In vivo Cardiac Effects of Mavacamten (MYK-461): Evidence for Negative Inotropy and Improved Compliance

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➢ I HAVE the following relationship(s) to disclose:
  ■ MyoKardia and QTest Labs (employment/consultant)
Background: HCM

- Hypertrophic cardiomyopathy (HCM) is a heritable cardiac disease characterized by *hyper-contractility* as well as *impaired ventricular relaxation and compliance*.
  - Impaired exercise capacity and cardiac reserve
  - Sarcomere disease (mutations)

- *Current* pharmacological management: clinically-available negative inotropes (β-AR blockers, ion-channel modulation)
  - Non-targeted
  - Potential to further impair relaxation/compliance (*other off-target effects*)
Background: A Potential Therapeutic Alternative

What is mavacamten (MYK-461)?
A novel clinical-stage small molecule that reduces contractility by DIRECT modulation of cardiac myosin / biomechanical cycle

Assess the *in vivo* cardiovascular profile of mavacamten
- What are the specificities of MAVA-mediated negative inotropy that are relevant in HCM?
- Can MAVA mechanism of action offer potential benefits beyond pure negative inotropy?

Why does mavacamten matter in HCM?
- Prevent/regress LV hypertrophy/fibrosis (murine HCM)
- Relieve LVOT Obstruction/SAM (feline HCM)
- Relieve LVOT Obstruction and improve exercise capacity (pVO2) (symptomatic oHCM)
  Heitner et al. Oral presentation (HFSA 2017)
Experimental Methods: ACUTE

• Healthy beagle dogs chronically instrumented
  ✓ Systemic/LV hemodynamics, LV dimensions, and aortic blood flow (CO)
  ✓ Load-independent LV function via pressure-volume relationships

CV profile before and after treatment:
  ➢ Mavacamten (MAVA) at 1.5 mg/kg PO (n = 8)
  ➢ Metoprolol (MET) at 2 mg/kg PO (n = 6)
  ✓ Data at PRE, 1, 3, 8, and 24hr post-dose (3HR)

Exp. A

Exp. B

Cardiac reserve via β-AR stimulation (DOB, dobutamine 1 to 10 µg/kg/min IV)
  - Before/after (MAVA, 1.5 mg/kg PO)
Exp. A: MAVA Depresses Systolic Function (acute, healthy dogs)

ACUTE, mavacamten:

- Depressed systolic function
- Preserved systemic pressures

**Graphs and Data**

- **Ees (%)**
  - Change (vs. PRE): -32% (vs. PRE) *: P < 0.05 vs. PRE

- **PRSW (%)**
  - Change (vs. PRE): -35% (vs. PRE) *

- **dP/dt_{max} (%)**
  - Change (vs. PRE): -28% (vs. PRE) *

- **EF (%)**
  - Change (vs. PRE): -28% (vs. PRE) *

- **CO (%)**
  - Change (vs. PRE): +3%

- **HR (%)**
  - Change (vs. PRE): +25%

- **MAP (%)**
  - Change (vs. PRE): +4%

- **SVR (%)**
  - Change (vs. PRE): +2%

- **N.S.**

*: P < 0.05 vs. PRE

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Exp. A: MAVA Improves LV Compliance (acute, healthy dogs)

**ACUTE, mavacamten:**

- Depressed systolic function
- Preserved systemic pressures

- Improved compliance/distensibility

![Graph showing LVV (mL) vs. LVP (mm Hg)]

**Graph Details:**
- PRE
- MAVA
- Improved compliance/distensibility

**Measurements:**
- EDV (%)
- EDP (mm Hg)
- EDPVR (mm Hg/mL)

**Statistical Significance:**
- *: P < 0.05 vs. PRE
- N.S.
Exp. A: Different end-diastolic profile vs. β-AR blocker (acute, healthy dogs)

**ACUTE, mavacamten:**

- Depressed systolic function
- Preserved systemic hemodynamics
- Improved compliance/distensibility

**Exp. A**

- **L V V (m L)**
- **L V P (m m H g)**
- **E D V (%)**
- **E D P (m m H g)**
- **E D P V R (m m H g /m L)**
- **E e s (%)**
- **P R S W (%)**
- **C h a n g e (v s . P R E )**
- **C h a n g e (v s . M E T )**

**Graph:**

- **PRE**
- **MAVA**

“+3%” vs. “+4”

“-25%” vs. “-15%”

“P < 0.05 vs. PRE”

“# : P < 0.05 vs. M E T”
Exp. B: MAVA Preserves β-AR Cardiac Reserve (acute, healthy dogs)

+DOB recruits systolic (↑dP/dt$_{max}$) and diastolic reserve (↓tau)
  - ↑ Stroke Volume (SV)

MAVA allows +DOB systolic recruitment, while enhancing diastolic reserve
- Preserve SV/CO gain

![Graphs showing changes in cardiac reserve with MAVA and +DOB](image_url)

**Diagram Legend**
- PRE
- CTRL (+DOB)
- MAVA (+DOB)

**Statistical Significance**
- *: P < 0.05 vs. CTRL

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Healthy beagle dogs dosed (oral gavage) once daily for up to 9M (39 weeks)

- **Vehicle** (VEH, n = 12)
- **MAVA** (n = 12): **LOW** and **SUPRA** (supra-therapeutic)
  - 0.18 mg/kg/day and either 0.3 (n = 6, males) or 0.45 mg/kg/day (n = 6, females).

- Echocardiograms taken prior (baseline), during (weeks 11 and 37),
  - Systolic/diastolic function and cardiac geometry
  - NT-proBNP levels
Exp. C: MAVA Preserves NT-proBNP, LAd, and E/e’ (chronic, healthy dogs)

**CHRONIC, mavacamten:**

- Sustained ↓EF and ↑EDV (unchanged NT-proBNP)

- Preserved LA dimensions and LV diastolic function
  - Preserved IVRT and E/A ratio

![Graph showing EF, EDV, NT-proBNP, HR, EF, EDV, LAd, E/e’ changes](image-url)
Conclusion

• MAVACAMTEN is a novel sarcomere-targeted modulator characterized by:
  - Negative inotropy
  - Improved myocardial compliance/distensibility (unlike metoprolol)
  - Preserved β-AR functional recruitment (enhanced lusitropic recruitment)

- Potential therapeutic advantage over beta-blockers
- Mechanistic support for the salutary observations in HCM

Direct myosin modulation with mavacamten in healthy animals has a unique in vivo hemodynamic profile characterized by negative inotropy with improved compliance
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- Mavacamten (MYK-461)

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