FULL PRESCRIBING INFORMATION

CAMZYOS 2.5 mg
CAMZYOS 5 mg
CAMZYOS 10 mg
CAMZYOS 15 mg
Capsules for oral use, containing mavacamten 2.5mg, 5mg, 10mg or 15mg per capsule.

The marketing of CAMZYOS is subject to a risk management plan (RMP) including a 'Patient Guide' and a 'Patient card'. The 'Patient Guide' and the 'Patient card' emphasize important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the Guide and the Card before starting treatment.

This product is marketed with Healthcare Professional (HCP) Guide providing important safety information.
Please ensure you are familiar with this material as it contains important safety information.

WARNING: RISK OF HEART FAILURE

CAMZYOS reduces left ventricular ejection fraction (LVEF) and can cause heart failure due to systolic dysfunction *[see Warnings and Precautions (5.1)]*.

Echocardiogram assessments of LVEF are required prior to and during treatment with CAMZYOS. Initiation of CAMZYOS in patients with LVEF <55% is not recommended. Interrupt CAMZYOS if LVEF is <50% at any visit or if the patient experiences heart failure symptoms or worsening clinical status *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]*.

Concomitant use of CAMZYOS with certain cytochrome P450 inhibitors or discontinuation of certain cytochrome P450 inducers may increase the risk of heart failure due to systolic dysfunction; therefore, the use of CAMZYOS is contraindicated with the following *[see Contraindications (4) and Warnings and Precautions (5.2)]*:

- **Moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors**
- **Moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers**

1 INDICATIONS AND USAGE

CAMZYOS is indicated for the treatment of adults with symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) to improve functional capacity and symptoms.

2 DOSAGE AND ADMINISTRATION

2.1 Initiation, Maintenance, and Interruption of Treatment

Treatment should be initiated and maintained under the supervision of a cardiologist.

Confirm absence of pregnancy and usage of effective contraception in females of reproductive potential *[see Warnings and Precautions (5.3)]*.

Initiation or up-titration of CAMZYOS in patients with LVEF <55% is not recommended.

The recommended starting dose is 5 mg orally once daily without regard to food; allowable subsequent doses with titration are 2.5 mg, 5 mg, 10 mg, or 15 mg orally once daily. The maximum recommended dose is 15 mg orally once daily.

Patients may develop heart failure while taking CAMZYOS. Regular LVEF and Valsalva left ventricular outflow tract (LVOT) gradient assessment is required for careful titration to achieve an appropriate target Valsalva LVOT gradient, while maintaining LVEF ≥50% and avoiding heart failure symptoms (see Figure 1 and Figure 2).

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 *[see Boxed Warning, Contraindications (4), Warnings and Precautions (5.2), Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

When initiating or titrating CAMZYOS, first consider LVEF then consider the Valsalva LVOT gradient and patient clinical status to guide appropriate CAMZYOS dosing. Follow the algorithms for Initiation (Figure 1) and Maintenance (Figure 2) for appropriate CAMZYOS dosing and monitoring schedules.

If LVEF <50% while taking CAMZYOS, interrupt treatment. Follow the algorithm for Interruption (Figure 3) for guidance on interrupting, restarting, or discontinuing CAMZYOS. If interrupted at 2.5 mg, either restart at 2.5 mg or discontinue permanently.

Figure 1: Initiation Phase

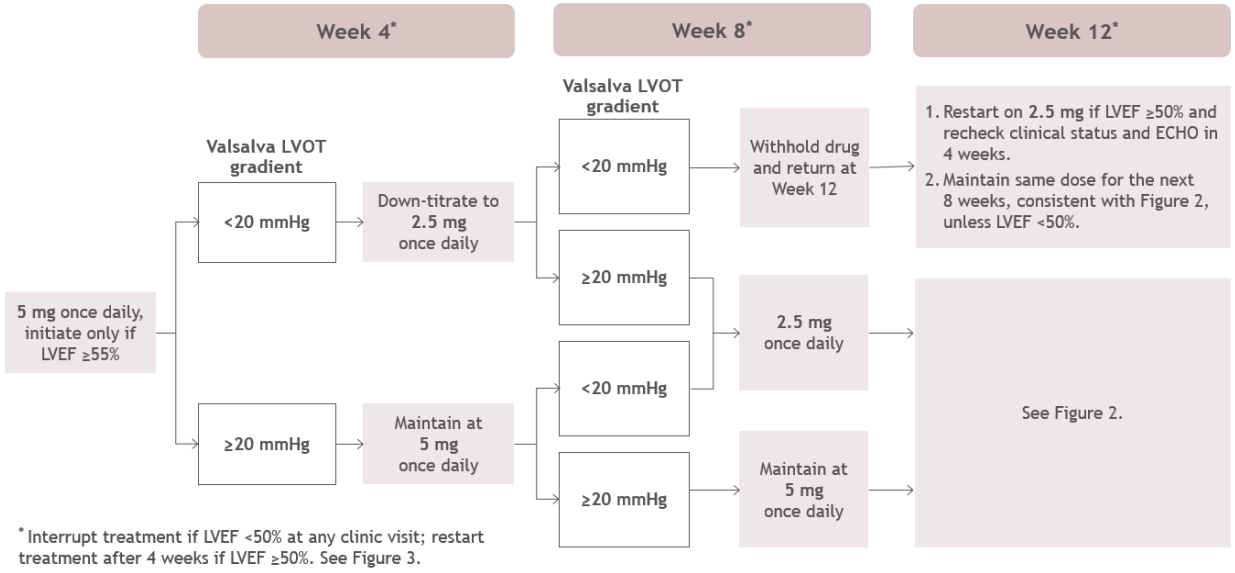


Figure 2: Maintenance Phase

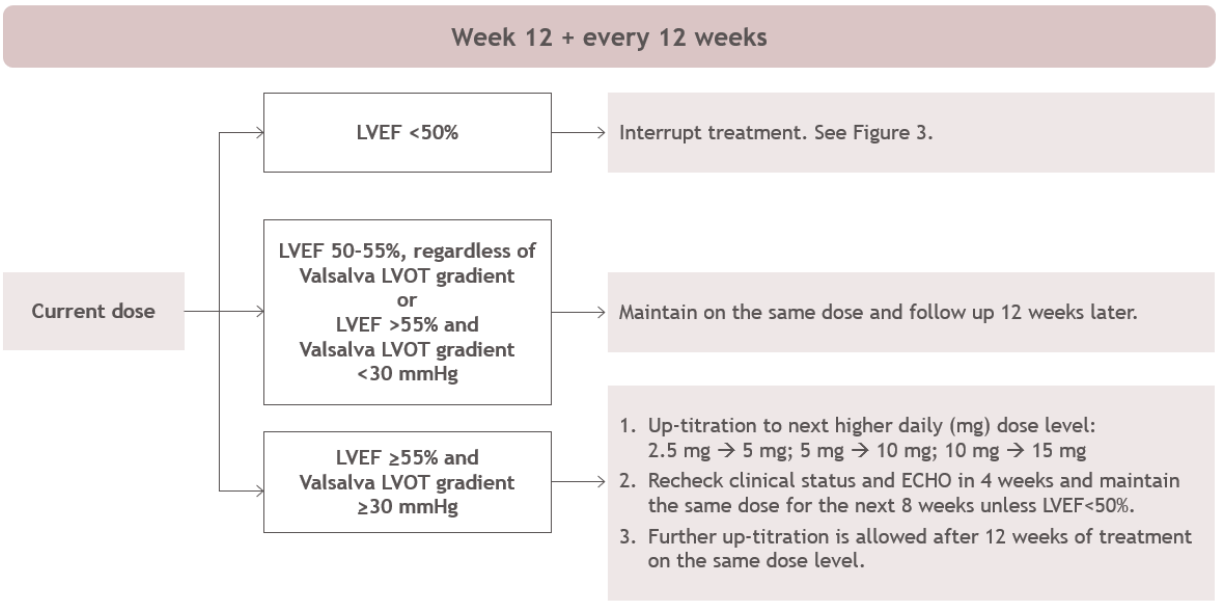
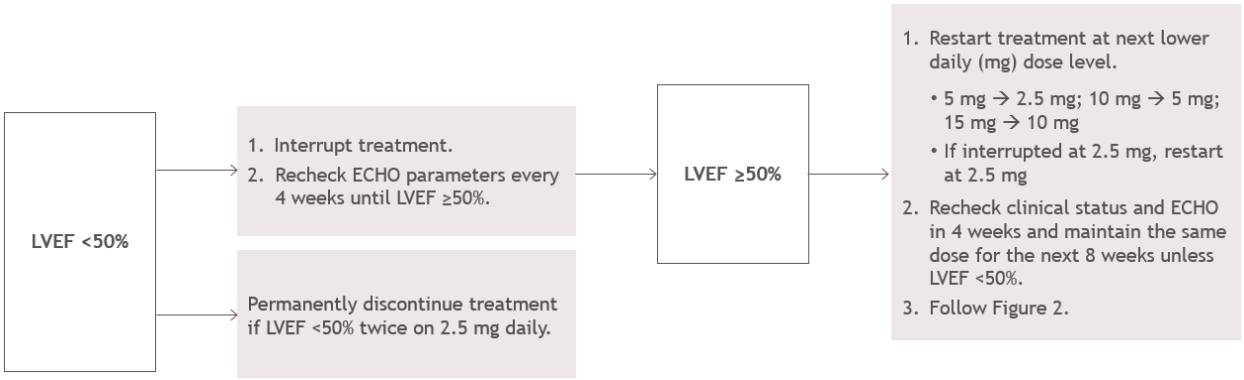


Figure 3: Treatment Interruption at Any Clinic Visit if LVEF <50%



Delay dose increases when there is intercurrent illness (e.g., serious infection) or arrhythmia (e.g., atrial fibrillation or other uncontrolled tachyarrhythmia) that may impair systolic function. Consider interruption of CAMZYOS in patients with intercurrent illness *[see Warnings and Precautions (5.1)]*.

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. Exact timing of dosing during the day is not essential, but two doses should not be taken on the same day.

Swallow capsules whole. Do not break, open, or chew the capsules as there is no data on using the capsules this way.

2.2 Concomitant Administration of Weak CYP2C19 or Moderate CYP3A4 Inhibitors

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

Reduce dosage of CAMZYOS by one level (i.e., 15 mg → 10 mg; 10 mg → 5 mg; or 5 mg → 2.5 mg) in patients who initiate a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor. Schedule clinical and echocardiographic assessment 4 weeks after inhibitor initiation, and do not up-titrate CAMZYOS until 12 weeks after inhibitor initiation. Avoid initiation of concomitant weak CYP2C19 and moderate CYP3A4 inhibitors in patients who are on stable treatment with 2.5 mg of CAMZYOS because a lower CAMZYOS once-daily dose is not available *[see Dosage and Administration (2.1), Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

CAMZYOS is available as capsules imprinted with “Mava” on capsules white body and with the strength on capsules cap as follows:

- 2.5 mg on light purple cap
- 5 mg on yellow cap
- 10 mg on pink cap

- 15 mg on gray cap

See also *How Supplied/Storage and Handling (16)*

4 CONTRAINDICATIONS

- Hypersensitivity to mavacamten or to any of the excipients listed in section 11.

CAMZYOS is contraindicated with concomitant use of:

- Moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors *[see Warnings and Precautions (5.2), Drug Interactions (7.1)]*
- Moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers *[see Warnings and Precautions (5.2), Drug Interactions (7.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Heart Failure

CAMZYOS reduces systolic contraction and can cause heart failure or totally block ventricular function. Patients who experience a serious intercurrent illness (e.g., serious infection) or arrhythmia (e.g., atrial fibrillation or other uncontrolled tachyarrhythmia) are at greater risk of developing systolic dysfunction and heart failure *[see Clinical Trial Experience (6.1)]*.

Assess the patient's clinical status and LVEF prior to and regularly during treatment and adjust the CAMZYOS dose accordingly *[see Dosage and Administration (2.1)]*. New or worsening arrhythmia, dyspnea, chest pain, fatigue, palpitations, leg edema, or elevations in N-terminal pro-B-type natriuretic peptide (NT-proBNP) may be signs and symptoms of heart failure and should also prompt an evaluation of cardiac function.

Asymptomatic LVEF reduction, intercurrent illnesses, and arrhythmias require additional dosing considerations *[see Dosage and Administration (2.1, 2.2)]*.

Initiation of CAMZYOS in patients with LVEF <55% is not recommended. Avoid concomitant use of CAMZYOS in patients on disopyramide, ranolazine, verapamil with a beta blocker, or diltiazem with a beta blocker as these medications and combinations increase the risk of left ventricular systolic dysfunction and heart failure symptoms and clinical experience is limited *[see Drug Interactions (7)]*.

5.2 CYP450 Drug Interactions Leading to Heart Failure or Loss of Effectiveness

CAMZYOS is primarily metabolized by CYP2C19 and CYP3A4 enzymes. Concomitant use of CAMZYOS and drugs that interact with these enzymes may lead to life-threatening drug interactions such as heart failure or loss of effectiveness *[see Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7.1)]*.

Advise patients of the potential for drug interactions, including with over-the-counter medications (such as omeprazole, esomeprazole). Advise patients to inform their healthcare provider of all

concomitant products prior to and during CAMZYOS treatment *[see Drug Interactions (7.1), Patient Counseling Information (17)]*.

5.3 Embryo-Fetal Toxicity

CAMZYOS may cause fetal toxicity when administered to a pregnant female, based on findings in animal studies. Confirm absence of pregnancy in females of reproductive potential prior to treatment and advise patients to use effective contraception during treatment with CAMZYOS and for 4 months after the last dose. CAMZYOS may reduce the effectiveness of combined hormonal contraceptives (CHCs). Advise patients using CHCs to use an alternative contraceptive method that is not affected by CYP450 enzyme induction or to add nonhormonal contraception *[see Drug Interactions (7.2) and Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential about the potential risk to the fetus with maternal exposure to CAMZYOS during pregnancy.

5.4 Sodium Content

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

5.5 Effects on ability to drive and use machines

Mavacamten has minor influence on the ability to drive and use machines. Dizziness may occur during use of mavacamten. Patients should be advised not to drive for use machines if they experience dizziness.

6 ADVERSE REACTIONS

The following adverse reaction is discussed in other sections of the labeling:

- Heart failure *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of CAMZYOS was evaluated in EXPLORER-HCM, a Phase 3, double-blind, randomized, placebo-controlled trial *[see Clinical Studies (14)]*. Of the 251 adults with obstructive HCM, 123 patients were treated with CAMZYOS 2.5-15 mg daily and 128 were treated with placebo. CAMZYOS-treated patients had a median duration of exposure of 30 weeks (range: 2-40 weeks).

Syncope (0.8%) was the only adverse drug reaction leading to discontinuation in patients receiving CAMZYOS.

Adverse reactions occurring in >5% of patients and more commonly on CAMZYOS than on placebo were dizziness (27% vs. 18%) and syncope (6% vs. 2%).

The safety of CAMZYOS in patients was further evaluated in VALOR-HCM, a Phase 3, double-blind, randomized, placebo-controlled trial *[see Clinical Studies (14)*]. Of the 112 adults with symptomatic obstructive HCM, 56 patients were treated with CAMZYOS 2.5-15 mg daily and 55 were treated with placebo. CAMZYOS-treated patients had a median duration of exposure of 17 weeks (range: 3-19 weeks).

There were no new adverse reactions identified in VALOR-HCM.

Effects on Systolic Function

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 CAMZYOS, mean (SD) absolute change from baseline in LVEF was -4% (8) in the CAMZYOS 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. In the EXPLORER-HCM trial, 7 (6%) patients in the CAMZYOS group and 2 (2%) patients in the placebo group experienced reversible reductions in LVEF to <50% (median 48%: range 35-49%) while on treatment. In 3 of the 7 CAMZYOS patients and 1 of the 2 placebo patients, these reductions were asymptomatic. In all 7 patients treated with CAMZYOS, LVEF recovered following interruption of CAMZYOS *[see Warnings and Precautions (5.1)].*

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important.

It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

https://sideeffects.health.gov.il

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect Plasma Concentrations of CAMZYOS

Mavacamten is primarily metabolized by CYP2C19 and to a lesser extent by CYP3A4 and CYP2C9. Inducers and inhibitors of CYP2C19 and moderate to strong inhibitors or inducers of CYP3A4 may affect the exposures of mavacamten *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*. (See Table 1)

Table 1: Established and Potentially Significant Pharmacokinetic Drug Interactions with CAMZYOS

Impact of Other Drugs on CAMZYOS

Moderate to Strong CYP2C19 Inhibitors or Strong CYP3A4 Inhibitors	
Clinical Impact	Concomitant use with a moderate to strong CYP2C19 or a strong CYP3A4 inhibitor increases mavacamten exposure, which may increase the risk of heart failure due to systolic dysfunction *[see Contraindications (4), Warnings and Precautions (5.2), Clinical Pharmacology (12.3)]*.
Prevention or Management	Concomitant use with a moderate to strong CYP2C19 inhibitor or a strong CYP3A4 inhibitor is contraindicated.
Moderate to Strong CYP2C19 Inducers or Moderate to Strong CYP3A4 Inducers	
Clinical Impact	Concomitant use with a moderate to strong CYP2C19 inducer or a moderate to strong CYP3A4 inducer decreases mavacamten exposure, which may reduce CAMZYOS' efficacy *[see Clinical Pharmacology (12.3)]*. The risk of heart failure due to systolic dysfunction may increase with discontinuation of these inducers as the levels of induced enzyme normalizes *[see Contraindications (4) and Warnings and Precautions (5.2)]*.
Prevention or Management	Concomitant use of a moderate to strong CYP2C19 inducer or a moderate to strong CYP3A4 inducer is contraindicated.
Weak CYP2C19 Inhibitors or Moderate CYP3A4 Inhibitors	
Clinical Impact	Concomitant use with a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor increases mavacamten exposure, which may increase the risk of adverse drug reactions *[see Warnings and Precautions (5.2)]*.
Prevention or Management	Initiate CAMZYOS at the recommended starting dosage of 5 mg orally once daily in patients who are on stable therapy with a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor. Reduce dose of CAMZYOS by one level (i.e., 15 to 10 mg, 10 to 5 mg, or 5 to 2.5 mg) in patients who are on CAMZYOS treatment and intend to initiate a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor. Avoid initiation of concomitant weak CYP2C19 and moderate CYP3A4 inhibitors in patients who are on stable treatment with 2.5 mg of CAMZYOS because a lower dose is not available *[see Dosage and Administration (2.2)]*.

7.2 Potential for CAMZYOS to Affect Plasma Concentrations of Other Drugs

Mavacamten is an inducer of CYP3A4, CYP2C9, and CYP2C19. Concomitant use with CYP3A4, CYP2C19, or CYP2C9 substrates may reduce plasma concentration of these drugs *[see Clinical Pharmacology (12.3)]*. Closely monitor when CAMZYOS is used in combination with CYP3A4, CYP2C19, or CYP2C9 substrates where decreases in the plasma concentration of these drugs may reduce their activity.

Hormonal Contraceptives: Progestin and ethinyl estradiol are CYP3A4 substrates. Concomitant use of CAMZYOS may decrease exposures of ethinyl estradiol and progestin *[see Clinical Pharmacology (12.3)]*, which may lead to contraceptive failure or an increase in breakthrough bleeding. Advise patients to use a contraceptive method that is not affected by CYP450 enzyme

induction (e.g., intrauterine system) or add nonhormonal contraception (such as condoms) during concomitant use and for 4 months after the last dose of CAMZYOS.

7.3 Drugs That Reduce Cardiac Contractility

Expect additive negative inotropic effects of CAMZYOS and other drugs that reduce cardiac contractility.

Avoid concomitant use of CAMZYOS in patients on disopyramide, ranolazine, verapamil with a beta blocker, or diltiazem with a beta blocker as these medications and combinations increase the risk of left ventricular systolic dysfunction and heart failure symptoms and clinical experience is limited *[see Warnings and Precautions (5.1)]*.

If concomitant therapy with a negative inotrope is initiated, or if the dose of a negative inotrope is increased, monitor LVEF closely until stable doses and clinical response have been achieved.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data, CAMZYOS may cause fetal harm when administered to a pregnant female. There are no human data on the use of CAMZYOS during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. The underlying maternal condition during pregnancy poses a risk to the mother and fetus *(see Clinical Considerations).* Advise pregnant females about the potential risk to the fetus with maternal exposure to CAMZYOS during pregnancy.

In animal embryo-fetal development studies, mavacamten-related decreases in mean fetal body weight, reductions in fetal ossification of bones, and increases in post-implantation loss (early and/or late resorptions) were observed in rats and increases in visceral and skeletal malformations were observed in both rabbits and rats at dose exposures similar to that achieved at the maximum recommended human dose (MRHD) (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

Clinical Considerations

Disease-Associated Maternal and Embryo-Fetal Risk

Obstructive HCM in pregnancy has been associated with increased risk for preterm birth.

Data

Animal Data

When mavacamten was administered orally to pregnant rats (0.3 to 1.5 mg/kg/day) during the period of organogenesis, increases in post-implantation loss, decreases in mean fetal body weight, reductions in fetal ossification of bones, 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 at a similar exposure as in humans at the MRHD. Plasma exposure (based on area under the concentration-time curve or AUC) at the no-effect dose for embryo-fetal development in rats is 0.3 times the exposure in humans at the MRHD.

When mavacamten was administered orally to pregnant rabbits (0.6 to 2.0 mg/kg/day) during the period of organogenesis, fetal malformations (visceral and skeletal) were increased at doses of 1.2 mg/kg/day and higher, with similar plasma exposure at 1.2 mg/kg/day as in humans at the MRHD. Visceral findings consisted of malformations of the great vessels (dilatation of pulmonary trunk and/or aortic arch). Skeletal malformations consisted of higher incidences of fused sternebrae at ≥1.2 mg/kg/day. Plasma exposure (AUC) at the no-effect dose for embryo-fetal development in rabbits is 0.4 times the exposure in humans at the MRHD.

In a pre/postnatal development study, mavacamten was administered orally to pregnant rats (0.3, to 1.5 mg/kg/day) 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 no-observed-adverse-effect level (NOAEL) was 1.5 mg/kg/day (the highest dosage level tested), with similar exposure (AUC) as in humans at the MRHD.

8.2 Lactation

Risk Summary

The presence of mavacamten in human or animal milk, the drug's effects on the breastfed infant, and the effects on milk production are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CAMZYOS and any potential adverse effects on the breastfed child from CAMZYOS or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Based on animal data, CAMZYOS may cause fetal harm when administered to a pregnant female *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)]*.

Pregnancy Testing

Confirm absence of pregnancy in females of reproductive potential prior to initiation of CAMZYOS.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with CAMZYOS and for 4 months after the last dose. Use of CAMZYOS may reduce the effectiveness of CHCs. Advise patients using CHCs to use an alternative contraceptive method or add nonhormonal contraception *[see Drug Interactions (7.2)]*.

8.4 Pediatric Use

The safety and effectiveness of CAMZYOS have not been established in pediatric patients.

8.5 Geriatric Use

Clinical trials included 319 patients dosed with CAMZYOS, 119 of whom were 65 years of age or older (37.3%), and 25 of whom (7.8%) were age 75 years or older. Safety, effectiveness, and pharmacokinetics were similar between patients ≥65 years and younger patients.

8.6 Hepatic Impairment

No dosage adjustment is required in patients with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment. Mavacamten exposure (AUC) increased up to 220% in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment compared to patients with normal hepatic function. However, no additional dose adjustment is required in patients with mild to moderate hepatic impairment with the recommended dose titration algorithm and monitoring plan. The effect of severe (Child-Pugh C) hepatic impairment is unknown *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Human experience of overdose with CAMZYOS is limited. CAMZYOS has been given as a single dose of up to 144 mg in patients with HCM. One subject administered a single dose of 144 mg experienced serious adverse events including vasovagal reaction, hypotension, and asystole, but the subject recovered. In healthy subjects, doses of up to 25 mg have been administered for up to 25 days, with 3 of 8 participants treated at the 25-mg dose level experiencing 20% or greater reductions in LVEF. An infant death was reported after accidental ingestion of three 15-mg capsules.

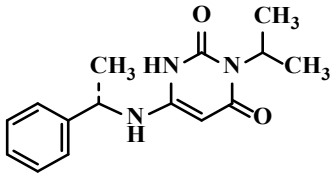
Systolic dysfunction is the most likely result of overdosage of CAMZYOS. Treatment of overdose with CAMZYOS consists of discontinuation of CAMZYOS treatment as well as medically supportive measures to maintain hemodynamic stability, including close monitoring of vital signs and LVEF and management of the clinical status of the patient. Overdose in humans can be life-threatening and result in asystole refractory to any medical intervention.

11 DESCRIPTION

CAMZYOS capsules for oral use contain mavacamten, a cardiac myosin inhibitor.

The chemical name of mavacamten is 3-(1-methylethyl)-6-[[(1S)-1-phenylethyl]amino]-2,4(1*H*,3*H*)-pyrimidinedione. The molecular formula is $C_{15}H_{19}N_3O_2$, and the molecular weight is 273.33 g/mol.

The structural formula of mavacamten is:



Mavacamten is a white to off-white powder that is practically insoluble in water and aqueous buffers at pH 2-10, sparingly soluble in methanol and ethanol, and freely soluble in DMSO and NMP.

CAMZYOS is supplied as immediate release Size 2 hard gelatin capsules, containing 2.5 mg, 5 mg, 10 mg, or 15 mg of mavacamten per capsule as active ingredient and the following inactive ingredients: mannitol, croscarmellose sodium, silica colloidal hydrated, hypromellose, magnesium stearate. The capsule shell contains gelatin, titanium dioxide, and: black iron oxide (Camzyos 2.5 mg and 15 mg), red iron oxide (Camzyos 2.5 mg and 10 mg), yellow iron oxide (Camzyos 5 mg) and black edible ink (shellac, propylene glycol, strong ammonia solution, potassium hydroxide, black iron oxide).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mavacamten is an allosteric and reversible inhibitor selective for cardiac myosin. Mavacamten modulates the number of myosin heads that can enter “on actin” (power-generating) states, thus reducing the probability of force-producing (systolic) and residual (diastolic) cross-bridge formation. Excess myosin actin cross-bridge formation and dysregulation of the super-relaxed state are mechanistic hallmarks of HCM. Mavacamten shifts the overall myosin population towards an energy-sparing, recruitable, super-relaxed state. In HCM patients, myosin inhibition with mavacamten reduces dynamic LVOT obstruction and improves cardiac filling pressures.

12.2 Pharmacodynamics

Left Ventricular Ejection Fraction and Left Ventricular Outflow Tract Obstruction

In the EXPLORER-HCM trial, patients achieved 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) changes from baseline in resting and Valsalva LVOT gradients were -39 (29) mmHg and -49 (34) mmHg, respectively, for the CAMZYOS group and -6 (28) mmHg and -12 (31) mmHg, respectively, for the placebo group. The reductions in Valsalva LVOT gradient were accompanied by decreases in LVEF, generally within the normal range. Eight weeks after discontinuation of CAMZYOS, mean LVEF and Valsalva LVOT gradients were similar to baseline.

Cardiac Structure

In EXPLORER-HCM, 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 (-7.4 [17.8] g/m2) versus an increase in LVMI in the placebo group (8.9 [15.3] g/m2). There was also a mean (SD) reduction from baseline in left atrial volume index (LAVI) in the mavacamten group (-7.5 [7.8] mL/m2) versus no change in the placebo group (-0.1 [8.7] mL/m2). The clinical significance of these findings is unknown.

Cardiac Biomarkers

In the EXPLORER-HCM trial *[see Clinical Studies (14)]*, reductions in a biomarker of cardiac wall stress, NT-proBNP, were observed by Week 4 and sustained through the end of treatment. At Week 30 compared with baseline, the reduction in NT-proBNP after mavacamten treatment was 80% greater than for placebo (proportion of geometric mean ratio between the two groups, 0.20 [95% CI: 0.17, 0.24]).

In the VALOR-HCM trial [see Clinical Studies (14)], a reduction in NT-proBNP was observed by Week 8 and sustained throughout treatment. At Week 16 compared with baseline, the reduction in NT-proBNP after mavacamten treatment was 67% greater than for placebo (proportion of geometric mean ratio between the two groups, 0.33 [95% CI: 0.27, 0.42]). At Week 16 compared with baseline, a reduction in cardiac troponin I after mavacamten treatment was 47% greater than for placebo (proportion of geometric mean ratio between the two groups, 0.53 [95% CI: 0.41, 0.70]).

The clinical significance of the NT-proBNP and troponin findings is unknown.

Cardiac Electrophysiology

In healthy volunteers receiving multiple doses of CAMZYOS, a concentration-dependent increase in the QTc interval was observed at doses up to 25 mg once daily. No acute QTc changes have been observed at similar exposures during single-dose studies. The mechanism of the QT prolongation effect is not known.

A meta-analysis across clinical studies in HCM patients does not suggest clinically relevant increases in the QTc interval in the therapeutic exposure range. 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 the HCM population. The effect of coadministration of CAMZYOS with other QT-prolonging drugs or in patients with potassium channel variants resulting in a long QT interval have not been characterized.

12.3 Pharmacokinetics

Mavacamten exposure increases generally dose proportionally after multiple once-daily doses of 1 mg to 15 mg. At the same dose level of CAMZYOS, 170% higher exposures of mavacamten are observed in patients with HCM compared to healthy subjects.

Absorption

Mavacamten has an estimated oral bioavailability of at least 85% and time to maximum concentration (T_{max}) of 1 hour.

Effect of Food

No clinically significant differences in mavacamten pharmacokinetics were observed following its administration with a high fat meal. The T_{max} was increased by 4 hours.

Distribution

Plasma protein binding of mavacamten is between 97 and 98%.

Elimination

Mavacamten has a variable terminal $t_{1/2}$ that depends on CYP2C19 metabolic status. Mavacamten terminal half-life is 6-9 days in CYP2C19 normal metabolizers (NMs), which is prolonged in CYP2C19 poor metabolizers (PMs) to 23 days. Drug accumulation occurs with an accumulation ratio of about 2-fold for C_{max} and about 7-fold for AUC in CYP2C19 NMs. The accumulation depends on the metabolism status for CYP2C19 with the largest accumulation observed in CYP2C19 PMs. At steady-state, the peak-to-trough plasma concentration ratio with once daily dosing is approximately 1.5.

Metabolism

Mavacamten is extensively metabolized, primarily through CYP2C19 (74%), CYP3A4 (18%), and CYP2C9 (8%).

Excretion

Following a single 25 mg dose of radiolabeled mavacamten, 7% of the dose was recovered in feces (1% unchanged) and 85% in urine (3% unchanged).

Specific Populations

No clinically significant differences in the pharmacokinetics of mavacamten were observed based on age (range: 18-82 years), sex, race, ethnicity, or mild (eGFR: 60 to 89 mL/min/1.73 m^2) to moderate (eGFR: 30 to 59 mL/min/1.73 m^2) renal impairment. The effects of severe (eGFR: 15 to 30 mL/min/1.73 m^2) renal impairment and kidney failure (eGFR: <15 mL/min/1.73 m^2; including patients on dialysis) are unknown.

Hepatic Impairment

Mavacamten exposures (AUC) increased up to 220% in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. The effect of severe (Child-Pugh C) hepatic impairment is unknown.

Drug Interactions

Clinical Studies and Model-Informed Approaches

Weak CYP2C19 Inhibitors: Concomitant use of mavacamten (15 mg) with omeprazole (20 mg) once daily increased mavacamten AUC_{inf} by 48% with no effect on C_{max} in healthy CYP2C19 NMs and rapid metabolizers (RMs; e.g., *1/*17).

Moderate CYP3A4 Inhibitors: Concomitant use of mavacamten (25 mg) with verapamil sustained release (240 mg) increased mavacamten AUC_{inf} by 16% and C_{max} by 52% in intermediate metabolizers (IMs; e.g., *1/*2, *1/*3, *2/*17, *3/*17) and NMs of CYP2C19. Concomitant use of mavacamten with diltiazem in CYP2C19 PMs is predicted to increase mavacamten AUC_{0-24h} and C_{max} up to 55% and 42%, respectively.

Strong CYP3A4 Inhibitors: Concomitant use of mavacamten (15 mg) with ketoconazole 400 mg once daily is predicted to increase mavacamten AUC_{0-24} and C_{max} up to 130% and 90%, respectively.

Strong CYP2C19 and CYP3A4 Inducers: Concomitant use of mavacamten (a single 15 mg dose) with a strong CYP2C19 and CYP3A4 inducer (rifampin 600 mg daily dose) is predicted to decrease mavacamten $AUC_{0\text{-}inf}$ and C_{max} by 87% and 22%, respectively, in CYP2C19 NMs, and by 69% and 4%, respectively, in CYP2C19 PMs.

CYP3A4 Substrates: Concomitant use of a 16-day course of mavacamten (25 mg on days 1 and 2, followed by 15 mg for 14 days) resulted in a 13% and 7% decrease in midazolam AUC_{inf} and C_{max}, respectively, in healthy CYP2C19 NMs. Following coadministration of mavacamten once daily in HCM patients, midazolam AUC_{inf} and C_{max} are predicted to decrease by 21 to 64% and 13 to 48%, respectively, depending on the dose of mavacamten and CYP2C19 phenotype.

CYP2C8 Substrates: Concomitant use of mavacamten once daily in HCM patients is predicted to decrease AUC and C_{max} of repaglinide, a CYP2C8 and CYP3A substrate, by 12 to 39%, depending on the dose of mavacamten and CYP2C19 phenotype.

CYP2C9 Substrates: Concomitant use of mavacamten once daily in HCM patients is predicted to decrease AUC and C_{max} of tolbutamide, a CYP2C9 substrate, by 33 to 65%, depending on the dose of mavacamten and CYP2C19 phenotype.

CYP2C19 Substrates: Concomitant use of mavacamten once daily in HCM patients is predicted to decrease AUC and C_{max} of omeprazole, a CYP2C19 substrate, by 48 to 67%, depending on the dose of mavacamten and CYP2C19 phenotype.

In Vitro Studies

CYP Enzymes: Mavacamten does not inhibit CYP1A2, CYP2B6, or CYP2C8. At clinically relevant concentrations, mavacamten is not an inhibitor of CYP2D6, CYP2C9, CYP2C19, or CYP3A4. Mavacamten is a CYP2B6 inducer.

Transporter Systems: Mavacamten does not inhibit P-gp, BCRP, BSEP, MATE1, MATE2-K, organic anion transporting polypeptides (OATPs), organic cation transporters (OCTs), or organic anion transporters (OATs).

12.5 Pharmacogenomics

Mavacamten AUC_{inf} increased by 241% and C_{max} increased by 47% in CYP2C19 poor metabolizers (PMs) compared to normal metabolizers (NMs) following a single dose of 15 mg mavacamten. Mean half-life is prolonged in CYP2C19 PMs compared to NMs (23 days vs. 6 to 9 days, respectively).

Polymorphic CYP2C19 is the main enzyme involved in the metabolism of CAMZYOS. An individual carrying two normal function alleles is a NM (e.g., *1/*1). An individual carrying two no function alleles is a PM (e.g., *2/*2, *2/*3, *3/*3).

The prevalence of CYP2C19 poor metabolizers differs depending on ancestry. Approximately 2% of individuals of European ancestry and 4% of individuals of African ancestry are PMs; the prevalence of PMs is higher in Asian populations (e.g., approximately 13% of East Asians).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

There was no evidence of carcinogenicity seen in a 6-month rasH2 transgenic mouse study at mavacamten doses of up to 2.0 mg/kg/day in males and 3.0 mg/kg/day in females, or in a 2-year rat study at mavacamten doses up to 0.6 mg/kg/day. The exposure-based (AUC) safety margins in mice and rats were up to 3X or 0.2X, respectively, compared to AUC exposures in humans at the MRHD.

In reproductive toxicity studies, there was no evidence of effects of mavacamten on mating and fertility in male or female rats at doses up to 1.2 mg/kg/day, or on the viability and fertility of offspring of dams dosed up to 1.5 mg/kg/day. Plasma exposure (AUC) of mavacamten at the highest dose tested was the same as in humans at the MRHD.

13.2 Animal Toxicology and/or Pharmacology

The safety of mavacamten has been evaluated in rats and dogs at multiple dose levels (0.06 to 10 mg/kg/day) orally. Noted toxicities, including echocardiographic findings, reduction in systolic function, cardiac dilation, and death, as well as increased heart weights in rats, were consistent with mavacamten's 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 NOAEL in rats and dogs were 0.1 and 0.3 times, respectively, human exposure (AUC) at the MRHD.

14 CLINICAL STUDIES

EXPLORER-HCM

The efficacy of CAMZYOS was evaluated in EXPLORER-HCM (NCT-03470545) a Phase 3, double-blind, randomized, placebo-controlled, multicenter, international, parallel-group trial in 251 adults with symptomatic NYHA class II and III obstructive HCM, LVEF ≥55%, and LVOT peak gradient ≥50 mmHg at rest or with provocation.

Patients on dual therapy with beta blocker and calcium channel blocker treatment or monotherapy with disopyramide or ranolazine were excluded. Patients with a known infiltrative or storage disorder causing cardiac hypertrophy that mimicked obstructive HCM, such as Fabry disease, amyloidosis, or Noonan syndrome with left ventricular hypertrophy, were also excluded.

Patients were randomized in a 1:1 ratio to receive either a starting dose of 5 mg of CAMZYOS or placebo once daily for 30 weeks. Treatment assignment was stratified by baseline NYHA functional class, baseline use of beta blockers, and type of ergometer (treadmill or exercise bicycle).

Groups were well matched with respect to age (mean 59 years), BMI (mean 30 kg/m^2), heart rate (mean 62 bpm), blood pressure (mean 128/76 mmHg), and race (90% Caucasian). Males comprised 54% of the CAMZYOS group and 65% of the placebo group.

At baseline, approximately 73% of the randomized patients were NYHA class II and 27% were NYHA class III. The mean LVEF was 74%, and the mean Valsalva LVOT gradient was 73 mmHg. About 10% had prior septal reduction therapy, 75% were on beta blockers, 17% were on calcium channel blockers, and 14% had a history of atrial fibrillation.

All patients were initiated on CAMZYOS 5 mg (or matching placebo) once daily, and the dose was periodically adjusted to optimize patient response (decrease in LVOT gradient with Valsalva maneuver) and maintain LVEF ≥50%. The dose was also informed by plasma concentrations of CAMZYOS.

In the CAMZYOS group, at the end of treatment, 49% of patients were receiving the 5-mg dose, 33% were receiving the 10-mg dose, and 11% were receiving the 15-mg dose. Three patients temporarily interrupted their dose due to LVEF <50%, of whom two resumed treatment at the same dose and one had the dose reduced from 10 mg to 5 mg.

Primary endpoint

The primary composite functional endpoint, assessed at 30 weeks, was defined as the proportion of patients who 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.

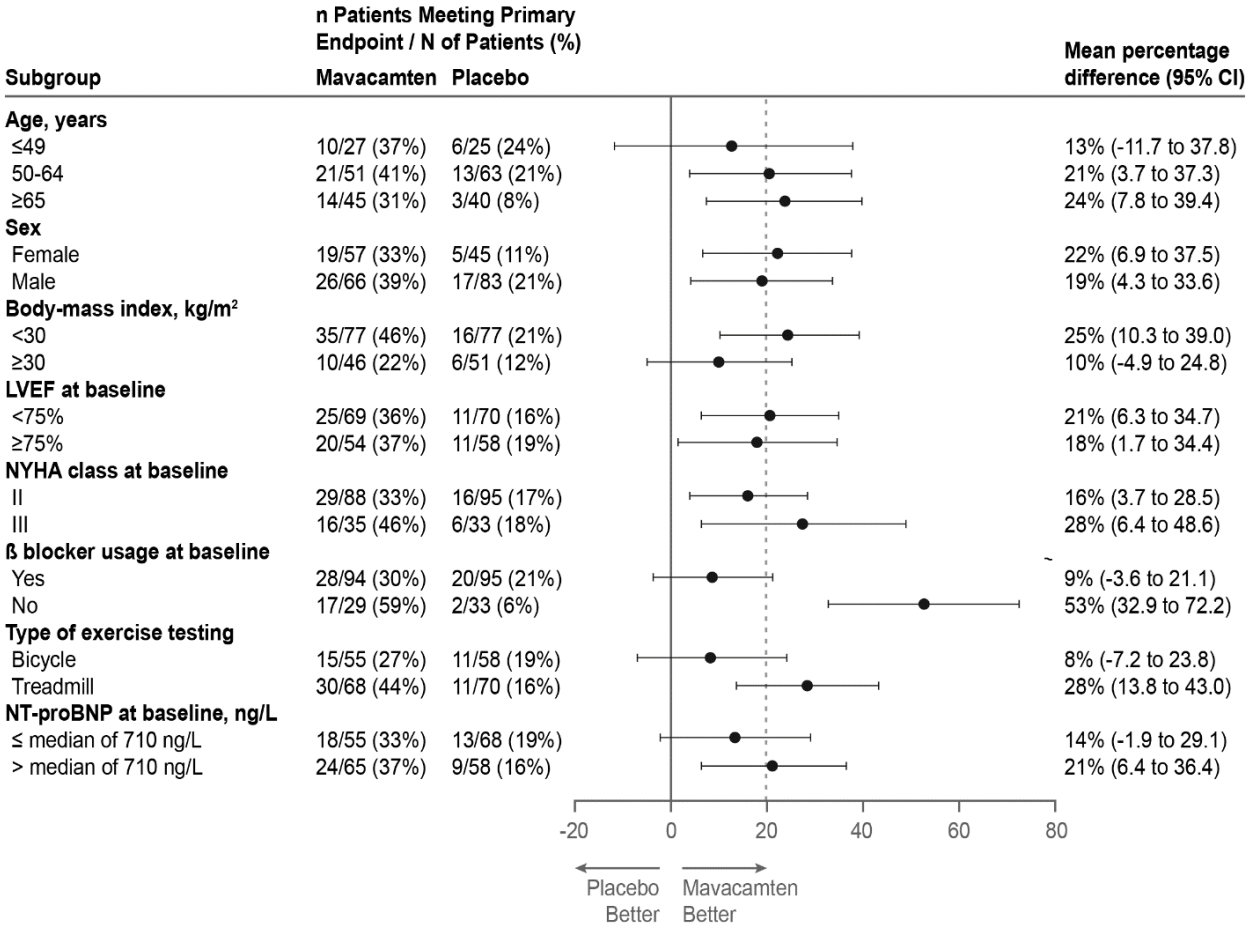
A greater proportion of patients met the primary endpoint at Week 30 in the CAMZYOS group compared to the placebo group (37% vs. 17%, respectively, p=0.0005; see Table 2).

Table 2: Primary Endpoint at 30 Weeks

	CAMZYOS n (%) N = 123	**Placebo n (%) N = 128**	**Difference (95% CI)**	**p-value**
Total responders	45 (37%)	22 (17%)	19% (9, 30)	0.0005
Change from baseline pVO_2 ≥1.5 mL/kg/min and decreased NYHA	41 (33%)	18 (14%)	19% (9, 30)	
Change from baseline pVO_2 ≥3 mL/kg/min and NYHA not increased	29 (23%)	14 (11%)	13% (3, 22)	

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 CAMZYOS across all subgroups analyzed (Figure 4).

Figure 4: Subgroup Analysis of the Primary Composite Functional Endpoint



The dashed vertical line represents the overall treatment effect and the solid vertical line (no effect) indicates no difference between treatment groups.

Note: The figure above presents effects in various subgroups, all of which are baseline characteristics.

The 95% confidence limits that are shown do not take into account the number of comparisons made and may not reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Although the benefit of mavacamten was smaller in patients on background beta blocker therapy compared to those who were not (attenuated improvement in pVO_2), analyses of other secondary endpoints (symptoms, LVOT gradient) suggest that patients might benefit from mavacamten treatment regardless of beta blocker use.

Secondary endpoints

The treatment effects of CAMZYOS 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 pVO_2, 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 CAMZYOS had greater improvement compared to the placebo group across all secondary endpoints (Table 3, Figure 5, Figure 6, Table 4, and Figures 7-10).

Table 3: Change from Baseline to Week 30 in Post-Exercise LVOT Gradient, pVO_2, and NYHA Class

	CAMZYOS N = 123	Placebo N = 128	Difference (95% CI)	p-value
Post-Exercise LVOT gradient (mmHg), mean (SD)	-47 (40)	-10 (30)	-35 (-43, -28)	<0.0001
pVO_2 (mL/kg/min), mean (SD)	1.4 (3.1)	-0.1 (3.0)	1.4 (0.6, 2.1)	<0.0006
Number (%) with NYHA Class improved ≥1	80 (65%)	40 (31%)	34% (22%, 45%)	<0.0001

Figure 5: Cumulative Distribution of Change from Baseline to Week 30 in LVOT Peak Gradient

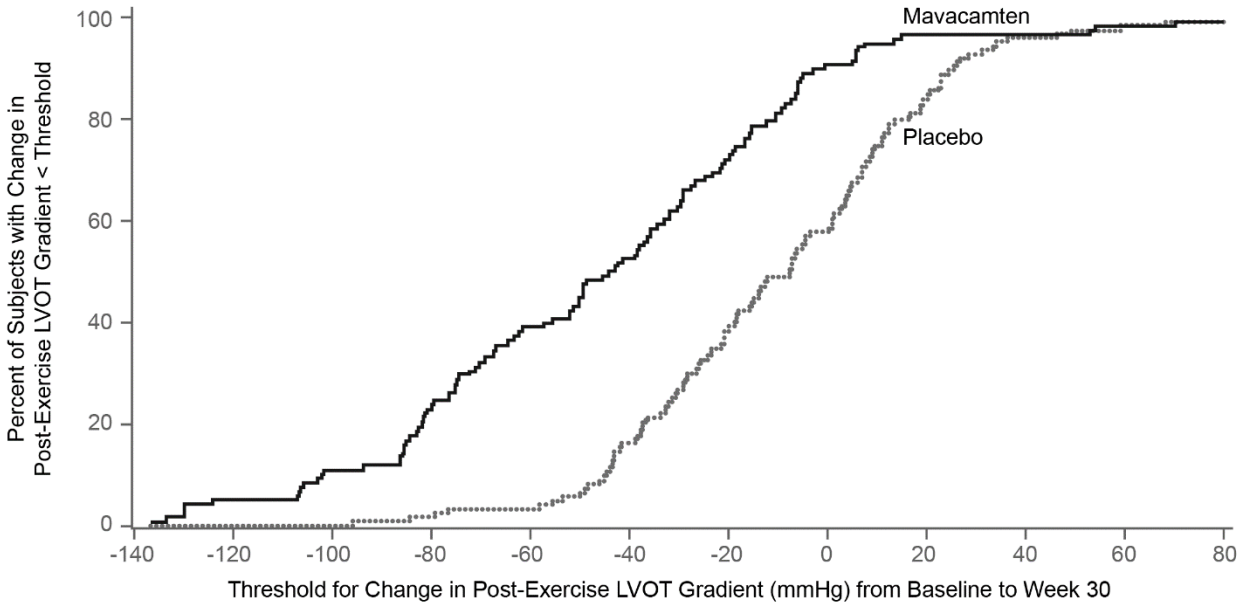


Figure 6: Cumulative Distribution of Change from Baseline to Week 30 in pVO_2

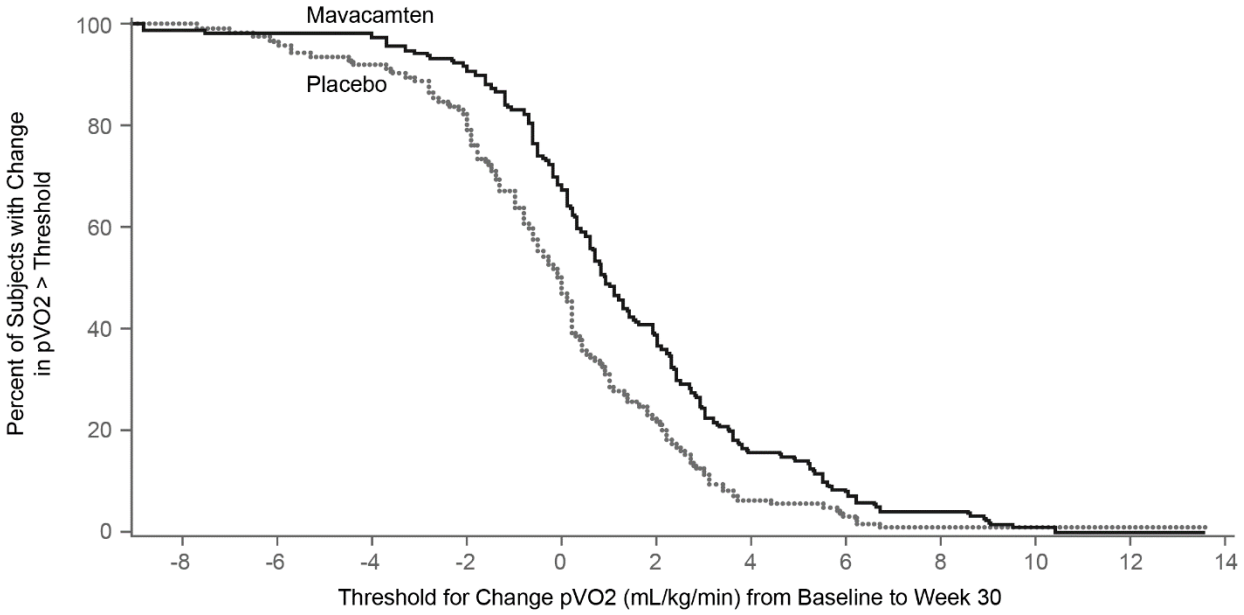


Table 4: Change from Baseline to Week 30 in KCCQ-23 CSS and HCMSQ SoB Domain

	Baseline, Mean (SD)		Change from Baseline to Week 30, Mean (SD)		Difference, LS Mean (95%CI) and p-value
	CAMZYOS	Placebo	CAMZYOS	Placebo	
KCCQ-23 CSS†	n=99 71 (16)	n=97 71 (19)	14 (14)	4 (14)	9 (5, 13) p<0.0001
KCCQ-23 TSS	71 (17)	69 (22)	12 (15)	5 (16)	
KCCQ-23 PL	70 (18)	72 (19)	15 (17)	4 (15)	
HCMSQ SoB‡	n=108 5 (3)	n=109 5 (3)	-3 (3)	-1 (2)	-2 (-2, -1) p<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 HCMSQ SoB domain score measures the frequency and severity of shortness of breath. The HCMSQ SoB domain score ranges from 0 to 18 with lower scores representing less shortness of breath.
Missing data were not imputed to summarize the baseline and change from baseline to Week 30 values. Difference in mean change from baseline between treatment groups was estimated using a mixed model for repeated measures.

Figure 7 shows the time course for changes in KCCQ-23 CSS. Figure 8 shows the distribution of changes from baseline to Week 30 for KCCQ-23 CSS.

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

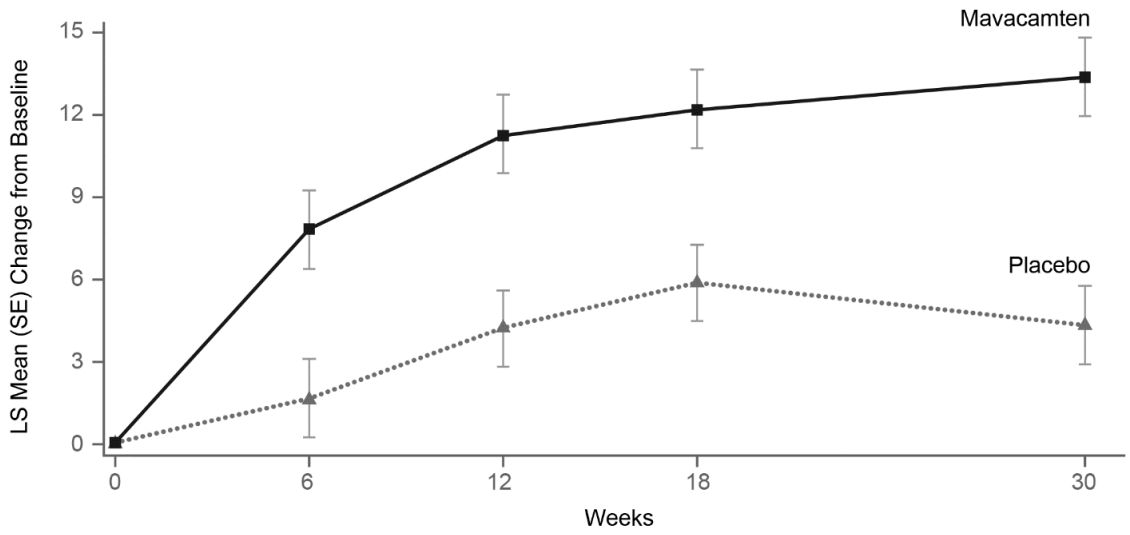
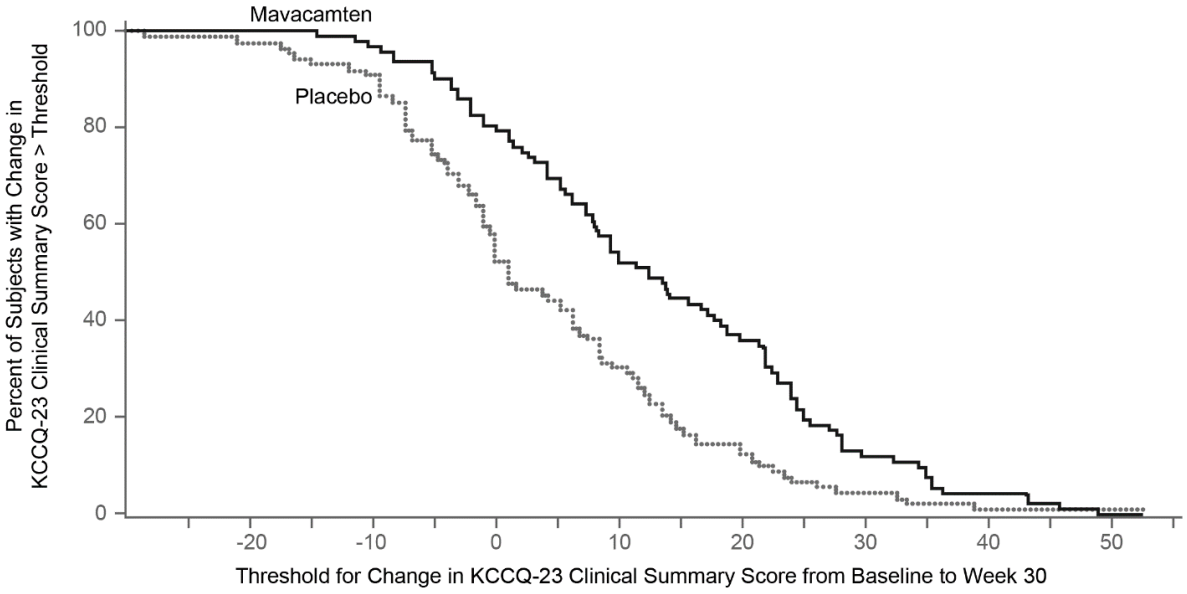


Figure 8: KCCQ-23 Clinical Summary Score: Cumulative Distribution of Change from Baseline to Week 30



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

Figure 9 shows the time course for changes in HCMSQ SoB. Figure 10 shows the distribution of changes from baseline to Week 30 for HCMSQ SoB.

Figure 9: HCMSQ Shortness of Breath Domain: Mean Change from Baseline Over Time

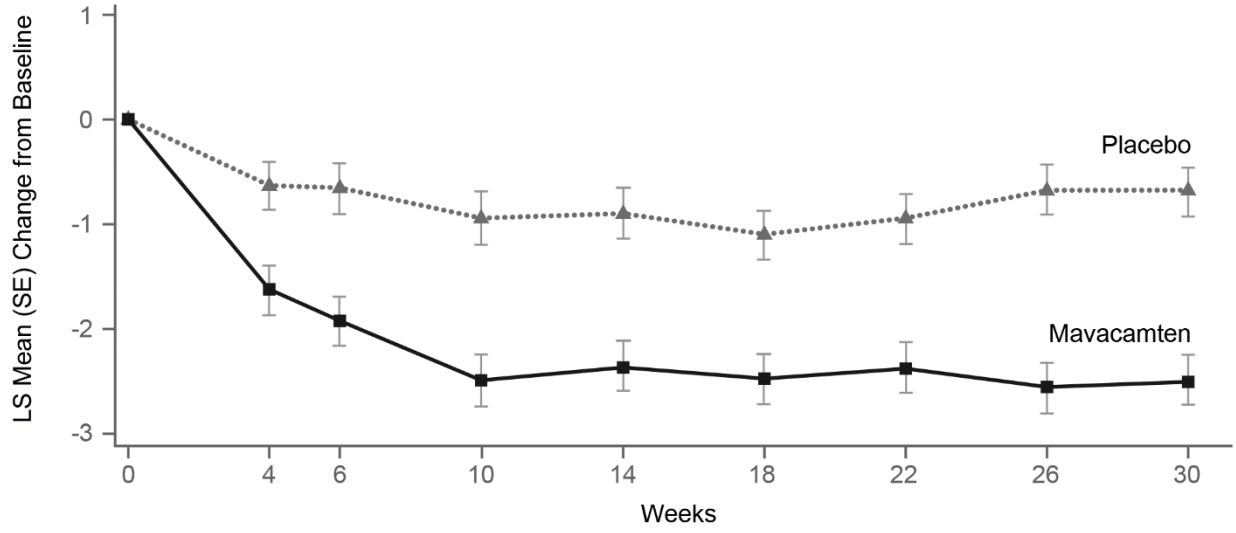
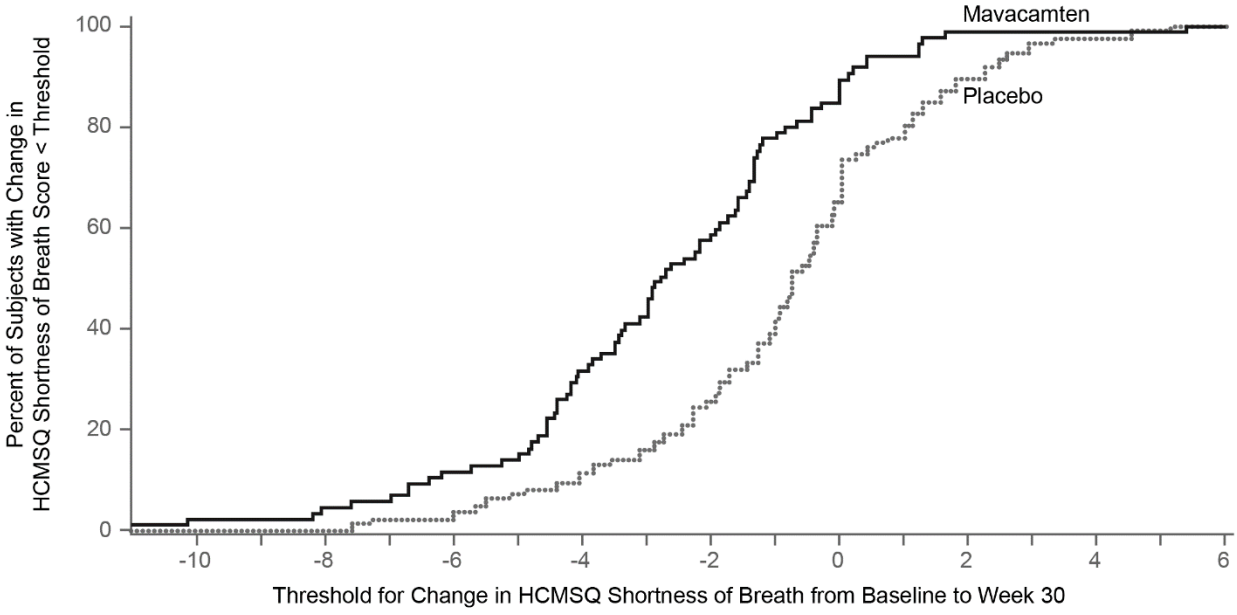


Figure 10: HCMSQ Shortness of Breath Domain: Cumulative Distribution of Change from Baseline to Week 30



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

VALOR-HCM

The efficacy of CAMZYOS was evaluated in VALOR-HCM, a Phase 3, double-blind, randomized, 16-week placebo-controlled trial in 112 patients (mean age of 60 years; 51% men; 93% ≥ NYHA class III) randomized 1:1 to receive treatment with CAMZYOS 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 CAMZYOS (2.5 mg, 5 mg, 10 mg, or 15 mg) or a placebo capsule once daily for 16 weeks. Dose adjustment was based on clinical echocardiogram parameters.

Primary endpoint

CAMZYOS 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 5).

Table 5: Primary Endpoint at 16 Weeks

	CAMZYOS n (%) n=56	**Placebo n (%) n=56**	**Treatment difference (95% CI)**	**p-value**
Primary efficacy composite endpoint	10 (18)	43 (77)	59% (44%, 74%)	<0.0001
Patient decision to proceed with SRT	2 (3.6)	2 (3.6)		
SRT-eligible based on guideline criteria*	8 (14)	39 (70)		
SRT status not evaluable (imputed as meeting guideline criteria)	0	2 (3.6)		

*NYHA Class III or IV, or Class II with exertion induced syncope or near syncope and dynamic LVOT gradient at rest or with provocation (i.e., Valsalva or exercise) ≥ 50 mmHg.

Secondary endpoints

The treatment effects of CAMZYOS on LVOT obstruction, functional capacity, and health status were assessed by change from baseline through Week 16 in post-exercise LVOT gradient, proportion of patients with improvement in NYHA class, and KCCQ-23 CSS.

Table 6: Change from Baseline to Week 16 in Secondary Endpoints

	CAMZYOS 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 (16)	2 (14)	10 (5, 15)	
KCCQ-23 PL, mean (SD)	10 (19)	2 (17)	10 (5, 16)	

[†]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**.**

Figure 11 shows the time course for changes in KCCQ-23 CSS. Figure 12 shows the distribution of changes from baseline to Week 16 for KCCQ-23 CSS.

Figure 11: KCCQ-23 Clinical Summary Score: Mean Change from Baseline Over Time

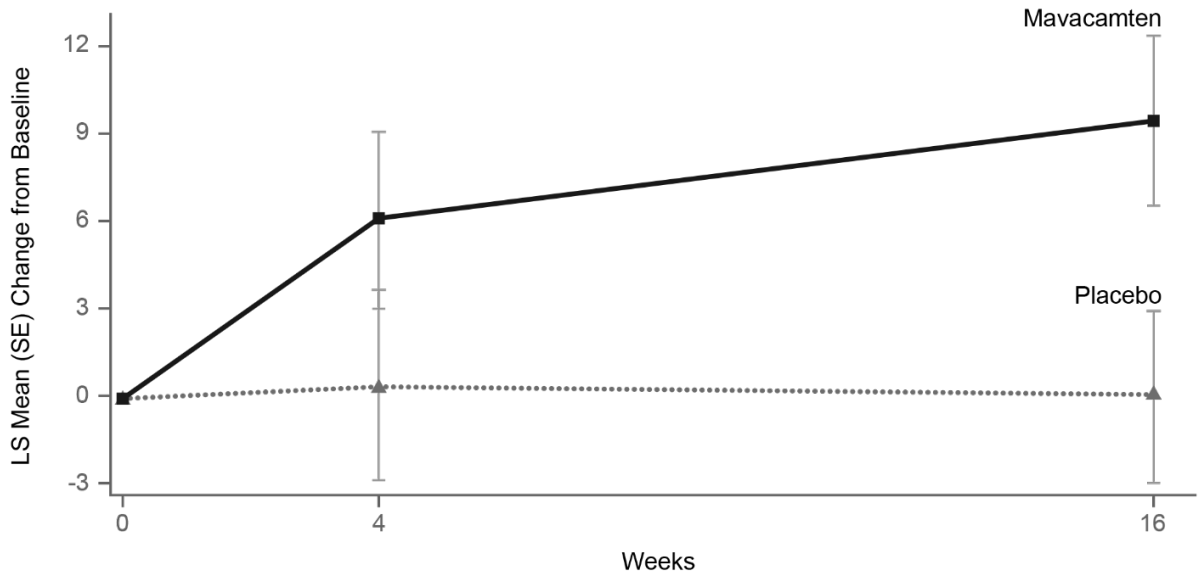
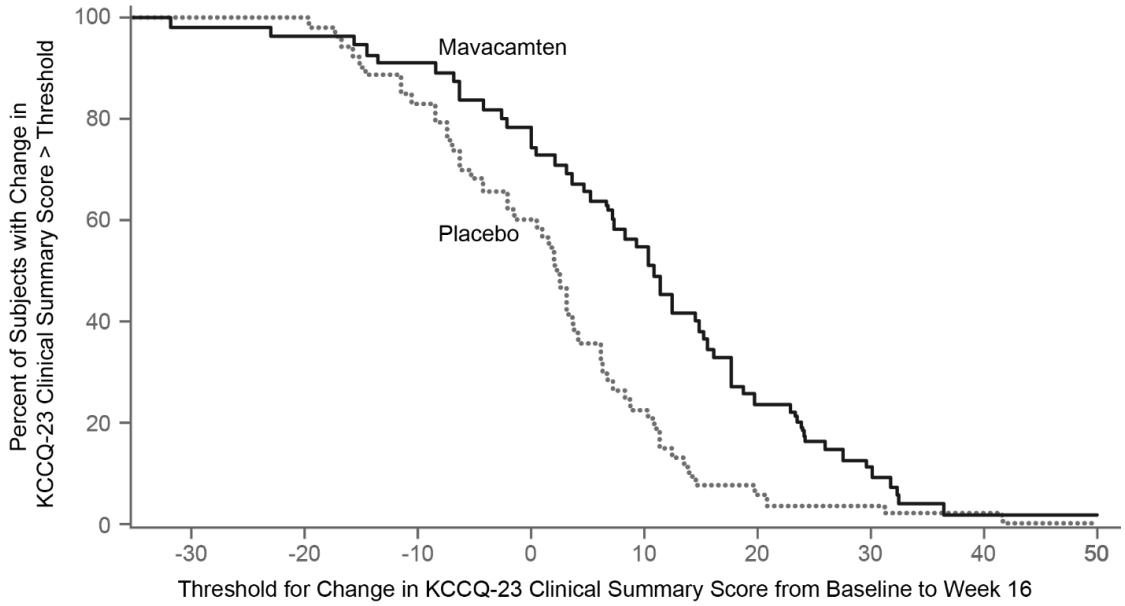


Figure 12: KCCQ-23 Clinical Summary Score: Cumulative Distribution of Change from Baseline to Week 16



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

16 HOW SUPPLIED/STORAGE AND HANDLING

CAMZYOS® is supplied as immediate release Size 2 hard gelatin capsules containing 2.5 mg, 5 mg, 10 mg, or 15 mg of mavacamten. White opaque capsule bodies are imprinted in black ink with “Mava”, and the opaque cap (Light purple for 2.5 mg, Yellow for 5 mg, Pink for 10 mg and Gray for 15 mg) is imprinted in black ink with the strength, both in radial direction. The capsule contains white to off-white powder. CAMZYOS capsules are available in Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE (ACLAR)) / Aluminium foil blisters containing 14 capsules.
Pack size of 14 or 28 capsules.
Not all pack sizes may be marketed.

Storage
Store below 30°C.
The expiry date of the product is indicated on the packaging materials.

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