A multicenter, randomized, double-blind, double-dummy, parallel group, active-controlled 8-week study to evaluate the effect of sacubitril/valsartan (LCZ696) versus valsartan on changes in NT-proBNP and safety and tolerability of in-hospital initiation in HFpEF patients with acute decompensated heart failure (ADHF) who have been stabilized during hospitalization.

Study Summary

July 2019
**Inclusion Criteria**

- NYHA II-III chronic HFpEF
- NT-proBNP > 400 pg/mL

**Design**

- 2 week placebo run-in
- Sacubitril/valsartan (LCZ696) 24/26 mg BID → 97/103 mg BID over 2-4 wks
- N = 266 evaluable

**Primary analysis:**

- Δ NT-proBNP from baseline to 12 weeks

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*Solomon et al. Lancet 2012;380:1387-95*
MINI-FOCUS ISSUE: HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFpEF)
STATE-OF-THE-ART REVIEW

Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction
Rationale and Design of the PARAGON-HF Trial

STUDY DESIGN

Sequential Single-Blind Run-In Period
Eligible patients who meet tolerability criteria at each safety/tolerability check visit are switched to the next study period

Randomized Double-Blind Long-Term Follow-Up Period
Follow-up visits occurred at 4, 16, 32, and 48 weeks and every 12 weeks thereafter. All patients are followed until target number of primary composite (CV deaths and total HF hospitalizations) occur or 26 months after randomization of the last patient elapse, whichever occurs last

-2 weeks
Screening period

1-4 weeks $^\S$
Valsartan single-blind run-in

2-4 weeks $^\P$
Sacubitril/Valsartan single-blind run-in

Safety/tolerability check

Safety/tolerability check and Randomizations (if eligible)

Sacubitril/Valsartan at a target dose of 97/103 mg bid
N~4800

Valsartan at a target dose of 160 mg bid

$^\S$ Eligible patients are exposed to valsartan 80 mg bid for 1 to 2 weeks. Patients on low pre-study angiotensin converting enzyme inhibitors or angiotensin receptor blocker doses or those with tolerability concerns are first started on valsartan 40 mg bid 1 to 2 weeks and then up-titrated to valsartan 80 mg bid for 1 to 2 weeks

$^\P$ Patients tolerating valsartan 80 mg bid for 1 to 2 weeks are switched to sacubitril/valsartan 49/51 mg bid for 2 to 4 weeks

Solomon SD, et al. JACC HF 2017
Study Purpose

- Multicenter, randomized study in patients with HFpEF (LVEF > 40%) stabilized during hospitalization for Acute Decompensated Heart Failure (ADHF) to evaluate:

1) Effect of sacubitril / valsartan (LCZ696) versus valsartan on changes in NT-proBNP

2) Safety and tolerability of in-hospital initiation of sacubitril/valsartan compared to valsartan
To assess the effect of in-hospital initiation of sacubitril/valsartan vs. valsartan on…

**Primary objective:**

- Time-averaged proportional change in NT-proBNP from baseline to weeks 4 and 8

**Secondary objectives include:**

- Reducing the rate of total heart failure re-hospitalizations at 8 weeks
- Change from baseline in biomarkers (hs-Troponin, ST2, urinary cGMP) at 4 and 8 weeks
- Incidence of adverse events of special interest during 8 weeks
  - Incidence of symptomatic hypotension
  - Incidence of hyperkalemia (potassium >5.5 mEq/L)
  - Incidence of angioedema
  - Incidence of worsening renal function, defined as an increase in serum creatinine of \( \geq 0.5 \text{ mg/dL} \) and worsening of the GFR by at least 25%
Study Design

N=616

Day -10 to Day -1
Day 1 Randomization
Week 1
Week 2
Week 4
Week 8
Week 10
Week 12

**Double-Blind**

**Open-Label**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Sacubitril/valsartan</th>
<th>Valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24/26 mg [50mg] BID</td>
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<td>80 mg BID</td>
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<tr>
<td>3</td>
<td>97/103 mg [200 mg] BID</td>
<td>160 mg BID</td>
</tr>
</tbody>
</table>
Patient Population (overview)

- Patients ≥40 years of age, male or female
- Currently hospitalized with acute decompensated HFpEF (LVEF > 40%) no earlier than 36 hours and up to 10 days after diagnosis while still hospitalized and hemodynamically stable:
  - SBP ≥100 mmHg for the preceding 6 hours prior to randomization; no symptomatic hypotension
  - No increase in IV diuretic within last 6 hours
  - No IV inotropic drugs for 24 hours
  - No IV vasodilators including nitrates within last 6 hours
- Elevated NT-proBNP during current hospitalization (pts not in a.fib: NTproBNP ≥ 800 pg/mL or BNP ≥ 250 pg/mL; pts in a.fib: NTproBNP ≥ 1600pg/mL or BNP ≥ 500 pg/mL)
- Patient has not taken an ACEi for at least 36 hours prior to randomization
- BMI ≤ 50 Kg/m² at randomization
Endpoints

- **Primary**: Proportional change in NT-proBNP from baseline to the average of weeks 4 and 8

- **Secondary**:
  - Cumulative number of heart failure re-hospitalizations at week 8
  - Proportional change in NT-proBNP from baseline to week 8
  - Proportional change from baseline at 4 and 8 weeks in the following biomarkers: hs-Troponin, ST2, urinary cGMP
  - Incidence of symptomatic hypotension, hyperkalemia (potassium >5.5 mEq/L), angioedema, worsening renal function during 8 weeks of treatment

- **Exploratory**:
  - Cumulative number of composite clinical events (CV death and total heart failure re-hospitalizations) for a given patient
  - Time to first occurrence of composite clinical endpoint that includes death and heart failure re-hospitalization
  - Time to first heart failure re-hospitalization
  - Incidence of re-hospitalization through day 30
  - Healthcare resource utilization (e.g., # days in hospital, ICU) at 8 weeks
  - Additional biomarker assessments
  - Patient-reported global evaluation of treatment effectiveness at 8 weeks
Back-Up
# Sacubitril/valsartan in HFpEF

**Where does PARAGLIDE-HF fit in?**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Comparator / Study Duration</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARAMOUNT</td>
<td>N=301 outpatients with chronic HFpEF, LVEF ≥ 45%, NT-proBNP &gt; 400 pg/mL</td>
<td>Valsartan 36 weeks</td>
<td>Change in NT-proBNP from baseline to 12 weeks</td>
</tr>
<tr>
<td>NCT00887588</td>
<td>Completed &amp; published</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARAGON-HF</td>
<td>N=4822 outpatients with chronic HFpEF, LVEF ≥ 45%, NT-proBNP &gt; 200 pg/mL if hospitalized in past 9 mo, &gt; 300 pg/mL if no recent HFH</td>
<td>Valsartan</td>
<td>Composite of CV death and total (first and recurrent) HF hospitalization</td>
</tr>
<tr>
<td>NCP01920711</td>
<td>ongoing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARALLAX</td>
<td>N=2500 outpatients with chronic HFpEF, LVEF ≥ 40%, NT-proBNP &gt; 220 pg/mL (no AF), &gt;600 pg/mL AF</td>
<td>Individualized medical therapy* 24 weeks</td>
<td>Co-primary: 1) Change from baseline in NT-ProBNP at week 12 2) Change from baseline in 6MWD at week 24</td>
</tr>
<tr>
<td>NCT03066804</td>
<td>ongoing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PERSPECTIVE</td>
<td>N=520 outpatients with chronic HFpEF, LVEF ≥ 40%, NT-proBNP ≥ 125 pg/mL</td>
<td>Valsartan 36 months</td>
<td>Change from baseline in CogState global cognitive composite score</td>
</tr>
<tr>
<td>NCT02884206</td>
<td>ongoing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARAGLIDE-HF</td>
<td>N=616 hospitalized patients with HFpEF, LVEF ≥ 40%, NT-proBNP ≥ 800 pg/mL (noAF), ≥ 1600 pg/mL AF</td>
<td>Valsartan 8 weeks DB + 4 weeks OL</td>
<td>Proportional change in NT-proBNP from baseline to the average of weeks 4 and 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*individualized medical therapy: patients on ACEi prior to study entry randomized to sacubitril/valsartan vs. enalapril; those on ARB prior to study entry randomized to sacubitril/valsartan vs. valsartan; those on no RASi prior to study entry randomized to sacubitril/valsartan vs placebo

Biomarkers – What is the significance of lowering NT-proBNP?

All-cause mortality

- <30% decrease in NTproBNP
- ≥30% decrease

Cumulative Risk

Study Day

0 20 40 60 80 100 120 140 160 180

0 0.05 0.10 0.15 0.20

0.47 (0.31, 0.69)
p=0.0001

All-cause death through day 180 in Relaxin in Acute Heart Failure study patients subdivided by percentage decrease in N-terminal pro–brain natriuretic peptide (NT-proBNP) from baseline to day 2

Metra et al. JACC 2013;61:196-206
Among patients with HFrEF who were hospitalized for ADHF, the in-hospital initiation of sacubitril/valsartan led to a greater ↓ in NT-proBNP and improved clinical outcomes compared with enalapril at 8 weeks.
## PIONEER-HF Safety

<table>
<thead>
<tr>
<th>Safety Events</th>
<th>Sacubitril/ Valsartan (n=440) (%)</th>
<th>Enalapril (n=441) (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening renal function&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.6</td>
<td>14.7</td>
<td>0.93 (0.67-1.28)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>11.6</td>
<td>9.3</td>
<td>1.25 (0.84-1.84)</td>
</tr>
<tr>
<td>Symptomatic hypotension</td>
<td>15.0</td>
<td>12.7</td>
<td>1.18 (0.85-1.64)</td>
</tr>
<tr>
<td>Angioedema events&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.2</td>
<td>1.4</td>
<td>0.17 (0.02-1.38)</td>
</tr>
</tbody>
</table>

PIONEER-HF enrolled HFrEF patients with acute decompensated heart failure who had been stabilized during hospitalization

<sup>a</sup> Increase in SCr ≥0.5 mg/dL(≥44 µmol/L) with simultaneous eGFR reduction of ≥25%

<sup>b</sup> Positively adjudicated angioedema cases. There was 1 positively adjudicated angioedema event in the sac/val group and 6 cases in the enalapril group

RR, Relative risk

Velazquez EJ, et al. NEJM 2018, DOI: 10;1056/NEJMoa1812851
The pivotal PARAGON-HF trial will provide information regarding the effect of sacubitril/valsartan compared with valsartan on clinical outcomes in patients with chronic HFpEF, initiating treatment in the outpatient setting.

- Further data will be needed regarding safety and tolerability of sacubitril/valsartan in:
  - Patients hospitalized due to acute decompensated HFpEF
  - Key US populations not broadly represented in PARAGON-HF (e.g., Black patients, those with newly diagnosed HF, morbidly obese)

PARAGLIDE-HF will complement PARAGON-HF, providing important information regarding the safety and tolerability of initiating sacubitril/valsartan therapy in hospitalized patients hemodynamically stabilized after an acute decompensated heart failure (ADHF) event in a broad US cohort of HFpEF patients.
Study objectives

Exploratory objectives:

- To examine the effect of sacubitril/valsartan vs. valsartan on:
  - Reducing the rate of the composite clinical endpoint of CV death and total (first and recurrent) heart failure (HF) re-hospitalization
  - Time to first occurrence of composite clinical endpoint that includes death and HF re-hospitalization
  - Time to first HF re-hospitalization
  - Incidence of re-hospitalization (all cause and HF-specific) through day 30
  - Medical resource utilization
    - doctor visits (planned vs. unplanned); urgent care visits; emergency room visits; hospitalizations, including length of stay and any procedures during hospitalization; and changes in treatment (addition/discontinuation of medication, dose adjustments)
  - Change from baseline in NT-ProBNP at week 1
  - Change in NT-ProBNP in the valsartan arm during the 4 week open label period
  - Change in biomarkers related to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury, and renal function, including estimated glomerular filtration rate (eGFR)
  - Patient global evaluation of treatment effectiveness (GETE) at 8 weeks
Population Inclusion criteria (1 of 2)

• Patients ≥40 years of age, male or female

• Currently hospitalized with acute decompensated HFP EF (LVEF > 40%) no earlier than 36 hours and up to 10 days after diagnosis while still hospitalized and hemodynamically stable:
  o SBP ≥100 mmHg for the preceding 6 hours prior to randomization; no symptomatic hypotension
  o No increase in IV diuretic within last 6 hours
  o No IV inotropic drugs for 24 hours
  o No IV vasodilators including nitrates within last 6 hours
• HFpEF with most recent LVEF > 40% (within past 3 months; may include current hospitalization)
  ➢ For EF measurements expressed as ranges, the average of the range end point values should be > 40%.

• Elevated NT-ProBNP (or BNP) during current hospitalization
  ➢ patients not in atrial fibrillation (afib) at the time of the biomarker assessment: NTproBNP ≥ 800 pg/mL or BNP ≥ 250 pg/mL
  ➢ patients in afib at the time of the biomarker assessment: NTproBNP ≥ 1600pg/mL or BNP ≥ 500 pg/mL

• Patient has not taken an ACEi for at least 36 hours prior to randomization
Population Exclusion criteria 1-7 (of 20)

- Any clinical event within the 90 days prior to randomization that could have reduced the LVEF (i.e., MI, CABG), unless an echo measurement was performed after the event confirming the LVEF to be >40%
- Currently taking Entresto™ (sacubitril/valsartan) or any prior use
- eGFR < 30ml/min/1.73 m² as measured by the simplified Modification of Diet in Renal Disease (MDRD) formula at most recent assessment prior to randomization and within 24 hours of randomization
- Serum potassium > 5.2 mEq/L at most recent assessment prior to randomization and within 24 hours of randomization
- Acute coronary syndrome, stroke, transient ischemic attack; cardiac, carotid or other major CV surgery; percutaneous coronary intervention (PCI) or carotid angioplasty, within 30 days of randomization
- Probable alternative diagnoses that in the opinion of the investigator could account for the patient’s HF symptoms (i.e. dyspnea, fatigue) such as significant pulmonary disease (including primary pulmonary HTN), anemia or obesity. Specifically, patients with the following are excluded:
  - Severe pulmonary disease including chronic obstructive pulmonary disease (COPD) (i.e. requiring home oxygen, chronic nebulizer therapy, chronic oral steroid therapy; or
  - Hemoglobin (Hgb) < 10 g/dL males and < 9.5 g/dL females; or
  - Body mass index (BMI) > 50 Kg/m² at randomization
- Isolated right HF in the absence of left-sided structural heart disease
Population Exclusion criteria 8-18 (of 20)

- History of hypersensitivity (i.e. including angioedema), known or suspected contraindications, or intolerance to any of the study drugs including ARNIs (i.e., sacubitril/valsartan), and/or ARBs
- Patients with a known history of angioedema due to any etiology
- Patients with a history of heart transplant or LVAD, currently on the transplant list, or with intent to implant LVAD or CRT device within the 12 week duration of the trial
- A cardiac or non-cardiac medical condition other than HF with an estimated life expectancy of < 3 months
- Known pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy including amyloid heart disease (amyloidosis)
- Life-threatening or uncontrolled dysrhythmia, including symptomatic or sustained ventricular tachycardia and atrial fibrillation or flutter with a resting ventricular rate >110 beats per minute (bpm)
- Clinically significant congenital heart disease felt to be the cause of the patient's symptoms and signs of HF
- Coronary or carotid artery disease or valvular heart disease likely to require surgical or percutaneous intervention within the 12 week duration of the trial
- Any surgical or medical condition, which in the opinion of the investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study
- Known hepatic impairment (as evidenced by total bilirubin > 3 mg/dL, or increased ammonia levels, if performed), or history of cirrhosis with evidence of portal hypertension such as varices
- Participation in any other clinical trial involving investigational agents or devices within the past 30 days
Initial dose

- Initial dose at randomization will be determined based on the patient’s previous dose of ACEi/ARB immediately prior to hospital admission for ADHF
  - For patients who were not being treated with ACEi/ARB at the time of presentation to hospital, the starting dose should be dose level 1
  - For patients previously treated with low dose of ACEi/ARB, the starting dose is dose level 1
  - For patients previously treated with high dose ACEi/ARB, the starting dose is dose level 2

<table>
<thead>
<tr>
<th>Dose Level</th>
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<th>Valsartan</th>
</tr>
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<tr>
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</table>
## Definition of low and high daily doses for common ACEi & ARBs

### Protocol Table 6-4

<table>
<thead>
<tr>
<th>ACEi/ARB</th>
<th>Low RASi stratum (total daily dose)</th>
<th>High RASi stratum (total daily dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACEis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>≤ 10 mg</td>
<td>&gt; 10 mg</td>
</tr>
<tr>
<td>Benazepril</td>
<td>≤ 20 mg</td>
<td>&gt; 20 mg</td>
</tr>
<tr>
<td>Captopril</td>
<td>≤ 100 mg</td>
<td>&gt; 100 mg</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>≤ 20 mg</td>
<td>&gt; 20 mg</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>≤ 10 mg</td>
<td>&gt; 10 mg</td>
</tr>
<tr>
<td>Moexipril</td>
<td>≤ 7.5 mg</td>
<td>&gt; 7.5 mg</td>
</tr>
<tr>
<td>Perindopril</td>
<td>≤ 4 mg</td>
<td>&gt; 4 mg</td>
</tr>
<tr>
<td>Quinapril</td>
<td>≤ 20 mg</td>
<td>&gt; 20 mg</td>
</tr>
<tr>
<td>Ramipril</td>
<td>≤ 5 mg</td>
<td>&gt; 5 mg</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>≤ 2 mg</td>
<td>&gt; 2 mg</td>
</tr>
<tr>
<td><strong>ARBs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>≤ 16 mg</td>
<td>&gt; 16 mg</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>≤ 400 mg</td>
<td>&gt; 400 mg</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>≤ 150 mg</td>
<td>&gt; 150 mg</td>
</tr>
<tr>
<td>Losartan</td>
<td>≤ 50 mg</td>
<td>&gt; 50 mg</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>≤ 10 mg</td>
<td>&gt; 10 mg</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>≤ 40 mg</td>
<td>&gt; 40 mg</td>
</tr>
<tr>
<td>Valsartan</td>
<td>≤ 160 mg</td>
<td>&gt; 160 mg</td>
</tr>
</tbody>
</table>
Sample size considerations

- Assuming a significance level of 0.05 and 85% power, a sample size of 616 patients would be needed to detect a 20% reduction in the geometric mean of the proportional change from baseline to an average of Weeks 4 and 8 in NT-proBNP for the sacubitril/valsartan treatment group assuming a common standard deviation of 0.85 and a 15% rate of missing/non-evaluable samples.

- A 23% difference was the difference seen in PARAMOUNT between sacubitril/valsartan vs. valsartan at 12 weeks in HFpEF outpatients. We are using a more conservative assumption of a 20% difference.

- The standard deviation estimate is supported by data from PIONEER.
Important differences from PIONEER-HF

- Randomization 36 hours – 10 days after diagnosis of ADHF while still hospitalized, with no ACEi within 36 hours prior to randomization
  - Allows for:
    - active therapy with FIRST DOSE of both arms of study medication: sacubitril/valsartan or valsartan
    - hospital discharge as early as 6 hours following FIRST DOSE of study medication

- Initial dose based on patient’s previous dose of ACEi/ARB immediately prior to hospital admission for ADHF

- No need for 36 hour washout when moving from double-blind to open-label phase at week 8, since no patients will be on ACEi

- In PARAGLIDE-HF (unlike PIONEER-HF), we will prospectively adjudicate all endpoints