MAVERICK-HCM: Phase 2, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Concentration-Guided Study to Evaluate Mavacamten (MYK-461) in Adults with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy

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Introduction

• Hypertrophic cardiomyopathy (HCM) is an autosomal dominant genetic disease defined clinically as unexplained left ventricular (LV) hypertrophy
• Pathogenesis of disease is associated with sarcomeric gene mutations resulting in hypercontractility, reduced compliance, and inefficient energy utilization
• MHC carries substantial lifelong morbidity, often associated with dynamic LV outflow tract (LVOT) obstruction; however, ~60% of HCM patients experience non-obstructive HCM (nHCM) with LVOT gradient <30 mmHg
• Patients with nHCM commonly report dyspnea and/or exercise intolerance
• Management options are extremely limited, with little other than cardiac transplantation for severely affected patients with HCM

The phase 2 MAVERICK-HCM study is designed to evaluate safety and tolerability and to provide proof of concept of mavacamten on biomarkers, cardiac function, and exercise capacity in nHCM

Mavacamten (formerly MYK-461)

• First-in-class small-molecule
• Selective allosteric modulator of cardiac myosin that inhibits cardiac myosin ATPase and reversibly attenuates cardiac contractility (Figure 1)
• Mavacamten re-populates the super-relaxed (SRX) "off" state of myosin
• Improves LV compliance in preclinical animal models (Selective allosteric modulator of cardiac myosin that inhibits cardiac myosin ATPase and reversibly attenuates cardiac contractility) – see poster #120
• Provided safety data to support the study of mavacamten in patients with HCM (phase 2 MAVERICK-HCM study) and provided safety data to support the study of mavacamten in patients with nHCM (phase 2 EXPLORER-HCM study)
• Improves LV compliance in patients with nHCM (phase 2 EXPLORER-HCM study) – see poster #120
• In the phase 2 open-label PIONEER-HCM study (NCT02842242) of patients with obstructive HCM, mavacamten:
  • Was well tolerated
  • Significantly reduced LVOT obstruction
  • Led to improvements in exercise capacity and symptoms
  • The results of the PIONEER-HCM study formed the rationale for the ongoing phase 3 EXPLORER-HCM study (randomized, double-blind, placebo-controlled trial to evaluate mavacamten in adults with hypertrophic cardiomyopathy – see poster #120)

Figure 1. Mavacamten Targets the Underlying Cause of HCM

Study Design

• Phase 2, multicenter, exploratory, randomized, double-blind, placebo-controlled study to evaluate safety and tolerability of mavacamten, and to generate pilot data on the effects of mavacamten on biomarkers, cardiac function, parameters of LV compliance, and exercise capacity in patients with symptomatic nHCM
• Primary objective: to evaluate the safety and tolerability of a 16-week course of mavacamten versus placebo
• Approximately 60 participants enrolled with ~20 participants in each group
  • Group 1: mavacamten QD (starting dose 5 mg) dose titrated according to plasma concentrations to achieve a target dose level
  • Group 2: placebo

Figure 2. Mavacamten Improves LV Compliance in Healthy Dogs (N=4)

Key Inclusion and Exclusion Criteria

Key Inclusion Criteria

• Age ≥18 years; body weight ≥45 kg
• Diagnosed with nHCM consistent with current American College of Cardiology Foundation/American Heart Association and European Society of Cardiology guidelines, with LV wall thickness ≥13 mm

Key Exclusion Criteria

• Persistent or permanent atrial fibrillation not treated with anticoagulation for at least 4 weeks prior to screening and/or is not adequately rate-controlled within 6 months
• History of resuscitated sudden cardiac arrest at any time or known appropriate implantable cardioverter defibrillator discharge within 6 months
• Paroxysmal, intermittent atrial fibrillation with atrial flutter at the time of screening
• Prolonged QT interval (QTcB >480 ms or any other ECG abnormality considered to pose a risk to participant safety

MAVERICK-HCM Trial Endpoints

Primary Endpoint

• Safety/tolerability, as measured by:
  • Frequency and severity of treatment-emergent adverse events and serious adverse events
  • Laboratory abnormalities
  • Use of cardiac rhythm abnormalities

Key Exploratory Endpoints

• Change from baseline to week 16 in the following:
  • Peak VO2, measured by CPET
  • End-systolic volume
  • EDD (mm Hg), EDPVR (mm Hg/mL), EDP (mm Hg)
  • Inability to perform exercise testing

Figure 3. Study Schema

Conclusions

• MAVERICK-HCM is leading a novel therapy aimed at improving symptom burden in HCM, a patient population currently lacking effective therapy

Reference


Author Disclosure Information

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