Chronic Treatment with a Mavacamten-like Myosin-modulator (MYK-581) Blunts Disease Progression in A Mini-pig Genetic Model of Non-obstructed Hypertrophic Cardiomyopathy: In Vivo Evidence For Improved Relaxation And Functional Reserve

del Rio CL1*, Yadav A1*, Ferguson B1*, Zambataro C1*, Smit T2#, Rohret F2#, Guo JL3#, Hargrave A3#, Grinde J3#, Sridhar V3#

1: MyoKardia (CA, USA); 2: Exemplar Genetics (IA, USA); 3: Texas A&M University (TX, USA)

DISCLOSURES: *: Employment/Ownership (MyoKardia, CA, USA) and #:Research Support (MyoKardia, CA, USA)
Hypertrophic cardiomyopathy (HCM) is a chronic disease characterized by **hypercontractility** and remodeling, as well as **impaired relaxation and compliance**.

- Diminished exercise capacity and cardiac reserve
- **Sarcomere disease (mutations)**
**Background: Hypothesis**

**Chronic Myosin-Modulation with MYK-581 can limit residual cross-bridges during diastole, blunting remodeling and improving compliance/relaxation in a mini-pig HCM model.**

*What is mavacamten (and MYK-581)?*

A novel clinical-stage small molecule that regulates contractility by **DIRECT** modulation of cardiac myosin (reduces ATPase activity)

- Inhibits the rate of phosphate release of β-cardiac myosin-S1 (preserves ADP release)
- Decreases the number of actin-binding heads transitioning from the weakly to the strongly bound state
  

- Stabilizes thick-filament, in particular, the super relaxed state (SRX) of myosin
  
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- Improves compliance/distensibility
  
METHODS: **Chronic** Experiment (Prevention)

- Cloned male MYH7 R403Q mutant (R403Q) mini-pig littermates (~1M old)
- Randomly assigned to either untreated (CTRL) or MYK (daily) for 12w

**Primary End-Points** (MYK vs. CTRL)

- **CTRL (n = 10)**
- **MYK (n = 10)**

- Increasing MYK-581 dose (5, 7.5, and 10 mg/day PO) to account for weight gain 6.4±0.3 to 28.3±1.1 kg (P < 0.05)

**Hemodynamic data collection**

- **β-AR reserve (DOB,10 µg/kg/min IV)**
  - **CTRL (n = 5)**
  - **MYK (n = 6)**

**ANES (ISO)**

**LV (hemodynamics +pressure/volume)**

**INVASIVE**

**ANES (ISO)**

**BASELINE**

**BLOOD**

**T1 map**

**TTE + β-AR (DOB IV)**

**NON-INVASIVE (IMAGING)**

**cMR (function, geometry, LGE, T1 mapping)**

- **CTRL (n = 10, 5.1 ± 0.1 M, 29.3 ± 1.6 kg)**
- **MYK (n = 10, 5.0 ± 0.1 M, 27.4 ± 1.4 kg)**
RESULTS: MYK Normalized LV/LA in MYH7 R403Q

✓ Blunted hyper-contractility w/ preserved CO
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- Blunted hyper-contractility with preserved CO
- Preserved LA size (blunted LV mass gain)
RESULTS: MYK Normalized LV/LA in MYH7 R403Q

✓ Blunted hyper-contractility w/ preserved CO
✓ Preserved LA size (blunted LV mass gain)
✓ …and LV structure
  • Reduced T1 times and Extracellular Volume (ECV) fraction
RESULTS: MYK Normalized Diastole in MYH7 R403Q

✓ Spared End-Diastolic Pressures (EDP) and Stiffness ($E_{ed}$)

- Preserving early relaxation

![Graphs showing EDP, $E_{ed}$, $\tau_w$, and $dP/dt_{min}$ comparisons between CTRL and MYK groups with statistical significance ($P < 0.05$).]
RESULTS: MYK Normalized Diastole in MYH7 R403Q

✓ Spared End-Diastolic Pressures (EDP) and Stiffness ($E_{ed}$)

- Preserved early relaxation

✓ Preserved β-AR reserve (dobutamine challenge)

- ↑ SV (MYK: $+15 \pm 4\%$ vs. $-14 \pm 6\%$, $P<0.05$)
- ↑ CO (MYK: $+60 \pm 8\%$ vs. $+26 \pm 2\%$, $P<0.05$)
Results: MYK Normalized Diastole in MYH7 R403Q

✓ Spared End-Diastolic Pressures (EDP) and Stiffness ($E_{ed}$)

- Preserving early relaxation

✓ Preserved $\beta$-AR reserve ...AND blunted mortality (0% vs. 40% in CTRL)
**CONCLUSIONS**

Chronic direct myosin modulation with **MYK-581** prevented cardiac remodeling characteristic of disease in a genetic HCM model, **preserving** diastolic function, cardiac reserve, left atrial size, and myocardial structure **in vivo**

*Mechanistic support for the (preliminary) observations in HCM*

Pharmacological Therapy in HF/Cardiomyopathy: The Next Important Indication or Agent?
2:05 p.m. – 2:10 p.m. ET
ORAL PRESENTATION: RF295: Precision Pharmacological Treatment for Obstructive Hypertrophic Cardiomyopathy With Mavacamten: One-Year Results From PIONEER-OLE
Lead author: Stephen B. Heitner, M.D., Oregon Health & Sciences University, Portland, OR

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- Texas A&M University
Background: HCM Mini-Pig Model

✓ MYH7 R403Q mutation in Yucatan background
**Background:** HCM Mini-Pig Model

- MYH7 R403Q mutation in Yucatan background

**Diagram:**
- Tension (mN/mm²) vs. pCa
- EF (%) vs. pCa
- Disarray Score (n.u.)
- Collagen Area (%)

**Graph:**
- WT vs. R403Q

**Figures:**
Background: HCM Mini-Pig Model

✓ Hyper-contractile

...but unchanged dP/dt_{max} (velocity)
Background: HCM Mini-Pig Model

- Hyper-contractile
  ...but unchanged $dP/dt_{\text{max}}$ (velocity)

- Diastolic Impairment

- Decreased compliance
**Background:** HCM Mini-Pig Model

- ✓ Hyper-contractile
  ...but unchanged $dP/dt_{max}$ (velocity)

- ✓ Diastolic Impairment
  - ➢ Decreased compliance and
  - ➢ Hindered relaxation
Background: HCM Mini-Pig Model

✓ Hyper-contractile

…but unchanged dP/dt_max (velocity)

✓ Diastolic Impairment

✓ Decreased β-AR cardiac reserve