A Contemporary Journey of a Drug from Bench to Bedside: Pivotal Trials of a Novel Compound

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Critical Care Franchise
Novartis Pharmaceuticals
Conflict of Interest

- Xing Li Wang is an employee of Novartis Pharmaceuticals Corporate
Who are the Players in Drug Development?
Likelihood of Approval and Phase Success in All Indications

Hay et al. Nature Biotech 2014;32:40-51
Schematic Flow of Drug Development

Classical Pathway

Identification of unmet medical needs
Target molecules, drug candidates, MoA

Preclinical evidence

Phase I
PK/PD profile
MTD, biomarkers

Phase II
PoC, DRF, Safety, Efficacy

Phase III
Pivotal Studies: Efficacy and Safety

Unmet medical needs
Identified pathogenesis
Defined drug target pathway
Efficacious dose range
Tolerable adverse events
Favorable risk/benefit profile

Registration

> 10 years
Drug Development: Target Disease and Drug Candidate

- **Unmet Medical Need**
  - Evaluate the disease landscape, demographics, severity, public health impact, epidemiology, etc
  - Evaluate the unmet medical need, existing standard of care and gaps in the treatment
  - Understand the pathogenesis of the target disease so that potential therapeutic targets can be identified

- **Established Mechanism of Action of the Candidate Drug**
  - Assess the mechanism of action of the candidate drug to see if it could have therapeutic impact

- **On Target Effects (Efficacy)**
  - Clear PK/PD profile with predictable efficacy dose range

- **Off Target Effects (Safety)**
  - Wide gap for the MTD

- Dissect previous studies of the candidate drug where trouble can be identified early

- Even all dots fit, it may not end up with an approvable drug
Phase I Design

- Mostly empirical rather than statistical
- Dose escalation to reach maximum tolerated dose (MTD) and dose limiting toxicity (DLT)
- Health volunteers and/or patients with intended target disease
- Safety and tolerability
- PK profiling
- PD observation
Phase II Clinical Trials

Rationales and Designs

- Rationale for dose: Phase II trial
  - To understand the dose response for safety and efficacy
    - To distinguish an effective dose from minimally or not effective dose
    - To distinguish a unsafe dose from a safe dose

- Key consideration for Phase II paradigms
  - Long term clinical safety
    - First real look at “risk-benefit”
  - Tie to safety assessment studies
    - Usually need ~1500 patients with 6 month safety and a minimum of ~100 with one year safety (Phase II and III together)

- Types of DRF Trial design
  - Cross-over; Dose titration; Parallel dose comparison; Dose escalation

- Statistical Model for DRF and PoC
  - Traditional (ANOVA); Adaptive (e.g. Bayesian); Modeling and Simulation; Pharmacometric model
Strategies in designing Phase II dose-range finding study

Dose Ranges: Phase I: > 500-fold; Phase II: > ~10-fold; Phase III: 1-4-fold
Phase III Trial Design: Points to Consider

- Primary question (Primary Endpoint) and secondary questions
- Study population (subset by inclusion/exclusion)
- Randomization processes (fixed or adaptive, stratification)
- Control (placebo, standard of care, active comparator, historical)
- Blindness (unblinded, single- double- blinded, matching controls)
- Sample size (effect size, p value, event rate, power, variability)
- Baseline assessment
- Recruitment
- Data collection and quality control (missing data)
- Adverse events
- Data analysis plan (confirmatory and exploratory analyses, ITT, mITT, PPT)
Phase III Design

- Randomized control studies
  - Event-driven or fixed sample size
  - Traditional fixed design or adaptive design
  - Parallel or staged

- Nonrandomized concurrent control studies

- Historical controls

- Cross-over designs

- Withdrawal designs

- Factorial designs

- Parallel or Run-in designs

- Superiority vs Non-inferiority
Challenges for Global Trials

Global or regional or country specific multicenter trials – How much heterogeneity or variation can we tolerate?
Challenges and Ideal Conditions

- **Challenges**
  - Heterogeneity in baseline patient characteristics may make a potentially effective drug *not approvable* for clinical use.
  - Ethnic specific variation in responses to drugs may make the selected *dose inadequate, not efficacious or unsafe*.
  - Variation in standard of care makes the comparison impossible.

- **Ideal conditions**
  - Homogeneous etiology of the target disease.
  - Homogeneous stage and clinical condition of the disease.
  - Homogeneous standard of care with 100% adherence.
  - Homogeneous comorbidities and concomitant medications.
  - Objective and readily measureable endpoints.
  - 100% compliance in treatment and follow-ups.
  - .......
Sources of Regional Variations

- **Intrinsic - genetic/race/ethnicity specific**
  - Variation in PK/PD profiles
  - Variation in dosing in reference to efficacy and safety
  - Variation in baseline patient characteristics and response to treatment

- **Extrinsic – social, cultural, lifestyle, nutritional, education, climates**
  - Variation in standard of care: criteria of diagnosis, availability of and access to treatment, threshold of hospitalization, alternative therapies
  - Variation in routines and standards of clinical practices: diagnostic procedures and treatments
  - Regulatory practice/GCP, healthcare policies and payment systems

- **Medical conditions**
  - Causes of the trial target disease
  - Comorbidities and concomitant medications

- **Variation in the trial endpoint event rates**
  - Variable causes and rates in mortality
  - Subjective definition patient reported endpoints
Example of Regional Variations in HF Registries

Ambrosy AP, et al. JACC 2014;63:1123-33

<table>
<thead>
<tr>
<th>Table 5: IV Therapies and Procedural Interventions for Representative HHF Registries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADHERE</strong></td>
</tr>
<tr>
<td>---</td>
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<tr>
<td><strong>IV Therapies</strong></td>
</tr>
<tr>
<td>Diuretics</td>
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<tr>
<td>Vasodilators</td>
</tr>
<tr>
<td>Inotropes</td>
</tr>
<tr>
<td><strong>Procedural Interventions</strong></td>
</tr>
<tr>
<td>Coronary angiography</td>
</tr>
<tr>
<td>PCI</td>
</tr>
<tr>
<td>CABG</td>
</tr>
<tr>
<td>Synchronized cardioversion</td>
</tr>
<tr>
<td>Pulmonary artery catheter</td>
</tr>
<tr>
<td>IABP</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
</tr>
<tr>
<td>Ultrafiltration</td>
</tr>
</tbody>
</table>

Values are %. *Estimate includes inotropes and vasopressors. †Overall inotrope utilization unavailable, but 22.3% of patients received dobutamine. ‡Continuous venovenous hemofiltration.

CABG = coronary artery bypass graft; IABP = intra-aortic balloon pump; IV = intravenous; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.
Kaplan-Meier Analysis for Cumulative Mortality by Region

Tolvaptan, an oral selective V(2)-vasopressin antagonist in EVEREST Trial

Blair JE, et al. JACC 2008;52:1640-8
Three Possible Ways for Global Trial Design

- One step: Single global trials with all countries included – simultaneous approval
- Sequential: US/EU first, followed with Asian bridging studies – delayed approval
- Parallel or staggered: US/EU as one and Asia as the other – simultaneous approval
Congestive Heart Failure
A Growing Global Epidemic and an Unmet Medical Need
Prevalence of Cardiovascular Disease in US
Mortality of HF versus stroke and common cancers

5-Year Age- and Sex-Adjusted Relative Survival

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure</td>
<td>62</td>
</tr>
<tr>
<td>Stroke</td>
<td>50</td>
</tr>
<tr>
<td>All Cancers Evaluated*</td>
<td>57</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>18</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>89</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>99</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>63</td>
</tr>
</tbody>
</table>

*Lung, breast, prostate, colorectal
Askoxylakis et al. *BMC Cancer* 2010;10:105
### Congestive Heart Failure and Acute Heart Failure: Acute or progressive symptoms of HF requiring hospitalization

#### Clinical presentation

<table>
<thead>
<tr>
<th>CONGESTION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary congestion / alveolar edema(^2)</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>breasts, chest X-ray pulmonary congestion</td>
<td>Rales</td>
</tr>
<tr>
<td>Systemic congestion(^1)</td>
<td>3rd heart sound</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Jugular venous distention</td>
</tr>
<tr>
<td>Renal dysfunction(^3)</td>
<td>Weight gain / peripheral edema</td>
</tr>
<tr>
<td></td>
<td>Increased creatinine</td>
</tr>
</tbody>
</table>

#### Hemodynamic presentation

- LV filling pressure increased
- PCWP (25–30 mmHg)
- Cardiac wall stress
- Elevated NT-pro-BNP
- Elevated troponin

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The pathophysiology of HF results in an increasingly downward spiral.

Myocardial/renal damage

There is a need for evidence-based treatments in acute HF

<table>
<thead>
<tr>
<th>Group</th>
<th>Medication</th>
<th>Class of recommendation</th>
<th>Level of evidence† (A–C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>IV loop diuretics</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>IV nitrates</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Sodium nitroprusside</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>IV opiates</td>
<td>Morphine</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Inotropes*</td>
<td></td>
<td>IIa or IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

†A=data derived from multiple RCTs or meta-analyses; B=data derived from a single RCT or large non-randomized studies; C=consensus of opinion of the experts and/or small studies, retrospective studies, registries

*Inotropic agents are not recommended unless the patient has hypotension (systolic blood pressure [SBP] <85 mmHg), hypoperfusion or shock due to safety concerns

IV=intravenous; RCT=randomized controlled trial

Adapted from McMurray et al. Eur Heart J 2012;33:1787–847

“The treatment of acute HF remains largely opinion-based with little good evidence to guide therapy”
ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012
McMurray et al. Eur Heart J 2012;33:1787–847
Development of Serelaxin for the Treatment of Acute Heart Failure

A classic development pathway
Serelaxin is a recombinant form of the human hormone relaxin-2 that acts directly on CV tissues

- Relaxin-2 is a naturally occurring peptide hormone which is elevated during pregnancy to adapt the maternal cardiovascular system to fluid overload, but is also present in male

- Structure of human relaxin-2: 53 amino acids (2 chains connected by 2 disulphide bonds)

- Human relaxin-2 is one of seven peptides in the relaxin family of hormones

- Relaxin-2 mediates its effects via specific G-protein-coupled receptors: RXFP1 (LGR7) and RXFP2 (LGR8)

- Cardiovascular tissues are equipped with relaxin receptors that are activated by circulating or regionally generated relaxin-2 to mediate diverse signaling pathways

Positive immunostaining for relaxin and precursor forms in both the endothelium and vascular smooth muscle of a small renal artery from a virgin female rat

Serelaxin (recombinant human relaxin-2) activates the relaxin receptor, which leads to several effects:

- ↓ Inflammation
- ↓ Fibrosis
- ↑ Vasodilation
- Renal effects
- Angiogenesis

The diagram shows the following interactions:

- ↓ TNF-α
- ↓ TGF-β
- ↓ Collagen deposition
- ↑ MMP
- ET-1
- ET₁₋₃₂
- NOS
- ↑ VEGF
- ET_B receptor

ET_B receptor = endothelin receptor type B; ET-1 = endothelin-1; MMP = matrix metalloproteinase; NO = nitric oxide; NOS = nitric oxide synthase; TGF = transforming growth factor; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.

Primary Hemodynamic Data

Rapid and sustained reduction in PCWP, no significant treatment difference in CI

Data represented as mean ± standard error, *p<0.05

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>PCWP: time-weighted average change from baseline</th>
<th>Serelaxin (n=32)</th>
<th>Placebo (n=31)</th>
<th>Treatment difference [95% confidence interval]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–8 h</td>
<td>-3.79 (0.50)</td>
<td>-1.08 (0.51)</td>
<td>-2.70 [-4.10, -1.31]</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>8–20 h</td>
<td>-4.90 (0.73)</td>
<td>-2.67 (0.74)</td>
<td>-2.24 [-4.28, -0.19]</td>
<td>0.0322</td>
<td></td>
</tr>
<tr>
<td>20–24 h</td>
<td>-4.41 (0.83)</td>
<td>-3.11 (0.85)</td>
<td>-1.30 [-3.63, 1.03]</td>
<td>0.27</td>
<td></td>
</tr>
</tbody>
</table>

Data represented in mmHg as least squares mean (standard error) change from baseline.
Time weighted average is based on area under the effect curve for the corresponding time interval.
Primary Renal Hemodynamic Data

*Increase in RPF with serelaxin, no treatment difference in GFR*

**Data represented as mean ± standard error, *p<0.05**

<table>
<thead>
<tr>
<th>Time interval</th>
<th>Serelaxin (N=28)</th>
<th>Placebo (N=37)</th>
<th>Treatment difference‡ (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–24 h</td>
<td>1.31 (1.05)</td>
<td>1.13 (1.04)</td>
<td>1.16 (1.05, 1.28)</td>
<td>0.0042</td>
</tr>
<tr>
<td>8–24 h</td>
<td>1.29 (1.05)</td>
<td>1.14 (1.05)</td>
<td>1.13 (1.01, 1.27)</td>
<td>0.0386</td>
</tr>
<tr>
<td>24–28 h</td>
<td>1.35 (1.05)</td>
<td>1.16 (1.05)</td>
<td>1.16 (1.03, 1.30)</td>
<td>0.0115</td>
</tr>
</tbody>
</table>

‡ Data presented as least squares geometric mean ratio to baseline (standard error), unless stated otherwise †Ratio of least squares geometric mean ratios
Pre-RELAX-AHF
Phase II Dose Range Finding Study
Pre-RELAX-AHF: study design

Phase IIb, multicenter (54 sites), international (8 countries), randomized, double-blind, placebo-controlled, parallel-group study in 234 patients with acute HF

AHF (dyspnea, BNP*, CXR)
SBP >125 mmHg
CrCl 30–75 mL/min

After ≥40 mg i.v. furosemide
Within 16 hours of presentation

Randomized 3:2:2:2:2
Stratified by site

Placebo (n=61)
Serelaxin 10 µg/kg/day (n=40)
Serelaxin 30 µg/kg/day (n=42)
Serelaxin 100 µg/kg/day (n=37)
Serelaxin 250 µg/kg/day (n=49)

0 6 12 24 48h 5d 14d 60d 180d
48 h study drug infusion
Post-discharge evaluations

* BNP ≥350 or NT-proBNP ≥1400 pg/mL
### Dose selection in Pre-RELAX-AHF

**Multidomain approach to dose selection**

30µg/kg/day provided best safety/efficacy profile

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=61</th>
<th>10 µg/kg/day N=40</th>
<th>30 µg/kg/day N=42</th>
<th>100 µg/kg/day N=37</th>
<th>250 µg/kg/day N=49</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Proportion of subjects with moderate/marked improvement by Likert at 6, 12 and 24hrs (Likert)</td>
<td>23% p=0.5</td>
<td>28% p=0.05</td>
<td>40% p=0.037</td>
<td>14% p=0.27</td>
<td>22% p=0.88</td>
</tr>
<tr>
<td>2. mean VAS AUC change from baseline to Day 5 (mm*hr)</td>
<td>1.679 (1.024-2.334) p=0.15</td>
<td>2.500 (1.570-3.430) p=0.11</td>
<td>2.567 (1.664-3.470) p=0.11</td>
<td>2.486 (1.531-3.441) p=0.15</td>
<td>2.155 (1.483-2.826) p=0.31</td>
</tr>
<tr>
<td>3. Incidence of worsening heart failure through Day 5 (%)</td>
<td>21.3% p=0.75</td>
<td>20.0% p=0.75</td>
<td>11.9% p=0.29</td>
<td>13.5% p=0.40</td>
<td>10.2% p=0.15</td>
</tr>
<tr>
<td>4. Mean length of hospital stay (days)</td>
<td>12.0 (10.1-13.9) p=0.36</td>
<td>10.9 (8.1-13.6) p=0.18</td>
<td>10.2 (8.3-12.1) p=0.18</td>
<td>11.1 (8.9-13.3) p=0.75</td>
<td>10.6 (8.7-12.4) p=0.2</td>
</tr>
<tr>
<td>5. Persistent renal impairment (Creatinine increase of 0.3 mg/dL or more at day 5 and 14)</td>
<td>6.8% p=0.87</td>
<td>7.5% p=0.87</td>
<td>7.3% p=0.9</td>
<td>10.8% p=0.47</td>
<td>15.2% p=0.19</td>
</tr>
<tr>
<td>Logistic regression odds ratio (95% Wald CI)</td>
<td>1.1 (0.2-5.4) p=0.87</td>
<td>1.1 (0.2-5.3) p=0.87</td>
<td>1.7 (0.4-7.4) p=0.47</td>
<td>2.4 (0.7-8.9) p=0.19</td>
<td></td>
</tr>
<tr>
<td>6. Mean # days alive and out of hospital through Day 60</td>
<td>44.2 (40.6-47.8) p=0.4</td>
<td>47.0 (42.9-51.2) p=0.16</td>
<td>47.9 (44.7-51.0) p=0.16</td>
<td>48.0 (44.6-51.3) p=0.4</td>
<td>47.6 (44.1-51.0) p=0.12</td>
</tr>
<tr>
<td>7. Proportion of subjects with CV death or re-hospitalization due to HF or renal failure through Day 60 (%)</td>
<td>17.2 p=0.32</td>
<td>10.1 p=0.32</td>
<td>2.6 p=0.053</td>
<td>8.4 p=0.23</td>
<td>6.2 p=0.85</td>
</tr>
<tr>
<td>Cox proportional hazard ratio (95% Wald CI)</td>
<td>0.55 (0.17-1.77) p=0.32</td>
<td>0.13 (0.02-1.03) p=0.053</td>
<td>0.46 (0.13-1.66) p=0.23</td>
<td>0.32 (0.09-1.17) p=0.85</td>
<td></td>
</tr>
<tr>
<td>8. Kaplan Meier estimate CV mortality to Day 180(%)</td>
<td>14.3</td>
<td>2.5</td>
<td>0</td>
<td>2.9</td>
<td>6.2</td>
</tr>
<tr>
<td>Cox proportional hazard ratio (95% Wald CI)</td>
<td>0.19 (0.02-1.57) p=0.14</td>
<td>0.0 p=0.04</td>
<td>0.22 (0.03-1.76) p=0.15</td>
<td>0.49 (0.13-1.9) p=0.51</td>
<td></td>
</tr>
<tr>
<td>Fisher’s exact test</td>
<td>p &lt;0.05</td>
<td>0.05 ≤ p &lt;0.20</td>
<td>p&lt;0.20 against</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
RELAX-AHF

Phase III pivotal study in AHF patients with normal or high blood pressure and mild to moderate renal impairment
RELAX-AHF: Study Design
Randomized, placebo-controlled study in a selected AHF patient population

Population
- 1161 hospitalized AHF patients with systolic blood pressure >125 mmHg at screening, eGFR 30-75 mL/min/1.73 m²

Inclusion criteria
- Dyspnea at rest or with minimal exertion, plus pulmonary congestion on radiograph
- BNP ≥ 350pg/mL or NT-pro-BNP ≥1400 pg/mL
- IV furosemide of at least 40 mg (or equivalent) at any time between admission and screening
RELAX-AHF: Key Efficacy Measures

Assessment of symptom relief, in-hospital benefits, Day 60 outcomes and 180 day mortality

**Timeline:**
- **D0**
- **D1**
- **D2**
- **D5**
- **D14/Index**
- **D60**
- **D180**

**Treatment**
- RLX/PBO 48h iv

**Primary EP**
- LIKERT
- VAS

**Secondary EP**
- DAOOH
- CV death or re-hospitalization
- CV death

**In-hospital benefits**
- LoS (index/ICU)
- WHF

**Out-patient benefits**

\[ p < 0.025 \text{ for either primary EP or } p < 0.05 \text{ for both primary EPs demonstrating dyspnea improvement} \]
Primary EP1: Dyspnea Assessment by the VAS (ITT)

Statistically significant improvement of dyspnea through Day 5

AUC with placebo, 2308 3082 AUC with serelaxin, 2756 2588 *P=0.0075

19.4% increase in AUC with serelaxin from baseline through day 5 (Mean difference of 447.7 mm-hr)

*P-value is based on a two-sided two sample t-test for serelaxin versus placebo comparing area under the curve (AUC, mm-hours) of change from baseline of dyspnea visual analog scale (VAS) from baseline to Day 5.

Source: Post-text table 14.2-1.1
Worsening Heart Failure

Serelaxin reduced the incidence of WHF and hence worsening dyspnea

Cumulative proportion of worsening heart failure to Day 5 (%)

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. PBO
*** HR estimate by Cox model, HR<1.0 favors serelaxin
CV Death through Day 180 (ITT)

Serelaxin significantly reduces CV mortality

HR 0.63 (0.41, 0.96); p=0.028

Placebo (N=580)
55 (9.5%)

Serelaxin (N=581)
35 (6.0%)

NNT = 29

Number of Events, n (%)*

[Source: Tables 14.2-17, 14.3.1-14.2]

* Adjudicated up to Day 60
Pre-specified Plasma Biomarkers

*Serelaxin may protect heart and kidney tissue and support cardiac unloading*

- **Troponin T**
  - Geometric mean change
  - Days
  - $p = 0.0126$
  - Prevention of cardiomyocyte loss

- **NT-pro-BNP**
  - Geometric mean change
  - Days
  - $p < 0.0001$
  - Alleviation of cardiac wall stress and decongestion

- **Cystatin C**
  - Geometric mean change
  - Days
  - $p = 0.0028$
  - Prevention of renal function loss

These changes have shown to be predictive of outcome value in AHF

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39 Strategies for Clinical Development - China 2014

**Novartis**
Treatment of AHF with Serelaxin

*Improvement in pathophysiological disease drivers resulting in mortality benefits*

**Efficacy**
- Serelaxin Infusion 48-hr
- Relief of Dyspnea and Congestion
- Prevention of worsening of heart failure and of renal function
- Prevention of heart and kidney tissue damage
- Reduction of all cause and CV mortality

**Safety**
- Controlled management of BP decrease
- Placebo-like incidence of AE
- Favorable clinical chemistry profile
- CV death drives All-cause death

RELAX-AHF confirmed observations made in Pre-RELAX on several parameters

Serelaxin may represent an important new treatment option for patients with AHF
Development of LCZ696 for the Treatment of Chronic Heart Failure

A innovative development pathway
Drugs that inhibit the renin-angiotensin system have modest effects on survival. Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF.
**LCZ696: Angiotensin Receptor Neprilysin Inhibition**

**Natriuretic and other vasoactive peptides***

- Vasorelaxation
- ↓ Blood pressure
- ↓ Sympathetic tone
- ↓ Aldosterone levels
- ↓ Fibrosis
- ↓ Hypertrophy
- ↑ Natriuresis/diuresis

---

**RAAS**

- Angiotensinogen (liver secretion)
- Ang I → Ang II

**Inhibiting**

- Vasoconstriction
- ↑ Blood pressure
- ↑ Sympathetic tone
- ↑ Aldosterone
- ↑ Fibrosis
- ↑ Hypertrophy

---

**Enhancing**

- Vasorelaxation
- ↓ Blood pressure
- ↓ Sympathetic tone
- ↓ Aldosterone levels
- ↓ Fibrosis
- ↓ Hypertrophy
- ↑ Natriuresis/diuresis

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*Neprilysin substrates listed in order of relative affinity for NEP: ANP, CNP, Ang II, Ang I, adrenomedullin, substance P, bradykinin, endothelin-1, BNP
Ang=angiotensin; ANP=atrial natriuretic peptide; AT₁=angiotensin II type 1; BNP=B-type natriuretic peptide; CNP=C-type natriuretic peptide; NEP=neprilysin; RAAS=renin angiotensin aldosterone system

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PARADIGM-HF: Study Design

Randomization

Single-blind run-in period

Double-blind period

Enalapril 10 mg BID

LCZ696 200 mg BID

(1:1 randomization)

Enalapril 10 mg BID

10 mg BID

100 mg BID

200 mg BID

2 weeks

1-2 weeks

2-4 weeks

Source: PARADIGM late breaker presentation Aug 31, 2014 by Milton Packer
10,521 patients screened at 1043 centers in 47 countries

- Did not fulfill criteria for randomization (n=2079)
- Randomized erroneously or at sites closed due to GCP violations (n=43)

8399 patients randomized for ITT analysis

- **LCZ696** (n=4187)
  - At last visit: 375 mg daily
  - 11 lost to follow-up

- **Enalapril** (n=4212)
  - median 27 months of follow-up
  - At last visit: 18.9 mg daily
  - 9 lost to follow-up
## PARADIGM-HF: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.8 ± 11.5</td>
<td>63.8 ± 11.3</td>
</tr>
<tr>
<td>Women (%)</td>
<td>21.0%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy (%)</td>
<td>59.9%</td>
<td>60.1%</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>29.6 ± 6.1</td>
<td>29.4 ± 6.3</td>
</tr>
<tr>
<td>NYHA functional class II / III (%)</td>
<td>71.6% / 23.1%</td>
<td>69.4% / 24.9%</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>122 ± 15</td>
<td>121 ± 15</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72 ± 12</td>
<td>73 ± 12</td>
</tr>
<tr>
<td>N-terminal pro-BNP (pg/ml)</td>
<td>1631 (885-3154)</td>
<td>1594 (886-3305)</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/ml)</td>
<td>255 (155-474)</td>
<td>251 (153-465)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Digitalis</td>
<td>29.3%</td>
<td>31.2%</td>
</tr>
<tr>
<td>Beta-adrenergic blockers</td>
<td>93.1%</td>
<td>92.9%</td>
</tr>
<tr>
<td>Mineralocorticoid antagonists</td>
<td>54.2%</td>
<td>57.0%</td>
</tr>
<tr>
<td>ICD and/or CRT</td>
<td>16.5%</td>
<td>16.3%</td>
</tr>
</tbody>
</table>

Source: PARADIGM late breaker presentation Aug 31, 2014 by Milton Packer
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

**Kaplan-Meier Estimate of Cumulative Rates (%)**

- **Enalapril** (n=4212)
  - Kaplan-Meier Estimate of Cumulative Rates (%)
  - Days After Randomization
- **LCZ696** (n=4187)
  - Kaplan-Meier Estimate of Cumulative Rates (%)
  - Days After Randomization

**HR = 0.80 (0.73-0.87)**
**P = 0.0000002 (1-sided)**
**Number needed to treat = 21**

Patients at Risk:
- LCZ696: 4187, 3922, 3663, 3018, 2257, 1544, 896, 249
- Enalapril: 4212, 3883, 3579, 2922, 2123, 1488, 853, 236

Source: PARADIGM late breaker presentation Aug 31, 2014 by Milton Packer
**PARADIGM-HF: Cardiovascular Death**

<table>
<thead>
<tr>
<th>Days After Randomization</th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>180</td>
<td>4056</td>
<td>4051</td>
</tr>
<tr>
<td>360</td>
<td>3891</td>
<td>3860</td>
</tr>
<tr>
<td>540</td>
<td>3282</td>
<td>3231</td>
</tr>
<tr>
<td>720</td>
<td>2478</td>
<td>2410</td>
</tr>
<tr>
<td>900</td>
<td>1716</td>
<td>1726</td>
</tr>
<tr>
<td>1080</td>
<td>1005</td>
<td>994</td>
</tr>
<tr>
<td>1260</td>
<td>280</td>
<td>279</td>
</tr>
</tbody>
</table>

**Kaplan-Meier Estimate of Cumulative Rates (%)**

**HR = 0.80 (0.71-0.89)**  
**P = 0.00004 (1-sided)**  
**Number need to treat = 32**

Source: PARADIGM late breaker presentation Aug 31, 2014 by Milton Packer
**PARADIGM-HF: All-Cause Mortality**

**Kaplan-Meier Estimate of Cumulative Rates (%)**

**Days After Randomization**

**Patients at Risk**

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>0</td>
<td>360</td>
<td>0</td>
</tr>
<tr>
<td>180</td>
<td>720</td>
<td>16</td>
</tr>
<tr>
<td>360</td>
<td>1080</td>
<td>32</td>
</tr>
<tr>
<td>540</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>720</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>900</td>
<td>0</td>
<td>835</td>
</tr>
<tr>
<td>1080</td>
<td>0</td>
<td>711</td>
</tr>
<tr>
<td>1260</td>
<td>0</td>
<td>835</td>
</tr>
</tbody>
</table>

**Source:** PARADIGM late breaker presentation Aug 31, 2014 by Milton Packer

**HR = 0.84 (0.76-0.93)**

**P < 0.0001**
## PARADIGM-HF: Effect of LCZ696 vs Enalapril on Primary Endpoint and Its Components

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (n=4187)</th>
<th>Enalapril (n=4212)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>914 (21.8%)</td>
<td>1117 (26.5%)</td>
<td>0.80 (0.73-0.87)</td>
<td>0.0000002</td>
</tr>
<tr>
<td><strong>Cardiovascular death</strong></td>
<td>558 (13.3%)</td>
<td>693 (16.5%)</td>
<td>0.80 (0.71-0.89)</td>
<td>0.00004</td>
</tr>
<tr>
<td><strong>Hospitalization for heart failure</strong></td>
<td>537 (12.8%)</td>
<td>658 (15.6%)</td>
<td>0.79 (0.71-0.89)</td>
<td>0.00004</td>
</tr>
</tbody>
</table>

* All p-values 1-sided

Source: PARADIGM late breaker presentation Aug 31, 2014 by Milton Packer
Angiotensin Neprilysin Inhibition With LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System

Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial

Source: PARADIGM late breaker presentation Aug 31, 2014 by Milton Packer
In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:

**LCZ696 was more effective than enalapril in . . .**

- Reducing the risk of CV death and HF hospitalization
- Reducing the risk of CV death by *incremental* 20%
- Reducing the risk of HF hospitalization by *incremental* 21%
- Reducing all-cause mortality by *incremental* 16%
- Incrementally improving symptoms and physical limitations

**LCZ696 was better tolerated than enalapril . . .**

- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema

Source: PARADIGM late breaker presentation Aug 31, 2014 by Milton Packer
For the last 25 years, the magnitude of the effect of ACE inhibitors on cardiovascular mortality (18%) has created an ethical mandate for their use in all patients with chronic heart failure who could tolerate treatment with these drugs.

The finding that LCZ696 has an 20% greater effect on cardiovascular mortality than ACE inhibitors strongly supports the conclusion that LCZ696 should replace current use of ACE inhibitors and angiotensin receptor blockers in the management of chronic heart failure.
Types of Clinical Research

- **Case Reports**
- **Observational**
  - Case control/retrospective
  - Cross sectional
  - Prospective
- **Drug Development**
  - Preclinical (animal studies, dose-responses, toxicology, etc)
  - Phase I [First in human, maximum tolerated dose (MTD), safety]
  - Phase II (Target patients, dose range, safety, efficacy)
  - Phase III (Efficacy, safety, label dose and patients for registration)
  - Phase IV (Post-approval safety and expanded populations)
Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms in Heart Failure

Endogenous vasoactive peptides

- natriuretic peptides
- adrenomedullin
- bradykinin
- substance P
- calcitonin gene-related peptide

Neprilysin inhibition

- Neurohormonal activation
- Vascular tone
- Cardiac fibrosis, hypertrophy
- Sodium retention

Inactive metabolites
LCZ696: Angiotensin Receptor Neprilysin Inhibition

**LCZ696**

- Angiotensin receptor blocker
- Inhibition of neprilysin
### The four essential goals for acute HF therapies

| **1. Improve signs and symptoms** | - Prompt relief of symptoms
- Relieve signs of congestion (reduction in edema, rales, JVP, weight) |
| **2. Improve in-hospital measures** | - Decrease in-hospital mortality
- Reduce length of stay
- Prevent worsening of HF in hospital (failure to improve or worsening signs and symptoms of HF despite therapy) |
| **3. Prevent end-organ damage** | - Prevent myocardial injury (troponin)
- Prevent renal dysfunction or injury (blood urea nitrogen, creatinine, cystatin C, other markers) |
| **4. Reduce post-discharge events** | - Decrease mortality
- Prevent re-hospitalization |