NEW DRUG APPROVAL

Brand Name	Camzyos™
Generic Name	mavacamten
Drug Manufacturer	Bristol Myers Squibb

New Drug Approval

FDA Approval Date: April 28, 2022

Review designation: Standard; Orphan

Type of review: Type 1 - New Molecular Entity; New Drug Application (NDA): 214998

Dispensing restrictions: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Hypertrophic cardiomyopathy is most often caused by abnormal genes in the heart muscle. These genes cause the walls of the heart chamber (left ventricle) to contract harder and become thicker than normal. The thickened walls become stiff. This reduces the amount of blood taken in and pumped out to the body with each heartbeat. In obstructive HCM, the wall (septum) between the two bottom chambers of the heart thickens. The walls of the pumping chamber can also become stiff. It may block or reduce the blood flow from the left ventricle to the aorta. Most people with HCM have this type. Hypertrophic cardiomyopathy (HCM) is the most common inherited (genetic) cardiovascular disorder, affecting approximately 1 in 500 individuals worldwide. However, only about 1 in 3200 people in the United States are diagnosed with HCM and experience symptoms. About two-thirds of patients with HCM are diagnosed with obstructive HCM. Patients with symptomatic obstructive HCM are at high risk of progressive disease, which can lead to atrial fibrillation, stroke, and death due to arrhythmias.

Efficacy

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 Valsalva 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/m2), 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 mixed venous oxygen tension (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.

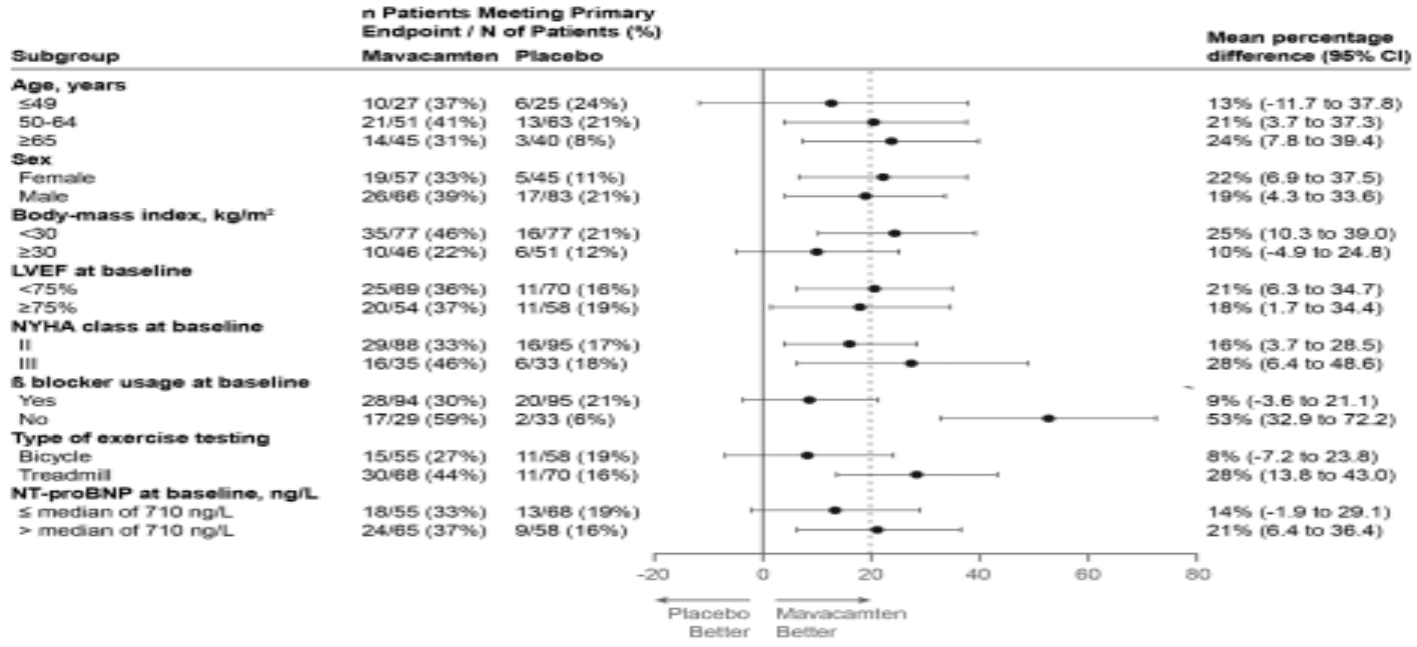
A greater proportion of patients met the primary endpoint at Week 30 in the Camzyos™ group compared to the placebo group (37% vs. 17%, respectively, p=0.0005).

Table 1: 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 ≥ 1.5 mL/kg/min and decreased NYHA	41 (33%)	18 (14%)	19% (9,30)	
Change from baseline pVO_2 ≥ 3 mL/kg/min and NYHA not increased	29 (23%)	14 (11%)	13% (3, 22)	

A range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes. Results of the primary analysis consistently favored Camzyos™ across all subgroups analyzed (Figure 1).

Figure 1: 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 pVO2, proportion of patients with improvement in NYHA class, Kansas City Cardiomyopathy Questionnaire-23 (KCCQ-23) Clinical Summary Score (CSS), and Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) Shortness of Breath (SoB) domain score. At Week 30, patients receiving Camzyos™ had greater improvement compared to the placebo group across all secondary endpoints.

Table 2: Change from Baseline to Week 30 in Post-Exercise LVOT Gradient, pVO2, and NYHA Class

	Camzyos™ N = 123	Placebo N = 128	Difference (95% CI)	p-value
Post-Exercise LVOT gradient (mm Hg), mean (SD)	-47 (40)	-10 (30)	-31 (-43, -23)	<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 2: Cumulative Distribution of Change from Baseline to Week 30 in LVOT Peak Gradient

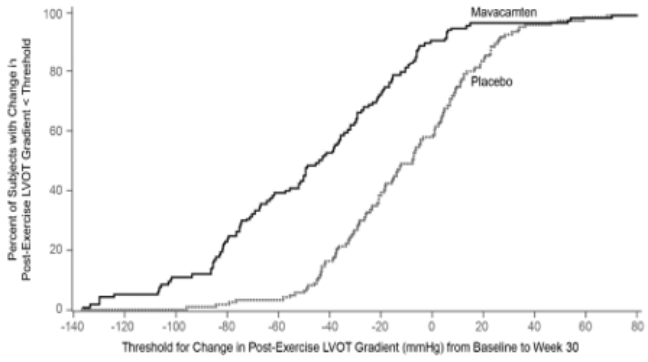


Figure 3: Cumulative Distribution of Change from Baseline to Week 30 in pVO_2

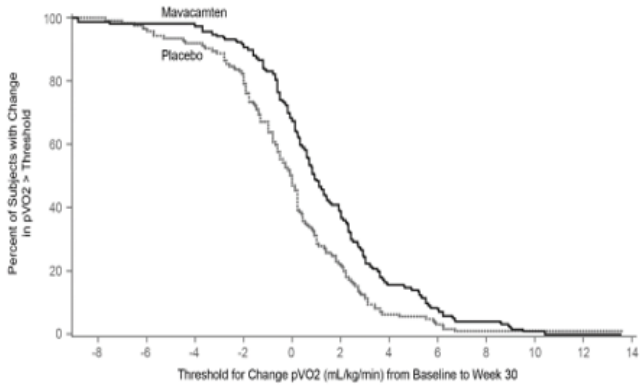


Table 3: Change from Baseline to Week 30 in KCCQ-23 CSS and HCMSQ SoB Domain

	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 4: shows the time course for changes in KCCQ-23 CSS. Figure 5: shows the distribution of changes from baseline to Week 30 for KCCQ-23 CSS.

Figure 4: KCCQ-23 Clinical Summary Score: Mean Change from Baseline Over Time

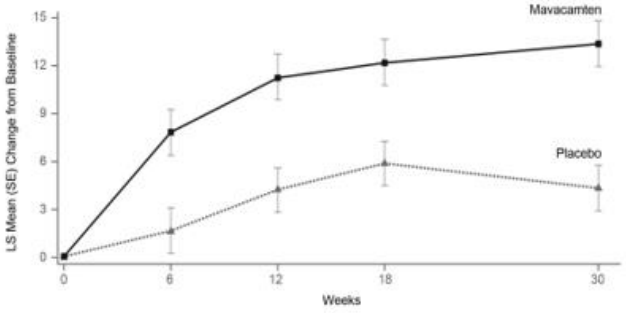
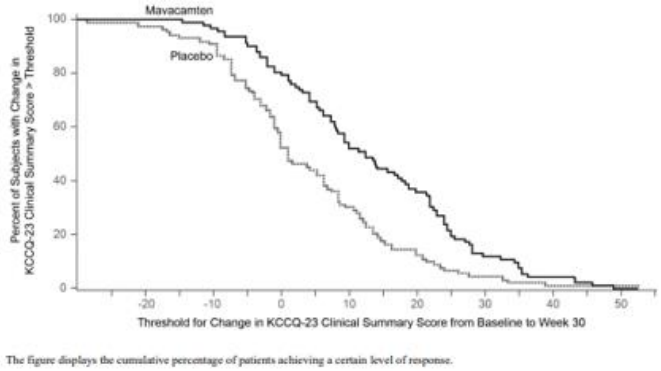


Figure 5: KCCQ-23 Clinical Summary Score: Cumulative Distribution of Change from Baseline to Week 30



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

Figure 6: shows the time course for changes in HCMSQ SoB. Figure 7: shows the distribution of changes from baseline to Week 30 for HCMSQ SoB.

Figure 6: HCMSQ Shortness of Breath Domain: Mean Change from Baseline Over Time

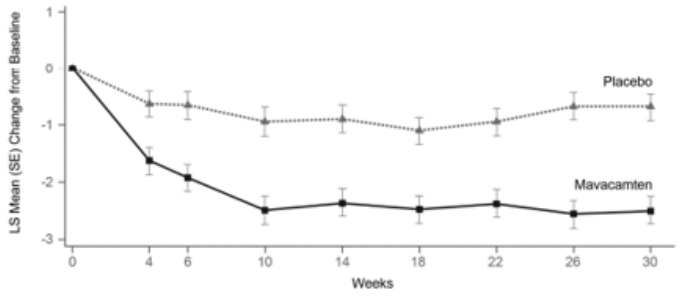
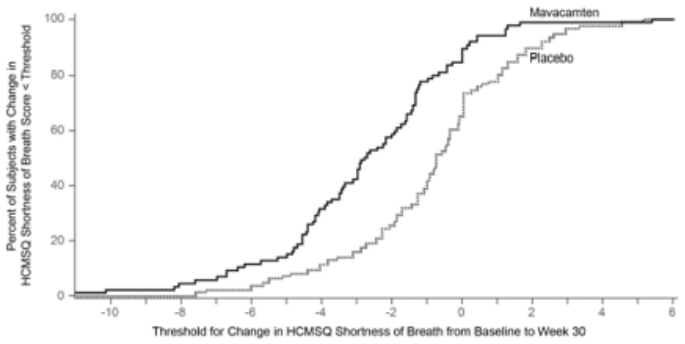


Figure 7: HCMSQ Shortness of Breath Domain: Cumulative Distribution of Change from Baseline to Week 30



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

Safety

ADVERSE EVENTS

Adverse reactions occurring in >5% of patients and more commonly on Camzyos™ than on placebo were dizziness (27%) and syncope (6%).

WARNINGS & PRECAUTIONS

- Heart Failure: Consider interruption of Camzyos™ in patients with intercurrent illness.
- CYP450 Drug Interactions Leading to Heart Failure or Loss of Effectiveness: Advise patients of the potential for drug interactions including with over-the-counter medications.
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential to use effective contraception until 4 months after the last dose. Use a contraceptive not affected by CYP450 enzyme induction or add nonhormonal contraception.
- Camzyos™ REMS Program: Camzyos™ is only available through a restricted program called the Camzyos™ REMS Program because of the risk of heart failure due to systolic dysfunction

CONTRAINDICATIONS

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

Clinical Pharmacology

MECHANISMS 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.

Dose & Administration

ADULTS

5 mg orally once daily, initially.

Adjust dose every 4 weeks during initiation phase and every 12 weeks during maintenance phase as needed based on patient clinical status and echocardiographic assessment of patient response.

Dose range: 2.5 to 15 mg/day. Interrupt treatment if left ventricular ejection fraction (LVEF) is less than 50% at any time.

PEDIATRICS

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

GERIATRICS

Refer adult dosing.

RENAL IMPAIRMENT

No dosage adjustment is required in patients 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 effect of severe (Child-Pugh C) renal impairment is unknown.

HEPATIC IMPAIRMENT

No dosage adjustment is required in patients with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment. The effect of severe (Child-Pugh C) hepatic impairment is unknown.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Capsules: 2.5 mg, 5 mg, 10 mg, and 15 mg