The Angiotensin Receptor Neprilysin Inhibitor LCZ696 in Heart Failure with Preserved Ejection Fraction

The Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejection fraction (PARAMOUNT) Trial

Scott D. Solomon, MD, Michael Zile, MD, Burkert Pieske, MD, Adriaan Voors, MD, Amil Shah, MD, Elisabeth Kraigher-Krainer, MD, Victor Shi, MD, Toni Bransford, MD, Madoka Takeuchi, MS, Jianjian Gong, PhD, Martin Lefkowitz, MD, Milton Packer, MD, John J.V. McMurray, MD for the PARAMOUNT Investigators
Disclosures

• Drs. Solomon, Zile, Pieske, Voors, Shah, Packer and McMurray have received research support and have consulted for Novartis.

• Drs. Shi, Bransford, Lefkowitz and Gong are employees of Novartis.

• Dr. Kraigher-Krainer and Ms. Takeuchi have no conflicts to report.
Heart failure with preserved ejection fraction (HFpEF) accounts for up to half of heart failure cases, and is associated with substantial morbidity and mortality.

Pharmacologic therapies that have been tested in clinical trials include beta-blockers, calcium-channel blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers; to date no therapies have been shown to improve clinical outcomes in this condition.

Several pathophysiologic mechanisms have been implicated in this disorder, including abnormalities of diastolic function and impaired natriuretic response to acute volume expansion.
LCZ696 – A First-in-Class Angiotensin Receptor Neprilysin Inhibitor

Natriuretic Peptide System
- pro-BNP
- BNP
- NT-pro BNP
- Neprilysin
- Inactive fragments
- Vasodilation
  - ▼ blood pressure
  - ▼ sympathetic tone
  - ▼ aldosterone levels
  - ▼ fibrosis
  - ▼ hypertrophy
  - Natriuresis/Diuresis

Heart Failure
- LCZ696

Renin Angiotensin System
- Angiotensinogen
  - (liver secretion)
- Angiotensin I
- Angiotensin II
- AT₁ receptor
- Vasoconstriction
  - ▲ blood pressure
  - ▲ sympathetic tone
  - ▲ aldosterone
  - ▲ fibrosis
  - ▲ hypertrophy

Inactive fragments:
- AHU377
- LBQ657
- Valsartan
Objectives and Hypothesis

- The PARAMOUNT trial was designed to test the safety and efficacy of LCZ696 in patients with HFpEF.

- We hypothesized that LCZ696 would reduce NT-proBNP to a greater extent than the ARB valsartan at 12 weeks, and would be associated with favorable changes in cardiac structure and function at 36 weeks.
Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Age ≥ 40 years
- Documented stable chronic heart failure (NYHA II-IV) with signs and symptoms of heart failure (Dyspnea on exertion/ Orthopnea/ Paroxysmal nocturnal dyspnea/ Peripheral edema)
- LVEF ≥ 45%
- Plasma NT-proBNP > 400 pg/ml at screening (Visit 1)
- On diuretic therapy prior to Visit 1, controlled systolic BP (<140 mm Hg, or BP <160 mm Hg if on 3 meds)
- eGFR ≥ 30 ml/min/1.73 m2 (MDRD)
- Patients with a potassium ≤5.2 mmol/l at Visit 1

Key Exclusion Criteria

- Patients with a prior LVEF reading <45%, at ANY time
- Patients who require treatment with both an ACE inhibitor and an ARB
- Isolated right heart failure due to pulmonary disease
- Dyspnea and/or edema from non-cardiac causes, such as lung disease, anemia, or severe obesity
- Presence of valvular heart disease, hypertrophic cardiomyopathy, infiltrative cardiomyopathy, restrictive cardiomyopathy, or pericardial disease
- Coronary disease requiring revascularization during the study
PARAMOUNT: Study Design

**Primary objective**

NT pro-BNP reduction from baseline at 12 weeks

**Secondary objectives**

- Echocardiographic measures of diastolic function, left atrial size, LV size and function, PASP
- HF symptoms, Clinical composite assessment and Quality of life (KCCQ)
- Safety and tolerability

Baseline randomization visit and visit at end of 12 weeks of core study

Clinicaltrials.gov NCT00887588
A sample size of 290 patients ensured at least 80% power to detect a 25% reduction in NT pro-BNP vs comparator

Primary endpoint (NT-proBNP) was evaluated as the ratio of the 12 week to baseline log-transformed NT-proBNP, and data are presented as geometric means

We performed a last observation carried forward analysis, as well as a completers only analysis and multiple imputation for missing values as sensitivity analyses.

All analyses of primary and secondary endpoints were adjusted for baseline values, and for the stratification strata (region and prior ACE/ARB use).
Patient Flow

685 patients screened

308 patients randomized

7 patients excluded from analyses for major GCP violations

LCZ696 200 mg, n=149 (100%) patients

Valsartan 160 mg, n=152 (100%) patients

12-week double-blind main period

130 (87.2%) completed 12 weeks

131 (86.2%) completed 12 weeks

24-week double-blind extension period

121 (81.2%) completed 36 weeks

120 (78.9%) completed 36 weeks
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>LCZ696</th>
<th>Valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=149</td>
<td>N=152</td>
</tr>
<tr>
<td>Mean age</td>
<td>70.9 (9.4)</td>
<td>71.2 (8.9)</td>
</tr>
<tr>
<td>Female gender (n, %)</td>
<td>57%</td>
<td>56%</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II (%)</td>
<td>81%</td>
<td>78%</td>
</tr>
<tr>
<td>Class III (%)</td>
<td>19%</td>
<td>21%</td>
</tr>
<tr>
<td>History of prior heart failure hospitalization (n, %)</td>
<td>40%</td>
<td>45%</td>
</tr>
<tr>
<td>Atrial Fibrillation at Screening (n, %)</td>
<td>27%</td>
<td>30%</td>
</tr>
<tr>
<td>History of Hypertension (n, %)</td>
<td>95%</td>
<td>92%</td>
</tr>
<tr>
<td>History of Diabetes (n, %)</td>
<td>41%</td>
<td>35%</td>
</tr>
<tr>
<td>eGFR &lt; 60 (%)</td>
<td>38%</td>
<td>45%</td>
</tr>
<tr>
<td>SBP/DBP median (interquartile range)</td>
<td>136 (130,145) / 80 (74, 85)</td>
<td>136 (126, 145) / 78 (70, 84)</td>
</tr>
<tr>
<td>NT-ProBNP geometric mean (95% CI)</td>
<td>794 (681, 925)</td>
<td>870 (740, 1022)</td>
</tr>
</tbody>
</table>
## Baseline Characteristics (2)

<table>
<thead>
<tr>
<th>Baseline Medications</th>
<th>LCZ696</th>
<th>Valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE Inhibitors (n, %)</strong></td>
<td>56%</td>
<td>53%</td>
</tr>
<tr>
<td><strong>ARBs (n, %)</strong></td>
<td>38%</td>
<td>41%</td>
</tr>
<tr>
<td><strong>ACE inhibitors or ARBs (n, %)</strong></td>
<td>93%</td>
<td>93%</td>
</tr>
<tr>
<td><strong>Diuretics (n, %)</strong></td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Beta-Blockers (n, %)</strong></td>
<td>79%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Aldosterone Antagonists (n, %)</strong></td>
<td>19%</td>
<td>23%</td>
</tr>
</tbody>
</table>

## Baseline Echocardiographic Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>LCZ696</th>
<th>Valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left Ventricular Ejection Fraction (%)</strong></td>
<td>58 (7.3)</td>
<td>58 (8.1)</td>
</tr>
<tr>
<td><strong>Left Ventricular Ejection Fraction ≥ 50%</strong></td>
<td>76%</td>
<td>82%</td>
</tr>
<tr>
<td><strong>Lateral Mitral Relaxation Velocity (E’) (cm/s)</strong></td>
<td>7.8 (2.7)</td>
<td>7.3 (2.9)</td>
</tr>
<tr>
<td><strong>Mitral Inflow to Mitral Relaxation Velocity Ratio (E/E’)</strong></td>
<td>12.4 (8.1)</td>
<td>13.0 (7.0)</td>
</tr>
<tr>
<td><strong>Left Atrial Dimension (cm)</strong></td>
<td>3.7 (0.45)</td>
<td>3.7 (0.54)</td>
</tr>
<tr>
<td><strong>Left Atrial Volume (ml)</strong></td>
<td>65.6 (22.7)</td>
<td>67.4 (28.4)</td>
</tr>
<tr>
<td><strong>Left Ventricular mass (g)</strong></td>
<td>145 (40.5)</td>
<td>150 (43.8)</td>
</tr>
</tbody>
</table>
Primary Endpoint: NT-proBNP at 12 Weeks

LCZ696/Valsartan: 0.77 (0.64, 0.92)  
P = 0.005

$p = 0.063$

NT-proBNP at 12 Weeks:

- Valsartan: 862 (733,1012)
- LCZ696: 783 (670,914)
- LCZ696/Valsartan: 605 (512, 714)
Similar Treatment Effect in All Predefined Subgroups

- **Age ≥ 65**: n = 207, n = 59
- **Age < 65**: n = 114, n = 152
- **Female**: n = 88, n = 178
- **Male**: n = 153, n = 109
- **SBP > 140**: n = 170, n = 96
- **SBP ≤ 140**: n = 217, n = 31
- **eGFR ≥ 60**: n = 190, n = 76
- **eGFR < 60**: n = 158, n = 108
- **Diabetes (no)**: n = 50, n = 214
- **Diabetes (yes)**: n = 158, n = 108
- **Atrial Fibrillation (no)**: n = 132, n = 134
- **Atrial Fibrillation (yes)**: n = 217, n = 31
- **Prior HF hospitalization (no)**: n = 132, n = 134
- **Prior HF Hospitalization (Yes)**: n = 217, n = 31
- **NYHA Class III**: n = 50, n = 214
- **NYHA class II**: n = 158, n = 108
- **NTproBNP ≤ median**: n = 207, n = 59
- **NTproBNP > median**: n = 114, n = 152

Interaction P-Value

- P = 0.57
- P = 0.69
- P = 0.07
- P = 0.18
- P = 0.02
- P = 0.49
- P = 0.85
- P = 0.62
- P = 0.70
- P = 0.57
Change in NT-proBNP over 36 weeks

- **Valsartan**
  - Week 0: $p = 0.005$
  - Week 36: $p = 0.20$

- **LCZ696**
  - Week 0: $p = 0.063$
  - Week 36: $p = 0.20$
Blood Pressure Reduction

<table>
<thead>
<tr>
<th>Change in Blood Pressure (mm Hg)</th>
<th>12 weeks</th>
<th>36 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCZ696</td>
<td>P = 0.001</td>
<td>P = 0.006</td>
</tr>
<tr>
<td>VALSARTAN</td>
<td>P = 0.09</td>
<td>P = 0.001</td>
</tr>
</tbody>
</table>

Note: Change in BP correlated poorly with change in NT-proBNP (r = 0.104, p=0.1). After adjustment for change in BP, the reduction in NT-proBNP between groups remained statistically significant (p=0.01).
Changes in Key Echocardiographic Measures

**Left Atrial Volume**

- **12 Weeks:**
  - LCZ696
  - Valsartan

- **36 Weeks:**
  - LCZ696
  - Valsartan

- Change in Left Atrial Volume (ml):
  - LCZ696: 
    - 12 Weeks: -2.0
    - 36 Weeks: -1.8
  - Valsartan:
    - 12 Weeks: -1.6
    - 36 Weeks: -1.4

**Left Atrial Width**

- **12 weeks:**
  - LCZ696
  - Valsartan

- **36 weeks:**
  - LCZ696
  - Valsartan

- Change in LA Width (cm):
  - LCZ696:
    - P = 0.07
  - Valsartan:
    - P = 0.03

**E/E’**

- **12 Weeks:**
  - LCZ696
  - Valsartan

- **36 Weeks:**
  - LCZ696
  - Valsartan

- Change in E/E’:
  - LCZ696:
    - P = 0.71
  - Valsartan:
    - P = 0.42

**Lateral E’**

- **12 weeks:**
  - LCZ696
  - Valsartan

- **36 weeks:**
  - LCZ696
  - Valsartan

- Change in Lateral Mitral Annular Relaxation Velocity (E’) (cm/s):
  - LCZ696:
    - P = 0.56
  - Valsartan:
    - P = 0.40

No Significant Changes in LV volumes, Ejection Fraction, or LV mass at 12 or 36 weeks
Change in NYHA Class

Week 12

LCZ696: P = 0.11
Valsartan:

Week 36

LCZ696: P = 0.05
Valsartan:
## Adverse Events and Laboratory Values

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (n=149)</th>
<th>Valsartan (n=152)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any Serious Adverse Event (SAE)</strong></td>
<td>22 (15%)</td>
<td>30 (20%)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td>1 (0.7%)</td>
<td>2 (1.3%)</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>All Cardiac</strong></td>
<td>9 (6.0%)</td>
<td>12 (7.9%)</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Heart Failure</strong></td>
<td>4 (2.7%)</td>
<td>6 (3.9%)</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>Any Adverse Event (AE)</strong></td>
<td>96 (64%)</td>
<td>111 (73%)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

### Adverse events of Interest

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (n=149)</th>
<th>Valsartan (n=152)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatic Hypotension</strong></td>
<td>28 (19%)</td>
<td>27 (18%)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Renal Dysfunction</strong></td>
<td>3 (2.0%)</td>
<td>7 (4.6%)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Hyperkalemia</strong></td>
<td>12 (8.1%)</td>
<td>9 (5.9%)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

### Abnormal Laboratory Values

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (n=149)</th>
<th>Valsartan (n=152)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium &gt; 5.5</td>
<td>24 (16%)</td>
<td>16 (11%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Potassium ≥ 6.0</td>
<td>5 (3.4%)</td>
<td>6 (4.2%)</td>
<td>0.97</td>
</tr>
<tr>
<td>≥ 50% decrease in eGFR</td>
<td>5 (3.4%)</td>
<td>4 (2.8%)</td>
<td>0.98</td>
</tr>
</tbody>
</table>
Conclusions

- We found that in patients with HFpEF, the angiotensin receptor neprilysin inhibitor LCZ696 reduced NT-proBNP, a marker associated with worse outcomes in HFpEF, to a greater extent than valsartan after 12 weeks of therapy. This reduction became evident at 4 weeks and was sustained to 36 weeks, though the between group difference was no longer significant.

- We further observed a reduction in left atrial size, indicative of reverse left atrial remodeling, and improvement in NYHA class in patients randomized to LCZ696 after 36 weeks, compared with those randomized to valsartan.

- LCZ696 was well tolerated.

- These hypothesis generating findings suggest that LCZ696 may have beneficial effects in patients with HFpEF and that further testing of this compound may be warranted in patients with this condition.
The angiotensin receptor nepriysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

Scott D Solomon, Michael Zile, Burkert Pieske, Adriaan Voors, Amil Shah, Elisabeth Kraigher-Krainer, Victor Shi, Toni Bransford, Madoka Takeuchi, Jianjian Gong, Martin Lefkowitz, Milton Packer, John V McMurray, for the Prospective comparison of ARNI with ARB on Management Of heart failure with preserved ejection fraction (PARAMOUNT) Investigators*

Summary

Background Heart failure with preserved ejection fraction is associated with substantial morbidity and mortality, but effective treatments are lacking. We assessed the efficacy and safety of LCZ696, a first-in-class angiotensin receptor nepriysin inhibitor, in patients with this disorder.

Methods PARAMOUNT was a phase 2, randomised, parallel-group, double-blind multicentre trial in patients with New York Heart Association (NYHA) class II–III heart failure, left ventricular ejection fraction 45% or higher, and NT-proBNP greater than 400 pg/mL. Participants were randomly assigned (1:1) by central interactive voice response system to LCZ696 titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily, and treated for 36 weeks. Investigators and participants were masked to treatment assignment. The primary endpoint was change in NT-proBNP, a marker of left ventricular wall stress, from baseline to 12 weeks; analysis included all patients randomly assigned to treatment groups who had a baseline and at least one postbaseline assessment. This trial is registered at Clinicaltrials.gov, number NCT00887588.