Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix.

Table of Contents

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4. Supplemental Methods

Censoring and handling of missing data

The censoring date for a non-fatal endpoint or an endpoint with non-fatal event as a component (even if fatal event is also another component) is defined as one of the following (whichever occurred first):

- Date when the patient withdrew informed consent
- Date of the patient's last visit (including telephone visit)
- Date of death
- Analysis cut-off date

The censoring date for a fatal endpoint (time-to-first event) is defined as one of the following (whichever occurred first):

- Date when the patient withdrew informed consent
- Patient's last known alive date
- Date of death
- Analysis cut-off date

We assumed all components: times to cutoff, non-CV death date, last known alive date, and last visit date are independent of time to the corresponding endpoint event. Cutoff and last visit date are administrative decided dates which are independent of the occurrence of the target event.

Sample Size re-estimation and interim analyses

"A sample size of 4,650 patients, randomized to LCZ696:ramipril using a 1:1 allocation ratio, was originally chosen with the aim to obtain at least 800 first primary events and at least 633 CV death or HF hospitalization events in this event-driven study. Eight hundred primary events provide at least 80% power assuming a true Relative Risk Reduction (RRR) of 18% (i.e. a hazard ratio of 0.82) for LCZ696 vs ramipril with statistical testing at the overall 2.5% 1-sided type I error rate (with strong control of the FWER).

Sample size re-estimation was planned and performed when approximately 1/2 of patients had been randomized and had reached the 3 month time point.

The estimated cumulative event rates based on the available blinded data were sizably lower than the originally assumed event rates for both the primary endpoint and the double composite endpoint, indicating that the original assumptions about the event rates may not hold.

Following the blinded sample size re-estimation, a sample size of 5,650 patients, randomized to LCZ696:ramipril using a 1:1 allocation ratio, was chosen with the aim to obtain at least 708 first primary endpoint events and at least 592 first CV death or HF hospitalization events in this event-driven study. Seven hundred eight primary endpoint events will provide 80% power assuming a true Relative Risk Reduction (RRR) of 19% (i.e. a hazard ratio of 0.81) for LCZ696 vs ramipril with statistical testing at the overall 2.5% 1-sided type I error rate (with strong control of the FWER). Five hundred ninety two first CV death or HF hospitalization events will provide 77.5% nominal power assuming a true RRR of 20% (for the ITT analysis) for this double composite endpoint for the same type I error rate.

One interim analysis for efficacy was initially planned. The cut-off time for the first interim analysis was planned to be when about two-thirds of the target number of 708 primary events were reported and adjudication-confirmed. Approximately 472 of adjudication-confirmed primary events (i.e., first CV deaths, HF hospitalizations, or outpatient HF events) were planned; 464 adjudication-confirmed primary events were included. In the first interim analysis, the analysis dataset was comprised of all patients who were randomized before the cutoff date.

A second interim analysis for efficacy was added in response to the potential impact from the COVID-19 pandemic, allowing the study to stop for overwhelming efficacy for the primary endpoint at one-sided alpha of 0.005. The second efficacy interim analysis included all patients randomized prior to 01-Mar-2020 and all primary endpoint events that occurred prior to 01-Mar-2020, approximately 80% of the target 708 total primary endpoint events in the PARADISE-MI study. The data collected prior to 01-Mar-2020 are generally considered not impacted by the COVID-19 pandemic at the global level. Accordingly, patients who do not have a primary endpoint event prior to 01-Mar-2020 were included in the second IA as censored.

Generalized Haybittle-Peto boundaries were adopted for the interim statistical comparisons between treatments. An alpha of 0.001 (1-sided) was spent at the first interim analysis, and an alpha corresponding to the nominal level of 0.005 (1-sided) was spent at the second interim analysis for the comparison of the primary endpoint. The rest of alpha (resulting in a nominal 1-sided 0.0244, with the currently specified target number of primary events of 708 and the planned addition of a second interim analysis to include 80% of the target 708 primary events, based on East version 6.4) was utilized at the final analysis. In the first interim analysis, as designed, the study could be stopped for superior efficacy only when both the primary endpoint and CV

death were significant at an alpha level of 0.001 (1-sided). In the second interim analysis, the study may be stopped for superior efficacy when the primary endpoint is significant at the alpha level of 0.005 (1-sided).

5. Supplemental Results

Incomplete follow-up

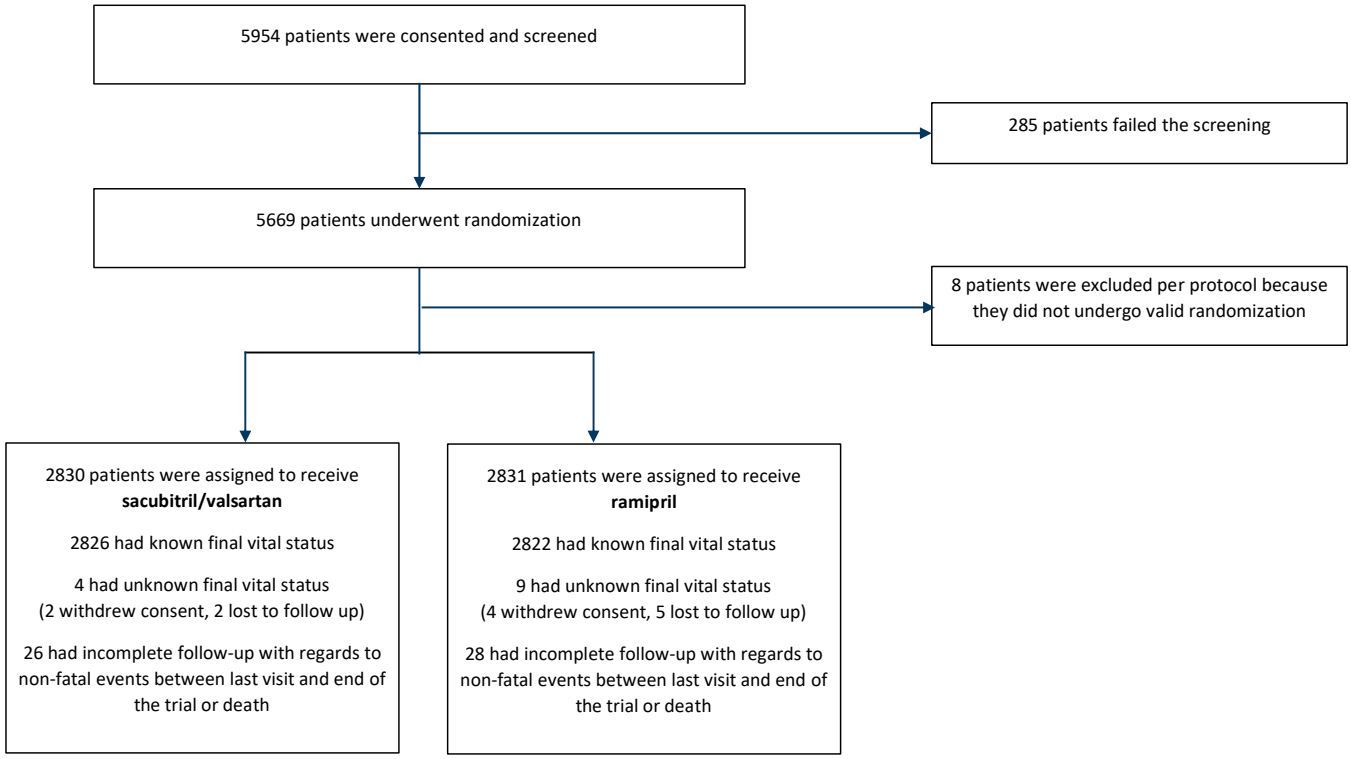
In 54 patients who had incomplete follow-up for non-fatal events subsequent to their last study visit (26 sacubitril/valsartan and 28 ramipril patients), the total patient-time contributed with incomplete follow-up was 9392 patient days.
For the 26 sacubitril/valsartan patients, the average time until last study visit was 658 days, followed by 164 days of incomplete follow-up. For the 28 ramipril patients, the average time until last study visit was 462 days, followed by 183 days of incompletely follow-up.

The total incomplete follow-up time experienced by the 26 sacubitril/valsartan patients was 4277 days, out of a total 1,961,142 days of follow-up for efficacy analyses (0.2%). In the 28 ramipril patients, the corresponding time with incomplete follow-up was 5115 days out of a total 1,951,643 days of follow-up (0.3%) for the ramipril group.

Competing Risks

The occurrence of non-CV death was less frequent than CV death (1.7% of patients vs 6.3%), occurred later than CV death (median non-CV death = Day 466 vs median CV-death = Day 132), and were distributed similarly between treatment arms (1.6% of sacubitril/valsartan patients vs 1.8% of ramipril patients). As such, non-CV death was not considered as a threat to the validity of the primary analysis.

6. **Supplementary Figure S1. Enrollment and Follow-up.**



7. **Supplementary Table S1. Detailed Inclusion and Exclusion Criteria**

Key Inclusion Criteria

1. Written informed consent must be obtained before any assessment is performed.
2. Male or female patients ≥ 18 years of age.
3. Diagnosis of spontaneous AMI based on the universal myocardial infarction (MI) definition* with randomization to occur between 12 hours and 7 days after index event presentation**.

Spontaneous AMI is defined when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia due to primary coronary event. Under these conditions, the following criteria have to be met for the diagnosis of spontaneous AMI:

- Detection of rise and/or fall of cardiac enzymes (cardiac troponin, cTn or the MB fraction of creatinine kinase, CKMB) with at least one value above the 99th percentile of the upper reference limit (URL) or the local laboratory MI diagnosis cut-off value, together with evidence of myocardial ischemia with at least one of the following:
    - Ischemic discomfort or other ischemia symptom(s)
    - Electrocardiogram (ECG) characteristics of STEMI or NSTEMI including new or presumably new significant ST-segment-T wave (ST-T) changes
    - Newly developed pathological Q waves or left bundle branch block (LBBB) in the ECG

  (*Patients with a spontaneous MI event determined to be secondary to another medical condition such as anemia, hypotension, or an arrhythmia OR thought to be caused by coronary vasospasm with documented normal coronary arteries are not eligible; patients with clinical presentation thought to be related to Takotsubo cardiomyopathy are also not eligible)

  (**Index MI presentation is the time of patient presentation at either the ER/ED, ICU/CCU or hospital ward etc., for the treatment of the index MI.)

4. Evidence of LV systolic dysfunction and/or‡ pulmonary congestion requiring intravenous treatment associated with the index MI event defined as:

- Left ventricular ejection fraction (LVEF) ≤ 40% assessed locally by echocardiography, magnetic resonance imaging, cardiac CT, radionuclide or contrast ventriculography after index MI presentation and prior to randomization. (These examinations may be performed as part of patient standard-of-care. In case multiple LVEF measurements have been performed during index event, the last one performed prior to randomization should be considered as the qualifying measurement), **and/or‡**
- Pulmonary congestion requiring intravenous treatment (diuretics, vasodilators, vasopressors and/or inotropes) during the index hospitalization supported by clinical assessment (worst Killip class‡‡, II or above) or radiological findings. Radiological evidence of pulmonary congestion is defined as pulmonary venous congestion with interstitial or alveolar edema and must be supported by at least one chest X-ray or CT scan.
  (‡ denotes that patients with either LVEF ≤40%, or pulmonary congestion requiring IV treatment, or both will qualify for this inclusion criterion)
  (‡‡ Killip class is defined as:
  - Class 1: No rales, no 3rd heart sound
  - Class 2: Rales in <½ lung field or presence of a 3rd heart sound
  - Class 3: Rales in >½ lung field–pulmonary edema
  - Class 4: Cardiogenic shock–determined clinically)

5. At least one of the following 8 risk factors:

- Age ≥ 70 years
- eGFR <60 mL/min/1.73 m2 based on Modification of Diet in Renal Disease (MDRD) formula at screening visit
- Type I or II diabetes mellitus
- Documented history of prior MI supported by ECG changes and/or elevation of cardiac enzymes consistent with MI diagnosis.
- Atrial fibrillation as noted by ECG, associated with index MI

- LVEF < 30% associated with index MI (In case multiple LVEF measurements have been performed during index event, the last one performed prior to randomization should be considered as the qualifying measurement.)
- Worst Killip class III or IV associated with index MI requiring intravenous treatment
- STEMI without reperfusion therapy within the first 24 hours after presentation

6. Hemodynamically stable defined as:
    - Systolic blood pressure (SBP) ≥ 100 mmHg at randomization for patients who received ACE inhibitor/angiotensin receptor blocker (ARB) during the last 24 hours prior to randomization (ACE inhibitor/ARB Yes patients)
    - SBP ≥ 110 mmHg at randomization for patients who did not receive ACE inhibitor/ARB during the last 24 hours prior to randomization (ACE inhibitor/ARB No patients)
    - No intravenous treatment with diuretics, vasodilators, vasopressors and/or inotropes during the last 24 hours prior to randomization.

Key Exclusion Criteria

1. Known history of chronic HF prior to randomization
2. Cardiogenic shock within the last 24 hours prior to randomization
3. Persistent clinical HF at the time of randomization
4. Coronary artery bypass graft (CABG) performed or planned for index MI
5. Clinically significant right ventricular MI as index MI
6. Symptomatic hypotension at screening or randomization
7. Patients with a known history of angioedema
8. Stroke or transient ischemic attack within one month prior to randomization
9. Known or suspected bilateral renal artery stenosis
10. Clinically significant obstructive cardiomyopathy
11. Open-heart surgery performed within one month prior to randomization or planned cardiac surgery within the 3 months after randomization

12. eGFR < 30 ml/min/1.73 m2 as measured by the Modification of Diet in Renal Disease (MDRD) formula at screening
13. Serum potassium > 5.2 mmol /L (or equivalent plasma potassium value) at randomization
14. Known hepatic impairment (as evidenced by total bilirubin > 3.0 mg/dL or increased ammonia levels, if performed), or history of cirrhosis with evidence of portal hypertension such as esophageal varices
15. Previous use of LCZ696 or EntrestoTM
16. Use of other investigational drugs within 30 days prior to screening
17. History of hypersensitivity to the study drugs or drugs of similar chemical classes
18. Known intolerance or contraindications to study drugs or drugs of similar chemical classes including ACE inhibitors, ARB or NEP inhibitors
19. Patients taking medications prohibited by the protocol that cannot be discontinued for the duration of the study
20. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin) within the past 3 years with a life expectancy of less than 1 year
21. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or extraction of study drug at investigators' discretion
22. History or evidence of drug or alcohol abuse within the last 12 months
23. Patients considered unsuitable for the study, including patients with psychiatric, behavioral or cognitive disorders, sufficient to interfere with the patient's ability to understand and comply with the protocol instructions or follow-up procedures
24. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test
25. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of investigational drug
26. Patients in atrial fibrillation at randomization are excluded from the echocardiographic substudy.

27. Patients with pulmonary fibrosis, or interstitial lung disease, current pneumonia, pneumonitis, pneumothorax, or chest pain, prior lung resection or lung transplantation, or current or prior lung or pleural cancer at randomization are excluded from the lung ultrasound assessment.

8. **Supplementary Table S2. Definitions of Endpoints**

I. FATAL ENDPOINT DEFINITIONS

The CEC will attribute cause of death according to the responsible underlying disease process rather than the immediate mechanism. Deaths will be classified as cardiovascular, non-cardiovascular, or unknown, and, where possible, further sub-classified as outlined below:

A. Cardiovascular Death

Cardiovascular death includes death classified in any of the following categories:

1. Fatal Myocardial Infarction (MI):

Fatal MI* may be adjudicated in any of the following three scenarios:

a. Death occurring within 14 days after a documented MI, in which there is no conclusive evidence of any other cause of death. Subjects who are being treated for a MI and who die as a result of complications of the MI (eg, sudden death, pump failure, or cardiogenic shock) will be classified as having had a MI-related death.

b. Autopsy evidence of a recent infarct with no conclusive evidence of any other cause of death.

c. An abrupt death that has characteristics suggestive of an acute infarct but does not meet the definition of a MI. Suggestive characteristics are:

- presentation with acute ischemic symptoms

AND one of the following:

- ECG changes indicative of an acute injury
- abnormal cardiac biomarkers
- *other evidence (eg, echocardiography, ventriculography, or scintigraphy) of new ventricular wall motion abnormality*

**Note, this includes Myocardial Infarction Type 3*

2. Heart Failure:

Death occurring in the context of clinically worsening symptoms and/or signs of heart failure (HF) without evidence of another cause of death.

Death occurring as a complication of the implantation of a ventricular assist device, cardiac transplant, or other surgery primarily for refractory HF.

Death occurring after referral to hospice specifically for progressive HF.

Note: If worsening HF is secondary to MI, then MI should be listed as the primary cause of death if the subject suffered an MI within 14 days of death (as above).

3. Sudden Death:

Death occurring unexpectedly in an otherwise stable subject. Further subclassification of sudden death will be as follows:

a. death witnessed or subject last seen alive <1 hour previously or

b. subject last seen alive ≥1 hr and < 24 hrs previously

4. Presumed Sudden Death

Death occurring unexpectedly in an otherwise stable subject last seen alive ≥24 hours previously, with circumstances suggestive of sudden death.

5. Presumed Cardiovascular Death:

Death likely due to a cardiovascular cause in which the available clinical data is insufficient to support a more specific cause of death.

6. Fatal Stroke:

Death occurring as a result of a documented stroke. Where possible, the stroke will be further classified as ischemic (non-hemorrhagic), ischemic (non-hemorrhagic) with hemorrhagic conversion, hemorrhagic, or unknown.

7. Fatal Pulmonary Embolism:

Death occurring as a direct result of a documented pulmonary embolism.

8. Cardiovascular Procedure-Related Death:

Death occurring during a cardiovascular procedure or as a result of complications related to a cardiovascular procedure (e.g. percutaneous coronary intervention), usually within 14 days. The CEC will subcategorize these deaths as related to percutaneous coronary intervention (PCI-related), coronary artery bypass-grafting (CABG-related), valvular procedures (valvular), or other cardiovascular procedures (other).

9. Other Cardiovascular Death:

Death resulting from a specifically documented cardiovascular cause other than those listed above.

B. Non-Cardiovascular Death

If an unequivocal and documented non-cardiovascular cause can be established as the primary cause of death, the event will be classified as non-cardiovascular. Non-cardiovascular deaths will be further classified into the following categories:

A. Infection

B. Malignancy

C. Pulmonary Failure

D. Gastrointestinal – Death due to GI-related abnormalities unrelated to liver or pancreas

E. Hepatic – Death related to primary liver or gallbladder abnormalities

F. Pancreatic – Death due to acute or chronic complications of pancreatic-related disorders

G. Renal Failure*

H. Accidental/Trauma

I. Suicide

J. Non Intracranial Hemorrhage (not related to CV surgery/procedure)

K. Other Non-CV (Specify)

* Renal Death is defined as death occurring from complications of renal failure (e.g. hyperkalemia, uremia, acidosis) while a patient receives renal replacement therapy (i.e. chronic dialysis or renal transplantation), or after a patient refuses or a physician withholds such therapy or in cases where dialysis is unavailable.

C. Unknown Death

Death in which insufficient data is available to make a reasonable differentiation of cardiovascular or non-cardiovascular cause of death.

II. NON-FATAL ENDPOINT DEFINITIONS

The CEC will receive for review and adjudication all occurrences of the following non-fatal endpoints:

A. Hospitalization for Heart Failure*

B. Outpatient Heart Failure Event

C. Myocardial Infarction (Non-Procedural and Post-Procedural)

D. Stroke

E. Resuscitated cardiac arrest

F. Hospitalization for Angina (exploratory endpoint)*

*Hospitalization criteria will be met if a subject has an unplanned admission to an acute care facility (i.e., hospital, emergency room, observation unit) requiring a change in calendar day from hospital presentation to discharge.

A1. Hospitalization for Heart Failure (HF)

Presentation to an acute care facility requiring an overnight hospitalization (change in calendar day) with an episode of heart failure requiring treatment meeting the following criteria:

1. Symptoms and signs of heart failure:

One or more of the following new or worsening symptoms consistent with heart failure:

a. Dyspnea

b. Orthopnea

c. Paroxysmal nocturnal dyspnea

d. Fatigue/ exercise intolerance

e. edema/anasarca

AND

Two or more of the following signs consistent with heart failure:

a. Rapid weight gain

b. Pulmonary edema or rales

c. Elevated jugular venous pressure

d. Radiologic signs of heart failure

e. Peripheral edema

f. Increasing abdominal distension or ascites

g. S3 gallop

h. Hepatojugular reflux

i. Elevated brain natriuretic peptide (BNP) or N-terminal pro-BNP (> most recent stable baseline value, if such baseline measurement is available)

j. Congestive hepatomegaly (i.e. not related to intrinsic liver disease)

k. Invasive/Non-invasive tests showing cardiac filling pressures or low cardiac output

AND

2. Treatment

Treatment with intravenous diuretics, intravenous vasodilators, intravenous inotropes, mechanical fluid removal (e.g., ultrafiltration or dialysis), or insertion of an intra-aortic balloon pump or other Mechanical Circulatory Support device for hemodynamic compromise. Initiation of standing oral diuretics or intensification (doubling) of the maintenance diuretic dose will also qualify as treatment.

Note: Adjudicated heart failure events associated with elevation in cardiac biomarkers (e.g. cardiac troponin) not thought to be evidence of an associated myocardial infarction will be noted by the CEC.

A2. Development of Heart Failure During Ongoing Hospitalization due to Non-HF Etiology

Presentation to an acute care facility requiring an overnight hospitalization (change in calendar day) for *another primary cause* in which a development of symptomatic heart

failure requiring treatment *spontaneously* occurs *without an inciting event** and meeting the following criteria:

1. Symptoms and signs of heart failure:

One or more of the following new or worsening symptoms consistent with heart failure:

a. Dyspnea
b. Orthopnea
c. Paroxysmal nocturnal dyspnea
d. Fatigue/ exercise intolerance
e. E**dema/anasarca**

AND

Two or more of the following signs consistent with heart failure:

a. Rapid weight gain
b. Pulmonary edema or rales
c. Elevated jugular venous pressure
d. Radiologic signs of heart failure
e. Peripheral edema
f. Increasing abdominal distension or ascites
g. S3 gallop
h. Hepatojugular reflux
i. Elevated brain natriuretic peptide (BNP) or N-terminal pro-BNP (> most recent baseline value, if a baseline measurement is available)
j. Congestive hepatomegaly (i.e. not related to intrinsic liver disease)
k. Invasive/Non-invasive tests showing cardiac filling pressures or low cardiac output

AND

3. Treatment

Treatment with IV diuretics for >3 consecutive calendar days and continuation of oral diuretics or augmentation of HF-specific medicines at time of discharge.

*Examples of inciting events include IV fluids, blood transfusions, and complications of planned valve surgery/CABG.

B. Outpatient Heart Failure Event

An urgent/unscheduled visit to an ED, acute/urgent care facility or outpatient clinic or a non-urgent office/practice or study visit for a primary diagnosis of HF that does not require an overnight hospital stay

1. Symptoms and signs of heart failure:

One or more of the following new or worsening symptoms consistent with heart failure:

a. Dyspnea
b. Orthopnea
c. Paroxysmal nocturnal dyspnea
d. Fatigue/ exercise intolerance
e. Edema/anasarca

AND

Two or more of the following signs consistent with heart failure:

a. Rapid weight gain
b. Pulmonary edema or rales
c. Elevated jugular venous pressure
d. Radiologic signs of heart failure
e. Peripheral edema
f. Increasing abdominal distension or ascites
g. S3 gallop
h. Hepatojugular reflux
i. Elevated brain natriuretic peptide (BNP) or N-terminal pro-BNP (> most recent baseline value, if a baseline measurement is available)
j. Congestive hepatomegaly (i.e. not related to intrinsic liver disease)

k. Invasive/Non-invasive tests with elevated cardiac filling pressures or low cardiac output

AND

2. Treatment

Initiation of standing oral loop diuretics or intensification (doubling) of the maintenance loop diuretic dose and *confirmed at outpatient visit at >28 days*, *or*

Intravenous diuretics, intravenous vasodilators, intravenous inotropes, or mechanical fluid removal (e.g., ultrafiltration or dialysis).

C. Myocardial infarction (MI)

Myocardial Infarction will be adjudicated by type according to the definitions below.

Definitions:

1) Non-Procedural MI

Cardiac markers:

Troponin > ULN (preferred) OR

CK-MB mass assay* > ULN (when troponin is not available)

** ULN should ideally reflect the 99th percentile of the upper reference limit (if not available,*

local ULN for MI diagnostic cut-off can also be acceptable). When multiple, appropriately timed values are available, a dynamic rise and/or fall is required (>20% change). When neither Troponin nor CKMB mass assay are measured, CK-MB activity ≥ 2x ULN will satisfy elevated CM criterion. When only a single value (high sensitivity troponin assay) is available, the absolute value should be >5x ULN.

AND

At least one of the following:

- Ischemic symptoms: rest or accelerated symptoms (pain, dyspnea, pressure) consistent with myocardial ischemia.

- ECG changes consistent with infarction:
- New significant Q waves (or R waves in V1-V2) in 2 contiguous leads in absence of previous LVH or conduction abnormalities.
- Evolving ST-segment to T-wave changes in 2 or more contiguous leads.
- Development of new LBBB.
- ST segment elevation requiring thrombolytics or PCI.

Non-procedural MI will be subclassified as:

1A. Spontaneous MI (Type 1)* Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

1B. Secondary MI (Type 2)* Myocardial infarction meeting the criteria for Type 1 MI, but secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension

* The protocol-defined endpoint event of non-fatal spontaneous MI includes both CEC adjudicated Type 1 and Type 2 MIs.

1C. Stent Thrombosis (Type 4b): Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

2) Procedural-related MI

Procedural MI will be subclassified as:

2A. PCI-related MI (Type 4a)

Cardiac markers**:

Assuming baseline biomarker levels < ULN, post-procedural elevation of cardiac biomarkers within 48 h meeting the thresholds below:

Troponin > 5xULN OR CK-MB > 5xULN

AND

In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

**In the absence of cardiac markers:

New pathological Q waves that are persistent upon discharge, or documentation of new wall motion abnormality (other than septal) will also meet criteria.

2B. CABG-related MI (Type 5)

Cardiac markers:

Assuming baseline biomarker levels < ULN, post-procedural elevation of cardiac biomarkers within 72 h meeting the thresholds below:

Troponin > 10xULN OR CK-MB > 10xULN

AND:

New pathological Q waves or LBBB, new native or graft vessel occlusion, or imaging evidence of loss of viable myocardium.

If it is determined that an MI has occurred, the type of myocardial infarction will be further classified by the CEC as follows:

ST segment elevation vs. Non-ST segment elevation Myocardial infarction: Defined based on the presence or absence of ST-segment elevations on the surface electrocardiogram (ECG) completed in association with the event. Where no ECG data (tracings or description) is available, events will be presumptively categorized as NSTEMI.

D. Non-Fatal Stroke

a. A focal neurological deficit of central origin lasting more than 24 hours (except for death within 24hrs), with or without imaging confirmation of cerebral infarction or intracerebral hemorrhage.

OR

b. A focal neurological deficit of central origin lasting less than 24 hours with corresponding imaging evidence of cerebral infarction or intracerebral hemorrhage.

OR

c. A focal neurological deficit of central origin lasting less than 24 hours that was treated with thrombolytic therapy or directed percutaneous intervention.

OR

d. A non-focal encephalopathy lasting more than 24 hours (except for death within 24hrs) with imaging evidence of cerebral infarction or hemorrhage adequate to account for the clinical state.

OR

e. Retinal artery ischemia

Subclassifications:

a. Ischemic (Non-hemorrhagic) Stroke – stroke with imaging suggesting ischemic changes

b .Ischemic (Non-hemorrhagic) Stroke with Hemorrhagic Conversion - stroke with evidence of hemorrhage on imaging, judged to be hemorrhagic transformation of a primary ischemic stroke

c. Hemorrhagic Stroke – stroke with evidence on imaging of intracerebral hemorrhage not due to transformation of an ischemic stroke

d. Unknown: when imaging is unavailable or inconclusive

*The deficit must be new, sudden in onset, and not attributable to any more likely alternative cause (e.g. tumor, trauma)

E. Resuscitated Cardiac Arrest

Sudden and unexpected cardiovascular collapse or cardiac arrest followed by successful active resuscitation requiring one of the following:

1) Chest compressions
2) Cardioversion

3) ICD firing

and with meaningful recovery after the event

This excludes fainting, vasovagal responses or other loss of consciousness not associated with cardiac arrest*.**

F. Hospitalization for Angina

1. Unplanned hospitalization for ischemic symptoms:

Rest or accelerated symptoms (pain, dyspnea, pressure) consistent with myocardial ischemia.

AND EITHER:

2A) Elevated cardiac markers (CK-MB or Troponin):

Not suggestive of acute myocardial infarction

OR:

2B) Ischemic ECG changes:

- ≥ 0.5mm transient ST segment depression in 2 contiguous leads.
- ≥ 1mm transient ST elevation of 2 contiguous leads.
- ≥ 2mm transient T wave change in 2 or more contiguous leads.
- ≥ 0.5mm ST segment change as compared to most recent ECG during the previous stable phase.

9. Supplementary Table S3. Angioedema Adjudication.

	Sacubitril/valsartan (n=2830)	Ramipril (n=2831)
Confirmed angioedema	14 (0.50%)	17 (0.60%)
Severity		
I - No treatment administered or antihistamines only	7 (0.25%)	9 (0.32%)
II - Treated with catecholamines or steroids	5 (0.18%)	3 (0.11%)
III - Hospitalized but no mechanical airway protection		
III a - No airway compromise	2 (0.07%)	5 (0.18%)
III b - With airway compromise		
IV - Mechanical airway protection or death from airway compromise		

10. **Supplementary Table S4. Reasons for screen failure in ineligible patients that had been consented and were not randomized.**

Reason*	**N=285**
Inclusion criteria not met	
Hemodynamically stable (as defined in the study protocol)	68
Evidence of LV systolic dysfunction and/or pulmonary congestion requiring intravenous treatment associated with the index MI event (as defined in the study protocol)	44
Diagnosis of spontaneous AMI (as defined in the study protocol) based on the universal MI definition with randomization to occur between 12 hours and 7 days after index event presentation	21
At least one of the following 8 risk factors (as defined in the study protocol)	15
Written informed consent must be obtained before any assessment is performed	3
Male or female patients = 18 years of age	1
Exclusion criteria met	
eGFR < 30 ml/min/1.73 m2 as measured by the Modification of Diet in Renal Disease (MDRD) formula at screening	24
Coronary artery bypass graft (CABG) performed or planned for index MI	12
Symptomatic hypotension at screening or randomization	12
Serum potassium > 5.2 mmol /L at randomization	8
Known history of chronic HF prior to randomization	7
Patients considered unsuitable for the study, including patients with psychiatric, behavioral or cognitive disorders	5
Persistent clinical HF at the time of randomization	5
Clinically significant right ventricular MI as index MI	3
History or evidence of drug or alcohol abuse within the last 12 months	3
Cardiogenic shock within the last 24 hours prior to randomization	2
Known intolerance or contraindications to study drugs or drugs of similar chemical classes including ACE inhibitors, ARB or NEP inhibitors	2
Previous use of LCZ696 or EntrestoTM	2
Stroke or transient ischemic attack within one month prior to randomization	2
Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or extraction of study drug at investigators' discretion	1
Clinically significant obstructive cardiomyopathy	1

	History of hypersensitivity to the study drugs or drugs of similar chemical classes	1
	History of malignancy of any organ system (other than localized basal cell carcinoma of the skin) within the past 3 years with a life expectancy of less than 1 year	1
	Known hepatic impairment (as evidenced by total bilirubin > 3.0 mg/dL or increased ammonia levels, if performed), or history of cirrhosis with evidence of portal hypertension such as esophageal varices	1
	Open-heart surgery performed within one month prior to randomization or planned cardiac surgery within the 3 months after randomization	1
	Patients taking medications prohibited by the protocol that cannot be discontinued for the duration of the study	1
	Patients with a known history of angioedema	1
	Use of other investigational drugs within 30 days prior to screening	1
	Women of child-bearing potential, unless they are using highly effective methods of contraception during dosing of investigational drug and for 7 days off of study drug	1
Number of subjects with missing inclusion/exclusion criteria		49

* Multiple reasons for screen failure may be provided.

11. Supplementary Table S5. Adverse Events of Special Interest.

Risk Category	Sacubitril/ Valsartan*	Ramipril*	Sacubitril/valsartan vs Ramipril Rate Ratio (95% CI)
Anaphylaxis	9 (0.3%)	9 (0.3%)	0.99 (0.39, 2.50)
Angioedema‡	14 (0.5%)	17 (0.6%)	0.82 (0.40, 1.66)
Cognitive impairment (Broad SMQ)	54 (1.9%)	60 (2.1%)	0.89 (0.62, 1.29)
Cognitive impairment (Narrow SMQ)	3 (0.1%)	10 (0.4%)	0.30 (0.08, 1.08)
Embryo-fetal toxicity or lethality	0 (0%)	0 (0%)	N/A
Hepatotoxicity	132 (4.7%)	167 (5.9%)	0.78 (0.62, 0.98)
Hyperkalemia	301 (10.7%)	285 (10.1%)	1.06 (0.90, 1.25)
Hypersensitivity (Broad SMQ)	322 (11.4%)	296 (10.5%)	1.09 (0.93, 1.28)
Hypersensitivity (Narrow SMQ)	195 (6.9%)	167 (5.9%)	1.17 (0.95, 1.44)
Hypotension	802 (28.3%)	620 (21.9%)	1.43 (1.29, 1.59)
Malignancy	85 (3.0%)	71 (2.5%)	1.19 (0.87, 1.64)
Neonatal or infantile toxicity through exposure from breast milk	0	0	N/A
Renal impairment (Broad SMQ)	329 (11.7%)	326 (11.6%)	1.01 (0.87, 1.18)
Renal impairment (Narrow SMQ)	265 (9.4%)	250 (8.9%)	1.06 (0.89, 1.26)
Statin drug-drug interaction	106 (3.8%)	129 (4.6%)	0.81 (0.62, 1.04)

*****Denominator may differ from Table 3 for the safety population excluding 25 patients who did not receive study drug.

‡Adjudicated and confirmed by the Angioedema Adjudication Committee.

12. **Supplementary Table S6. Serious Adverse Events by Primary System Organ Class.**

(Patients with any exposure to study drug)	Sacubitril/valsartan N = 2820		Ramipril N = 2816	
Primary Category*	**N**	**%**	**N**	**%**
Any serious adverse event	1146	40.6	1126	40.0
Blood and lymphatic system disorders	48	1.7	38	1.3
Cardiac disorders	572	20.3	615	21.8
Congenital, familial and genetic disorders	0		1	0.04
Ear and labyrinth disorders	5	0.2	7	0.2
Endocrine disorders	1	0.04	1	0.04
Eye disorders	12	0.4	9	0.3
Gastrointestinal disorders	100	3.5	97	3.4
General disorders and administration site conditions	139	4.9	147	5.2
Hepatobiliary disorders	25	0.9	25	0.9
Immune system disorders	3	0.1	2	0.1
Infections and infestations	218	7.7	200	7.1
Injury, poisoning and procedural complications	62	2.2	74	2.6
Investigations	25	0.9	33	1.2
Metabolism and nutrition disorders	62	2.2	56	2.0
Musculoskeletal and connective tissue disorders	35	1.2	32	1.1
Neoplasms benign, malignant and unspecified (including cysts and polyps)	73	2.6	66	2.3
Nervous system disorders	141	5.0	126	4.5
Pregnancy, puerperium and perinatal conditions	1	0.04	0	
Product issues	3	0.1	7	0.2
Psychiatric disorders	11	0.4	19	0.7
Renal and urinary disorders	82	2.9	61	2.2
Reproductive system and breast disorders	12	0.4	5	0.2
Respiratory, thoracic and mediastinal disorders	118	4.2	116	4.1
Skin and subcutaneous tissue disorders	22	0.8	11	0.4
Social circumstances	1	0.04	2	0.1
Surgical and medical procedures	0		1	0.04
Vascular disorders	96	3.4	80	2.8

*The primary category for each serious adverse event was assigned by the local investigator.