New Therapies for Acute Heart Failure:

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Disclosures

• Grant Support and/or Consulting
  – NIH/NHLBI
  – Novartis
  – Amgen
  – Trevena
  – Roche Diagnostics
  – Otsuka
  – Celladon
  – St Judes
  – Singulex

• I will discuss investigational agents that are not currently approved by the US FDA
Acute Heart Failure Hospitalizations

1.0 Million Hospitalizations a Year and Rising

The majority of patients hospitalized with HF were previously hospitalized with HF

30-Day Rehospitalization Rates in HF
24.8%
(Medicare)

United States: 1979-2006 Source: NHDS/NCHS, NHLBI. Hospital Compare 2007-2010
Estimated Direct and Indirect Costs of HF in US

- Hospitalization: $20.9 (53.3%)
- Lost Productivity/Mortality*: $4.1 (11.9%)
- Home Healthcare: $3.8 (10.5%)
- Drugs/Other Medical Durables: $3.2 (8.2%)
- Physicians/Other Professionals: $2.5 (6.4%)
- Nursing Home: $4.7 (9.7%)

Total Cost: $39.2 billion

[Reference: Heart Disease and Stroke Statistics—2010 Update: A Report From the AHA
Circulation, Feb 2010; 121: e46 - e215.]
State of the Art ADHF Therapy

1974

- Diuretics
- Vasodilators
- Oxygen
- Consider inotropic therapy

2007

Fonarow, GC et al. AHJ 2007
Current Treatments of Acute Heart Failure

Diuretics
- Reduce fluid volume

Vasodilators
- Decrease preload and/or afterload

Inotropes
- Augment contractility
Novel Therapies in AHF

• Serelaxin (Phase III)

• Omecamtiv Mecarbil (Phase IIb)

• TRV027 (Phase Ila)
Pregnancy & the Heart

Relaxin mediates physiologic hemodynamic adjustments to pregnancy

Pharmacologic use of relaxin may produce these beneficial effects in heart failure

<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>Creatinine Clearance (mL/min)</td>
<td>45% Increase</td>
</tr>
</tbody>
</table>

Relaxin

- Naturally-occurring peptide
- Found in men and women
- Normal hormone of pregnancy
- Women “exposed” for 9 months to increased plasma concentrations: 0.8-1.6 ng/ml pregnancy*
- Benign safety profile

PreRELAX: Phase II

Relaxin 30 µg/kg/d compared to Placebo:
H.R. 0.00 (0.00–0.98); p<0.05

Kaplan-Meier Event-free Survival (%)

Days

Teerlink, Lancet, 2010
RELAX-AHF: study design

• A Phase III, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of serelaxin, in addition to standard therapy, in subjects hospitalized for AHF

Randomized:
1,161 patients hospitalized with AHF, normal-to-elevated SBP and mild-to-moderate renal impairment

Screening
Screening occurred after ≥40 mg i.v. furosemide

Presentation <16 h

Double-blind, randomized treatment period

Placebo (n=580)
Serelaxin 30 µg/kg/d (n=581)

In addition to standard therapy‡

48 h study drug infusion (i.v.) period

06122448 h 5 d

Post-discharge evaluation period

14 d 60 d 180 d

‡Standard therapy permitted at physician’s discretion

AHF=acute heart failure; d=day; h=hour; i.v.=intravenous; SBP=systolic blood pressure
RELAX AHF: Endpoints

N = 1161

Timeline:
- D0
- D1
- D2
- D5
- D14/Index
- D60

Treatment:
- Serelaxin
- Placebo

Primary EP:
- Likert: 6, 12, 24 h
- VAS AUC: 0-100 mm; 0, 6, 12, 24h, D2-D5

Secondary EP:
- Days Alive Out of Hospital
- CV death + HF/RF Re-hospitalization
- CV death

Biomarkers
- WHF
- LoS (index/ICU)

In-hospital benefits
- p<0.025 for either 1° Dyspnea EP
- or p<0.05 for both 1° Dyspnea EPs

Out-patient benefits

Duke Medicine
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

Teerlink et al. Lancet 2012
1° Endpoint: Dyspnea Relief (Likert)

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

Serelaxin

- 6 hr: p=0.113, n=180
- 12 hr: p=0.051, n=205
- 24 hr: p=0.086, n=256
- 6, 12, and 24 hr: p=0.702, n=150

n=180, n=205, n=256, n=288, n=362, n=389, n=150, n=156

Teerlink et al. Lancet 2012
CV Death through Day 180

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

HR 0.63 (0.41, 0.96); p=0.028
NNT = 29

Placebo (N=580)
55 (9.5%)
Serelaxin (N=581)
35 (6.0%)

Teerlink et al. Lancet 2012
Index Hospitalization LOS

Index Hospitalization Length of Stay (Days)

- Placebo: *p=0.039
- n=580
- Serelaxin: n=581

Length of ICU/CCU Stay (Days)

- Placebo: *p=0.029
- n=578
- Serelaxin: n=574

Teerlink et al. Lancet 2012
Biomarkers and Outcomes in RELAX-AHF

Serelaxin affected multiple biomarkers associated with long term outcomes: A mechanism for a long term effect?

Metra, M et al. JACC 2013
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

Stay tuned…..

Duke Medicine
RELAX-AHF 2: Study Design

Randomized, placebo-controlled study in a selected AHF patient population

N = 6375

**Primary EP:**
CV mortality at 180 days
Novel Therapies in AHF

- Serelaxin (Phase III)
- Omecamтив Mecarbil (Phase IIb)
- TRV027 (Phase IIa)
Current Treatments of Acute Heart Failure

Diuretics
- Reduce fluid volume

Vasodilators
- Decrease preload and/or afterload

Inotropes
- Augment contractility
Inotropes in Acute Heart Failure

“Let’s get out of here.”
Omecamtiv Mecarbil
A Cardiac Myosin Activator

• Preclinical
  – Selective activator of cardiac myosin
  – Prolongs duration of systole by
    o Increasing entry rate of myosin into force-producing state
    o Thus increasing overall number of active cross-bridges
  – No increase in myocyte calcium
  – No change in \( \frac{dP}{dt_{\text{max}}} \)
  – No increase in \( \text{MVO}_2 \)
  – Increases stroke volume

Omecamtiv Mecarbil
(MW = 401.43)

Malik FI, et al. Science 2011
How Does a Cardiac Myosin Activator Work?

The Chemical and Mechanical Cycles are Linked

The Actin–Myosin Cycle

Omecamtiv mecarbil increases the number of independent force generators (myosin heads) interacting with the actin filament

“More hands pulling on the rope”

Omecamtiv increases the transition rate from weak to strong binding states

Malik FI, et al. Science 2011
Omecamtiv Mecarbil Does Not Alter the Ca\textsuperscript{2+} Transient

Rat Adult Cardiac Myocytes

**Contractility Transient**
- Basal
- **Omecamtiv mecarbil** 200 nM

**Calcium Transient**
- Basal
- **Omecamtiv mecarbil** 200 nM

**Contractility Transient**
- Basal
- **Isoproterenol** 2 nM

**Calcium Transient**
- Basal
- **Isoproterenol** 2 nM

Malik FI, et al. Science 2011
**Omecamtiv Mecarbil: Dog Heart Failure Model**

*Increases the Duration but not the Velocity of Contraction*

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

![Graph showing time-dependent elastance](image)

- **Dobutamine**
  - Baseline
  - $T_{E_{\text{max}}}$
  - $T_{E_{\text{min}}}$

- **Omecamtiv mecarbil**
  - Baseline
  - $T_{E_{\text{min}}}$

**MVO$_2$**

- Increased
- Unchanged

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Malik FI, et al. Science 2011
Increases in Systolic Ejection Time Underlie Increases in Cardiac Function

Δ Stroke Volume (mL)

Δ Fractional Shortening (% points)

Δ Ejection Fraction (% points)

Δ = placebo corrected change from baseline
Mean ± SEM

Pharmacodynamic Effects of Omecamtiv in HF
Study Design: Sequential Dosing Cohort

Cohort 1
- Omecamtiv
- 1:1 Randomization (n≈200)
- Placebo

Cohort 2
- Omecamtiv
- 1:1 randomization (n≈200)
- Placebo

Cohort 3
- Omecamtiv
- 1:1 randomization (n≈200)
- Placebo

Pharmacokinetic simulations

Cohort 1
- 7.5 mg/hr @ 0-4 hr
- 1.5 mg/hr @ 4-48 hr
- Target: 115 ng/mL
- Cmax: 30-250 ng/mL
- SET: ~3-28 msec

Cohort 2
- 15 mg/hr @ 0-4 hr
- 3 mg/hr @ 4-48 hr
- Target: 230 ng/mL
- Cmax: 75-500 ng/mL
- SET: ~8-55 msec

Cohort 3
- 20 mg/hr @ 0-4 hr
- 4 mg/hr @ 4-48 hr
- Target: 310 ng/mL
- Cmax: 125-700 ng/mL
- SET: ~14-78 msec

Primary Efficacy Endpoint:
Dyspnoea Response (Likert Scale)

Pooled Placebo

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dyspnoea Response Rate (% Responders)</th>
<th>Response Rate Ratio*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled Placebo</td>
<td>41%</td>
<td>1.03</td>
<td>(0.79, 1.35)</td>
</tr>
<tr>
<td>OM Cohort 1</td>
<td>42%</td>
<td>1.15</td>
<td>(0.90, 1.47)</td>
</tr>
<tr>
<td>OM Cohort 2</td>
<td>47%</td>
<td>1.23</td>
<td>(0.97, 1.55)</td>
</tr>
<tr>
<td>OM Cohort 3</td>
<td>51%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Ratio of response rate to Pooled Placebo

p-value of a CMH test among all 3 Placebo arms = 0.32
# Secondary Efficacy Endpoint: Worsening Heart Failure (WHF)

<table>
<thead>
<tr>
<th>Within 7 days of IP initiation</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>Death or WHF*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes - n(%)</td>
<td>52 (17)</td>
<td>13 (13)</td>
<td>9 (9)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Relative risk</td>
<td>0.67</td>
<td>0.54</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.38, 1.18)</td>
<td>(0.28, 1.04)</td>
<td>(0.27, 1.08)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.151</td>
<td>0.054</td>
<td>0.067</td>
<td></td>
</tr>
<tr>
<td>WHF*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes - n(%)</td>
<td>51 (17)</td>
<td>13 (13)</td>
<td>8 (8)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Relative risk</td>
<td>0.68</td>
<td>0.49</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.38, 1.21)</td>
<td>(0.24, 0.98)</td>
<td>(0.28, 1.09)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.179</td>
<td>0.034</td>
<td>0.075</td>
<td></td>
</tr>
</tbody>
</table>

*Worsening heart failure is defined as clinical evidence of persistent or deteriorating heart failure requiring at least one of the following treatments:
- Initiation, reinstitution or intensification of IV vasodilator
- Initiation of IV positive inotropes, or IV vasopressors
- Initiation of ultrafiltration, hemofiltration, or dialysis
- Initiation of mechanical ventilatory or circulatory support
Troponin-I Change from Baseline (ng/mL) Compared with Pooled Placebo

<table>
<thead>
<tr>
<th>Time</th>
<th>Troponin Change from Baseline (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 hours</td>
<td>Median: 0.044, (Q1, Q3): 0.023, 0.080</td>
</tr>
<tr>
<td>15 hours</td>
<td>Median: 0.060, (Q1, Q3): 0.028, 0.141</td>
</tr>
<tr>
<td>24 hours</td>
<td>Median: 0.044, (Q1, Q3): 0.030, 0.084</td>
</tr>
<tr>
<td>48 hours</td>
<td>Median: 0.056, (Q1, Q3): 0.026, 0.092</td>
</tr>
<tr>
<td>Day 4</td>
<td></td>
</tr>
<tr>
<td>Day 6</td>
<td></td>
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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
Development of Omecamtiv Mecarbil

**Phase 1-2a**
- Well-characterized PK
- Echo PD at > 100-300 ng/mL
- Increased risk at > 1200 ng/mL

**Phase 2b**
- Further characterize PK in AHF
- Evaluate safety, tolerability, echo PD, and clinical efficacy

**Phase 3**
- Evaluate safety, tolerability, and clinical efficacy

**Availability of IV and PO formulations enable evaluation of omecamtiv mecarbil across a range of heart failure patient populations**
Novel Therapies in AHF

- Serelaxin (Phase III)
- Omecamtiv Mecarbil (Phase IIb)
- TRV027 (Phase IIa)
Duke Cardiologist Wins 2012 Nobel Prize
Angiotensin receptor activation in AHF is both maladaptive and beneficial.
Full AT1R antagonism

- Vasoconstriction
  - ↓ blood pressure

- Na⁺ & fluid retention
  - ↓ fluid retention
  - ↓ cardiac output

- Cardiac contractility

AT1R

GRK

Gα

β-arrestin

ARB
Selective B-arrestin biased ligand

Vasoconstriction
↓ blood pressure

Na⁺ & fluid retention
↓ fluid retention

Cardiac contractility
preserve cardiac output
TRV027: a selective β-arrestin biased ligand
Phase 2a hemodynamic study design

TRV027 (µg/kg/min) vs Time (hours)

- Baseline
- Escalation
- Continuous infusion
- Washout

- Max = 10 µg/kg/min
- Max = 3 µg/kg/min
- Max = 1 µg/kg/min

Cohort 1 (n = 6)
Cohorts 2+4 (n = 12)
Cohort 3 (n = 6)
Placebo (n=8, 2 per cohort)
Sustained, reversible reduction in MAP by TRV027 in high PRA subjects

Changes in MAP during and after study drug infusion

- PBO (n=8)
- normal PRA (n=13)
- high PRA (n=11)

Soergal, ACC 2013
Dose response on MAP in high PRA subjects

"high PRA" = PRA > 5.8

* both high PRA subjects from Cohort 3 had dosing or sampling irregularities and were excluded
TRV027: BLAST-AHF

- Biased Ligand of Angiotensin II Study in Acute Heart Failure

- Phase IIb study in launching in late 2013
Conclusions

- AHF remains major public health problem
- Few new therapies have been developed over last 40 years
- Many promising new therapies currently in development with unique biologic mechanisms and potential to improve acute symptoms and post-discharge outcomes
Clinical Trials of Pharmacological Therapies in Acute Heart Failure Syndromes
Lessons Learned and Directions Forward

G. Michael Felker, MD, MHS; Peter S. Pang, MD; Kirkwood F. Adams, MD; John G.F. Cleland, MD; Gad Cotter, MD; Kenneth Dickstein, MD; Gerasimos S. Filippatos, MD; Gregg C. Fonarow, MD; Barry H. Greenberg, MD; Adrian F. Hernandez, MD, MHS; Sadiya Khan, MD; Michel Komajda, MD; Marvin A. Konstam, MD; Peter P. Liu, MD; Aldo P. Maggioni, MD; Barry M. Massie, MD; John J. McMurray, MD; Mandeep Mehra, MD; Marco Metra, MD; John O'Connell, MD; Christopher M. O'Connor, MD; Ileana L. Pina, MD; Piotr Ponikowski, MD; Hani N. Sabbah, PhD; John R. Teerlink, MD; James E. Udelson, MD; Clyde W. Yancy, MD; Faiez Zannad, MD, PhD; Mihai Gheorghiade, MD; on behalf of the International AHFS Working Group
“The rumors of the death of acute heart failure research have been greatly exaggerated.”