Prevention of Worsening Heart Failure by Serelaxin in Patients Admitted for Acute Heart Failure: Results from RELAX-AHF

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Presenter Disclosure Information

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• Financial Disclosure
  – J.R. Teerlink received research grants and consulting fees from Novartis as Co-Principal Investigator of RELAX-AHF and RELAX-AHF-2, as Executive Committee Member of RELAX-AHF-Asia, and as US National Leader for PARADIGM-HF
  – Funding for RELAX-AHF was from Novartis Pharma AG
Serelaxin has potential multi-mechanistic effects which may address the pathophysiology of AHF

1. **Myocardial overload;**
   - **↓** Myocardial overload;
   - **↑** Renal function

2. **Cell preservation**
   - **↓** Inflammation
     - **↓** Inflammatory cell infiltration
     - **↓** Oxidative stress
   - **↑** Tissue healing
     - **↑** Angiogenesis
     - **↑** Stem cell survival

3. **ECM remodeling**
   - **↑** ECM remodeling
   - **↓** Myocardial overload;
   - **↑** Renal function

- **Remodeling**
  - **↑** Matrix metalloproteinases
  - **↓** Vessel stiffness

- **Fibrosis**
  - **↓** Collagen synthesis
  - **↑** Collagen breakdown

- **Cell survival**
  - **↓** Oxidative stress
  - **↓** Apoptosis
  - **↓** Ca²⁺ overload
  - **↓** Infarct size

*Selective dilation of pre-constricted vessels; AHF=acute heart failure; ECM=extracellular matrix; ET-1=endothelin-1; GFR=glomerular filtration rate; NO=nitric oxide; RBF=renal blood flow; SVR-systemic vascular resistance

Adapted from Du et al. Nat Rev Cardiol 2010;7:48–58
RELAX-AHF: Study design

1,161 patients hospitalized for AHF

Screening

Entry Criteria:
• Dyspnea, Congestion on CXR, Elevated BNP/nt-ProBNP
• SBP >125 mmHg
• eGFR 30-75 ml/min/1.73m²
• ≥40 mg IV furosemide

Excluded:
• Acute Coronary Syndrome
• High dose nitrates

Double-blind, randomized treatment and follow up period

Placebo (n=580)

Serelaxin 30 µg/kg/d (n=581)

Presentation ≤16 h

48 h study drug infusion period

Post-discharge evaluation period

Standard HF therapy
During study investigators free to use any concomitant medications incl. nitrates according to clinical judgment

1° Endpoint: 
Visual Analog Scale Area Under the Curve Composite

19.4% increase in AUC with serelaxin from baseline through day 5 (Mean difference of 448 mm-hr)

AUC with placebo, 2308 ± 3082
AUC with serelaxin, 2756 ± 2588
p=0.0075

1° Endpoint: Visual Analog Scale Area Under the Curve Composite through 5 Days

Visual Analog Scale AUC With Worst Score Assignment

- No dyspnea
- Severe dyspnea
- Worsening heart failure requiring IV or mechanical interventions
- Death

Numerical scores over time

Worst score
Definition of Worsening HF through Day 5 in RELAX-AHF

- Worsening signs and/or symptoms of heart failure that require an intensification of intravenous therapy for heart failure or mechanical, ventilatory or circulatory support.
- Such treatment can include the institution or uptitration of IV furosemide, IV nitrates or any other IV medication for heart failure, or institution of mechanical support such as mechanical ventilation, IABP, etc.
- Medications for heart failure (such as IV treatment for hypertension control) can be added for reasons other than worsening heart failure.
# Baseline Characteristics of Patients With WHF vs. Non-WHF in RELAX-AHF

<table>
<thead>
<tr>
<th></th>
<th>WHF (n=106)</th>
<th>Non-WHF (n=1055)</th>
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</thead>
<tbody>
<tr>
<td><strong>Age (year)</strong></td>
<td>72.6</td>
<td>72.0</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>69</td>
<td>62</td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td>141</td>
<td>142</td>
</tr>
<tr>
<td><strong>HF hospitalization in past year (%)</strong></td>
<td>35.8</td>
<td>34.0</td>
</tr>
<tr>
<td><strong>CHF 1 month prior (%)</strong></td>
<td>80.2</td>
<td>72.6</td>
</tr>
<tr>
<td><strong>NYHA (%) - II&amp;III / IV</strong></td>
<td>84.9/12.8</td>
<td>80.0/16.0</td>
</tr>
<tr>
<td><strong>LVEF (mean %)</strong></td>
<td>36.4</td>
<td>38.9</td>
</tr>
<tr>
<td><strong>LVEF &lt;40% (%)</strong></td>
<td>63.4</td>
<td>53.9</td>
</tr>
<tr>
<td><strong>Ischemic heart disease (%)</strong></td>
<td>51.9</td>
<td>51.9</td>
</tr>
<tr>
<td><strong>Atrial fibrillation at screening (%)</strong></td>
<td>49.1</td>
<td>40.6</td>
</tr>
<tr>
<td><strong>Diabetes mellitus (%)</strong></td>
<td>50.0</td>
<td>47.2</td>
</tr>
<tr>
<td><strong>Time to randomization (hr)</strong></td>
<td>7.6</td>
<td>7.9</td>
</tr>
<tr>
<td><strong>VAS score (mm)</strong></td>
<td>44.2</td>
<td>44.2</td>
</tr>
<tr>
<td><strong>NT-proBNP (pg/mL)</strong></td>
<td>6146</td>
<td>4963</td>
</tr>
<tr>
<td><strong>hs-troponin T (µg/L)</strong></td>
<td>0.041</td>
<td>0.034</td>
</tr>
</tbody>
</table>
Patients With Worsening Heart Failure Had Prolonged Use of Intravenous Diuretics

Patients Without In-Hospital Worsening Heart Failure vs. Patients With In-Hospital Worsening Heart Failure

Dose of intravenous diuretics as furosemide equivalents (mg/day)

Day 0 1 2 3 4 5 0 1 2 3 4 5

Data presented as mean ± 95% CI

Patients without worsening heart failure (n=1037-1052) and with worsening heart failure (n=98-106)

(p<0.00001)
Patients With Worsening Heart Failure Had Higher Levels of Cardiac and Renal Biomarkers

Shown are changes from baseline. P values refers to comparison of patients with and without worsening heart failure and are based on t-test.
Patients With Worsening Heart Failure had Prolonged Intensive Care and Hospital Stay

Patients with worsening heart failure (n=99) and without worsening heart failure (n=1055)
Excludes patients who died through Day 5. Data presented as mean ± 95% CI

Length of Index ICU/CCU Stay

- Patients with worsening heart failure: Δ=4.9 days
- Patients without worsening heart failure: Δ=8.0 days

Length of Initial Hospital Stay

- Patients with worsening heart failure: Δ=8.0 days
- Patients without worsening heart failure: Δ=4.9 days

p<0.00001
Patients with worsening heart failure had increased risk of all-cause death.

Mortality Hazard Ratio (95% CI)
- 30-day: 2.86 (1.07, 7.65); p=0.0367
- 60-day: 3.42 (1.68, 6.97); p=0.0007
- 180-day: 1.98 (1.14, 3.43); p=0.0148

Patients who died prior to Day 5 are excluded.

Patients With Worsening Heart Failure Treated Only with IV Diuretics

• Prolonged duration of intravenous therapy
• Longer stay in ICU/CCU (+2.9 d; p=0.00005) and initial hospitalization (+5.4 d; p<0.00001)*
• Numerically greater mortality at
  – 60 days (3.1% vs 5.2%; HR 1.70 (0.5-5.6); p=NS)
  – 180 days (8.2% vs 12.1%; HR 1.53 (0.7-3.3); p=NS)**

* P values based on a t-test
**P value based on Wald test; Excludes patients who died through Day 5.
Incidence of In-Hospital Worsening HF or Death Through Day 5

Placebo (N=573)  Serelaxin (N=570)

Cumulative proportion (%)

p<0.001 to Day 5

* P<0.05;  ** P<0.005;  *** P<0.001 using logistic regression.

P value to Day 5 based on Wilcoxon test
Time to Event Analysis of Worsening Heart Failure Through Day 5

K-M Estimate (%)

HR: 0.53 (0.36, 0.79)  
p=0.0016

Placebo (N=580)  
Serelaxin (N=581)

Placebo  
12.2%

Serelaxin  
6.7%

Days

Serelaxin  
581  575  564  560  546  542
Placebo  
580  567  544  527  519  513
Rescue Interventions Used to Respond to In-Hospital Worsening Heart Failure

<table>
<thead>
<tr>
<th>Rescue Interventions</th>
<th>Placebo (N=580)</th>
<th>Serelaxin (N=581)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients who died or had in-hospital worsening or rehospitalization for HF through Day 5</td>
<td>69</td>
<td>37</td>
</tr>
<tr>
<td>IV inotropes and/or mechanical ventilation or circulatory support (± IV vasodilators ± IV diuretics)</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>IV vasodilators (± IV diuretics)</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>IV diuretics only</td>
<td>38</td>
<td>19</td>
</tr>
</tbody>
</table>

One patient on placebo experienced HF rehospitalization at Day 4
3 patients died prior to Day 5 without preceding WHF in each treatment group
### Worsening Heart Failure Events With More Intensive Rescue Intervention

<table>
<thead>
<tr>
<th>Patients with WHF event included in the analysis of the 5-day primary endpoint</th>
<th>Placebo (N=580)</th>
<th>Serelaxin (N=581)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who died or who experienced WHF leading to rehospitalization within 5 days</td>
<td>69</td>
<td>37</td>
</tr>
<tr>
<td>Patients with WHF within 5 days treated with IV positive inotropic drug or mechanical intervention</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Patients with WHF within 5 days treated with new IV nitrates or IV nitroprusside</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Patients with WHF within 5 days treated with reinitiation or doubling of daily dose of IV diuretic</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>24</td>
</tr>
</tbody>
</table>

P=0.003

One patient on placebo experienced HF rehospitalization at Day 4
3 patients died prior to Day 5 without preceding WHF in each treatment group
### Recurrent Worsening Heart Failure Through Day 5

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=580)</th>
<th>Serelaxin (N=581)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with recurrent WHF events through Day 5</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>In-hospital WHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV inotropes, and/or mechanical ventilation, and/or ultrafiltration</td>
<td>8*</td>
<td>0</td>
</tr>
<tr>
<td>IV nitrates and/or vasodilators</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>IV diuretics</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

* Placebo: IV inotropes n=6, mechanical ventilation n=1, and ultrafiltration n=1
Serelaxin Reduced Both First and Recurrent Worsening Heart Failure Events Through Day 5

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N=580)</th>
<th>Serelaxin (N=581)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode of worsening heart failure or death within 5 days</td>
<td>69 (11.9%)</td>
<td>37 (6.4%)</td>
</tr>
<tr>
<td>Recurrent worsening heart failure or death with prior event within 5 days</td>
<td>15 (2.6%)</td>
<td>4 (0.7%)</td>
</tr>
<tr>
<td>All worsening heart failure events and deaths within 5 days*</td>
<td>85</td>
<td>41</td>
</tr>
</tbody>
</table>

HR: 0.48 (0.32, 0.73)  
p=0.0005

* Presented as numbers of events
Conclusions

In RELAX-AHF…

- Worsening heart failure was related to
  - Prolonged intravenous therapy duration
  - Elevations in markers of cardiac injury, myocardial stretch and renal dysfunction
  - Lengthened ICU/CCU and overall hospitalization stay
  - Increased mortality
Conclusions

In RELAX-AHF...

• Serelaxin treatment resulted in
  – Marked decrease in worsening heart failure
  – Decreased recurrent worsening heart failure
  – Reduced worsening heart failure events in patients with all categories of rescue therapy, ranging from those treated only with IV diuretics to those treated only with more intensive therapies
RELAX-AHF: All-Cause Mortality

HR 0.63 (95% CI 0.43–0.93)  
\( p = 0.02 \)

Placebo: 65 deaths (11.3%)  
Serelaxin: 42 deaths (7.3%)  

>6,300 Patients admitted for Acute Heart Failure  
Primary endpoint: Cardiovascular mortality through 180 days  
Currently enrolling in 30 countries
San Francisco Veterans Affairs Medical Center

Thank you!
RELAX-AHF Study Organization

- Co-PIs: M Metra (IT), JR Teerlink (US)
- Executive Committee: G Cotter (US), BA Davison (US), GM Felker (US), G Filipatos (GR), BH Greenberg (US), P Ponikowski (PL), TM Severin (CH), SL Teichman (US), E Unemori (USA), AA Voors (NL).
- Steering Committee: KF Adams (US), M Dorobantu (RO), L Grinfeld (AR), G Jondeau (FR), A Marmor (IL), J Masip (ES), PS Pang (US), K Werdan (DE).
- DSMB: BM Massie-Chair (US), M Böhm (DE), E Davis (US), G Francis (US), S Goldstein (US).
- Sponsor: Corthera, Inc. (a Novartis affiliate company)
- Coordinating Center: Momentum Research, Inc.
## RELAX-AHF Investigators

<table>
<thead>
<tr>
<th>Country</th>
<th>Investigators</th>
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</thead>
<tbody>
<tr>
<td>Argentina (71 pts):</td>
<td>GM Ferrari; A Quiroga; A Fernandez; E Perna; MS Ramos; L Guzman; G Cursack; O Allall; MG Masuelli; C Rapallo.</td>
</tr>
<tr>
<td>France (21):</td>
<td>A Cohen-Solal; M Galinier; G Jondeau; R Isnard.</td>
</tr>
<tr>
<td>Germany (78):</td>
<td>H-G Olbrich; V Mitrovic; K Werdan; S Felix; T Heitzer; G Cieslinski; K Stangl.</td>
</tr>
<tr>
<td>Hungary (151):</td>
<td>J Tomcsányi; D Apró; K Tóth; A Vértes; G Lupkovics; Z László; A Cziraki.</td>
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<td>Israel (210):</td>
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</tr>
<tr>
<td>Italy (77):</td>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>Romania (153):</td>
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</tr>
<tr>
<td>Spain (18):</td>
<td>J Masip; D Pascual; MG Bueno; R Muñoz.</td>
</tr>
<tr>
<td>USA (114):</td>
<td>S Meymandi; P Levy; PS Pang; C Clark; G Fermann; KF Adams, Jr.; B Bozkurt; J Fulmer; D Mancini; T Vittorio; R Zolty; BH Greenberg; E Chung; V Florea; J Heilman III; A Storrow; MR Costanzo; G Lamas; M Greenspan; M Klapolz; J Martinez-Arraras; WF Peacock; N Saleh; R Small; JR Teerlink; B Trichon; D Wencker.</td>
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