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HEALTH TECHNOLOGY BRIEFING JANUARY 2021

Mavacamten for hypertrophic cardiomyopathy

NIHRIO ID	13071	NICE ID	10536
Developer/Company	Bristol-Myers Squibb	UKPS ID	659841

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Mavacamten is currently being developed for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adults. Hypertrophic cardiomyopathy (HCM) is a genetic condition whereby areas of heart muscle become thickened and stiff. Blood decreases in the left ventricular volume and narrowing of the left ventricular outflow tract (LVOT) is classified as obstructive HCM (oHCM). HCM is a genetic condition that is caused by a change or fault (or mutation) in one or more genes. The most common symptoms are shortness of breath, palpitations, chest pain and light-headedness. Patients with oHCM can develop serious complications such as atrial fibrillation, heart failure, malignant ventricular arrhythmias, and sudden cardiac death (SCD).

Mavacamten, intended for oral administration, is the first therapeutic candidate in a new class of direct myosin (protein involved in muscle contraction) inhibitors. It targets excessive contractility and impaired relaxation, heart muscle energetics and compliance, with the intent of correcting the abnormal function of the HCM heart. If licensed, mavacamten in addition to the current standard of care would offer an additional treatment options for adult patients with symptomatic oHCM.

PROPOSED INDICATION

Treatment of adults with symptomatic oHCM.[1,a]

TECHNOLOGY

DESCRIPTION

Mavacamten (MYK-461) is a first-in-class, small molecule, selective allosteric inhibitor of cardiac myosin ATPase specifically developed to target the underlying pathophysiology of hypertrophic cardiomyopathy, by reducing actin–myosin cross-bridge formation, thereby reducing contractility and improving myocardial energetics.[2] It is intended to reduce resting and dynamic left ventricular outflow tract (LVOT) obstruction in patients with oHCM by normalising the function of myosin protein in hypercontractile hearts, regardless of the presence of a sarcomeric gene mutation.[3]

Mavacamten is currently in clinical development for the treatment of oHCM in adult patients, in addition to the current standard of care.[a] In the phase III clinical trial (EXPLORER-HCM, NCT03470545), patients were assigned to receive once-daily orally administered treatment with mavacamten (starting at 5 mg) for 30 weeks.[1,2]

INNOVATION AND/OR ADVANTAGES

In the absence of randomised trials, guideline-recommended pharmacological therapy is administered on an empirical basis and includes β blockers or non-dihydropyridine calcium channel blockers, as well as disopyramide for individuals refractory to first-line therapy.[2] Despite management with β-blockers or non-dihydropyridine calcium-channel blockers, symptoms and disease burden persist for many patients with oHCM, and therapeutic options are limited.[3] Moreover, the use of these drugs is limited by side-effects, and often does not provide optimal control of LVOT gradients and symptoms, leaving an unmet burden of disease in many patients.[2]

In the phase 2 PIONEER-HCM trial, in patients with oHCM, treatment with mavacamten led to improvements in post-exercise LVOT gradients, exercise capacity, and symptoms, and was generally well tolerated, with most adverse effects being mild or moderate, self-limiting, and unrelated to the study drug.[2,3] In the phase III EXPLORER-HCM clinical trial, treatment with mavacamten improved exercise capacity, LVOT obstruction, New York Heart Association functional class, and health status in patients with obstructive hypertrophic cardiomyopathy.[2]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Mavacamten does not currently have Marketing Authorisation in the EU/UK for any indication.

Mavacamten was granted:

- a Paediatric Investigation Plan (EMEA-002231-PIP01-17) for the treatment of oHCM the EMA in March 2019[4]
- a Breakthrough Therapy Designation by the US FDA for the treatment of symptomatic oHCM in July 2020.[5]

Mavacamten is currently in phase II/III clinical trials for the treatment of HCM, oHCM and non-oHCM.[6]

[a] Information provided by Bristol-Myers Squibb on UK PharmaScan

Serious adverse events associated with mavacamten reported in clinical studies were generally mild and include atrial fibrillation, syncope, stress cardiomyopathy, diverticulitis, infection, contusion and forearm fracture.[2,7]

PATIENT GROUP

DISEASE BACKGROUND

HCM is the most frequently occurring inherited cardiovascular disease. It is a genetically determined heart muscle disease with most HCM cases (60 to 70 percent) caused by the mutations in genes encoding proteins of the cardiac sarcomere.[8] This complex disease can be broadly defined by pathologically enhanced cardiac actin–myosin interactions, with core pathophysiological features that include hypercontractility, diastolic abnormalities, and dynamic LVOT obstruction.[2] HCM generally affects the left ventricle and particularly the septum. However, it can also affect the right ventricle.[9]

The most commonly responsible genes for HCM are *MYH7*, *MYBPC3*, *TNNT2*, and *TNNI3*.[10] Between 30 and 50% of those mutations are found in the gene that encodes human β-cardiac myosin, the motor that powers ventricular contraction.[8] A child of someone with HCM has a 50% chance of inheriting the condition.[11] Other causes of HCM include:[12]

- Heightened sympathetic stimulation due to excess catecholamine secretion or decreased uptake.
- Abnormally thickened coronary arteries which may not dilate normally. This may lead to ongoing myocardial ischemia, that eventually leads to ventricular fibrosis and compensatory hypertrophy.
- Abnormal microcirculation that prevents the normal contractile function of the myofibrils.

HCM is characterised by a wall thickness of 15mm or more.[9] Symptoms of HCM include shortness of breath, chest pain, palpitations, light headedness and fainting, however, many affected individuals have no symptoms.[10,11] People with HCM have an increased risk of sudden death, even if they have no other symptoms of the condition.[10]

HCM can be classified as obstructive or non-obstructive. The degree of obstruction is dependent upon contractility and loading conditions. It most commonly affects the ventricular septum (about 2/3 of patients), although any portion of the left ventricle can be affected. Dynamic outflow obstruction is due to systolic anterior motion (SAM) of the anterior leaflet of the mitral valve.[12] Patients with oHCM are often symptomatic and can have atrial fibrillation, heart failure, and malignant ventricular arrhythmias.[2] Complications of HCM include stroke and sudden cardiac death.[9]

CLINICAL NEED AND BURDEN OF DISEASE

Recent studies suggest that approximately 20 million people worldwide are affected by HCM, well beyond the population initially thought, although it is estimated that only 10% of cases are clinically identified and only 6% are symptomatic.[13] HCM is thought to be the commonest inherited cardiac condition and affects around 1 in 500 people in the UK.[9] According to a population-based cohort (CALIBER, linked primary care, hospital and mortality records in England, period 1997–2010, among the 3,3 million eligible CALIBER patients HCM was found in 4 per 10,000 (1,375 cases).[14] HCM can affect adults, children and both men and women.[9]

In an autopsy study in England and Wales covering 1996-1998, there were 184 deaths per year from HCM (about 15% of all deaths from cardiomyopathy) of which one third (65) were in

people without symptoms. Most (110) of the 184 deaths each year were in people over age 55. Under age 55 there were only 37 deaths each year in asymptomatic people, out of an estimated 60,000 people with the disorder in the population. Of the 37 deaths, 14 (20%) occurred in relation to physical activity and 2 after competitive sport.[15] Another autopsy study in England between 1994-2003 identified 453 sudden cardiac deaths (SCDs) with 6.2% attributed to HCM.[16] The annual risk of SCDs in contemporary medical literature is less than one per cent per year and fortunately only a small proportion of HCM patients die suddenly.[17]

The 2019-2020 Hospital Episodes Statistics for England recorded a total of 1,046 finished consultant episodes (FCEs) for oHCM (ICD-10-CM: I42.1), resulting in 681 hospital admissions and 3,961 FCE bed days and 203 day cases.[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Suspected HCM cases may be referred to a cardiologist for specialist advice and diagnostic tests.[9] Currently there is no cure for HCM, however, treatments are available to help control symptoms and prevent complications.[9,11]

When medication is not effective or in cases of dangerous arrhythmias, implanted devices may be needed to reverse these arrhythmias. These devices include ICDs (implantable cardioverter defibrillator) and pacemakers. On rare occasions a pacemaker may be used to treat the symptoms of LVOTO. An intervention may be needed reducing or removing the area of thickened heart muscle to reduce the obstruction and help the blood to flow through the heart. A small number of people may have a transplant if their heart is in severe failure and not responding to treatment. [9]

In some people with obstructive hypertrophic cardiomyopathy, they may need to have either:[19]

- an injection of alcohol into their heart – this is to reduce part of the muscle in the septum
- a septal myectomy – heart surgery to remove part of the thickened septum (the mitral valve may be repaired at the same time, if necessary).

CURRENT TREATMENT OPTIONS

There are currently no approved pharmacological treatment options for this indication and patient population.

Medication may be needed to control blood pressure, correct an abnormal heart rhythm, prevent blood clots or other symptoms. These include:[9,19]

- Beta-blockers
- Calcium channel blockers
- Anti-arrhythmic medication
- Anticoagulants
- Diuretics

Non-surgical reduction of the myocardial septum is recommended by NICE for the treatment of outflow tract obstruction in patients with oHCM.[20]

PLACE OF TECHNOLOGY

If licensed, mavacamten, in addition to the current standard of care, would offer an additional treatment option for adult patients with symptomatic oHCM.

CLINICAL TRIAL INFORMATION

Trial	**VALOR-HCM; NCT04349072; MYK-461-017;** A Randomized, Double-blind, Placebo-controlled Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy Who Are Eligible for Septal Reduction Therapy **Phase III** – Recruiting **Location(s):** USA **Primary completion date:** Sep 2024
Trial design	Randomised, parallel assignment, quadruple-blinded
Population	N=100; adults subjects diagnosed with symptomatic oHCM who are eligible for septal reduction therapy (SRT) based on American College of Cardiology Foundation/American Heart Association (ACCF/AHA) 2011 and/or European Society of Cardiology (ESC) 2014 guidelines; aged 18 years and older
Intervention(s)	Mavacamten administered once-daily orally
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: SRT Status [Time frame: 16 weeks] See trial record for full list of other outcomes
Results (efficacy)	–
Results (safety)	–

Trial	**MAVA-LTE; NCT03723655; MYK-461-007;** A Long-Term Safety Extension Study of Mavacamten (MYK-461) in Adults With Hypertrophic Cardiomyopathy Who Have Completed the MAVERICK-HCM (MYK-461-006) or EXPLORER-HCM (MYK-461-005) Trials (MAVA-LTE) **Phase II/III** – Enrolling by invitation **Location(s):** EU (incl. UK), USA and Israel **Primary completion date:** Sep 2025
Trial design	Randomised, parallel assignment
Population	N=310; adult subjects diagnosed with symptomatic oHCM who have completed the Parent Study (MAVERICK-HCM or EXPLORER-HCM); aged 18 years and older
Intervention(s)	Active treatment with mavacamten (administered orally) for: • Group 1: participants with base target trough concentration • Group 2: participants with higher target trough concentration • Group 3: participants dose titrated to clinical response
Comparator(s)	No comparator
Outcome(s)	Primary outcome: Frequency and severity of treatment-emergent adverse events and serious adverse events [Time frame: 252 weeks]
Results (efficacy)	–
Results (safety)	–

Trial	**EXPLORER-HCM;** NCT03470545; **MYK-461-005;** A Randomized, Double Blind, Placebo Controlled Clinical Study to Evaluate Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy **Phase III** – Completed **Location(s):** EU (incl. UK), USA and Israel **Study completion date:** May 2020
Trial design	Randomised, parallel assignment, quadruple-blinded
Population	N=251; adults diagnosed with symptomatic oHCM; aged 18 years and older
Intervention(s)	Mavacamten (starting at 5 mg) for 30 weeks administered once-daily orally[2]
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: Percentage of participants achieving a clinical response [Time frame: 30 weeks] See trial record for full list of other outcomes
Results (efficacy)	Patients on mavacamten had greater reductions than those on placebo in post-exercise LVOT gradient (−36 mm Hg, 95% CI −43·2 to −28·1; p<0·0001), greater increase in pVO_2 (+1·4 mL/kg per min, 0·6 to 2·1; p=0·0006), and improved symptom scores (KCCQ-CSS +9·1, 5·5 to 12·7; HCMSQ-SoB −1·8, −2·4 to −1·2; p<0·0001). 34% more patients in the mavacamten group improved by at least one NYHA class (80 of 123 patients in the mavacamten group *vs* 40 of 128 patients in the placebo group; 95% CI 22·2 to 45·4; p<0·0001).[2]
Results (safety)	Safety and tolerability were similar to placebo. Treatment-emergent adverse events (AEs) were generally mild and include atrial fibrillation, syncope, stress cardiomyopathy, diverticulitis, infection, contusion and forearm fracture. One patient died by sudden death in the placebo group.[2]

Trial	**PIONEER-HCM;** NCT02842242; **MYK-461-004;** A Phase 2 Open-label Pilot Study to Evaluate Efficacy, Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of MYK-461 in Subjects With Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction **Phase II** – Completed **Location(s):** USA **Primary completion date:** Nov 2017	**PIONEER-OLE**; NCT03496168; MYK-461-008; An Open-Label Extension Study of Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy Previously Enrolled in Study MYK-461-004 (PIONEER) **Phase II** – Active, not recruiting **Location(s):** USA **Primary completion date:** Jan 2022
Trial design	Non-randomised, single assignment, open label	Non-randomised, single assignment, open label
Population	N=21; adult subjects diagnosed with symptomatic HCM (hypertrophied and non-dilated left ventricle in absence of systemic or other known	N=12; adults subjects diagnosed with oHCM who previously participated in PIONEER-HCM; aged 18 years and older

	cause), with LV wall thickness ≥ 15 mm at time of initial diagnosis or ≥ 13 mm with a positive family history of HCM, aged 18 to 70 years	
Intervention(s)	Patients were administered orally:[3] • Cohort A: 10 to 20 mg/d mavacamten without background medications • Cohort B: 2 to 5 mg/d mavacamten with β-blockers allowed	Starting dose of 5 mg/d mavacamten, administered orally; titration at week 6 to an individualized dose (5, 10, or 15 mg)[21]
Comparator(s)	No comparator	No comparator
Outcome(s)	Primary outcome: Change in post-exercise peak LVOT gradient from baseline to week 12 [Time Frame: baseline and week 12] See trial record for full list of other outcomes	Primary outcome: Frequency and severity of adverse events and serious adverse events. [Time frame: up to 120 weeks]
Results (efficacy)	See trial record	–
Results (safety)	See trial record	–

ESTIMATED COST

The cost of mavacamten is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (TA314). June 2014.
- NICE interventional procedure guidance. Non-surgical reduction of the myocardial septum (IPG40). February 2004.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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

OTHER GUIDANCE

- The New European Society of Cardiology. Guidelines on Hypertrophic Cardiomyopathy. 2015.[22]
- European Society of Cardiology. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. 2014.[23]
- American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA). 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic

Cardiomyopathy: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2011.[24]

ADDITIONAL INFORMATION

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