Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): Results from a Double-blind, Randomized, Placebo-controlled, Multicenter Study

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Omecamtiv Mecarbil (OM) is a Novel Selective Cardiac Myosin Activator

Mechanochemical Cycle of Myosin

OM increases the entry rate of myosin into the tightly-bound, force-producing state with actin

“More hands pulling on the rope”

- Increases duration of systole
- Increases stroke volume
- No increase in myocyte calcium
- No change in dP/dt\(_{\text{max}}\)
- No increase in MVO\(_2\)

OM-induced Increases in Systolic Ejection Time (SET) Underlie the Improvements in Cardiac Function

Healthy Volunteers vs. Stable HF Patients

Δ Stroke Volume (mL)

Δ Fractional Shortening (% points)

Δ Ejection Fraction (% points)

Δ = placebo corrected change from baseline
Mean ± SEM


SEM, standard error of the mean

Δ SET (msec)
COSMIC-HF
Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure

• Primary Objectives
  – To select an oral modified release formulation and dose for chronic twice daily (BID) dosing in patients with HFrEF (Escalation Phase)
  – To characterize pharmacokinetics (PK) over 20 weeks of treatment with selected formulation (Expansion Phase)

• Secondary Objectives
  – To evaluate the safety and tolerability of the oral formulation
  – To measure changes in SET, stroke volume, left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), and heart rate (HR) over 20 weeks of oral dosing
  – To evaluate the effect over 20 weeks of oral dosing on N-terminal pro-B-type natriuretic peptide (NT-proBNP)
Study Design

**Escalation Phase**
Select a modified-release formulation and dose(s)
Dosing for 7 days
Intensive PK
~40 patients/cohort

**Cohort 1**
(3 formulations)
- Matrix-F₁
  - 25 mg BID
- Matrix-F₂
  - 25 mg BID
- SCT-F₂
  - 25 mg BID
- Placebo

**Cohort 2**
(3 formulations)
- Matrix-F₁
  - 50 mg BID
- Matrix-F₂
  - 50 mg BID
- SCT-F₂
  - 50 mg BID
- Placebo

**Expansion Phase**
Evaluate a PK-based titration regimen vs placebo
Dosing for 20 weeks
Echocardiograms
~450 patients

**Expansion Cohort**
(1 formulation)
- Matrix-F₁
  - 25 mg BID
- Matrix-F₁
  - 25 mg then 50 mg BID
- Placebo

BID, twice a day
Expansion Phase

- Randomization 1:1:1
- Placebo (n = 149)
- 25 mg BID (n = 150)
- 25 mg BID → 50 mg BID (PK-titration; n = 149)
- Dose adjustment
- End of IP Administration
- End of Study Visit

Study drug administration

Dose escalation from 25 mg BID to 50 mg BID based on OM trough concentration at Week 2
Titration was blinded

PK sampling

Echo

↑ Intensive PK sampling
Echo, echocardiographic parameters; IP, investigational product
Key Inclusion and Exclusion Criteria

**Key Inclusion Criteria**
- $\geq 18$ and $\leq 85$ years of age
- History of chronic HF
- Treated with stable, optimal heart failure therapy
- NYHA class II or III
- LVEF $\leq 40\%$
- NT-proBNP $\geq 200$ pg/mL ($\geq 1200$ pg/mL if AFib at screening)

**Key Exclusion Criteria**
- NYHA class IV
- Severe uncorrected valvular heart disease
- Acute MI, unstable angina, or persistent angina at rest within 30 days prior to randomization
- Systolic BP $> 160$ mmHg or $< 90$ mmHg, or diastolic BP $> 90$ mmHg, or HR $> 110$ bpm or HR $< 50$ bpm at screening
- eGFR $< 30$ mL/min/1.73 m$^2$ at screening

AFib, Atrial fibrillation; BP, blood pressure; bpm, beats per minute; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association
# Key Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>448 Patients Enrolled</th>
<th>Placebo (n = 149)</th>
<th>OM 25 mg BID (n = 150)</th>
<th>All PK Titration (n = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>64 (10)</td>
<td>63 (10)</td>
<td>63 (12)</td>
</tr>
<tr>
<td>Male, %</td>
<td>80</td>
<td>85</td>
<td>84</td>
</tr>
<tr>
<td>White, %</td>
<td>91</td>
<td>95</td>
<td>94</td>
</tr>
<tr>
<td><strong>Disease characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease, %</td>
<td>60</td>
<td>65</td>
<td>67</td>
</tr>
<tr>
<td>LVEF (%), mean (SD)</td>
<td>29 (7)</td>
<td>29 (8)</td>
<td>29 (7)</td>
</tr>
<tr>
<td>NYHA class II, %</td>
<td>70</td>
<td>68</td>
<td>72</td>
</tr>
<tr>
<td>NYHA class III, %</td>
<td>30</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>Persistent atrial fibrillation or flutter, %</td>
<td>22</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>41</td>
<td>47</td>
<td>37</td>
</tr>
</tbody>
</table>

SD, standard deviation
# Key Baseline Concomitant Medications and Lab Values

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 149)</th>
<th>OM 25 mg BID (n = 150)</th>
<th>All PK Titration (n = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troponin I (ng/mL), median (Q1, Q3)</td>
<td>0.025 (0.016, 0.041)</td>
<td>0.022 (0.016, 0.039)</td>
<td>0.022 (0.016, 0.042)</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL), median (Q1, Q3)</td>
<td>1719 (699, 3242)</td>
<td>1538 (634, 3427)</td>
<td>1719 (881, 3060)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²), mean (SD)</td>
<td>65 (19)</td>
<td>63 (19)</td>
<td>65 (19)</td>
</tr>
<tr>
<td><strong>Concomitant medications, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>71</td>
<td>69</td>
<td>65</td>
</tr>
<tr>
<td>ARBs</td>
<td>24</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>98</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>MRAs</td>
<td>59</td>
<td>58</td>
<td>63</td>
</tr>
<tr>
<td>Diuretics other than MRAs</td>
<td>84</td>
<td>85</td>
<td>90</td>
</tr>
</tbody>
</table>
### Preliminary PK Results

<table>
<thead>
<tr>
<th>Week 12</th>
<th>25 mg OM (n = 146)</th>
<th>PK-titration 25 mg OM (n = 58)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PK-titration 25 to 50 mg OM (n = 78)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>All PK-Titration (n = 141)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{predose}}$, mean (SD), ng/mL</td>
<td>160 (72)</td>
<td>221 (87)</td>
<td>289 (126)</td>
<td>261 (116)</td>
</tr>
<tr>
<td>$C_{\text{max}}$, mean (SD), ng/mL</td>
<td>197 (75)</td>
<td>258 (85)</td>
<td>359 (137)</td>
<td>317 (141)</td>
</tr>
</tbody>
</table>

- The maximum concentration was 453 ng/mL and 812 ng/mL for the 25 mg BID and the PK-titration groups, respectively.

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<sup>a</sup> includes data from only those subjects with available PK data

$C_{\text{predose}}$, concentration prior to OM administration; $C_{\text{max}}$, maximum observed concentration
LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; SE, standard error; SET, systolic ejection time
Efficacy of OM

LS Mean (SE) Change (mm)

**LVESD**

- Placebo 25 mg
- 25 mg (no titration)
- 25 → 50 mg
- All PK Titration

p = 0.173

LS Mean (SE) Change (mL)

**LVESV**

- Placebo 25 mg
- 25 mg (no titration)
- 25 → 50 mg
- All PK Titration

p = 0.019

p = 0.003

p = 0.005

LS Mean (SE) Change (mm)

**LVEDD**

- Placebo 25 mg
- 25 mg (no titration)
- 25 → 50 mg
- All PK Titration

p = 0.190

p = 0.013

LS Mean (SE) Change (mL)

**LVEDV**

- Placebo 25 mg
- 25 mg (no titration)
- 25 → 50 mg
- All PK Titration

p = 0.062

p = 0.021

p = 0.003

LS Mean (SE) Change (mL)

**LVESV**

- Placebo 25 mg
- 25 mg (no titration)
- 25 → 50 mg
- All PK Titration

p = 0.019

p = 0.003

p = 0.005

LVESD left ventricular end systolic diameter, LVEDD left ventricular end diastolic diameter, LVESV left ventricular end systolic volume, LVEDV left ventricular end diastolic volume.
NT-proBNP, N-terminal of the prohormone brain natriuretic peptide
## Cardiac Troponin I

<table>
<thead>
<tr>
<th>Troponin I (ng/mL)</th>
<th>Placebo (n = 149)</th>
<th>25 mg (n = 150)</th>
<th>25 mg (n = 58)</th>
<th>50 mg (n = 78)</th>
<th>PK-guided titration arm (n = 146)</th>
<th>All PK Titration (n = 146)</th>
<th>Pooled OM (n = 296)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.025</td>
<td>0.022</td>
<td>0.024</td>
<td>0.021</td>
<td>0.025</td>
<td>0.025</td>
<td>0.022</td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>0.016, 0.041</td>
<td>0.016, 0.039</td>
<td>0.016, 0.034</td>
<td>0.016, 0.046</td>
<td>0.016, 0.042</td>
<td>0.016, 0.040</td>
<td></td>
</tr>
<tr>
<td><strong>Change to Week 20</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.000</td>
<td>0.001</td>
<td>0.006</td>
<td>0.007</td>
<td>0.006</td>
<td>0.006</td>
<td>0.004</td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>-0.007, 0.004</td>
<td>0.000, 0.012</td>
<td>0.000, 0.022</td>
<td>0.000, 0.024</td>
<td>0.000, 0.024</td>
<td>0.000, 0.019</td>
<td></td>
</tr>
<tr>
<td><strong>Change to Week 24</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.000</td>
<td>0.000</td>
<td>0.001</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>-0.006, 0.008</td>
<td>-0.002, 0.009</td>
<td>-0.002, 0.016</td>
<td>-0.005, 0.005</td>
<td>-0.003, 0.010</td>
<td>-0.003, 0.009</td>
<td></td>
</tr>
</tbody>
</table>

Number of increased troponin events adjudicated by CEC for MI = 0/278

- cTnI > 0.04 ng/mL (99%URL) when prior undetectable OR
- cTnI > 0.03 ng/mL (10%CoV) greater than prior when prior detectable

*a Excludes 3 patients that were not dosed*
## Adjudicated Clinical Events

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Placebo (n = 149)</th>
<th>25 mg (n = 150)</th>
<th>25 mg (n = 58)</th>
<th>50 mg (n = 78)</th>
<th>All PK Titration (n = 146)</th>
<th>Pooled OM (n = 296)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospitalization</strong></td>
<td>24 (16)</td>
<td>24 (16)</td>
<td>10 (17)</td>
<td>11 (14)</td>
<td>26 (18)</td>
<td>50 (17)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>11 (7)</td>
<td>9 (6)</td>
<td>4 (7)</td>
<td>5 (6)</td>
<td>10 (7)</td>
<td>19 (6)</td>
</tr>
<tr>
<td>MI</td>
<td>1 (1)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (1)</td>
<td>1 (&lt; 1)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>-</td>
<td>1 (1)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (&lt; 1)</td>
</tr>
<tr>
<td>Chest pain (non-MI/UA)</td>
<td>1 (1)</td>
<td>2 (1)</td>
<td>2 (3)</td>
<td>-</td>
<td>2 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Other categories</td>
<td>15 (10)</td>
<td>14 (9)</td>
<td>5 (9)</td>
<td>7 (9)</td>
<td>15 (10)</td>
<td>29 (10)</td>
</tr>
<tr>
<td><strong>MI (nonfatal)</strong></td>
<td>1 (1)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Investigator-reported</td>
<td>1 (1)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CEC-reported</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total MI</td>
<td>2 (1)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (1)</td>
<td>1 (&lt; 1)</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>4 (3)</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>1 (1)</td>
<td>3 (2)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>CV Death</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>1 (1)</td>
<td>2 (1)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

CEC, Clinical Events Classification; MI, myocardial infarction; UA, unstable angina

*a Excludes 3 patients that were not dosed
## Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 149)</th>
<th>25 mg (n = 150)</th>
<th>25 mg (n = 58)</th>
<th>50 mg (n = 78)</th>
<th>All PK Titration (n = 146)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Pooled OM (n = 296)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any AE</strong></td>
<td>91 (61)</td>
<td>92 (61)</td>
<td>35 (60)</td>
<td>53 (68)</td>
<td>95 (65)</td>
<td>187 (63)</td>
</tr>
<tr>
<td><strong>Most-common</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>8 (5)</td>
<td>11 (7)</td>
<td>5 (9)</td>
<td>6 (8)</td>
<td>13 (9)</td>
<td>24 (8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (3)</td>
<td>14 (9)</td>
<td>5 (9)</td>
<td>3 (4)</td>
<td>9 (6)</td>
<td>23 (8)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (4)</td>
<td>8 (5)</td>
<td>5 (9)</td>
<td>4 (5)</td>
<td>10 (7)</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>13 (9)</td>
<td>5 (3)</td>
<td>2 (3)</td>
<td>5 (6)</td>
<td>8 (5)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5 (3)</td>
<td>8 (5)</td>
<td>2 (3)</td>
<td>3 (4)</td>
<td>5 (3)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>Leading to study</td>
<td>12 (8)</td>
<td>8 (5)</td>
<td>5 (9)</td>
<td>1 (1)</td>
<td>12 (8)</td>
<td>20 (7)</td>
</tr>
<tr>
<td>discontinuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SAEs</td>
<td>30 (20)</td>
<td>35 (24)</td>
<td>12 (21)</td>
<td>15 (19)</td>
<td>32 (22)</td>
<td>68 (23)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Excludes 3 patients that were not dosed  
<sup>b</sup> Treatment Emergent Adverse Events Occurring in ≥ 5% of patients
## Cardiac Serious Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 149)</th>
<th>25 mg (n = 150)</th>
<th>25 mg (n = 58)</th>
<th>50 mg (n = 78)</th>
<th>All PK Titration (n = 146)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Pooled OM (n = 296)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac SAEs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>19 (13)</td>
<td>18 (12)</td>
<td>7 (12)</td>
<td>7 (9)</td>
<td>17 (12)</td>
<td>35 (12)</td>
</tr>
<tr>
<td>Cardiac failure acute</td>
<td>4 (3)</td>
<td>3 (2)</td>
<td>1 (2)</td>
<td>3 (4)</td>
<td>5 (3)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Cardiac failure congestive</td>
<td>1 (1)</td>
<td>3 (2)</td>
<td>1 (2)</td>
<td>2 (3)</td>
<td>3 (2)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>-</td>
<td>3 (2)</td>
<td>1 (2)</td>
<td>-</td>
<td>1 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>1 (1)</td>
<td>2 (1)</td>
<td>1 (2)</td>
<td>-</td>
<td>1 (1)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Excludes 3 patients that were not dosed
Conclusions

• Pharmacokinetics
  – The pharmacokinetic-based dose titration reliably controlled patient exposure to omecamtiv mecarbil in the PK-titration group

• Efficacy
  – Improvements in SET, stroke volume, and LVEF
  – Decreases in cardiac dimensions and volumes
  – Decreases in HR and NT-proBNP

• Safety
  – Overall SAE profile and tolerability similar to placebo
  – Small increase in troponin I without imbalance in cardiac adverse events

• Perspective
  – Magnitude of cardiac effects observed in this trial may potentially translate into improvements in clinical outcomes
Committees

**Executive Committee:** John R. Teerlink (Chair), Michael Felker, John JV McMurray, Scott D. Solomon.

**Data Monitoring Committee:** Marvin A. Konstam (Chair), Javed Butler, Henry John Dargie, Barry Greenberg, James L. Januzzi, Jr., Julie A. Johnson, Joseph Massaro.

**Clinical Events Committee:** G. Michael Felker (Chair), Mark P. Donahue, Zubin J. Eapen, Adrian F. Hernandez, Robert J. Mentz.

**National Leaders:** Kirkwood Adams (USA), John Cleland (United Kingdom), Justin Ezekowitz (Canada), Assen Goudev (Bulgaria), Peter McDonald (Australia), Marco Metra (Italy), Veselin Mitrovic (Germany), Piotr Ponikowski (Poland), Jindrich Spinar (Czech Republic), Janos Tomcsanyi (Hungary), Hans Vanderckhove (Belgium), Adriaan Voors (Netherlands).