

**Category**

Best Biotechnology Product

**Drug / Device Name**

Camzyos® (mavacamten)

**Compound/ Tech Name**

mavacamten

**Trade Name**

Camzyos

**Date of Approval**

2022-04-28

**Indications**

Camzyos is a cardiac myosin inhibitor 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.

**Therapeutic Categories**

cardiovascular, first-in-class cardiac myosin inhibitor, small molecule

**Background information and need for drug/device**

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder characterized by heart muscle thickening, hyperdynamic contraction and impaired relaxation not explained by another cardiac or systemic disease. Its prevalence in the general population is 1 in 500. Patients with HCM are often symptomatic, experiencing shortness of breath, fatigue, impaired exercise tolerance and reduced quality of life. Over time, HCM patients are at risk for developing arrhythmias, syncope, heart failure, or sudden death.

A foundational decade of discovery in HCM occurred between 1958 and 1968 when it was first recognized by Dr Eugene Braunwald and colleagues that muscular hypertrophy could obstruct outflow from the left ventricle (LV), that the obstruction is provokable, that non-obstructive forms also exist, and that HCM can be familial with autosomal dominant transmission. By the mid-1960s the first efforts to treat the debilitating symptoms of HCM arose, including medical treatment with beta blockade (BB) and surgical myectomy. For the ensuing 50 years, medical therapy for HCM changed very little. Beta blockers, calcium channel blockers and/or disopyramide became the mainstay, being recommended on an empiric basis for symptoms due to limited data and no randomized evidence. Invasive procedures and surgery remained the only options for the most severely affected patients, thus leaving a significant unmet medical need.

Since identification of the first mutations in the beta cardiac myosin heavy chain gene in 1990, HCM

has been recognized as a disease of the sarcomere, the fundamental unit of cardiac contraction. By 2013, synthesis and development of mavacamten, a small molecule inhibitor selective for cardiac myosin, which showed disease prevention in a genetic mouse model of HCM, opened a long-awaited pathway for clinical development.

The availability of Camzyos as medical therapy is helping to transform treatment of symptomatic obstructive HCM by offering an effective targeted treatment option for this patient population.

Attached Files:

- Response 1 attachment 1 Camzyos FDA approval PR.pdf

### **History of the development of the drug/device**

The Camzyos journey started in 2012 when MyoKardia (later acquired by BMS) was founded to discover and develop targeted therapies for serious cardiovascular disorders. The founders, Christine and Jonathan Seidman, Leslie Leinwand, and James Spudich, brought deep experience regarding HCM genetics, the molecular basis of muscle contraction, and molecular motors, particularly myosin-actin interaction. Recognizing that the complex cycle of contraction is dysregulated in HCM leading to hypercontractility, impaired relaxation, and inefficient use of cellular energy (ATP), initial therapeutic strategies aimed to counterbalance these effects. The seminal finding that HCM mutations disrupt the energy sparing closed state of myosin compared to healthy heart drove the search for a mechanism that would reduce the number of actin-myosin cross-bridges, not compete with ATP, nor impact cycle kinetics or prolong diastole.

Mavacamten (MYK-461), an allosteric inhibitor selective for cardiac myosin, was synthesized and met the desired criteria. Mavacamten stabilizes myosin in a resting state, reduces myosin-actin cross-bridging, and shifts the overall myosin population towards a super-relaxed state in the HCM heart. Both in vitro and in vivo, mavacamten reduces cardiac contractility, targeting the underlying abnormality in HCM. Encouraging clinical activity observed in the Phase 2 trial led to an accelerated development path. Early results were highlighted at the 2017 Heart Failure Society of America meeting.

By mid-2019, the pivotal, global, randomized EXPLORER-HCM trial was enrolled with 251 symptomatic, obstructive HCM patients. Clinical results from the 30-week treatment showed improved functional capacity, LVOT obstruction, and symptoms compared to placebo and were published in Lancet and presented at the European Society of Cardiology in 2020. The same year, EXPLORER-HCM was recognized among the top research advances by the American Heart Association, a testament to the therapy's transformative nature.

The FDA granted mavacamten US Orphan Drug and Breakthrough Therapy Designations and subsequently approved Camzyos in April 2022.

Attached Files:

- Response 2 attachment 6 Olivotto Lancet 2020.pdf
- Response 2 attachment 7 Bristol Myers Squibb to Present Data Supporting its Cardiovascular Portfolio.pdf

### **Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition**

Camzyos is a first-in-class myosin inhibitor that addresses an unmet medical need in the treatment of HCM. It shifts the existing treatment paradigm from symptom management to addressing the

underlying pathophysiology and represents a significant leap forward for patients with limited options.

In 2022 Camzyos was one of 37 novel drug approvals by the FDA, and the only one for heart disease. EXPLORER-HCM was the first positive randomized, phase 3 trial in obstructive HCM. The composite primary endpoint evaluated improvement in exercise and functional capacity; specifically designed with relevance to the patients' condition. Beyond the primary endpoint, analyses from EXPLORER have revealed disease modifying effects of the drug that are fueling additional research. The CMR imaging substudy was the first to show favorable impact of drug treatment on cardiac structure in HCM (significant reductions in LV hypertrophy and left atrial volume). Artificial-intelligence analysis of electrocardiograms, show reductions in HCM risk scores with treatment compared to placebo. Research of treatment over longer duration and in other forms of the disease are underway.

Due to heterogeneity of HCM, different patient journeys, and individual preferences, it is important to provide physicians and patients with a range of treatment options. Following EXPLORER-HCM, a second phase 3 trial was conducted to evaluate the effect of Camzyos in symptomatic obstructive HCM patients who, despite maximal medical therapy, were referred and actively considering septal reduction therapy (SRT). VALOR-HCM randomized 112 patients and showed a significantly reduced fraction of patients meeting guideline criteria for SRT compared to placebo after 16 weeks treatment. Outcomes through 32 weeks also showed sustained reduction in the proportion proceeding to SRT or remaining eligible. These findings have implications for future disease management.

Camzyos is an innovative and effective new therapy that has changed the treatment paradigm for patients with symptomatic obstructive HCM.

Attached Files:

- Response 3 Attachment 1 Novel Drug Approvals for 2022 \_ FDA.pdf

**Please provide appropriate references (ie Pubmed links)**

- 1) A small-molecule inhibitor of sarcomere contractility suppresses hypertrophic cardiomyopathy in mice. <https://pubmed.ncbi.nlm.nih.gov/26912705/>
- 2) Deciphering the super relaxed state of human beta-cardiac myosin and the mode of action of Mavacamten from myosin molecules to muscle fibers  
<https://pubmed.ncbi.nlm.nih.gov/30104387/>
- 3) Mavacamten Treatment for obstructive hypertrophic cardiomyopathy: A Clinical Trial  
<https://pubmed.ncbi.nlm.nih.gov/31035291/>
- 4) Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomized, double-blind, placebo-controlled, phase 3 trial  
<https://pubmed.ncbi.nlm.nih.gov/32871100/>
- 5) Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): health status analysis of a randomized, double-blind, placebo-controlled phase 3 trial  
<https://pubmed.ncbi.nlm.nih.gov/34004177/>
- 6) Effect of Mavacamten on the echocardiographic features in symptomatic patients with obstructive

hypertrophic cardiomyopathy

<https://pubmed.ncbi.nlm.nih.gov/34915982/>

7) Validation of the Kansas City Cardiomyopathy Questionnaire in Symptomatic Obstructive Hypertrophic Cardiomyopathy

<https://pubmed.ncbi.nlm.nih.gov/35902155/>

8) Development of the Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ): A new patient reported outcome (PRO) instrument

<https://pubmed.ncbi.nlm.nih.gov/35653062/>

9) Longitudinal Psychometric Analysis of the Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) Using Outcomes from the Phase III EXPLORER-HCM Trial

<https://pubmed.ncbi.nlm.nih.gov/35718845/>

10) Mavacamten favorably impacts cardiac structure in obstructive hypertrophic cardiomyopathy: EXPLORER-HCM cardiac magnetic resonance substudy analysis

<https://pubmed.ncbi.nlm.nih.gov/33190524/>

11) Assessment of disease status and treatment response with artificial intelligence-enhanced electrocardiography in obstructive hypertrophic cardiomyopathy

<https://pubmed.ncbi.nlm.nih.gov/35272798/>

12) Myosin inhibition in patients with obstructive hypertrophic cardiomyopathy referred for septal reduction therapy

<https://pubmed.ncbi.nlm.nih.gov/35798455/>

13) Dose-blinded myosin inhibition in patients with obstructive hypertrophic cardiomyopathy referred for septal reduction therapy: outcomes through 32 weeks

<https://pubmed.ncbi.nlm.nih.gov/36335531/>

14) Effects of Mavacamten on measures of cardiopulmonary exercise testing beyond peak oxygen consumption: a secondary analysis of the EXPLORER-HCM randomized trial

<https://pubmed.ncbi.nlm.nih.gov/36652223/>

15) Pathophysiology and treatment of hypertrophic cardiomyopathy: New Perspectives

<https://link.springer.com/article/10.1007/s11897-021-00523-0>