A Novel Oral Myosin Modulator (MYK-461) for the Treatment of Obstructive Hypertrophic Cardiomyopathy: Initial Single Ascending Dose Data in Healthy Volunteers and Patients

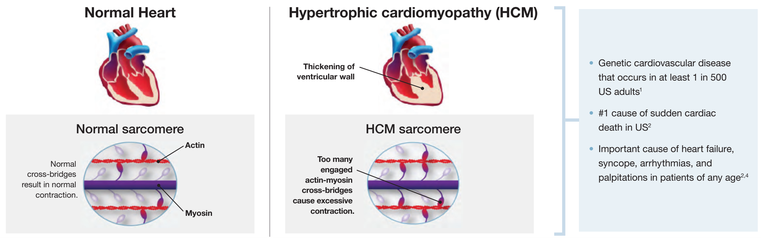
Martin Maron[1], Euan Ashley[2], Thomas Blok[3], Marc Evanchik[4], Eric M. Green[4], Joseph Lambing[4], Steven Lester[5], Kenneth Mahaffey[2], Svetlana Markova[4], Anjali Owens[6], James Ritter[7], Andrew Wang[8], and Jonathan Fox[4]

[1]Tufts Medical Center, Boston MA, [2]Stanford University Hospital, Stanford, CA, [3]Jasper Clinic, Kalamazoo, MI, [4]MyoKardia, Inc., [5]Mayo Clinic, AZ, [6]Hospital of the University of Pennsylvania, Philadelphia, PA, [7]Quintiles Drug Research Unit at Guy's Hospital, London, UK, and [8]Duke University Medical Center, Durham, NC

Introduction

- Hypertrophic cardiomyopathy (HCM), the most common genetic cardiovascular disease, is associated with increased risk for atrial fibrillation, stroke, heart failure (HF), and sudden death[1,2]
- HCM mutations in the genes encoding the cardiac sarcomere result in hypercontractile left ventricular (LV) function and increased wall thickness, which contribute to LV outflow tract (LVOT) obstruction, a major cause of limiting symptoms including angina and shortness of breath[3,4] **(Figure 1)**
- There are no specific FDA-approved medical therapies for HCM. Current treatments include off-label use of agents to address disease symptoms rather than the underlying disease pathophysiology[5,6]
- MYK-461, a novel oral myosin modulator, targets the underlying defect in myosin activity. Preclinical studies in a murine model of HCM have shown that MYK-461 inhibits the morphologic, histopathologic, and molecular changes characteristic of HCM without compromising skeletal muscle[7]
- To assess the safety and tolerability of MYK-461, we conducted two phase 1, single ascending dose (SAD) trials in patients with HCM and in healthy volunteers

Figure 1. Genetic mutations in sarcomere proteins lead to HCM



- Genetic cardiovascular disease that occurs in at least 1 in 500 US adults[1]
- #1 cause of sudden cardiac death in US[2]
- Important cause of heart failure, syncope, arrhythmias, and palpitations in patients of any age[2,4]

Methods

- **Study MYK-461-002** was a randomized, double-blind, placebo-controlled SAD trial
  - N=48 healthy volunteers (age 18-60 years)
  - Six cohorts (n=8/cohort)
  - Randomized 6:2, active:placebo
  - Each cohort received a single dose of 1, 2, 6, 12, 24, or 48 mg MYK-461 or placebo
- **Study MYK-461-001**[a] was an open-label SAD trial
  - N=15 patient volunteers with HCM (age 18-60 years)
  - Two patients with Valsalva-provoked outflow gradients, New York Heart Association (NYHA) class I-II, and LV ejection fraction (LVEF) ≥65%
  - Participants received a single dose of 48 (n=4), 96 (n=6), or 144 (n=5) mg MYK-461
- In both studies, assessments included echocardiographic assessment of LVEF, LV fractional shortening (LVFS), and LV velocity-time integral (LV-VTI) at baseline and 2, 3, 4, 24, and 48 hours post-dose
- Primary endpoint: safety and tolerability of a single dose of MYK-461, assessed by adverse events (AEs)
- Exploratory endpoints: pharmacodynamic profile of MYK-461, as assessed via changes in LVEF, LVFS, and LVOT velocity-time integral

[a]Study MYK-461-001 has concluded, but the database is not yet locked.

Abbreviations: AE, adverse event; HCM, hypertrophic cardiomyopathy; HF, heart failure; LV, left ventricle; LVEF, LV ejection fraction; LVFS, LV fractional shortening; LVOT, LV outflow tract; LV-VTI, LV velocity-time integral; NYHA, New York Heart Association; oHCM, obstructive HCM; PK, pharmacokinetics; SAD, single ascending dose; SEM, standard error of the mean.

Results

Table 1. Participant demographics and baseline characteristics

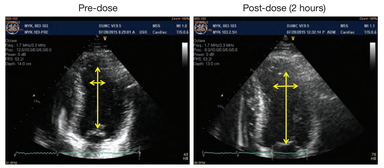
Parameter	Study MYK-461-001 HCM Patients N=15	Study MYK-461-002 Healthy Volunteers N=48
Sex, No. (%)		
Male	7 (47)	48 (100)
Age, mean (SD), y	41.3 (14.7)	32.7 (9.1)
NYHA class, No. (%)		
I	13 (87)	NA
II	2 (13)	NA
LVEF, mean (SD), %	65 (2.3)	NA
Maximal LV wall thickness, mean (SD), cm	1.9 (0.4)	NA

NA, not available.

Study MYK-461-001[a]

- Mild to moderate AEs occurring in ≥2 patients with HCM included headache, heartburn, nausea, dizziness, and fatigue
- One serious AE occurred in a patient administered 144 mg MYK-461, reported as a transient episode of hypotension and asystole presumably due to vasovagal reaction, which resolved without therapeutic intervention

Figure 2. MYK-461 reduces LV contractility



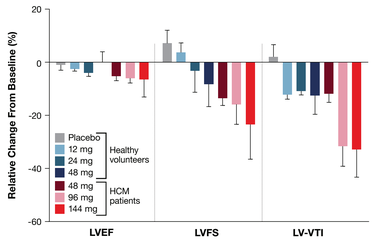
- Echocardiographs from 1 patient, taken at baseline and 2 hours post-dose, demonstrated reduced LV contractility following administration of 48 mg MYK-461 **(Figure 2)**

Study MYK-461-002

- All AEs were mild to moderate; AEs occurring in ≥2 patients included dizziness, headache, contact dermatitis, and catheter-site reaction
- No serious AEs
- Overall, findings for AEs were similar in the MYK-461 and placebo groups

- Dose-dependent reductions in measures of LV contractility (LVEF, LVFS, and LV-VTI) were observed in both healthy volunteers and patients with HCM **(Figures 2 and 3)**

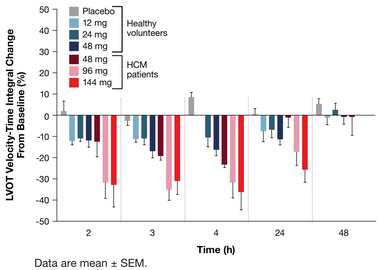
Figure 3. Mean percentage change from baseline to 2 hours post-dose for each echocardiographic measure of LV contractility following a single dose of MYK-461



Data are mean ± SEM.

- The effects of a single dose of MYK-461 on LVOT velocity-time integral were reversible and followed the time course of MYK-461 plasma levels. These effects were maintained for up to 48 hours in healthy volunteers and patients with HCM **(Figure 4)**
- Similar dose-dependent effects were observed for LVEF and LVFS

Figure 4. Change in LVOT velocity-time integral over 48 hours following a single dose of MYK-461



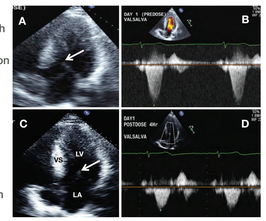
Data are mean ± SEM.

- Two HCM patients had provocable LVOT gradient with Valsalva maneuver at baseline (28 mm Hg and 42 mm Hg). In both cases, gradient was greatly diminished (5 mm Hg and 9 mm Hg, respectively) after administration of a single 96-mg dose of MYK-461 **(Figure 5)**

Figure 5. Elimination of LVOT gradient in an HCM study patient following a single 96-mg dose of MYK-461

(A) Four-chamber echocardiogram with Valsalva maneuver prior to administration of MYK-461 showed systolic anterior motion of the mitral valve (SAM) with septal contact (arrow).

(B) Corresponding Doppler indicated an outflow gradient of 42 mm Hg.

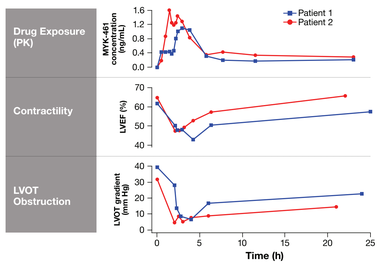


(C) An echocardiogram from the same patient following administration of 96 mg MYK-461 showed no SAM (arrow).

(D) The corresponding Doppler indicated normal LVOT velocities.

- Pharmacokinetic and pharmacodynamic results from the 2 patients with provocable LVOT gradient demonstrated concentration-dependent reductions in LVEF and LVOT gradient **(Figure 6)**

Figure 6. Reduction in LVEF and LVOT gradient over 24 hours



Conclusions

- HCM is an important, underrecognized genetic heart disease characterized by hypercontractile function and increased wall thickness, and is an important cause of atrial fibrillation, stroke, HF, and sudden death
- MYK-461 was generally well tolerated by patients with HCM and by healthy volunteers
- MYK-461 was associated with dose- and concentration-dependent reductions in LV contractility in patients with HCM and in healthy volunteers
- MYK-461 decreased LV contractility and LVOT gradient in 2 patients in a concentration-dependent manner
- These data support the advancement of MYK-461 into the phase 2 PIONEER-HCM study, a pilot study of symptomatic patients with obstructive HCM (oHCM) in an outpatient setting

References

1. Semsarian C, Ingles J, Maron MS, Maron BJ. *J Am Coll Cardiol.* 2015;65:1249-1254.
2. Maron BJ, Ommen SR, Semsarian C, Spirito P, Olivotto I, Maron MS. *J Am Coll Cardiol.* 2014;64:83-99.
3. Alfares AA, Kelly MA, McDermott G, et al. *Genet Med.* 2015;17(11):880-888.
4. Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, Aeppli DM. *JAMA.* 1999;281(7):650-655.
5. Maron BJ, Maron MS. *Lancet.* 2013;381(9862):242-255.
6. Spoladore R, Maron MS, D'Amato R, Camici PG, Olivotto I. *Eur Heart J.* 2012;33(14):1724-1733.
7. Green EM, Wakimoto H, Anderson RL, et al. *Science.* 2016;351(6273):617-621.

Disclosures: TB, SL, KM, MM, and AW have received consulting fees from MyoKardia. EA is the founder of Personalis Inc. ME, JF, JL, EG, and SM are employees of, and/or own shares in, MyoKardia. KM has received research funding from Amgen, Daiichi, J&J, Medtronic, St. Jude, and Tenax; has received consultant fees from the American College of Cardiology, AstraZeneca, BARonova, Bayer, Boehringer Ingelheim, Bio2 Medical, Bristol-Myers Squibb, Cubist, Eli Lilly, Elsevier, Epson, Forest, GSK, J&J, Medtronic, Merck, Mt. Sinai Hospital, Omthera, Portola, Purdue, Springer, The Medicines Company, Theravance, Vindico, and WebMD; and holds stock in BioPrint Fitness. AW has received research grants from MyoKardia and Gilead Sciences and consulting fees from Heart Metabolics. AO has no disclosures to report.

MyoKardia