Protocol for the Heart Failure Clinical Research Network Entresto™ (**L**CZ696) **I**n Advanced Heart **F**ailur**e (LIFE Study)**

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The Heart Failure Network Research Group
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Distributed by:
Heart Failure Network Coordinating Center
Duke Clinical Research Institute
Duke University
P.O. Box 17969
Durham, NC 27715

Study Funding: National Heart, Lung, and Blood Institute
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Project Officer: Patrice Desvigne-Nickens, MD

Network Chair:	Eugene Braunwald, MD
Protocol Principal Investigator:	Douglas L. Mann, MD
Protocol Development Team:	Michael M. Givertz, MD Randall C. Starling, MD Justin Vader, MD
Sponsor/ Coordinating Center:	Kevin J. Anstrom, PhD Adrian F. Hernandez, MD Duke Clinical Research Institute Durham, NC
Biomarker Core Laboratory:	Russell Tracy, PhD University of Vermont Burlington, VT

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACEI	Angiotensin-Converting Enzyme Inhibitor
AE	Adverse Event
ARB	Angiotensin Receptor Blocker
AUC	Area Under the Curve
CC	Coordinating Center
Cr	Creatinine
CRF	Case Report Form
DCRI	Duke Clinical Research Institute
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
ER	Emergency Room
GDMT	Guideline Directed Medical Therapy
GFR	Glomerular Filtration Rate
HF	Heart Failure
HFN	Heart Failure Clinical Research Network
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
ITT	Intention To Treat
IRB	Institutional Review Board
IV	Intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
LV	Left Ventricular
LVAD	Left Ventricular Assist Device
LVEDP	Left Ventricular End Diastolic Pressure
LVEF	Left Ventricular Ejection Fraction
m	Meters
mmHG	Millimeters of mercury
mmol/L	Millimole per liter
MDRD	Modification of Diet in Renal Disease
NHLBI	National Heart, Lung, and Blood Institute
NT-proBNP	Pro-B-type Natriuretic Peptide
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PCW	Pulmonary Capillary Wedge
PO	“Per os,” or by mouth
PPI	Patient Package Insert
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
VO_2	Oxygen Consumption

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3 EXECUTIVE SUMMARY

Title	Entresto™ (**L**CZ696) **I**n Advanced Heart **F**ailur**e (LIFE Study)**
Indication	New York Heart Association (NYHA) Class IV heart failure with a reduced ejection fraction (EF ≤ 35%).
Location	Approximately 40 clinical centers in the United States
Brief Rationale	Patients with advanced heart failure with reduced ejection fraction (HFrEF) have extremely high morbidity and mortality with 1 year outcomes of death and hospitalization of approximately 50%.[1,2] For the most advanced heart failure patients, the evidence base for medical treatment is limited with consensus guidelines recommending consideration for either cardiac transplant or ventricular assist device, or palliative care. [3] The PARADIGM-HF trial showed that LCZ696, which consists of the neprilysin inhibitor sacubitril and the ARB valsartan, improved morbidity and mortality in patients with chronic HFrEF in comparison to enalapril.[1] However, limited experience with advanced heart failure patients was gained from patients enrolled in the trial. Additionally, experience is needed on the use of, and outcomes with, LCZ696 in patients unable to tolerate target doses of ACEI/ARB compared to reduced doses of LCZ696. **Hypothesis:** In patients with symptomatic heart failure due to left ventricular systolic dysfunction, treatment with LCZ696 for 24 weeks will improve NT-proBNP levels, which reflect hemodynamic and clinical status, compared to treatment with valsartan.
Study Design	This study will be a randomized, double-blinded trial of advanced heart failure subjects with 1:1 randomization to either LCZ696 (sacubitril and valsartan) or valsartan. Study drug will be administered in a double-dummy fashion, in which subjects take active (LCZ696 or valsartan) and placebo. Approximately 400 subjects will be randomized into the study.
Treatment	LCZ696 (sacubitril and valsartan) plus placebo or valsartan plus placebo
Primary Objective and Endpoint	The proportional change from baseline in the AUC for NT-proBNP levels measured at 2, 4, 8, 12 and 24 weeks
Secondary Objectives and Endpoints	1. Days alive and out of hospital at 24 weeks, not listed for transplant (Status 1A, 1B or 1-4) or undergoing transplant, implanted with an LVAD, maintained or started on continuous inotropic therapy for ≥ 7 days, or has had two hospital admissions for HF (other than the index admission*) *The days alive and out of hospital will end on the day of the second readmission. 2. Tolerability measured as:

	a) Number of subjects achieving a target dose of 25%, 50% or 100% of valsartan or LCZ696 b) Number of subjects developing hypotension (SBP ≤ 85 mmHg) with symptoms c) Number of subjects developing worsening renal function (eGFR <20 ml/min/1.73m²) d) Number of subjects developing moderate (≥ 5.5 mmol/L) or severe (≥ 6 mmol/L) hyperkalemia

4 OBJECTIVES

4.1 Primary Objectives

To evaluate the effects of LCZ696 compared to valsartan on the proportional change from baseline in the AUC for NT-proBNP levels at 2, 4, 8, 12, and 24 weeks.

Hypothesis: In patients with symptomatic, advanced heart failure due to left ventricular systolic dysfunction, treatment with LCZ696 for 24 weeks will improve NT-proBNP levels, which reflect hemodynamic and clinical status, compared to treatment with valsartan.

4.2 Secondary Objectives

1. To evaluate the effects of LCZ696 compared to valsartan over 24 weeks on days alive and out of hospital at 24 weeks, not listed for transplant (Status 1A, 1B or 1-4) or undergoing transplant, implanted with an LVAD maintained or started on continuous inotropic therapy for ≥ 7 days, or has had two hospital admissions for HF (other than the index admission*)
   *The days alive and out of hospital will end on the day of the second readmission.

2. To determine tolerability measured as:
   a. Number of subjects achieving a target dose of 25%, 50% or 100% of valsartan or LCZ696
   b. Number of subjects developing hypotension (SBP ≤ 85 mmHg) with symptoms
   c. Number of subjects developing worsening renal function (eGFR < 20 ml/min/1.73 m^2)
   d. Number of subjects developing moderate (≥ 5.5 mmol/L) or severe (≥ 6 mmol/L) hyperkalemia

4.3 Tertiary Objectives

1. To evaluate the effects of LCZ696 compared to valsartan over 24 weeks on:
   a. Time to death
   b. Time to first HF hospitalization
   c. Time to death or first HF hospitalization
   d. Total HF hospitalizations
   e. Number of subjects on continuous inotropic therapy ≥ 7 days after discharge from the index hospitalization.
   f. Number of subjects, listed for transplant (status 1A, 1B or 1-4), transplanted or implanted with an LVAD
   g. Change in eGFR and cystatin C levels compared to baseline. Renal function will be assessed at baseline, 4, 8, 12, and 24 weeks.
   h. Number of subjects with unanticipated use of IV diuretics (outpatient, ER or inpatient)

i. Change in AUC in the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 4, 12, and 24 weeks compared to baseline
j. The change in the AUC for the ratio of NT-proBNP/BNP from baseline to 2, 4, 8, 12, and 24 weeks

4.4 Exploratory Objective

Modified Clinical Composite endpoint including Death, LVAD or Heart Transplant (including Listing status of 1A, 1B or 1-4), Multiple HF Hospital Admissions, Single HF admission

5 BACKGROUND

Patients with advanced HFrEF have extremely high morbidity and mortality with 1 year outcomes of death and hospitalization of approximately 50%.[1,3] Although ACEI/ARBs, beta-blockers and spironolactone are currently approved for use in patients with advanced heart failure (NYHA class IV), the overall morbidity and mortality in this class of patients remains unacceptably high. For the most advanced heart failure patients, the evidence base for medical treatment is limited with consensus guidelines recommending consideration for either cardiac transplant or ventricular assist device, or palliative care.[3]

Recently, a new class of therapeutic agent, a dual angiotensin receptor blocker (ARB) angiotensin receptor blocker neprilysin inhibitor (ARNIs) has been approved for use in patients with NYHA class II-IV heart failure. LCZ696 is an ARNI consisting of the neprilysin inhibitor sacubitril (AHU377) and the ARB valsartan. Neprilysin (NEP) is a membrane bound enzyme (peptidase) that can be “shed” and circulated in a biologically active form in the circulation. NEP catalyzes the degradation of a number of endogenous peptides, including natriuretic peptides, angiotensin II, bradykinin, substance and amyloid β peptide, which has been implicated in Alzheimer’s disease. In heart failure, NEP inhibition leads to increased circulating levels of these vasoactive peptides, thereby offsetting the deleterious effects of neurohormonal over activation, that contribute to peripheral vasoconstriction, sodium retention, and maladaptive left ventricular remodeling. In small clinical trials in patients with heart failure with a preserved ejection fraction or who had hypertension, LCZ696 had hemodynamic and neurohormonal effects that were greater than those of an ARB alone.

6 PRELIMINARY STUDIES (STUDY RATIONALE)

The PARADIGM-HF trial showed that LCZ696 improved morbidity and mortality in patients with chronic HFrEF in comparison to enalapril.[2] In PARADIGM-HF, 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less were randomized to receive LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to evidence

based medical therapy for heart failure. The primary outcome variable for the trial was a composite of death from cardiovascular causes or hospitalization for heart failure. The trial was stopped early for benefit in the LCZ696 treatment arm. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril treatment arm (HR 0.80; 95% CI, 0.73 - 0.87; P < 0.001). Moreover, there was a significant overall mortality benefit for LCZ696 when compared to enalapril (HR 0.84; 95% CI, 0.76 - 93; P <0.001). Despite the striking clinical benefits for LCZ696 in the PARADIGM-HF trial, limited experience with advanced heart failure patients was gained from patients enrolled in the trial. In the PARADIGM-HF trial a total of 33 patients (0.8%) with class IV heart failure were randomized to the treatment arm with LCZ696. Moreover, a recent study by Vodovar in patients with acute decompensated heart failure suggests that high circulating levels of endogenous B-type natriuretic peptide (BNP) and proBNP are capable of inhibiting the enzymatic activity of circulating NEP,[4] raising the possibility that the NEP inhibition may be less effective in patients with more advanced heart failure.

Because the information on the effects of sacubitril/valsartan in patients with NYHA class IV heart failure is limited, the updated 2016 ACC/AHA/HFSA guidelines for the treatment of heart failure do not endorse the use of sacubitril/valsartan in patients with NYHA class IV heart failure[5]

Accordingly, additional experience is needed on the use of, and outcomes with LCZ696 in patients unable to tolerate target doses of ACEI/ARB.

7 STUDY DESIGN

7.1 Screening / Baseline

Subjects will have an initial screening evaluation, including baseline laboratory tests as well as an assessment of LV ejection fraction, at which time preliminary subject eligibility will be determined. The LV ejection fraction may have been obtained within the prior 12 months by 2-D echocardiogram, LV angiogram or radionuclide scintigraphy. Willing subjects meeting entry criteria will be consented. Those who meet all entry criteria and are interested in study participation will be enrolled.

Enrolled subjects will complete baseline assessments and undergo a run-in period of 3-7 days with LCZ696 50 mg (equivalent to Entresto™ 24/26 mg) po BID prior to randomization. For subjects taking an ACEI, the ACEI will be withheld for ≥ 36 hours prior to first dose of LCZ696.

7.2 Randomization Phase

This will be a 2-arm randomized, double-blind, controlled trial with an active treatment arm (valsartan).

Subjects who tolerate the run-in period with LCZ696 will be randomized 1:1 to LCZ696 or valsartan. Subjects will be randomized using procedures determined by the Coordinating Center

(CC) to one of the two treatment groups.

7.3 Study Intervention Phase

Study treatment will be titrated to the target dose of 200 mg LCZ696 (equivalent to Entresto™ 97/103 mg) as two 100 mg LCZ696 and 2 placebo tablets po BID or valsartan 160 mg (two 80 mg valsartan and 2 placebo tablets) po BID.* Randomized subjects will receive the first dose of study drug as follows:

- For subjects not previously taking ACEI or ARB, previously taking ACEI or ARB at a low dose*, or subjects who have an eGFR < 30 mL/min/1.73m², the starting dose of valsartan will be 40 mg po BID and the starting dose of LCZ696 will be 50 mg po BID.
- For subjects taking an ARB at greater than low dose†, the starting dose of valsartan will be 80 mg po BID and the starting dose of LCZ696 will be 100 mg po BID.
- For subjects taking an ACEI at greater than low dose†, the ACEI will be withheld for ≥ 36 hours prior to randomization. The starting dose of valsartan will be 80 mg po BID and the starting dose of LCZ696 will be 100 mg po BID.

* Per package insert, the valsartan compounded in Entresto™ is more bioavailable than the valsartan in other marketed formulations. The dose equivalence for valsartan compounded in Entresto™ compared to valsartan prepared alone (Entresto™ dose = marketed valsartan dose) is as follows: 26 mg=40 mg, 51 mg=80 mg, 103 mg=160 mg.

† Low dose is defined as 24 hour dose of ≤ 10 mg lisinopril, ≤ 5 mg ramipril, ≤ 50 mg losartan, ≤ 10 mg olmesartan, or other dose equivalent.

Dose adjustments will be performed every 2 weeks by doubling the dose of LCZ696 or valsartan up to the target maximum dose. The doses of LCZ696 are 50 mg (one 50 mg active and 1 placebo tablet), 100 mg (one 100 mg active and 1 placebo tablet) and 200 mg (two 100 mg active and 2 placebo tablets). These doses are equivalent to 24/26 mg, 49/51 mg, and 97/103 mg commercial Entresto™, respectively. The doses of valsartan are 40mg (one 40 mg active and 1 placebo tablet), 80 mg (one 80 mg active and 1 placebo tablet), and 160 mg (two 80 mg active and 2 placebo tablets). The criteria for doubling the dose will be based on systolic blood pressure (a SBP > 90 mmHg is required for up titration), changes in renal function (maximum serum creatinine of 2.0 mg/dL), and the absence of symptoms of hypotension. For those not tolerating the current dose of study drug, the dose will be down-titrated to the previous tolerated dose. Subjects will return to clinic for follow-up visits at 2, 4, 8, 12, 24 and 26 weeks after randomization.

8 STUDY FLOW DIAGRAM

Screening / Study Visit 0: Enrollment
- Informed Consent
- Baseline Evaluation for eligibility
- Discontinue ACEI 36 hours before start of run-in phase, if applicable

Assessments: physical examination, review of medications, KCCQ questionnaire, and local laboratory testing, pregnancy test (if applicable)

Visit 1: Begin 3-7 day run-in phase
- Ensure first dose of LCZ696 ≥ 36 hours after last ACEI dose

Assessments: interim history, review of medications, physical examination, local laboratory testing, and AE monitoring
- Start LCZ696 50 mg po BID for 3-7 days

Visit 2: End of Run-in/Randomization (If run-in phase tolerated)
Randomize subject and administer 1st dose of LCZ696 or valsartan
If previously taking no ACEI/ARB, low-dose ACEI/ARB*, or GFR < 30 ml/min/1.73m^2 ensure ACEI was discontinued and the last dose of ACEI was ≥ 36 hours ago, then
- LCZ696 50 mg po BID or valsartan 40 mg po BID (1 active and 1 placebo tablet po BID)

If previously taking greater than low-dose ARB
- LCZ696 100mg po BID or valsartan 80 mg po BID (1 active and 1 placebo tablet po BID)

If previously taking greater than low dose ACEI, ensure ACEI was discontinued and the last dose of ACEI ≥ 36 hours ago, then
- LCZ696 100 mg po BID or valsartan 80 mg po BID (1 active and 1 placebo tablet po BID)

Assessments: interim history, review medications, physical examination, routine laboratory testing, core laboratory testing (BNP, NT-proBNP and Cystatin C), and AE monitoring

Visit 3: 2 weeks post-randomization
First dose titration:
If tolerating current dose (SBP > 90 mmHg, Cr ≤ 2.0 mg/dL, and no symptoms of hypotension) then double dose.
- Maximum dose LCZ696 200 mg po BID or Valsartan 160 mg po BID (2 active and 2 placebo tablets po BID)

If not tolerating dose, reduce to previously tolerated dose.

Assessments: interim history, review of medications, physical examination, routine laboratory testing, core laboratory testing (BNP, NT-proBNP), and AE monitoring

The Screening visit and Visit 1 may be combined at the investigator's discretion for subjects who are stable, and for whom lab results have been reviewed as long as the investigator ensures the 1st dose of LCZ696 is ≥ 36 hours after last ACEI dose (if applicable).
If not combined, Visit 1 should take place within 7 days of the Screening Visit

Visit 4: 4 weeks post-randomization
Second dose titration:
If tolerating current dose (SBP > 90 mmHg, Cr ≤ 2.0 mg/dL, and no symptoms of hypotension) then double dose.

- Maximum dose LCZ696 200 mg po BID or valsartan 160 mg po BID (2 active and 2 placebo tablets po BID)

If not tolerating dose, reduce to previously tolerated dose
Assessments: interim history, review of medications, physical examination, KCCQ, routine laboratory testing, core laboratory testing (BNP, NT-proBNP and Cystatin C), and AE monitoring

Visit 5: 8 weeks post-randomization
Continue LCZ696 or valsartan at highest tolerated dose
Assessments: interim history, review of medications, routine laboratory testing, core laboratory testing (BNP, NT-proBNP and Cystatin C), and AE monitoring.

Visit 6: 10 weeks post-randomization
Continue LCZ696 or valsartan at highest tolerated dose
Subjects should be contacted via telephone to assess dosing compliance, record the occurrence of applicable AEs, and remind the subject of the date and time of their next in-person visit.

Visit 7: 12 weeks post-randomization
Continue LCZ696 or valsartan at highest tolerated dose
Assessments: interim history, review of medications, physical examination, KCCQ, routine laboratory testing, core laboratory testing (BNP, NT-proBNP and Cystatin C), and AE monitoring.

Visit 8: 16 weeks post-randomization
Continue LCZ696 or valsartan at highest tolerated dose
Subjects should be contacted via telephone to assess dosing compliance, record the occurrence of applicable AEs, and remind the subject of the date and time of their next in-person visit.

Visit 9: 20 weeks post-randomization
Continue LCZ696 or valsartan at highest tolerated dose
Subjects should be contacted via telephone to assess dosing compliance, record the occurrence of applicable AEs and events of interest, and remind the subject of the date and time of their next in-person visit.

Visit 10: 24 weeks post-randomization
End treatment phase and begin follow-up phase
Discontinue study medication
Assessments: interim history, review of medications, physical examination, KCCQ, routine laboratory testing, core laboratory testing (BNP, NT-proBNP and Cystatin C), and AE monitoring.

Visit 11: 2 weeks following end of study drug / 26 weeks post randomization
Final follow-up visit
Assessment: phone call to assess clinical stability and any applicable AEs.

* Low dose is defined as 24 hour dose of ≤ 10 mg lisinopril, ≤ 5 mg Ramipril, ≤ 50 mg Losartan, ≤ 10 mg Olmesartan, or other dose equivalent.

9 PATIENT POPULATION

9.1 Study Population

It is anticipated that approximately 400 subjects meeting eligibility criteria listed below will be randomized into the study. Subjects suitable for this protocol are individuals with advanced HF and a LVEF≤ 35%. Subjects may be currently hospitalized or non-hospitalized.

9.2 Inclusion Criteria

Key inclusion criteria

1. Advanced HFrEF defined as including ALL
    a. LVEF≤ 35% documented during the preceding 12 months
    b. NYHA class IV symptomatology, defined as chronic dyspnea or fatigue at rest or on minimal exertion in the previous 3 months, or patients who require chronic inotropic therapy
    c. Minimum of 3 months GDMT for HF and/or intolerant to therapy
2. Systolic blood pressure ≥ 90 mmHg
3. Serum NT-proBNP ≥ 800 pg/mL OR BNP ≥ 250 pg/mL (most recent - less than 3 months old)
4. Any one or more of the following objective findings of advanced HF including:

a. Current inotropic therapy or use of inotropes in the past 6 months
b. ≥ 1 hospitalization for heart failure in the past 6 months (not including the index hospitalization for inpatient participants)
c. LVEF ≤ 25% (within the past 12 months)
d. Peak VO2 < 55% predicted or peak VO2 ≤ 16 for men or ≤ 14 for women (Respiratory Exchange Ratio (RER) ≥ 1.05) (within the past 12 months)
e. 6 min walk test distance < 300 m (within the past 3 months)

5. Age ≥18 years and ≤ 85 years
6. Signed Informed Consent form

9.3 Exclusion Criteria

1. Currently taking Entresto™
2. History of hypersensitivity or intolerance (unmodifiable) to Entresto™, an ACEI or ARB as well as known or suspected contraindications (including hereditary angioedema) to the study drugs.
3. Estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73 m2 at baseline
4. Co-morbid conditions that may interfere with completing the study protocol (e.g. recent history of drug or alcohol abuse) or cause death within 1 year
5. Symptomatic hypotension at randomization or systolic blood pressure < 90 mmHg
6. Serum potassium > 5.5 mmol/L
7. Severe liver dysfunction (Childs-Pugh Class C)
8. Acute coronary syndrome within 4 weeks as defined by electrocardiographic (ECG) changes and biomarkers of myocardial necrosis (e.g. troponin) in an appropriate clinical setting (chest discomfort or anginal equivalent)
9. Planned or recent (≤ 4 weeks) PCI, coronary artery bypass grafting, or biventricular pacing
10. Currently hospitalized and listed status 1A, 1B or 1-4 for heart transplant
11. Current or scheduled for LVAD implantation within 30 days of study enrollment
12. Active infection (current use of oral or IV antimicrobial agents)
13. Primary hypertrophic or infiltrative cardiomyopathy, acute myocarditis, constrictive pericarditis or tamponade
14. Complex congenital heart disease
15. Concomitant use of aliskiren in patients with diabetes or renal impairment (eGFR <60 mL/min/1.73 m²)
16. Known pregnancy or anticipated pregnancy within the next 6 months or breastfeeding mothers
17. Enrollment in any other investigational clinical trial within 30 days prior to screening
18. Inability to comply with study procedures

10 TREATMENT

10.1 Intervention

This will be a 2-arm randomized, double-blind, controlled trial with an active treatment arm (valsartan). The therapeutic intervention will be treatment with either LCZ696 or valsartan.

Study drug will be given for 24 weeks following a run-in phase. Subjects will be given a starting dose of LCZ696 or valsartan and up-titrated (if tolerated) to the target maintenance dose as described in section 7.3. For those not tolerating the current dose of study drug, the dose will be down-titrated to the previous tolerated dose.

In order to maintain the study blind, study drug will be administered in a double-dummy design, where subjects will take both active drug (either LCZ696 or valsartan) and placebo.

10.2 Drug Dispensing

LCZ696, valsartan, and their respective matching placebos will be manufactured and provided for study sites by Novartis Pharmaceuticals. LCZ696 will be supplied in bottles containing 50 mg (low dose) tablets or 100 mg (high dose) tablets or matching placebo. Valsartan will be supplied in bottles containing 40 mg (low dose) or 80 mg (high dose) tablets, or matching placebo. Subjects will receive a sufficient supply of study drug at each study visit to last until the next study visit. Drug storage, inventory, accountability, and dispensing will be managed at each study site. Subjects will be instructed to take the medication as required by the protocol and compliance will be assessed at each visit (as described in the protocol).

10.3 Drug Administration

Subjects will take LCZ696 plus placebo or valsartan plus placebo twice daily by mouth, according to the Dosing Guidelines below. The total number of pills taken will be 2-4 pills, twice per day.

10.4 Dosing Guidelines

The study will begin with a 3-7 day run-in period in which all subjects will be administered LCZ696 50 mg po BID. For those subjects taking ACEI prior to the run-in period, the first dose of LCZ696 will be withheld ≥ 36 hours after last ACEI dose. After stopping LCZ696, a 36 hour washout period is required before resuming an ACEI.

Subjects tolerating the LCZ696 in the run-in period will be randomized to either LCZ696 or valsartan. Doses will be assigned in the following fashion:
If previously taking no ACEI/ARB, low-dose ACEI/ARB†, or eGFR < 30 ml/min/1.73m^2, ensure ACEI has been discontinued and the last dose was ≥ 36 hours ago, then

- LCZ696 50 mg plus placebo po BID or valsartan 40 mg plus placebo po BID

If previously taking greater than low dose ARB†

- LCZ696 100 mg plus placebo po BID or valsartan 80 mg plus placebo po BID*

If previously taking greater than low dose ACEI†, ensure ACEI was discontinued and the last dose was ≥ 36 hours ago, then

- LCZ696 100 mg plus placebo po BID or valsartan 80 mg plus placebo po BID*

* At Investigator discretion, study drug may be started at the low dose (LCZ696/placebo 50 mg po BID or valsartan/placebo 40 mg po BID) if there are any concerns regarding tolerability at the 100 mg / 80 mg dose.

Two weeks after randomization, upward dose titration will occur among subjects tolerating their current dose (SBP > 90 mmHg, creatinine (Cr) ≤ 2.0 mg/dL, and no symptoms of hypotension). This will consist of doubling the dose up to a maximum dose LCZ696 200 mg po BID (two 100 mg tablets plus 2 placebo tablets po BID) or valsartan 160 mg po BID (two 80 mg tablets and 2 placebo tablets po BID). For those not tolerating the current dose of study drug, the dose will be down-titrated to the previous tolerated dose.

Two weeks after the prior dose titration visit and four weeks after randomization, further dose titration will occur among subjects tolerating their current dose (SBP > 90 mmHg, Cr ≤ 2.0 mg/dL, and no symptoms of hypotension). This will consist of doubling the dose up to a maximum dose LCZ696 200 mg po BID or valsartan 160 mg po BID. For those not tolerating the current dose of study drug, the dose will be down-titrated to the previous tolerated dose. The total duration of study drug treatment will be 24 weeks.

With regard to the transition of therapy after the conclusion of the study period, this will be left to clinician discretion without unblinding. Since valsartan/sacubitril is available clinically, we will advise physicians to determine what is most appropriate clinically. Because we will not know which treatment a subject was assigned, we are recommending treating physicians will initiate an angiotensin-receptor blocker initially in open-label fashion if there is a concern about hypotension. Treating physicians can transition patients to valsartan/sacubitril as clinically indicated.

† Low dose is defined as 24 hour dose of ≤ 10 mg lisinopril, ≤ 5 mg ramipril, ≤ 50 mg losartan, ≤ 10 mg olmesartan, or other dose equivalent.

10.5 Drug Storage Requirements

Study mediation must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study drug and placebo should be stored according to the instructions specified on the drug labels.

10.6 Drug accountability

Subjects are instructed to return all used, partly used and unused trial product at each study

visit. Returned trial product(s) (used, partly used or unused including empty packaging material) must be stored separately from the non-allocated trial product(s) until drug accountability has been reconciled. The investigators will keep track of all received, used, partly used and unused trial products.

10.7 Destruction

Used and unused study drug may be destroyed at the site according to accepted pharmacy practice, local and national guidelines, using the site's destruction procedure after receiving written authorization for study drug destruction from the Coordinating Center. A copy of the site drug destruction Standard Operating Procedure (SOP) should be maintained in the Pharmacy section of the Regulatory Binder. Study drug destruction should be documented in the comments section of the Subject Specific Drug Accountability Log.

10.8 Randomization, Stratification and Blinding

Subjects will be consented and enrolled at the first study visit. This will be followed by a run-in phase. Subjects who successfully tolerate the study drug during the run-in phase will be randomized at the second study visit. Subjects will be randomized using procedures determined by the CC to one of 2 treatment groups. Subjects will be randomized in a 1:1 allocation ratio using a permuted block design with stratification based on the clinical center and atrial fibrillation status. Subjects will be randomized using a permuted block randomization to ensure relatively equal distribution of subjects to each arm within each site.

Blinding of the study, with respect to treatment groups, will be preserved by the use of matching placebo, identical in appearance to the active study drugs. The investigator may be asked at the end of the trial if they had obtained any information which may have led to the unbinding of treatment.

10.9 Unblinding

The investigative sites will be given access to the treatment code for their Subjects for emergency unblinding ONLY by calling the CC. Any suspected study drug-related events should be treated as though the subject received LCZ696. Nevertheless, in the rare event of necessary unblinding, the CC medical monitor must be contacted to discuss a given case. Randomization data are kept strictly confidential, accessible only to authorized persons, until the time of unblinding.

10.10 Concomitant Medication

Subjects should be treated with standard HF strategies (diuretics for congestion, blood pressure control and heart rate control if subject is in atrial fibrillation) as per recommended guidelines. Subjects may not take ARBs (other than blinded study drug) during the study, and ACE inhibitors and direct renin inhibitors are prohibited during the study.

11 RECRUITMENT AND SCREENING PROCEDURES

11.1 Common Recruitment Procedures

All subjects presenting to the participating study centers with signs and symptoms suggestive of HF will be screened by a study coordinator. Subjects meeting eligibility criteria will be approached regarding participation in this study.

11.2 Estimated Enrollment Period

This study will randomize approximately 400 subjects at approximately 40 clinical centers in the U.S. The anticipated enrollment period is approximately 18 months.

11.3 Informed Consent

Study center clinicians will explain to eligible subjects the purpose of the study, study interventions and evaluations, and the potential risks and benefits of participation, and will answer any questions. If a subject agrees to participate in the study, they will review and sign the site specific IRB approved informed consent form (ICF).

11.4 Confidentiality and HIPAA Requirements

All information collected on study subjects will be stored in a confidential manner using the procedures in place at each participating center. Only approved study personnel will have access to data collected as part of the study. Consented study subjects will be identified by a subject ID number on all study documents. Data will be transmitted to the CC in a secure manner, and stored securely at the CC using standard Duke Clinical Research Institute (DCRI) operating procedures.

11.5 Protections of Human Subjects

Protections for human subjects of research are required under Department of Health and Human Services (HHS) regulations at 21 CFR parts 50, 56, and 312.

11.6 Summary of the Risks and Benefits

Blood draws: The risks of drawing blood include bleeding at the puncture site, bruising and pain. These occur in a very small portion of the population.

Valsartan: Angiotensin receptor blockers, the class to which valsartan belongs, have been shown to reduce mortality in patients with heart failure and reduced ejection fraction (HFrEF). These agents are recommended in all patients with HFrEF who are intolerant to ACE inhibitors (I, LOE A) and are a reasonable alternative to ACE inhibitors as first-line therapy (IIa, LOE A). The risks for valsartan use in this study are the same as open-label use of valsartan in adherence to guideline-directed medical therapy. The most common adverse reactions are dizziness, hypotension, diarrhea, arthralgia, back pain, fatigue and hyperkalemia. Valsartan is

teratogenic and contraindicated in pregnancy. Valsartan should be used with caution in the setting of concomitant non-steroidal anti-inflammatory drugs, lithium, other potassium-sparing diuretics, and other inhibitors of the renin-angiotensin aldosterone system.

LCZ696 (sacubitril/valsartan): The use of LCZ696 compared to the guideline-indicated ACE inhibitor enalapril reduced mortality was shown in the PARADIGM trial to reduce the hazard ratio for cardiovascular death and mortality by 20%. The updated 2016 ACC/AHA/HFSA guidelines for the treatment of heart failure recommend the use of sacubitril/valsartan in patients with NYHA II-III heart failure (I, LOE B-R).[5] Few enrollees in the PARADIGM trial had NHYHA Class IV heart failure and enrollment required systolic blood pressure > 100 mmHg at the time of enrollment. The risks and benefits of LCZ696 among patients with advanced heart failure and lower enrollment blood pressure are not known, which is the rationale for this trial. The known risks of Entresto™ overlap with those of valsartan alone, with some initial considerations. In the PARADIGM trial, use of LCZ696 was associated with a greater incidence of angioedema than the comparator drug enalapril (0.5% vs. 0.2%). The risk of angioedema with LCZ696 compared to enalapril was relatively greater among Black patients (2.4% vs. 0.5%). Patients with a history of angioedema are contraindicated from taking this drug. Trial data indicate adverse reactions occurring ≥5% are hypotension, hyperkalemia, cough, dizziness, and renal failure. Symptomatic hypotension in PARAGON was more common among patients taking LCZ696 than enalapril (18% vs. 12%).

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Women of child-bearing potential must have a negative pregnancy test prior to initiating study drug. When pregnancy is detected, discontinue study drug as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimesters of pregnancy. There is no information regarding the presence of sacubitril/valsartan in human milk, the effects on the breastfed infant, or the effects on milk production. Sexually active subjects must agree to use appropriate contraception as long as they are taking study drug. Medically acceptable contraceptives include:

- surgical sterilization (such as a tubal ligation or hysterectomy)
- approved hormonal contraceptives (such as birth control pills, patches, implants or injections)
- barrier methods (such as a condom or diaphragm) used with a spermicide, or
- Intrauterine device (IUD)

12 VISIT SCHEDULE AND ASSESSMENTS

12.1 Baseline Evaluation and Randomization Visit

A complete schedule of assessments throughout the study is given in Appendix A.

Screening/Study Visit 0 (Enrollment)

This visit will include the screening and informed consent process followed by a baseline assessment including:

- Medical history including etiology and duration of HF, documented history of HF visits within 6 months
- Confirmation of ejection fraction ≤35% within the last 12 months
- Physical examination including height and weight
- NYHA class assessment
- Review of medications
- KCCQ quality of life questionnaire
- Local laboratory testing, including the following:
  - Sodium
  - Potassium
  - Chloride
  - CO2/bicarbonate
  - Total calcium
  - Magnesium
  - Blood Urea Nitrogen (BUN)
  - Creatinine

  For Screening/Study Visit 0 only - Standard of care labs are acceptable, using results within 24 hours prior for hospitalized patients and within 7 days prior for outpatients.
- Serum pregnancy test on all women of childbearing potential
- Discontinue ACEI 36 hours prior to the start of the run-in phase, if applicable

Study Visit 1 (Begin run-in phase)

Visit 1 should take place within 7 days of the screening visit. This visit will begin the 3-7 day run-in period. All subjects will be administered LCZ696 50 mg po BID. For those subjects taking ACEI prior to the run-in period, ensure that the ACEI has been discontinued and last dose of ACEI was ≥ 36 hours prior to the first dose of LCZ696.

Assessments at this visit include:

- Interim history
- Review of medications
- Physical examination with NYHA class assessment
- Local laboratory testing (creatinine, BUN, electrolytes – see visit 0 for labs to be collected)
- Adverse event monitoring.

For subjects who are stable and for whom lab results have been reviewed, the Screening Visit and Visit 1 may be combined at the investigator's discretion as long as the investigator ensures the 1st dose of LCZ696 is ≥ 36 hours after last ACEI dose (if applicable).

Study Visit 2 (End run-in phase / Begin Randomization)

At this visit, those subjects tolerating the LCZ696 in the run-in period will be randomized to either LCZ696 or valsartan. Randomization should occur immediately following the end of the run-in phase. If the subject cannot return to the clinic within 7 days of starting the run-in phase,

the subject should continue to take LCZ696 po BID until the randomization visit and site personnel should notify the CC. Subjects who fail the open-label run-in phase should receive a follow-up contact approximately 2 weeks after the last dose of study drug.

Doses will be assigned in the following fashion:
If previously taking no ACEI/ARB, low-dose ACEI/ARB†, or eGFR < 30 ml/min/1.73m^2 ensure ACEI has been discontinued and the last dose of ACEI was ≥36 hours ago, then

- LCZ696 50 mg po plus placebo BID or valsartan 40 mg po BID plus placebo

If previously taking greater than low dose ARB†

- LCZ696 100 mg po plus placebo BID or valsartan 80 mg po BID plus placebo*

If previously taking greater than low dose ACEI†, ensure ACEI has been discontinued and the last dose of ACEI was ≥ 36 hours ago, then

- LCZ696 100 mg po plus placebo BID or valsartan 80 mg po BID plus placebo*

† Low dose is defined as 24 hour dose of ≤ 10 mg lisinopril, ≤ 5 mg Ramipril, ≤ 50 mg Losartan, ≤ 10 mg Olmesartan, or other dose equivalent.
* At Investigator discretion, study drug may be started at the low dose (LCZ696/placebo 50 mg po BID or valsartan/placebo 40 mg po BID) if there are any concerns regarding tolerability at the 100 mg / 80 mg dose.)

Study drug will be supplied in kits (containing both active and placebo tablets) and will be administered as follows:

- 50 mg LCZ696 / 40 mg valsartan = one low-dose active tablet and one low-dose placebo tablet po BID
- 100 mg LCZ696 / 80 mg valsartan = one high-dose active tablet and one high-dose placebo tablet po BID
- 200 mg LCZ696 / 160 mg valsartan = two high-dose active tablets and two high-dose placebo tablets po BID

Assessments at this visit include:

- Interim history
- Review of medications
- Physical examination with NYHA class assessment
- Routine laboratory testing (creatinine, BUN, electrolytes – see visit 0 for labs to be collected)
- Core laboratory testing (Cystatin C, BNP, NT-proBNP)
- Adverse event monitoring

12.2 Follow-up Evaluations

Study Visit 3 (Dose Titration / 2 weeks post-randomization +/- 3 days)
At this visit, two weeks after randomization, upward dose titration will occur among subjects tolerating their current dose (SBP > 90 mmHg, Cr ≤ 2.0 mg/dL, and no symptoms of

hypotension). This will consist of doubling the dose up to a maximum dose LCZ696 200 mg po BID or valsartan 160 mg po BID. For those not tolerating the current dose of study drug, the dose will be down-titrated to the previous tolerated dose.
Assessments at this visit include:

- Interim history
- Review of medications
- Physical examination with NYHA class assessment
- Routine laboratory testing (creatinine, BUN, electrolytes – see visit 0 for labs to be collected)
- Core laboratory testing (BNP, NT-proBNP)
- Adverse event monitoring.

Study Visit 4 (Dose Titration / 4 weeks post-randomization +/- 3 days)

At this visit, two weeks after the prior dose titration visit and four weeks after randomization, further dose titration will occur among subjects tolerating their current dose (SBP > 90 mmHg, Cr ≤ 2.0 mg/dL, and no symptoms of hypotension). This will consist of doubling the dose up to a maximum dose LCZ696 200 mg po BID or valsartan 160 mg po BID. For those not tolerating the current dose of study drug, the dose will be down-titrated to the previous tolerated dose.
Assessments at this visit include:

- Interim history
- Review of medications
- Physical examination with NYHA class assessment
- Routine laboratory testing (creatinine, BUN, electrolytes – see visit 0 for labs to be collected)
- Core laboratory testing (Cystatin C, BNP, NT-proBNP)
- KCCQ questionnaire
- Adherence and tolerance assessment
- Adverse event monitoring.

Study Visit 5 (8 weeks after randomization +/- 5 days)

Subjects will continue taking study drug at the highest tolerated dose. If the study drug has not yet been titrated to the maximal dose, or if the dose of study drug was previously down-titrated, it may be up-titrated, at the physician's discretion. If there are any concerns regarding tolerability, the dose may be down-titrated per investigator discretion.
Assessments at this visit include:

- Interim history
- Review of medications
- Routine laboratory testing (creatinine, BUN, electrolytes – see visit 0 for labs to be collected)
- Core laboratory testing (Cystatin C, BNP, NT-proBNP)
- Adherence and tolerance assessment
- Adverse event monitoring

Study Visit 6 (10 weeks after randomization +/- 5 days)
Subjects should be contacted via telephone to assess dosing compliance, record the occurrence of applicable adverse events and events of interest, and remind the subject of the date and time of their next in-person visit.

Study Visit 7 (12 weeks after randomization +/- 5 days)
Subjects will continue taking study drug at the highest tolerated dose. If the study drug has not been titrated to the maximal dose, or if the dose of study drug was previously down-titrated, it may be up-titrated again, at the physician's discretion. If there are any concerns regarding tolerability, the dose may be down-titrated per investigator discretion.

Assessments at this visit include:

- Interim history
- Review of medications
- Physical examination with NYHA class assessment
- Routine laboratory testing (creatinine, BUN, electrolytes – see visit 0 for labs to be collected)
- Core laboratory testing (Cystatin C, BNP, NT-proBNP)
- KCCQ questionnaire
- Adherence and tolerance assessment
- Adverse event monitoring

Study Visits 8 and 9 (16 and 20 weeks after randomization +/- 5 days)
Subjects should be contacted via telephone to assess dosing compliance, record the occurrence of applicable adverse events and events of interest, and remind the subject of the date and time of their next in-person visit.

Study Visit 10 (24 weeks after randomization (+/- 5 days)/ End of treatment phase / Begin follow-up phase)
Subjects will discontinue study medication.

Assessments at this visit include:

- Interim history
- Review of medications
- Physical examination with NYHA class assessment
- Routine laboratory testing (creatinine, BUN, electrolytes – see visit 0 for labs to be collected)
- Core laboratory testing (Cystatin C, BNP, NT-proBNP)
- KCCQ questionnaire
- Adherence and tolerance assessment
- Adverse event monitoring

After this visit, the study phase is complete. If the subject is to be given an ACEI, a 36 hour wash-out period is required after the last dose of study drug before starting the ACEI.

Study Visit 11 (26 weeks after randomization +/- 3 days)
A final phone visit is conducted approximately 2 weeks after study visit 10 to assess clinical stability and any applicable adverse events.

Study Drug Interruption:
If a subject should stop taking study medication for any reason before completing the 24 weeks of study drug dosing, an attempt should be made to restart the study drug at the last tolerated dose when the subject is stable, per physician discretion. If the treating physician decides to stop study medication and start the patient on an ACEI, then a 36 hour wash-out period is required after the last dose of study drug before starting the ACEI. All subjects will complete all study assessments through study visit 11, regardless of whether they have received the full 24 weeks of study drug treatment.

Unscheduled Visits:
If the Investigator determines that a participant should be brought to the clinic to be evaluated for a potential change in study drug dose between scheduled study visits, an "unscheduled visit" should be done. Study drug dose changes will be recorded in the eCRF.
Assessments at this visit include:

- Interim history
- Review of medications
- Physical examination
- Routine laboratory testing (creatinine, BUN, electrolytes – see visit 0 for labs to be collected)
- Adverse event monitoring

12.3 Phone and Other Media Follow-up

General procedures: At Study Visit 1, subjects and study staff will define optimal times and phone numbers for the protocol-specified phone contacts to encourage compliance with study procedures.

During the follow-up visits, the subject will receive:

- Reminder of appropriate study drug dose for the stage of the protocol.
- Reminder to maintain study dosing diary and discussion regarding dosing compliance
- Encouragement of activity within the limits of their HF symptoms
- Confirm plans for future study visits
- Confirm need to bring study drug and dosing diary to future study visits.

13 OUTCOME DETERMINATIONS

13.1 Primary Endpoint

The proportional change from baseline in the AUC for NT-proBNP levels measured at 2, 4, 8, 12 and 24 weeks.

13.2 Secondary Endpoints

1. Days alive and out of hospital at 6 months, not listed for transplant (status 1A, 1B or 1-4) or undergoing transplant, implanted with an LVAD, maintained or started on continuous inotropic therapy for ≥ 7 days, or has had two hospital admissions for HF (other than the index admission*). If a patient meets the pre-specified secondary endpoint of 2 hospital admissions for heart failure (other than the index admission), the patient can remain on study drug or be started on open label sacubitril/valsartan, at the treating physician's discretion, while remaining in the trial.

*The days alive and out of hospital will end on the day of the second readmission.

2. Tolerability measured as:
    a) Number of subjects achieving a target dose of 25%, 50% or 100% of valsartan or LCZ696
    b) Number of subjects developing hypotension (SBP ≤ 85 mmHg) with symptoms
    c) Number of subjects developing worsening renal function (eGFR < 20 ml/min/1.73 m^2)
    d) Number of subjects developing moderate (≥ 5.5 mmol/L) or severe (≥ 6 mmol/L) hyperkalemia

13.3 Tertiary Endpoints

1. Time to death
2. Time to first HF hospitalization
3. Time to death and first HF hospitalization
4. Total number of HF hospitalizations
5. Number of subjects on continuous inotropic therapy ≥ 7 days after discharge from the index hospitalization
6. Number of subjects, listed for transplant (status 1A, 1B or 1-4), transplanted or implanted with an LVAD
7. Change in eGFR and cystatin C levels compared to baseline. Renal function will be assessed at baseline, 4, 8, 12, and 24 weeks
8. Number of subjects with unanticipated use of IV diuretics (outpatient, ER or inpatient)
9. Change in AUC in the KCCQ at 4, 12 and 24 weeks compared to baseline
10. The change in the AUC for the ratio of NT-proBNP/BNP from baseline to 2, 4, 8, 12 and 24 weeks

13.4 Exploratory Endpoints

Modified Clinical Composite endpoint including Death, LVAD or Heart Transplant (including Listing status of 1A, 1B or 1-4), Multiple HF Hospital Admissions, Single HF admission

14 METHODS TO PROMOTE ADHERENCE

14.1 Protocol Training

Protocol training and adherence will be a major focus of the investigator training. Based on our experience in prior studies, identifying and correcting non-adherence is best accomplished in a stepped approach. The site will be responsible for managing subject compliance with study drug administration and visit compliance.

14.2 Data Quality Reports

Site personnel are responsible for ensuring that all procedures required by the protocol are performed as outlined and that the data is collected and reported accurately and per established guidelines. The CC will generate and review data quality reports and will follow-up with study site personnel as needed to ensure adherence. Routine data quality reports will also be provided to the sites. Significant non-adherence issues will be discussed with the Executive Committee.

15 SAFETY MONITORING AND REPORTING

15.1 Institutional Review Boards

All sites will submit the study protocol, consent form, and other study documents to their IRB for approval. The approval letter for each clinical center will be reviewed by the CC. Any amendments to the protocol, other than minor administrative changes, must be approved by each IRB before they are implemented.

15.2 Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in a subject, whether or not considered drug or biologic related. An AE can therefore be any undesirable sign, symptom or medical condition occurring after starting study drug, even if the event is not considered to be related to the pharmaceutical product. Study drug includes the drug under evaluation, and any reference drug given during any phase of the trial.

15.3 Suspected Adverse Reaction Definition

A suspected adverse reaction (SAR) is any adverse event for which there is a reasonable possibility that the drug caused the event. “Reasonable possibility” suggests there is a causal

relationship between the drug and the adverse event. “Suspected adverse reaction” implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

15.4 Serious Adverse Events (SAE)

An adverse event or suspected adverse reaction is considered serious if the investigator or sponsor believes any of the following outcomes occurred:

- Death
- Life-threatening AE: Places the subject at immediate risk of death at the time of the event as it occurred. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Inpatient hospitalization or prolongation of hospitalization.
- Congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition above.

This determination is based on the opinion of either the investigator or sponsor (e.g., if either believes it is serious, it must be considered serious).

15.5 Laboratory Test Abnormalities

For laboratory test abnormalities that meet the definition of an SAE, that required the subject to have the investigational product discontinued or interrupted or required the subject to receive specific corrective therapy, the clinical diagnosis rather than the laboratory term will be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

15.6 Assessment of Causal Relationship

A medically-qualified investigator must assess the relationship of any AE to the use of study drug, based on available information, using the following guidelines:

- **Not related:** There is not a reasonable causal relationship to the investigational product and the adverse event.
- **Unlikely related:** No temporal association or the cause of the event has been identified, or the drug or biologic cannot be implicated.
- **Possibly related:** There is reasonable evidence to suggest a causal relationship between the drug and adverse event.
- **Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

15.7 Assessment of Adverse Event Severity

The determination of adverse event severity rests on medical judgment of a medically-qualified Investigator. The severity of AEs will be graded using the following definitions:

- **Mild:** Awareness of sign, symptom, or event, but easily tolerated;
- **Moderate:** Discomfort enough to cause interference with usual activity and may warrant intervention;
- **Severe:** Incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention.

15.8 Expectedness

The expectedness of an AE or Suspected Adverse Reaction (SAR) shall be determined according to the most current patient package insert (PPI). Any AE that is not identified in nature, severity, or specificity in the current PPI is considered unexpected. Events that are mentioned in the PPI as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but not specifically mentioned as occurring with the particular drug under investigation are considered unexpected.

15.9 Anticipated Disease Related Events and Events of Interest

The following are anticipated, disease-related events in patients with HF or anticipated events of interest in patients with heart failure taking valsartan or valsartan/sacubitril:

- **Arrhythmias:** This refers to both atrial and ventricular arrhythmias.
- **Sudden Cardiac Death:** This refers to witnessed cardiac arrests and sudden deaths without an otherwise apparent cause such as trauma or malignancy.
- **Acute coronary syndrome:** This refers to unstable angina, non ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial (STEMI).
- **Unplanned hospitalization, ER visit or clinic visit for worsening HF:** This refers to treatment for acute heart failure such as receiving intravenous diuretics.
- **Cerebrovascular event:** This refers to cerebrovascular accidents (stroke) of any cause (hemorrhagic, ischemic, or embolic) and transient ischemic attack (TIA).
- **Venous thromboembolism:** This includes both deep venous thrombosis and pulmonary embolus.
- **Lightheadedness, Presyncope, or Syncope:** This includes dizziness, lightheadedness, or fainting from any cause.
- **Worsening renal function:** This refers to acute kidney injury, typically defined as a decrease in eGFR ≥ 20% over 48 hours, or progressive loss of renal function over time.
- **LVAD implantation:** This refers to implantation of a temporary or durable LVAD.
- **Cardiac Transplantation**
- **Hyperkalemia $\geq$ 5.5 mEq/L**
- **Acute renal failure with serum creatinine > 2.5 mg/dL**
- **Angioedema**
- **Symptomatic hypotension**

Anticipated events will not be captured as AEs/SAEs during the study, but will be entered on the appropriate electronic case report form (eCRF) module ("Events of Interest" page).

15.10 Recording and Reporting of Adverse Events

The site Investigator is responsible for monitoring the safety of subjects enrolled into the study at the study sites. For this study, non-serious AEs will not be collected on the safety reporting page of the eCRF, but should be documented in the source documents and followed according to local standard of care. Events significant enough to necessitate modification of study drug dosing will be captured on the appropriate eCRF module ("Study Drug Dosing" page).

All SAEs, except for those anticipated events listed above, occurring from signed informed consent through study visit 11 will be captured on the SAE eCRF. Subjects that have screen failed will be followed for SAEs until two weeks post last study drug dose. Unless exempted as described above**,** all SAEs, whether or not deemed drug-related or expected, must be reported by the investigator or qualified designee within 24 hours of first becoming aware of the event. For this study, the cause of death will be reported on either the SAE or Events of interest (EVNINT) eCRF, as well as the Death eCRF page. The investigator or qualified designee will enter the required information regarding the SAE into the appropriate module of the eCRF, which will automatically result in distribution of the information to DCRI Safety Surveillance. DCRI Safety Surveillance will share all SAE reports with Novartis Pharmaceuticals. If the eCRF system is temporarily unavailable, the event, including the investigator-determined causality to study drug should be reported via the back-up paper SAE form to DCRI Safety Surveillance. Upon return of the availability of the electronic data capture (EDC) system, the SAE information must be entered into the eCRF.

Any misuse or abuse of the study drug, other medication errors and uses outside of what is foreseen in the protocol (irrespective of whether a clinical event has occurred) must also be reported to DCRI.

15.11 Follow-up of Adverse Events

When additional relevant information becomes available, the Investigator will record follow-up information according to the same process used for reporting the initial event as described above. The Investigator will follow all reportable events until resolution, stabilization or the event is otherwise explained.

DCRI Safety Surveillance will follow all SAEs until resolution, stabilization, until otherwise explained or until the subject completes the final follow-up, whichever occurs first. Investigators are also responsible for promptly reporting AEs to their reviewing IRB/EC in accordance with local requirements. The Data Safety Monitoring Board (DSMB) will review detailed safety data approximately every 3 months throughout the study.

15.12 Suspected Unexpected Serious Adverse Reaction

AEs that meet the criteria of serious, related to study drug, and unexpected per PPI, qualify for expedited reporting to the regulatory authorities. The site Investigator will assess all SAE's occurring at his/her site and evaluate for "unexpectedness" and relationship to study drug. The site Investigator is required to complete and submit a voluntary MedWatch Report for events confirmed by DCRI Safety Medical Monitor, as serious, study drug related and unexpected at: https://www.accessdata.fda.gov/scripts/medwatch/.

A copy of this report should be kept at the site and also forwarded to the DCRI Coordinating Center and to DCRI Safety Surveillance.

15.13 Pregnancy

Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, must be reported to DCRI within the same timelines as a serious adverse event. The pregnancy will be recorded on the appropriate paper pregnancy tracking form. The pregnancy will be followed until final outcome. Any associated AEs or SAEs that occur to the mother or fetus will be recorded in the AE/SAE eCRF, within the EDC system. The pregnancy outcome of a female partner to a male study participant will not be followed. DCRI will share all pregnancy reports with Novartis Pharmaceuticals.

16 STATISTICAL METHODS AND DATA ANALYSIS

16.1 General Design Issues

All planned analyses will be prospectively defined for this study and approved by the CC prior to unblinding of data. The statistical analysis plan (SAP) will contain detailed information regarding the data analysis. The SAP will be finalized prior to trial completion and will be approved by the coordinating center statistical team as well as the National Heart, Lung, and Blood Institute (NHLBI) program officer.

Analysis of the LIFE Study will be based on intention to treat (ITT). That is, subjects will be analyzed (and endpoints attributed) according to the treatment strategy to which subjects are randomized, regardless of subsequent additional post-randomization treatment and medical care. The ITT population will correspond to all randomized subjects.

Statistical comparisons will be performed using two-sided significance tests. Baseline demographic and clinical variables will be summarized for each randomized arm of the study. Descriptive summaries of the distribution of continuous variables will be presented in terms of percentiles (e.g., median, 25th and 75th percentiles) along with means and standard deviations. Categorical variables will be summarized in terms of frequencies and percentages.

In addition, exploratory analyses will be performed to help explain and understand findings

observed from the planned analyses. Statistical tests with a 2-sided p-value <0.05 will be considered statistically significant, unless otherwise stated. Analyses will be performed using SAS software (SAS Institute, Inc, Cary, NC).

16.2 Sample Size Justification and Randomization

Subjects will be randomized in a 1:1 allocation ratio using a permuted block design with stratification based on the clinical center and atrial fibrillation status. We plan to randomize 400 subjects with planned follow-up of 26 weeks. The primary efficacy endpoint is the proportional change from baseline in the AUC for NT-proBNP levels measured at 2, 4, 8, 12 and 24 weeks.

Based on recent Heart Failure Clinical Research Network (HFN) trials with similar follow-up requirements, we are anticipating a dropout / withdrawal of consent rate of approximately 5%. However, due to deaths and other sample collection issues we anticipate as many as 20-25% of subjects will not have NT-proBNP data at the week 24 assessment.

For the primary analysis, the AUC data will be log transformed and subjects missing the NT-proBNP data at the week 24 assessment will be assigned the last observation carried forward (LOCF). Based on a 2-sample t-test with type I error of 0.05 two-sided, the total sample size of 400 randomized subjects will provide 80% and 90% power to detect a differences of 19% and 21% for LCZ696 compared to valsartan. The PARAMOUNT phase II clinical trial observed a 23% greater reduction in NT-proBNP for LCZ696 compared to valsartan at 12 weeks post-randomization in patient population with HFpEF. [6] The HF Network investigators believe a 20% reduction in NT-proBNP would be considered a clinically significant improvement, and this level of change falls within a range considered clinically meaningful in a recent comparative effectiveness review published by AHRQ. [7]
Sensitivity analyses will examine the influence of the imputation for the informatively missing data. For the complete case analysis, the total sample size of 400 subjects will provide approximately 80% and 95% power to detect reductions of 20% and 25% for LCZ696 compared to valsartan, respectively. These calculations were based on a two-sample t-test and assume that the standard deviation of the log-transformed 180-day AUC measure is 0.70.[8]

Another secondary analysis of the AUC data for NT-proBNP will be conducted using a Wilcoxon nonparametric test with a worst-rank imputation based on the time-to-death.[9] A sample size of 190 subjects per group with available data will provide 80% power to detect the probability of 0.58 that an LCZ696 subject will have a better response than a valsartan subject. Similarly the sample size will provide 90% power to detect the probability of 0.60 that an LCZ696 subject will have a better response than a valsartan subject.

For the composite endpoint of all-cause mortality or first HF re-admission, we anticipate a 40% event rate at 24-weeks in the valsartan arm. The total sample size of 400 subjects will provide approximately 88% power to detect a difference of 40% vs. 25% for the LCZ696 arm. Similarly, there will be 55% power to detect a difference of 40% vs. 30%. The calculations were performed

using nQuery 7.0 and assume a 0.05 type I error rate (two-sided) with 1:1 randomization.

16.3 Interim Analyses and Safety Reviews

Interim examinations of key safety and process data will be performed at regular intervals during the course of the trial. It is anticipated that the DSMB will review the accumulating data at predetermined intervals (approximately every 3 months). In addition, a summary of clinical events and adverse events will be sent to the Chair of the DSMB monthly for review. The DSMB will receive a full report 4 times each year and the Chair can call a meeting of the full DSMB at any time. The CC will create regular reports to track subject enrollment reports, rates of adherence with the assigned treatment strategy, and frequency of protocol violations. Prior to each meeting, the CC will conduct any requested statistical analyses and prepare a summary report along with the following information: subject enrollment reports, rates of adherence with the assigned treatment, and description of SAEs. The DSMB will review data masked by study group (such as X vs. Y). An interim review will be conducted using the first 200 patients randomized with analysis starting after the last of the 200 patients complete study follow-up.

16.4 Analysis of the Primary Endpoint

A general linear model will be used to estimate and statistically compare the log-transformed AUCs in the NT-proBNP values between the two treatment groups. Each individual will have one response based on the log of the proportional change from baseline in the AUC from the 2, 4, 8, 12, and 24 week measurements. Missing data for the NT-proBNP assessment at week 24 will be assigned the last observation carried forward (LOCF). The treatment effect will be summarized using a point estimate and 95% confidence interval.

Sensitivity analyses will examine the influence of the imputation for the informatively missing data and the possibility for outliers due to clinical changes including atrial fibrillation status. For a set of analyses, missing data for the NT-proBNP assessment at week 24 will be assigned a value corresponding to 2.5 and 5 times the baseline NT-proBNP value. The linear models will include covariates for the treatment group indicator variable, log of the baseline NT-proBNP, and atrial fibrillation status. A complete case analysis will be conducted to examine the sensitivity of the overall findings to the imputation algorithm. A nonparametric sensitivity analysis will compare the AUC data for NT-proBNP using a Wilcoxon test with a worst-rank imputation based on the time-to-death. [9]

16.5 Analysis of Secondary, Tertiary and Exploratory Endpoints

The key secondary endpoint, *days alive and out of hospital at 6 months, not listed for transplant (status 1A, 1B or 1-4)* or undergoing transplant*, implanted with an LVAD,maintained or started on continuous inotropic therapy for ≥ 7 days, or has had two hospital admissions for HF (other than the index admission*)*, will be analyzed using a regression model with indicator variables for the treatment assignment and atrial fibrillation at enrollment. For time-to-event endpoints, the

Cox regression model for survival data will be used to test the statistical significance of differences in mortality between the treatments. Kaplan-Meier curves will be generated to graphically display the mortality rates as a function of time from randomization in each treatment. Continuous endpoint data will be modelled using general linear models. Mixed models will be used for the analysis of longitudinal data. The unmatched win ratio approach of Pocock et al. will be used to analyze the modified composite endpoints.[11]

17 DATA MANAGEMENT PROCEDURES

17.1 Overview of Data Management

The CC will have primary responsibility for data management, including the development of data collection systems, data monitoring processes, and data storage and back-up. State-of-the-art technology will be used for the management of the network's data.

17.2 Data Security

Access to databases will be controlled centrally by the CC through user passwords linked to appropriate privileges. This protects the data from unauthorized changes and inadvertent loss or damage. Database and web servers will be secured by a firewall and through controlled physical access. Database back-up will be performed daily using standard procedures in place at the CC. All disk drives that provide network services, and all user computers, will be protected using virus-scanning software.

17.3 Publication Policy

Dissemination of preliminary information can adversely affect the objectivity of study data. For this reason, investigators will not be allowed to perform subset analyses at any point before the conclusion of the study, and any data, other than safety data, cannot be used for publication or reporting outside of this study until the study is completed or discontinued by the DSMB or HFN Steering Committee.

18 STUDY ADMINISTRATION

18.1 Data and Safety Monitoring Board

A DSMB has been appointed by the NHLBI for the HFN, and will function as the DSMB for this trial. This committee consists of a group of highly experienced individuals with extensive pertinent expertise in HF and clinical trials. The DSMB will advise the HFN Steering Committee regarding the continuing safety of current subjects and those yet to be recruited, as well as the continuing validity and scientific merit of the trial. Safety data, summarized at the treatment level, will be assessed approximately every 3 months by the DSMB. The safety analyses will be based on the entire ITT population. Safety will be evaluated by comparing the occurrence of AEs and changes in laboratory values of the active treatment arm compared to the active

control arm.

18.2 Coordinating Center

The DCRI will function as the CC for this trial as specified by the National Institute of Health and NHLBI HFN grant.

18.3 Biomarker Core Laboratory

The University of Vermont will serve as the core laboratory for measurement of HFN biomarkers. Plasma specimens will be collected at Study Visits 2, 3, 4, 5, 7, and 10 (0, 2, 4, 8, 12, and 24 weeks from randomization), processed at the clinical centers according to the procedures provided by the core laboratory, and shipped to the core laboratory on dry ice (Refer to Biomarker Core Laboratory Manual of Procedures). Any subjects who agree to participate in the HFN biorepository sub-study will have samples collected at the clinical sites and stored at the University of Vermont biomarker core laboratory.

19 REGULATORY ISSUES

19.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol. These procedures are designed to ensure adherence to Good Clinical Practice, as described in the following documents:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

The investigator agrees to adhere to the instructions and procedures described in the protocol and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

19.2 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC). Documentation that the protocol and informed consent have been approved by the IRB/IEC must be given to the Coordinating Center before study initiation. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

19.3 Informed Consent

The investigator or designee must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment

or relationship with the treating physician.

The informed consent form(s) must be submitted by the investigator for IRB/IEC approval. The Coordinating Center will supply template informed consent forms, which comply with regulatory requirements, and are appropriate for the study. Any changes to the template consent form suggested by the Investigator must be agreed to by the Coordinating Center before submission to the IRB/IEC, and a copy of the approved version must be provided to the Coordinating Center after IRB/IEC approval.

20 MONITORING

A CC monitor may visit sites during the study to verify that data collection is being handled properly. In addition, monitors may provide in-service training, review source, and address questions from site investigators and coordinators as needed. Remote monitoring activities will also be conducted to monitor compliance with the study protocol.

21 APPENDICES

21.1 Appendix A - Schedule of Assessments

Visit number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Time of Visit	Enrollment	Run-in*	1st dose	Dose titration (2 weeks)	Dose titration (4 weeks)	8 weeks	10 weeks	12 weeks	16 weeks	20 weeks	24 weeks	26 weeks	Unscheduled Visit for dose adjustment
Inclusion/Exclusion criteria	x		x										
Information & Informed consent	x												
Physical examination	x	x	x	x	x			x			x		x
KCCQ questionnaire	x				x			x			x		
Dispense study medication		x[1]	x	x	x	x		x			x		x
Laboratory test (routine)+	X^	x	x	x	x	x		x			x		x
Laboratory test (core)			x[2]	x[3]	x[2]	x[2]		x[2]			x[2]		
Adverse events		x	x[4]	x	x	x	x	x	x	x	x		x
Telephone follow-up							x		x	x			
Telephone Safety Assessment												x	

* The Screening visit and Visit 1 may be combined at the investigator's discretion for subjects who are stable and for whom lab results have been reviewed as long as the investigator ensures the 1st dose of LCZ696 ≥ 36 hours after last ACEI dose (if applicable). If not combined, Visit 1 should take place within 7 days of the Screening Visit

\+ Local lab tests include the following: Sodium, Potassium, Chloride, CO2/Bicarbonate, Total Calcium, Magnesium, BUN, Creatinine

^ For Screening/Study Visit 0 only - Standard of care labs are acceptable, using results within 24 hours prior for hospitalized patients and within 7 days prior for outpatients.

[1] Open-label LCZ696 (50 mg po BID) during run-in phase

[2] BNP, NT-proBNP and Cystatin C

[3] BNP and NT-proBNP only

[4] Run-in failure patients should be contacted approximately 2 weeks after their last dose of study drug.

21.2 Appendix B - New York Heart Association Functional Classification

Class	NYHA Classification [10]
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitations of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

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