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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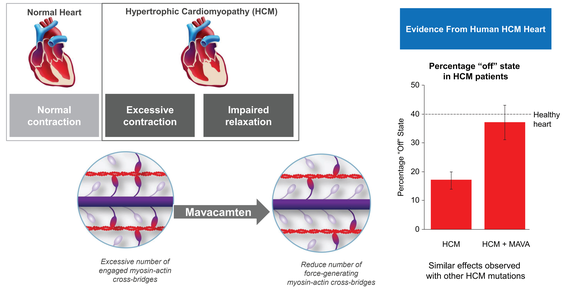
Introduction

- Hypertrophic cardiomyopathy (HCM) is an autosomal dominant genetic disease defined clinically as unexplained left ventricular (LV) hypertrophy[1]
- Pathogenesis of disease is associated with sarcomeric gene mutations resulting in hypercontractility, reduced compliance, and inefficient energy utilization
- HCM carries substantial lifelong morbidity, often associated with dynamic LV outflow tract (LVOT) obstruction; however ~30% of HCM patients experience non-obstructive HCM (nHCM) with LVOT gradient <30 mmHg
- Patients with nHCM commonly report dyspnea and/or angina and may progress to advanced heart failure
- Management options are extremely limited, with little other than cardiac transplantation for severely affected patients with nHCM
- The phase 2 MAVERICK-HCM study is designed to evaluate safety and tolerability and to provide pilot data on the effects of mavacamten on biomarkers, cardiac function, and exercise capacity in nHCM

Mavacamten (formerly MYK-461)

- First-in-class oral 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 (**Figure 2**) and clinical studies (AHA 2018 Abstract SaMDP120)
- Improves passive elastance during diastole, enabling the heart to refill

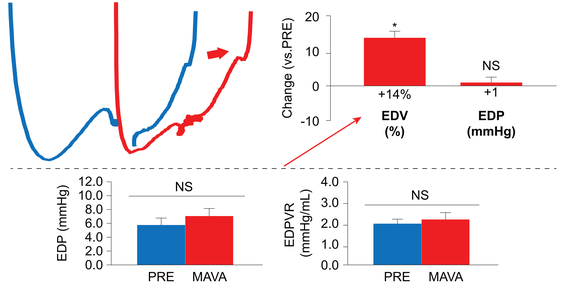
Figure 1. Mavacamten Targets the Underlying Cause of HCM



MAVA, mavacamten.
Adapted with permission from Anderson RL, et al. *Proc Natl Acad Sci U S A*. 2018;115:E8143-E8152.

- 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 symptomatic obstructive cardiomyopathy – see poster SA1264) and provided safety data to support the study of mavacamten in patients with nHCM (phase 2 MAVERICK-HCM study)

Figure 2. Mavacamten Improves LV Compliance in Healthy Dogs (N=8)

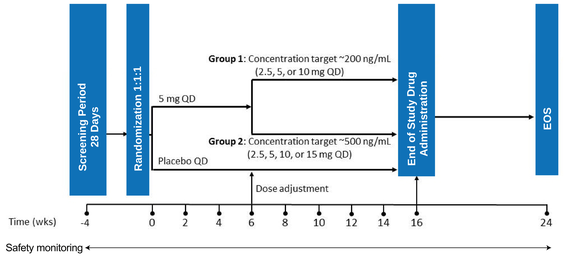


*P<0.05 vs. PRE.
Acute mavacamten administration in healthy dogs causes a rightward shift in the pressure-volume loop consistent with improved compliance/distensibility. There was a statistically significant increase of +14% EDV with MAVA vs. predose conditions and no significant change in EDP.
EDP: end diastolic pressure; EDPVR, end diastolic pressure volume relationship; EDV, end diastolic volume; MAVA, mavacamten; NS, not significant; PRE, predose.
Del Rio CL, et al. Presented at the Scientific Sessions of the American Heart Association; November 11-15, 2017, Anaheim, CA.

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 each in three groups:
  - Group 1: mavacamten once daily (QD) (starting dose 5 mg) with dose titrated according to plasma concentrations to achieve a base target trough concentration
  - Group 2: mavacamten QD (starting dose 5 mg) with dose titrated to achieve a higher target concentration
  - Group 3: placebo QD
- Doses of mavacamten used in this study will be 2.5, 5, 10, and 15 mg
- Background HCM therapy (beta blocker or calcium channel blocker) allowed
- Assessments include (see Study Schema; **Figure 3**):
  - Echocardiography to evaluate LVEF and parameters of diastolic function
  - Standardized cardiopulmonary exercise testing (CPET) with measurement of peak oxygen consumption (pVO_2)
  - Drug concentration (pharmacokinetics [PK])
  - N-terminal pro b-type natriuretic peptide (NT-proBNP) levels at rest and after exercise
  - Cardiac rhythm monitoring (48-hour Holter) at screening and end of treatment
  - Symptoms and quality of life (patient-reported outcomes [PROs])

Figure 3. Study Schema



QD, once daily; wks, weeks.

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 ≥15 mm, *or*
  - LV wall thickness ≥13 mm with a positive family history of HCM
- LV ejection fraction ≥55%
- LVOT peak gradient at rest *AND* during Valsalva *AND* post-exercise <30 mmHg
- Maximal intracavitary gradient at rest *AND* during Valsalva *AND* post-exercise <30 mmHg
- New York Heart Association (NYHA) class II or III symptoms
- Elevated NT-proBNP at rest (>300 pg/mL)
- Safety laboratory parameters within normal limits

Key Exclusion Criteria

- Known infiltrative or storage disorder causing increased LV wall thickness (phenocopies)
- Inability to perform exercise testing
- History of syncope or sustained ventricular tachyarrhythmia with exercise within the past 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 fibrillation at the time of screening
- 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
- Treatment with disopyramide or ranolazine
- QT interval with Fridericia correction >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
  - Vital signs
  - Cardiac rhythm abnormalities

Key Exploratory Endpoints

- Change from baseline to week 16 in the following:
  - Peak VO_2 measured by CPET
  - Echocardiographic measures of systolic and diastolic function
  - NYHA functional class
  - NT-proBNP at rest and after maximal exercise
  - PROs
  - Daily step count measured by accelerometer

Conclusions

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

Reference

1. Marian AJ, Braunwald E. *Circ Res*. 2017;121:749-70.

Author Disclosure Information

S. Heitner, A. Wang, S. Lester: Consultant/Advisory Board; Modest; MyoKardia. **D. Jacoby:** Consultant/Advisory Board; Modest; MyoKardia, Abbott, Alnylam, Deerfield. Consultant/Advisory Board; Significant; Admera. **T. Carlson, D. Zhang, A. Sehnert:** Employment; Significant; MyoKardia. **C. Ho:** Other Research Support; Significant; MyoKardia. Honoraria; Modest; MyoKardia. Consultant/Advisory Board; Significant; MyoKardia.

This study was funded by MyoKardia and Sanofi.