

## **1. PRODUCT NAME**

KOPOZGO 2.5mg capsules

KOPOZGO 5mg capsules

KOPOZGO 10mg capsules

KOPOZGO 15mg capsules

## **2. NAME AND STRENGTH OF ACTIVE SUBSTANCE**

Mavacamten; 2.5mg, 5mg, 10mg, 15mg

## **3. INDICATIONS AND USAGE**

KOPOZGO 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.

## **4. DOSAGE AND ADMINISTRATION**

### **4.1. Initiation, Maintenance, and Interruption of Treatment**

Confirm absence of pregnancy and usage of effective contraception in females of reproductive potential [*see Warnings and Precautions (7.3)*].

Initiation or up-titration of KOPOZGO 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 once daily. The maximum recommended dose is 15 mg orally once daily.

Patients may develop heart failure while taking KOPOZGO. 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  $\geq$ 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 Contraindications (6), Warnings and Precautions (7.2), Drug Interactions (9.1) and Clinical Pharmacology (13.3)*].

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

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

Figure 1. Initiation Phase

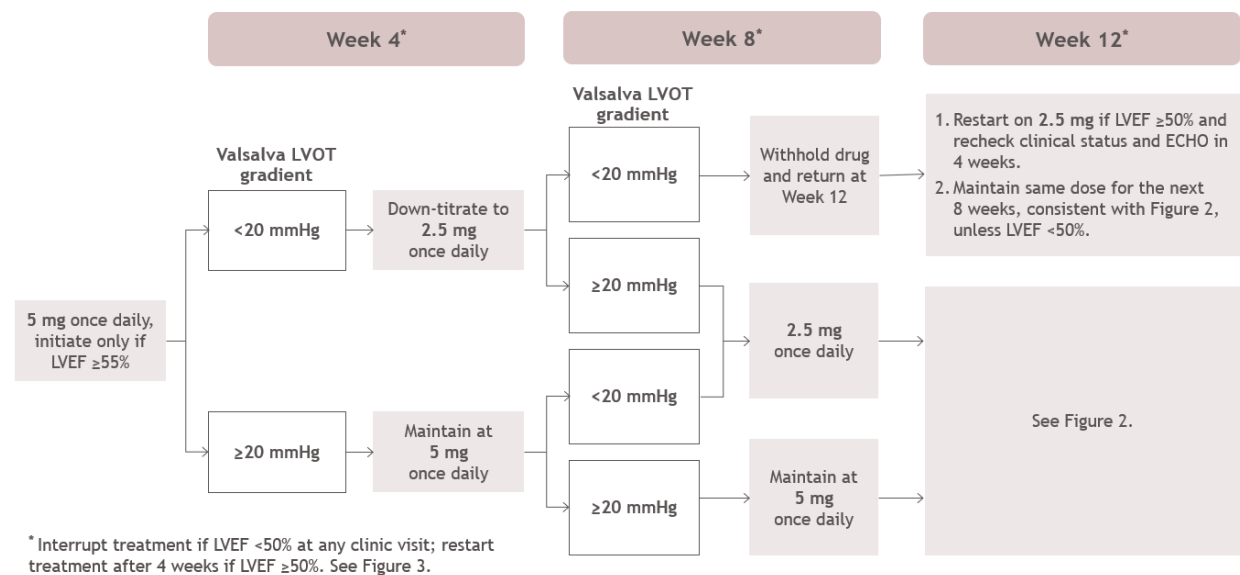


Figure 2. Maintenance Phase

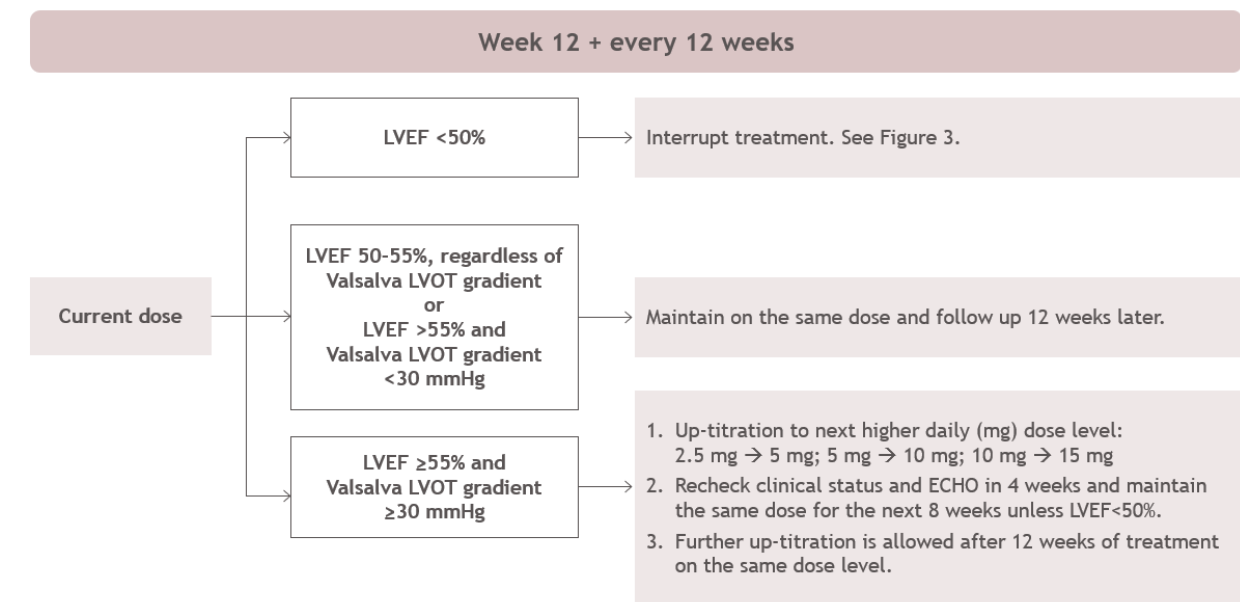
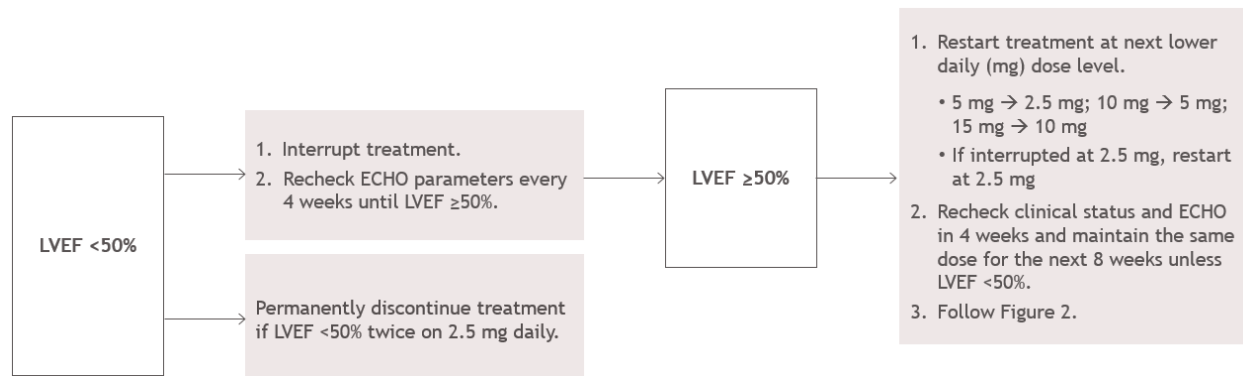


Figure 3. Treatment Interruption at Any Clinic Visit if LVEF <50%



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 KOPOZGO in patients with intercurrent illness [see *Warnings and Precautions (7.1)*].

#### 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.

## **4.2. Concomitant Administration of Weak CYP2C19 or Moderate CYP3A4 Inhibitors**

Initiate KOPOZGO 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 KOPOZGO 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 KOPOZGO 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 KOPOZGO because a lower KOPOZGO once-daily dose is not available [see *Dosage and Administration (4.1)*, *Drug Interactions (9.1)*].

## **5. DOSAGE FORMS AND STRENGTHS**

KOPOZGO is available as capsules imprinted with the strength and “Mava” in the following strengths:

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

- 15 mg – gray cap

## 6. CONTRAINDICATIONS

KOPOZGO is contraindicated with concomitant use of:

- Moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors [*see Warnings and Precautions (7.2), Drug Interactions (9.1)*]
- Moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers [*see Warnings and Precautions (7.2), Drug Interactions (9.1)*]

## 7. WARNINGS AND PRECAUTIONS

### 7.1. Heart Failure

KOPOZGO 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) or those undergoing major cardiac surgery may be at greater risk of developing systolic dysfunction and heart failure.

Assess the patient's clinical status and LVEF prior to and regularly during treatment and adjust the KOPOZGO dose accordingly [*see Dosage and Administration (4.1)*]. 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 (4.1, 4.2)*].

Initiation of KOPOZGO in patients with LVEF <55% is not recommended. Avoid concomitant use of KOPOZGO 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 (9)*].

### 7.2. CYP450 Drug Interactions Leading to Heart Failure or Loss of Effectiveness

KOPOZGO is primarily metabolized by CYP2C19 and CYP3A4 enzymes. Concomitant use of KOPOZGO and drugs that interact with these enzymes may lead to life-threatening drug interactions such as heart failure or loss of effectiveness [*see Contraindications (6), Warnings and Precautions (7.1), and Drug Interactions (9.1)*].

Advise patients of the potential for drug interactions, including with medications such as omeprazole, esomeprazole, or cimetidine. Advise patients to inform their healthcare provider of all concomitant products prior to and during KOPOZGO treatment [*see Drug Interactions (9.1)*].

### 7.3. Embryo-Fetal Toxicity

KOPOZGO 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 KOPOZGO and for 4 months after the last dose. CHCs containing a combination of ethinyl estradiol and norethindrone may be used with mavacamten. However, KOPOZGO may reduce the effectiveness of certain other combined hormonal contraceptives (CHCs). If these CHCs are used, advise patients to add nonhormonal contraception (such as condoms) during concomitant use and for 4 months after the last dose of KOPOZGO [see *Drug Interactions (9.2)* and *Use in Specific Populations (10.1, 10.3)*].

## 8. ADVERSE REACTIONS

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

- Heart failure [see *Warnings and Precautions (7.1)*]

### 8.1. 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 KOPOZGO was evaluated in EXPLORER-HCM, a Phase 3, double-blind, randomized, placebo-controlled trial [see *Clinical Studies (15)*]. Of the 251 adults with obstructive HCM, 123 patients were treated with KOPOZGO 2.5-15 mg daily and 128 were treated with placebo. KOPOZGO-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 KOPOZGO.

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

The safety of KOPOZGO in patients was further evaluated in VALOR-HCM, a Phase 3, double-blind, randomized, placebo-controlled trial [see *Clinical Studies (15)*]. Of the 112 adults with symptomatic obstructive HCM, 56 patients were treated with KOPOZGO 2.5-15 mg daily and 55 were treated with placebo. KOPOZGO-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 KOPOZGO, mean (SD) absolute change from baseline in LVEF was -4% (8) in the KOPOZGO 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 KOPOZGO 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 KOPOZGO patients and 1 of the 2 placebo patients, these reductions were asymptomatic. In all 7 patients treated with KOPOZGO, LVEF recovered following interruption of KOPOZGO [see *Warnings and Precautions (7.1)*].

## 9. DRUG INTERACTIONS

### 9.1. Potential for Other Drugs to Affect Plasma Concentrations of KOPOZGO

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 (7.2)* and *Clinical Pharmacology (13.3)*]. (See Table 1)

**Table 1: Established and Potentially Significant Pharmacokinetic Drug Interactions with KOPOZGO**

#### Impact of Other Drugs on KOPOZGO

| <b>Moderate to Strong CYP2C19 Inhibitors or Strong CYP3A4 Inhibitors</b>         |                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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 <i>Contraindications (6)</i> , <i>Warnings and Precautions (7.2)</i> , <i>Clinical Pharmacology (13.3)</i> ].                                                                                                                                          |
| Prevention or Management                                                         | Concomitant use with a moderate to strong CYP2C19 inhibitor or a strong CYP3A4 inhibitor is contraindicated.                                                                                                                                                                                                                                                                                                                                       |
| <b>Moderate to Strong CYP2C19 Inducers or Moderate to Strong CYP3A4 Inducers</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Clinical Impact                                                                  | Concomitant use with a moderate to strong CYP2C19 inducer or a moderate to strong CYP3A4 inducer decreases mavacamten exposure, which may reduce KOPOZGO' efficacy [see <i>Clinical Pharmacology (13.3)</i> ]. The risk of heart failure due to systolic dysfunction may increase with discontinuation of these inducers as the levels of induced enzyme normalizes [see <i>Contraindications (6)</i> and <i>Warnings and Precautions (7.2)</i> ]. |
| Prevention or Management                                                         | Concomitant use of a moderate to strong CYP2C19 inducer or a moderate to strong CYP3A4 inducer is contraindicated.                                                                                                                                                                                                                                                                                                                                 |
| <b>Weak CYP2C19 Inhibitors or Moderate CYP3A4 Inhibitors</b>                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

|                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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 <i>Warnings and Precautions</i> (7.2)].                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Prevention or Management | <p>Initiate KOPOZGO 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.</p> <p>Reduce dose of KOPOZGO by one level (i.e., 15 to 10 mg, 10 to 5 mg, or 5 to 2.5 mg) in patients who are on KOPOZGO treatment and intend to initiate a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor.</p> <p>Avoid initiation of concomitant weak CYP2C19 and moderate CYP3A4 inhibitors in patients who are on stable treatment with 2.5 mg of KOPOZGO because a lower dose is not available [see <i>Dosage and Administration</i> (4.2)].</p> |

## 9.2. Potential for KOPOZGO to Affect Plasma Concentrations of Other Drugs

### Certain CYP3A4, CYP2C9, and CYP2C19 Substrates

Mavacamten is an inducer of CYP3A4, CYP2C9, and CYP2C19. Concomitant use with CYP3A4, CYP2C9, or CYP2C19 substrates may reduce plasma concentration of these drugs [see *Clinical Pharmacology* (13.3)]. Closely monitor when KOPOZGO is used with concomitant CYP3A4, CYP2C9, or CYP2C19 substrates unless otherwise recommended [see *Dosage and Administration* (4.2)]

### Certain Combined Hormonal Contraceptives (CHC)

Progestin and ethinyl estradiol are CYP3A4 substrates. Concomitant use of KOPOZGO may decrease exposures of certain progestins [see *Clinical Pharmacology* (13.3)], which may lead to contraceptive failure. CHCs containing a combination of ethinyl estradiol and norethindrone may be used with mavacamten, but if other CHCs are used, advise patients to add nonhormonal contraception (such as condoms) during concomitant use and for 4 months after the last dose of KOPOZGO.

## 9.3. Drugs That Reduce Cardiac Contractility

Expect additive negative inotropic effects of KOPOZGO and other drugs that reduce cardiac contractility. Avoid concomitant use of KOPOZGO 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* (7.1)]

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.

## 10. USE IN SPECIFIC POPULATIONS

### 10.1. Pregnancy

#### Risk Summary

Based on animal data, KOPOZGO may cause fetal harm when administered to a pregnant female. There are no human data on the use of KOPOZGO 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 KOPOZGO 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*).

#### 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  $\geq 1.2$  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.



## **10.2. 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 KOPOZGO and any potential adverse effects on the breastfed child from KOPOZGO or from the underlying maternal condition.

## **10.3. Females and Males of Reproductive Potential**

Based on animal data, KOPOZGO may cause fetal harm when administered to a pregnant female [see *Warnings and Precautions (7.3) and Use in Specific Populations (10.1)*].

### Pregnancy Testing

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

### Contraception

#### *Females*

Advise females of reproductive potential to use effective contraception during treatment with KOPOZGO and for 4 months after the last dose. CHCs containing a combination of ethinyl estradiol and norethindrone may be used with mavacamten. However, KOPOZGO may reduce the effectiveness of certain other combined hormonal contraceptives (CHC). If these CHCs are used, advise patients to add nonhormonal contraception (such as condoms) during concomitant use and for 4 months after the last dose of KOPOZGO [see *Drug Interactions (9.2)*].

## **10.4. Pediatric Use**

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

## **10.5. Geriatric Use**

Clinical trials included 319 patients dosed with KOPOZGO, 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  $\geq 65$  years and younger patients.

## **10.6. 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 (13.3)*]

## 11. OVERDOSAGE

### Clinical Experience and Effects

- Cardiovascular effects may include reduced LVEF (left ventricular ejection fraction), heart failure, hypotension, and asystole refractory to medical intervention.
- Neurological effects may include dizziness and syncope.
- An infant death was reported after accidental ingestion of three 15 mg capsules (45 mg).
- An adult administered a single dose of 144 mg developed a vasovagal reaction, hypotension, and asystole, but the subject recovered.

### Management

Discontinue KOPOZGO treatment.

Provide medically supportive measures to maintain hemodynamic stability and monitor left ventricular function.

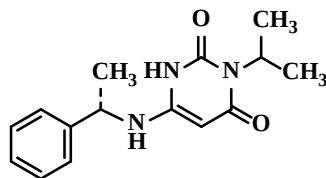
Consider administering activated charcoal (pediatric dose is 1 g/kg; adult dose is 50 g) within 2 hours of ingestion in addition to other supportive measures. The benefit of activated charcoal is negligible after 6 hours [see *Clinical Pharmacology* (12.3)].

## 12. DESCRIPTION

KOPOZGO 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*)-pyrimidin-2-one]. The molecular formula is C<sub>15</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>, 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.

KOPOZGO 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: croscarmellose sodium, hypromellose, magnesium stearate (non-bovine), mannitol, and silicon dioxide. The capsule shell contains black edible ink, black iron oxide, gelatin, red iron oxide, titanium dioxide, and yellow iron oxide.

## 13. CLINICAL PHARMACOLOGY

### 13.1. 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.

### 13.2. 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 KOPOZGO 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 KOPOZGO, 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/m<sup>2</sup>) versus an increase in LVMI in the placebo group (8.9 [15.3] g/m<sup>2</sup>). 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<sup>2</sup>) versus no change in the placebo group (-0.1 [8.7] mL/m<sup>2</sup>). The clinical significance of these findings is unknown.

#### Cardiac Biomarkers

In the EXPLORER-HCM trial [see *Clinical Studies (15)*], 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 (15)*], 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 KOPOZGO, 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. In the VALOR-HCM study, there was no further lengthening of QTcF when KOPOZGO was added to disopyramide. The effect of coadministration of KOPOZGO with other QT-prolonging drugs or in patients with potassium channel variants resulting in a long QT interval have not been characterized.

### **13.3. Pharmacokinetics**

Mavacamten exposure increases dose proportionally following multiple once-daily doses of 1 mg to 15 mg. At the same dose level of KOPOZGO, 170% higher exposures of mavacamten are observed in patients with HCM compared to healthy subjects. Mavacamten accumulation is approximately 100% for  $C_{max}$  and approximately 600% for AUC in CYP2C19 normal metabolizers (NMs). The accumulation is dependent upon the CYP2C19 metabolism status with the largest accumulation occurring in CYP2C19 poor metabolizers (PMs). At steady-state, the peak-to-trough mavacamten plasma concentration ratio with once daily dosing is approximately 1.5.

#### Absorption

Mavacamten has an estimated oral bioavailability of at least 85% and median time to maximum concentration ( $T_{max}$ ) of 1 to 2 hours.

#### *Effect of Food*

No clinically significant differences in mavacamten AUC were observed following its administration with a high fat meal.

#### 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 to 9 days in CYP2C19 normal metabolizers (NMs), which is prolonged in CYP2C19 poor metabolizers (PMs) to 23 days.

#### 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<sup>2</sup>) to moderate (eGFR: 30 to 59 mL/min/1.73 m<sup>2</sup>) renal impairment. The effects of severe (eGFR: 15 to 30 mL/min/1.73 m<sup>2</sup>) renal impairment and kidney failure (eGFR: <15 mL/min/1.73 m<sup>2</sup>; 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<sub>inf</sub> by 48% with no effect on C<sub>max</sub> 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<sub>inf</sub> by 16% and C<sub>max</sub> 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<sub>0-24h</sub> and C<sub>max</sub> 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<sub>0-24</sub> and C<sub>max</sub> 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<sub>0-inf</sub> and C<sub>max</sub> 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) decreased AUC<sub>inf</sub> and C<sub>max</sub>, of midazolam by 13% and 7%, respectively, in healthy subjects. Following coadministration of mavacamten once daily in HCM patients at the upper end of the therapeutic range, midazolam AUC<sub>inf</sub> and C<sub>max</sub> are predicted to decrease up to 45% and 24% respectively.

*Certain combined oral contraceptives:* No clinically significant differences in ethinyl estradiol and norethindrone exposure were observed in healthy female subjects with CYP2C19 NM phenotype following concomitant use of a combined oral contraceptive containing ethinyl estradiol and norethindrone with a 17-day course of mavacamten (25 mg on days 1 and 2, followed by 15 mg for 15 days). The impact of mavacamten on oral contraceptives containing other progestins is unknown.

*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 up to 27% and 19%, respectively, 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 up to 54% and 23%, respectively, 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 up to 48% and 17%, respectively, depending on the dose of mavacamten and CYP2C19 phenotype.

*Activated Charcoal:* Mavacamten  $AUC_{0-72h}$  and  $AUC_{0-infinity}$  was reduced by 14% and 34%, respectively, following administration of 50 g activated charcoal with sorbitol 2 hours after ingestion of a single mavacamten 15 mg dose. Administration of activated charcoal 6 hours after the mavacamten dose had minimal effect on mavacamten exposure.

#### In Vitro Studies

*CYP Enzymes:* Mavacamten does not inhibit CYP1A2, CYP2B6, CYP2C8, 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).

### **13.5. 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 KOPOZGO. 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).

## **14. NONCLINICAL TOXICOLOGY**

### **14.1. 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.

## **14.2. 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.

## **15. CLINICAL STUDIES**

### **EXPLORER-HCM**

The efficacy of KOPOZGO was evaluated in EXPLORER-HCM 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  $\geq 55\%$ , and LVOT peak gradient  $\geq 50$  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 KOPOZGO 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<sup>2</sup>), heart rate (mean 62 bpm), blood pressure (mean 128/76 mmHg), and race (90% Caucasian). Males comprised 54% of the KOPOZGO 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 KOPOZGO 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  $\geq 50\%$ . The dose was also informed by plasma concentrations of KOPOZGO.

In the KOPOZGO 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  $\geq 1.5$  mL/kg/min plus improvement in NYHA class by at least 1 or improvement of  $pVO_2$  by  $\geq 3.0$  mL/kg/min plus no worsening in NYHA class.

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

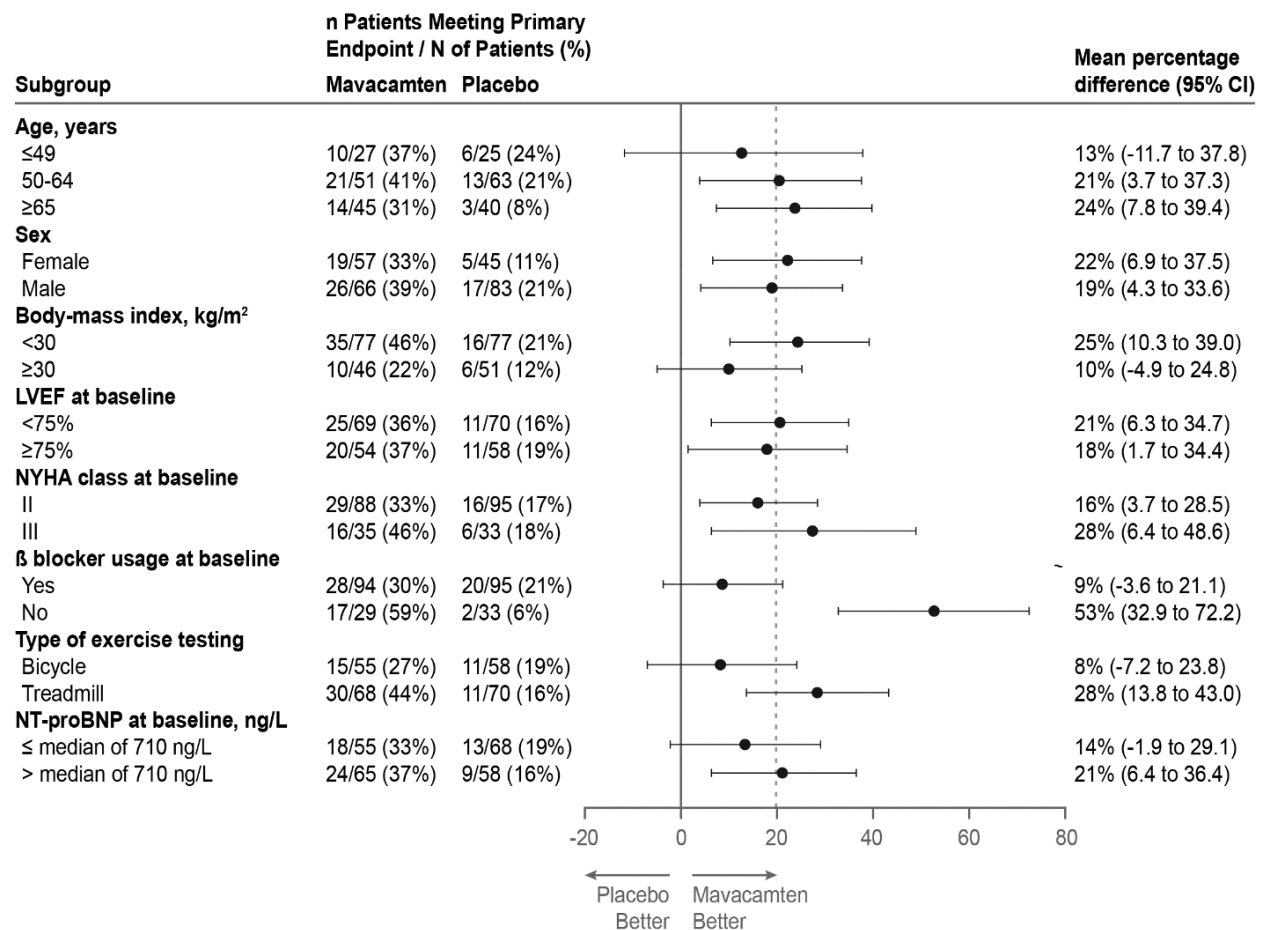
**Table 2: Primary Endpoint at 30 Weeks**

|                                                                            | <b>KOPOZGO<br/>n (%)<br/>N = 123</b> | <b>Placebo<br/>n (%)<br/>N = 128</b> | <b>Difference<br/>(95% CI)</b> | <b>p-value</b> |
|----------------------------------------------------------------------------|--------------------------------------|--------------------------------------|--------------------------------|----------------|
| Total responders                                                           | 45 (37%)                             | 22 (17%)                             | 19% (9, 30)                    | 0.0005         |
| Change from baseline<br>$pVO_2 \geq 1.5$ mL/kg/min and<br>decreased NYHA   | 41 (33%)                             | 18 (14%)                             | 19% (9, 30)                    |                |
| Change from baseline<br>$pVO_2 \geq 3$ mL/kg/min and<br>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 KOPOZGO 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<sub>2</sub>), analyses of other secondary endpoints (symptoms, LVOT gradient) suggest that patients might benefit from mavacamten treatment regardless of beta blocker use.

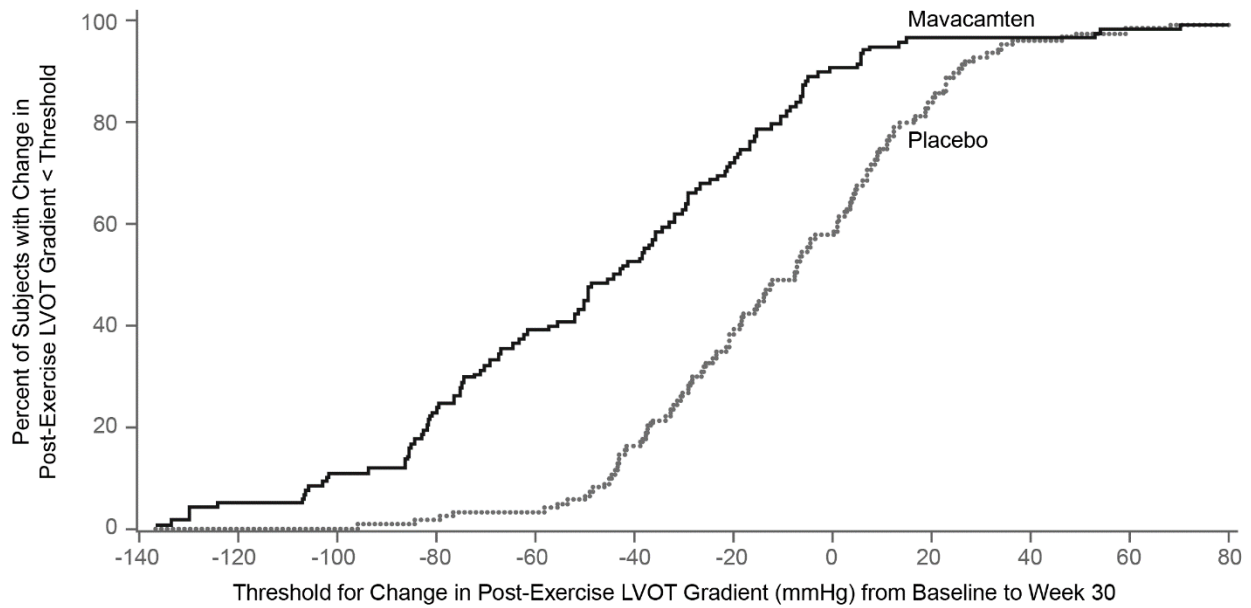
### Secondary endpoints

The treatment effects of KOPOZGO 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<sub>2</sub>, 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 KOPOZGO had greater improvement compared to the placebo group across all secondary endpoints (Table 3, Figure 5, Figure 6, Table 4, and Figures 7-10).

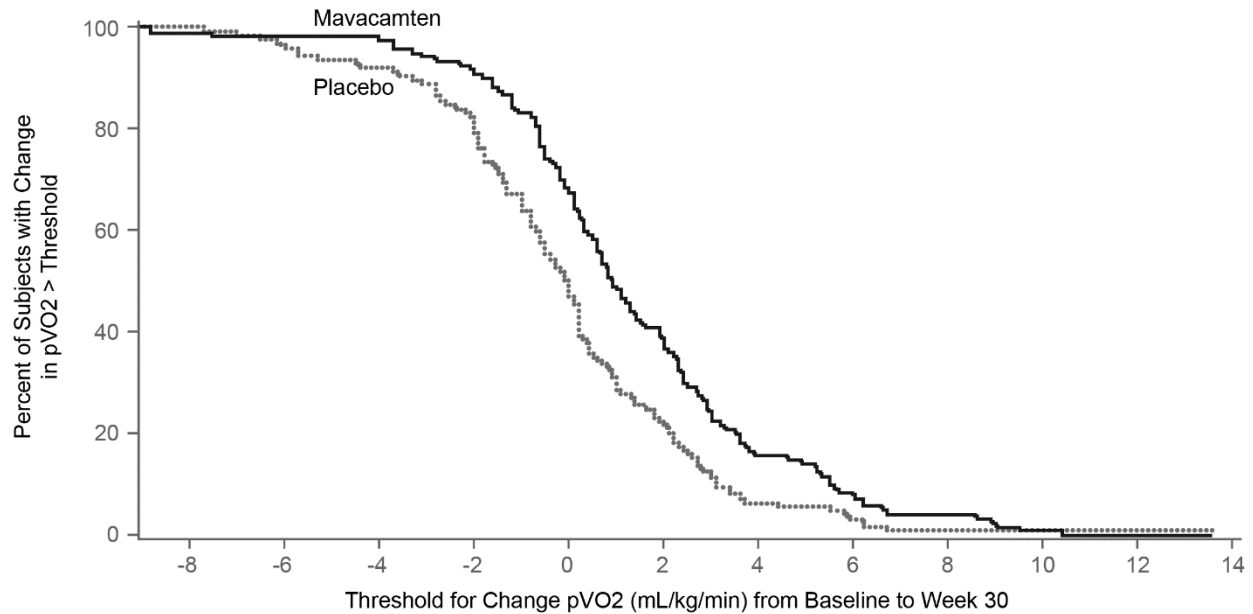
**Table 3: Change from Baseline to Week 30 in Post-Exercise LVOT Gradient, pVO<sub>2</sub>, and NYHA Class**

|                                               | <b>KOPOZGO<br/>N = 123</b> | <b>Placebo<br/>N = 128</b> | <b>Difference (95% CI)</b> | <b>p-value</b> |
|-----------------------------------------------|----------------------------|----------------------------|----------------------------|----------------|
| Post-Exercise LVOT gradient (mmHg), mean (SD) | -47 (40)                   | -10 (30)                   | -35 (-43, -28)             | <0.0001        |
| pVO <sub>2</sub> (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 $\geq 1$  | 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<sub>2</sub>**



**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 |
|--------------------------|---------------------|-----------------|--------------------------------------------|---------|-----------------------------------------|
|                          | KOPOZGO             | Placebo         | KOPOZGO                                    | Placebo |                                         |
| KCCQ-23 CSS <sup>†</sup> | n=99<br>71 (16)     | n=97<br>71 (19) | 14 (14)                                    | 4 (14)  | 9 (5, 13)<br>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 <sup>‡</sup>   | n=108<br>5 (3)      | n=109<br>5 (3)  | -3 (3)                                     | -1 (2)  | -2 (-2, -1)<br>p<0.0001                 |

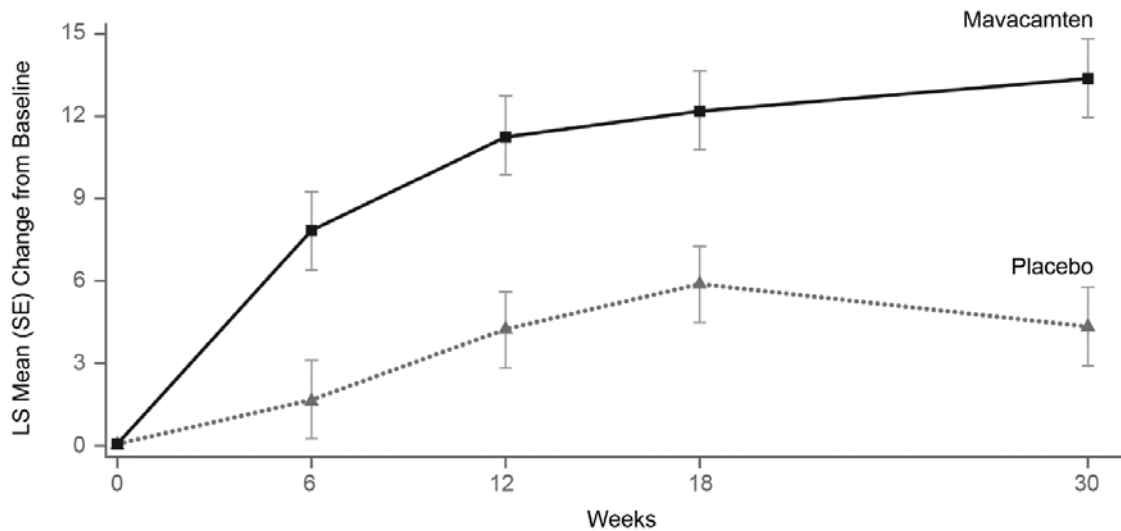
<sup>†</sup>The KCCQ-23 CSS is derived from the Total Symptom Score (TSS) and the Physical Limitations (PL) score of the KCCQ-23. The CSS ranges from 0 to 100 with higher scores representing less severe symptoms and/or physical limitations.

<sup>‡</sup>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.

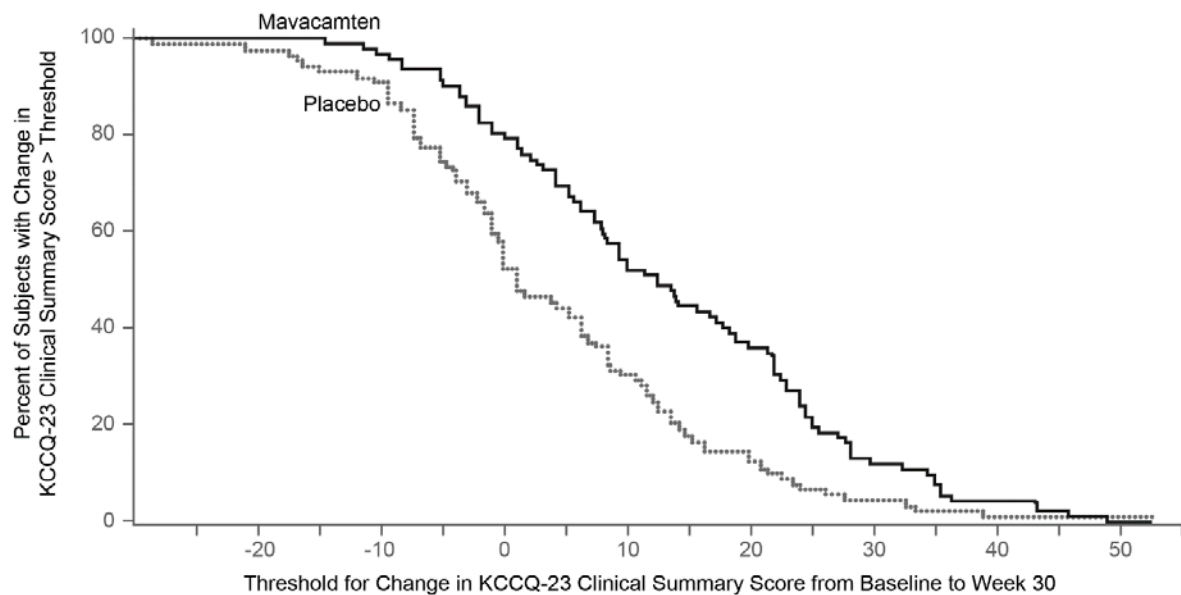
Missing data were not imputed to summarize the baseline and change from baseline to Week 30 values. Difference in mean change from baseline between treatment groups was estimated using a mixed model for repeated measures.

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**



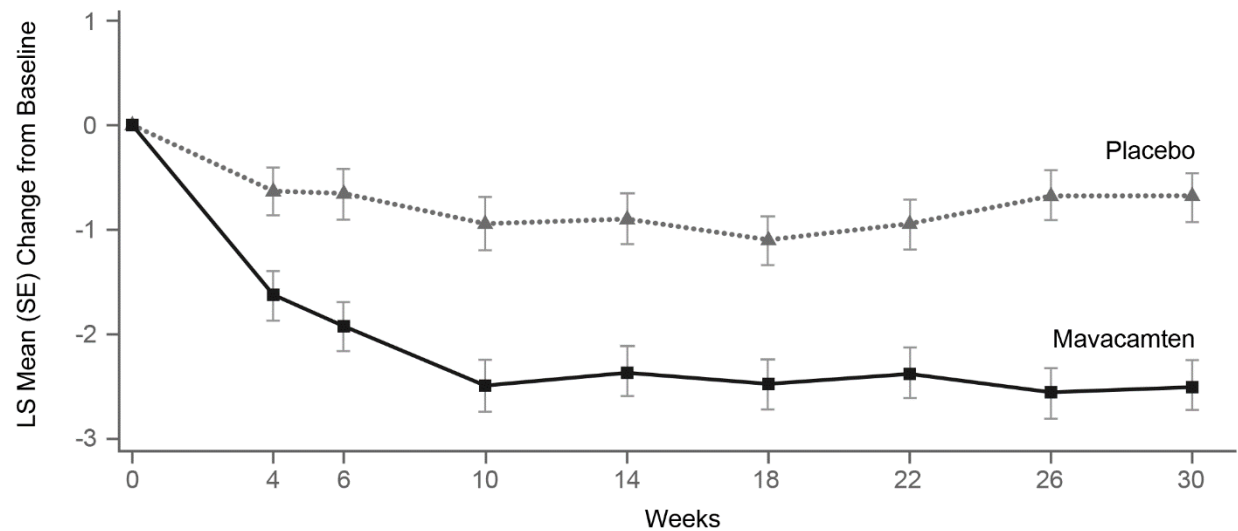
**Figure 8. KCCQ-23 Clinical Summary Score: Cumulative Distribution of Change from Baseline to Week 30**



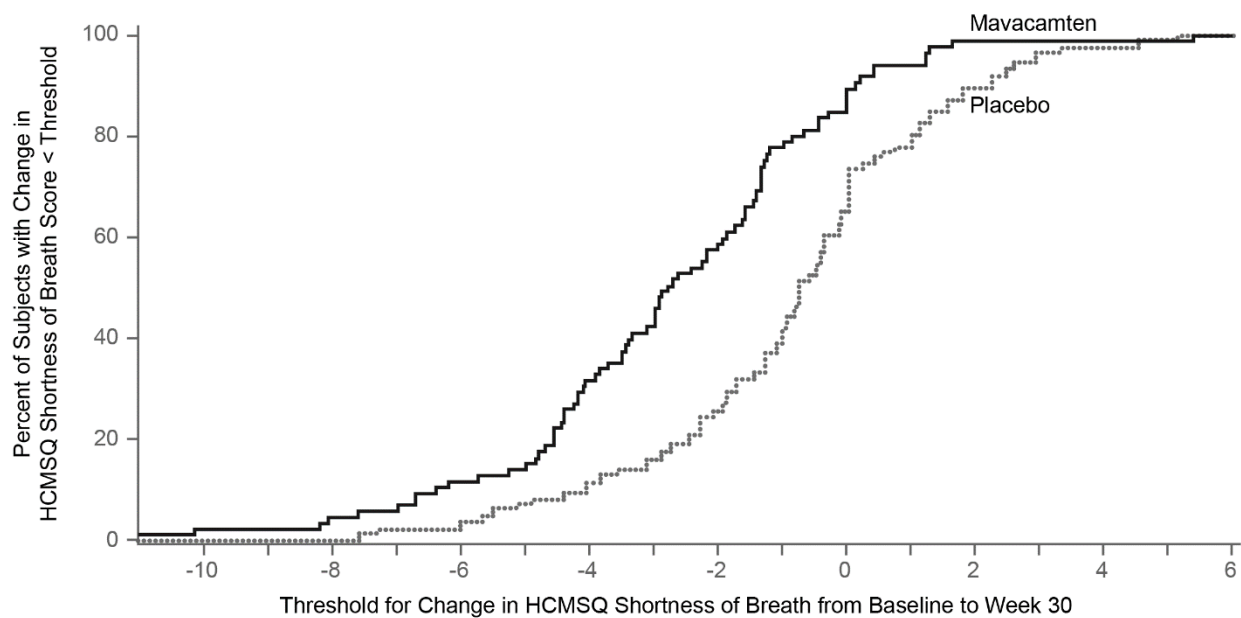
The figure displays the cumulative percentage of patients achieving a certain level of response.

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 KOPOZGO 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%  $\geq$  NYHA class III) randomized 1:1 to receive treatment with KOPOZGO 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  $\geq 50$  mmHg at rest or with provocation, and LVEF  $\geq 60\%$ . Patients must have been referred or under active consideration within the past 12 months for SRT and actively considering scheduling the procedure.

Patients received KOPOZGO (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*

KOPOZGO 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  $\geq 50$  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**

|                                                                  | <b>KOPOZGO</b><br><b>n (%)</b><br><b>n=56</b> | <b>Placebo</b><br><b>n (%)</b><br><b>n=56</b> | <b>Treatment</b><br><b>difference</b><br><b>(95% CI)</b> | <b>p-value</b> |
|------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|----------------------------------------------------------|----------------|
| <b>Primary efficacy composite endpoint</b>                       | 10 (18)                                       | 43 (77)                                       | 59%<br>(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)  $\geq 50$  mmHg.

### *Secondary endpoints*

The treatment effects of KOPOZGO 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.

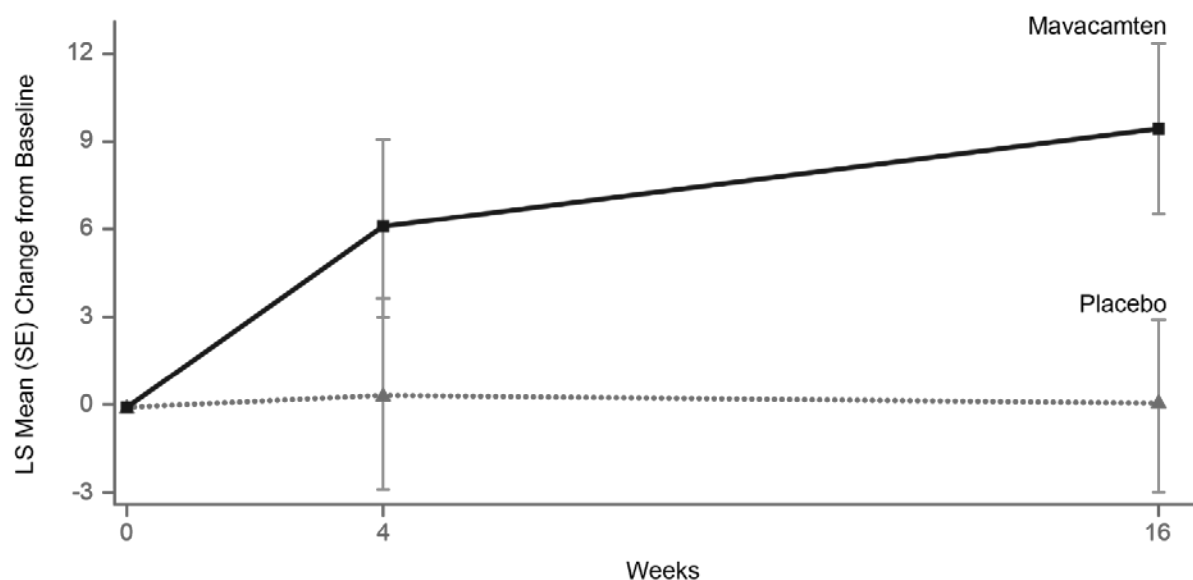
**Table 6: Change from Baseline to Week 16 in Secondary Endpoints**

|                                               | <b>KOPOZGO<br/>n = 56</b> | <b>Placebo<br/>n = 56</b> | <b>Difference<br/>(95% CI)</b> | <b>p-value</b> |
|-----------------------------------------------|---------------------------|---------------------------|--------------------------------|----------------|
| Post-Exercise LVOT gradient (mmHg), mean (SD) | -39<br>(37)               | -2<br>(29)                | -38<br>(-49, -28)              | <0.0001        |
| Number (%) with NYHA Class improved $\geq 1$  | 35<br>(63%)               | 12<br>(21%)               | 41<br>(25%, 58%)               | <0.0001        |
| KCCQ-23 CSS <sup>†</sup> , mean (SD)          | 10<br>(16)                | 2<br>(12)                 | 9<br>(5, 14)                   | <0.0001        |
| KCCQ-23 TSS, mean (SD)                        | 10<br>(16)                | 2<br>(14)                 | 10<br>(5, 15)                  |                |
| KCCQ-23 PL, mean (SD)                         | 10<br>(19)                | 2<br>(17)                 | 10<br>(5, 16)                  |                |

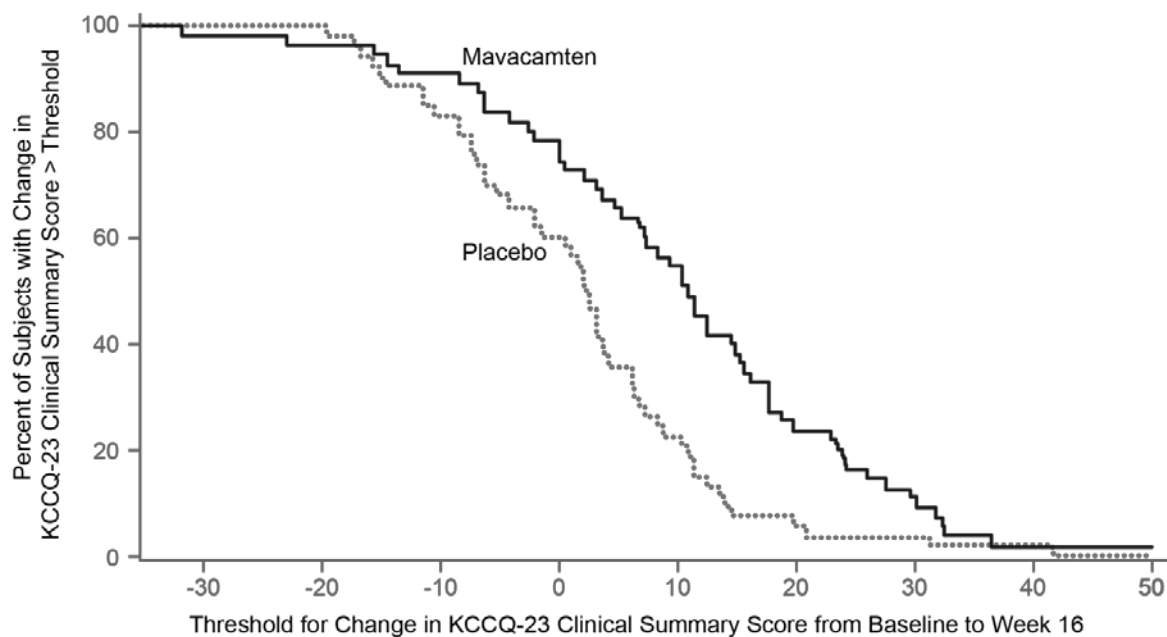
<sup>†</sup>The KCCQ-23 CSS is derived from the Total Symptom Score (TSS) and the Physical Limitations (PL) score of the KCCQ-23. The CSS ranges from 0 to 100 with higher scores representing less severe symptoms and/or physical limitations. The KCCQ-23 TSS and the KCCQ-23 PL are exploratory endpoints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

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

KOPOZGO is supplied as immediate release Size 2 hard gelatin capsules containing 2.5, 5, 10, or 15 mg of mavacamten. White opaque capsule bodies are imprinted with “Mava”, and the opaque cap is imprinted with the strength. The capsule contains white to off-white powder. KOPOZGO capsules are available in blisters of 14 capsules, as listed in the table below:

| Strength | Capsule Cap  |
|----------|--------------|
| 2.5 mg   | Light purple |
| 5 mg     | Yellow       |
| 10 mg    | Pink         |
| 15 mg    | Gray         |

Not all strengths and pack sizes may be marketed.

### Storage

Do not store above 30°C.

## **17. EFFECTS ON ABILITY TO DRIVE AND USE MACHINE**

KOPOZGO 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.

### **Product Registration Holder**

DKSH Malaysia Sdn Bhd  
B-11-01, The Ascent, Paradigm  
No. 1 Jalan SS 7/26A, Kelana Jaya  
47301 Petaling Jaya  
Selangor Darul Ehsan

### **Date of Revision of the Text**

6 June 2024