

EMERGING ROLE OF MAVACAMTEN IN PRECISION MEDICINE FOR HYPERTROPHIC CARDIOMYOPATHY

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ABSTRACT

Mavacamten is a first-in-class, orally administered, selective allosteric inhibitor of beta-cardiac myosin ATPase. Its novel mechanism directly targets the core pathophysiology by reducing the formation of actin-myosin cross-bridges, shifting myosin heads towards a relaxed, energy-sparing state. This action decreases myocardial contractility and alleviates LVOT obstruction in an exposure-dependent manner. Hypertrophic cardiomyopathy (HCM), a prevalent genetic myocardial disorder, is characterized by hypercontractility which often leads to dynamic left ventricular outflow tract (LVOT) obstruction in the obstructive phenotype (oHCM). Traditional pharmacotherapies, such as beta-blockers and calcium channel blockers, offer symptomatic relief but are non-specific and often inadequate. Critically, the VALOR-HCM trial demonstrated that mavacamten substantially reduced the proportion of patients eligible for septal reduction therapy (SRT), positioning it as a potent non-invasive alternative. Mavacamten is extensively metabolized primarily by the polymorphic CYP2C19 enzyme, resulting in a highly variable half-life (6–9 days in normal metabolizers, approximately 23 days in poor metabolizers). Mavacamten represents a paradigm shift from symptomatic management to a disease-specific approach for oHCM. While long-term data and strategies for managing its complex pharmacogenetics continue to evolve, it establishes a foundational advance in the medical management of this condition.

KEYWORDS: Cardiomyopathy; mavacamten; heart failure; actin-myosin cross-bridge; stenosis; hypertrophy.

INTRODUCTION

Mavacamten is a allosteric and selective reversible inhibitor of cardiac myosin ATPase approved by the FDA in April 2022 for adults suffering from symptomatic obstructive hypertrophic cardiomyopathy (oHCM),^[1] particularly those with sarcomeric mutations leading to excessive myosin-actin cross-bridging, hypercontractility, and left ventricular outflow tract (LVOT) obstruction. By binding to myosin heads in various states, Mavacamten stabilizes an energy conserving conformation that reduces actin interaction

and inhibits the release of phosphate during the ATPase cycle, thus mitigating the systolic force and LVOT gradients by at least 50 mmHg^[2], as demonstrated in studies like EXPLORER-HCM. This action effectively decreases myocardial oxygen demand and diastolic filling pressures while maintaining ejection fraction above 50%. Mavacamten shows superior efficacy compared to conventional therapies like beta blockers or disopyramide by directly addressing the sarcomere dynamics, resulting in significant clinical improvements such as enhanced peak VO₂^[1-2], NYHA class shifts (37%

improvement vs. 17% for placebo), and better quality of life as reflected in the VALOR-HCM study.

Administered orally in doses ranging from 2.5 to 15 mg daily and primarily metabolized by CYP2C19/3A4 with a half-life of 6-23 days, Mavacamten necessitates REMS monitoring due to potential side effects like drops in left ventricular ejection fraction (LVEF), dizziness, atrial fibrillation, and interactions with CYP enzyme

modulators.^[3]

PATHOPHYSIOLOGY

In Hypertrophic Cardiomyopathy (HCM), a genetic mutation shifts myosin heads from a resting state to an active one. This causes hypercontractility, excessive energy use, and structural changes that eventually block blood flow.^[4-5-6-7]

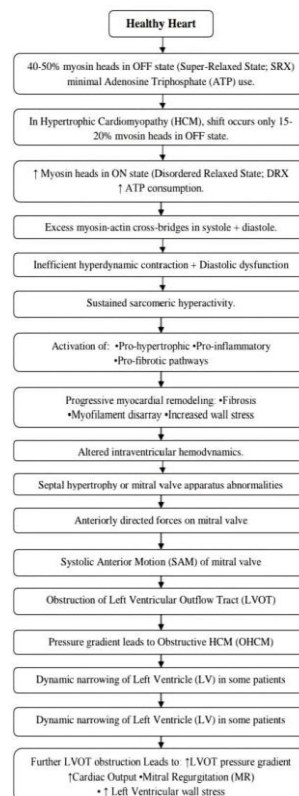
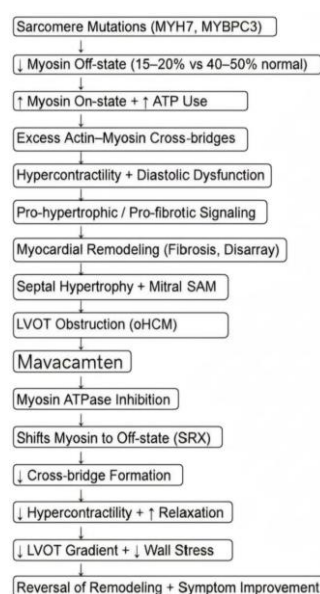


Fig. 1: Pathophysiology of Mavacamten.

MECHANISM OF ACTION



[8-9-10]

Fig. 2: Mechanism of Action Mavacamten.

PHARMAKOKINETICS

1. Absorption

Mavacamten is orally administered and reaches peak plasma concentrations (T_{max}) within 1–2 hours. Food has minimal effect on absorption.^[11]

2. Distribution

The drug has a large volume of distribution and is highly protein-bound (~97%).

3. Metabolism

It is extensively metabolized by CYP2C19 (primary)^[12], CYP3A4, and CYP2C9. Poor metabolizers show

increased systemic exposure.

4. Elimination

Elimination half-life is 6–9 days. Excretion occurs mainly as metabolites.

5. Drug–Drug Interactions

CYP2C19/3A4 inhibitors increase exposure; inducers decrease therapeutic levels.^[11-13]

6. Pharmacokinetic Variability

Genetic polymorphisms (CYP2C19) cause major variability. Renal/hepatic impairment has modest effects.

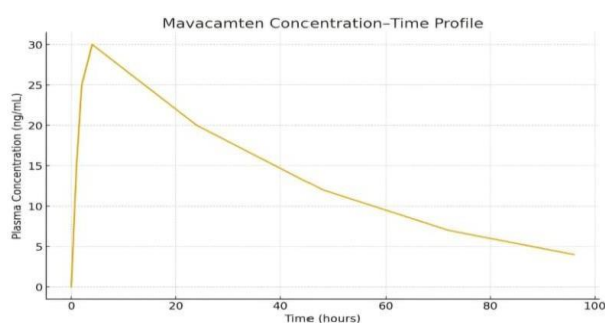


Fig. 3: Pharmacokinetic Profile Chart.

CLINICAL TRIALS

Introduction to Clinical Trials of Mavacamten:-

1. Background

Mavacamten (formerly MYK-461) is a selective cardiac myosin inhibitor developed to treat Hypertrophic Cardiomyopathy (HCM). HCM is characterized by Left Ventricular Hypertrophy (LVH), reduced compliance of the heart muscle^[14], Left Ventricular Outflow Tract Obstruction (LVOTO) in many patients, and associated diastolic dysfunction leading to exercise intolerance.^[15]

2. Purpose of Developing Mavacamten

Existing treatments including β -blockers (beta blockers)^[15-17], CCBs (calcium channel blockers) and disopyramide (an anti-arrhythmic agent) mainly provide symptomatic relief and do not target the fundamental mechanism of the disease.^[16] Therefore, mavacamten was developed in order to reduce excessive actin–myosin cross-bridge formation, improve diastolic filling, reduce LVOTO, and ultimately improve functional status and exercise capacity.

3. Overview of Clinical Trial Phases

The clinical development of mavacamten consists of three principal phases.

A. Phase 1 Trials

Phase 1 studies primarily evaluated safety, pharmacokinetics (PK)^[14], referring to how the drug moves in the body, and pharmacodynamics (PD), referring to how the drug affects cardiac physiology. These early investigations showed a dose-dependent reduction in Left ventricular Ejection Fraction (LVEF)^[17], established safe dose-titration strategies, and

demonstrated the necessity for regular echocardiography (ECHO) monitoring.

B. Phase 2 Trials

The PIONEER-HCM study (Pilot Investigation of Mavacamten in Obstructive Hypertrophic Cardiomyopathy) was conducted in patients with obstructive HCM (oHCM). The trial demonstrated decreases in LVOT gradients, improvement in NT-proBNP (N-terminal pro-B-type natriuretic peptide)^[18], and better exercise tolerance, supporting continued development of mavacamten in larger trials.

4. Overall Clinical Impact of Mavacamten Trials

A. Physiological Effects

Across studies, mavacamten has been shown to reduce hypercontractility, improve diastolic compliance, and lower LVOTO.

B. Clinical Benefits

These physiological improvements translate into enhanced peak VO_2 (exercise capacity), improved NYHA functional class, better KCCQ quality-of-life scores, and a reduced need for Septal Reduction Therapy (SRT).

C. Safety

The principal safety concern noted was reduction in LVEF^[23], which requires regular echocardiography monitoring; importantly, this decrease is reversible when the drug is withheld.

Case study:- Mavacamten in Hypertrophic Cardiomyopathy.

1. 1. Purpose

The purpose of clinical evaluation was to determine the safety, efficacy, and clinical outcomes of mavacamten (MYK-461). A total of six major clinical trials—PIONEER-HCM, MAVERICK-HCM, EXPLORER-HCM, VALOR-HCM, EXPLORER-CN, and HORIZON-HCM—were analyzed to assess effects on LVOT gradients^[17-18], NYHA class, biomarkers, quality of life, and adverse events. HCM is a genetic disorder that results in left ventricular hypertrophy and diastolic dysfunction.^[18] Two phenotypes exist: obstructive HCM (oHCM), defined by an LVOT gradient ≥ 50 mmHg, and non-obstructive HCM (nHCM), in which no significant gradient is present. Traditional therapies including β -blockers, verapamil and disopyramide provide only

symptomatic benefit, while invasive Septal Reduction Therapy (SRT), using surgery or alcohol ablation, is reserved for severe disease. Mavacamten^[16], as a first-in-class myosin ATPase inhibitor, reduces pathological hypercontractility and therefore targets the disease mechanism directly.

3. Outcomes

Across all trials, sample sizes ranged from 21 to 251 participants with mean ages between 52 and 65 years, and male predominance except in MAVERICK and HORIZON.^[15] Dosing strategies ranged from 2.5–15 mg/day, titrated according to LVEF and LVOT gradient, with a minimum follow-up duration of 16 weeks.

Trial	Year	Type	Setting	Population
PIONEER-HCM	2019	Phase II open-label	USA (5 centers)	oHCM
MAVERICK-HCM	2020	Phase II randomized	USA (35 centers)	nHCM
EXPLORE R-HCM	2020	Phase III RCT	13 countries (68)	oHCM
VALOR-HCM	2023	Phase III RCT	USA (19 centers)	oHCM (SRT candidates)
EXPLORE R-CN	2023	Phase III RCT	China (12 centers)	oHCM
HORIZON	2024	Phase III single-arm	Japan	oHCM

Fig. 4: Table A-Trial Characteristics.

Trial	N	Age (yrs)	Male %	Dose Strategy
PIONEER	21	57	57%	2–20 mg/day
MAVERICK	59	54	42%	Target serum concentration
EXPLORER	251	60	59%	Titration to LVOTG <30 mmHg
VALOR	112	60	51%	2.5–15 mg/day
EXPLORER-CN	81	52	72%	Start 2.5 mg/day; titrate
HORIZON	38	65	34%	Start 2.5 mg/day; titrate

Fig. 5: Table B- Population & Dose Summary.

SUMMARY

- Sample sizes: 21 → 251 participants.
- Mean age: 52–65 years.
- Males predominated in most trials except MAVERICK & HORIZON.
- Dosing: 2.5–15 mg/day, titrated based on LVEF & LVOT gradient.
- Follow-up: Minimum 16 weeks.

4. Safety

Common adverse effects observed included decreases in LVEF, atrial fibrillation, sinus node dysfunction, fatigue, dizziness, headache, nausea and dyspnea. Serious concerns centered around systolic dysfunction (LVEF <50%)^[19], requiring careful monitoring. Discontinuation was rare and no mavacamten-related deaths were

reported.

5. Limitations Identified

Important limitations included small sample sizes, short follow-up periods (16–30 weeks)^[20], the presence of single-arm or open-label designs, limited ethnic diversity, potentially conservative dosing strategies leading to under-treatment, and a lack of long-term systolic dysfunction data.

6. Interpretation

The strengths of mavacamten trials include strong and consistent reductions in LVOT obstruction, improvements in NYHA class^[21], exercise capacity and biomarkers, high tolerability, and a significant reduction in the need for invasive SRT. Importantly, mavacamten

is the first drug to target the fundamental mechanism of sarcomeric hypercontractility. However, the drug appears less effective in non-obstructive HCM; long-term safety remains to be established, and issues of cost and access have not been addressed.

7. CONCLUSION

Mavacamten represents a highly effective and non-invasive therapy for obstructive HCM, demonstrating meaningful improvement across multiple clinical endpoints including LVOT gradient reduction, NYHA improvement, biomarker reduction and structural remodeling on cardiac MRI.^[20-21] Although the safety profile is generally favorable, regular LVEF monitoring remains essential. Future studies must include larger, ethnically diverse samples and longer follow-up periods.^[22] Overall, mavacamten represents a transformative treatment option for oHCM, especially for patients who are unsuitable candidates for surgical septal reduction.

MARKETED FORMULATION

Brand Name	Content	Company Name	Dose (Available Strengths)
Camzyos	Mavacamten (selective allosyeric cardiac myosin inhibitor)	Bristol Myers Squibb	2.5mg, 5mg, 10mg, and 15mg oral capsule

[27-28]

Fig. 6: Marketed Formulation.

CONCLUSION

Mavacamten has truly revolutionized treatment for people with symptomatic obstructive hypertrophic cardiomyopathy (oHCM), helping them breathe easier, move better and feel less limited by reducing heart outflow blockages. It's sold only as easy to swallow oral capsules in 2.5 mg, 5 mg, 10 mg and 15 mg doses branded as Camzyos in the US and Europe or Kopozgo in India, with careful dose adjustments needed through special monitoring programs to avoid rare but serious heart risks; no tablets or liquid versions exist on the market. Mavacamten is set to become a go to option in tailored heart care, though better access and fresh formulations could make it even more practical.

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FUTURE ROLE

Hypertrophic cardiomyopathy (HCM) is an inherited heart condition in which the heart muscle becomes abnormally thick, making it harder for the heart to pump blood effectively and increasing the risk of abnormal heart rhythms. For many years^[24], treatment has mainly focused on easing symptoms such as breathlessness and chest pain, rather than addressing the underlying cause of the disease itself. Mavacamten represents an important step forward in the treatment of HCM.^[25] As a selective cardiac myosin inhibitor, it works directly on the heart muscle to reduce excessive contraction—the key problem driving the disease.

Clinical studies have shown that mavacamten can improve patients' ability to exercise and significantly reduce obstruction to blood flow from the heart, positioning it as a cornerstone therapy for symptomatic HCM.^[26]

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