Summary Report of Benefit-Risk Assessment

CAMZYOS CAPSULES 2.5 MG, 5 MG, 10 MG AND 15 MG

NEW DRUG APPLICATION

Active Ingredient(s)	Mavacamten
Product Registrant	Bristol-Myers Squibb (Singapore) Pte. Ltd
Product Registration Number	SIN16804P, SIN16805P, SIN16806P, SIN16807P
Application Route	Abridged evaluation
Date of Approval	14 June 2023

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A INTRODUCTION

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

The active substance, mavacamten, is an oral cardiac myosin inhibitor, which prevents excessive myosin-actin cross-bridge formation that brings about the hyper-cardiac contractility and left ventricular hypertrophy in HCM. The reduction in myocardial contractility attenuates the force of ejection flow and lessens the venturi effect responsible for anterior mitral valve leaflet displacement into the left ventricular outflow tract (LVOT) and worsening of LVOT obstruction.

Camzyos is available as capsule containing 2.5 mg, 5 mg, 10 mg and 15 mg of mavacamten. Other ingredients in the capsule are croscarmellose sodium, hypromellose, magnesium stearate (non-bovine), mannitol, and silicon dioxide. Ingredients in the capsule shell include black edible ink, black iron oxide, gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The black edible ink contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, and potassium hydroxide.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, mavacamten, is manufactured at Ash Stevens LLC, Michigan, USA and micronised at Catalent Micron Technologies Inc., Pennsylvania, USA. The drug product, Camzyos capsule, is manufactured at Patheon Inc., Ontario, Canada..

Drug substance

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications were established in accordance with ICH Q6A guideline and the impurity limits were appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been appropriately validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance at 25ºC with a re-test period of 60 months. The packaging is double polyethylene (PE) bags in high-density polyethylene (HDPE) container.

Drug product

The capsules are manufactured using a standard manufacturing process.

The manufacturing site involved is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications were established in accordance with ICH Q6A guideline and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been appropriately validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 24 months when stored at or below 30ºC. The container closure system is polyvinyl chloride/ polychlorotrifluoroethylene (PVC/Aclar) clear blister containing 14 capsules.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of mavacamten in the treatment of oHCM was based on one pivotal Phase III study, EXPLORER-HCM. This was a double-blind, randomised, placebo-controlled, multicentre, parallel group study in adult subjects with symptomatic oHCM of NYHA functional classification II or III, left ventricular ejection fraction (LVEF) ≥55%, and LVOT peak gradient ≥50 mmHg at rest or with provocation.

Study participants were randomised (1:1) to receive either mavacamten or placebo for 30 weeks. Randomisation was stratified by baseline NYHA functional class (II or III), baseline use of beta-blockers (yes or no), planned type of ergometer used during the study (treadmill or exercise bicycle), and consent for the cardiac magnetic resonance imaging (CMR) substudy (yes or no). The starting dose of study drug was mavacamten 5 mg or matching placebo once daily (QD). The dose was periodically adjusted to achieve mavacamten plasma trough concentrations <700 ng/mL while optimising patient response (decrease in LVOT gradient with Valsalva manoeuvre) and maintaining LVEF ≥50%.

The primary efficacy endpoint was a composite functional response at 30 weeks, 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. The primary endpoint was considered appropriate as increase in pVO_2 during exercise testing reflects improvement in exercise and functional capacity in patients with symptomatic oHCM. The inclusion of NYHA class as a component of the primary endpoint strengthens the validity of clinical response and a change in NYHA class of 1 or more represents a clinically meaningful improvement. The secondary endpoints assessed in the study included the 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.

A total of 251 patients were randomised into the study: 123 patients in the mavacamten group and 128 patients in the placebo group. The treatment groups were well matched with respect to age (mean 58.5 years), BMI (mean 29.4 kg/m^2), heart rate (mean 63 bpm), blood pressure (mean 128.4/75.8 mmHg), and race (91.2% Caucasian, 2.4% Asian). Males comprised 53.7%

of the mavacamten group and 64.8% of the placebo group. At baseline, 72.9% of the randomised patients were NYHA class II and 27.1% were NYHA class III. The mean LVEF was 74%, and the mean Valsalva LVOT gradient was 73 mmHg. A total of 7.6% of the subjects had prior septal reduction therapy, 75.3% of the patients were on beta-blockers and 16.7% of the patients were on calcium channel blockers; 13.9% of the patients had a history of atrial fibrillation.

Study EXPLORER-HCM met its primary endpoint. The proportion of subjects with a positive response on the composite primary endpoint was statistically significantly greater in the mavacamten group compared to the placebo group (36.6% vs 17.2%, between-group difference of 19.4%; 95% CI: 8.67, 30.13; p=0.0005).

Mavacamten treatment was also superior to placebo for all secondary endpoints on change from baseline to Week 30 in post-exercise LVOT peak gradient (between-group difference -35 mmHg; 95% CI: -43.2, -28.1; p<0.0001), change from baseline to Week 30 in pVO_2 (between-group difference -1.4 mL/kg/min; 95% CI: 0.59, 2.12; p=0.0006), ≥1 NYHA class improvement responder at Week 30 (between-group difference 33.8%; 95% CI: 22.15, 45.43; p<0.0001), change from baseline to Week 30 in KCCQ-23 CSS (between-group difference 9.1; 95% CI: 5.5, 12.7; p<0.0001), and change from baseline to Week 30 in HCMSQ SoB domain score (between-group difference -1.8; 95% CI: -2.40, -1.20; p<0.0001).

Subgroup analyses of the primary efficacy endpoint showed that the treatment difference in the proportion of responders in the mavacamten group compared to placebo was 8.7% among beta-blocker users versus 52.6% among non-beta-blocker users. Also, there was an attenuated improvement in pVO_2 in the subgroup of subjects receiving beta-blockers at baseline compared to those who did not receive beta-blockers (the between-group differences were 1.1 vs 2.2 mL/kg/min, respectively; interaction p=0.016). The results for post-exercise LVOT peak gradient, proportion of patients with NYHA class improvement and the patient reported outcomes (PROs) demonstrated consistent treatment effects of mavacamten irrespective of beta-blocker use. Overall, the effect of mavacamten was blunted when taken together with beta-blocker but given that no harm was observed with this combination, the combination use was not restricted. The results of the subgroup findings have been reflected in the package insert for the prescriber to make an informed and individualised judgement on the initiation and continuation of mavacamten treatment in patients on background beta-blocker therapy.

Summary of Efficacy Results (Study EXPLORER-HCM)

Primary Endpoint	**Mavacamten (N=123)**	**Placebo (N=128)**	**Treatment difference (95% CI)**	**p-value**
Proportion of subjects who achieved the composite functional endpoint at Week 30, n (%)	45 (36.6)	22 (17.2)	19.4 (8.67, 30.13)	0.0005
Secondary Endpoints	**Mavacamten (N=123)**	**Placebo (N=128)**	**LS mean treatment difference (95% CI)**	**p-value**
Mean (SD) change from baseline to Week 30 in	-47 (40.3)	-10 (29.6)	-35 (-43.2, -28.1)	<0.0001

post-exercise LVOT peak gradient (mmHg)				
Mean (SD) change from baseline to Week 30 in pVO_2 (mL/kg/min)	1.4 (3.12)	-0.05 (3.02)	1.4 (0.59, 2.12)	0.0006
Proportion of subjects who improved by ≥1 NYHA class from baseline to Week 30, n (%)	80 (65.0)	40 (31.3)	Odds Ratio 4.28 (2.45, 7.99)	<0.0001
Mean (SD) change from baseline to Week 30 in KCCQ-23 CSS	13.6 (14.42)	4.2 (13.68)	9.1 (5.46, 12.66)	<0.0001
Mean (SD) change from baseline to Week 30 in HCMSQ SoB domain score	-2.8 (2.68)	-0.9 (2.41)	-1.8 (-2.40, -1.20)	<0.0001

Overall, the efficacy of mavacamten in the treatment of patients with symptomatic oHCM was adequately demonstrated based on robust and consistent improvements across numerous clinically relevant objective and subjective parameters.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of mavacamten was based primarily on safety data derived from the pivotal EXPLORER-HCM study, comprising a total of 251 patients who received at least one dose of study treatment: 123 subjects in the mavacamten group and 128 subjects in the placebo group. The median duration of treatment (excluding time off drug due to temporary interruptions) was 7.0 months for both treatment groups.

Overview of Safety Profile

AE	Mavacamten (N=123) n (%)	Placebo (N=128) N (%)
Any adverse event (AE)	108 (87.8)	104 (81.3)
Grade ≥3 AE	12 (9.8)	14 (10.9)
Serious AE (SAE)	14 (11.4)	12 (9.4)
AE with a fatal outcome	0	1 (0.8)
AE leading to discontinuation of study drug	2 (1.6)	0

Dizziness was the most common AE reported in EXPLORER-HCM and it was reported more frequently in the mavacamten group compared to placebo (21.1% vs 13.3%). The majority of dizziness AEs in both groups were reported as mild. The proportion of subjects with dyspnoea, headache, upper respiratory tract infection, back pain, cough, gastrooesophageal reflux disease, arthralgia and syncope were also higher in the mavacamten group compared to placebo. Nevertheless, the differences between groups were small (<5%) and the events were generally mild in severity.

Treatment-Emergent Adverse Events Reported for ≥5% of Subjects in Either Treatment Group During the Treatment-Emergent Period (Day 1 to Week 38)

Adverse Event	Mavacamten	Placebo

	(N=123) n (%)	(N=129) n (%)
Total Number of AEs	536	495
Subjects with ≥1 AE	108 (87.8)	104 (81.3)
Dizziness	26 (21.1)	17 (13.3)
Dyspnoea	18 (14.6)	13 (10.2)
Nasopharyngitis	15 (12.2)	19 (14.8)
Headache	15 (12.2)	10 (7.8)
Atrial fibrillation	10 (8.1)	10 (7.8)
Upper respiratory tract infection	10 (8.1)	6 (4.7)
Back pain	10 (8.1)	8 (6.3)
Cough	10 (8.1)	4 (3.1)
Gastrooesophageal reflux disease	7 (5.7)	3 (2.3)
Palpitations	7 (5.7)	10 (7.8)
Fatigue	7 (5.7)	7 (5.5)
Arthralgia	7 (5.7)	2 (1.6)
Syncope	7 (5.7)	2 (1.6)
Diarrhoea	5 (4.1)	7 (5.5)
Angina pectoris	3 (2.4)	7 (5.5)

The incidence of discontinuation due to AEs was low overall (1.6%), indicating that the AEs were tolerated by the majority of patients. Two subjects in the mavacamten group discontinued the treatment due to AEs of atrial fibrillation and syncope.

The incidences of SAEs were similar between the treatment groups (11.4% in the mavacamten group vs 9.4% in the placebo group). Syncope (2.4% vs 0.8%) and stress cardiomyopathy (1.6% vs 0%) were more frequently reported in the mavacamten group compared to placebo. Review of the individual cases of SAEs did not reveal particular safety concerns. Syncope was likely related to the patients' underlying condition of oHCM. As for stress cardiomyopathy, casual relation to mavacamten treatment was unlikely as both affected subjects continued with the treatment after the event without any recurrence of cardiac event.

The reduction of cardiac contractility by mavacamten resulted in small mean decrease in LVEF (~4%) during 30 weeks of mavacamten treatment compared with placebo. The risk did not present a major safety concern with mavacamten as the reduction was reversible with treatment discontinuation. The small reduction in the LVEF did not translate into an increase in the risk of systolic dysfunction since the incidence of heart failure was similar between the mavacamten and placebo group (2.4% in mavacamten group vs 3.9% in placebo).

Overall, mavacamten was well-tolerated with the majority of the events being mild in severity. The principal safety concern of mavacamten is the risk of heart failure due to systolic dysfunction resulting from an excessive pharmacologic effect of mavacamten. Nevertheless, the risk of heart failure was low and could be mitigated via careful and frequent monitoring of LVEF and increased patients' awareness to identify signs and symptoms of heart failure to seek prompt treatment. Adequate warnings on this risk, including recommendations for regular monitoring, have been included in the package insert.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Symptom burden in HCM, particularly oHCM, has profound impact on patients' quality of life. The most frequent symptoms in patients with oHCM are shortness of breath and chest pain, with resulting reduced exercise tolerance. There are currently no approved disease-specific pharmacological therapies for oHCM. Pharmacologic agents (e.g., beta-blockers, calcium channel blockers, antiarrhythmics) used in the management of HCM are targeted at symptom relief, and have limited clinical evidence to support the efficacy and safety in the treatment of oHCM. Therefore, there is an unmet medical need for a targeted therapy that addresses the underlying disease pathophysiology of oHCM.

In the pivotal Study EXPLORER-HCM, mavacamten was superior to placebo in terms of the composite primary endpoint measuring pVO_2 and NYHA class (response rate 36.6% vs 17.2%; treatment difference 19.4%; 95% CI: 8.67, 30.13; p=0.0005) in subjects with symptomatic oHCM. Superiority compared to placebo was also demonstrated in terms of the secondary endpoints, showing reduction in post-exercise LVOT gradient (treatment difference -35 mmHg; 95% CI: -43.2, -28.1; p<0.0001), reduction in pVO_2 (treatment difference -1.4 mL/kg/min; 95% CI: 0.59, 2.12; p=0.0006), improvement in NYHA class by at least 1 (treatment difference 33.8%; 95% CI: 22.15, 45.43; p<0.0001), and improvement in health status as measured by the KCCQ-23 CSS (treatment difference 9.1; 95% CI: 5.5, 12.7; p<0.0001) and HCMSQ SoB domain score (treatment difference -1.8; 95% CI: -2.40, -1.20; p<0.0001).

Dizziness was the most common AE and occurred more frequently in the mavacamten group compared to placebo (21.1% vs 13.3%). Other AEs reported more frequently in the mavacamten group compared to placebo included dyspnoea (14.6% vs 10.2%), headache (12.2% vs 7.8%), cough (8.1% vs 3.1%), upper respiratory tract infection (8.1% vs 4.7%), back pain (8.1% vs 6.3%), gastrooesophageal reflux disease (5.7% vs 2.3%), arthralgia (5.7% vs 1.6%) and syncope (5.7% vs 1.6%). The differences between groups for these AEs were small (<5%) and the events were mostly mild in severity.

Heart failure due to systolic dysfunction is an exaggerated on-target mavacamten effect of reduction in hypercontractility. The incidence of heart failure AEs reported in the clinical studies was low and the risk can be mitigated by individualised dose titration with frequent monitoring of LVEF as well as increased patients' awareness on the signs and symptoms of heart failure and to seek prompt treatment.

Overall, considering the robust and consistent efficacy demonstrated across numerous objective and subjective parameters, and the safety profile that is acceptable in the target patient population, the benefit-risk profile of mavacamten in the treatment of patients with symptomatic NYHA class II-III oHCM was considered positive.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Camzyos for the treatment of adults with symptomatic NYHA class II-III obstructive hypertrophic cardiomyopathy to improve functional capacity and symptoms was deemed favourable and approval of the product registration was granted on 14 June 2023.

APPROVED PACKAGE INSERT AT REGISTRATION

CAMZYOS CAPSULES 2.5MG, 5MG, 10MG, 15MG
FULL PRESCRIBING INFORMATION

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

Confirm absence of pregnancy and usage of effective contraception in females of reproductive potential *[see Warnings and Precautions (5.4)]*.

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

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

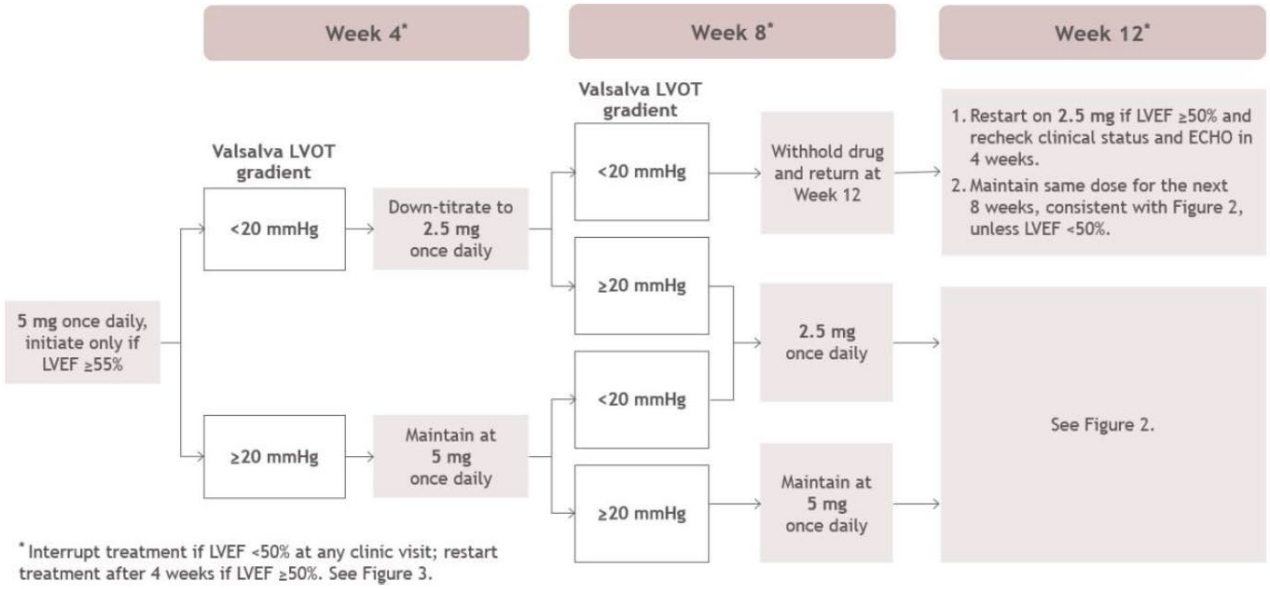
Patients may develop heart failure while taking CAMZYOS. Regular LVEF and Valsalva left ventricular outflow tract (LVOT) gradient assessment is required for careful titration to achieve an appropriate target Valsalva LVOT gradient, while maintaining LVEF ≥50% and avoiding heart failure symptoms (see Figure 1 and Figure 2). Additional assessment of LVEF is recommended if clinical status changes or in patients with a serious intercurrent illness such as infection or arrhythmia (including atrial fibrillation or other uncontrolled tachyarrhythmia).

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 (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



* Interrupt treatment if LVEF <50% at any clinic visit; restart treatment after 4 weeks if LVEF ≥50%. See Figure 3.

Figure 2. Maintenance Phase

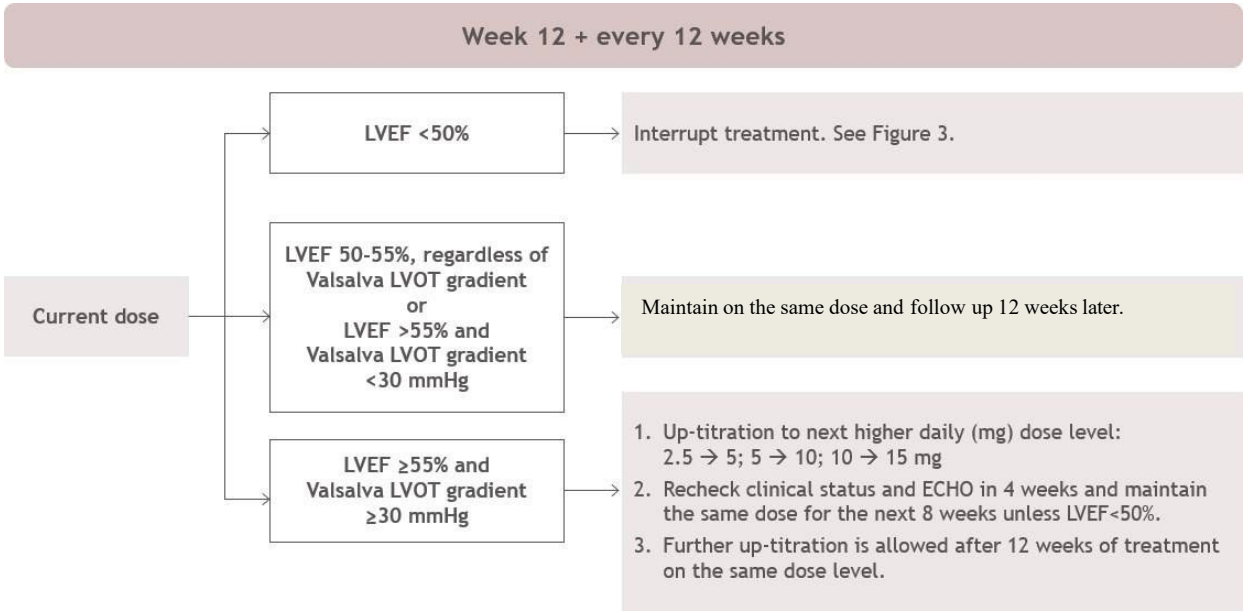
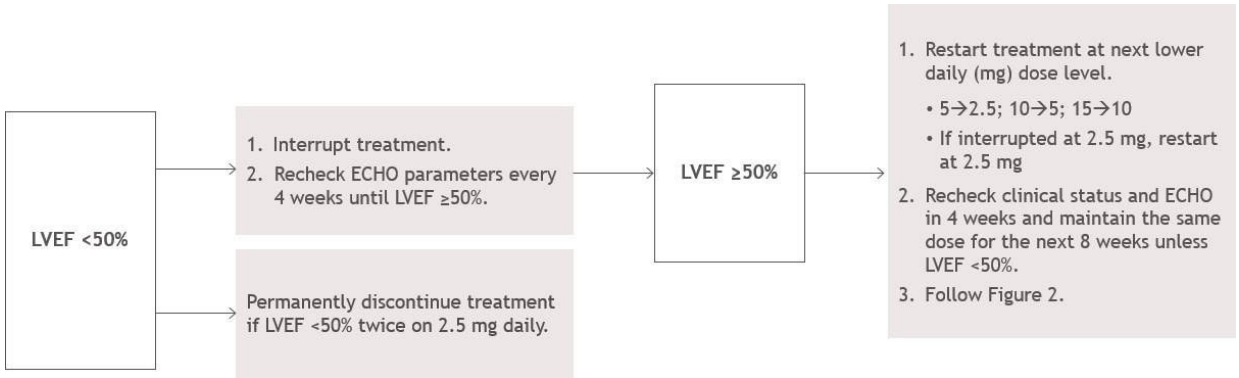


Figure 3. Treatment Interruption at Any Clinic Visit if LVEF <50%



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.

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 ➔ 10 mg; 10 ➔ 5 mg; or 5 ➔ 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 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

4. CONTRAINDICATIONS

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 were excluded from the clinical study of CAMZYOS in obstructive HCM (EXPLORER-HCM). Concomitant use of CAMZYOS with disopyramide in combination with verapamil or diltiazem has been associated with left ventricular systolic dysfunction and heart failure symptoms in patients with obstructive HCM *[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, or cimetidine). 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 (15)]*.

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.

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%) and atrial fibrillation (0.8%) were the only adverse drug reaction leading to discontinuation in patients receiving CAMZYOS.

Adverse events reported by ≥ 5% of subjects in any treatment group are provided in Table 1.

Table 1 Treatment-emergent Adverse Events Reported in ≥ 5% of Subjects in Any Treatment Group in pivotal clinical study

System organ class and Preferred Term	CAMZYOS (N = 123) N (%)	Placebo (N = 129) N (%)
Cardiac disorders		
Atrial fibrillation	10 (8.1)	10 (7.8)
Palpitations	7 (5.7)	10 (7.8)
Angina pectoris	3 (2.4)	7 (5.5)
Gastrointestinal disorders		
Diarrhoea	5 (4.1)	7 (5.5)
Gastrooesophageal reflux disease	7 (5.7)	3 (2.3)
General disorders and administration site conditions		
Fatigue	7 (5.7)	7 (5.5)
Infections and infestations		
Nasopharyngitis	15 (12.2)	19 (14.8)
Upper respiratory tract infection	10 (8.1)	6 (4.7)
Musculoskeletal and connective tissue disorders		
Back pain	10 (8.1)	8 (6.3)
Arthralgia	7 (5.7)	2 (1.6)
Nervous system disorders		
Dizziness	26 (21.1)	17 (13.3)
Headache	15 (12.2)	10 (7.8)

Syncope	7 (5.7)	2 (1.6)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	18 (14.6)	13 (10.2)
Cough	10 (8.1)	4 (3.1)

The treatment-emergent period is defined as the date of the first dose of study drug to the date of the last dose of study drug plus 56 days.

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)]*.

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 2)

Table 2: 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.

7.3. Drugs That Reduce Cardiac Contractility

Expect additive negative inotropic effects of CAMZYOS and other drugs that reduce cardiac contractility. In the EXPLORER-HCM trial, 119 of 123 patients who received CAMZYOS received concomitant therapy with beta blockers (n=94), verapamil (n=19), or diltiazem (n=6).

Avoid concomitant use of CAMZYOS with disopyramide in combination with verapamil or diltiazem because such use has been associated with left ventricular systolic dysfunction and heart failure symptoms *[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*).

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 (5.4) 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 263 patients dosed with CAMZYOS, 95 of whom were 65 years of age or older (36.1%), and 17 of whom (6.5%) 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 (11.3)]*.

9. 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.

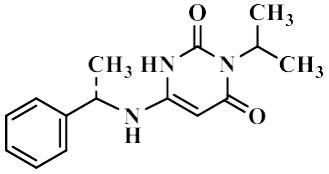
Systolic dysfunction is the most likely result of overdosage of CAMZYOS. Treatment of overdose with CAMZYOS consists of discontinuation of CAMZYOS treatment as well as medically supportive measures to maintain hemodynamic stability, including close monitoring of vital signs and LVEF and management of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

10. 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, 5, 10, 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. The black edible ink contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, and potassium hydroxide.

11. CLINICAL PHARMACOLOGY

11.1 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.

11.2 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/m^2) versus an increase in LVMI in the placebo group (8.9 [15.3] g/m^2). There was also a mean (SD) reduction from baseline in left atrial volume index (LAVI) in the mavacamten group (-7.5 [7.8] mL/m^2) versus no change in the placebo group (-0.1 [8.7] mL/m^2). 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]). The clinical significance of these 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 QT-prolonging drugs or in patients with potassium channel variants resulting in a long QT interval have not been characterized.

11.3 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 15% 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 $AUC_{0\text{-}24h}$ 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 $AUC_{0\text{-}24}$ 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).

11.4 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).

12 NONCLINICAL TOXICOLOGY

12.1 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, which resulted in exposures (AUC) that were 1.8- and 3-fold in males and females, 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.

12.2 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.

13 CLINICAL STUDIES

Obstructive Hypertrophic Cardiomyopathy

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.

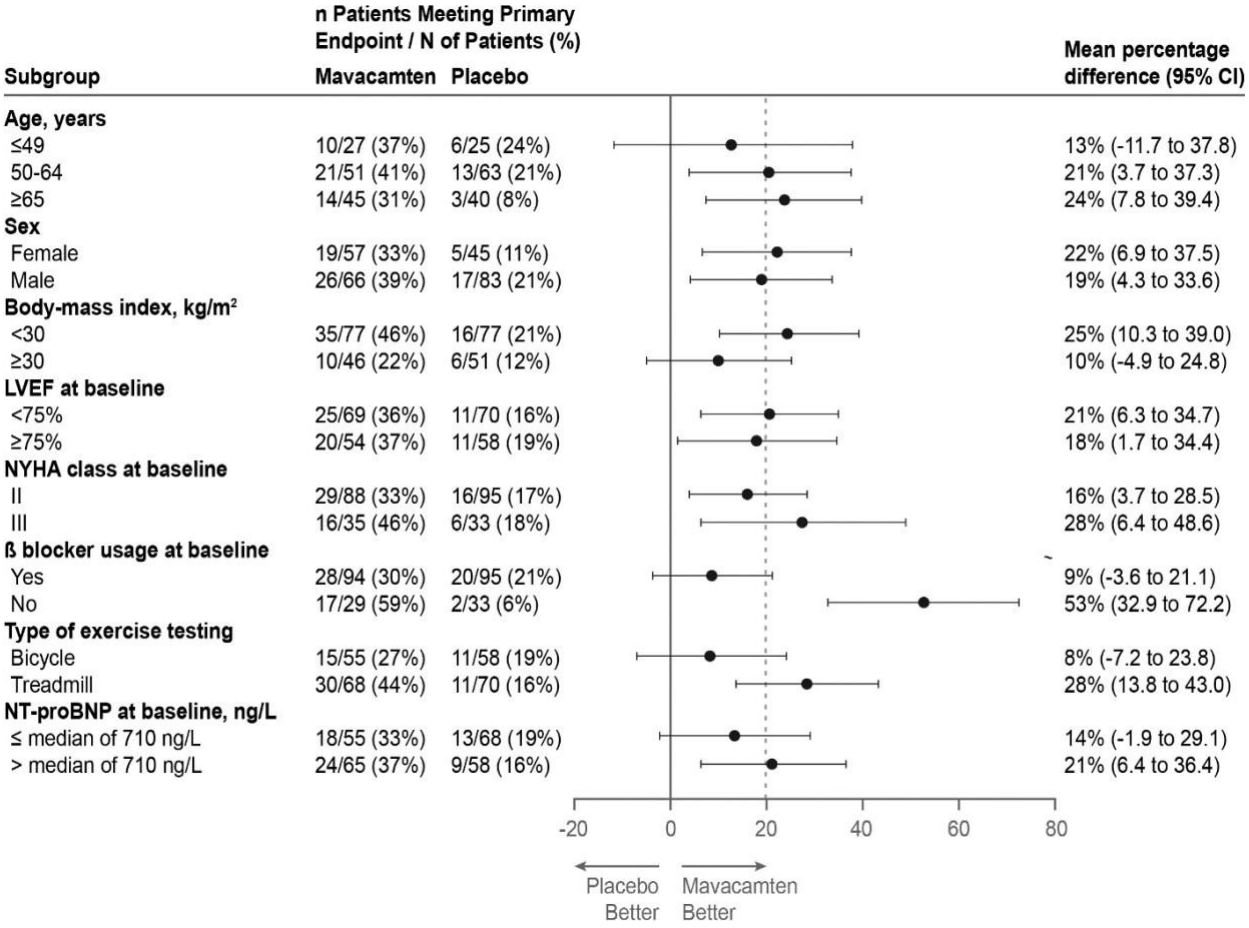
A greater proportion of patients met the primary endpoint at Week 30 in the CAMZYOS group compared to the placebo group (37% vs. 17%, respectively, p=0.0005; see Table 3).

Table 3: Primary Endpoint at 30 Weeks

	CAMZYOS N = 123	Placebo N = 128	Difference (95% CI)	p-value
Total responders	45 (37%)	22 (17%)	19% (9, 30)	0.0005
Change from baseline $pVO_2 \geq 1.5$ mL/kg/min and decreased NYHA	41 (33%)	18 (14%)	19% (9, 30)	
Change from baseline $pVO_2 \geq 3$ 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 4, Figure 5, Figure 6, Table 5, and Figures 7-10).

Table 4: 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

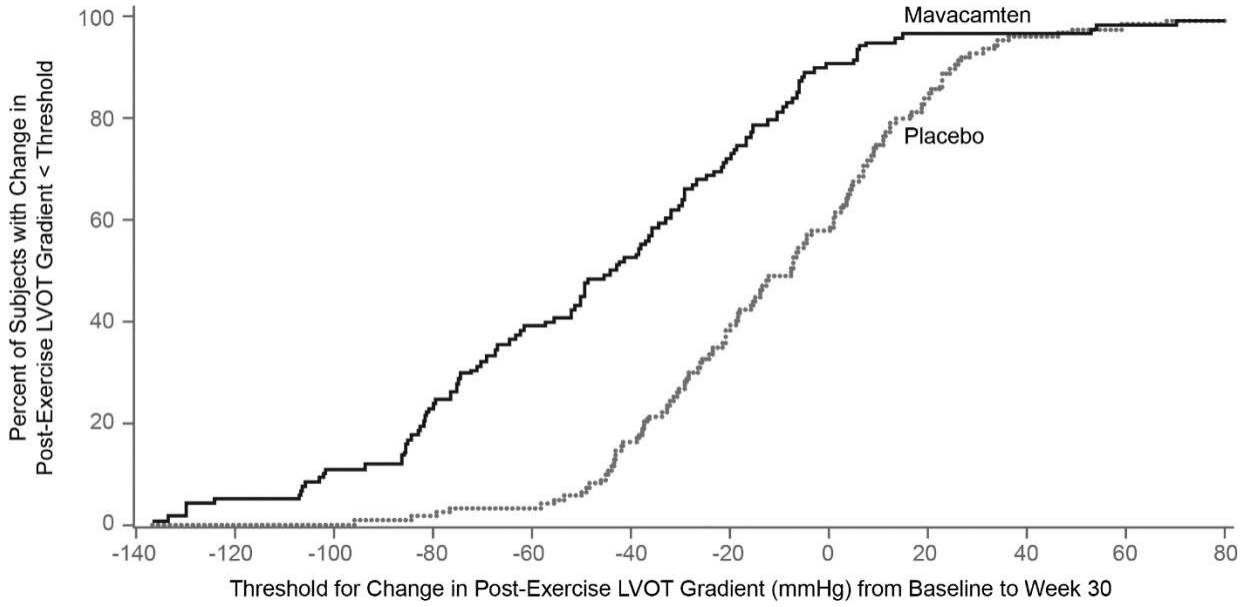


Figure 6: Cumulative Distribution of Change from Baseline to Week 30 in pVO_2

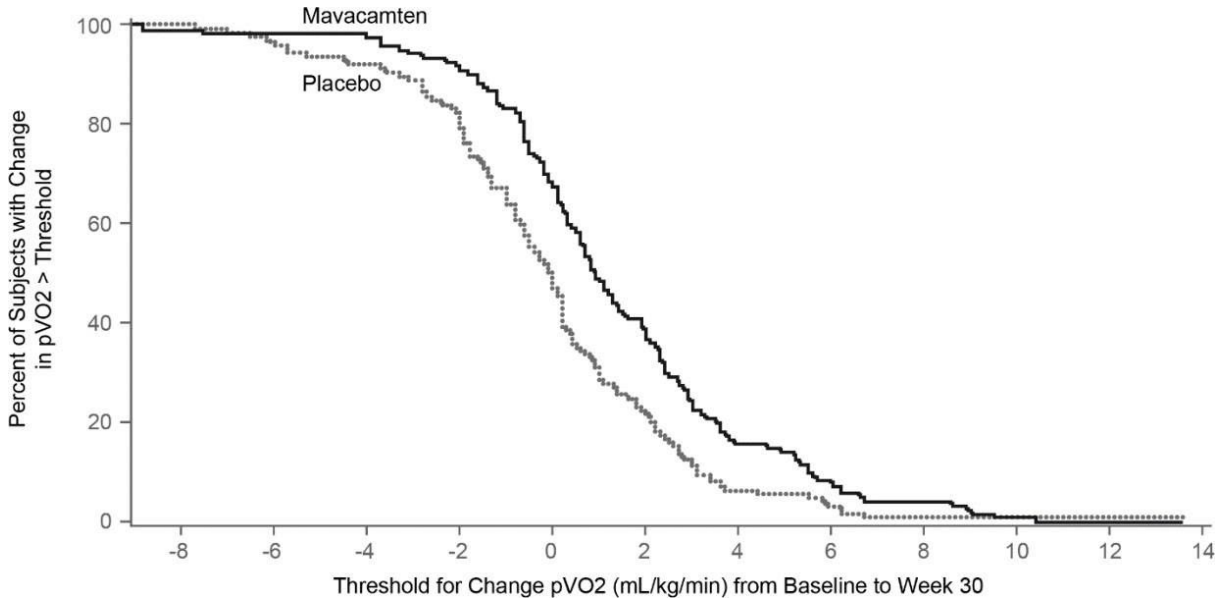


Table 5: Change from Baseline to Week 30 in KCCQ-23 CSS and HCMSQ SoB Domain

	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

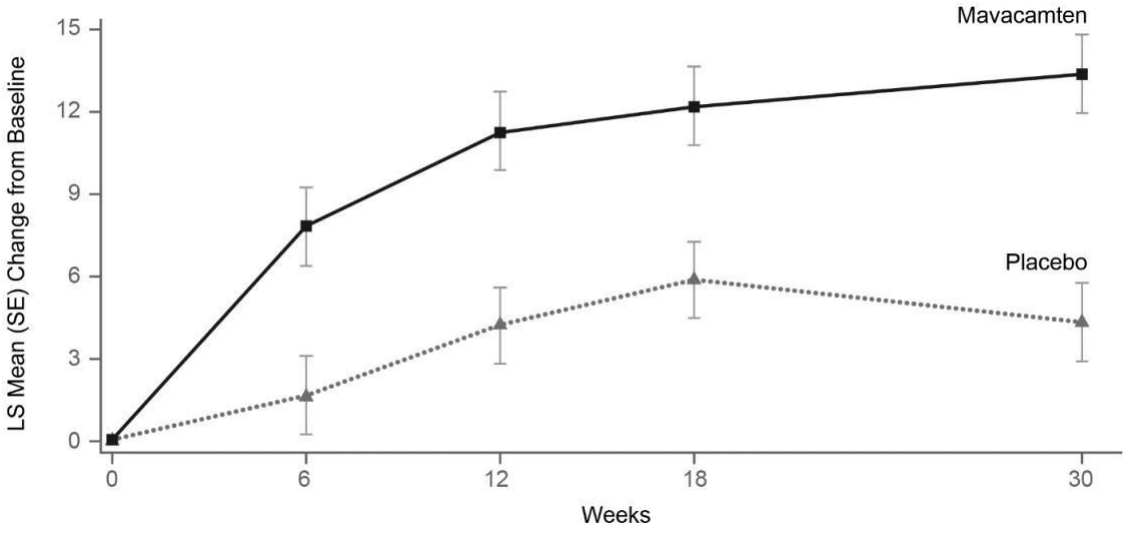
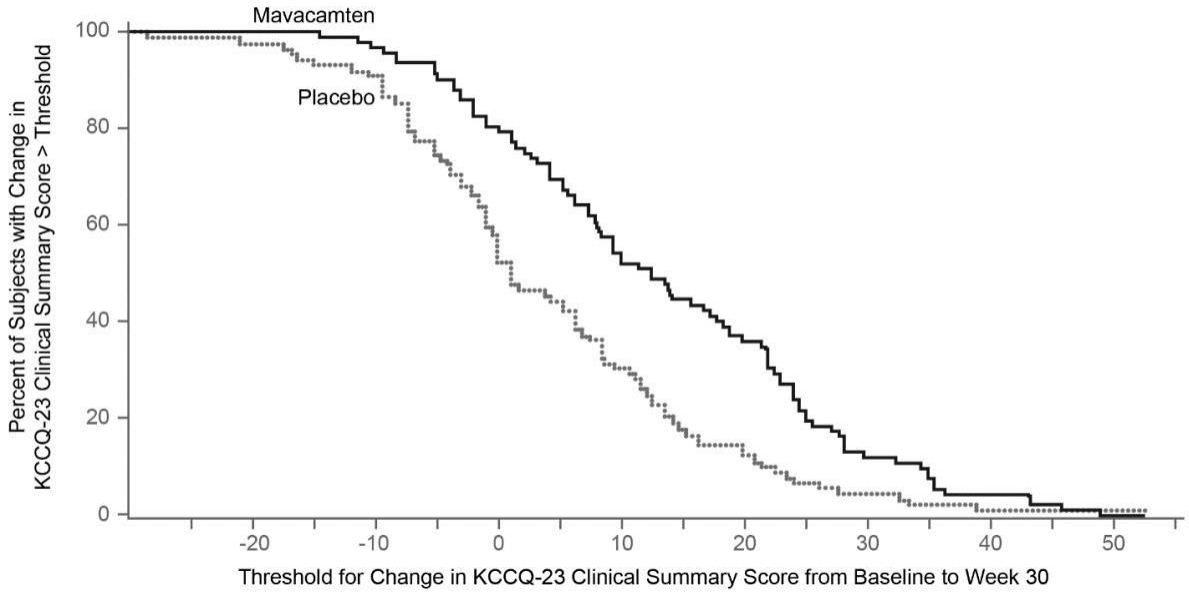


Figure 8: KCCQ-23 Clinical Summary Score: Cumulative Distribution of Change from Baseline to Week 30



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

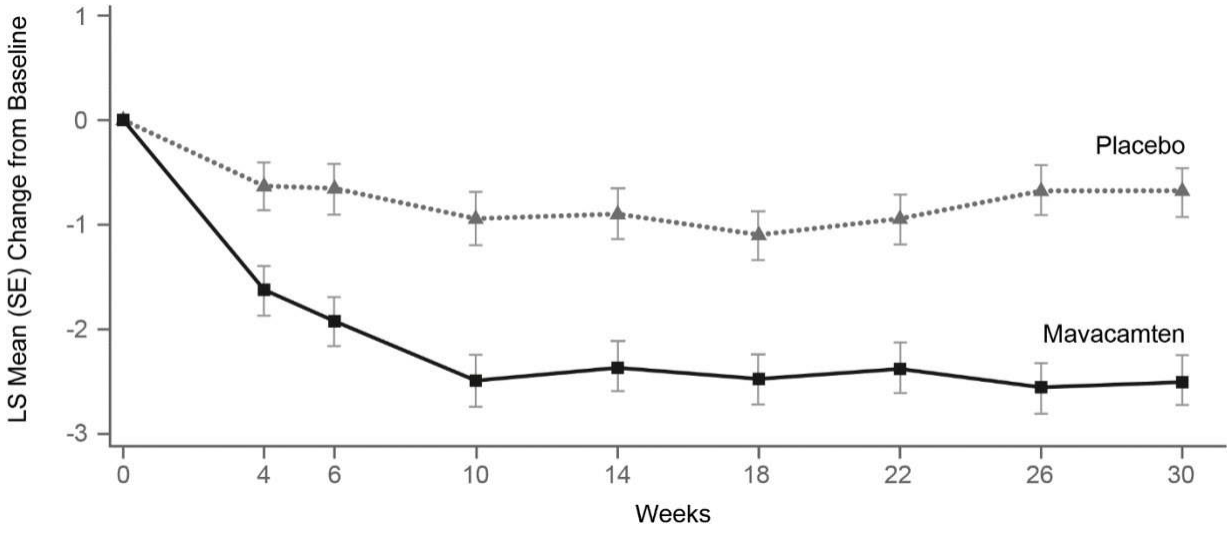
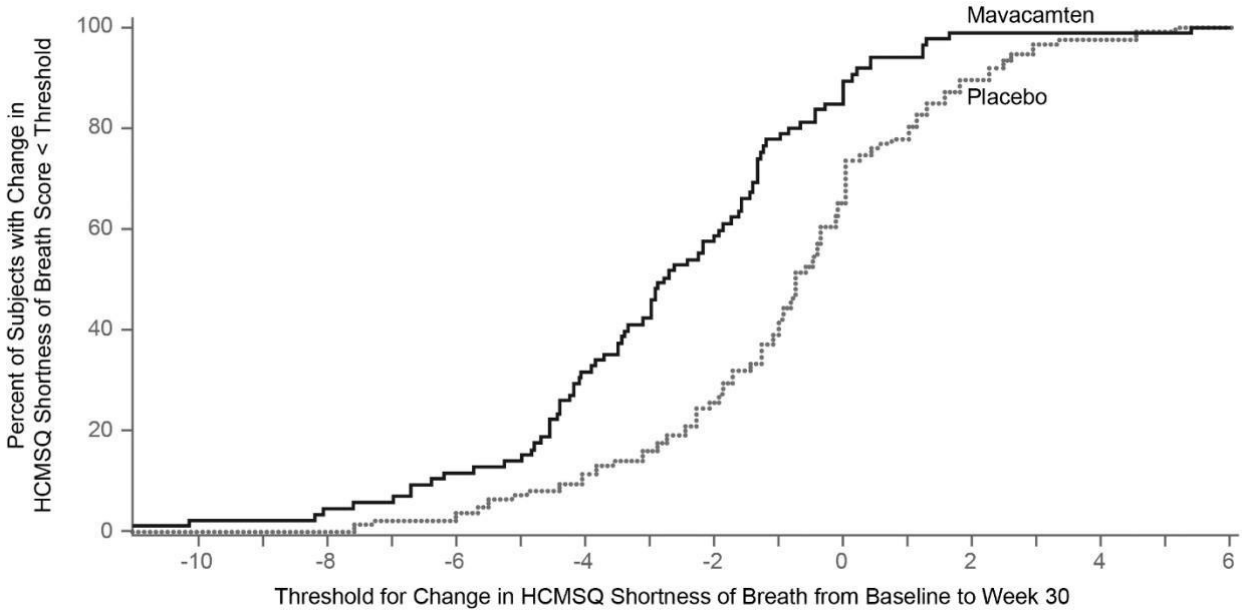


Figure 10: HCMSQ Shortness of Breath Domain: Cumulative Distribution of Change from Baseline to Week 30



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

14. HOW SUPPLIED/STORAGE AND HANDLING

CAMZYOS™ 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. CAMZYOS capsules are supplied in PVC/Aclar clear blister with Alu foil lidding in cartons of 28 capsules.

Storage

Store at or below 30°C.

15. PATIENT COUNSELING INFORMATION

Heart Failure

Inform patients that cardiac function monitoring must be performed using echocardiography to monitor for heart failure *[see Warnings and Precautions (5.1)]*. Advise patients to report any signs or symptoms of heart failure immediately to their healthcare provider.

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant products, including over-the-counter medications (such as omeprazole, esomeprazole, or cimetidine) and supplements, prior to and during CAMZYOS treatment.

Embryo-Fetal Toxicity

Advise pregnant females and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraception during treatment with CAMZYOS and for 4 months after the last dose. Advise patients using CHCs to use an alternative contraceptive method or add nonhormonal contraception because CAMZYOS may decrease the efficacy of CHCs *[see Drug Interactions (7.2), Use in Specific Populations (8.3)]*.

Instructions for Taking CAMZYOS

CAMZYOS capsules should be swallowed whole. Advise patients that if they miss a dose of CAMZYOS, to take the dose as soon as possible that day and the next scheduled dose should be taken at the usual time the following day. The patient should not take two doses in the same day.

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