flow, the condition is called nonobstructive HCM (nHCM). This is caused by excessive binding of myosin and actin (proteins involved in muscle contraction) in the heart muscle, which leads to abnormally increased contractions in the heart. This affects the hearts' ability to pump blood around the body effectively, and can cause symptoms including dizziness, fatigue, heart murmurs and swelling of legs, ankles and/or abdomen. Patients with nHCM are at risk of serious conditions such as sudden cardiac death and stroke. Currently, treatment strategies for nHCM are aimed at managing symptoms, and there are no licensed therapies available for treating the underlying cause of disease.

Mavacamten is a 'cardiac myosin inhibitor', given as an oral tablet. Mavacamten binds to myosin, preventing it from attaching to actin, which reduces the excessive connections between these two proteins. This allows the heart muscle to relax more, and has been shown to reduce heart muscle stress, which can be associated with serious adverse events such as sudden cardiac death. If licenced, mavacamten would offer an additional treatment option to adult patients with nHCM.

Proposed Indication

Treatment of adults with symptomatic non-obstructive hypertrophic cardiomyopathy (nHCM).[1]

Technology

Description

Mavacamten (BMS-986427, MYK-461) is an allosteric and reversible cardiac myosin inhibitor.[2] Myosin inhibitors are capable of modifying the myosin-actin mechochemistry.[3] Mavacamten modulates the number of myosin heads that can enter power-generating states, returning the probability of force-producing systolic and residual diastolic cross-bridge formation to normal in patients with nHCM.[2] Cardiac myosin inhibition by mavacamten normalises contractility, reduces dynamic left ventricular outflow tract and improves cardiac filling pressures.[2]

Mavacamten is in phase III clinical development for treatment of symptomatic nHCM.[1] The proposed treatment regime for nHCM has not been confirmed. Mavacamten is given as oral tablets.[2]

Key Innovation

nHCM is associated with significant adverse events such as atrial fibrillation, stroke or sudden cardiac death.[4] Current treatment strategies focus on managing arrhythmias, particularly atrial fibrillation, and attempting to improve left ventricular (LV) filling or congestion with beta-blockers, verapamil, and diuretics.[5] However, there are no treatment options currently available addressing the underlying disease process of nHCM. If patients do not respond to pharmacological therapies, they may require surgery such as septal myectomy or heart transplantation.[6] Mavacamten has the potential to modify nHCM disease pathophysiology and improve symptoms associated with nHCM by altering contractile mechanics of cardiomyocytes.[5] Mavacamten treatment has led to a reduction in biomarkers associated with myocardial wall stress and injury in previous trials EXPLORER-HCM and MAVERICK-HCM (N-terminal pro–B-type natriuretic peptide and cardiac troponin I).[5,7] Evidence suggests mavacamten is well tolerated by the majority of patients.[5] If licensed, mavacamten will offer an additional treatment option for patients with nHCM, who currently have limited treatment strategies.

Regulatory & Development Status

Mavacamten is marketed in the UK for treatment of symptomatic obstructive HCM in adults patients with New York Heart Association (NYHA) class II to III.[8]

Mavacamten is in phase III/II clinical development for obstructive HCM.[9]

Patient Group

Disease Area and Clinical Need

HCM is a genetic disorder characterised by LV hypertrophy.[10] HCM can be oHCM or nHCM; oHCM means the blood flow from the heart is reduced by the thickening of the heart's muscular wall, nHCM means blood flow from the heart is not reduced by the thickening of the heart's muscular wall.[11] A child of someone with HCM has a 50% chance of inheriting the condition.[12] The most common disease gene is TNNI3, other less commonly involved genes include TNNT2, ACTC1, MYH7, MYBPC3, TTN, TPM1, MYPN, MYL3, and MYL2.[13] Most of these mutations promote actin-myosin cross-bridge formations in cardiomyocytes, leading to hyperdynamic contraction and increased energy consumption.[14] HCM is characterised by thickening of the myocardium, resulting in left ventricular hypertrophy, and in some cases the septum is also thickened.[12,15] While there is no significant blocking of blood flow in nHCM, the LV may

become stiff.[16] This compromises the functional ability of the LV, affecting the hearts ability to pump blood around the body.[17] Symptoms of nHCM can include dizziness, fatigue, heart murmurs and oedema of ankles, legs and/or abdomen.[17]

Approximately 1 in 500 people in the UK have a form of HCM.[12] The proportion of HCM cases that are nHCM in the UK is approximately 32%.[18] Between 2022-2023, there were 1,409 finished consult episodes (FCE) for other hypertrophic cardiomyopathies (ICD10 code I42.2) in England, resulting in 601 day cases and 4,196 FCE bed days.[19] A US-based cohort study described annual nHCM mortality as <1%, however found patients with nHCM were at greater risk of adverse related disease events such as ventricular arrythmia, atrial fibrillation or stroke.[4]

Recommended Treatment Options

There are currently no approved pharmacological treatment options specifically for nHCM. Treatment options are available to help control symptoms and prevent other health issues. These include pharmacological drugs (such as diuretics, beta blockers and cardiac myosin inhibitors), medical devices (e.g., pacemaker), catheter ablation, or septal myectomy (a type of heart surgery).[12]

Clinical Trial Information

Trial	**ODYSSEY-HCM; NCT05582395;EudraCT 2021-005329-26;** A randomized, double-blind, placebo-controlled clinical study to evaluate mavacamten in adults with symptomatic non-obstructive hypertrophic cardiomyopathy **Phase III –** Active, not recruiting **Locations:** 12 EU countries, the UK, United States, and other countries **Primary completion date:** March 2025
Trial Design	Randomised, double blinded, parallel assignment.
Population	N = 420 (estimated). Subjects with diagnosis of HCM (unexplained LV hypertrophy with non-dilated ventricular chambers in the absence of other cardiac or systemic disease), with LV wall thickness ≥15mm or ≥13mm with positive family history of HCM, peak LV outflow tract pressure gradient <30 mmHg at rest and <50 mmHg with provocation (Valsalva maneuver and stress echocardiography), NYHA class II or III, and aged 18 and older.
Intervention(s)	Patients were administered specified dose of mavacamten on specified days.
Comparator(s)	Matched placebo.
Outcome(s)	Primary outcomes: - Change from baseline in Kansas City cardiomyopathy questionnaire (23-item) clinical summary score at week 48 - Change from baseline in peak oxygen consumption at week 48 See trial record for full list of all outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Mavacamten is already marketed in the UK, the cost of 28 capsules is £1,073.20.[20]

Relevant Guidance

NICE Guidance

No relevant NICE guidance identified.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cardiology: Inherited Cardiac Conditions (All ages). A09/S/c

Other Guidance

- Ommen S, Ho C, Asif I, Balaji S, Burke M *et al*. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the Management of Hypertrophic Cardiomyopathy: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. 2024.[21]
- European Society of Cardiology. 2023 ESC Guidelines for the management of cardiomyopathies ESC Clinical Practice Guidelines. 2023.[13]

Additional Information

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.