PIONEER-HCM: A Phase 2 study of Mavacamten (formerly MYK-461) in Symptomatic Obstructive Hypertrophic Cardiomyopathy Patients

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HFSA 2017
Hypertrophic Cardiomyopathy (HCM)

- HCM is the most common monogenic disease of the myocardium
- HCM is characterized by excessive myocardial contractility, left ventricular hypertrophy and reduced compliance
- Obstructive HCM occurs as a result of asymmetric LVH, abnormal MV and sub-valvular apparatus, and resultant SAM-septal contact
- Earlier onset of severe HF symptoms and/or death vs. non-obstructive HCM
- Medical management is limited to drugs (e.g. beta-blockers) or invasive procedures
- Invasive interventions are associated with significant morbidity & mortality

Mavacamten (formerly MYK-461)

- **Mavacamten**
  - Oral small molecule
  - Selective allosteric modulator of cardiac myosin ATPase
  - In HCM mutant mice, mavacamten prevented hypertrophy, reduced myocyte disarray & interstitial fibrosis compared with placebo

- **Phase 1 studies:**
  - Dose-dependent reduction in cardiac contractility in volunteers & patients
  - Favorable safety profile observed across a number of doses
  - One SAE observed (vasovagal); all other AEs mild to moderate

Mavacamten, a modulator of cardiac myosin, reduces LVOT gradient in symptomatic obstructive HCM patients
Key Inclusion and Exclusion Criteria &
Statistical Plan for Cohort A

Key Inclusion Criteria

- 18-70 years old with symptomatic (NYHA functional class ≥ II) HCM
- LVOT gradient ≥ 30 mmHg (resting) and ≥ 50 mm Hg (post-exercise peak LVOT gradient)
- LVEF ≥ 55%
- Patients discontinued beta-blockers, CCB and disopyramide >14 days prior to screening

Key Exclusion Criteria

- History of syncope with exercise within the past 6 months
- History of VT or persistent atrial fibrillation or atrial fibrillation at screening
- History of obstructive coronary artery disease

Statistical Analysis Plan

- Within patient change from baseline to week 12 were evaluated using Wilcoxon Signed Rank test against null hypothesis of zero change
PIONEER-HCM: Cohort A Study Design

Screening

Mavacamten

Washout

starting daily dose

adjusted daily dose

< 60 kg: 10mg

≥ 60 kg: 15mg

Increase by 5mg or 10 mg

No change

Decrease by 5mg

Dose Adjustment (based on LVEF at W4)

<table>
<thead>
<tr>
<th></th>
<th>Scr</th>
<th>D1</th>
<th>W1</th>
<th>W2</th>
<th>W3</th>
<th>W4</th>
<th>W5</th>
<th>W6</th>
<th>W7</th>
<th>W8</th>
<th>W12</th>
<th>W16</th>
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<td></td>
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<tr>
<td>Rest echo</td>
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</tbody>
</table>

W = Week; D = day; Scr = Screening
PIONEER–HCM Trial Endpoints

**Primary Endpoint:**
- Change in post-exercise peak LVOT gradient from baseline to Week 12

**Key Secondary & Exploratory Endpoints:**
- Proportion of patients achieving post-exercise peak gradient <30 mmHg at Week 12
- Change from Week 12 to Week 16 in post-exercise peak LVOT gradient
- Change in LVEF from baseline to Week 12
- Change in dyspnea symptom score from baseline to Week 12
- Change in pVO2 and VE/VCO2 from baseline to Week 12
- Change in NYHA Class from baseline to Week 12
- Change in N-terminal pro B-type natriuretic peptide (NT-proBNP) from baseline to Week 12
### Baseline Characteristics in PIONEER (Part A)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tr>
<td>Number of patients</td>
<td>N = 11</td>
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<tr>
<td>Number of sites</td>
<td>5</td>
</tr>
<tr>
<td>Age, yrs; mean (min-max)</td>
<td>56 (22-70)</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>64</td>
</tr>
<tr>
<td>NYHA Class, %</td>
<td>64% Class II</td>
</tr>
<tr>
<td></td>
<td>36% Class III</td>
</tr>
<tr>
<td>Hx of Paroxysmal Atrial Fib</td>
<td>N = 1</td>
</tr>
<tr>
<td>Hx of Septal Myectomy</td>
<td>N = 1</td>
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<tr>
<td>Previous β Blocker Therapy</td>
<td>N = 9</td>
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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Resting LVEF, % mean ± SD</td>
<td>70 ± 7</td>
</tr>
<tr>
<td>Exercise LVEF, % mean ± SD</td>
<td>76 ± 8</td>
</tr>
<tr>
<td>Resting LVOT Gradient, mmHg mean ± SD</td>
<td>68 ± 34</td>
</tr>
<tr>
<td>Exercise LVOT Gradient, mmHg mean ± SD</td>
<td>125 ± 60</td>
</tr>
<tr>
<td>Peak VO₂, mL/kg/min mean ± SD</td>
<td>20.7 ± 7.4</td>
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</tbody>
</table>
Primary Endpoint:
Rapid Reduction in Post-Exercise LVOT Gradient

* p=0.002 vs baseline
† N<11 due to pt who terminated study early or missing data
Primary Endpoint:
Rapid Reduction in Post-Exercise LVOT Gradient

- Post-Exercise LVOT Gradient, mmHg

* $p=0.002$ vs baseline

† $N<11$ due to pt who terminated study early or missing data

HFSA 2017
Concordant Change in Resting LVOT Gradient and EF

W = week  † N<11 due to pt who terminated study early or missing data
### Significant Improvement in Peak VO$_2$ by Week 12

**Additional CPET Parameters**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 12</th>
<th>Change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE/VCO$_2$</td>
<td>32.2 ± 5.44</td>
<td>30.3 ± 6.10</td>
<td>-2.19 ± 5.46</td>
<td>0.164</td>
</tr>
<tr>
<td>Circulatory Power</td>
<td>3276 ± 1535</td>
<td>4400 ± 2040</td>
<td>1075 ± 932</td>
<td>0.0098</td>
</tr>
</tbody>
</table>

† N<11 due to pt who terminated study early

![Graph showing Significant Improvement in Peak VO$_2$](image-url)
Rapid Improvement in Dyspnea Over Time

Dyspnea NRS Improvement

Baseline W1 W2 W3 W4 W5† W6† W7† W8 W12† W16†

Mean Median

W = week

*p=0.002 vs baseline
† N<11 due to pt who terminated study early or missing data

Mean

Median

W = week

Washout Period

Rapid Improvement in Dyspnea Over Time

Mean

Median

W = week

Washout Period

*p=0.002 vs baseline
† N<11 due to pt who terminated study early or missing data

Mean

Median

W = week

Washout Period
Improvement in NYHA Functional Class

Mean change -0.9 ± 0.7 W12 vs baseline; p=0.016
• 5 subjects with 1 class improvement
• 2 subjects with 2 class improvement

† N<11 due to pt who terminated study early or missing data
Change in NT-proBNP

* $p=0.08$

† $N<11$ due to pt who terminated study early or missing data
Safety Events

- Most AEs were mild (77%) to moderate (21%)
- Most AEs were unrelated to mavacamten (64%)
- One SAE
  - Hx of paroxysmal AF
  - Withdrawal of β blocker and disopyramide to participate in the study
  - Pt cardioverted, but AF (2nd AE) recurred requiring hospitalization and anti-arrhythmic therapy
  - Pt elected to stop study drug at week 4
- No increase in hs-troponin
- Independent Data Monitoring Committee found no safety concerns

## Non-Serious Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th># of events</th>
<th># assessed related to study drug</th>
<th># of patients</th>
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<tbody>
<tr>
<td>Headache</td>
<td>4</td>
<td>1</td>
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<tr>
<td>LVEF Reduction</td>
<td>3</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Nausea</td>
<td>3</td>
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<tr>
<td>Atrial Fibrillation</td>
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<tr>
<td>Dizziness</td>
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<tr>
<td>Dyspnea Exertional</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Peripheral Edema</td>
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<tr>
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URTI = upper respiratory tract infection; UTI = urinary tract infection;
Summary

- All patients had a reduction in post-exercise LVOT gradient
  - All 10 achieved ≤ 50 mmHg; 8 of 10 patients ≤ 30 mmHg
- All patients had a rapid reduction in resting LVOT gradient by week 2
- Peak VO2, NYHA class, dyspnea NRS and NT-pro BNP improved with mavacamten treatment
- Reversibility of mavacamten treatment effect was observed during washout period (Week 12 to Week 16)
- Most adverse events were mild to moderate & unrelated to mavacamten
Conclusion

Mavacamten reduced post-exercise LVOT gradient to below hemodynamic significance in symptomatic oHCM

Global Phase 3 Trial Currently Being Planned (EXPLORER-HCM)
Acknowledgements

Thank you to all the patients, caregivers, investigators & sites teams.

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• Andrew Wang, MD - Duke University Medical Center
• Richard Bach, MD - Washington University
• Marty Maron, MD - Tufts Medical Center
• MyoKardia Team
Back-up slides
## Studies Using Peak VO2 as an Endpoint

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>n</th>
<th>Intervention</th>
<th>Change in peak VO$_2$ mL/kg/min</th>
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<tbody>
<tr>
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<td>24</td>
<td>Myectomy</td>
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<td>BiV Pacing</td>
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