For the use of a Registered Medical Practitioners or a hospital or a laboratory only.

To be sold by retail only under the prescription of Cardiologist only

Mavacamten Capsules

KOPOZGO®

1. GENERIC NAME

Mavacamten hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsules contains either 2.5, 5, 10 or 15 mg of mavacamten.

Mavacamten 2.5 mg capsules	Light purple opaque cap, hard capsule, size 2, imprinted with “2.5 mg” in black, and white opaque body imprinted with “Mava” in black, both in radial direction.
Mavacamten 5 mg capsules	Yellow opaque cap, hard capsule, size 2, imprinted with “5 mg” in black, and white opaque body imprinted with “Mava” in black, both in radial direction.
Mavacamten10 mg capsules	Pink opaque cap, hard capsule, size 2, imprinted with “10 mg” in black, and white opaque body imprinted with “Mava” in black, both in radial direction.
Mavacamten 15 mg capsules	Gray opaque cap, hard capsule, size 2, imprinted with “15 mg” in black, and white opaque body imprinted with “Mava” in black, both in radial direction.

For the full list of excipients, *see section 7*

3. DOSAGE FORM AND STRENGTH

Mavacamten 2.5 mg 5 mg, 10 mg, 15 mg hard capsules

Immediate release hard capsules. For oral use.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Mavacamten is indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Recommended dosage

The recommended starting dose of mavacamten is 5 mg orally once daily. The capsule should be swallowed whole with water and can be taken with or without food.

Monitoring on treatment:

It is important to regularly monitor the patient's symptoms of obstructive HCM, left ventricular outflow tract (LVOT) gradient with Valsalva maneuver and left ventricular ejection fraction (LVEF) using echocardiogram assessments.

Once an individualized maintenance dose is achieved, patients should be assessed every 12 weeks.

If at any visit the patient's LVEF is < 50%, the treatment should be interrupted for 4 weeks and until LVEF returns to ≥ 50%.

Assessment of LVEF is recommended if clinical status changes or in patients with a serious intercurrent illness such as infection or arrhythmia (including atrial fibrillation or other uncontrolled tachyarrhythmia) (*see section 4.4*).

Testing prior to initiation with mavacamten:

Prior to initiating treatment with mavacamten, assess LVEF by echocardiography (*see section* 4.4). Treatment should not be initiated in patients with LVEF < 55 %.

Treatment Initiation:

The patient should be assessed for early clinical response 4 and 8 weeks after treatment initiation.

Week 4 visit

If LVOT gradient with Valsalva maneuver is < 20 mmHg, the dose should be decreased to 2.5 mg once daily. If LVOT gradient with Valsalva maneuver is ≥ 20 mmHg and LVEF remains ≥ 50%, maintain 5 mg once daily.

Week 8 visit

If LVOT gradient with Valsalva maneuver is ≥ 20 mmHg and LVEF remains ≥ 50%, the dose of 2.5 mg or 5 mg once daily should be maintained. If LVOT gradient with Valsalva maneuver is < 20 mmHg, the dose should be decreased from 5 mg to 2.5 mg; patients who are already on the 2.5 mg dose should have their treatment paused until week 12.

All patients should return at week 12 for re-assessment.

Treatment Maintenance:

Week 12 visit

Patients who have not had their treatment paused may have their dose increased by one level (e.g., 2.5 to 5 mg; 5 to 10 mg) if LVEF ≥ 55% and LVOT gradient with Valsalva maneuver ≥ 30 mmHg. A 4-week follow-up visit is required for any dose increase.

If the patient's LVEF is between 50% to 55%, regardless of Valsalva LVOT gradient or LVEF > 55% and Valsalva LVOT gradient < 30 mmHg the patient should maintain their current dose.

Patients withheld 2.5 mg treatment at week 8 should be reassessed and if LVEF ≥ 50% can restart their treatment on 2.5 mg, regardless of LVOT gradient. A 4-week follow-up assessment visit will be required to determine if the patient should maintain 2.5 mg dose for 8 weeks.

Treatment Interruption if LVEF < 50%

If at any clinical visit LVEF is < 50%, treatment should be interrupted. Restart treatment after 4 weeks at one lower dose level (e.g., 5 to 2.5 mg; 10 to 5 mg; 15 to 10 mg) if LVEF ≥ 50%. Patients on 2.5 mg who temporarily interrupted treatment on two consecutive occasions because their LVEF remains < 50% should discontinue treatment.

Subsequent 12-weekly assessment visits

The patient's individualized daily dose of mavacamten will be either 2.5, 5, 10 or 15 mg. The maximum dose is 15 mg once daily.

If during future 12-weekly assessment visits the patient's obstructive HCM symptoms have not improved and the LVOT gradient is ≥ 30 mmHg, a further dose increase by one level may be considered in patients with an LVEF ≥ 55% up to a maximum daily dose of 15 mg.

Dose increases should not occur more frequently than every 12 weeks. Following any dose increase, LVOT gradient with Valsalva maneuver and LVEF should be assessed after 4weeks, and the patient should return 8 weeks later (then resume 12-weekly visits).

Dose increases are not recommended if the patient is experiencing an intercurrent illness such as infection or arrhythmia (including atrial fibrillation or other uncontrolled tachyarrhythmia) which may impair systolic function.

Missed or delayed doses

If a dose is missed, it should be taken as soon as possible, and the next scheduled dose should be taken at the usual time the following day. Two doses should not be taken on the same day.

Renal impairment

No dosage adjustment is needed in patients with mild (eGFR 60 to < 90 mL/min/1.73m^2) to moderate (eGFR 30 to < 60 mL/min/1.73m^2) renal impairment. Caution should be used in patients with severe (eGFR < 30 mL/min/1.73m^2) renal impairment, as mavacamten not been studied in this population (*see section 5.3*)

Hepatic impairment

No dosage adjustment is required for patients with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment. Caution should be used in patients with severe (Child-Pugh class C) hepatic impairment, as mavacamten has not been studied in this population.

Pediatric and adolescent

The safety and efficacy of mavacamten in pediatric patients aged less than 18 years of age have not been established. No data are available.

Geriatric

No dosage adjustment is required in patients 65 years and older (*see section 5.3*).

Concomitant therapy

Initiate mavacamten at the recommended starting dosage of 5 mg orally once daily in patients who are on stable therapy with a CYP2C19 or CYP3A4 inhibitor, or with a CYP2C19 or CYP3A4 inducer.

Follow Table 1 for guidance regarding patients who initiate or modify treatment with agents that are inhibitors or inducers of CYP450.

Table 1: Dose modification with concomitant medicinal products

Concomitant medicinal product	Dosage modification / monitoring
Inhibitors	
• Initiation or dose increase of: - strong CYP2C19 inhibitor	• Decrease mavacamten by one dose level or pause treatment if on 2.5 mg • Monitor LVEF 4 weeks later, and subsequently resume the patients monitoring and titration schedule
• Initiation, or dose adjustment of: - moderate or weak CYP2C19 inhibitor - strong or moderate CYP3A4 inhibitor	• Consider additional monitoring of LVEF • Adjust mavacamten dose based on clinical assessment
Inducers	
• Discontinuation of: - strong CYP2C19 inducer - strong CYP3A4 inducer	• Monitor LVEF 4 weeks after inducer discontinuation, subsequently resume the monitoring and titration schedule

4.3 CONTRAINDICATIONS

None.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Drug-class–specific warnings and precautions

None.

Product-specific warnings and precautions

Heart failure due to systolic dysfunction

Mavacamten reduces LVEF and may cause heart failure due to systolic dysfunction defined as symptomatic LVEF < 50%. Patients with a serious intercurrent illness such as serious infection or

arrhythmia (including atrial fibrillation or other uncontrolled tachyarrhythmia) or those undergoing major cardiac surgery may be at greater risk of systolic dysfunction and progress to heart failure. New or worsening dyspnea, chest pain, fatigue, palpitations, leg oedema or elevations in N-terminal pro-B-type natriuretic peptide (NT-proBNP) may be signs and symptoms of systolic dysfunction and should prompt an evaluation of cardiac function. LVEF should be measured prior to initiating treatment and closely monitored thereafter. Treatment interruption may be necessary to ensure that LVEF remains ≥ 50% (*see section 4.2*).

Risk of heart failure or loss of response to mavacamten due to drug-drug interactions

Mavacamten is primarily metabolized by cytochrome P450 (CYP) 2C19 and CYP 3A4 enzymes which may lead to the following drug interactions (*see section* 4.5 and 5.3):

- Starting or increasing the dose of a strong or moderate CYP3A4 inhibitor or any CYP2C19 inhibitor may increase risk of heart failure due to systolic dysfunction.
- Stopping or decreasing dose of a strong or moderate CYP3A4 inhibitor or any CYP2C19 inhibitor may lead to a loss of therapeutic response to mavacamten.
- Starting a strong CYP3A4 or strong CYP2C19 inducer may lead to a loss of therapeutic response to mavacamten.
- Stopping a strong CYP3A4 or strong CYP2C19 inducer may increase risk of heart failure due to systolic dysfunction.

Prior to and during mavacamten treatment, the potential for drug interactions, including over-the-counter medications (such as omeprazole or esomeprazole), should be considered. Dose adjustment of mavacamten and close monitoring may be required in patients initiating or discontinuing treatment with, or changing the dose of, a strong or moderate CYP 3A4 inhibitor or any CYP2C19 inhibitor or strong inducers of CYP2C19 or CYP3A4. Intermittent administration of these medicines is not recommended (*see section 4.5*).

Concomitant use of negative inotropes

There is limited data on the use of mavacamten with disopyramide or the use of mavacamten in patients taking beta blockers in combination with verapamil or diltiazem. Therefore, caution should be used when taking these concomitant medications or combinations and patients should be closely monitored for systolic dysfunction (*see section* 4.5).

Embryo-fetal toxicity

Based on animal studies, mavacamten may cause embryo-fetal harm when administered to a pregnant woman (*see section* 6.1). Women of childbearing potential and women becoming pregnant while receiving the treatment should be informed of the potential risk to the fetus. Women of childbearing potential must use highly effective contraception during treatment with mavacamten and for at least 4 months after discontinuing treatment.

4.5 DRUG INTERACTION

Effect of other drugs on mavacamten

Mavacamten is primarily metabolized by CYP2C19 and to a lesser extent by CYP3A4. Strong CYP3A4 inhibitors/inducers or any CYP2C19 inhibitors/inducers may thus affect the clearance of mavacamten increase/decrease mavacamten plasma concentration.

CYP2C19 and CYP3A4 inhibitors

Coadministration of mavacamten with a weak CYP2C19 inhibitor or a strong or moderate CYP3A4 inhibitor resulted in an increase in mavacamten plasma concentration.

Initiation or dose increase of concomitant use with a strong CYP2C19 inhibitor (including, but not limited to, fluoxetine, fluconazole, fluvoxamine), dose adjustment of mavacamten and monitor LVEF 4 weeks later, and subsequently resume the patients monitoring and titration schedule are recommended (*see section* 4.2).

Initiation or dose adjustment of concomitant use with moderate or weak CYP2C19 inhibitor (including, but not limited to, omeprazole, esomeprazole, voriconazole) or a strong or moderate CYP3A4 inhibitor (including, but not limited to clarithromycin, ketoconazole, posaconazole, voriconazole, ritonavir, cobicistat, telaprevir, grapefruit juice, diltiazem, verapamil), increased clinical assessments and dose adjustment should be considered (*see section* 4.2).

Intermittent administration of CYP2C19 inhibitors (such as omeprazole or esomeprazole) is not recommended (*see section* 4.4 and 5.3).

CYP2C19 and CYP3A4 inducers

Coadministration of mavacamten with any CYP2C19 or a strong CYP3A4 inducer (including, but not limited to, rifampicin, enzalutamide, apalutamide, phenytoin, mitotane, dabrafenib,

carbamazepine, St. John's wort) may result in a decrease in mavacamten plasma concentration. If discontinuing concomitant treatment with a strong CYP2C19 or CYP3A4 inducer, monitor LVEF 4 weeks after inducer discontinuation, subsequently resume the monitoring and titration schedule (*see section* 4.2).

Effect of mavacamten on other drugs

See section 5.3.

Other interactions

Drugs That Reduce Cardiac Contractility

In the EXPLORER-HCM study, 119 of 123 patients who received mavacamten received concomitant therapy with either beta blockers (n=94), verapamil (n=19), or diltiazem (n=6) (*see section* 5.3).

In the VALOR-HCM study, 53 of the 56 patients who received mavacamten during the randomized-controlled period received concomitant therapy with the following medications (alone or in combination with other treatment): beta blocker (n=45), verapamil or diltiazem (n=16), and/or disopyramide (n=14). In the overall study, including patients who were treated with mavacamten after the double-blind period, 37 of 112 patients (33%) received mavacamten with combination background HCM therapy; 22 of 112 patients (20%) received disopyramide as monotherapy or in combination with other treatments and no evidence of systolic dysfunction was observed. There is limited information available on the potential for a pharmacodynamic interaction between mavacamten and other drugs that also reduce cardiac contractility (*see section* 5.2). If treatment with a new negative inotrope is initiated, or if the dose of a negative inotrope is increased, in a patient receiving mavacamten, close medical supervision with echocardiographic monitoring of LVEF should be provided until stable doses and clinical response have been achieved (*see section* 4.4).

4.6 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PAEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

Pregnancy

There are no adequate data on the developmental risk associated with the use of mavacamten in pregnant females. Based on animal data, mavacamten may cause fetal harm when administered to a pregnant female (*see section* 6).

Mavacamten should not be administered to patients who are pregnant. Females of reproductive potential who undergo therapy with mavacamten should be informed of the potential hazard to the fetus and should be advised to avoid becoming pregnant prior to or during treatment and for at least 4 months after discontinuation.

If the patient becomes pregnant while receiving the drug, the patient should be informed of the potential hazard to the fetus.

Lactation

It is unknown whether mavacamten or its metabolites are excreted in human milk. Because of the unknown adverse effects of mavacamten in breastfed newborns/infants, a decision must be made whether to discontinue breast-feeding during treatment and for 4 months after the last dose or to discontinue treatment, taking into account the benefit of breast-feeding for the child and the benefit of treatment for the woman.

Females and Males of Reproductive Potential

In a reproductive toxicology study mavacamten had no effect on fertility in male or female rats (*see section* 6.1).

Reproductive considerations

Pregnancy testing

Confirm a negative pregnancy test in women of reproductive potential prior to initiation of treatment (*see section* 4.4 and 6.1)

Contraception

Advise females of reproductive potential to avoid becoming pregnant and to use highly effective contraception during treatment with mavacamten and for at least 4 months after discontinuing treatment.

Labor and delivery

None.

Pediatric use

Not applicable.

Geriatric use

None

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Mavacamten may have minor influence on the ability to drive and use machines. Dizziness may occur following administration of mavacamten. Patients should be advised not to drive or use machines if they experience dizziness.

4.8 UNDESIRABLE EFFECTS

Clinical experience

The safety of mavacamten was evaluated in EXPLORER-HCM, a Phase 3, double-blind, randomized, placebo-controlled trial. Of the 251 oHCM adult patients in this trial, either 123 patients were treated with a daily dose of 2.5 mg, 5 mg, 10 mg or 15 mg of mavacamten and 128 were treated with placebo. Mavacamten treated patients received a median duration of exposure of 30.4 weeks (range: 1.6 to 40.3 weeks).

The population characteristics were median age 59 years (range: 26 to 82) with 36.1% of patients ≥65 years and 6.5% of patients ≥75 years, 94% White, 54% male.

Two patients out of 123 (1.6%) in the mavacamten group and no patients (0%) in the placebo group discontinued trial drug.

The frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1,000); and very rare (<1/10,000). Within each category, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Adverse Reaction	Frequency	
		Mavacamten	Placebo
Nervous system disorders	Dizziness	Very common (21.1%)	(13.3%)
Cardiac disorders	Heart failure	Common (2.4%)	(2.3%)
	Systolic dysfunction[a]	Common (6.5%)	(1.6%)

[a] Defined as LVEF <50% with or without symptoms.

The safety of mavacamten in patients was further evaluated in VALOR-HCM, a Phase 3, double-blind, randomized, placebo-controlled trial. Of the 112 adults with symptomatic obstructive HCM, 56 patients were treated with mavacamten 2.5-15 mg daily and 55 were treated with placebo. Mavacamten-treated patients had a median duration of exposure of 17 weeks (range: 3-19 weeks).

There were no adverse drug reactions leading to discontinuation in patients receiving mavacamten.

Adverse reaction occurring in > 5% of patients and more commonly on mavacamten than on placebo was dizziness (13% vs. 6%).

Effects on Systolic Function

In the EXPLORER-HCM trial, 7 (6%) patients in the mavacamten group and 2 (2%) patients in the placebo group experienced reversible reductions in LVEF < 50% (median 48%: range 35-49%) while on treatment. None of the 7 patients receiving mavacamten had systolic dysfunction leading to heart failure. In 3 of the 7 mavacamten patients and in 1 of the 2 placebo patients, these reductions were observed without other clinical manifestations (e.g., symptoms). In all 7 patients treated with mavacamten, LVEF recovered following interruption of mavacamten, and they completed the study (*see section* 4.4).

4.9 OVERDOSE

Human experience of overdose with mavacamten is limited. Mavacamten been given as a single dose of up to 144 mg in patients with HCM. There was one serious adverse reaction of vasovagal

reaction, hypotension, and asystole lasting 38 seconds reported at that dose. In healthy subjects, doses of up to 25 mg have been administered for up to 25 days. Three out of 8 participants treated at the 25 mg dose level experienced 20% or greater reductions in LVEF. Systolic dysfunction is the most likely result of overdosage of mavacamten.

Management of overdose

If warranted, treatment of overdose with mavacamten consists of discontinuation of mavacamten treatment as well as medically supportive measures to maintain hemodynamic status (e.g., initiation of inotropic support with adrenergic agents), including close monitoring of vital signs and LVEF and management of the clinical status of the patient.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 15 mg dose of mavacamten resulted in mavacamten AUC geometric mean ratio of 0.658 and 1.14, respectively. Mean apparent half-life of mavacamten geometric mean ratio was 0.648 and 1.02, respectively. Timely administration of activated charcoal resulted in a more rapid decrease in mavacamten blood levels and may be considered in the management of mavacamten overdose or accidental ingestion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Mavacamten is a selective, allosteric, and reversible cardiac myosin inhibitor. Mavacamten modulates the number of myosin heads that can enter power-generating states, thus reducing, (or in HCM normalizing), the probability of force-producing systolic and residual diastolic cross-bridge formation. Mavacamten also shifts the overall myosin population towards an energy-sparing, but recruitable, super-relaxed state. Excess cross-bridge formation and dysregulation of the super-relaxed state of myosin are mechanistic hallmarks of HCM, which can result in hyper-contractility, impaired relaxation, excess energy consumption, and myocardial wall stress. In HCM patients, myosin inhibition with mavacamten normalizes contractility, reduces dynamic LVOT obstruction, and improves cardiac filling pressures and biomarkers of cardiac stress, improving symptoms and exercise capacity.

5.2 Pharmacodynamics Properties

LVEF

A reduction in ejection fraction is expected with mavacamten treatment. In the EXPLORER-HCM trial, mean (SD) resting LVEF was 74% (6) at baseline in both treatment groups. Consistent with the mechanism of action of mavacamten, reductions in mean (SD) absolute change from baseline in LVEF was -4% (8) in the mavacamten group and 0% (7) in the placebo group over the 30-week treatment period. At Week 38, following an 8-week interruption of trial drug, mean LVEF was similar to baseline for both treatment groups.

LVOT obstruction

In the EXPLORER-HCM trial, patients achieved significant reductions in mean resting and provoked (Valsalva) LVOT gradient by Week 4 which were sustained throughout the 30-week trial. At Week 30, the mean (SD) change from baseline in resting and Valsalva LVOT gradients were -39 (29) mmHg and -49 (34) mmHg, respectively, for the mavacamten group and -6 (28) mmHg and -12 (31) mmHg, respectively, for the placebo group. The clinically significant reductions in LVOT gradient were mediated by the mechanism of action of mavacamten, which resulted in small decreases in LVEF, attenuating the hypercontractility typical of obstructive HCM while maintaining LVEF within the normal range. The reductions in LVOT gradient while maintaining stable heart rate and systemic blood pressure demonstrate improvement in forward blood flow. At Week 38, following 8 weeks of trial drug washout, mean LVEF and LVOT gradients were similar to baseline for both treatment groups.

Cardiac Structure

In EXPLORER-HCM trial, echocardiographic measurements of cardiac structure showed a mean (SD) reduction from baseline at Week 30 in left ventricular mass index (LVMI) in the mavacamten group of -7.4 (17.8) g/m^2 versus an increase in LVMI in the placebo group of 9.0 (15.3) g/m^2. There was also a mean (SD) reduction from baseline in left atrial volume index (LAVI) in the mavacamten group -7.5 (7.8) mL/m^2 versus no change in the placebo group with -0.1 (8.7) mL/m^2.

Cardiac Biomarkers

In the EXPLORER-HCM trial, reductions in a biomarker of cardiac wall stress, N-terminal pro-B-type natriuretic peptide (NT-proBNP), were observed by Week 4 and sustained through the end of treatment. At Week 30 ratio to baseline geometric mean was 0.20 for mavacamten and 1.02 for placebo (proportion of geometric mean ratio between the two arms 0.20, [95% CI: 0.17, 0.24]);

therefore, the reduction in NT-proBNP after mavacamten treatment was 80% greater than for placebo.

Cardiac Electrophysiology

In HCM, the QT interval may be intrinsically prolonged due to the underlying disease, in association with ventricular pacing, or in association with drugs with potential for QT prolongation commonly used in HCM population. An exposure-response analysis across all clinical studies in HCM patients has shown a concentration-dependent shortening of the QTcF interval. The mean placebo corrected change from baseline in obstructive HCM patients was -8.7 ms (upper and lower limit of the 90% CI -6.7 ms and -10.8 ms, respectively) at the median steady-state C_{max} of 452 ng/mL. Patients with longer baseline QTcF intervals tended to display the greatest shortening. In the EXPLORER-HCM trial, there was no evidence of an increase in clinical events suggestive of ventricular arrhythmias (e.g., sudden deaths, or seizures) in the mavacamten group compared to placebo. In the VALOR-HCM trial, there was no further lengthening of QTcF when mavacamten was added to disopyramide. There is limited experience on co-administration of mavacamten with other QT prolonging drugs or in patients with potassium channel variants resulting in a long QT interval.

Consistent with nonclinical findings in normal hearts, in one clinical trial in healthy subjects sustained exposure to mavacamten at supratherapeutic levels leading to marked depression of systolic function was associated with QTc prolongation (< 20 ms). No acute QTc changes have been observed at comparable (or higher) exposures after single doses.

Preclinical studies to investigate the observed QTc prolongation in healthy hearts in animals demonstrated no proarrhythmic and/or torsadogenic potential either *in vivo*, *in vitro*, and/or *in silico,* and confirmed that the QTc prolongation observed in healthy hearts is not the result of an off-target direct effect of mavacamten on late-repolarization currents like hERG ion channel activity and/or trafficking. The findings in healthy hearts are attributed to an adaptive response to the cardiac mechanical/functional changes (marked mechanical LV depression) occurring in response to myosin inhibition in hearts with normal physiology and LV contractility.

5.3 Pharmacokinetics Properties

Mavacamten has a variable terminal $t_{1/2}$ that depends on CYP 2C19 metabolic status (6-9 days in normal metabolizers and 23 days in poor metabolizers). Exposure to mavacamten increased approximately dose proportionally between 2 mg and 48 mg.

Absorption

Mavacamten is readily absorbed (t_{max} of 1 hour) after oral administration with an estimated oral bioavailability of approximately 85% within the clinical dose range. The increase in mavacamten exposure is generally dose proportional after multiple once daily doses of mavacamten (2 mg to 48 mg).

Effect of Food

A high fat, high calorie meal delayed absorption resulting in a t_{max} of 4 hours in the fed state compared to 1 hour in the fasted state. Administration with food resulted in a 12% decrease in $AUC_{0\text{-inf},}$ however this decrease is not considered clinically significant. Mavacamten may be administered with or without regard to food.

Distribution

Specific studies to assess distribution of mavacamten have not been conducted in humans, however data are consistent with a high volume of distribution. Plasma protein binding of mavacamten is 97 to 98% in clinical studies. The blood-to-plasma concentration ratio is 0.79.

Based upon measurements of mavacamten in semen of 10 male subjects who received either an 18.5 mg (n=4) or 25 mg (n=6) dose for up to 28 days, the mean (SD) mavacamten semen-to-plasma ratio was 0.039 (0.0047) and 0.044 (0.016), respectively.

Metabolism

Mavacamten is extensively metabolized, primarily through CYP 2C19 (74%), CYP 3A4 (18%), and CYP 2C9 (7.6%). Three metabolites have been detected in human plasma. The exposure of the most abundant metabolite MYK-1078 in human plasma was less than 4% of the exposure of mavacamten, and the other two metabolites had exposures less than 3% of the exposure of mavacamten indicating these would have minimal to no impact on the overall activity of mavacamten.

Elimination

Mavacamten is cleared from plasma primarily by metabolism through cytochrome P450 enzymes. Terminal half-life is 6-9 days in CYP 2C19 normal metabolizers (NM). Drug accumulation occurs with an accumulation ratio about 2-fold for C_{max} and about 7-fold for AUC. At steady-state, the peak-to-trough plasma concentration ratio with once daily dosing is approximately 1.5. Inter subject pharmacokinetic (PK) variability is moderate, with a coefficient of variation for exposure in of approximately 30 to 50% for C_{max} and AUC.

CYP2C19 Poor Metabolizers

After a single dose of 15 mg mavacamten, C_{max} and AUC_{inf} increased by 47% and 241%, respectively, in CYP2C19 PM compared to NM. Mean half-life is prolonged in CYP2C19 PM compared to NM (23 days vs 6-9 days, respectively). The incidence of CYP 2C19 PM ranges from approximately 2% in Caucasian to 18% in Asian populations.

Excretion

Following a single 25 mg dose of ^{14}C labeled mavacamten, 7% and 85% of the total radioactivity was recovered in the feces and urine, respectively. Unchanged drug accounted for approximately 1% and 3% of the administered dose in the feces and urine, respectively.

Special populations

No clinically significant differences in the pharmacokinetics of mavacamten were observed using population PK modeling based on age, sex, race or ethnicity.

Renal impairment

Approximately 3% of a mavacamten dose is excreted in the urine as parent drug. A population PK analysis, which comprised eGFR levels down to 29.5 mL/min/1.73m^2, demonstrated no correlation between renal function and exposure. A dedicated PK study has not been conducted in patients with severe renal impairment (< 30 mL/min/1.73m^2) (*see section* 4.2).

Hepatic impairment

A single dose PK study was conducted in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, as well as a control group with normal hepatic function. Mavacamten exposures (AUC) increased 3.2-fold and 1.8-fold in patients with mild and moderate

impairment, respectively, compared to patients with normal hepatic function. There was no effect of hepatic function on $C_{max,}$ consistent with no change in the rate of absorption and/or volume of distribution. A dedicated PK study has not been conducted in patients with severe (Child-Pugh Class C) hepatic impairment (*see section* 4.2).

Geriatric

Clinical trials included 319 patients dosed with mavacamten, 119/319 (37.3%) patients were age 65 years or older, and 25/319 (7.8%) were age 75 years or older. Safety, effectiveness, and pharmacokinetics were consistent between elderly patients (≥ 65 years) and younger patients (18 to < 65 years) (*see section* 4.2).

Pediatric and adolescent

The safety and efficacy of mavacamten in pediatric patients aged less than 18 years of age have not been established. No data are available.

Gender

Biological sex has no effect on mavacamten exposure; no dose adjustment based on sex is required.

Race

Race (Caucasian, African American, and Asian) has no effect on mavacamten exposure; no dose adjustment based on race is required.

Drug Interaction Studies

CYP 2C19 Inhibitor Effect on Mavacamten

Coadministration of mavacamten (15 mg) with the weak CYP 2C19 inhibitor omeprazole (20 mg) resulted in a 48% increase in mavacamten AUC_{inf} with no effect on C_{max}.

CYP 3A4 Inhibitor Effect on Mavacamten

Coadministration of mavacamten (25 mg) with the moderate CYP 3A4 inhibitor verapamil sustained release (240 mg) resulted in a 16% and 52% increase in mavacamten AUC_{inf} and C_{max}, respectively. These changes were not considered clinically significant.

Coadministration of mavacamten (15 mg) with the strong CYP 3A4 inhibitor itraconazole (200 mg) is predicted by modeling to result in an increase of up to 59% and 40% in AUC_{0-24} and C_{max}, respectively.

CYP 2C19 and CYP 3A4 inducers Effect on Mavacamten

Coadministration of mavacamten with a strong CYP2C19 and CYP3A4 inducer (rifampicin) following a 7-day lead-in induction period, is predicted by physiologically based pharmacokinetic (PBPK) modelling to result in a decrease in mavacamten of up to 60% and 7% in AUC_{0-t} and C_{max}, respectively, in CYP2C19 normal metabolizers (NM). In CYP2C19 poor metabolizers (PM), a decrease of up to 69% and 4% in AUC0-t and Cmax, respectively, is predicted. Mavacamten clearance is expected to increase for both NM and PM by 2.5-fold and 3.2-fold, respectively, under induction conditions.

Effect of Mavacamten on CYP3A4 Substrates

Coadministration of a 16-day course of mavacamten (25 mg on days 1 and 2, followed by 15 mg for 14 days) resulted in a decrease in midazolam plasma concentration (13% and 7% in AUC_{inf} and C_{max}, respectively). This change was not considered clinically significant.

Coadministration of a 17-day course of mavacamten (25 mg on days 1 and 2, followed by 15 mg for 15 days) did not decrease the exposure to ethinyl estradiol and norethindrone, which are the components of typical oral contraceptives and substrates for CYP3A4.

Effect of Mavacamten on CYP Substrates

Based on pre-clinical data, at clinically relevant concentrations, mavacamten is not an inhibitor of CYP 1A2, 2B6, 2C8, 2D6, 2C9, 2C19, or 3A4.

Effect of Mavacamten on Transporters

In vitro data indicate that mavacamten is not an inhibitor of major efflux transporters (P-gp, BCRP, BSEP, MATE1, or MATE2-K) at therapeutic concentrations, nor is it an inhibitor of major uptake transporters (organic anion transporting polypeptides [OATPs], organic cation transporters [OCTs], or organic anion transporters [OATs]) at therapeutic concentrations.

CLINICAL TRIAL INFORMATION

EXPLORER-HCM trial

The efficacy of mavacamten was evaluated in EXPLORER-HCM a Phase 3, double-blind, randomized, placebo-controlled, multicenter, international, parallel-group trial in 251 adult patients with symptomatic NYHA class II and III obstructive hypertrophic cardiomyopathy (HCM), left ventricular ejection fraction (LVEF) ≥ 55%, and LVOT peak gradient ≥ 50 mmHg at rest or with provocation. The majority of patients received background HCM treatment for a total of 96% of patients in mavacamten arm (beta blockers 76%, calcium channel blockers 20%) and of 87% in the placebo arm (beta blockers 74%, calcium channel blockers 13%).

Patients were randomized in a 1:1 ratio to receive either a starting dose of 5 mg of mavacamten (n=123) or placebo (n=128) once daily for 30 weeks. The dose was periodically adjusted to optimize patients' response (decrease in LVOT gradient with Valsalva maneuver), maintain LVEF ≥ 50%, and was further guided by plasma concentrations of MAVACAMTEN.

Treatment assignment was stratified by baseline disease severity NYHA functional class (II or III), current treatment with beta blockers (yes or no), type of ergometer (treadmill or exercise bicycle) used for assessment of peak oxygen consumption (pVO_2), and consent for the CMR sub study (yes or no). Patients on background dual therapy with beta blocker and calcium channel blocker treatment or disopyramide or ranolazine were excluded. Patients with known infiltrative or storage disorder causing cardiac hypertrophy that mimicked obstructive HCM, such as Fabry disease, amyloidosis, or Noonan syndrome with LV hypertrophy, were also excluded.

Tables 2 and 3 describes the patient demographics and baseline characteristics.

Table 2: Patient Demographics

Characteristics	Mavacamten N=123	Placebo N=128
Age (years)		
Mean (minimum, maximum)	59 (26, 82)	59 (18, 81)
Sex, n (%)		
Male	66 (54)	83 (65)
Female	57 (46)	45 (35)
Mean body mass index, kg/m^2 (SD)	30 (5)	29 (6)

Mean heart rate, beats/min (SD)	63 (10)	62 (11)
Mean blood pressure, mm Hg (SD)		
Systolic	128 (16)	128 (15)
Diastolic	75 (11)	76 (10)
Race, n (%)		
American Indian or Alaska Native	0	1 (1)
Asian	4 (3)	2 (1)
Black or African American	1 (1)	5 (4)
Unknown	3 (2)	6 (5)
White	115 (94)	114 (89)
Ethnicity		
Hispanic or Latino	8 (7)	4 (3)
Not Hispanic or Latino	114 (93)	119 (93)

Table 3: Baseline Disease Characteristics

Characteristics	Mavacamten N=123	Placebo N=128
NYHA functional class, n (%)		
NYHA Class II	88 (72)	95 (74)
NYHA Class III	35 (28)	33 (26)
Background HCM therapy, n (%)		
Beta blockers	94 (76)	95 (74)
Calcium channel blockers*	25 (20)	17 (13)
Echocardiography parameters		
Mean interventricular septum thickness, mm (SD)	17 (3)	17 (3)
Systolic anterior motion of mitral valve, n (%)	97 (82)	102 (81)
Mean LAVI (SD), mL/m^2	40 (12)	41 (14)
Mean LVEF (SD), (%)	74 (6)	74 (6)
Mean LVOT gradient with Valsalva maneuver, mmHg (SD)	72 (32)	74 (32)
Mean LVOT gradient post-exercise, mmHg (SD)	86 (34)	84 (36)

Critical cardiac history		
Atrial fibrillation, n (%)	12 (10)	23 (18)
Implantable Cardioverter Defibrillator (ICD), n (%)	27 (22)	29 (23)
Prior invasive septal reduction therapies, n (%)	11 (9)	8 (6)

* Non-dihydropyridine calcium channel blockers; SD = Standard deviation

In the EXPLORER-HCM trial, 81% (100/123) of patients were receiving either the 5 mg or 10 mg dose at the end of the treatment period, with 49% (60/123) receiving the 5 mg dose. During the EXPLORER-HCM trial, three of 7 patients on mavacamten had LVEF < 50% prior to the Week 30 visit and temporarily interrupted their dose; two patients resumed treatment at the same dose and one patient had the dose reduced from 10 mg to 5 mg.

Primary endpoint-

The primary endpoint was comprised of a composite of change at Week 30 in exercise capacity measured by pVO_2 and symptoms measured by NYHA functional classification, defined as an improvement of pVO_2 by ≥ 1.5 mL/kg/min and an improvement in NYHA class by at least 1 or an improvement of pVO_2 by ≥ 3.0 mL/kg/min and no worsening in NYHA class.

A greater proportion of patients met the primary endpoint at Week 30 in the mavacamten group compared to the placebo group (36.6% vs 17.2%, respectively, p=0.0005) (see Table 4).

Table 4: Analysis of the Primary Composite Endpoint

	Mavacamten N = 123	Placebo N = 128	Treatment difference (95% CI)	p-value
Patients Achieving Primary Endpoint at Week 30, n (%)	45 (37%)	22 (17%)	19 (8.67, 30.13)	0.0005
Patients with Change from Baseline in pVO_2 ≥ 1.5 mL/kg/min and Improvement in NYHA Class ≥ 1 at Week 30, n (%)	41 (33%)	18 (14%)	19 (8.99 –29.55)	

Patients with Change from Baseline in pVO_2 ≥ 3.0 mL/kg/min and No Worsening in NYHA Class at Week 30, n (%)	29 (24%)	14 (11%)	13 (3.39 – 21.89)	

A range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes. Results of the primary analysis consistently favored mavacamten across all subgroups analyzed.

Secondary endpoints-

The treatment effects of Mavacamten on LVOT obstruction, functional capacity, and health status were assessed by change from baseline through Week 30 in post-exercise LVOT peak gradient, change in pVO2, proportion of patients with improvement in NYHA class, Kansas City Cardiomyopathy Questionnaire-23 (KCCQ-23) Clinical Summary Score (CSS), and Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) Shortness of Breath (SoB) domain score. At Week 30, patients receiving mavacamten had greater improvement compared to placebo group across all secondary endpoints (see Table 5, Figure 1, Figure 2).

Table 5: Analysis of secondary endpoints

	Mavacamten	Placebo
Change from baseline post-exercise LVOT peak gradient at Week 30, mmHg	N = 123	N = 128
Mean (SD)	-47 (40)	-10 (30)
Treatment difference (95% CI)	-35 (-43, -28)	
p-value	<0.0001	
Change from baseline to Week 30 in pVO_2, mL/kg/min	N = 123	N = 128
Mean (SD)	1.4 (3)	-0.05 (3)
Treatment difference (95% CI)	1.4 (0.6, 2)	
p-value	<0.0006	
Patients with improvement of NYHA class ≥ 1 at Week 30	N = 123	N = 128
N, (%)	80 (65%)	40 (31%)
Treatment difference (95% CI)	34 (22, 45)	
p-value	<0.0001	

Change from baseline to Week 30 in KCCQ-23 CSS†	N = 92	N = 88
Mean (SD)	14 (14)	4 (14)
Treatment difference (95% CI)	9 (5, 13)	
p-value	<0.0001	
Baseline	N = 99	N = 97
Mean (SD)	71 (16)	71 (19)
Week 30	N = 108	N = 113
Mean (SD)	82 (16)	73 (20)
Change from baseline to Week 30 in HCMSQ SoB domain score‡	N = 85	N = 86
Mean (SD)	-2.8 (2.7)	-0.9 (2.4)
Treatment difference (95% CI)	-1.8 (-2.4, -1.2)	
p-value	< 0.0001	
Baseline	N = 108	N = 109
Mean (SD)	4.9 (2.5)	4.5 (3.2)
Week 30	N = 92	N = 97
Mean (SD)	2.0 (2.6)	3.7 (3.0)

† The KCCQ-23 CSS is derived from the Total Symptoms Score (TSS) and the Physical Limitations (PL) score of the KCCQ-23. The Clinical Summary Score (CSS) ranges from 0 to 100, with higher scores representing better health status.

‡ The HCMSQ SoB domain score measures frequency and severity of shortness of breath. The HCMSQ Shortness of Breath (SoB) domain score ranges from 0 to 18, with lower scores representing less shortness of breath.

Figure 1: Cumulative Distribution of Change from Baseline to Week 30 in LVOT Peak Gradient

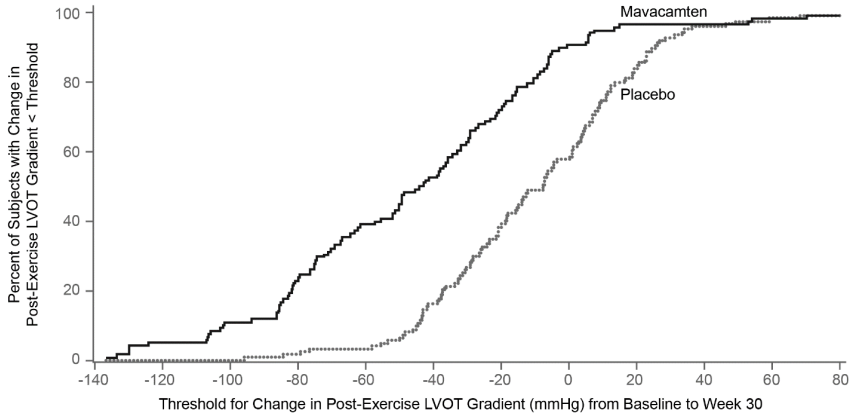
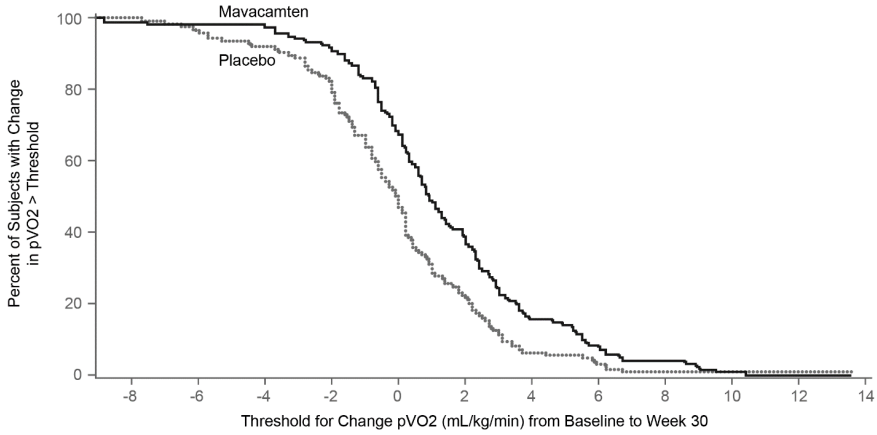
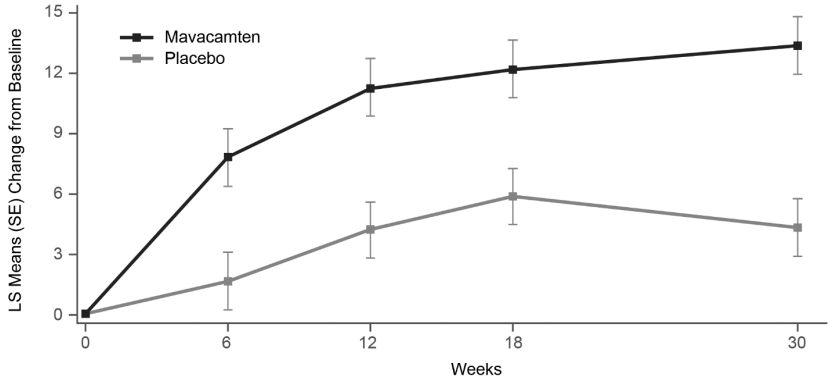


Figure 2: Cumulative Distribution of Change from Baseline to Week 30 in pVO_2



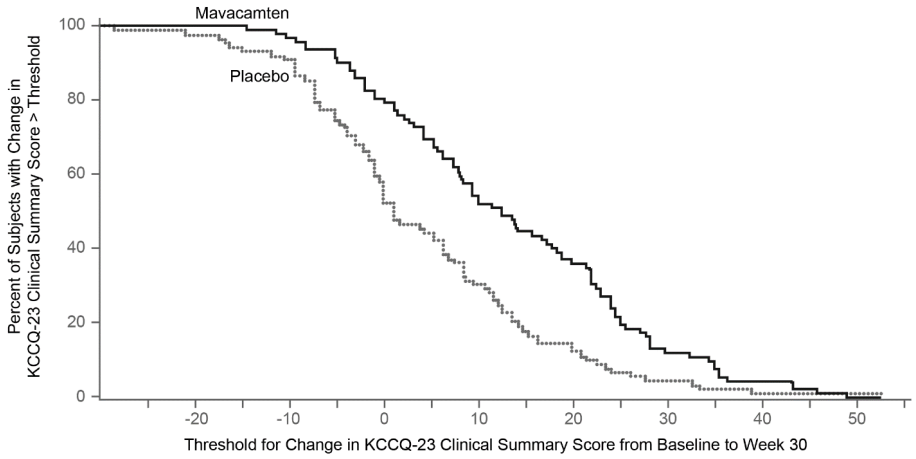
The KCCQ-23 CSS favored Mavacamten compared to placebo at Week 30. The mean improvement from baseline on the KCCQ-23 CSS was greater in the Mavacamten group compared to the placebo at Week 30 ($p<0.0001$), with effects observed as early as 6 weeks (Figure 3).

Figure 3: KCCQ-23 CSS: Mean Change from Baseline Over Time



The proportion of patients with improved KCCQ-23 CSS from baseline to Week 30 was higher at various levels of improvement for the mavacamten-treated group compared to the placebo group (see Figure 4).

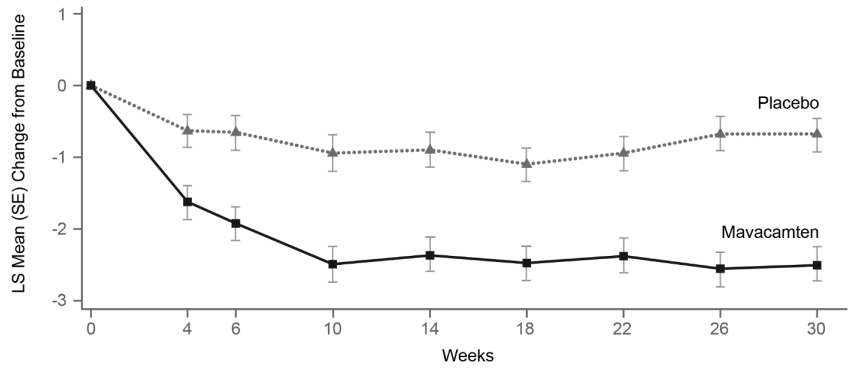
Figure 4: KCCQ-23 CSS: Cumulative Distribution of Change from Baseline to Week 30



The figure displays the cumulative percentage of patients achieving a certain level of response.

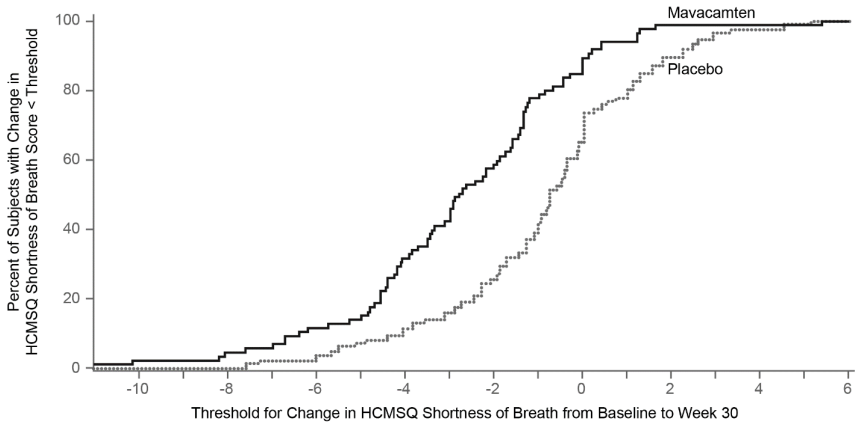
The HCMSQ SoB domain favored mavacamten compared to placebo at Week 30. The mean improvement from baseline on the HCMSQ SoB domain was greater in the mavacamten group compared to the placebo at Week 30 ($p<0.0001$), with effects observed as early as 4 weeks (Figure 5).

Figure 5: HCMSQ Shortness of Breath Domain: Mean Change from Baseline Over Time



The proportion of patients with improved HCMSQ SoB scores from baseline to Week 30 was higher at various levels of improvement for the mavacamten -treated group compared to the placebo group (see Figure 6).

Figure 6: HMCSQ Shortness of Breath Domain: Cumulative Distribution of Change from Baseline to Week 30



The figure displays the cumulative percentage of patients achieving a certain level of response.

VALOR-HCM

The efficacy of mavacamten was evaluated in VALOR-HCM, a Phase 3, double-blind, randomized, 16-week placebo-controlled trial in 112 patients (mean age of 60.3 years; 50.9% men; 92.9% ≥ NYHA class III) randomized 1:1 to receive treatment with mavacamten or placebo. At baseline, all patients had symptomatic obstructive HCM and were SRT eligible.

Patients with severely symptomatic drug refractory obstructive HCM (including 33% on any combination of beta-blocker, calcium channel blocker and/or disopyramide; 20% were on disopyramide alone or in combination with other treatment), and NYHA class III/IV or class II with exertional syncope or near syncope, were included in the study. Patients were required to have LVOT peak gradient ≥50 mmHg at rest or with provocation, and LVEF ≥60%. Patients must have been referred or under active consideration within the past 12 months for SRT and actively considering scheduling the procedure.

Patients received mavacamten (2.5, 5, 10, or 15 mg) or a placebo capsule once daily for 16 weeks. Dose adjustment was based on clinical echocardiogram parameters.

Primary endpoint

Mavacamten was shown to be superior to placebo in reducing the proportion of patients who met the primary endpoint (the composite of patient decision to proceed with SRT prior to or at Week

16 or met SRT eligibility (LVOT gradient of ≥ 50 mmHg and NYHA class III-IV, or class II with exertional syncope or near syncope) at Week 16 (18% vs. 77%, respectively, p<0.0001; see Table 6).

Table 6: Primary Endpoint at 16 Weeks

	Mavacamten N=56	**Placebo N=56**	**Treatment difference (95% CI)**	**p-value**
Primary efficacy composite endpoint	10 (17.9)	43 (76.8)	58.9 (44.0, 73.9)	<0.0001
Patient decision to proceed with SRT	2 (3.6)	2 (3.6)		
SRT-eligible based on guideline criteria	8 (14.3)	39 (69.6)		
SRT status not evaluable (imputed as meeting guideline criteria)	0	2 (3.6)		

Secondary endpoints

The treatment effects of mavacamten on LVOT obstruction, functional capacity, health status, and cardiac biomarkers were assessed by change from baseline through Week 16 in post-exercise LVOT gradient, proportion of patients with improvement in NYHA class, KCCQ-23 CSS, NT-proBNP, and cardiac troponin I. In the VALOR-HCM study, hierarchical testing of secondary efficacy endpoints showed significant improvement in the mavacamten group compared to the placebo group (Table 7).

Table 7: Change from Baseline to Week 16 in Secondary Endpoints

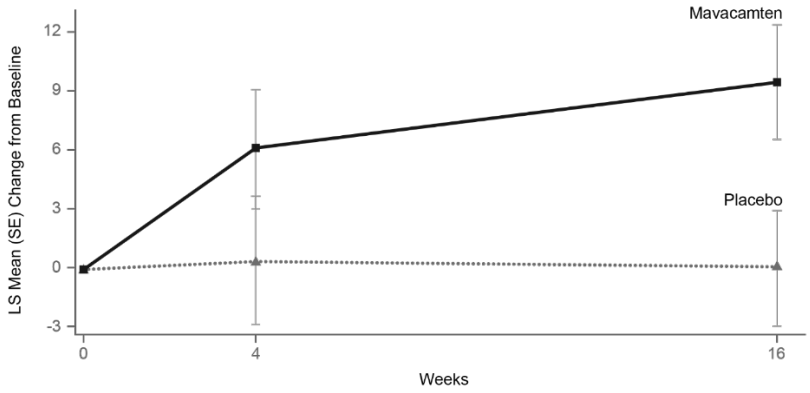
	Mavacamten N = 56	**Placebo N = 56**	**Difference (95% CI)**	**p-value**
Post-Exercise LVOT gradient (mmHg), mean (SD)	-39 (37)	-2 (29)	-38 (-49, -28)	<0.0001
Number (%) with NYHA Class improved ≥1	35 (63%)	12 (21%)	41 (25%, 58%)	<0.0001
KCCQ-23 CSS[†], mean (SD)	10 (16)	2 (12)	9 (5, 14)	<0.0001
KCCQ-23 TSS, mean (SD)	10	2	10	

	(16)	(14)	(5, 15)	
KCCQ-23 PL, mean (SD)	10 (19)	2 (17)	10 (5, 16)	
NT-proBNP (ng/L), geometric mean ratio to baseline	0.35	1.13 (n=53)	0.33 (0.27, 0.42)	<0.0001
Cardiac Troponin I (ng/L), geometric mean ratio to baseline	0.50	1.03 (n=53)	0.53 (0.40, 0.70)	<0.0001

†The KCCQ-23 CSS is derived from the Total Symptom Score (TSS) and the Physical Limitations (PL) score of the KCCQ-23. The CSS ranges from 0 to 100 with higher scores representing less severe symptoms and/or physical limitations. The KCCQ-23 TSS and the KCCQ-23 PL are exploratory endpoints in the VALOR-HCM study.

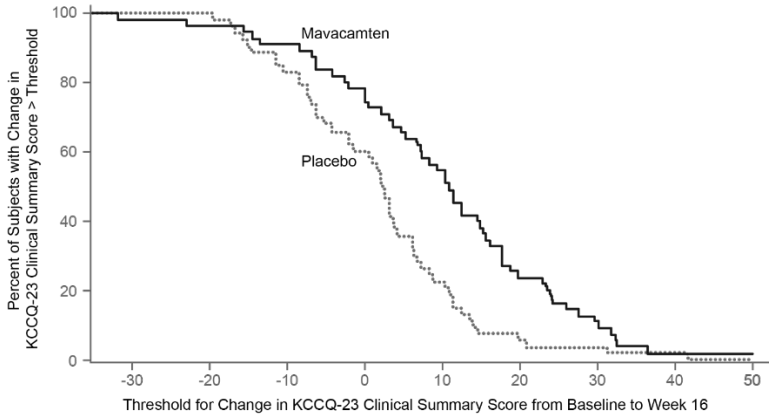
The KCCQ-23 CSS favored mavacamten compared to placebo at Week 16. The mean improvement from baseline on the KCCQ-23 CSS was greater in the mavacamten group compared to the placebo at Week 30 ($p<0.0001$), with effects observed as early as 4 weeks (Figure 7).

Figure 7: KCCQ-23 Clinical Summary Score: Mean Change from Baseline Over Time



The proportion of patients with improved KCCQ-23 CSS from baseline to Week 16 was higher at various levels of improvement for the mavacamten-treated group compared to the placebo group.

Figure 8: KCCQ-23 Clinical Summary Score: Cumulative Distribution of Change from Baseline to Week 16



The figure displays the cumulative percentage of patients achieving a certain level of response.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Carcinogenesis, mutagenesis, impairment of fertility

Mavacamten was not found to be genotoxic in a reverse mutation bacterial test (Ames test), a human in vitro lymphocyte clastogenicity assay, or a rat in vivo micronucleus assay.

There was no evidence of carcinogenicity at the highest mavacamten doses tested in a 6-month rasH2 transgenic mouse study or a 2-year rat study. Exposures (AUC) in mice were up to 3-fold higher compared to the MRHD, while exposures (AUC) in rats were up to 0.2-fold compared to the MRHD.

In reproductive toxicity studies, there was no evidence of effects of mavacamten on mating and fertility in male or female rats or in the viability and fertility of offspring of dams at any dose tested. Plasma exposures (AUC) of mavacamten at the highest doses tested are less than in humans at the MRHD.

Animal toxicology

The safety of mavacamten has been evaluated in rats and dogs dosed for up to 6 and 9 months, respectively. Noted toxicities, including echocardiographic findings of reduced systolic performance and cardiac dilation, death, due to heart failure, and, in rats, increased heart weights

likely secondary to cardiac hypertrophy in response to decreased contractility, were consistent with the mavacamten mechanism of action and primary pharmacological activity. Other findings included cardiac osseous metaplasia in rats and QTc prolongation in dogs. Plasma exposures (AUC) at the no observed adverse effect level NOAEL in rats and dogs respectively are lower than those in humans at the MRHD.

Embryo-fetal Development

When mavacamten was administered orally to pregnant rats during the period of organogenesis, decreased mean fetal body weight, and increases in post implantation loss and fetal malformations (visceral and skeletal) were observed in the high dose group (1.5 mg/kg/day). Visceral malformations (heart malformation in fetuses, including one total situs inversus) and increased incidences of skeletal malformations (mainly fused sternebrae) were observed. Plasma exposure (AUC) at the no effect dose for embryo-fetal development in rats and rabbits are less than those in humans at the MRHD.

When mavacamten was administered orally to pregnant rabbits during the period of organogenesis, fetal malformations (visceral and skeletal) were increased at doses of 1.2 mg/kg/day and higher. Visceral findings consisted of malformations of the great vessels (dilatation of pulmonary trunk and/or aortic arch) noted in 4 fetuses from 4 litters at 2.0 mg/kg/day. Skeletal malformations consisted of higher incidences of fused sternebrae (38 fetuses from 10 litters) at 2.0 mg/kg/day. Plasma exposure (AUC) at the no effect dose for embryo-fetal development in rabbits is less than those in humans at the MRHD.

In a pre- and post-natal development study, mavacamten was administered orally to pregnant rats from gestation Day 6 to lactation/post-partum Day 20. No adverse effects were observed in the dams or offspring exposed daily from before birth (in utero) through lactation. The maternal exposure was inferred from the embryo-fetal developmental toxicity study dosed at the same level, and the exposure was less than the MRHD.

7. DESCRIPTION

Mavacamten hard capsules for oral use contains mavacamten, a selective allosteric cardiac myosin inhibitor.

Pharmacotherapeutic group: Cardiac therapy; ATC code: C01EB24

List of excipients-

Capsule content: Silica, colloidal hydrated, Mannitol (E421), Hypromellose (E464)

Croscarmellose sodium (E468), Magnesium stearate

Capsule shell: All strengths- Gelatin, Titanium dioxide (E171)

Approved colors used:

Mavacamten 2.5 mg hard capsules- Iron oxide black (E172), Iron oxide red (E172)

Mavacamten 5 mg hard capsules-Iron oxide yellow (E172)

Mavacamten 10 mg hard capsules- Iron oxide red (E172)

Mavacamten 15 mg hard capsules- Iron oxide black (E172)

Printing ink: Iron oxide black (E172), Shellac (E904), Propylene glycol (E1520), Ammonia solution, concentrated (E527), Potassium hydroxide (E525)

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf life

Refer to the outer carton, for the expiry date

8.3 Packaging information

Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminum foil blister containing 14 hard capsules.

Pack size of 1x14 and 2x14 hard capsules. Not all pack sizes may be marketed in the country.

8.4 Storage and handing instructions

Store at or below 30°C

9. Patient Counselling Information

Please refer to section 4.4 and section - 4.6 for patient counselling information.

10. Details of Manufacturer

Manufactured by: M/s. Bristol Myers Squibb Company, New Jersey having premises at Swords Laboratories Unlimited Company, T/A Bristol Myers Squibb, Pharmaceutical Operations, External Manufacturing Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867, Ireland

Imported by: Bristol-Myers Squibb India Private Limited, Bldg.B-4, Gala No. 3B & 4B, Citylink Warehousing Complex, Mumbai Nashik Highway, Vadape Village, Taluka: Bhiwandi – 16, District: Thane Z5, Pin- 421302, Maharashtra, India

Marketed by: Bristol-Myers Squibb India Private Limited, 6th floor, Tower 1, One International Center, S.B. Marg, Elphinstone (W), Mumbai - 400013, Maharashtra, India

11. Details of permission or licence number with date

Form CT-20 Permission No. IMP-ND-18/2024 dated 08.10.2024

12. Date of revision

Date– 12 Mar 2025

Document Version Number 02

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