Efficacy and Safety of Ninerafaxstat, a Novel Cardiac Mitotrope, in Patients with Symptomatic Nonobstructive Hypertrophic Cardiomyopathy

(Results of IMPROVE-HCM)

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The *Unmet* Treatment Need in *Nonobstructive* HCM

- **Nonobstructive HCM** (<30 mmHg at rest/exercise)
- **50% NYHA Class II-III**
- **10% End-Stage HF**

- **Beta-Blocker**
- **Calcium Channel Blocker**
- **Heart Transplant**

Unmet Treatment Need
Diastolic Dysfunction in Nonobstructive HCM

LV Relaxation:
- LV Hypertrophy
- Myocardial Ischemia

Heavily Energy Dependent

Altered LV Diastolic Filling/Low Stroke Vol

LV Distensibility:
- LV Hypertrophy
- Disarray
- Interstitial Fibrosis
- Replacement Scar

Limiting Symptoms and Decreased Exercise Capacity
Energy Deficiency is a Primary Consequence of HCM Disease Expression

Energetic Cost of Contraction/Relaxation

PCr/ATP Ratio

Microvascular Ischemia

Exacerbates Primary Energy Deficiency
Energy Deficiency is a Primary Consequence of HCM Disease Expression

For these reasons...

Myocardial Energetics Represent an Attractive Therapeutic Target

**Mitotropes** = Drugs that influence myocardial energetics
Ninerafaxstat is a Mitotrope that Influences Cardiac Energetics

Ninerafaxstat

niacin

trimetazidine (TMZ)

IMB-102

carboxy-8814

Approved in some countries for treatment of angina since 1970s & in current ESC treatment guidelines (Class 2a recommendation)
Ninerafaxstat is a Mitotrope that Influences Cardiac Energetics

Partial Inhibition of Fatty Acid Oxidation
No Drug Monitoring
No Hemodynamic Effect
Ninerafaxstat: Mechanism of Action
Optimizes Efficiency of ATP Generation to Enhance Cardiac Function

- Partial inhibition of mitochondrial fatty acid oxidation
- Shift of cardiac metabolism from using fatty acids towards glucose
- Recoupling glycolysis and glucose oxidation
- ↑ Efficiency of ATP production per molecule of O₂
**IMPROVE-HCM - Key Inclusion Criteria and Endpoints**

### Study Design and Endpoints

- Randomized and blinded prospective trial for 12 weeks
- Orally administered ninerafaxstat 200 mg MR BID vs. Placebo
- Evaluating:
  - Safety and Tolerability
  - CPET Measures (pVO$_2$ and $V_E/VCO_2$)
  - KCCQ-CSS
  - Echocardiographic Variables
  - NT-proBNP

### Key Inclusion Criteria

- 18-80 years old
- LV wall thickness of $\geq 15$ mm
- LV Outflow Tract Gradient $< 30$ mmHg at rest and with exercise
- Baseline LVEF $\geq 50$
- CPET:
  - pVO$_2$ $\leq 80\%$ predicted for age & gender
  - RER $\geq 1.05$
IMPROVE-HCM - Clinical Trial Design

Ninerafaxstat MR 200mg bid + SoC

Placebo + SoC

Study Visits
- Screen
  - Consent
  - CPET
  - ECHO
  - Labs
- Baseline
  - KCCQ-23
  - NYHA Class
  - Biomarkers
- Week 6
  - KCCQ-23
  - NYHA Class
  - Biomarkers
  - ECHO
- Week 12
  - KCCQ-23
  - NYHA Class
  - CPET
  - ECHO
  - Biomarkers
  - Labs
- Week 14
- Safety
- Follow-up visit

End of Study
## IMPROVE-HCM – Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 33)</th>
<th>Ninerafaxstat (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Years), Mean (SD)</strong></td>
<td>56 (13)</td>
<td>58 (11)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>16 (48)</td>
<td>14 (41)</td>
</tr>
<tr>
<td><strong>NYHA Functional Class, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>20 (61)</td>
<td>20 (59)</td>
</tr>
<tr>
<td>Class III</td>
<td>12 (36)</td>
<td>12 (35)</td>
</tr>
<tr>
<td><strong>Maximal LV Wall Thickness (mm), Mean (SD)</strong></td>
<td>17 (4)</td>
<td>17 (3)</td>
</tr>
<tr>
<td><strong>LVEF (%), Mean (SD)</strong></td>
<td>68 (4)</td>
<td>63 (5)</td>
</tr>
<tr>
<td><strong>LA Diameter (mmHg), Mean (SD)</strong></td>
<td>36 (5)</td>
<td>43 (7)</td>
</tr>
<tr>
<td><strong>pVO2 (mL/kg/min), Mean (SD)</strong></td>
<td>20 (4)</td>
<td>18 (4)</td>
</tr>
<tr>
<td><strong>pVO2 % predicted age and gender, % (SD)</strong></td>
<td>62 (11)</td>
<td>59 (9)</td>
</tr>
<tr>
<td><strong>Ve/VCO2, Mean (SD)</strong></td>
<td>33 (5)</td>
<td>31 (4)</td>
</tr>
<tr>
<td><strong>NT-proBNP (pg/mL), Mean (SD)</strong></td>
<td>712 (1150)</td>
<td>606 (634)</td>
</tr>
</tbody>
</table>
**IMPROVE-HCM – Ninerafaxstat was well tolerated**

- **Treatment Emergent Serious Adverse Events**
  - Placebo: 2 patients (6%)
    - Sepsis; hypoxia (post CPET)
  - Ninerafaxstat: 4 patients (11%)
    - COVID pneumonia; CABG; pyelonephritis; abdominal abscess

- **≥1 Treatment-emergent adverse event**
  - Placebo: 20 patients (61%)
  - Ninerafaxstat: 24 patients (71%)

- **Most TEAE were mild to moderate**

- **Ninerafaxstat was associated with no significant change in LV EF, blood pressure or heart rate at Week 12**
Efficacy of Ninerafaxstat on Heart Failure Symptom Burden by KCCQ-CSS (ITT Population)

LS mean difference = 3.2 (-2.9, 9.2)
P value = 0.2
Efficacy of Ninerafaxstat on Heart Failure Symptom Burden by KCCQ-CSS (Patients Limited at Baseline)

≤80 KCCQ-CSS at Baseline

- Ninerafaxstat: N=18
- Placebo: N=17

LS mean difference = 9.4 (0.3, 18.5)
P=value = 0.04

≥5 Point Change in KCCQ: Clinically Meaningful

NYHA Class III at Baseline

- Ninerafaxstat: N=12
- Placebo: N=11

LS mean difference = 13.6 (1.4, 25.9)
P=value = 0.03
Efficacy of Ninerafaxstat on Exercise Capacity by $V_E/VCO_2$

(ITT Population)

LS mean difference = -2.1 (-3.6, -0.6)
P value = 0.005

$\geq 1$ Unit $V_E/VCO_2$ Slope
Associated with Risk
Death/Transplant

Placebo Corrected
Decrease
Of 2 Units in
$V_E/VCO_2$:
Clinically Meaningful Improvement

Ninerafaxstat
N=29

Placebo
N=30

Ninerafaxstat
BL  Week 12
Placebo
BL  Week 12

LS mean difference = -2.1 (-3.6, -0.6)
P value = 0.005
Efficacy of Ninerafaxstat on Exercise Capacity by $V_E/VCO_2$
(Patients Limited at Baseline)

$\leq 80$ KCCQ-CSS at Baseline

NYHA Class III at Baseline

Week 12

BL

20 30 40 50

LS mean difference = -2.1 (-3.8, -0.3)
P value = 0.02

$V_E/VCO_2$
(Baseline $\leq 80$)

Ninerafaxstat
N=18

Placebo
N=16

Ninerafaxstat
N=11

Placebo
N=11

Week 12

BL

20 30 40 50

LS mean difference = -3.0 (-4.9, -1.0)
P value = 0.004

$V_E/VCO_2$
(NYHA Class III at Baseline)
# IMPROVE-HCM – pVO$_2$, Key Echo Parameters and Biomarkers

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ninerafaxstat (N=34)</th>
<th>Placebo (N=33)</th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Change from baseline</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>pVO$_2$ (ml/kg/min)</strong></td>
<td>29 (85.3)</td>
<td>0.013 ± 2.03</td>
<td>30 (90.9)</td>
</tr>
<tr>
<td><strong>LA Size (mm)</strong></td>
<td>27 (79)</td>
<td>-0.09 ± 0.29</td>
<td>32 (97%)</td>
</tr>
<tr>
<td><strong>Average E/e’</strong></td>
<td>27 (79.4)</td>
<td>0.27 ±3.4</td>
<td>31 (93.9)</td>
</tr>
<tr>
<td><strong>Median NT-proBNP</strong> (ng/L) (min, max)</td>
<td>29 (85.3)</td>
<td>342 (54, 6123)</td>
<td></td>
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</table>
Conclusions

- In this Phase 2 proof-of-concept study, ninerafaxstat, a novel investigational cardiac mitotrope, was safe and well tolerated in nonobstructive HCM.

- Treatment with ninerafaxstat was associated with significant improvement in functional capacity measured by $V_E/VCO_2$, an important and prognostic submaximal CPET variable in HCM.

- In those nonobstructive HCM patients limited at baseline, ninerafaxstat significantly improved limiting symptoms with favorable change in KCCQ-CCS score.

- These results support progression to larger Phase 3 study in symptomatic nonobstructive HCM to investigate if targeted therapy at optimizing cardiac energetics may fulfill an important unmet treatment need in this disease.