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 Marion1, Euan Ashley2, Thomas Blok3, Marc Evanichik4, Eric M. Green4, Joseph Lambing4, Steven Lester5, Kenneth Mahaffey2, Svetlana Markova4, Anjali Owens5, James Ritter7, Andrew Wang8, and Jonathan Fox4

1Tufts Medical Center, Boston MA, 2Stanford University Hospital, Stanford, CA, 3Jasper Clinic, Kalamazoo, MI, 4Mykardia, Inc., 5Mayo Clinic, AZ, 6Mayo University of the Pennsylvania, Philadelphia, PA, 7Quintiles Drug Research Unit at Guy’s Hospital, London, UK, and 8Duke 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.
• HCM mutations in the genes encoding the cardiac sarcomere result in transcript variance and increased wall thickness, which contribute to LV outflow tract (LVOT) obstruction, an important cause of limiting symptoms including angina and shortness of breath.1,2 (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.3–4
• 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.5
• 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.

Methods

• Study MYK-461-001 was a randomized, double-blind, placebo-controlled SAD trial
  – N=48 healthy volunteers (age 18-60 years)
  – Six cohorts (12 cohorts/64)
  – 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 was an open-label SAD trial
  – N=15 patient volunteers with HCM (age 18-60 years)
  – Two patients withValsalva-provoked outflow gradients, New York Heart Association (NYHA) class II, and LV ejection fraction (LVEF) >65%.
  – Participants received a single dose of 48, 60, 96, or 144 mg MYK-461.
• In both studies, assessments included echocardiographic assessment of LV function, LV fractional shortening (LVFS), LV velocity-time integral (LV-VTI), and LV ejection fraction (LVEF) 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 LV-VTI velocity-time integral

Table 1. Participant demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study MYK-461-001</th>
<th>Study MYK-461-002</th>
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<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>52.1 (12.3)</td>
<td>56.7 (8.8)</td>
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<td>Sex, % male</td>
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<td>50</td>
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<td>NYHA class, No. (%):</td>
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</tr>
<tr>
<td>II</td>
<td>12</td>
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<td>III</td>
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<td>IV</td>
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<td>1</td>
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<td>LVEF, mean (SD), %</td>
<td>65 (2.3)</td>
<td>67 (2.7)</td>
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<tr>
<td>LVOT gradient, mean (SD), mm/Hg</td>
<td>33 (10)</td>
<td>32 (8)</td>
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<tr>
<td>LV-VTI, mean (SD), cm²/second</td>
<td>0.6 (0.2)</td>
<td>0.6 (0.2)</td>
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</table>

Results

• Dose-dependent reductions in measures of LV contractility (LVEF, LVFS, LV-VTI) were observed in both healthy volunteers and patients with HCM (Figures 2 and 3).
• Two HCM patients had provocative LVOT gradient with Valsalva maneuver at baseline (28 mm Hg and 42 mm Hg), respectively; after administration of a single 96-mg dose of MYK-461 (Figure 5).

Figure 3. Mean percentage change from baseline to 24 hours post-dose for each echocardiographic measure of LV contractility following a single dose of MYK-461 (Figure 2)

Figure 4. Change in LVOT velocity-time integral over 48 hours following a single dose of MYK-461 (Figure 2)

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

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

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

Conclusions

• HCM is an important, underrecognized genetic heart disease characterized by hypertrophic cardiomyopathy and increased wall thickness. It 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 decreased LVOT and LV-VTI velocity-time integral 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 (hHCM) in an outpatient setting.

References


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Abbreviations: LA, left atrium; LV, left ventricle; LVOT, LV outflow tract; LVEF, LV ejection fraction; LVFS, LV fractional shortening; LV-VTI, LV velocity-time integral; NYHA, New York Heart Association; and PK, pharmacokinetics.

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