Serelaxin, A Novel Treatment for Acute Heart Failure-
The RELAX-AHF Trial

Prof. John R. Teerlink, MD, FAHA
University of California, San Francisco
and San Francisco VA Medical Center

Prof. Marco Metra, MD
University of Brescia, Brescia, Italy

on behalf of the RELAX-AHF Executive and Steering Committees, Investigators & Patients
Pregnancy & the Heart

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>PREGNANCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Output (L/min)</td>
<td>20% Increase</td>
</tr>
<tr>
<td>Systemic Vascular Resistance (dyn.s.cm²)</td>
<td>30% Decrease</td>
</tr>
<tr>
<td>Global Arterial Compliance (mL/mm Hg)</td>
<td>30% Increase</td>
</tr>
<tr>
<td>Renal Blood Flow (mL/min/1.73m²)</td>
<td>50-85% Increase</td>
</tr>
<tr>
<td>Creatinine Clearance (mL/min/1.73m²)</td>
<td>40-65% Increase</td>
</tr>
</tbody>
</table>

- Relaxin has been shown to mediate these changes, as well as to have anti-ischemic, anti-inflammatory, anti-fibrotic effects.
- Relaxin is elevated through 9 months of pregnancy and mediates physiologic hemodynamic adjustments to growing baby.
- Pharmacologic use of serelaxin may produce these beneficial effects in acute heart failure.

Pre-RELAX-AHF


- 234 patient, dose finding Phase II study
- Optimal dose across multiple clinical outcome domains was 30mcg/kg/d
- Serelaxin had trends to:
  - Improved dyspnea relief
  - Decreased congestion
  - Reduced diuretic use
  - Less worsening of heart failure
  - Shorter length of stay
  - Reduced days alive out of hospital
  - Improved cardiovascular and all-cause survival
- No significant adverse events
- No hypotension SAEs; Hypotension AEs similar to placebo

CV Death (KM)

<table>
<thead>
<tr>
<th>Events</th>
<th>n (KM%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=42)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Serelaxin (n=172)</td>
<td>5 (3%)</td>
</tr>
</tbody>
</table>

HR 0.25 (0.08-0.79) P=0.019
Objectives and Hypothesis

• Based upon the hypothesis-generating results of Pre-RELAX-AHF, the RELAX-AHF trial was designed to test the efficacy and safety of serelaxin in patients with acute heart failure (AHF).

• We hypothesized that serelaxin (30 mcg/kg/d iv) would improve dyspnea to a greater extent than placebo by one or both measures at 24 hours (Likert) and/or 5 days (VAS AUC), and improve other clinical outcomes.
Inclusion and Exclusion Criteria

Key Inclusion Criteria

• Hospitalized for AHF
  – Dyspnea at rest or with minimal exertion
  – Pulmonary congestion on chest radiograph
  – BNP ≥ 350 pg/mL or NT-pro-BNP ≥ 1400 pg/mL
• Received ≥40 mg IV furosemide (or equivalent) at any time between admission to emergency services (either ambulance or hospital, including the ED) and the start of screening for the study
• Systolic blood pressure > 125 mmHg
• Impaired renal function on admission (sMDRD eGFR 30-75 mL/min/1·73 m²)
• Randomised within 16 hours from presentation
• Age ≥ 18 years of age
• Body weight < 160 kg

Key Exclusion Criteria

• Current or planned treatment with any IV therapies [i.e. other vasodilators, (nesiritide), positive inotropic agents and vasopressors] or mechanical circulatory, renal, or ventilatory support, with the exception of IV furosemide (or equivalent), or of IV nitrates if patient has screening SBP >150 mmHg
• AHF and/or dyspnea from arrhythmias or non-cardiac causes, such as lung disease, anemia, or severe obesity
• Infection or sepsis requiring IV antibiotics
• Pregnant or breast-feeding
• Stroke within 60d; ACS within 45d; major surgery within 30d
• Presence of acute myocarditis, significant valvular heart disease, hypertrophic/ restrictive/ constrictive cardiomyopathy
Key Efficacy Measures

Timeline: D0 D1 D2 D5 D14/Index D60 D180

Treatment
Serelaxin/Placebo

Primary EP
Likert
6, 12, 24 h

VAS AUC
0-100 mm; 0, 6, 12, 24h, D2-D5

p<0.025 for either 1° Dyspnea EP or p<0.05 for both 1° Dyspnea EPs

Secondary EP
Days Alive Out of Hospital

CV death+ HF/RF

Re-hospitalization

Biomarkers

WHF

LoS (index/ICU)

In-hospital benefits

Out-patient benefits

CV death
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (N=580)</th>
<th>Serelaxin (N=581)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean 72.5</td>
<td>71.6</td>
</tr>
<tr>
<td>Systolic BP at baseline (mmHg)</td>
<td>Mean 142.1</td>
<td>142.2</td>
</tr>
<tr>
<td>Heart Rate at Baseline (bpm)</td>
<td>Mean 80.4</td>
<td>78.9</td>
</tr>
<tr>
<td>Respiratory Rate at baseline (breaths/ min)</td>
<td>Mean 22.0</td>
<td>21.8</td>
</tr>
<tr>
<td>HF Hospitalization (in the past year)</td>
<td>% 31.2</td>
<td>37.2*</td>
</tr>
<tr>
<td>Most Recent Ejection Fraction</td>
<td>Mean 38.7</td>
<td>38.6</td>
</tr>
<tr>
<td>&lt; 40%</td>
<td>% 54.9</td>
<td>54.7</td>
</tr>
<tr>
<td>NYHA (1 month prior to admission)</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>% 46.7</td>
<td>43.7</td>
</tr>
<tr>
<td>IV</td>
<td>% 17.0</td>
<td>14.4</td>
</tr>
<tr>
<td>Medical History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>% 87.9</td>
<td>85.4</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>% 54.0</td>
<td>52.3</td>
</tr>
<tr>
<td>Stroke or Other Cerebrovascular event</td>
<td>% 14.5</td>
<td>12.6</td>
</tr>
<tr>
<td>Atrial fibrillation/ atrial flutter at presentation</td>
<td>% 42.4</td>
<td>40.1</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>% 46.9</td>
<td>48.0</td>
</tr>
</tbody>
</table>
## Patient population (2)

<table>
<thead>
<tr>
<th>Parameter (n’ placebo/n’ serelaxin)</th>
<th>Placebo (N=580)</th>
<th>Serelaxin (N=581)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Concomitant Heart Failure Meds at Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors %</td>
<td>55.2</td>
<td>53.9</td>
</tr>
<tr>
<td>ARB %</td>
<td>16.7</td>
<td>15.1</td>
</tr>
<tr>
<td>Beta-blocker %</td>
<td>70.2</td>
<td>66.6</td>
</tr>
<tr>
<td>Aldosterone antagonist %</td>
<td>29.8</td>
<td>33.2</td>
</tr>
<tr>
<td>Digoxin %</td>
<td>18.6</td>
<td>20.7</td>
</tr>
<tr>
<td><strong>Time from present. to random. (hr)</strong></td>
<td>Mean</td>
<td>7.9</td>
</tr>
<tr>
<td><strong>Duration of study drug administration (hr)</strong></td>
<td>Mean</td>
<td>43.8</td>
</tr>
<tr>
<td><strong>IV nitrates at randomisation</strong> %</td>
<td>7.2</td>
<td>6.7</td>
</tr>
<tr>
<td><strong>NT-proBNP (mg/L)</strong> Geometric Mean</td>
<td>5003</td>
<td>5125</td>
</tr>
<tr>
<td><strong>Troponin T (pg/ml)</strong> Geometric Mean</td>
<td>0.036</td>
<td>0.034</td>
</tr>
<tr>
<td>eGFR (MDRD; mL/kg/1.73m²) Mean</td>
<td>53.3</td>
<td>53.7</td>
</tr>
</tbody>
</table>

** Core lab values
1° Endpoint: Dyspnea Relief (VAS AUC)

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: Dyspnea Relief (Likert)

Proportion of subjects with moderately or markedly better dyspnea by Likert by time point

- Placebo
- Serelaxin

**p value by Chi-square test**
2° Endpoint: CV Death or HF/RF
Re-hospitalization through Day 60

K-M estimate for time to first event (%)

- **Placebo**
  - HR = 1.03 (0.75, 1.42)
  - p = 0.862
- **Serelaxin**
  - HR = 1.03 (0.75, 1.42)
  - p = 0.862

Composite event components (%)

- **CV death**:
  - % subjects: HR = 0.7, p = 0.236
  - n = 27 (Placebo), n = 19 (Serelaxin)
- **HF/RF re-hospitalization**:
  - % subjects: HR = 1.2, p = 0.300
  - n = 50 (Placebo), n = 60 (Serelaxin)

* p value by log rank test
**HR estimate by Cox model
2° Endpoint: Days Alive and Out of Hospital through Day 60

Serelaxin
N=(581)

Average days of index hospitalization: 8.9
Average days alive and out of hospital: 48.3
Average days re-hospitalized: 2.6
Average days dead: 1.2

Placebo
N=(580)

Average days of index hospitalization: 9.5
Average days alive and out of hospital: 47.7
Average days re-hospitalized: 1.9
Average days dead: 1.8

Days Alive Out of Hospital = total follow-up time (D60) - days in hospital or dead
*p value by 2-sided Wilcoxon rank sum test
CV Death through Day 180

K-M estimate CV death (ITT) (%)

HR 0.63 (0.41, 0.96); p=0.028

NNT = 29
Signs and Symptoms of Congestion

Signs and Symptoms of Congestion at Day 2

- **DOE**
  - None: 100%
  - Mild: 90%
  - Moderate: 70%
  - Severe: 50%
  - *p*=0.02

- **Orthopnea**
  - None: 100%
  - Mild: 90%
  - Moderate: 70%
  - Severe: 50%
  - *p*=0.002

- **Edema**
  - None: 100%
  - Mild: 90%
  - Moderate: 70%
  - Severe: 50%
  - *p*=0.01

- **Rales**
  - None: 100%
  - Mild: 90%
  - Moderate: 70%
  - Severe: 50%
  - *p*=0.008

- **JVP**
  - None: 100%
  - Mild: 90%
  - Moderate: 70%
  - Severe: 50%
  - *p*=0.06

*p* value by 2-sided Wilcoxon rank sum test of change from baseline.

Patients %

- None
- Mild
- Moderate
- Severe

- 0
- 20
- 40
- 60
- 80
- 100

- None
- 1 pillow
- 2 pillows
- >30

- None
- 1+
- 2+
- 3+

- None
- 1/3
- 1/3-2/3
- >2/3

- None
- <1/3
- 1/3-2/3
- >2/3

- None
- <6 cm
- 6-10 cm
- >10 cm

- None
- <6 cm
- 6-10 cm
- >10 cm

- None
- <6 cm
- 6-10 cm
- >10 cm
Worsening Heart Failure (WHF) was defined as worsening signs and/or symptoms of HF that required an intensification of IV therapy for heart failure or mechanical ventilatory or circulatory support.

*p value by Wilcoxon test
**p value by log rank test for Serelaxin vs. Placebo; HR estimate by Cox model, HR<1.0 favors Serelaxin
Intravenous Diuretic Use

Total daily dose IV diuretics (mg)

Placebo
Serelaxin

*p value by t test

*p=0.0078
*p=0.0003
*p=0.0103

IV diuretics use (cumulative total dose from day 1-5 (mg))

*N=573
*N=572

*p=0.0057
Index Hospitalization Length of Stay (Days)

*p=0.039

n=580

n=581

Length of ICU/CCU Stay (Days)

*p=0.029

n=578

n=574

Patients still in the hospital at Day 60 are censored at Day 60. Patients who died in-hospital are imputed as the maximum +1 day.

*p value by 2-sided Wilcoxon rank sum test
### Incidence of AEs/SAEs to Day 14

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo (N=570) n (%)</th>
<th>Serelaxin (N=568) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects with any AE</strong></td>
<td>320 (56.1)</td>
<td>305 (53.7)</td>
</tr>
<tr>
<td>Subjects with any drug-related AE[1]</td>
<td>46 (8.1)</td>
<td>47 (8.3)</td>
</tr>
<tr>
<td>Subjects with AE leading to study drug d/c</td>
<td>22 (3.9)</td>
<td>26 (4.6)</td>
</tr>
<tr>
<td>Hypotension-related AE (through day 5)</td>
<td>25 (4.4)</td>
<td>28 (4.9)</td>
</tr>
<tr>
<td>Renal Impairment-related AE (through day 5)</td>
<td>49 (8.6)</td>
<td>26 (4.6)*</td>
</tr>
<tr>
<td><strong>Subjects with any SAE</strong></td>
<td>78 (13.7)</td>
<td>86 (15.1)</td>
</tr>
<tr>
<td>Subjects with any drug-related SAEs</td>
<td>2 (0.4)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Subjects with SAE leading to drug d/c</td>
<td>3 (0.5)</td>
<td>5 (0.9)</td>
</tr>
<tr>
<td>Serious AE with an outcome of death</td>
<td>15 (2.6)</td>
<td>10 (1.8)</td>
</tr>
</tbody>
</table>

The number of subjects with any AE includes all AEs and SAEs reported through Day 14.
Non-serious AEs were collected through Day 5, SAEs through Day 14.
### Biomarkers

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Placebo</th>
<th>Serelaxin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NT-proBNP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(≥30% decrease at Day 2)</td>
<td>Yes</td>
<td>315 (58.0%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>228 (42.0%)</td>
</tr>
<tr>
<td><strong>Creatinine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(≥0.3 mg/dl Increase at Day 2)</td>
<td>Yes</td>
<td>108 (19.8%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>437 (81.2%)</td>
</tr>
<tr>
<td><strong>Troponin T</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(≥20% Increase at Day 2)</td>
<td>Yes</td>
<td>145 (27.2%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>389 (72.8%)</td>
</tr>
<tr>
<td><strong>ALT</strong></td>
<td>mg/dL</td>
<td>-2.3</td>
</tr>
</tbody>
</table>

*p = 0.0002  
**p < 0.0001  
***p < 0.0010
Conclusions

In selected patients with AHF, early treatment with serelaxin for 48 h improved:

• Dyspnea relief: VAS AUC
• In-hospital signs and symptoms of AHF
• In-hospital end organ dysfunction/ damage
• In-hospital worsening of heart failure
• 180-day CV and all-cause mortality

…but had no effect on rehospitalizations.

Serelaxin use in AHF was safe with few hypotensive events and adverse events similar to placebo.
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

- **Argentina (71 patients):** GM Ferrari; A Quiroga; A Fernandez; E Perna; MS Ramos; L Guzman; G Cursack; O Allall; MG Masuelli; C Rapallo.
- **France (21):** A Cohen-Solal; M Galinier; G Jondeau; R Isnard.
- **Germany (78):** H-G Olbrich; V Mitrovic; K Werdan; S Felix; T Heitzer; G Cieslinski; K Stangl.
- **Hungary (151):** J Tomcsányi; D Apró; K Tóth; A Vértés; G Lupkovics; Z László; A Cziraki.
- **Israel (210):** A Marmor; S Goland; A Katz; R Zimlichman; D Aronson; A Butnaru; M Omary; XA Piltz; D Zahger.
- **Italy (77):** M Metra; A Mortara; M Balbi; F Cosmi; S DiSomma; MC Brunazzi.
- **Netherlands (10):** AA Voors; PEF Bemdemacher; G-J Milhous; PL van Haelst; P Dunselman.
- **Poland (258):** P Ponikowski; P Jankowski; A Wysokinski; M Dluzniewski; J Stepinska; W Tracz; M Krzeminska-Pakula; J Grzybowski; K Loboz-Grudzień.
- **Romania (153):** D-D Ionescu; CS Stamate; M Dorobantu; C Pop; A Matei; T Nanea; M Radoi; A Salajan.
- **Spain (18):** J Masip; D Pascual; MG Bueno; R Muñoz.
- **United States of America (114):** 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 Klapholz; J Martinez-Arraras; WF Peacock; N Saleh; R Small; JR Teerlink; D Wencker.