



Mavacamten: First Approval

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Accepted: 15 June 2022 / Published online: 8 July 2022
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Abstract

Mavacamten (Camzyos™) is an oral small-molecule cardiac myosin inhibitor developed by MyoKardia, Inc., a wholly owned subsidiary of Bristol Myers Squibb, for the treatment of hypertrophic cardiomyopathy (HCM) and diseases of diastolic dysfunction. In April 2022, mavacamten was approved for use in the USA in the treatment of adults with symptomatic New York Heart Association (NYHA) class II-III obstructive HCM to improve functional capacity and symptoms. This article summarizes the milestones in the development of mavacamten leading to this first approval for the treatment of adults with symptomatic NYHA class II-III obstructive HCM.

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<https://doi.org/10.6084/m9.figshare.20057537>

Mavacamten (Camzyos™): Key points

A cardiac myosin inhibitor developed by MyoKardia, Inc., a wholly owned subsidiary of Bristol Myers Squibb, for the treatment of HCM and diseases of diastolic dysfunction

Received its first approval on 28 April 2022 in the USA

Approved for use in the treatment of adults with symptomatic NYHA class II-III obstructive HCM to improve functional capacity and symptoms

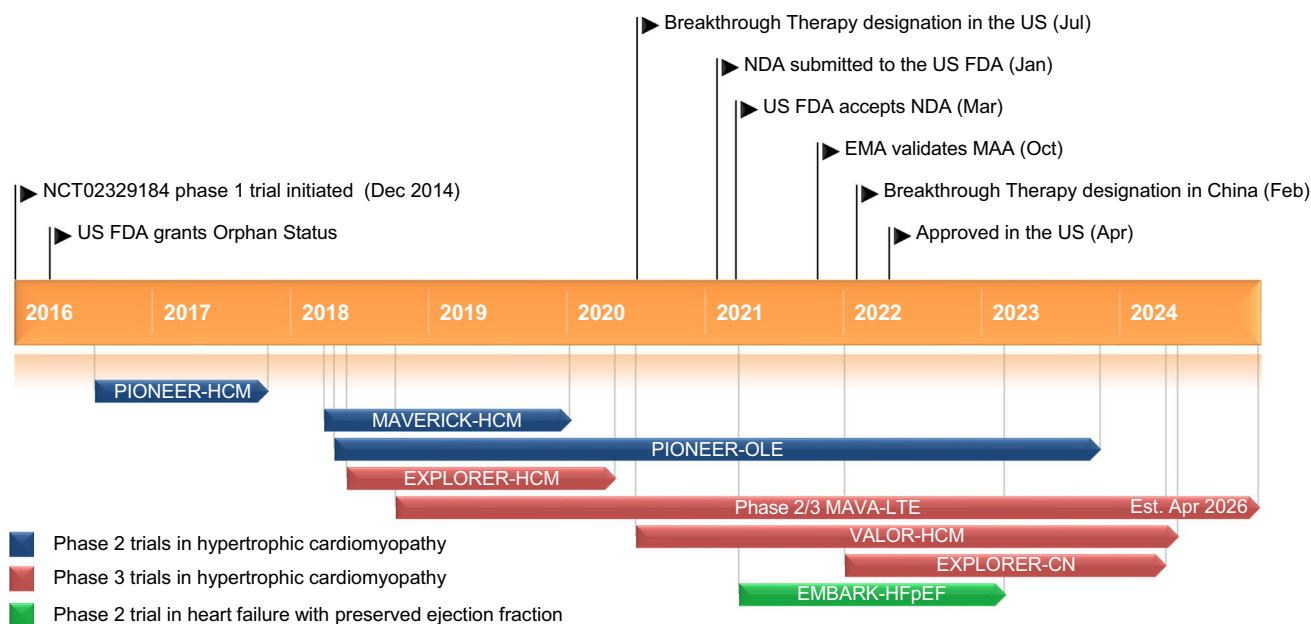
1 Introduction

Hypertrophic cardiomyopathy (HCM) is one of the most common genetic cardiac disorders, affecting between 0.16% (1 in 625) and 0.29% (1 in 344) of the general adult population [1, 2]. It is characterized by primary left ventricular (LV) cardiac hypertrophy (with the greatest hypertrophy affecting the basal interventricular septum), decreased compliance and myocardial fibrosis. LV outflow obstruction at rest or on provocation is seen in approximately two-thirds of patients with HCM [1–6]. Dynamic LV outflow tract (LVOT) obstruction resulting from systolic anterior motion of the mitral valve is also common [2]. Although LV diastolic dysfunction often occurs, LV ejection fraction (LVEF) is preserved or increased [2]. HCM is recognised as a disease of the cardiac sarcomere [7]. Histological features of HCM include myocyte hypertrophy and disarray and interstitial fibrosis [2, 7]; at a molecular level, excess myosin actin cross-bridge formation and dysregulation of the super-relaxed state are evident [7, 8]. While HCM has a relatively benign course in most affected individuals, it is associated with chronic, progressive heart failure symptoms. It is also associated with an increased risk of atrial fibrillation and stroke and/or with sudden cardiac death, especially in adolescents and younger adults [2]. Current treatment for obstructive HCM focuses on pharmacological management of symptoms (e.g., β -blockers, non-dihydropyridine calcium channel blockers, disopyramide) and nonpharmacological options such as implantable cardiac defibrillators or septal reduction therapy (SRT) [6, 9, 10]. While some

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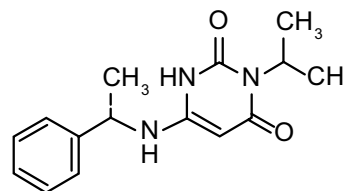
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patients benefit from pharmacological treatment, these agents often do not provide good control of LVOT gradients and symptoms, may not be well tolerated and do not target the underlying mechanisms and pathophysiology of HCM [4, 6].

Mavacamten (Camzyos™) is a small-molecule allosteric and reversible inhibitor of cardiac myosin ATPase [7, 8, 11]. It targets the sarcomere hypercontractility that is one of the characteristics of HCM [8, 12] and inhibits excessive myosin actin cross-bridge formation, shifting the overall myosin population towards an energy-sparing, recruitable, super-relaxed state [8]. Mavacamten received its first approval on 28 April 2022 in the USA for the treatment of adults with symptomatic New York Heart Association (NYHA) class II-III obstructive HCM to improve functional capacity and symptoms [8] and is under evaluation in the EU for the treatment of obstructive HCM [13]. The recommended starting dose of mavacamten is 5 mg once daily without regard to food; allowable subsequent doses with titration are 2.5, 5, 10, or 15 mg once daily. Regular LVEF and Valsalva (provoked) LVOT gradient assessment is required for careful dose titration to achieve an appropriate target Valsalva LVOT gradient, while maintaining LVEF \geq 50% and avoiding heart failure symptoms. Daily dosing takes weeks to reach steady-state drug levels and therapeutic effects, and genetic variation in metabolism and drug interactions can cause large differences in exposure. Algorithms for initiation and maintenance dosing, patient monitoring schedules, and guidance for treatment interruption or discontinuation are provided in the prescribing information and should be followed [8].

The US prescribing information for mavacamten contains a boxed warning regarding heart failure. Mavacamten reduces LVEF and can cause heart failure due to systolic dysfunction [8]. Consequently, mavacamten is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Camzyos REMS PROGRAM. Echocardiogram assessments of LVEF are required prior to and during treatment with mavacamten. Initiation of mavacamten treatment in patients with LVEF $<$ 55% is not recommended; if LVEF is $<$ 50% at any visit or if the patient experiences heart failure symptoms or worsening clinical status, mavacamten treatment should be interrupted. Coadministration of mavacamten with disopyramide in combination with verapamil or diltiazem should be avoided because such use has been associated with left ventricular systolic dysfunction and heart failure symptoms in patients with obstructive HCM [8]. Concomitant use of mavacamten with moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors, or with moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers is contraindicated. Mavacamten dosage adjustments may be required when concomitant administration of weak CYP2C19 inhibitors (e.g., omeprazole)



Chemical structure of mavacamten

or moderate CYP3A4 inhibitors (e.g., verapamil, diltiazem) is required. Avoid initiating concomitant weak CYP2C19 and moderate CYP3A4 inhibitors in patients who are on stable treatment with mavacamten 2.5 mg once daily, because a lower once-daily dose is not available. Mavacamten may cause fetal toxicity when administered to a pregnant female, based on findings in animal studies and effective contraception is advised during treatment and for 4 months after the last dose [8].

1.1 Company Agreements

In November 2020, Bristol Myers Squibb announced that they had closed the acquisition of MyoKardia, Inc. and that MyoKardia had become a wholly owned subsidiary of Bristol Myers Squibb [14]. In October 2020, Bristol Myers Squibb had announced a definitive merger agreement under which it would acquire MyoKardia [15].

In August 2020, MyoKardia and LianBio entered into a licensing agreement to develop and commercialize mavacamten in China, Hong Kong, Macau, Taiwan, Thailand and Singapore [16, 17]. The partnership will initially pursue a registration strategy for mavacamten in China for obstructive HCM (including a registrational phase 3 trial [16]), with plans for additional indications to follow consistent with MyoKardia's development strategy [17].

In July 2019, MyoKardia re-acquired the US royalty rights to mavacamten from Sanofi [18]. In January 2019, MyoKardia regained worldwide rights to all programs (including those for mavacamten) covered under its license and collaboration agreement with Sanofi. The collaboration was not extended beyond the initial research term (which had commenced in August 2014 [19] and ended on December 2018 [20]) and was fully concluded on 1 April 2019 [20].

2 Scientific Summary

2.1 Pharmacodynamics

Mavacamten exerts its effect through the myosin-S1 motor and modulates multiple steps of the myosin chemomechanical cycle [12]. Contractility of cardiac myofibrils is modulated by ATPase activity; in vitro, mavacamten reduces steady-state ATPase activity by inhibiting the rate of phosphate release from β -cardiac myosin-S1 (the rate-limiting step of the myosin chemomechanical cycle) [12, 21]. Mavacamten also decreases the number of myosin heads that can enter "on actin" (power-generating) states, and reduces the probability of force-producing (systolic) and residual (diastolic) cross-bridge formation [8, 12, 22, 23]. In in vitro studies of isolated cells, muscle fibre preparations and engineered human heart tissue models, mavacamten stabilized cardiac myosin, inhibited cardiac muscle hypercontractility and improved active lusitropic function of cardiac muscles [12, 21, 24–30].

In a feline model of HCM, mavacamten reduced contractility, eliminated systolic anterior motion of the mitral valve and relieved LVOT pressure gradients in a dose-dependent manner [31]. Administration of mavacamten early in the course of the disease in a genetic mouse model of HCM (harbouring heterozygous human mutations in the myosin heavy chain) suppressed the development of ventricular hypertrophy, cardiomyocyte disarray and myocardial fibrosis and attenuated hypertrophic and profibrotic gene expression [21].

In the phase 2, placebo-controlled, dose-ranging MAVERICK-HCM (NCT03442764) safety and tolerability trial ($n = 59$), geometric mean N-terminal pro-B-type natriuretic peptide (NT-proBNP; a biomarker of cardiac wall stress) levels were reduced from baseline to a greater extent with mavacamten than placebo (-435 vs -6 pg/mL; $p = 0.0005$) in adults with symptomatic NYHA class II/III non-obstructive HCM [32]. Reductions from baseline in geometric mean cardiac troponin I levels were seen with mavacamten, but not with placebo (-0.008 vs $+0.001$ ng/mL; $p = 0.009$) [32]. Patients who completed MAVERICK-HCM were eligible to enrol in the MAVERICK-LTE cohort of the 5-year MAVA-LTE (NCT03723655) trial. Reductions in median NT-proBNP with mavacamten treatment at weeks 24 and 48 of treatment in the MAVERICK-LTE cohort were comparable with those seen in MAVERICK-HCM [33].

Treatment with mavacamten reduced LVOT obstruction, LV mass, left atrial (LA) volume and NT-proBNP in patients with symptomatic obstructive HCM in the 30-week, phase 3, randomized, placebo-controlled EXPLORER-HCM trial ($n = 251$; NCT05174416) [4, 34, 35]. Greater reductions from baseline in mean resting and Valsalva LVOT gradients were seen in mavacamten than placebo recipients; at 30 weeks, resting LVOT gradient was 14.1 vs 45.9 mmHg, respectively (baseline values 51.7 and 51.1 mmHg) and Valsalva LVOT gradients were 24.8 vs 62.7 mmHg (baseline values 72.4 and 73.9 mmHg) [4]. Mavacamten relieved LVOT obstruction (post-exercise gradient < 30 mmHg) in 57% of patients (vs 7% of patients in the placebo group) and reduced the gradient to below the standard threshold for invasive septal reduction therapy (< 50 mmHg) in 74% of patients (vs 21% in the placebo group) [4]. These improvements with mavacamten were seen from week 4 of treatment onwards. A complete response (a reduction in all LVOT gradients to < 30 mmHg and reaching NYHA class I) was achieved in 27% mavacamten recipients compared with 1% of placebo recipients [4]. Mean resting LVEF at baseline was 74.1% and 74.2% in the mavacamten and placebo arms, respectively [4]. Decreases in LVEF accompanied reductions in Valsalva LVOT gradient in the mavacamten arm, but these were generally within the normal range (mean absolute change from baseline in LVEF over the 30-week period of -3.9%); the mean LVEF reduction in the placebo group was -0.01% . At week 38, following the 8-week treatment interruption, mean LVEF in both treatment arms was similar to baseline [4, 8].

Reductions in NT-proBNP in the mavacamten arm of EXPLORER-HCM were observed by week 4 and were maintained throughout treatment. At week 30, the reduction in NT-proBNP from baseline in the mavacamten group was 80% greater than in the placebo group and the reduction in high-sensitivity cardiac troponin I was 41% greater [4]. Interim, longer-term data from the EXPLORER-LTE cohort of MAVA-LTE extension study showed that clinically meaningful improvements in LVOT gradients and reductions in NT-proBNP consistent with those seen with mavacamten in the 30-week EXPLORER-HCM trial which were evident at 48 weeks ($n = 206$) and up to 84 weeks ($n = 66$) of mavacamten treatment. At week 84, 83.5% of patients had LVOT gradients < 30 mmHg and NT-proBNP had reduced from baseline by 63% [36, 37]. Reductions in NT-proBNP were significantly associated with improvements in several echocardiographic parameters of cardiac structure and function in mavacamten recipients, the strongest of which was the association with the reduction in resting LVOT gradient ($p < 0.0001$) [34].

In patients with mitral valve systolic anterior motion at baseline in the EXPLORER-HCM trial (94 mavacamten and 97 placebo recipients), significantly more mavacamten than placebo recipients showed complete resolution after 30 weeks of treatment (80.9% vs 34.0%; $p < 0.0001$) [34]. Mavacamten recipients also showed a mean reduction from baseline in LV mass index at 30 weeks, whereas placebo recipients showed a mean increase (-7.4 vs $+8.9$ g/m²; $p < 0.0001$). LA volume index (LAVI) was reduced to a greater extent with mavacamten than placebo (-7.5 vs -0.1 mL/m²; $p < 0.0001$), and this was associated with significantly improved peak O₂ consumption ($p = 0.04$). Lateral E/e' (-3.8 vs $+0.04$; $p < 0.0001$) and septal E/e' (-3.5 vs -0.3 ; $p < 0.0001$) were also significantly improved with mavacamten. Significant improvements in LAVI, lateral E/e' and septal E/e'

with mavacamten were evident from week 18 onwards [34]. In a cardiac magnetic resonance substudy of EXPLORER-HCM ($n = 35$ patients randomized; 17 to mavacamten, 18 to placebo), significantly greater reductions in mean LV mass index (primary endpoint) from baseline to week 30 were seen with mavacamten (-17.4 vs -1.6 g/m²; $p < 0.0001$). LV mass (between-group difference -30.0 g; $p < 0.0001$) and maximum LAVI (mean between group difference -10.3 mL/m²; $p = 0.0004$) were also reduced to a greater extent in the mavacamten arm [35].

A meta-analysis of the clinical studies of mavacamten in patients with HCM did not show clinically relevant increases in the QTc interval in the therapeutic exposure range [8]. After administration of multiple doses of mavacamten in healthy volunteers, a concentration-dependent increase in the QTc interval was seen at doses up to 25 mg; however, no acute changes in QTc interval were seen at similar exposures after a single dose of the drug. The mechanism of this QT prolongation is unknown [8]. Nonclinical data indicates that mavacamten is not torsadogenic [38].

2.2 Pharmacokinetics

The pharmacokinetics of once-daily oral mavacamten are generally dose proportional over a dose range of 1–15 mg [8]. In patients with HCM, exposures of mavacamten are 170% higher than those in healthy individuals receiving the same dose. The estimated oral bioavailability of mavacamten is $\geq 85\%$ and T_{\max} is 1 h. Administration with food (a high fat meal) has no clinically significant effect on mavacamten pharmacokinetics. Mavacamten is highly protein bound in plasma (97–98%). The peak-to-trough plasma concentration ratio of mavacamten at steady state after once daily dosing is ≈ 1.5 [8].

Features and properties of mavacamten

Alternative names	Camzyos; HCM 1; MAVA-Bristol Myers Squibb/MyoKardia; MYK-461; SAR-439152
Class	Cardiovascular therapies; Ethylamines; Heart failure therapies; Pyrimidinones; Small molecules
Mechanism of action	Cardiac myosin inhibitors
Route of administration	Oral
Pharmacodynamics	Stabilizes cardiac myosin; decreases the number of myosin heads that can enter “on actin” states and reduces the probability of systolic and diastolic cross-bridge formation. Reduces LVOT obstruction, LV mass, LA volume and NT-proBNP levels
Pharmacokinetics	Median T_{\max} 1 h, 97–98% plasma protein bound. Extensively metabolized in the liver, primarily via CYP2C19 (74%), CYP3A4 (18%) and CYP2C9 (8%); elimination depends on polymorphic CYP2C19 status (mean AUC_{∞} $\uparrow 241\%$, mean C_{\max} $\uparrow 47\%$, $t_{1/2}$ \uparrow to 23 days in CYP2C19 poor metabolizers). Mainly excreted in urine
Adverse events	
Most frequent	Dizziness, syncope
Occasional	Reversible \downarrow in LVEF to $< 50\%$
ATC codes	
WHO ATC code	C01E-B24 (Mavacamten)
EphMRA ATC code	C1 (Cardiac Therapy)
Chemical name	3-(1-methylethyl)-6-[[[(1S)-1-phenylethyl]amino]-2,4(1 <i>H</i> ,3 <i>H</i>)-pyrimidinedione

Mavacamten is extensively metabolized in the liver, primarily via CYP2C19 (74%), CYP3A4 (18%) and CYP2C9 (8%) [8]. Mavacamten elimination is variable and depends largely on polymorphic CYP2C19 status. Normal metabolizers carry two normal function alleles, whereas poor metabolizers carry two nonfunctional alleles. A small proportion of individuals with European ($\approx 2\%$) or African ($\approx 4\%$) ancestry are poor metabolizers; the prevalence of poor metabolizers is higher in Asian populations (e.g., $\approx 13\%$ in East Asians). After a single 15 mg dose, mavacamten exposure is increased (AUC_{∞} by 241% and C_{\max} by 47%) in CYP2C19 poor metabolizers compared with normal metabolizers, and $t_{1/2}$ is prolonged (23 vs 6–9 days, respectively). In CYP2C19 normal metabolizers, the accumulation ratio for C_{\max} is ≈ 2 -fold and that for AUC is ≈ 7 -fold. Accumulation in CYP2C19 poor metabolizers is considerably greater than in CYP2C19 normal metabolizers [8].

Mavacamten is primarily excreted in urine. After administration of a single 25 mg dose of radiolabelled mavacamten, 85% of the dose was recovered in urine (3% as the unchanged drug) and 7% in faeces (1% as the unchanged drug) [8].

In patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, mavacamten exposure (AUC) increased up to 220%; however, no additional dosage adjustment is required with the recommended dose titration algorithm and monitoring plan in this patient group. The effect of severe (Child-Pugh C) hepatic impairment on mavacamten pharmacokinetics is unknown. Mild to moderate renal

impairment had no clinically significant effect on the pharmacokinetics of mavacamten; the effects of severe renal impairment and kidney failure on mavacamten pharmacokinetics is unknown [8].

In vitro, mavacamten does not inhibit CYP1A2, CYP2B6, or CYP2C8 and at clinically relevant drug concentrations does not inhibit CYP2D6, CYP2C9, CYP2C19, or CYP3A4; however, mavacamten induces CYP3A4, CYP2C9, CYP2C19 and CYP2B6. Mavacamten does not inhibit the transporters P-gp, BCRP, BSEP, MATE1, MATE2-K, OATPs, OCTs or OATs [5, 8].

Inducers and inhibitors of CYP2C19 and moderate to strong inhibitors or inducers of CYP3A4 may affect the mavacamten exposure [8]. Coadministration of mavacamten with moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors increases mavacamten exposure, while coadministration with moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers decreases mavacamten exposure, both of which may have a clinical impact on patient management. Concomitant use of mavacamten and drugs that are CYP3A4, CYP2C19, or CYP2C9 substrates may decrease plasma concentration of these drugs and close monitoring is required. As the hormonal contraceptive components progestin and ethinyl estradiol are CYP3A4 substrates, alternative contraceptive methods are required during concomitant use and for 4 months after the last mavacamten dose [8]. Consult mavacamten prescribing information for detailed information regarding guidance on the management of potential drug interactions [8].

Key clinical trials of mavacamten

Drug(s)	Indication	Phase	Status	Location	Sponsor(s)	Identifier
Mavacamten, placebo	Symptomatic oHCM	3	Active	USA	MyoKardia, Inc. ^a	NCT04349072; VALOR-HCM
Mavacamten, placebo	Symptomatic oHCM	3	Active	China	LianBio	NCT05174416; EXPLORER-CN; CTR20212890
Mavacamten, placebo	Symptomatic oHCM	3	Completed	Global	MyoKardia, Inc. ^a	NCT03470545; EXPLORER-HCM; EudraCT 2017-002530-23
Mavacamten	oHCM, nHCM	2/3	Active	Global	MyoKardia, Inc. ^a	NCT03723655; MAVA-LTE; EudraCT 2018-004039-64
Mavacamten,	Symptomatic oHCM	2	Active	USA	MyoKardia, Inc. ^a	NCT03496168; PIONEER-OLE
Mavacamten	Symptomatic oHCM	2	Completed	USA	MyoKardia, Inc. ^a	NCT02842242; PIONEER-HCM
Mavacamten, placebo	Symptomatic nHCM	2	Completed	USA	MyoKardia, Inc. ^a	NCT03442764; MAVERICK-HCM
Mavacamten,	HF with preserved ejection fraction	2	Active	USA	MyoKardia, Inc. ^a	NCT04766892; EMBARK-HFpEF

HF heart failure, *n/oHCM* non obstructive/obstructive hypertrophic cardiomyopathy

^aMyoKardia, Inc., a wholly owned subsidiary of Bristol Myers Squibb

2.3 Therapeutic Trials

2.3.1 Phase 3 Trials

Treatment with mavacamten improved cardiac function in adult patients with symptomatic obstructive HCM in the phase 3 randomized, double-blind, placebo-controlled EXPLORER-HCM (NCT03470545) [4]. Significantly more mavacamten ($n = 123$) than placebo ($n = 128$) recipients achieved either improvement of peak oxygen consumption (pVO_2) by ≥ 1.5 mL/kg/min plus improvement in NYHA class by at least 1 or improvement of pVO_2 by ≥ 3.0 mL/kg/min plus no worsening in NYHA class at 30 weeks [37% vs 17%, respectively; $p = 0.0005$ (primary composite functional endpoint)]. More than twice as many mavacamten than placebo recipients had a change from baseline in $pVO_2 \geq 1.5$ mL/kg/min and a decreased NYHA class (33% vs 14%) or a change from baseline in $pVO_2 \geq 3$ mL/kg/min with no increase in NYHA class (23% vs 11%) [4, 8]. Treatment with mavacamten also significantly improved LVOT obstruction, functional capacity and health status compared with placebo. Significant changes versus placebo from baseline to week 30 were evident in post-exercise LVOT gradient (mean -47 vs -10 mmHg, respectively; $p < 0.0001$), pVO_2 (mean $+1.4$ vs -0.1 mL/kg/min; $p < 0.0006$), and the number of patients with NYHA Class improved ≥ 1 (65% vs 31%; $p < 0.0001$). Measures of health-related quality of life [Kansas City Cardiomyopathy Questionnaire-23 Clinical Summary Score (KCCQ-23 CSS), KCCQ-23 overall score, Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness of Breath (HCMSQ SoB) subscore [4, 8, 39, 40], EuroQoL 5-dimension 5-level (EQ-5D-5L) index score and EuroQoL visual analog scale (EQ-VAS) score] were all improved from baseline to a significantly greater extent with mavacamten than placebo ($p < 0.05$) [41]. Additional assessment using cardiopulmonary exercise testing showed that mavacamten significantly improved other parameters of exercise performance compared with placebo ($p < 0.05$ vs placebo for peak VE/VCO_2 , peak metabolism equivalents, peak circulatory power, peak exercise time, VE/VCO_2 slope and ventilatory power) [42].

Interim, longer-term data from the EXPLORER-LTE cohort of the 5-year MAVA-LTE (NCT03723655) extension study showed that clinically meaningful improvements in NYHA Class and shortness of breath with exercise consistent with those seen with mavacamten in EXPLORER-HCM were evident in mavacamten recipients at 48 weeks ($n = 206$) and up to 84 weeks ($n = 66$). 68% of patients improved by ≥ 1 NYHA class and the proportion of patients with NYHA class III disease decreased from 29% at baseline to 4.9% at 48 weeks. The proportion of patients with shortness of breath with exercise halved between baseline and 48 weeks (from 94% to 45%) [36, 37].

Eligible patients in EXPLORER-HCM had symptomatic NYHA class II and III obstructive HCM, LVEF $\geq 55\%$, at least one LVOT peak gradient ≥ 50 mmHg at rest or with provocation, and Valsalva LVOT peak gradient > 30 mmHg and were randomized to receive either a starting dose of mavacamten 5 mg or placebo once daily for 30 weeks. The dose was periodically adjusted to optimize patient response (i.e., a decrease in Valsalva LVOT gradient) and maintain LVEF $\geq 50\%$. At baseline, $\approx 73\%$ of patients were NYHA class II and $\approx 27\%$ were NYHA class III, mean LVEF was 74% and mean Valsalva LVOT gradient was 73 mmHg. 92% of trial participants remained on background β -blockers or calcium-channel blockers. Exclusion criteria included dual β -blocker and calcium channel blocker treatment, monotherapy with disopyramide or ranolazine and known infiltrative or storage disorders [4, 6]. 231 of 244 patients from EXPLORER-HCM were enrolled in the EXPLORER-LTE cohort of MAVA-LTE, a long-term dose-blinded extension study that also enrolled patients from the phase 2 MAVERICK-HCM trial. Patients restarted/started treatment with mavacamten (5 mg once daily on study entry), with subsequent dose adjustments using echo-guided titration to achieve therapeutic targets [36, 37].

Preliminary results of the phase 3, randomized, double-blind, placebo-controlled VALOR-HCM trial (NCT04349072) indicate that treatment with mavacamten significantly reduced the need for SRT in patients with severely symptomatic drug-refractory obstructive HCM who met guideline criteria of eligibility for SRT [43]. After 16 weeks of treatment, the percentage of patients who proceeded with SRT prior to or at week 16 or remained eligible for SRT at week 16 (primary composite endpoint [44]) was significantly lower with mavacamten (10/56 patients) than with placebo (43/56) [(17.9% vs 76.8%; $p < 0.0001$]. Significantly more mavacamten than placebo recipients had improved ≥ 1 NYHA Class (62.5% vs 21.4%; $p < 0.0001$) and improvements in KCCQ-23 CSS average scores (10.4 ± 16.1 vs 1.9 ± 12.0 ; $p < 0.0001$) at week 16. Post-exercise LVOT peak gradient was also decreased from baseline to a greater extent in the mavacamten group (-39.1 vs -1.8 mmHg) at week 16 [43]. VALOR-HCM was a 138-week trial that consisted of a 2-week screening period followed by a 16-week placebo-controlled treatment period, a 16-week active blinded treatment period, a 96-week long-term extension and an 8-week post-treatment follow-up visit [44]. The study enrolled 112 patients with symptomatic obstructive HCM (NYHA Class III-IV or Class II with exertional syncope or near syncope) who met the 2011 ACC/AHA Guideline criteria for SRT (LVOT gradient of ≥ 50 mm Hg and

NYHA Class III-IV or Class II with syncope) and were referred for SRT. Trial participants were receiving maximally tolerated standard HCM treatment and remained on this throughout the study [43]. During the placebo-controlled dosing period, patients were randomized to receive mavacamten 5 mg or placebo once daily followed by echo-guided dose titration at weeks 4, 8, and 12. In the active-controlled period, mavacamten recipients continued on mavacamten and placebo recipients received mavacamten 5 mg, followed by echo-guided dose titration at weeks 20, 24 and 28. Patients continued mavacamten treatment during the long-term extension, from week 32 to week 128 [44].

2.3.2 Phase 2 Trial

Mavacamten reduced LVOT obstruction and improved exercise capacity and dyspnoea in patients with symptomatic obstructive HCM in the phase 2 open-label PIONEER-HCM trial (NCT02842242) [45]. Patients ($n = 21$) were divided into two treatment cohorts: cohort A ($n = 11$) received mavacamten 10–20 mg day with no background HCM treatment and cohort B ($n = 10$) received mavacamten 2 mg/day, increasing to 5 mg/day at the end of week 4 if the decrease in resting LVOT gradient was $< 50\%$ from baseline, while continuing prior β -blocker treatment. At 12 weeks, mean postexercise LVOT gradient was significantly reduced from baseline (primary endpoint) in both treatment cohorts [cohort A mean change -89.5 mm Hg ($p = 0.008$); cohort B mean change -25.0 mm ($p = 0.02$)]. In both cohorts, peak VO_2 increased (mean change from baseline of 3.5 and 1.7 mL/kg/min, respectively) and dyspnoea scores improved (mean change from baseline of -3.1 and -3.0). In the 13 patients who re-initiated treatment with mavacamten in the PIONEER-OLE (NCT03496168) extension study, significant reductions from baseline in mean post-exercise LVOT gradient were noted at the 48-week assessment; the extent of improvements at this timepoint were comparable to those achieved in PIONEER-HCM [46]. Eligible patients in PIONEER-HCM had a diagnosis of HCM based on the presence of LV hypertrophy, LVOT obstruction and NYHA functional class II or III [45]. Patients who had completed PIONEER-HCM were eligible to enrol in the 3-year PIONEER-OLE (NCT03496168) [46].

2.4 Adverse Events

Mavacamten was generally well tolerated in clinical trials in patients with symptomatic obstructive HCM. Treatment-emergent adverse events (TEAEs) were reported in 88% of mavacamten 2.5–15 mg once daily recipients ($n = 123$) and 79% of placebo recipients ($n = 128$) in the phase 3 randomized, double-blind, placebo-controlled EXPLORER-HCM trial (NCT03470545) [4]. Dizziness (27% vs 18%) and

syncope (6% vs 2%) were the most frequent adverse reactions occurring in $> 5\%$ of patients and at a higher incidence in the mavacamten arm [8]. Serious adverse events occurred in 8% of mavacamten recipients and 9% of placebo recipients; the most frequent serious adverse events were atrial fibrillation (2% vs 3%), syncope (2% vs 1%) and stress cardiomyopathy (2% vs 0%) [4]. The only adverse drug reaction leading to discontinuation of mavacamten treatment in EXPLORER-HCM was syncope (0.8%) [8]. Reversible reductions in LVEF to $< 50\%$ (median 48%) were evident in 7 (6%) mavacamten and 2 (2%) placebo recipients during treatment; reductions were asymptomatic in 3 mavacamten recipients and 1 placebo recipient. LVEF recovered after treatment interruption in all 7 mavacamten recipients (3 mavacamten recipients had a temporary interruption; 2 resumed treatment at the same dose and 1 had the dose reduced from 10 mg to 5 mg) [8]. The median duration of mavacamten exposure in EXPLORER-HCM was 30 weeks (range 2–40 weeks) [8]. In the phase 2 MAVERICK-HCM trial ($n = 58$), treatment-emergent adverse events were reported in 90% of mavacamten and 68% of placebo recipients; the most frequent adverse event occurring with a higher incidence in the mavacamten group was dizziness (17.9% vs 5.3%) [32].

Most TEAEs reported in the EXPLORER-LTE ($n = 137$) [47] and MAVERICK-LTE ($n = 43$) [33] cohorts of MAVALTE (NCT03723655) were mild or moderate in severity and were not related to mavacamten treatment. In the MAVERICK-LTE cohort [33], nine patients temporarily discontinued treatment because of LVEF $< 50\%$; eight patients resumed treatment at a lower mavacamten dose after recovery of LVEF and one discontinued treatment permanently. In EXPLORER-LTE, 12 patients temporarily discontinued treatment because of LVEF $< 50\%$; 7 patients resumed mavacamten treatment and 5 discontinued treatment permanently [48]. In the EXPLORER-LTE cohort ($n = 231$) [48], TEAEs of any severity were reported in 87.0% of patients; serious adverse events were reported in 14.7%. Drug-related TEAEs were reported in 17.3% of patients; drug-related cardiovascular TEAEs occurred in 8.2% [48].

In the phase 3, randomized, double-blind, placebo-controlled VALOR-HCM trial (NCT04349072) in patients with severely symptomatic drug-refractory obstructive HCM receiving mavacamten, no patients permanently discontinued therapy due to LVEF $\leq 30\%$, with none experiencing serious adverse events of congestive heart failure, syncope or sudden cardiac death, according to preliminary safety findings [43].

2.5 Ongoing Clinical Trials

Ongoing trials of mavacamten in HCM consist of the phase 3 VALOR-HCM (NCT04349072) study, MAVALTE (NCT03723655), a long-term open-label extension trial that has enrolled patients from MAVERICK-HCM and

EXPLORER-HCM and the phase 2 open-label extension of PIONEER (PIONEER-OLE; NCT03496168). The phase 3 EXPLORER-CN (NCT05174416) study in Chinese patients with symptomatic obstructive HCM is recruiting. DISCOVER-HCM, a prospective registry study, will assess real-world safety and effectiveness of mavacamten in patients with symptomatic HCM in the USA. A phase 2 proof-of-concept trial of mavacamten in patients with heart failure and preserved ejection fraction (EMBARC-HFpEF; NCT04766892) is recruiting.

3 Current Status

Mavacamten received its first approval on 28 April 2022 for the treatment of adults with symptomatic NYHA class II-III obstructive HCM to improve functional capacity and symptoms in the USA [8, 49].

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40265-022-01739-7>.

Declarations

Funding The preparation of this review was not supported by any external funding.

Authorship and Conflict of interest During the peer review process the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made by the authors on the basis of scientific completeness and accuracy. Susan J. Keam is a contracted employee of Adis International Ltd/Springer Nature, and declares no relevant conflicts of interest. All authors contributed to the review and are responsible for the article content.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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