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 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 breath1,2 (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 pathology3,4 (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 muscle5).

To assess the safety and tolerability of MYK-461, we conducted two phase-1, single ascending dose (SAD) studies 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 (hydrc/ost)
    - Randomized 6:2, active:placebo
    - Six cohorts (n=8/cohort)
    - N=48 healthy volunteers (age 18-60 years)
- **Study MYK-461-002** was a randomized, double-blind, placebo-controlled 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%
  - Each cohort received a single dose of 1, 2, 6, 12, 24, or 48 mg MYK-461 or placebo

Results

- **Table 1. Participant demographics and baseline characteristics**
- **Table 2. Pharmacokinetic and pharmacodynamic results**

- **Figure 3. Mean percentage change from baseline in LVOT velocity-time integral following a single 48-mg dose of MYK-461**
- **Figure 4. Change in LVEF and LVOT velocity-time integral after 48 hours following a single dose of MYK-461**

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 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


Disclosures