Heart failure with preserved ejection fraction (HFpEF) accounts for up to 50% of all heart failure (HF) cases and is associated with substantial morbidity and mortality.

To date both angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have reduced EF unless an echo measurement performed after the primary endpoint analysis rather than a time-to-first event analysis. This may be on a subgroup of HFpEF patients. RAAS blockade is used in the majority of patients with HFpEF to treat comorbidities. Valsartan was chosen as the comparator as it is a commonly used ARB and its use will standardize RAAS treatment for the comparator arm of the trial.

A novel secondary endpoint, atrial fibrillation (AF), is being included in PARAMOUNT-HF. AF is most common arrhythmia in patients with HF, its prevalence increases with the severity of HF, and its occurrence is frequently associated with symptom deterioration and increased morbidity.

Primary and secondary objectives

Primary objective

The primary objective of this trial is to compare LCZ696 to valsartan in reducing the rate of the composite endpoint of CV death and total (first and recurrent) HF hospitalizations in patients with HFpEF.

Secondary objective

To compare LCZ696 to valsartan in reducing the rate of the composite endpoint of CV death and total non-fatal strokes, and total non-fatal myocardial infarctions (MIs). Total is defined as the first and all recurrent events.

To compare LCZ696 to improve NYHA functional classification at 8 months.

To compare LCZ696 to valsartan in delaying the time to new onset AF in patients with no history of AF and without AF on electrocardiogram (ECG) at baseline.

To compare LCZ696 to valsartan in delaying to all-cause mortality.

Figure 2. Summary of results of the PARAMOUNT trial

Table 1. Key trial committees

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>CHAIR</th>
<th>MemBERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steering Committee</td>
<td>Scott D. Solomon, MD</td>
<td></td>
</tr>
<tr>
<td>Medical Science Steering Committee</td>
<td>Mark Pfeffer, MD</td>
<td></td>
</tr>
<tr>
<td>End-Point Committee</td>
<td>John J. McMurray, MD</td>
<td></td>
</tr>
<tr>
<td>Safety Committee</td>
<td>Paul O’Donnell, MD</td>
<td></td>
</tr>
<tr>
<td>Monitoring Committee</td>
<td>Daniel L. Halpryn, MD</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Mechanism of action of LCZ696

Figure 3. Trial design

Methods

PARAGON-HF will assess the effect of LCZ696 on outcomes (cardiovascular [CV] death and total – first and recurrent – HF hospitalization) in patients with HFpEF.

Criteria

Table 2. Key inclusion criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Symptom(s) of HF requiring treatment with diuretic(s) for HF for ≥30 days</td>
</tr>
<tr>
<td>2.</td>
<td>Symptom(s) of HF requiring treatment with diuretic(s) for HF for ≥30 days</td>
</tr>
</tbody>
</table>

Table 3. Key exclusion criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Patients with active malignancy</td>
</tr>
<tr>
<td>2.</td>
<td>Patients with severe left ventricular systolic dysfunction (LVEF &lt;20% by echocardiogram)</td>
</tr>
</tbody>
</table>

Figure 4. Key inclusion criteria

Figure 5. Key exclusion criteria

REFERENCES


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