New inotropes in the management of acute heart failure

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Disclosure

VM has received consultancy fees/honoraria from Bayer HealthCare AG, Novartis, and CardioPep Pharma GmbH.
Impact of Acute Heart Failure

In-hospital

Within 60 days of admission

30-50% dead or rehospitalised

4-6% mortality

1 year

20-30% mortality

50% mortality

1 year

5 years

70% mortality

10 years

2. Dickenstein et al/ Eur Heart J 2008; 29:2388-442
3. Chen et al. JAMA 2011;306:1669-78
Plus ça change, plus c’est la même chose

MEDICAL INTELLIGENCE

CURRENT CONCEPTS
Cardiac Decompensation

ALBERTO RAMÍREZ, M.D., AND WALTER H. ABELMANN, M.D.

- Morphine
- Oxygen (NIV)
- Loop diuretic
  - (Turniquet/phlebotomy)
- Inotropes
  - (Digitalis/aminophylline/Isoproterenol)
- Nitroglycerin/nitroprusside phentolamine
- Cardioversion/pacing/IABP
<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>Symptoms</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPTIME-CHF</td>
<td>Milrinone</td>
<td>-</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>PDE-III Inh.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=951</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVEREST</td>
<td>Tolvaptan</td>
<td>+</td>
<td>Neutral</td>
</tr>
<tr>
<td></td>
<td>Vasop. V$_2$-Ant.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=4.133</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VERITAS</td>
<td>Tezosentan</td>
<td>-</td>
<td>Neutral</td>
</tr>
<tr>
<td></td>
<td>Endothelin-Ant.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=1.448</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SURVIVE</td>
<td>Levosimendan</td>
<td>-</td>
<td>Neutral</td>
</tr>
<tr>
<td></td>
<td>Ca$^{2+}$ Sensitizer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=1.327</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROTECT</td>
<td>Rolofylline</td>
<td>-</td>
<td>Neutral</td>
</tr>
<tr>
<td></td>
<td>Adenosine A$_1$-Ant.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=2.033</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCEND-HF</td>
<td>Nesiritide</td>
<td>-</td>
<td>Neutral</td>
</tr>
<tr>
<td></td>
<td>Natr. Pept. BNP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=7.141</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatment of acute heart failure
Well almost an evidence free zone
### Summary of guidelines (treatment)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>ESC</th>
<th>ACC/AHA</th>
<th>Canadian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>I C</td>
<td>I C</td>
<td>-</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>I B</td>
<td>I B</td>
<td>I B</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>I B</td>
<td>IIa C</td>
<td>I B</td>
</tr>
<tr>
<td>Non-invasive ventilation</td>
<td>IIa B</td>
<td>-</td>
<td>IIa B</td>
</tr>
<tr>
<td>Inotropes</td>
<td>IIa B</td>
<td>I C/IIb C</td>
<td>I B</td>
</tr>
<tr>
<td>Invasive monitoring</td>
<td>IIa B/IIa C</td>
<td>I C/IIa C</td>
<td>I B</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>IIa B</td>
<td>IIa B</td>
<td>None</td>
</tr>
<tr>
<td>Coronary reperfusion</td>
<td>I C</td>
<td>IIa C</td>
<td>None</td>
</tr>
</tbody>
</table>

Not a single evidence-level A recommendation!
**β-receptor dependent inodilators**

Catecholamines *in ADHF*

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**meta analysis**

16 Trials, 474 Pts: Dobutamin, „highly dosed“ - Dopamin

⇒ **Symptoms** ↓ (NYHA $\Delta - 0.7$)

(OR 1.50; 95%CI 0.51–3.92)

⇒ **Lethality** ↑ (OR 50; 95% CI 0.51 – 3.92)

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*Thackray et al: Eur J Heart Failure 2002;4:515-529*
INOTROPES MAY INCREASE MORTALITY IN ACUTE HEART FAILURE

O’Connor et al., Am Heart J 1999
Indirect Mechanism

↑ Calcium

↑ Heart Rate

↓ Blood Pressure

↑ Oxygen Demand

↓ Efficiency

↑ Arrhythmias
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008

Oxygen/NIV
Loop diuretic ± vasodilator
Clinical evaluation

- SBP > 100 mmHg
  - vasodilator
    - (NTG, nitroprusside, nesiritide), levosimendan
- SBP 90-100 mmHg
  - vasodilator and/or inotrope
    - (dobutamine, PDEI, levosimendan)
- SBP < 90 mmHg
  - consider preload correction with fluids inotrope (dopamine)

Good response
stabilize and initiate diuretic, ACEI/ARB, β-blocker

Poor response
inotrope
vasopressor
mechanical support
consider PAC

Dickstein EHJ 2008
New drugs on the horizon

Myosine Activator
(Omecamptiv Mecarbil)

Vasoactive Peptid
(Relaxin)

ECE + NEP-Inhibitors
(Daglutril)

sGC-Modulators
(Cinaciguat, Riociguat)

New Natriuretic Peptides
(Ularitide, Nesiritide, CD-NP)

Na⁺-K⁺ +SERCA-ATPase
Inhibitors
(Istaroxime)

AGE-Breakers
(TRC 4185)

Aldosterone Syntase
Inhibitors
(LCI, FAD 286)

MRA
(BAY 94-8862)
Small Molecules Can Improve Cardiac Function…

Indirect Mechanisms
PKA phosphorylates proteins throughout the myocyte

Intracellular [Ca\(^{2+}\)] increases
But They Compromise Cardiac Performance

Indirect Mechanisms

PKA phosphorylates proteins throughout the myocyte

Intracellular \([\text{Ca}^{2+}]\) increases

- Contractility
- Heart rate
- Blood Pressure
- \(O_2\) Demand
- Efficiency
- Arrhythmias

Dobutamine (\(\beta\)-agonist), Milrinone (PDE3\(_i\))
Potential Advantages of Targeting the Sarcomere

Therapeutic Hypothesis

Directly target the sarcomere
Ø PKA activation
Intracellular [Ca\(^{2+}\)] unchanged
Contractility
Heart rate?
Blood Pressure?
O\(_2\) Demand?
Efficiency?
Arrhythmias?
Effective Drug?
Inotropes

Omecamptiv Mecarbil

and Direct Cardiac Myosin Activation
Postulated Mechanism of Action for Cardiac Myosin Activators

Cardiac myosin activators increase the number of “independent force generators” (myosin heads) interacting with the actin filament.

Chemical and mechanical cycles are linked

Cardiac myosin activators increase the actin-myosin transition rate from weak to strong binding states.

The Sarcomere: The Basic Contractile Unit of Muscle

Omecamtiv Mecarbil a Cardiac Myosin Activator

Omecamtiv Mecarbil Binds to the Mechanochemical Domain of Myosin

Vale and Milligan, Science 2000

Omecamtiv Mecarbil
(MW = 401.43)

Malik et al, 2011
Omecamtiv Mecarbil: Dog Heart Failure Model

Increases Duration but not Velocity of Contraction

Time-dependent Elastance \([E(t)]\)

Dobutamine

Baseline

MVO\(_2\) Increased

Omecamtiv mecarbil

Baseline

MVO\(_2\) Unchanged

Malik et al, 2011
Omecamtiv Mecarbil: Rat Adult Cardiac Myocytes Does Not Alter the Ca^{2+} Transient

Malik et al, 2011
Omecamtiv Mecarbil: Dog Heart Failure Model
Cardiac Function and Hemodynamics

Shen YT, et al. 2010

WT: Wall thickening
FS: Fractional shortening
SET: Systolic ejection time
dP/dt: Rate of pressure change
HR: Heart Rate
MAP: Mean Arterial Pressure
TPR: Total Peripheral Resistance
LAP: Left Atrial Pressure
SV: Stroke Volume
CO: Cardiac Output

Change from Baseline (%)

4 hr

24 hr

Circulation
Heart Failure
Shen YT, et al. 2010
Omecamtiv Mecarbil: Dog Heart Failure Model
Does not Increase Oxygen Consumption

CBF : Coronary Blood Flow
CSO2 : Coronary Sinus Oxygen Content
MVO2 : Myocardial Oxygen Consumption

Shen YT, et al. 2010
Overview of Completed Phase 1-2a Development Program

<table>
<thead>
<tr>
<th>Phase 1 Healthy Volunteers (N = 124)</th>
<th>Phase 2 Heart Failure Subjects (N = 776)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CY 1111</strong>  First in human 6 hr IV (N = 35)</td>
<td><strong>CY 1121</strong>  PK, PD, safety, and tolerability ≤ 72 hr IV (N = 45)</td>
</tr>
<tr>
<td><strong>CY 1011</strong>  Oral bioavailability 1 hr IV, 1 PO dose, fasted/fed (N = 10)</td>
<td><strong>CY 1221</strong>  Safety/tolerability in ischemic cardiomyopathy 20 hr IV followed by 7 d PO (N = 94)</td>
</tr>
<tr>
<td><strong>CY 1013</strong>  Oral drug-drug interaction (CYP 2D6/3A4) 1 PO dose (N = 25)</td>
<td><strong>CY 1124</strong>  PD and Energetics 2 hrs IV (N = 2)</td>
</tr>
<tr>
<td><strong>CY 1015</strong>  Single- and multiple-dose PK ≤ 7 days PO (N = 40)</td>
<td><strong>CY 1021</strong>  MR and IR PK 10 days PO (N = 35)</td>
</tr>
<tr>
<td><strong>CY 1016</strong>  MR and IR PK 1 PO dose (N = 14)</td>
<td>ATOMIC-AHF PK,PD,safety and efficacy in ADHF 48hrs IV (N=600)</td>
</tr>
</tbody>
</table>

600 subjects studied – 569 exposed to omecamtiv mecarbil for up to 3 days IV and 10 days PO
CY 1111
Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenous *Omecamtiv Mecarbil* in Healthy Volunteers

Dose-dependent augmentation of cardiac systolic function with the selective cardiac myosin activator, omecamtiv mecarbil: a first-in-man study

John R Teerlink, Cyril P Clarke, Khalil G Saikali, Jacqueline H Lee, Michael M Chen, Rafael D Escandon, Lyndsey Elliott, Rachel Bee, Mohammad Reza Habibzadeh, Jonathan H Goldman, Nelson B Schiller, Fady I Malik, Andrew A Wolff

*Lancet* 2011; 378: 667–75
Increases in Systolic Ejection Time Underlie Increases in Cardiac Function

$\Delta$ = placebo corrected change from baseline
Mean ± SEM

Δ Stroke Volume (mL)

Δ Fractional Shortening (% points)

Δ Ejection Fraction (% points)

Δ SET (msec)
The effects of the cardiac myosin activator, omecamtiv mecarbil, on cardiac function in systolic heart failure: a double-blind, placebo-controlled, crossover, dose-ranging phase 2 trial


Lancet 2011; 378: 676–83
OM proof of concept study (45 patients)

Study CY 1121: Systolic ejection time
Placebo Corrected Change from Baseline

Δ SET (msec)  
LSM ± SEM

<100  >100-200  >200-300  >300-400  >400-500  >500

[CK-452]  (ng/mL)

p value for correlation < 0.0001

* p < 0.05
** p < 0.01
*** p < 0.001
Study CY 1121: Stroke volume and heart rate
Placebo Corrected Change from Baseline

Δ Stroke Volume (mL)
(Baseline 69 mL)

Δ Heart Rate (bpm)
(Baseline 66 bpm)

p value for correlation < 0.0001

p value for correlation = 0.0003

* p < 0.05  ** p < 0.01  *** p < 0.001
OM proof of concept study (45 patients)

Study CY 1121: LV end systolic volume and end diastolic volume

Placebo Corrected Change from Baseline

Δ LV ESV (mL)  
(Baseline 168 mL)

Δ LV EDV (mL)  
(Baseline 243 mL)

CK-452 [ng/mL]  
<100 >100-200 >200-300 >300-400 >400-500 >500

p value for correlation < 0.0001  
p value for correlation = 0.0005

* p < 0.05  ** p < 0.01  *** p < 0.001
CY 1121: Effect of Omecamtiv Mecarbil in a Subject with Stable Heart Failure

24 hour infusion
Peak [omecamtiv mecarbil] = 378 ng/mL

<table>
<thead>
<tr>
<th></th>
<th>SET (msec)</th>
<th>LVOT SV (mL)</th>
<th>EF (%)</th>
<th>HR (bpm) – supine ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Baseline</td>
<td>Baseline</td>
<td>Baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td>Omecamtiv mecarbil</td>
<td>216</td>
<td>311</td>
<td>23</td>
<td>54</td>
</tr>
<tr>
<td>Placebo</td>
<td>234</td>
<td>225</td>
<td>26</td>
<td>24</td>
</tr>
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CY 1121: Effect of Omecamtiv Mecarbil in a Subject with Stable Heart Failure

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</tr>
<tr>
<td>Omecamtiv mecarbil</td>
<td>216</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>Placebo</td>
<td>234</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>24 hrs</td>
<td>311</td>
<td>54</td>
<td>23</td>
</tr>
<tr>
<td>24 hrs</td>
<td>225</td>
<td>24</td>
<td>18</td>
</tr>
</tbody>
</table>
ATOMIC-AHF

**Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure**
(ClinicalTrials.gov NCT01300013)

- 48 hr infusion of omecamtiv mecarbil vs. placebo
- Ascending dose cohorts (200 pts per cohort)
- Pts admitted for decompensated heart failure with dyspnea; EF≤40%; within 24 hrs of initial i.v. diuretic
OM aktuelle klinische Studie (geplant 600 Pat.)

Study 20100754: Sequential dosing design

Randomized, double-blind, placebo-controlled, sequential cohort trial in subjects with LVSD and hospitalization for AHF

1:1 randomization

Omepram IV: target conc ~115 ng/mL

Placebo IV

1:1 randomization

Omepram IV: target conc ~230 ng/mL

Placebo IV

1:1 randomization

Omepram IV: target conc ~310 ng/mL

Enrollment and Treatment of Low Dose Cohort

Enrollment and Treatment of Medium Dose Cohort

Enrollment and Treatment of High Dose Cohort

DMC data review and recommendation for next dose level

DMC data review and recommendation for next dose level
**Baseline Characteristics (1)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pooled Placebo (N = 303)</th>
<th>Cohort 1 OM (N = 103)</th>
<th>Cohort 2 OM (N = 99)</th>
<th>Cohort 3 OM (N = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>66 (11)</td>
<td>65 (12)</td>
<td>67 (10)</td>
<td>68 (10)</td>
</tr>
<tr>
<td>Gender – male, %</td>
<td>76</td>
<td>76</td>
<td>82</td>
<td>76</td>
</tr>
<tr>
<td>Region, %</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>53</td>
<td>45</td>
<td>56</td>
<td>62</td>
</tr>
<tr>
<td>North America</td>
<td>25</td>
<td>37</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>Australia</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Western Europe</td>
<td>21</td>
<td>18</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Ischaemic heart disease, %</td>
<td>62</td>
<td>62</td>
<td>59</td>
<td>66</td>
</tr>
<tr>
<td>Years from HF diagnosis, mean (SD)</td>
<td>6 (6)</td>
<td>6 (6)</td>
<td>6 (5)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Most recent LVEF (%), mean (SD)</td>
<td>26 (8)</td>
<td>26 (8)</td>
<td>25 (7)</td>
<td>28 (7)</td>
</tr>
<tr>
<td>Persistent Atrial Fibrillation or Flutter, %</td>
<td>33</td>
<td>29</td>
<td>32</td>
<td>36</td>
</tr>
<tr>
<td>Diabetes Mellitus, %</td>
<td>45</td>
<td>49</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>81</td>
<td>84</td>
<td>81</td>
<td>82</td>
</tr>
</tbody>
</table>

*p < 0.05 for a difference in cohorts 1-3 Placebo arms compared to each other*
## Baseline Characteristics (2)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pooled Placebo (N = 303)</th>
<th>Cohort 1 OM (N = 103)</th>
<th>Cohort 2 OM (N = 99)</th>
<th>Cohort 3 OM (N = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg), mean (SD)</td>
<td>119 (18)*</td>
<td>118 (18)</td>
<td>117 (17)</td>
<td>117 (15)</td>
</tr>
<tr>
<td>Heart rate (beats/min), mean (SD)</td>
<td>78 (13)</td>
<td>78 (13)</td>
<td>79 (13)</td>
<td>78 (14)</td>
</tr>
<tr>
<td>Dyspnoea Numerical Rating Scale (NRS), Mean (SD)</td>
<td>6 (2)</td>
<td>6 (2)</td>
<td>6 (2)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>ACE inhibitors/Angiotensin Receptor Blockers, %</td>
<td>78</td>
<td>79</td>
<td>74</td>
<td>84</td>
</tr>
<tr>
<td>Beta blocker, %</td>
<td>86*</td>
<td>90</td>
<td>87</td>
<td>90</td>
</tr>
<tr>
<td>Digoxin, %</td>
<td>20</td>
<td>28</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>Mineralocorticoid Receptor Antagonist, %</td>
<td>55</td>
<td>54</td>
<td>59</td>
<td>58</td>
</tr>
<tr>
<td>Ivabradine, %</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Troponin-I, median (URL 0.04 ng/mL)</td>
<td>0.044*</td>
<td>0.060</td>
<td>0.044</td>
<td>0.056</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL), median</td>
<td>9026</td>
<td>7674</td>
<td>10488</td>
<td>10416</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²), mean (SD)</td>
<td>53 (18)*</td>
<td>52 (18)</td>
<td>53 (19)</td>
<td>50 (18)</td>
</tr>
<tr>
<td>Time from presentation to randomisation, mean (SD)</td>
<td>15 (8)*</td>
<td>12 (8)</td>
<td>16 (10)</td>
<td>15 (9)</td>
</tr>
</tbody>
</table>

*p < 0.05 for a difference in cohorts 1-3 Placebo arms compared to each other; URL= upper reference limit
Primary Efficacy Endpoint: Dyspnoea Response (Likert Scale)

Pooled Placebo

Overall p-value = 0.33

<table>
<thead>
<tr>
<th>Pooled Placebo</th>
<th>OM Cohort 1</th>
<th>OM Cohort 2</th>
<th>OM Cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>41%</td>
<td>42%</td>
<td>47%</td>
<td>51%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response Rate Ratio*</th>
<th>1.03</th>
<th>1.15</th>
<th>1.23</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% CI</td>
<td>(0.79, 1.35)</td>
<td>(0.90, 1.47)</td>
<td>(0.97, 1.55)</td>
</tr>
</tbody>
</table>

*Ratio of response rate to Pooled Placebo
p-value of a CMH test among all 3 Placebo arms = 0.32
Supplemental Primary Analysis: Dyspnoea Response (Likert Scale)

Paired Placebo

<table>
<thead>
<tr>
<th>Placebo Cohort 1</th>
<th>OM</th>
<th>Placebo Cohort 2</th>
<th>OM</th>
<th>Placebo Cohort 3</th>
<th>OM</th>
</tr>
</thead>
<tbody>
<tr>
<td>41%</td>
<td>42%</td>
<td>46%</td>
<td>47%</td>
<td>37%</td>
<td>51%</td>
</tr>
</tbody>
</table>

Response rate ratio: ratio of response rate to Placebo within each cohort

<table>
<thead>
<tr>
<th>Response Rate Ratio</th>
<th>1.02</th>
<th>1.02</th>
<th>1.41</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% CI</td>
<td>(0.74, 1.42)</td>
<td>(0.76, 1.37)</td>
<td>(1.02, 1.93)</td>
</tr>
</tbody>
</table>
Troponin-I Change from Baseline (ng/mL) Compared with Pooled Placebo

<table>
<thead>
<tr>
<th>Time</th>
<th>Baseline TnI (ng/mL) Median</th>
<th>Pooled Placebo Median</th>
<th>Cohort 1 Median</th>
<th>Cohort 2 Median</th>
<th>Cohort 3 Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 hours</td>
<td>0.023, 0.080</td>
<td>0.023, 0.080</td>
<td>0.028, 0.141</td>
<td>0.030, 0.084</td>
<td>0.026, 0.092</td>
</tr>
<tr>
<td>15 hours</td>
<td>0.044</td>
<td>0.044</td>
<td>0.060</td>
<td>0.044</td>
<td>0.056</td>
</tr>
<tr>
<td>24 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Q1, Q3: Quartiles
## Change in Heart Rate and SBP

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>OM concentration range (ng/ml)</td>
<td></td>
<td>≥88-200</td>
<td>&gt;200-300</td>
<td>&gt;300-787</td>
</tr>
<tr>
<td>Heart Rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS means</td>
<td>-4.3</td>
<td>-4.4</td>
<td>-6.3</td>
<td>-6.5</td>
</tr>
<tr>
<td>Difference from control</td>
<td>-0.1</td>
<td>-2.0</td>
<td>-2.3</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(-1.4, 1.1)</td>
<td>(-3.6, -0.4)</td>
<td>(-3.9, -0.6)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.835</td>
<td>0.016</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Linear regression slope</td>
<td></td>
<td></td>
<td></td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS means</td>
<td>-4.6</td>
<td>-4.4</td>
<td>-4.0</td>
<td>-2.2</td>
</tr>
<tr>
<td>Difference from control</td>
<td>0.3</td>
<td>0.6</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(-1.2, 1.7)</td>
<td>(-1.2, 2.4)</td>
<td>(0.6, 4.2)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.719</td>
<td>0.521</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Linear regression slope</td>
<td></td>
<td></td>
<td></td>
<td>p = 0.0017</td>
</tr>
</tbody>
</table>

N: number of patients in the bin, n: number of observations in the bin. Heart rate measured by ECG. Control = observations in Placebo + PK below quantification limit. PK bin concentration analysis: repeated measures analysis of covariance. Linear regression slope analysis: repeated measures multiple linear regression.
Omecamtiv Mecarbil: Development Across Continuum of Care

IV and oral formulations enable evaluation of omecamtiv mecarbil across a range of heart failure patient populations.
Summary

• Efficacy
  – OM did not meet the 1° endpoint of dyspnoea relief
  – Appeared to improve dyspnoea in Cohort 3
  – Trends towards reduction of worsening HF

• Safety
  – Overall SAE profile and tolerability similar to placebo
  – Increase in troponin; no clear relationship to OM concentration
  – Numerical imbalance in MIs in Cohort 3
  – No evidence of pro-arrhythmia

• Pharmacology
  – PK similar to healthy volunteers and stable HF patients
  – Systolic ejection time significantly increased consistent with MOA
  – Small fall in heart rate & rise in systolic BP at higher doses
Thank You!
Study Objectives

**Primary**
- Evaluate the effect of 48 hours of intravenous (IV) omecamtiv mecarbil (OM) compared with placebo on dyspnea in subjects with left ventricular systolic dysfunction hospitalized for acute heart failure (AHF)

**Secondary**
- Assess the safety and tolerability of 3 dose levels of IV omecamtiv mecarbil (OM) compared with placebo in subjects with left ventricular systolic dysfunction hospitalized for AHF
- Evaluate the effects of 48 hours treatment with IV OM on dyspnea (different measurement than primary), patient global assessment (PGA), change in NT-pro BNP and short-term clinical outcomes
- Characterize PK of OM, including major metabolites, following IV infusion and evaluate the relationship between OM plasma concentration and echocardiographic parameters in subjects with acute heart failure
ATOMIC-AHF: Inclusion Criteria

KEY Eligibility Criteria – Inclusion

- Male/female ≥ 18 and ≤ 85 years of age at the time of randomization
- History of chronic heart failure (defined as requiring treatment for heart failure for a minimum of 30 d before hospitalization)
- History of left ventricular ejection fraction (LVEF) ≤ 40% (echocardiogram, radionuclide ventriculography, cardiac magnetic resonance imaging, or contrast ventriculography) without an intervening value of > 40%
- Dyspnea, due to heart failure, at rest or with minimal exertion
- Screening BNP ≥ 400 pg/mL or NT-proBNP ≥ 1600 pg/mL during screening (BNP ≥ 600 pg/mL or NT-proBNP ≥ 2400 pg/mL if the subject has atrial fibrillation)
Omecamtiv Mecarbil: Pharmacodynamics and Tolerability are Concentration-dependent

- Increase in echo indices of cardiac function as low as > 100-300 ng/mL
- Increased risk of intolerance and ischemia (> 1200 ng/mL)

Dosing regimens focus on target concentrations of 100-500 ng/mL so that vast majority of subjects do not approach 1000 ng/mL.
### PK/PD Substudy Endpoint: Change in Systolic Ejection Time (SET)

<table>
<thead>
<tr>
<th>PK Concentration Bin Analysis</th>
<th>Control</th>
<th>OM Concentration Bin 1</th>
<th>OM Concentration Bin 2</th>
<th>OM Concentration Bin 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>OM concentration range (ng/ml)</td>
<td></td>
<td>≥88-200</td>
<td>&gt;200-300</td>
<td>&gt;300-787</td>
</tr>
<tr>
<td>Change in SET (msec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N(n)</td>
<td>45 (88)</td>
<td>10 (18)</td>
<td>15 (23)</td>
<td>12 (19)</td>
</tr>
<tr>
<td>LS mean</td>
<td>-6.7</td>
<td>16.6</td>
<td>26.9</td>
<td>46.4</td>
</tr>
<tr>
<td>Difference from control</td>
<td>23.4</td>
<td>33.6</td>
<td>53.2</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>(7.4, 39.4)</td>
<td>(19.8, 47.4)</td>
<td>(38.0, 68.3)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.005</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Baseline systolic ejection time for all patients was 258 msec. N: number of patients in the bin, n: number of observations in the bin; Control = observations in Placebo + PK below quantification limit; PK bin concentration analysis: repeated measures analysis of covariance; Linear regression slope analysis: repeated measures multiple linear regression.
Efficacy Endpoints

Primary:
• Dyspnoea symptom response (7-point Likert scale) through 48 hours

Secondary:
• Death (any cause) and/or worsening heart failure within 7 days
• Dyspnoea area under the curve (AUC) (baseline to 5\textsuperscript{th} day or discharge) as measured by subject self-assessed Numerical Rating Scale (NRS)
• Dyspnoea by 7-point Likert scale at each scheduled assessment
• Patient Global Assessment response through 48 hours
• Change from baseline in NT-proBNP
• Length of initial hospital stay
• Days alive out of hospital until day 30

PK/PD (Echo) Sub-study
ATOMIC-AHF

Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure

Objective:

- To evaluate the safety, pharmacokinetics/pharmacodynamics, and efficacy of IV omecamtiv mecarbil (OM) in patients with acute heart failure (AHF)

Hypothesis:

- At least 1 dose level of IV OM will be well tolerated and will result in improvement of dyspnoea in subjects with left ventricular systolic dysfunction hospitalised for AHF
Study Design

Randomised, double-blind, placebo-controlled, sequential cohort study

Omeicamiv mecarbil IV

Placebo IV

MANDATORY IN-HOSPITAL STAY

Time (hrs) 0 4 6 15 24 48 72 96 Day 6/DC Day 30 EOS Month 6

Study drug administration

1st EP dyspnoea response

PK sampling
all subjects
PK/PD sub-study
Cardiac troponin/CK-MB
Echo (PK/PD sub-study)

* Randomisation within 24 hours of initial IV diuretic (Amendment 2)
OM aktuelle klinische Studie (geplant 600 Pat.)

Study 20100754: Design

Sequential cohort enrollment of low, medium and high dose target AMG 423 plasma concentrations: 115, 230, 310 ng/mL

- Minimal in-hospital follow-up until 24 hrs after ending IP
- Minimal telemetry until 12 hrs after ending IP
- Earliest Discharge on Day 4
- Study assessments: Daily until discharge or day 8, whichever is earlier
- On day of discharge

Mandatory in-hospital stay

- Presentation for AHF
- Screening
- Randomization 1:1
- Omecamtiv mecarbil IV
- Placebo IV
- Randomization within 16 hours of presentation

Time:
- 0 hr
- 4 hrs
- 48 hrs
- 72 hrs “Day 4”
- Day 30 EOS
- Month 6

Vital Status (phone call)