**EXPLORER-HCM: Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled Study to Evaluate Mavacamten (Formerly MYK-461) in Adults With Symptomatic 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 myocardial efficiency unfavourable milieu.
- Approximately 70% of patients have LV outflow tract (LVOT) obstruction.
- For some patients, HCM may carry substantial lifelong morbidity.
- Despite knowledge of the disease for >50 years, few randomized studies have been conducted and therapeutic options are limited, resulting in unmet medical need

**Mavacamten (formerly MYK-461)**

- First-in-class oral small molecule
- In HCM mutant mice, prevented hypertrophy, reduced myocyte disarray and improved cardiac function.
- Mavacamten re-populates the super-relaxed (SRX) “Off” state of myosin
- First-in-class oral small molecule
- Need
- Despite knowledge of the disease for >50 years, few randomized studies have been conducted and therapeutic options are limited, resulting in unmet medical need.

**Study Design**

- Phase 3, double-blind, randomized, placebo-controlled, multicenter, international, parallel-group study
- Primary objective is to compare a 30-week course of mavacamten with placebo on clinical response comprising exercise capacity and clinical symptoms.
- Approximately 220 participants with HCM will be enrolled.
- Cardiac magnetic resonance (CMR) substudy: 80 participants

**Statistical Power**

- Assuming that 50% and 25% of patients in the active and control arms, respectively, will achieve the clinical response at the end of the 30-week dosing period, the proposed sample size of 110 subjects per arm will provide 96% power at the two-sided 5% statistical significance level.

**Key Inclusion and Exclusion Criteria**

- **Inclusion Criteria**
  - At least 18 years old with diagnosed HCM consistent with current American College of Cardiology Foundation/American Heart Association and European Society of Cardiology guidelines.
  - LVOT gradient at screening TTE of ≥50 mmHg at rest or with provocation.
  - NYHA functional class I or II symptoms
  - Ability to perform an upright CPET and has a respiratory exchange ratio (RER) ≥1.0

- **Exclusion Criteria**
  - Known infiltrative or storage disorder causing cardiac hypertrophy (phenocopies)
  - History of syncope or sustained ventricular tachyarrhythmias with exercise within 6 months.
  - History of neussulated sudden cardiac arrest (at any time) or history of appropriate implantable cardiac defibrillator discharage for life-threatening ventricular arrhythmias within 6 months.
  - Paroxysmal or persistent atrial fibrillation present at time of screening.
  - Persistent or paroxysmal atrial fibrillation not treated with anticoagulation for at least 4 weeks prior to screening and/or not adequately rate controlled within 6 months prior to screening.
  - Treatment or planned treatment with beta blocker or calcium channel blocker allowed.

**Conclusions**

- EXPLORER-HCM is a pivotal phase 3 trial testing a novel therapy to improve symptom burden and functional capacity in oHCM.
- By targeting an underlying mechanism of disease, this type of therapy has the potential to modify natural history.

**References**