Protocol

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

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This supplement contains the following items:

1. Original protocol, final protocol, and a summary of the protocol changes;
2. Original statistical analysis plan and final statistical analysis plan.

NOVARTIS

Clinical Development and Medical Affairs

LCZ696

Clinical Trial Protocol CLCZ696BUS01

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

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List of abbreviations

ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ADHF	acute decompensated heart failure
AE	adverse event
AF	atrial fibrillation
AHF	acute heart failure
ALT	alanine aminotransferase
ANCOVA	analysis of covariance model
ANP	arial natriuretic peptide
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
AST	aspartate aminotransferase
AUC	area under the curve
b.i.d.	twice a day
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
Bpm	beats per minute
CHF	chronic heart failure
CFR	US Code of Federal Regulations
CDS	Core Data Sheet (for marketed drugs)
COPD	Chronic obstructive pulmonary disease
CPO	Country Pharma Organization
CRA	clinical research associate (site monitor)
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRTD	Cardiac resynchronization therapy device
CSR	Clinical Study Report
CTL	Clinical Trial Leader
CV	cardiovascular

DBP	diastolic blood pressure
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
Echo	echocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
eGFR	estimated glomerular filtration rate
cGMP	cyclic guanosine monophosphate
EOS	end of study
ER	emergency room
HF	heart failure
HfrEF	heart failure with reduced ejection fraction
hs-Troponin	high sensitivity troponin
HTN	hypertension
IA	interim analysis
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	investigator notification
i.v.	intravenous
IRB	Institutional Review Board
IVRS	Interactive voice response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
LFT	Liver function test (raised serum transaminases and/or bilirubin levels)
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
LVESV	left ventricular end systolic volume
LVH	left ventricular hypertrophy

MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
mm Hg	millimeter mercury
MUGA	multi gated acquisition scan
NEP	neutral endopeptidase
NEPi	neutral endopeptidase inhibitor
NP	natriuretic peptide
NT-proBNP	N-terminal pro-brain natriuretic peptide
PCI	percutaneous coronary intervention
PGA	Patient Global Assessment
QoL	Quality of Life
RAAS	renin angiotensin aldosterone system
SAE	serious adverse event
SBP	systolic blood pressure
SUSAR	Suspected Unexpected Serious Adverse Reactions
ULN	upper limit of normal
USPI	United States prescribing information/package insert

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Period	A subdivision of a cross-over study
Premature subject/patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the

	drug being tested in the study

Protocol summary

Protocol number	CLCZ696BUS01
Title	A multicenter, randomized, double-blind, double-dummy, parallel group, active-controlled 8-week study to evaluate the effect of sacubitril and valsartan (LCZ696) versus enalapril on changes in NT-proBNP and safety and tolerability of in-hospital initiation of sacubitril and valsartan compared to enalapril in HFrEF patients who have been stabilized following hospitalization for acute decompensated heart failure (ADHF)
Brief title	In hospital initiation of sacubitril and valsartan vs. enalapril to assess changes in NT-proBNP through 8 weeks of treatment following an episode of acute decompensated heart failure.
Sponsor and Clinical Phase	Novartis Phase IIIb/IV
Investigation type	Interventional
Study type	Multicenter, randomized, double-blind, parallel group, active-controlled
Purpose and rationale	The purpose of this study is to assess the effect of in hospital initiation of sacubitril and valsartan tablets vs. enalapril on time averaged proportional change in NT-proBNP in patients hospitalized for acute decompensated heart failure (ADHF) and reduced ejection fraction (left ventricular ejection fraction (LVEF) ≤ 40%). Hospitalization for acute decompensated heart failure identifies patients at increased risk of death and re-hospitalization following discharge. This increased risk justifies intervention with novel treatment strategies initiated prior to hospital discharge to improve patient outcomes.
Primary Objective(s)	The primary objective of this study is to assess the effect of in hospital initiation of sacubitril and valsartan tablets vs. enalapril on the time-averaged proportional change of NT-proBNP from baseline in patients who have been stabilized following hospitalization for acute decompensated heart failure and reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤ 40%). Weeks 4 and 8 will be included in the analysis (primary analysis time point).
Secondary Objectives	To examine the effect of sacubitril and valsartan tablets vs. enalapril on change in: • Incidence of symptomatic hypotension during 8 weeks of treatment • Incidence of hyperkalemia (Potassium >5.5 mEq/L) during 8 weeks of treatment • Incidence of angioedema during 8 weeks of treatment • Biomarkers: high sensitivity-Troponin (hs-Troponin), urinary cGMP at 4 and 8 weeks; and BNP:NT-proBNP ratio
Exploratory Objectives	• Time to first occurrence of composite clinical endpoint that includes death, heart failure re-hospitalization, requirement of LVAD, listed for cardiac transplantation, unplanned acute HF visits requiring i.v. diuretics, additional heart failure drug or increase in >50% of the diuretic dose. • Change from baseline at Weeks 1 and 2 in NT-proBNP

	• Incidence of re-hospitalization, ED visit or unplanned outpatient clinic visits due to worsening HF symptoms • Need for advanced heart failure therapies (including but not limited to i.v. inotropes, LVAD, transplantation) • Patient centered outcomes including the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Patient Global Assessment (PGA) at 4 weeks and 8 weeks post randomization • Change in biomarkers related to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury, and renal function, including estimated glomerular filtration rate (eGFR) • Change from Week 8 in NT-proBNP in the enalapril arm during the 4 week open label period • Medical resource utilization • Incidence of worsening renal function during 8 weeks of treatment, defined as an increase in serum creatinine of ≥0.5mg/dl from the values measured at baseline
Study design	This study will use a randomized, double-blind, double-dummy, active-controlled, parallel group design. Eligible patients hospitalized for ADHF will be randomized within 48 hours and up to five days of admission, while still hospitalized. Patients randomized to sacubitril and valsartan will require a 36-hour wash-out from prior ACEi/ARB treatment prior to first dose of active study treatment. At the time of randomization, patients will have been stabilized, defined for this study as SBP ≥ 110 mg Hg for the preceding 24 hours, no increase in i.v. diuretic dose for 24 hours prior to randomization, and did not receive i.v. inotropic drugs or i.v. vasodilators including nitrates for 24 hours prior to randomization; and meeting all other inclusion and none of the exclusion criteria. Patients will be randomized to sacubitril and valsartan or enalapril. Initial dose will be determined by the blood pressure at the time of randomization. Study treatment will be titrated to the target dose of sacubitril and valsartan 97/103 mg bid and enalapril 10 mg bid. Titration will be based on blood pressure at the time of the visit. Dose adjustments will be allowed per protocol defined safety and tolerability criteria. At the end of the 8-week treatment period, patients will enter a 4-week follow up period on open label sacubitril and valsartan.
Population	The study population will consist of male and female patients, ≥ 18 years of age, admitted to hospital for acute decompensated heart failure. The goal is to randomize a total of approximately 736 patients to sacubitril and valsartan or enalapril in a 1:1 ratio in approximately 100 centers in the United States. At the time of randomization, patients will have been stabilized, defined for this study as SBP ≥ 110 mm Hg for the preceding 24 hours, no increase in i.v. diuretic dose for 24 hours prior to randomization, and did not receive i.v. inotropic drugs or i.v. vasodilators including nitrates for 24 hours prior to randomization; and meeting all other inclusion and none of the exclusion criteria.
Inclusion criteria	Patients eligible for inclusion in this study have to fulfill all of the following criteria: 1. Written informed consent must be obtained before any assessment is performed.

	2. Patients ≥ 18 years of age, male or female. 3. Currently hospitalized for ADHF. Patients with a diagnosis of acute heart failure had to have symptoms and signs of fluid overload (i.e. jugular venous distention, edema or rales on auscultation or pulmonary congestion on chest x-ray) at time of hospitalization. 4. Eligible patients will be randomized no earlier than 48 hours and up to 5 days after presentation while still hospitalized as long as they meet the following definition of stable status: Stable for at least 24 hours defined by:SBP ≥ 110 mm Hg for the preceding 24 hours, no increase in i.v. diuretic dose for 24 hours prior to randomization, and did not receive i.v. inotropic drugs or i.v. vasodilators including nitrates for 24 hours prior to randomization. 5. LVEF ≤40% via any local measurement within the past 6 months using echocardiography, multi gated acquisition scan (MUGA), CT scanning, MRI or ventricular angiography provided no subsequent study documenting an EF of >40%. 6. Elevated NT-proBNP ≥ 1600pg/mL OR BNP ≥400 pg/mL. 7.
Exclusion criteria	Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients. 1. Currently taking sacubitril and valsartan tablets or any use within the past 30 days. 2. Enrollment in any other clinical trial involving an investigational agent or investigational device. 3. History of hypersensitivity to any of the study drugs, including history of hypersensitivity to drugs of similar chemical classes, or allergy to ACEIs, ARBs, or NEP inhibitors as well as known or suspected contraindications to the study drugs. 4. Previous history of intolerance to sacubitril and valsartan, ACEI or ARB standard of care doses despite appropriate and gradual up-titration. 5. Patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy. 6. Requirement of treatment with both ACE inhibitor and ARB. 7. Symptomatic hypotension and/or a systolic blood pressure (SBP) < 110 mm Hg at screening or at randomization. 8. eGFR < 30 ml/min/1.73 m2 as measured by the simplified Modification of Diet in Renal Disease (MDRD) formula at screening. 9. Serum potassium > 5.2 mEq/L at screening. 10. Acute coronary syndrome, stroke, transient ischemic attack; cardiac, carotid or other major CV surgery; percutaneous coronary intervention (PCI) or carotid angioplasty, within the 3 months prior to Visit 1. 11. Primary cause of dyspnea due to non-cardiac causes, such as acute or chronic respiratory disorders or infections (i.e., severe chronic obstructive pulmonary disease, bronchitis, pneumonia) which may interfere with the ability to interpret the primary cause of dyspnea. 12. Known history of respiratory disorders requiring the daily use of IV or

	oral steroids; current need for intubation or the current use of IV or oral steroids for chronic obstructive pulmonary disease (COPD). 13. Coronary or carotid artery disease likely to require surgical or percutaneous intervention within the 6 months after Visit 1. 14. Implantation of a cardiac resynchronization therapy device (CRTD) within the prior 3 months from Visit 1or intent to implant a CRTD. 15. History of heart transplant or patients who are on a transplant list or with left ventricular assistance device (LVAD). 16. Isolated right HF due to severe pulmonary disease. 17. Diagnosis of peripartum or chemotherapy induced cardiomyopathy within the 12 months prior to Visit 1. 18. Treatment with Vaughn Williams Type Ic anti-arrhythmic agents (e.g., Flecainide, propafenone, moricizine). 19. Documented untreated ventricular arrhythmia with syncopal episodes within the 3 months prior to Visit 1. 20. Symptomatic bradycardia or second or third degree heart block without a pacemaker. 21. Presence of hemodynamically significant mitral and/or aortic valve disease. 22. Presence of other hemodynamically significant obstructive lesions of left ventricular outflow tract, including aortic and sub-aortic stenosis. 23. Known presence of bilateral renal artery stenosis. 24. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past year with a life expectancy of less than 1 year. 25. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or extraction of study drug, including but not limited to any of the following: a. History of active inflammatory bowel disease during the 12 months prior to visit 1. b. History of peptic ulcer disease without successful eradication of H. pylori. c. Gastrointestinal/rectal bleeding during the 3 months prior to visit 1. d. Current treatment with cholestyramine or colestipol resins. 26. Known hepatic impairment (as evidenced by total bilirubin > 3 mg/dL, or increased ammonia levels, if performed), or history of cirrhosis with evidence of portal hypertension such as varices. 27. 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 hCG laboratory test. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they are using two birth control methods. The two methods can be a double barrier method (if accepted by the local regulatory authority and ethics committee) or a barrier method plus a hormonal method
Investigational and reference therapy	All eligible patients will be randomized to receive either sacubitril and valsartan or enalapril. The following study treatment will be provided for the

	8-week double blind double dummy treatment period: sacubitril and valsartan tablets + matching placebo or enalpril tablets + matching placebo. Open-label sacubitril and valsartan tablets will be provided for the open label extension
Efficacy assessments	Primary: Time-averaged proportional change from baseline in NT-proBNP. Weeks 4 and 8 will be included in the analysis.Secondary: Biomarkers: hs-Troponin, urinary cGMP and BNP to NT-proBNP ratio Exploratory: Time to first occurrence of composite clinical endpoint that includes death, heart failure re-hospitalization, requirement of LVAD, listed for cardiac transplantation, unplanned acute HF visits requiring i.v. diuretics, additional heart failure drug or increase in >50% of the diuretic dose. Change from baseline at Weeks 1 and 2 in NT-proBNP Incidence of re-hospitalization or unplanned heart failure visits Need for advanced heart failure therapies (including but not limited to i.v. inotropes, LVAD, transplantation) Patient centered outcomes including the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Patient Global Assessment (PGA) at 4 weeks and 8 weeks post randomization. Change in biomarkers related to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury, and renal function, including estimated glomerular filtration rate (eGFR). Change in NT-proBNP in the enalapril arm during the 4 week open label period Medical resource utilization Incidence of worsening renal function during 8 weeks of treatment, defined as an increase in serum creatinine of ≥ 0.5 mg/dl from the values measured at baseline
Safety assessments	Change from baseline in serum creatinine of ≥0.5mg/dl with at least a 25% decrease in eGFR Incidence of symptomatic hypotension Incidence of hyperkalemia (serum potassium ≥5.5 mEq/l) Incidence of angioedema In addition, safety will be assessed through physical exam, vital signs, laboratory evaluations, other adverse events and serious adverse events. The Data Monitoring Committee (DMC) will monitor safety.
Data analysis	The primary hypothesis to be tested is that the ratio of the geometric means of NT-Pro BNP (average of Weeks 4 and 8/baseline) for the sacubitril and valsartan tablets and enalapril groups are equal (H0) versus the ratio of the geometric means of NT-Pro BNP are not equal (Ha). For NT-proBNP, the time-averaged proportional change from baseline in a logarithmic scale will be analyzed using an analysis of covariance (ANCOVA) model using data

	from Weeks 4 and 8 with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate.The estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0. For worsening renal function, a logistic regression model with treatment and baseline value as covariates having fixed effects will be run. Incidences of symptomatic hypotension, hyperkalemia and angioedema will be calculated, along with relative risk of sacubitril and valsartan vs. enalapril and 95% confidence intervals of the relative risk. For biomarkers including BNP to NT-proBNP ratio, hs-Troponin, and urinary cGMP, the time-averaged proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model using the data from Weeks 4 and 8 with treatment as a fixed effect factors and the logarithmic baseline biomarker value as a covariate For each of Weeks 4 and 8 the estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0. For BNP to NT-proBNP ratio and urinary cGMP at Weeks 1 and 2, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate, using observed data. For each of Weeks 1 and 2 the estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0. Analyses of the secondary variables will be based on the full analysis set. The assessment of safety will be based primarily on the frequency of adverse events, SAEs, and laboratory abnormalities. Safety analyses will be performed based on the Safety Set. There will be no inferential analyses of the safety data. Assuming a significance level of 0.05 and 85% power, a sample size of 736 patients would be needed to detect an 18% reduction in the geometric mean of the time-averaged proportional change from baseline (average of Weeks 4 and 8) in NT-proBNP for the sacubitril and valsartan treatment group assuming a value of 0.95 for the enalapril group, a common standard deviation of 0.85 and a 10% loss to follow-up rate.

1 Introduction

1.1 Background

Heart failure is a major public health issue. More than 5 million Americans have heart failure (HF) and treatment costs for HF are approximately $31 billion annually (Go et al 2014). Outcomes for patients after a hospitalization for HF remain disappointingly poor. The 1-year mortality rate after a HF hospitalization is 20-30%, and this number has been relatively unchanged over the past decade (Chen et al 2011, Loehr et al 2008).

The current state of treatments for patients hospitalized with acute heart failure (AHF) is focused around maintaining previously established guideline directed medical therapy, optimizing volume status, and initiating beta-blockers if indicated (Yancy et al 2013, Gattis et al 2004). Unfortunately, recent clinical trials employing a variety of additional in-hospital interventions have failed to improve post-discharge outcomes (Binanany et al 2005, Konstam et al 2007, Massie et al 2010, O'Connor et al 2011). Thus, therapeutic options to improve post-discharge survival free of recurrent HF hospitalizations for patients hospitalized for AHF are limited.

In addition, while intravenous diuretics are nearly universally required for symptom relief during a HF hospitalization (Gheorghiade et al 2005), they activate the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system and may provoke renal dysfunction (Felker et al 2012). Activation of the RAAS plays a fundamental role in the pathophysiology of HF (Braunwald 2013, Giverta 2001), and although therapies to block adverse neurohormonal activation are well established and improve clinical outcomes in chronic HF with reduced ejection fraction (Yancy et al 2013, McMurray et al 2012), they have not been extensively tested among patients hospitalized with AHF. Further reducing RAAS activation during the period following a HF hospitalization may hold promise to change the trajectory of poor post-discharge outcomes for patients with HF.

Volume expansion and congestion during AHF leads to the synthesis and release of counter-regulatory natriuretic peptides from the myocardium: A-type natriuretic peptide (ANP) responding predominantly to atrial distention and B-type natriuretic peptide (BNP) to ventricular wall stress. The precursor molecule of BNP is a propeptide (proBNP108) that when cleaved, results in the generation of the biologically active BNP and the release in the circulation of a biologically inert aminoterminal fragment called N-terminal prohormone of Brain Natriuretic Peptide (NT-proBNP). This fragment is a largely stable peptide that can be measured in serum. Both BNP and NT-proBNP are useful to aid the diagnosis or exclusion of HF (Yancy et al 2013). The PROTECT study was a small study (N=151) that demonstrated that NT-proBNP guided therapy was superior to standard of care in reducing total cardiovascular events, improved quality of life and impact on cardiac remodeling in patients with chronic reduced ejection fraction (Januzzi 2011). A larger on-going study is looking to evaluate whether treatment directed therapy based on NT-proBNP levels will provide benefit to patients compared to standard of care in patients with reduced ejection fraction (Felker 2014).

Patients developing an AHF episode are known to have markedly elevated levels of BNP and NT-proBNP, which are reduced following adequate treatment and normalization of their cardiac decompensation. In the RELAX AHF trial, it was shown that patients that have a higher NT-proBNP level during an AHF hospitalization have a worse prognosis (Metra et al. 2013). Therefore, it is important to evaluate therapeutic strategies that can lead to superior reductions in NT-proBNP in patients hospitalized due to an AHF episode.

Sacubitril and valsartan combination tablet is an orally available, first in class, combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin receptor blocker that targets complementary pathways, RAAS inhibition via an Angiotensin II receptor blockade and natriuretic peptide augmentation via neprilysin inhibition. This novel agent may also hold promise in modifying the poor outcomes currently observed after a hospitalization for AHF, especially in the initial high-risk post-hospitalization period.

Preliminary studies

Sacubitril and valsartan has been evaluated for safety and efficacy in patients with chronic heart failure. The PARAMOUNT study was a randomized, double-blind, active-controlled phase 2 trial of 308 patients with HF with preserved ejection fraction (Left ventricular ejection fraction (LVEF) ≥45%) (Solomon et al 2012). Patients enrolled in the study received sacubitril and valsartan tablets titrated to 200 mg twice daily or valsartan titrated to 160 mg twice daily. The primary end point of the study was change in NT-proBNP levels from baseline to 12 weeks. NT-proBNP levels were significantly reduced at 12 weeks in the sacubitril and valsartan group compared with the valsartan group (sacubitril and valsartan: baseline, 783 pg/mL [95% CI 670 to 914], 12 weeks 605 pg/mL [95% CI512-714]; valsartan: baseline, 862 pg/mL [95% CI 733-1012], 12 weeks 835 pg/mL [95% CI 710-981]; ratio: sacubitril and valsartan /valsartan, 0.77, 95% CI 0.64 to 0.92, p=0.005. The sacubitril and valsartan combination was well tolerated and had a similar adverse effect profile to valsartan. The PARAGON-HF trial is now enrolling 4300 similar patients with chronic HF with preserved ejection fraction (LVEF ≥ 45%) to test whether the favorable effect of sacubitril and valsartan combination tablet in reducing NT-proBNP seen in PARAMOUNT translates into a reduction in the composite end point of cardiovascular morbidity and total (first and recurrent) HF hospitalizations.

The PARADIGM-HF study was a large randomized, double-blind, active-controlled trial of 8442 patients with symptomatic, chronic HF with reduced ejection fraction (LVEF ≤ 40%) (McMurray et al 2013, McMurray et al 2014). Patients enrolled in the study started in a single blind sequential run-in phase with enalapril 10 mg twice daily and after a washout period of 36 hours, went on to sacubitril and valsartan combination tablet at 200 mg daily to assess for safety and tolerability. Those patients who completed the run-in phase were then randomized and received sacubitril and valsartan combination tablet titrated to 200 mg twice daily or enalapril 10 mg twice daily. The trial was stopped prematurely after a median follow-up of 27 months upon the recommendation of the data safety monitoring board due to compelling evidence in favor of sacubitril and valsartan. . Patients receiving sacubitril and valsartan combination tablet, compared to enalapril, were noted to have reduced risk of the primary outcome of composite of death from cardiovascular causes or hospitalization for HF (HR0.80, 95% CI 0.73-0.87). The hazard ratio for all-cause mortality was 0.84 (95% CI, 0.76-0.93) and

for hospitalization for HF was 0.79 (95% CI 0.71-0.89) (McMurray et al 2014). In PARADIGM-HF, 8385 patients had a baseline NT-proBNP obtained. Results were consistent with the primary composite endpoint regardless of whether the NT-proBNP was less than or equal to the median values compared to higher than median values (USPI Entresto, figure 4). Additionally, a subset of patients had biomarkers obtained at baseline, visit 3 (end of enalapril run-in), visit 5 (end of sacubitril and valsartan combination tablet run-in), 4 weeks after randomization, and at 8 months after randomization. The ratio of NT-proBNP to baseline levels was 25% lower in the sacubitril and valsartan combination tablet group compared to the enalapril group at 4 weeks and 8 months post-randomization (both $p<0.0001$). Conversely, BNP levels were approximately 23% higher in the sacubitril and valsartan combination tablet group compared to the enalapril group at 4 weeks and 8 months post-randomization (both $p<0.0001$). These findings are consistent with NT-proBNP not being a substrate of neprilysin, whereas BNP is a substrate of neprilysin; levels of BNP reflect the action of the drug whereas NT-proBNP levels reflect the effect of the sacubitril and valsartan combination on the heart [PARADIGM-HF data on file, [Packer 2014]].

Table 1-1 Adverse reactions occurring at an incidence of >5% of patients in the double-blind period of PARADIGM-HF were as follows:

	Sacubitril and valsartan (N=4203) %	Enalapril (N=4220) %
Hypotension	18	12
Hyperkalemia	12	14
Cough	9	13
Dizziness	6	5
Renal failure/acute renal failure	5	5

Angioedema occurred at rate of 0.5% in the sacubitril and valsartan arm compared to 0.2% in the enalapril arm (ENTRESTO USPI).

The combination of sacubitril and valsartan was evaluated in a multicenter, randomized, double-blind, and parallel group design in heart failure patients with reduced ejection fraction to assess the safety and tolerability of two different titration regimens (NCT01922089). Patients were stratified on low RAAS inhibition (whether they were ACEi/ARB naïve or receiving ≤10 mg daily of enalapril or ≤ 160 mg daily of valsartan (or equivalent doses of other ACEi/ARBs)) or high RAAS inhibition stratum. This high RAAS inhibition stratum was defined as receiving > 10 mg daily of enalapril or > 160 mg daily of valsartan or equivalent doses of other ACEi or ARBs). The patients underwent dosing with 50 mg BID during the open-label run-in period of 5 days, and then were randomized to titration of the target dose of 97/103 mg twice daily over 6 weeks (conservative up-titration) compared to three weeks (condensed up-titration). 540 patients entered the run-in period and 498 were randomized. The primary endpoint was the proportion of patients experiencing pre-specified adverse events (AEs) and pre-specified laboratory assessment outcomes. The results were

presented at the European Society of Cardiology Heart Failure meeting in 2015. The combination of sacubitril and valsartan demonstrated an acceptable safety and tolerability profile regardless of the up-titration regimen. After excluding non-adverse events discontinuations or death-related discontinuations, >76% of patients achieved and maintained the target dose of 97/103 twice daily for 12 weeks. Achievement of target dose was possible even in patients who required dose interruption or down-titration during the study period, and rates of AEs were generally lower than in the PARADIGM-HF trial. Hypotension occurred in 9.7% of the condensed regimen compared to 8.4% in the conservative regimen; renal dysfunction occurred in 7.3% of condensed compared to 7.6% in the conservative regimen, hyperkalemia occurred in 7.7% in the condensed regimen compared to 4.4% in the conservative regimen and angioedema occurred in 0.0% in the condensed regimen compared to 0.8% in the conservative regimen.ENTRESTO™ (sacubitril and valsartan) received FDA approval on 07July2015. It is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA class II-IV) and reduced ejection fraction. It is usually administered in conjunction with other heart failure therapies in place of an ACE inhibitor or other ARB. The approved dosages are 24/26 mg, 49/51 mg, and 97/103 mg twice daily. During the prior clinical studies 24/26 mg, 49/51 mg, and 97/103 mg were referred to as 50 mg, 100 mg and 200 mg, respectively.

The present study will be the first study to examine sacubitril and valsartan combination tablet administration during AHF and whether it can safely mitigate the adverse neuro-hormonal activation that persists and contributes to the unacceptably high adverse event rate currently observed in the first months after hospitalization for AHF as determined by the effect on NT-proBNP in this patient population. Importantly, although it is likely that clinical events (i.e., death, hospitalizations, etc.) will occur in the patients randomized in the present study, there is not enough statistical power to assess the effect on these hard clinical outcomes and therefore this trial will not include differences in the rate of mortality or HF hospitalizations as part of the primary or secondary endpoints. These endpoints will only be analyzed for the purpose of safety evaluation.

1.2 Purpose

The purpose of this study is to assess the effect of in hospital initiation of sacubitril and valsartan vs. enalapril on time averaged proportional change in NT-proBNP in patients who have been stabilized following hospitalization for acute decompensated heart failure (ADHF) and reduced ejection fraction (left ventricular ejection fraction (LVEF) ≤ 40%).

2 Study objectives

2.1 Primary objective(s)

The primary objective of this study is to assess the effect of in hospital initiation of sacubitril and valsartan vs. enalapril on the time-averaged proportional change of NT-proBNP from baseline in patients who have been stabilized following hospitalization for ADHF and reduced

ejection fraction (left ventricular ejection fraction [LVEF] ≤ 40%). Weeks 4 and 8 will be included in the analysis (primary analysis time point).

2.2 Secondary objectives

To examine the effect of sacubitril and valsartan vs. enalapril on:

- Incidence of symptomatic hypotension during 8 weeks of treatment
- Incidence of hyperkalemia (Potassium >5.5 mEq/L) during 8 weeks of treatment
- Incidence of angioedema during 8 weeks of treatment
- Biomarkers: hs-Troponin (high sensitivity), urinary cGMP and BNP to NT-proBNP ratio at 4 and 8 weeks

2.3 Exploratory objectives

- To examine the effect of sacubitril and valsartan vs. enalapril on time to first occurrence of composite clinical endpoint that includes death, heart failure re-hospitalization, requirement of LVAD, listed for cardiac transplantation, unplanned acute HF visits requiring i.v. diuretics, additional heart failure drug or increase in >50% of the diuretic dose.
- To examine the effect of sacubitril and valsartan vs. enalapril on change from baseline at Weeks 1 and 2 in NT-proBNP
- To examine the effect of sacubitril and valsartan vs. enalapril on incidence of re-hospitalization, ED visit or unplanned outpatient clinic visits due to worsening HF symptoms
- To examine the effect of sacubitril and valsartan vs. enalapril on the need for advanced heart failure therapies (including but not limited to i.v. inotropes, LVAD, transplantation)
- To examine the effect of sacubitril and valsartan vs. enalapril on patient centered outcomes including the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Patient Global Assessment (PGA) at 4 weeks and 8 weeks post randomization.
- To examine the effect of sacubitril and valsartan vs. enalapril on change in biomarkers related to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury, and renal function, including estimated glomerular filtration rate (eGFR).
- Change in NT-proBNP in the enalapril arm during the 4 week open label period
- To examine the effect of sacubitril and valsartan vs. enalapril on medical resource utilization
- To examine the effect of sacubitril and valsartan vs. enalapril on incidence of worsening renal function during 8 weeks of treatment, defined as an increase in serum creatinine of ≥0.5mg/dl

3 Investigational plan

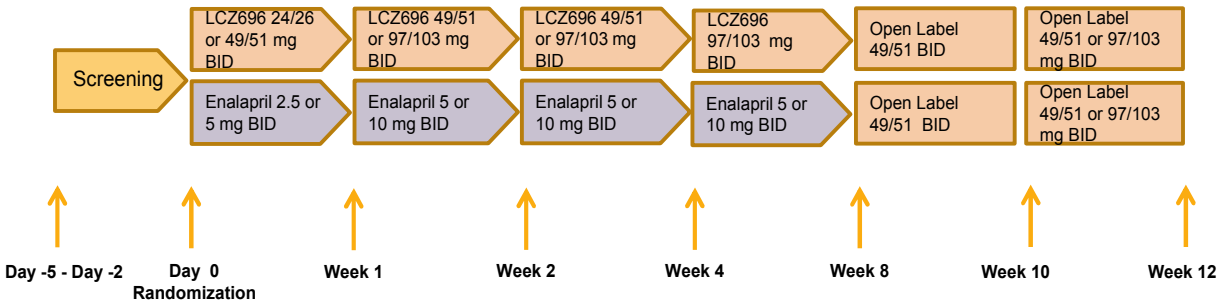
3.1 Study design

This study will use a randomized, double-blind, double-dummy, active-controlled, parallel group design. Eligible patients hospitalized for ADHF will be randomized within 48 hours and up to five days of admission while still hospitalized. Patients randomized to sacubitril and valsartan will require a 36-hour wash-out from prior ACEi/ARB treatment prior to first dose of active study treatment. Therefore, these patients will receive both enalapril matching placebo and sacubitril and valsartan matching placebo for the first day of treatment (2 doses). Patients randomized to the enalapril treatment arm will not require a washout of prior ACEi/ARB treatment, and will receive active enalapril and sacubitril and valsartan matching placebo from randomization. All patients will remain in the hospital until after they receive their third dose of study medication (the day after randomization) which can be no less than 36 hours from randomization.

At the time of randomization, patients will have been stabilized, defined for this study as SBP ≥ 110 mg Hg for the preceding 24 hours, no increase in i.v. diuretic dose for 24 hours prior to randomization, and did not receive i.v. inotropic drugs or IV vasodilators including nitrates for 24 hours prior to randomization; and meeting all other inclusion and none of the exclusion criteria.

Patients will be randomized to sacubitril and valsartan or enalapril. Initial dose will be determined by the blood pressure at the time of randomization. Study treatment will be titrated to the target dose of sacubitril and valsartan 97/103 mg bid (Dose Level 3) and enalapril 10 mg bid. Titration will be based on blood pressure at the time of the visit. Dose adjustments will only be allowed if indicated per protocol defined safety and tolerability criteria and investigator judgement. At the end of the 8-week treatment period ALL patients will need to have a 36 hour washout from study treatment prior to starting the open label extension to ensure that the blinding of the core study is maintained. To facilitate this washout, patients will be instructed NOT to take study medication on the day of their final visit and to start their open label treatment the following day. All patients will start open label treatment on sacubitril and valsartan 49/51 mg BID (Dose level 2) and will have their dose titrated to the desired dose of 97/103mg according to the United States Prescribing Information (USPI) or based on clinical need and investigator judgement.

Figure 3-1 Study design



3.2 Rationale of study design

Hospitalization for ADHF identifies patients at increased risk of death and re-hospitalization following discharge. This increased risk justifies intervention with novel treatment strategies initiated prior to hospital discharge to improve patient outcomes. Both the PARAMOUNT and PARADIGM-HF trials demonstrated reductions in the NT-proBNP compared to the comparator enalapril and valsartan, respectively, in both the chronic reduced ejection fraction and preserved ejection fraction heart failure patients. PARADIGM-HF demonstrated reductions in the NT-proBNP values seen at both 4 weeks and 8 months post randomization in the arm receiving the combination of the sacubitril and valsartan compared to the enalapril arm. In the current protocol, the primary endpoint of NT-proBNP will be evaluated at both the 4 and 8 week intervals to better assess the short-term benefit/risk ratio of sacubitril and valsartan compared to enalapril in patients who have been stabilized from an ADFH hospitalization in the setting of reduced ejection fraction.

The need for a 36-hour wash-out period is required per the FDA approved USPI label because there is a potential for increased risk for angioedema in patients who receive both an ACE inhibitor and the combination of sacubitril and valsartan. The requirement to stop the ARB is because there is an ARB contained within sacubitril and valsartan combination. The open-label period of 4 weeks provides the opportunity for every patient to receive sacubitril and valsartan and evaluate the change in NT-proBNP and other biomarkers in patients who had been previously receiving enalapril, while still being monitored for safety outcomes.

3.3 Rationale of dose/regimen and duration of treatment

Sacubitril and Valsartan 97/103 mg BID was selected as the target dose and is the USPI approved target dose. This dose of sacubitril and valsartan delivers similar exposures of valsartan as Diovan 160 mg BID, the maximal approved Diovan dose for heart failure and the dose recommended in international guidelines for the treatment of heart failure. In addition, biomarker analysis (increase in ANP and cGMP) indicates that this sacubitril dose delivers approximately 90% of its maximal neutral endopeptidase (NEP) inhibition. Dosing with 97/103 mg twice daily is to ensure sustained NEP inhibition over 24 hours, which is thought to be critical for patients with heart failure. The PARADIGM-HF study had a median duration of 27 months with patients treated up to 4.3 years. In the PARADIGM-HF study,

patients could have been hospitalized within the past year, but 37% never had a prior hospitalization. However, there is no data on the short-term benefit/risk ratio of starting sacubitril and valsartan while in the hospital after a patient has been stabilized after an ADHF episode.

Additionally, the duration of the double-blind period also limits the patients' exposure to the current standard of care, enalapril, based on the superior results obtained with sacubitril and valsartan in the PARADIGM-HF trial. Sacubitril and valsartan (Entresto™) is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction and this is usually administered in conjunction with other heart failure therapies in place of an ACE inhibitor or other ARB.

3.4 Rationale for choice of comparator

Treatment with ACEI has been well established as the standard of care for RAAS blockade and is recommended by treatment guidelines as a 1A recommendation for all patients with CHF and reduced LVEF, unless ACEI-intolerant. As a well-studied ACEI in heart failure, enalapril has been selected as the comparator for this study with a target dose of 10 mg BID The 10 mg BID dose was the same target dosage studied in the SOLVD study and is the dose that was chosen in the PARADIGM-HF trial.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

Patients randomized to the sacubitril and valsartan treatment arm will be given matching placebo doses of both sacubitril and valsartan and enalapril on the day of randomization to fulfill the requirement for a washout prior to sacubitril and valsartan treatment initiation. The first active dose of sacubitril and valsartan treatment will be the next day after randomization to allow a 36 hour wash out period to minimize the interaction between an ACEi and sacubitril in potentiating the development of angioedema. Patients randomized to the enalapril treatment arm do not require a washout, but will receive sacubitril and valsartan matching placebo in addition to active enalapril on the day of randomization.

Since this is a double blind study, **all** study patients must remain in the hospital for at least a part of the day following randomization even though the 36 hour wash out is only required for patients randomized to sacubitril and valsartan.. This will allow for the first dose of active sacubitril and valsartan to be administered in the hospital and will ensure that the blind is maintained.

All patients will be allowed to continue receiving the rest of their background cardiovascular (CV) medications. The risk to patients in this trial will be minimized by compliance with the eligibility criteria and close clinical monitoring. A Data Monitoring Committee (DMC) will also monitor the study for all safety considerations, since this population represents a patient population who are being initiated on study drug during the same hospitalization for admission for acute decompensated heart failure.

4 Population

The study population will consist of male and female patients, ≥ 18 years of age, admitted to hospital for acute decompensated heart failure. The goal is to randomize a total of approximately 736 patients to sacubitril and valsartan or enalapril in a 1:1 ratio in approximately 100 centers in the United States. At the time of randomization, patients will have been stabilized, defined for this study as SBP ≥ 110 mg Hg for the preceding 24 hours, no increase in i.v. diuretic dose for 24 hours prior to randomization, and did not receive i.v. inotropic drugs or i.v. vasodilators including nitrates for 24 hours prior to randomization; and meeting all other inclusion and none of the exclusion criteria.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Patients ≥ 18 years of age, male or female.
3. Currently hospitalized for ADHF. Patients with a diagnosis of acute heart failure had to have symptoms and signs of fluid overload (i.e. jugular venous distention, edema or rales on auscultation or pulmonary congestion on chest x-ray) at time of hospitalization.
4. Eligible patients will be randomized no earlier than 48 hours and up to 5 days after presentation while still hospitalized as long as meet the following definition of stable status: Stable for at least 24 hours defined by: SBP ≥ 110mm Hg for the preceding 24 hours, no increase in i.v. diuretic dose for 24 hours prior to randomization, and did not receive i.v. inotropic drugs or i.v. vasodilators including nitrates for 24 hours prior to randomization.
5. LVEF ≤40% via any local measurement within the past 6 months using echocardiography, multi gated acquisition scan (MUGA), CT scanning, MRI or ventricular angiography provided no subsequent study documenting an EF of >40%.
6. Elevated NT-proBNP ≥ 1600pg/mL OR BNP ≥400 pg/mL.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Currently taking sacubitril and valsartan or any use within the past 30 days.
2. History of hypersensitivity to any of the study drugs, including history of hypersensitivity to drugs of similar chemical classes, or allergy to ACEIs, ARBs, or NEP inhibitors as well as known or suspected contraindications to the study drugs.
3. Previous history of intolerance to sacubitril and valsartan combination, ACEI or ARB standard of care doses despite appropriate and gradual up-titration.
4. Currently enrolled in any other clinical trial involving any investigational agent or investigational device.

5. Patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy.
6. Requirement of treatment with both ACE inhibitor and ARB.
7. Symptomatic hypotension and/or a systolic blood pressure (SBP) < 110 mm Hg at screening or at randomization.
8. eGFR < 30 ml/min/1.73 m^2 as measured by the simplified Modification of Diet in Renal Disease (MDRD) formula at screening.
9. Serum potassium > 5.2 mEq/L at screening.
10. Acute coronary syndrome, stroke, transient ischemic attack; cardiac, carotid or other major CV surgery; percutaneous coronary intervention (PCI) or carotid angioplasty, within the 3 months prior to Visit 1.
11. Primary cause of dyspnea due to non-cardiac causes, such as acute or chronic respiratory disorders or infections (i.e., severe chronic obstructive pulmonary disease, bronchitis, pneumonia) which may interfere with the ability to interpret the primary cause of dyspnea.
12. Known history of respiratory disorders requiring the daily use of i.v. or oral steroids; current need for intubation or the current use of i.v. or oral steroids for chronic obstructive pulmonary disease (COPD).
13. Coronary or carotid artery disease likely to require surgical or percutaneous intervention within the 6 months after Visit 1.
14. Implantation of a cardiac resynchronization therapy device (CRTD) within the prior 3 months from Visit 1or intent to implant a CRTD.
15. History of heart transplant or patients who are on a transplant list or with left ventricular assistance device (LVAD).
16. Isolated right HF due to severe pulmonary disease.
17. Diagnosis of peripartum or chemotherapy induced cardiomyopathy within the 12 months prior to Visit 1.
18. Treatment with Vaughn Williams Type Ic anti-arrhythmic agents (e.g., Flecainide, propafenone, moricizine).
19. Documented untreated ventricular arrhythmia with syncopal episodes within the 3 months prior to Visit 1.
20. Symptomatic bradycardia or second or third degree heart block without a pacemaker.
21. Presence of hemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation secondary to left ventricular dilatation.
22. Presence of other hemodynamically significant obstructive lesions of left ventricular outflow tract, including aortic and sub-aortic stenosis.
23. Known presence of bilateral renal artery stenosis.
24. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past year with a life expectancy of less than 1 year.
25. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or extraction of study drug, including but not limited to any of the following:

1. History of active inflammatory bowel disease during the 12 months prior to visit 1.
2. History of peptic ulcer disease without successful eradication of H. pylori.
3. Gastrointestinal/rectal bleeding during the 3 months prior to visit 1.
4. Current treatment with cholestyramine of colestipol resins.

25 Known hepatic impairment (as evidenced by total bilirubin > 3 mg/dL, or increased ammonia levels, if performed), or history of cirrhosis with evidence of portal hypertension such as varices.

26 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 hCG laboratory test.

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they are using two birth control methods. The two methods can be a double barrier method (if accepted by the local regulatory authority and ethics committee) or a barrier method plus a hormonal method

- Adequate barrier methods of contraception include: diaphragm, condom (by the partner), intrauterine device (copper or hormonal), sponge or spermicide. Hormonal contraceptives include any marketed contraceptive agent that includes an estrogen and/or a progesterone agent.
- Reliable contraception should be maintained throughout the study and for 7 days after study drug discontinuation.
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL and estradiol < 20 pg/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational and control treatment

Table 5-1 Investigational and comparator treatment

All eligible patients will be randomized to receive either sacubitril and valsartan or enalapril. The following study treatment will be provided:

Treatment	Minimum dose	Maximum dose	Frequency	Admin. Route

Treatment	Minimum dose	Maximum dose	Frequency	Admin. Route
sacubitril and valsartan	24/26 mg	97/103 mg	BID	oral
sacubitril and valsartan matching placebo				oral
Enalapril	2.5 mg	10 mg	BID	oral
Enalapril matching placebo				oral

Table 5-2 Treatment Dose Levels

Dose Level	sacubitril and valsartan	Enalapril
1	24/26 mg BID	2.5 mg BID
2	49/51 mg BID	5.0 mg BID
3	97/103 mg BID	10 mg BID

Both sacubitril and valsartan and enalapril and their matching placebos will be packaged and labeled by the sponsor in accordance with the US Code of Federal Regulations governing handling of investigational treatments, and will be dispensed by the study physician.

Matching placebo will also be needed for sacubitril and valsartan combination tablet and matching placebo for the enalapril for the first day of treatment to allow for the 36-hour washout required for patients randomized to the sacubitril and valsartan treatment arm.

Each participating hospital will be provided with a central supply kit containing dose levels 1 and 2 and their matching placebos. Bottles will be numbered and assigned via an interactive voice response system (IVRS). Treatment for the day of randomization will be provided to the patients from the hospital kit. Treatment for the second day of dosing onwards, also assigned via IVRS, will be provided in bottles and or blister packs for the patients to take home upon discharge.

Patients not tolerating the target dose of sacubitril and valsartan 97/103 mg bid or enalapril 10 mg bid will be titrated down to the lower dose level (including active medication and matching placebos), at the investigator's discretion, based on the defined safety and tolerability criteria.

Sacubitril and valsartan dose or enalapril dose levels may be increased to the targeted desired dose of 97/103mg twice daily or enalapril 10 BID (Dose level 3) on an every 2 week basis or earlier if based on clinical need and investigator judgement.

This study is designed as a double-blind, double-dummy trial to ensure the blinding during the entire course of the study. To maintain the blinding, patients will be required to take their assigned active treatment tablet along with placebo matching the opposite treatment twice daily.

All study sites will be provided with a Treatment Manual describing the treatment packaging and treatment instructions.

5.1.2 Additional study treatment

Treatment	# of patients	Minimum dose	Maximum dose	Frequency	Admin. Route
Open-label sacubitril and valsartan	736	49/51 mg	97/103 mg	BID	oral

Open-label sacubitril and valsartan will be packaged and labeled by the sponsor in accordance with the US Code of Federal Regulation governing handling of investigational treatments, and will be dispensed by the study physician. Open-label treatment will be provided for a 4-week follow up. Patients entering the open label phase will be given dose level 2 and titrated according to the USPI. Adjustment of the sacubitril and valsartan or enalapril dose levels may be increased on an every 2-4 week basis per USPI to the desired target maintenance dose of 97/103 mg or increased within a 1-2 week time period based on clinical need and/or investigator judgement.

5.2 Treatment arms

Patients will be randomized in a 1:1 ratio to either sacubitril and valsartan or enalapril.

5.3 Treatment assignment, randomization

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio.

Eligible patients will be randomized no earlier than 48 hours after presentation at the hospital and no later than within 5 days of admission, while still hospitalized, via IVRS to one of the treatment arms. The investigator or his/her delegate will contact the IVRS after confirming that the patient fulfills all the study entry criteria. The IVRS will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify which bottle from the centralized hospital supply the patient will be dosed for the first day and a unique medication number for the first package of investigational treatment to be dispensed to the patient. The initial dose will be determined by the patient's blood pressure at the time of the call to the IVRS.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IVRS provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Initial dose at randomization will be determined by systolic blood pressure (SBP).

Dose adjustments to lower dose levels may be made at any time at both scheduled and unscheduled visit only if clinically indicated for blood pressure control/tolerability reasons. Dose adjustments to increase dose levels may be made at any time at both scheduled and unscheduled visits based on clinical need or investigator judgement.

Subsequent supplies of study drug will be assigned in the following manner. The investigator or his or her delegate will call the IVRS and provide the patient's number. The IVRS will ask the caller whether there is a change in the dose level of the study drug. If the caller indicates that there is no change in the dose level, the IVRS will provide the unique medication numbers of the study drug with the same dose level that was dispensed at the previous dispensing. If the caller indicates that the dose level has changed since the last dispensing, the IVRS will ask the caller which dose level should be dispensed. The caller will enter the dose level to dispense or whether no study drug should be dispensed (in case of study drug withdrawal). If applicable, the IVRS will provide the unique medication numbers for the study drug supplies that should be dispensed at the new dose level.

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the exception of the IVRS provider generating the randomization code, members of the DMC and the independent biostatistician assigned to the DMC. (2) The identity of the treatments will be concealed by the use of investigational treatments that are identical in packaging, labeling, and schedule of administration, appearance, taste and odor.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.11) and at the conclusion of the study.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed by the 4-digit site number (e.g., 0501, 0502 etc.) assigned by Novartis and a 5-digist sequential number assigned by the investigator (e.g., 00001, 00002, etc.). Hence a 9-digit study patient identification number, e.g., 050100001. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IVRS and provide the assigned patient study identification number along with the requested identifying information for the patient to register them into the IVRS. The site will enter this number on the electronic case report form (eCRF) in the electronic data capture system (EDC). The Screen Failure eCRF which includes demographic information must be completed for patients who fail to be randomized.

5.5.2 Dispensing the investigational and comparator treatment

Each study site will be supplied by Novartis with investigational and comparator treatment in packaging of identical appearance. Each hospital will be provided a kit for Day 1 of treatment, from which all patients will be provided their first 2 doses. This kit will include dose levels 1 and 2 and their matching placebos. Since the first day of treatment is placebo only for patients randomized to the sacubitril and valsartan arm in order to facilitate the required 36-hour washout, the bottles assigned for the sacubitril and valsartan treatment arm will all contain placebos. Patients will receive their first 2 doses from the centralized hospital supply. The third dose of treatment will be provided from the patient supply that will be sent home with the patient upon discharge.

The investigational and control treatment packaging will have a 2-part label. A unique randomization number is printed on each part of this label which corresponds to one of the 2 treatment arms and a dose level. Investigator staff will identify the investigational treatment package(s) to dispense to the patient by contacting the IVRS and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational and comparator treatment

Investigational and comparator treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all investigational and comparator treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Medication labels will include storage conditions but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of investigational and comparator treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused investigational or comparator treatment and packaging at the end of the study or at the time of discontinuation of treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational and comparator treatment, packaging, drug labels, and a copy of the completed drug accountability log according to the instructions provided by Novartis or its agents.

5.5.3.2 Handling of other study treatment

Each study site will be supplied by Novartis with open-label sacubitril and valsartan for the 4-week open-label follow up period. The IVRS will need to be called to receive drug shipments prior to dispensing.

The open-label sacubitril and valsartan packaging will have a 2-part label. Investigator staff will identify the treatment package(s) to dispense to the patient by contacting the IVRS and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

Open-label sacubitril and valsartan treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all open-label sacubitril and valsartan treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Medication labels will include storage conditions but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of open-label sacubitril and valsartan treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site visits or remotely and at the completion of the study. Patients will be asked to return all unused open-label treatment and packaging at the end of the study or at the time of discontinuation of treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused open-label treatment, packaging, drug labels, and a copy of the completed drug accountability log according to the instructions provided by Novartis or its agents.

5.5.4 Instructions for prescribing and taking study treatment

All medication for the duration of the study will be provided by Novartis. Eligible patients will be randomized via IVRS to either sacubitril and valsartan or enalapril. Patients randomized to the sacubitril and valsartan arm will receive sacubitril and valsartan matching placebo for the first day of treatment to fulfill the required 36-hour wash-out period (in addition to enalapril matching placebo). Patients randomized to enalapril will not require a washout and will receive active treatment on the first day of treatment, in addition to sacubitril and valsartan matching placebo. The first day of dosing will be provided from a centralized hospital supply containing dose levels 1 and 2 and matching placebos.

From the second day of treatment (third dose), patients will be provided with sufficient medication to last until the next scheduled visit. In order to adequately blind the study, patients will be required to take a total of two tablets (one tablet from the sacubitril and valsartan / sacubitril and valsartan matching placebo pack and one tablet from the enalapril/enalapril matching placebo pack) twice a day for the duration of the study.

Initial dose at randomization will be determined by systolic blood pressure (SBP).

- All patients with a systolic blood pressure (SBP) between 110-120 mm Hg will start at Dose level 1 (2.5 mg Enalapril or 24/26 mg sacubitril and valsartan, BID).
- Patients with a SBP ≥ 120 mm Hg will start at dose level 2 (5 mg enalapril or 49/51 mg sacubitril and valsartan, BID).
- Patients will be titrated to the next dose level at Weeks 1 and 2 (Visits 3 and 4) with the goal of reaching the target dose for dose level 3 (10 mg enalapril or 97/103 mg sacubitril and valsartan, BID) by week 2 (Visit 4).
- Patients should be titrated to the next dose level at week 1 only if their SBP is >110 mm Hg and at week 2 if their SBP is > 100 mm Hg.

Dose titration will proceed according to the following table:

Table 5-3 Dose titration schedule based on SBP

Visit	Previous dose level	Systolic Blood pressure mm Hg*	Start/remain/tit rate to: Dose level
Baseline (Visit 2)	N/A	<120	1
	N/A	≥120	2
1 Week (Visit 3)**	1	<110	1
	1	≥110	2
	2	<110	2
	2	≥110	3
2 weeks (Visit 4)	1	<100	1
	1	≥100	2
	2	<100	2
	2	≥100	3
4 Weeks (Visit 5)	1	<100	1
	1	≥100	2
	2	<100	2
	2	≥100	3
6 Weeks (Visit 6)	1	<100	1
	1	≥100	2
	2	<100	2
	2	≥100	3

*Dose level assigned based on BP measurement at the time of randomization/drug dispensing call to IVRS

**Up titration may be done prior to the week 1 visit for patients who were started at dose level 1 who were previously on high dose RAS blockade (>10 mg enalapril total daily dose or > 160 mg valsartan total daily dose or equivalent doses of other ACEi or ARB).

Dose adjustments to lower dose levels may be made at any time at both scheduled and unscheduled visits only if indicated for blood pressure control/tolerability reasons.

Study medication should be taken with a glass of water with or without food. If the patient misses taking any study drug dose, he/she should take it as soon as possible, unless it is almost time for the following scheduled dose. In this case, the patient should skip the missed dose and return back to his/her regular study drug administration schedule.

All dosage prescribed and dispensed to the patient and all dose changes during the study must be recorded in the IVRS and on the Dosage Administration Record eCRF.

The investigator should promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable to take the study treatment as prescribed for any reason.

All patients that complete 8 weeks of treatment will proceed with a 4-week follow up on open-label sacubitril and valsartan. Patients will be instructed not to take any medication on the day of the final visit and will start their open label treatment the next day to facilitate the 36-hour wash out. All patients will have the wash out in order to maintain the blinding of the core study. All patients entering the open-label phase will receive dose level 2 and will be titrated to the next dose level according to the USPI on an every 2-4 week basis to the desired target maintenance dose of 97/103 mg or increased within a 1-2 week time period based on clinical need and/or investigator judgement.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Every attempt should be made to maintain patients on the target study drug dose level for as long a duration as possible throughout the study. If, however, in the opinion of the investigator, a patient is unable to tolerate the protocol-specified target dose, the investigator should consider whether dose adjustments of concomitant medications may rectify the situation before reducing the dose of study treatment. If adjustment of the concomitant medications is not possible or does not alleviate the side effects of concern, the investigator may down-titrate the dose of the study drug to the previous dose level. If needed, the study drug may be stopped completely, but the patient should continue to attend the study visits and be followed until the completion of the study. Patients may restart their current dose of study drug following an interruption of treatment, based on investigator judgment.

Study drug dose level adjustments should be mainly based on overall safety and tolerability with special focus on hyperkalemia, symptomatic hypotension and clinically significant decrease in eGFR/increase in serum creatinine (defined as a serum creatinine of ≥0.5mg/dl with at least a 25% decrease in eGFR).

Adjustment of study drug dose level

If necessary, the patient may be down-titrated to the next lower dose level. The patient may continue receiving the lower dose level for a recommended period of 1 to a maximum of 4 weeks. Re-challenge to titrate back up to the target dose level should be attempted at 2 weeks. It must be noted that the desired dose of study medication is the highest dose (dose level 3), but patient tolerability and safety must be taken into account.

If the tolerability issues are not alleviated despite down-titration by one dose level, the investigator may lower the study drug dose further to the next lower level for 1 to a maximum of 4 weeks, up to temporary withdrawal of the study drug. Again, once stable, the patient should be re-challenged with up-titration to the next higher dose level in an attempt to bring back the patient gradually to the target study drug dose level (dose level 3). The investigator may choose the next dose level for down- or up-titration according to his or her clinical judgment. The IVRS should be contacted to register any changes in the patient's study drug dose level, including in cases of temporary and permanent withdrawal of the study drug, and to obtain the medication numbers of the study drug supplies required for the new study drug dose level.

In some instances, according to the safety and tolerability criteria and the investigator's judgment, dose level 1 or 2 could be maintained if he/she considers that the patient's condition would not allow any further up-titration to the target dose of study medication (level 3). In this case it would be acceptable to maintain the patient at dose level 1 or level 2, whichever is the higher and tolerated dose level by the patient, but reasons for not getting to dose level 3 need to be clearly described in the eCRF.

Study drug restart after temporary treatment interruption

Study drug should be reintroduced in those who temporarily discontinue it as soon as medically justified in the opinion of the investigator.

Once the investigator considers the patient's condition appropriate for receiving the study drug, the investigator should re-start the patient on the study drug at the most appropriate and allowable dose level per his/her medical judgment. If tolerated, the patient should be up-titrated up to dose level 3 every 1 to 4 weeks, as per the investigator's judgment. Patients re-started on the study drug will retain their original randomization and study identification numbers. Should the patient not tolerate the re-start study drug dose level, he/she may be down-titrated again (if appropriate) or discontinue the study medication..

Study visits should occur as close as possible to the pre-defined visit schedule. The timeframe between the regular visits should be maintained as scheduled, irrespective of the number of unscheduled visits that may be performed in between, according to the visit and time schedule described in Table 6-1.

Any changes in the study drug dose level, including temporary/permanent withdrawal or re-start of the study drug, must be recorded on the Dosage Administration Record eCRF and registered in the IVRS.

In case of pregnancy discovered during the study, the patient should be instructed to stop taking the study drug immediately.

5.5.6 Rescue medication

Guidance on handling hyperkalemia, hypotension, and renal dysfunction are provided to investigators in the appendices. Patients may receive open-label ACEIs and/or ARBs during the study **ONLY** if the study medication has been discontinued either temporarily or permanently. A 36 hour wash-out period is required when switching from or to an ACE inhibitor. Use of rescue medication must be recorded in on the Concomitant medications/Significant non-drug therapies eCRF.

5.5.7 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded on the Concomitant medications/Significant non-drug therapies eCRF.

ACEIs and ARBs:

Patients' pre-study ACEIs/ARBs will be replaced with the study medication.

The concomitant use of open-label ACEIs or ARBs is strictly prohibited while the patient is receiving study medication. If the investigator believes that addition of an ACEI or ARB is necessary, then study drug must be discontinued. Study medication should be stopped 36 hours prior to addition of open-label ACEI. If not already treated with aldosterone antagonist, consideration should be given to adding this therapy rather than an ACEI or and ARB, while monitoring renal function.

Other heart failure and cardiovascular medication

If a patient's condition warrants any change in concomitant heart failure or cardiovascular medications, changes may be made at the investigator's discretion.

Oral diuretics may be used and may be adjusted throughout the study duration at the discretion of the investigator.

Medications known to raise potassium levels

Potassium sparing diuretics, potassium supplements, aldosterone antagonists, and any other medications known to raise potassium levels should be used with caution while the patient is receiving study medication due to the increased possibility of occurrence of hyperkalemia. Potassium levels should be monitored regularly especially in those who are receiving these medications.

Concomitant administration of renin inhibitors, such as aliskiren, is prohibited.

Phosphodiesterase-5 (PDE-5) inhibitors

PDE-5 inhibitors should be used with caution while the patient is receiving study medication due to the increased possibility of occurrence of hypotension.

Neseritide and intravenous nitrates

The concomitant admission of sacubitril and valsartan with neseritide and intravenous nitrates has not been studied. Concomitant use of neseritide will not be permitted during the study.

Other medications

Bile acid sequestering agents such as cholestyramine or colestipol are prohibited to avoid interference with study drug absorption.

5.5.8 Discontinuation of study drug

Patients may voluntarily discontinue the study drug for any reason at any time.

Study drug must be discontinued under the following circumstances:

- Withdrawal of consent
- Pregnancy
- Use of prohibited concomitant medication
- Any protocol deviation that constitutes a risk to the patient
- Investigator believes that continuation of study drug may be detrimental to the patient's well-being

Study medication may be discontinued at the investigator's discretion if any of the following occur:

- Any severe suspected drug related AE
- Suspected occurrence of angioedema. A patient with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator to determine if it constitutes a reason for discontinuation of study medication.
- Depending on the serum potassium, blood pressure, or eGFR, patients may need to have their study drug dose or the dose of another concomitant medication reduced or discontinued; or, if appropriate, have potentially contributing agents adjusted. Refer to appendices for treatment guidelines for hyperkalemia, hypotension or renal dysfunction, respectively.

In the case of study drug discontinuation, every effort must be made to complete an end of study visit and obtain follow up health status information for any patients that withdraw from the study. If the patient refuses, he/she should be contacted by telephone in place of protocol-specified visits unless the patient expressly refuses such contacts.

The investigator must notify the IVRS of any study drug discontinuation and record it on the drug administration eCRF.

5.5.9 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a patient does not want to participate in the study anymore and does not want any further visits or assessments and does not want any further study related contacts and does not allow analysis of already obtained biologic material. If a patient withdraws consent, the sites must request permission from patients who withdraw consent for a final telephone contact for patient health status.

At the time a patient withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information. Study drug must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

5.5.10 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

5.5.11 Emergency breaking of assigned treatment code

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IVRS. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Clinical Trial Lead (CTL) that the code has been broken.

It is the investigator’s responsibility to ensure that there is a procedure in place in case of an emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, study treatment name if available, patient number, and instructions for contacting Novartis Country Pharma Organization CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case an emergency treatment code break is required at a time when the investigator and backup are unavailable.

5.5.12 Study completion and post-study treatment

At the end of study visit, patients will be asked to return all remaining study drug. The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

When the patient has completed all scheduled study assessments, the investigator must call the IVRS to record the patient completion in the IVRS.

5.5.13 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

All assessments are listed in Table 6-1. Assessments that are to be reported in the clinical database are marked with an 'x'. Assessments that will only be reported in the source documentation are marked with an 's'. Patients should be seen for all visits on the designated day or as close to it as possible, with an allowed visit window of ± 3 days for post baseline visits.

The screening period may begin following an admission to hospital for ADHF. Eligible patients may be randomized once it is confirmed that they meet all inclusion criteria and none of the exclusion criteria.

Patients may be contacted for safety evaluations for 30 days after the last dose of the 4-week open-label follow-up period. Documentation of attempts to contact the patient should be recorded in the source documentation.

Unscheduled visits for safety/medication evaluation/unscheduled assessments are permitted at any time during the study.

Table 6-1 Assessment schedule

Visit number	1	2	3	4	5	6	7	8	9
Phase	**screening**	**Treatment**						**Titration**	**4 week f/u**
Week	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**~12**
Day	**-5 to 0**	**1**	**7**	**14**	**28**	**42**	**54**	**70**	**84**
Informed consent	s								
Inclusion/exclusion criteria	x	x							
Demography/ medical history	x								
Heart failure and CV disease history	x								
ECG	x								
Physical exam	x			X (cardiac related only)			x		x
Height and weight	x	x	x	x	x	x	x		x
Vital signs	x	x	x	x	x	x	x	x	x
Waist/hip circumference	x								
HF signs and symptoms	x	x	x	x	x	x	x	x	x
HF and CV medications	x	x	x	x	x	x	x		x
Conmeds	x	x	x	x	x	x	x	x	x
AE/SAE	x	x	x	x	x	x	x	x	x
Pregnancy test[4]	x				x		x		x
Plasma BNP and NT-proBNP	x	x	x	x	x		x		x
Plasma/serum biomarkers[1]		x		x	x		x		x
Spot urine biomarkers[2]		x	x	x	x		x		x
eGFR	x	x	x	x	x		x	x	x
Urinalysis	x	x		x	x		x		
Chemistry	x	x	x	x	x		x	x	x
Hematology	x	x					x		
IVRS call	x	x	x	x	x	x	x	x	x
Randomization		x							
Dispense treatment		x	x	x	x	x	X[5]	x	
Drug accountability			x	x	x	x	x	x	x
Angioedema assessment	x	x	x	x	x	x	x	x	x

Visit number	1	2	3	4	5	6	7	8	9
Phase	**screening**	**Treatment**						**Titration**	**4 week f/u**
Week	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**~12**
Day	**-5 to 0**	**1**	**7**	**14**	**28**	**42**	**54**	**70**	**84**
PRO (KCCQ, PGA)		x			x		x		x
Medical Resource utilization									x
Study completion – randomized treatment							x		
Study completion – open label period									x
Post study completion follow up[3]									x[3]

[1] includes cardiac, renal, and drug mechanism of action biomarkers
[2] include urinary markers such as cGMP.
[3]Health status phone call 4 weeks after study completion (16 weeks).
[4]Urine pregnancy test will be done at Visit 2 at the local laboratory.
[5]At week 8, patients will receive open label sacubitril and valsartan and be instructed to not take study medication on the day of the final visit in order to fulfill the washout requirement

6.1 Information to be collected on screening failures

All patients who have signed informed consent but are not randomized will have the study completion page for the screening visit, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race, ethnicity and source of patient referral. Relevant medical history/current medical condition data includes data until the start of study drug. Where possible, diagnoses and not symptoms, will be recorded. HF medications and other CV medications will be recorded in eCRFs separately from other medications. Likewise, detailed HF history and other relevant CV medical history will be recorded on eCRFs separately from other medical history.

6.3 Treatment exposure and compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the care giver. This information should be captured in the source document at each visit. Patient compliance should be at least 80% during the double-blind treatment period. The investigator and/or study personnel will counsel the patient if

compliance is below 80%. Study drug accountability will also be determined by the site monitor while performing routine site visits and at the completion of the study.

Duration of double-blind study drug exposure will be calculated based upon the start and stop dates recorded in the eCRF.

6.4 Efficacy

The efficacy end points are:

Primary:

Time-averaged proportional change from baseline in NT-proBNP. Weeks 4 and 8 will be included in the analysis.Secondary:

- Biomarkers: hs-Troponin, urinary cGMP and BNP toNT-proBNP ratio

Exploratory:

- Time to first occurrence of composite clinical endpoint that includes death, heart failure re-hospitalization, requirement of LVAD, listed for cardiac transplantation, unplanned acute HF visits requiring i.v. diuretics, additional heart failure drug or increase in >50% of the diuretic dose.
- Change in NT-proBNP at Weeks 1 and 2
- Incidence of re-hospitalization or unplanned heart failure visits
- Need for advanced heart failure therapies (including but not limited to i.v. inotropes, LVAD, transplantation)
- Patient centered outcomes including the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Patient Global Assessment (PGA) at 4 weeks and 8 weeks post randomization.
- Change in biomarkers related to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury, and renal function, including estimated glomerular filtration rate.
- Change in NT-proBNP in the enalapril arm during the 4 week open label period
- Medical resource utilization
- Incidence of worsening renal function during 8 weeks of treatment, defined as an increase in serum creatinine of ≥0.5mg/dl from the values measured at baseline

6.4.1 Heart failure signs and symptoms

Signs and symptoms of heart failure will be reviewed by the investigator at all visits during the study. The signs and symptoms evaluation may include, but are not limited to, paroxysmal nocturnal dyspnea, fatigue, edema, dyspnea at rest, dyspnea upon effort, orthopnea, rales, jugular venous distention, presence of a third heart sound. NYHA classification will be assessed and scored at each visit.

6.4.2 Estimated glomerular filtration rate (eGFR)

The eGFR to determine eligibility of the patient for screening into the trial will be calculated at Visit 1 from the serum creatinine concentration measured at the local laboratory. The eGFR will be further calculated from creatinine concentration measured at Visits 2, 3, 4, 5, and 7 (randomization, weeks 1, 2, 4, 8/end of study), visit 8 and 9, titration visit (Week 10) and end of extension (Week 12) at the central laboratory. The eGFR calculation will be based on the Abbreviated Modification of Diet in Renal Disease (MDRD) study equation [Levey, et al 2007].

6.4.3 Biomarkers

BNP and NT-proBNP will be obtained in all patients by using the local laboratory at Visit 1 to determine eligibility; and using the central laboratory at Visits 2, 3, 4, 5 and 7 (randomization, weeks 1, 2, 4, and 8), and at the end of the open label extension, Visit 9 (Week 12).

In addition, biomarker measurements will be obtained from serum and plasma samples at Visits 2, 4, 5 and 7 (randomization, 2, 4 and 8 weeks), to determine effects of treatment on biomarkers of CV, CHF or renal risk. Spot urine will be collected at Visits 2, 3, 4, 5, 7 and 9 (randomization, weeks 1, 2, 4, 8 and 12) to measure urinary cGMP.

The selected biomarkers to be studied will be those believed to be relevant to the pathophysiology of the disease processes of heart failure and renal dysfunction. Biomarkers studies may include, but are not limited to those accessing cardiac and renal benefit or biomarkers related to the study drug mechanism of action such as:

- Neurohormones BNP and NT-proBNP
- hs-Troponin (will not be measured at Week 2)
- Cystatin c
- ST2
- eGFR (MDRD calculation)
- urinary cGMP
- other biomarkers related to cardiac fibrosis/remodelling, tissue perfusion/injury, renal function/injury or other pathophysiologies involved in ADHF

Evaluation of Neprilysin measurement at baseline as a predictor of clinical outcome may be added depending on availability of a validated assay and sample handling requirements. The list may be changed or expanded further as new relevant biomarkers may be discovered during this study and after its completion. As such, serum and plasma will be bio-banked for analysis of yet to be identified diagnostic biomarkers. Details of sample collection, handling and shipment will be provided to investigators in the laboratory manual.

6.4.4 Appropriateness of efficacy measurements

The selected efficacy variables for this study including changes in NT-proBNP and other biomarkers concentrations, as well as heart failure signs and symptoms are standard for the evaluation of therapeutic agents in a heart failure population.

6.5 Safety

- Incidence of worsening renal function, defined as an increase in serum creatinine of ≥0.5mg/dl and worsening of the eGFR by at least 25%
- Incidence of symptomatic hypotension
- Incidence of hyperkalemia (Potassium >5.5 meq/l)
- Incidence of angioedema

Safety assessments will consist of monitoring and recording of all adverse events and serious adverse events, evaluation of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations.

6.5.1 Physical examination

A complete physical exam will be performed at Visits 1, 7 and 9 (screening, weeks 8 and 12). It will include the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and vascular and neurological examinations. If indicated based on medical history, and/or symptoms, rectal, external genitalia, breast and pelvic exams will be performed. The Visit 4 9Week 2) physical exam will only be a cardiac care exam.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the start of the study drug must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's eCRF. Significant findings made after the start of study drug which meet the definition of an adverse event must be recorded on the Adverse Event screen of the eCRF.

6.5.2 Vital signs

Vital signs will be assessed at every visit. This will include blood pressure and pulse measurements. BP will be measured using a standard sphygmomanometer with an appropriate sized cuff and the non-dominant arm in the sitting position after 5 minutes of rest. Every effort should be made to use the same arm for the patient for all vital signs assessments and where possible, the same person doing the assessment.

6.5.3 Height, weight and waist/hip circumference

Height in centimeters if possible, body weight to the nearest 0.1 kg without shoes, will be measured at all visits. Waist/hip circumference to the nearest centimeter will be measured at Visits 1, 2, 5 and 7.

6.5.4 Angioedema

Angioedema is a type of abrupt swelling that occurs under the skin and/or mucous membranes and is often localized to the head, neck, throat, and/or tongue, but may occur elsewhere, including the genitalia and intestines. Severe cases may be associated with airway compromise. Although, the mechanism is not fully understood, bradykinin has been implicated as the putative mediator. Therefore, medications that raise the levels of endogenous bradykinin by inhibiting the enzymes responsible for its breakdown, such as

ACE, aminopeptidase P, and NEP, may result in this potentially dangerous side effect. All suspected cases of angioedema, regardless of suspected causality, must be reported. The angioedema eCRF must be completed and the Novartis Medical Monitor must be notified.

If the angioedema event meets SAE criteria, the investigator must ensure that an SAE form is completed and submitted to Novartis Drug Safety and Epidemiology.

6.5.5 Laboratory evaluations

The local hospital laboratory will be used to for all laboratory evaluations required to determine eligibility. A central laboratory will be used for analysis of all collected specimens from baseline through the final visit. Details on the collections, shipment of samples and reporting of results by the central laboratory will be provided to investigators in the laboratory manual. Results from the local hospital laboratory will be recorded in the laboratory evaluations eCRF.

Clinically notable laboratory findings are defined in Appendix 1.

Local laboratory assessments may be performed on an as-needed basis for unscheduled visits.

Laboratory values that exceed the boundaries of a notable laboratory abnormality must be commented on by the investigator in the Comments screen of the patient's eCRF and additional laboratory evaluations should be performed, as judged appropriate by the investigator. If the laboratory abnormality induces clinical signs or symptoms, or requires therapeutic intervention, then the diagnosis or medical condition must be entered on the AEs screen of the patient's eCRF. If the laboratory abnormality is the primary reason for an unforeseen hospitalization or otherwise fulfills the seriousness category of an AE, then the procedure for rapid notification of SAEs must be followed. Likewise, if the laboratory abnormality leads to discontinuation from the study drug (temporarily or permanently), the patient must be followed until the abnormality resolves or until it is judged to be permanent. This investigation may include continued monitoring by repeat laboratory testing or by performing additional laboratory tests as deemed necessary by the investigator or the Novartis medical monitor.

6.5.5.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured at Visits 1 (local lab), 2 and 7 (central lab).

6.5.5.2 Clinical chemistry

Blood urea nitrogen (BUN), glucose, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), alkaline phosphatase, sodium, potassium, chloride, calcium, hemoglobin A1C, total protein, albumin, uric acid, and lipid profile will be measured at Visits 1 (local lab), 2, 3, 4, 5, 7 and 9 (central lab).

6.5.5.3 Urinalysis

Dipstick-test determination of specific gravity, pH, blood, total protein, bilirubin, ketones, and leukocytes will be measured at Visits 1 (local lab) 2, 4, 5 and 7 (central lab). If dipstick is

positive, a qualitative microscopic determination, including white blood cells high power field (WBCs/HPF) and red blood cells high power field (RBCs/HPF) will be performed.

6.5.6 Pregnancy and assessments of fertility

All female patients of childbearing potential will have a serum pregnancy test (hCG) performed at Visit 1 (local lab) and Visits 5, 7 and 9 (central lab). In addition, these patients will have a urine pregnancy test conducted in the hospital laboratory at Visit 2. If any of these tests are positive, the patient must be discontinued from the study.

6.5.7 Appropriateness of safety measurements

The majority of safety assessments selected for this study are standard for the evaluation of patients with heart failure.

6.6 Other assessments

6.6.1 The Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Patient Global Assessment (PGA)

The KCCQ is a self-administered questionnaire and requires, on average, 4-6 minutes to complete. It contains 23 items, covering physical function, clinical symptoms, social function, self-efficacy and knowledge, and Quality of Life (QoL), each with different Likert scaling wording, including limitations, frequency, bother, change in condition, understanding, levels of enjoyment and satisfaction. A change of 5 points on the scale scores, either as a group mean difference or an intra-individual change appears to be clinically significant, based on comparisons of changes in the scale scores to clinical indicators and patient global reports of change. The KCCQ is a valid, reliable and responsive health status measure for patients with CHF and may serve as a clinically meaningful outcome in CV clinical research, patient management and quality assessment [Green et al 2000].

The HF symptoms and physical limitation domains scores show the best correlation for improvements following a CHF exacerbation [Green et al 2000]. Thus, one of the secondary endpoints is a clinical summary score based on the HF symptoms and physical limitation domains scores of the KCCQ. All other domains will be analyzed as exploratory endpoints, as the instruments will be administered as a whole.

The KCCQ questionnaire will be completed at Visits 2, 5, 7 and 9.

The KCCQ is available in a number of validated translations. However, patients in whose language a validated translation of the KCCQ is not available will be exempt from completing this instrument.

The patient global assessment (PGA) is a seven-point patient self-evaluation scale. At Visit 2 (randomization), the investigator should call the patient's attention to how he/she feels about his/her condition at that time and to explain that periodically the patient will be asked to rate how he/she feels at this point in the study. Subsequently, patients will be asked to rate how well they feel compared to Visit 2 (randomization/baseline) [COPERNICUS Investigators 2002]. This evaluation is combined with the NYHA functional class, one of the most reliable instruments for rating HF patients' functionality, and with occurrence of death and

hospitalization for heart failure to arrive at an overall evaluation of whether a patient is considered to have improved, worsened, or unchanged after a pre-specified period of time [Packer 2001].

The PGA will be conducted at Visits 2, 5, 7 and 9.

6.6.2 Medical resource utilization

The effect of treatment on medical resource utilization will be assessed during the 4-week open-label period. This will include doctor visits, hospitalizations including any procedures during hospitalization, and changes in treatment (addition of medication, dose adjustments).

7 Safety monitoring

7.1 Adverse events

Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during any phase of the study. Medical conditions/diseases present before starting study drug are only considered AEs if they worsen after starting study drug. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All AEs must be recorded on the Adverse Events CRF with the following information.

1. the severity grade [mild, moderate, severe]
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.2**.**

All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this AE; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the AE should be recorded on the Adverse Event CRF.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Novartis may request additional information on specific adverse events of interest and may make requests to perform additional diagnostic tests to further assess the safety profile of the study medications. Such information may include diagnostic procedure reports, discharge

summaries, autopsy reports, and other relevant information that may help in assessing the reported adverse event. All additional information will be de-identified prior to collection by Novartis or its agents.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
    - is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to DS&E as per section 7.2.2.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

In addition if required by the local health authority or ethics committee, the investigator should report all expected and unexpected serious adverse events to these authorities and also inform the institutional review board at the study institution.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety and Epidemiology (DS&E) Department. The telephone number of the contact persons in the local department of DS&E, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If a SAE is unexpected, i.e., the event is not previously documented in the Investigator's Brochure (new occurrence) and is suspected to be related to the Novartis study drug, **this event is considered a Suspected Unexpected Serious Adverse Reaction (SUSAR)**. A DS&E associate may urgently require further information from the investigator for Health Authority reporting purposes. **In general, it is Novartis policy to unblind SUSARs for regulatory reporting. If the unblinding shows that the Novartis drug is involved,** Novartis will issue an Investigator Notification (IN) to inform all investigators participating in any study with the same drug that this SUSAR has been reported. In addition, SUSARs will be collected and reported to the competent authorities and relevant ethics committees as per United States regulatory requirements in the USA.

An external independent DMC will be appointed and will review efficacy and safety data of the ongoing trial on a regular basis. DMC opinion and recommendations will be notified by

Novartis as soon as possible to the competent authorities and the ECs where they qualify for expedited reporting.

7.3 Pregnancy reporting

In case a patient becomes pregnant, or plans to become pregnant, the study drug must be interrupted before contraception is discontinued (or, from the date the pregnancy becomes known) for the entire duration of the pregnancy and lactation period (or, for the entire duration that contraception is discontinued). To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis DS&E Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome.

Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.4 Reporting angioedema-like events

It is important that the investigator pays special attention to any swelling or edema that may resemble angioedema or angioedema-like events that may be reported by patients. If such an event occurs, the investigator will complete an Adjudication Questionnaire for an Angioedema-like Event form (provided by Novartis) to summarize the event, its treatment, and its ultimate outcome and communicate this report to Novartis as soon as possible. Follow-up reports must be communicated to Novartis as soon as new information regarding the event becomes available. All hospital records related to the event must be communicated to Novartis.

Occasionally, the investigator may be contacted by the Novartis regarding AEs that were reported on behalf of patients that may resemble an angioedema-like event. The investigator or his/her delegated staff must complete the required report forms and supply the required medical records for such events, regardless of whether the investigator views the event in question as angioedema or not.

All angioedema reports will be forwarded to an angioedema adjudication committee by Novartis for assessment.

Submission of an angioedema report is not a substitution for the submission of a SAE report. If an angioedema-like event satisfies the definition of a SAE, the investigator must submit a SAE report in addition to the Adjudication Questionnaire for an Angioedema-like Event.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and (e)CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized monitor. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the (e)CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the (e)CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRFs) using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before review of the data by the CRO working on behalf of Novartis. Prior to database lock, the Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

CRO staff working on behalf of Novartis, review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any

required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to CRO staff who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to the designated CRO.

Randomization codes and data about all study drug dispensed to the patient and all dosage changes will be tracked using an Interactive Voice Response System (IVRS). The system will be supplied by a vendor, who will also manage the IVRS database. The IVRS database will be sent electronically to the designated CRO.

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis. The occurrence of reportable protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Head of Biometrics and the Medical Unit Head.

8.4 Data Monitoring Committee

An external data monitoring committee (DMC) independent of Novartis will be appointed to review the incidence of the pre-specified clinical events including major cardiac events, serious adverse events, the rate and distribution of adverse events, and relevant laboratory findings on an ongoing basis. If it is deemed necessary for internal decision making due to patient safety, an interim analysis will be conducted by an independent statistical group.

The membership of the DMC and the responsibilities of the DMC and Novartis will be defined in a separate document entitled ‘Data Monitoring Committee Charter’. The DMC Charter will include information about data flow, purpose and timing of DMC meetings, guidance in the decision making process, communication strategy, procedures for ensuring confidentiality, procedure to address conflicts of interest and statistical monitoring guidelines.

8.5 Adjudication Committee

It is important that the investigator pays special attention to any swelling or edema that may resemble angioedema or angioedema-like events that may be reported by patients. There will be a separate eCRF for angioedema events. If such an event occurs, the investigator will complete an Adjudication Questionnaire for an Angioedema-like Event form (provided by Novartis) to summarize the event, its treatment, and its ultimate outcome and communicate

this report to Novartis as soon as possible. Follow-up reports must be communicated to Novartis as soon as new information regarding the event becomes available. All hospital records related to the event must be communicated to Novartis.

Occasionally, the investigator may be contacted by the Novartis regarding AEs that were reported on behalf of patients that may resemble an angioedema-like event. The investigator or his/her delegated staff must complete the required report forms and supply the required medical records for such events, regardless of whether the investigator views the event in question as angioedema or not.

All angioedema reports will be forwarded to an angioedema adjudication committee by Novartis for assessment.

Submission of an angioedema report is not a substitution for the submission of a SAE report. If an angioedema-like event satisfies the definition of a SAE, the investigator must submit a SAE report in addition to the Adjudication Questionnaire for an Angioedema-like Event.

9 Data analysis

A designated Contract Research Organization will perform the statistical analysis.

It is planned that the data from all centers that participate in this protocol will be combined, so that an adequate number of subjects will be available for analysis.

Unless otherwise specified, all statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

Efficacy, safety, and other data will be summarized. For continuous variables, summary statistics (mean, standard deviation, median, 25th and 75th percentiles, interquartile range, minimum, and maximum) at each time point and for change from baseline to each time point will be reported by treatment group.

9.1 Analysis sets

The following patient sets will be used for the statistical reporting and analyses:

The Randomized Set will consist of all randomized patients.

The Full Analysis Set (FAS) will consist of all randomized patients with the exception for those patients who have not been qualified for randomization and have not received study drug, but have been inadvertently randomized into the study. Following the intent-to-treat principle, patients will be analyzed according to the treatment to which they were assigned at randomization. Efficacy variables will be analyzed based on the FAS as the primary set.

The Safety Set (SAF) will consist of all randomized patients who received at least one dose of study drug. Patients will be included in the analysis according to the treatment actually received. The Safety Set will be used for the analyses of safety variables.

The Per-Protocol (PP) set will be a subset of the FAS which will consist of the patients who do not have major deviations from the protocol procedures in the double-blind study stage.

Major protocol deviations will be pre-specified prior to unblinding treatment codes for analyses. This supplemental efficacy set will be used to support the primary analysis results.

9.2 Patient demographics and other baseline characteristics

Baseline value is defined as the last non-missing assessment prior to the first dose of randomized study medication, including the matching placebos, unless specified otherwise in the protocol.

Summary statistics will be provided by treatment group for demographics and baseline characteristics, including age, age group (<65 years vs. ≥65 years; <75 years vs. ≥75 years), sex, race, ethnicity, weight, height, body mass index (BMI), category of prior CHF medication, prior HF hospitalization, NYHA class, NT-proBNP, BNP, and vital signs. BMI will be calculated as weight (kg) / height^2 (m^2) from the collected height and weight at Visit 1 (Screening Visit). Continuous variables will be summarized using n, mean, standard deviation, median, 25th and 75th percentiles, interquartile range, minimum, and maximum. Geometric means will be used to summarize the NT-proBNP results. Categorical variables will be summarized using frequency and percentage.

The Randomized Set and FAS will be the patient sets for the above analyses.

9.3 Treatments

The overall duration on the double-blind study drug will be summarized by treatment group using mean, standard deviation, median, 25th and 75th percentiles, interquartile range, minimum, and maximum. Additionally, the number and percentage of patients will be summarized by treatment group for duration category.

Concomitant medications and significant non-drug therapies, prior to and after the randomization date will be summarized by therapeutic class, preferred term, and treatment group.

The number and percentage of patients on different HF background medications will be tabulated by treatment at baseline and during the double-blind stage.

The Safety Set will be used for the above analyses.

9.4 Analysis of the primary variable(s)

9.4.1 Variables

The primary efficacy variable is the time-averaged proportional change from baseline in NT-proBNP. Weeks 4 and 8 will be included in the analysis (primary analysis time point).

9.4.2 Statistical model, hypothesis, and method of analysis

The primary hypothesis to be tested is that the ratio of the geometric means of NT-proBNP (average of Weeks 4 and 8/baseline) for the sacubitril and valsartan and enalapril groups are equal (H0) versus the ratio of the geometric means of NT-proBNP are not equal (Ha).

For NT-proBNP, the time-averaged proportional change from baseline in a logarithmic scale will be analyzed using an analysis of covariance (ANCOVA) model using data from Weeks 4 and 8 with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate The estimated treatment effect in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0.

The change from baseline log-transformed NT-proBNP will be calculated as log (post-dose value) – log (baseline value). Geometric means (presented as a ratio to baseline) will be calculated by exponentially back-transforming the LS means based on the ANCOVA model.

9.4.3 Handling of missing values/censoring/discontinuations

The analysis will be performed based on all available data in the FAS and based on likelihood method with an assumption of missing at random for missing data.

9.4.4 Supportive analyses

T-tests comparing treatment groups using change from log (baseline) to log (Week 8) values and log (Week 4) values will be performed.

In addition to the primary analysis, the primary efficacy variable will also be analyzed using the same analysis model in the PP Set as supportive.

9.5 Analysis of secondary and exploratory variables

9.5.1 Secondary variables

Incidences of symptomatic hypotension, hyperkalemia and angioedema will be calculated, along with the relative risk of sacubitril and valsartan vs. enalapril and 95% confidence intervals of the relative risk.

For biomarkers including BNP to NT-proBNP ratio, hs-Troponin, and urinary cGMP, the time-averaged proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model using the data from Weeks 4 and 8 with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariateThe estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0.

For BNP to NT-proBNP ratio and urinary cGMP at Weeks 1 and 2, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. For each of Weeks 1 and 2 the estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0.

Analyses of the secondary variables will be based on the FAS.

9.5.2 Exploratory variables

Exploratory variables:

1. Time to first occurrence of composite clinical endpoint that includes death, heart failure re-hospitalization, requirement of LVAD, listed for cardiac transplantation, unplanned acute HF visits requiring i.v. diuretics, additional heart failure drug or increase in >50% of the diuretic dose
2. Change from baseline at Weeks 1 and 2 in NT-proBNP
3. Need for re-hospitalization, ED visit, or unplanned outpatient clinic visits due to worsening HF symptoms
4. Need for advanced heart failure therapies (including but not limited to i.v. inotropes, LVAD, transplantation)
5. Patient centered outcomes including the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Patient Global Assessment (PGA) at 4 weeks and 8 weeks post randomization
6. Change in biomarkers related to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury, and renal function, including estimated glomerular filtration rate (eGFR)
7. Change from Week 8 in NT-proBNP in the enalapril arm during the 4 week open label period
8. Medical resource utilization
9. Incidence of worsening renal function during 8 weeks of treatment, defined as an increase in serum creatinine of ≥0.5 mg/dl from the value measured at baseline

For the composite variable (exploratory variable 1), Kaplan-Meier estimates of the rates of the composite event will be presented, and treatment groups will be compared using a log- rank test. Kaplan-Meier plots will be presented. Hazard ratios and 95% CIs will be estimated from a Cox proportional hazard regression model with treatment as a factor.

For NT-proBNP at Weeks 1 and 2, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. For each of Weeks 1 and 2 the estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0.

Within exploratory variable 3, the time to first hospitalization will be analyzed presenting Kaplan-Meier estimates and testing with the log rank test.

Within exploratory variables 3 and 4, categorical variables will be analyzed using a logistic regression model with treatment as a factor.

Within exploratory variable 3, the number of re-hospitalizations and number of heart failure visits requiring diuretics will be analyzed using a negative binomial regression model with the count data as the dependent variable and treatment group as a fixed-effect factors and log(follow-up duration) as the off-set. The model will estimate event rates (intensities/risks)

and their 95% confidence intervals will be provided by treatment group. The treatment comparison will be performed through the estimated ratio and its 95% confidence interval.

Within exploratory variables 3 and 4, for variables representing a number of days, the mean differences between treatment groups will be compared using an analysis of variance model with treatment group as a factor. The estimated treatment difference and its 95% confidence interval will be provided.

Analysis of KCCQ clinical summary score as continuous variable

The KCCQ instrument includes several domains. Only the domains that address HF symptoms and physical limitations will be analyzed. The clinical summary score of KCCQ is computed as the mean of the following available domain scores:

- Physical limitation score
- Total HF symptom score

The clinical summary score at weeks 4 and 8 of KCCQ will be analyzed based on a repeated measures ANCOVA model in which treatment, visit, and treatment-by-visit interaction will be included as fixed-effect factors and baseline value as a covariate, with a common unstructured covariance for each treatment group. The primary treatment comparison between sacubitril and valsartan and enalapril is to be made at Week 8. The analysis will be performed based on all available data in the FAS and based on likelihood method. The estimated treatment effect with the associated confidence interval at Week 8 will be provided.

Responder analyses based on the number of patients with at least 5 points improvement or deterioration of the KCCQ clinical summary score will be performed using logistic regression models. The list of explanatory variables in the logistic regression model will be determined when the Statistical Analysis Plan is prepared prior to database lock.

The Physician's Global Assessment will be analyzed at Weeks 4 and 8, using Cochran-Mantel-Haenszel (CMH) test for different row (treatment) means based on the modified ridit scores.

For biomarkers related to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury, and renal function, a proportional change from baseline in a logarithmic scale will be analyzed using a repeated measures ANCOVA model using the data from Weeks 2, 4 and 8 with treatment, week and treatment-by-week interaction as fixed effect factors and the logarithmic baseline biomarker value as a covariate, using observed data. The unstructured working correlation matrix will be used. For each of Weeks 2, 4 and 8 the estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0.

For NT-pro BNP, change from Week 8 to Week 12 in a logarithmic scale will be summarized by treatment group.

The medical resource utilization data analysis is described in Section 9.5.4.

For worsening renal function, a logistic regression model with treatment and baseline creatinine value as covariates having fixed effects will be run.

Analyses of the exploratory variables will be based on the FAS.

9.5.3 Other safety variables

The safety and tolerability assessments are listed below:

- AEs and SAEs
- Sitting systolic, diastolic BP, and pulse pressure
- Heart rate
- Laboratory values

The assessment of safety will be based primarily on the frequency of adverse events, SAEs, and laboratory abnormalities. Other safety data will be summarized as appropriate.

The incidence of treatment-emergent adverse events (new or worsened) will be summarized by primary system organ class, preferred term, severity, and relationship to study drug. In addition, the incidence of death, SAEs, and AEs leading to discontinuation will be summarized separately by primary system organ class and preferred term.

Laboratory data will be summarized by presenting shift tables using extended reference ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (mean, median, standard deviation, 25th and 75th percentiles, interquartile range, minimum and maximum) and by the flagging of notable values in data listings.

Data from other tests (e.g., ECG or vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

Safety analyses will be performed based on the Safety Set. There will be no inferential analyses of the safety data.

9.5.4 Resource utilization

Data relating to resource utilization will be used to describe medical resources used by the study participants. Only descriptive statistics of resources utilization data will be provided by treatment group.

9.5.5 Pharmacokinetics

Not Applicable.

9.5.6 Pharmacogenetics and pharmacogenomics

Not applicable.

9.5.7 Biomarkers

See Sections 9.4 and Section 9.5 for a description of the methods used to analyze the biomarkers. Any other biomarkers collected but not specifically mentioned in Sections 9.4 or 9.5 will be analyzed in the same manner.

9.5.8 PK/PD

Not applicable.

9.6 Interim analyses

No interim analysis is planned.

9.7 Sample size calculation

Assuming a significance level of 0.05 and 85% power, a sample size of 736 patients would be needed to detect an 18% reduction in the geometric mean of the time-averaged proportional change from baseline (average of Weeks 4 and 8) in NT-proBNP for the sacubitril and valsartan treatment group assuming a value of 0.95 for the enalapril group, a common standard deviation of 0.85 and a 10% loss to follow-up rate. The estimates are based on the day 5 to day 14 data from the RELAX-AHF study. The standard deviation estimate is supported by data from PARADIGM.

The assumption of a 18% reduction in the geometric mean for NT-proBNP for the sacubitril and valsartan treatment group vs. the enalapril group is consistent with NT-proBNP results seen in PARADIGM (26% and 25% relative reduction of sacubitril and valsartan vs. enalapril at Week 4 and Month 8 respectively), PARAMOUNT (23% relative of sacubitril and valsartan vs. valsartan at Week 12) and RELAX-AHF (19% relative reduction of serelaxin vs. placebo at Day 2).

Table 9-1 Sample size and power for various rate of reduction in sacubitril and valsartan group given alpha =0.05 and 10% drop out rate:

Change in GM for enalapril	Common SD	Relative reduction in GM for sacubitril and valsartan group compared to enalapril group	Change in GM for sacubitril and valsartan group	Power	Total sample size after adjusting for 10% drop out rate
.95	.85	15%	.81	85%	1096
.95	.85	15%	.81	90%	1280
.95	.85	18%	.78	85%	736
.95	.85	18%	.78	90%	860
.95	.85	20%	.76	85%	582
.95	.85	20%	.76	90%	680

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated

agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in section 7 Safety Monitoring should be followed.

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13 Appendix 1: Clinically notable laboratory values and vital signs

Clinically notable laboratory abnormalities for selected tests based on a percent change from baseline:

Hematology

RBC count	>50% increase, >20% decrease
Hemoglobin	>50% increase, >20% decrease
Hematocrit	>50% increase, >20% decrease
WBC count	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease

Blood Chemistry

ALT (SGPT)	>150% increase
AST (SGOT)	>150% increase
BUN	>50% increase
Creatinine	>50% increase
Total bilirubin	>100% increase
CPK	>300% increase
Alkaline phosphatase	>100% increase
Potassium	>20% increase, >20% decrease
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease
Uric acid	>50% increase

14 Appendix 2: Treatment guidelines for hyperkalemia (serum potassium greater than or equal to 5.5 mEq/L)

General principles

Elevation of potassium levels above the predefined values should be repeated and confirmed before any action is taken.

Any patient who experiences a potassium level ≥ 5.5 mEq/L confirmed by repeated testing after randomization requires regular, repeated checks of potassium concentration (beyond that prescribed in the protocol) until it is clear that the potassium concentration is stable and not rising into the range of concern (≥ 5.5 mEq/L).

Patients with elevated potassium value will be managed according to the corrective actions outlined below and the investigator's clinical judgement. Hyperkalemia should be followed until resolution.

Recommended corrective action for management of hyperkalemia

Serum potassium > 5.3 and less than or equal to 5.5 mEq/L

- Confirm potassium concentration in a non-hemolyzed sample
- Reinforce low potassium diet and restriction of food/drinks with high potassium content (e.g. orange juice, melon, bananas, low-salt substitutes etc.)
- Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia. Consider reduction in dose or discontinuation of these agents:
- Aldosterone antagonists (if they are believed to be the most likely cause of hyperkalemia)
- Potassium-sparing diuretics (e.g. amiloride and triamterene) including in combination products with thiazide or loop diuretics
- Potassium supplements, e.g., potassium chloride
- Salt substitutes
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Cyclo-oxygenase-2 (COX-2) inhibitors
- Trimethoprim and trimethoprim-containing combination products, such as Bactrim® and Septra® (trimethoprim/sulfamethoxazole fixed combination)
- Herbal Supplements:
- For example, Noni juice, alfalfa (*Medicago sativa*), dandelion (*Taraxacum officinale*), horsetail (*Equisetum arvense*), nettle (*Urtica dioica*), milkweed, lily of the valley, Siberian ginseng, hawthorn berries
- Repeat serum potassium measurement within 3 to 5 days
- If serum potassium remains > 5.3 and ≤ 5.5 mEq/L, regularly monitor serum potassium levels to ensure stability (suggested once monthly)
- Consider down-titration of study medication, according to investigator's medical judgment.

Serum potassium > 5.5 and < 6.0 mEq/L

- Confirm potassium concentration in a non-hemolyzed sample
- Consider down-titration or temporarily discontinue study drug according to investigator medical judgment.
- Apply all measures outlined for serum potassium > 5.3 and ≤ 5.5 mEq/L
- Repeat serum potassium measurement after 2-3 days
- If serum potassium < 5.5 mEq/L, consider resumption of study drug at lower dose with repeat potassium within 5 days

Serum potassium greater than or equal to 6.0 mEq/L

- Immediately discontinue study drug
- Confirm potassium concentration in a non-hemolyzed sample
- Urgently evaluate patient and treat hyperkalemia as clinically indicated
- Apply all measures outlined for serum potassium > 5.3 and < 6.0 mEq/L
- If serum potassium < 5.5 mEq/L, consider resumption of study drug at lower dose with repeat potassium within 5 days

15 Appendix 3: Guidelines for the management of blood pressure

Guidelines

1. Investigator should monitor blood pressure closely
2. If symptomatic hypotension occurs:
    a. Correct any treatable cause, e.g. hypovolemia
    b. If hypotension persists, any antihypertensive drug and non-disease-modifying drugs, such as diuretics, CCBs, nitrates, and α-blockers, should be down-titrated or stopped first before down-titration of the study drug is considered
3. If hypotension persists, the study drug should be down-titrated or even temporarily withdrawn. The dose re-challenge and medication adjustment guidelines described in Section 5.5.5 should be adhered to as much as possible.

16 Appendix 4: Guidelines for the management of renal dysfunction

General principles:

Glomerular filtration rate in HF patients depends on intrinsic renal function and on a balance between afferent and efferent glomerular arterial tonicity. This tonicity is partly regulated by a stimulation of angiotensin II and could be affected by either study medication. Moreover, renal dysfunction may develop or may deteriorate in some patients after study drug administration. These recommendations have been developed to guide the investigators in managing patients with renal dysfunction after randomization.

Two types of response to serum creatinine increase are described:

Surveillance situation

If, at any time after randomization, eGFR decreases by ≥ 25% from baseline (or if serum creatinine concentration increase to 2.5 mg/dL [221 μmol/L]), the investigator will check for potentially reversible causes of renal dysfunction such as:

- Non-steroidal anti-inflammatory drug intake, antibiotics, or other treatments known to affect creatininemia

- Volume decrease, including that resulting from excessive dosing of diuretics
- Urinary infection
- Urinary tract obstruction
- Study medication

Action situation

If a patient eGFR decreases by ≥ 40% from baseline (or if serum creatinine concentration rises above 3 mg/dL (265 μmol/L), the investigator will check for potentially reversible causes of renal dysfunction (see above).

If the investigator judges that study medication has to be stopped, he/she will have to contact the Novartis medical monitor or his/her designee. Thereafter, serum creatinine assessments will have to be repeated at least each week until levels return to acceptable values. If study medication was stopped, every effort will be done to restart it again, according to clinical conditions

17 Appendix 5: Kansas City Cardiomyopathy Questionnaire

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some may mainly feel shortness of breath while others mainly fatigue. Please indicate how limited you have been by **heart failure** (for example, shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Please put an **X** in one box on each line

Activity	**Extremely** limited	**Quite a bit** limited	**Moderately** limited	**Slightly** limited	**Not at all** limited	**Limited for other reasons or did not do the activity**
Dressing yourself	☐	☐	☐	☐	☐	☐
Showering or having a bath	☐	☐	☐	☐	☐	☐
Walking 100 yards on level ground	☐	☐	☐	☐	☐	☐
Doing gardening, housework or carrying groceries	☐	☐	☐	☐	☐	☐
Climbing a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Jogging or hurrying (as if to catch a bus)	☐	☐	☐	☐	☐	☐

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (for example, shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** are now…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
☐	☐	☐	☐	☐	☐

3. Over the past 2 weeks, how many times have you had **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
☐	☐	☐	☐	☐	☐

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
☐	☐	☐	☐	☐	☐

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
☐	☐	☐	☐	☐	☐

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every night	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
☐	☐	☐	☐	☐

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse (for example, regularly weighing yourself, eating a low salt diet etc.)?

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
☐	☐	☐	☐	☐

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
☐	☐	☐	☐	☐

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Completely dissatisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I have felt that way **all of the time**	I have felt that way **most of the time**	I have **occasionally** felt that way	I have **rarely** felt that way	I have **never** felt that way
☐	☐	☐	☐	☐

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please put an **X** in one box on each line

Activity	**Extremely** limited	**Quite a bit** limited	**Moderately** limited	**Slightly** limited	**Not at all** limited	**Limited for other reasons or did not do the activity**
Hobbies, recreational activities	☐	☐	☐	☐	☐	☐
Working or doing household chores	☐	☐	☐	☐	☐	☐
Visiting family or friends	☐	☐	☐	☐	☐	☐
Intimate or sexual relationships	☐	☐	☐	☐	☐	☐

NOVARTIS

Clinical Development

LCZ696

Clinical Trial Protocol CLCZ696BUS01

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

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List of abbreviations

ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ADHF	acute decompensated heart failure
AE	adverse event
AF	atrial fibrillation
AHF	acute heart failure
ALT	alanine aminotransferase
ANCOVA	analysis of covariance model
ANP	arial natriuretic peptide
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
AST	aspartate aminotransferase
AUC	area under the curve
b.i.d.	twice a day
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
Bpm	beats per minute
CHF	chronic heart failure
CFR	US Code of Federal Regulations
CDS	Core Data Sheet (for marketed drugs)
COPD	Chronic obstructive pulmonary disease
CPO	Country Pharma Organization
CRA	clinical research associate (site monitor)
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRTD	Cardiac resynchronization therapy device
CSR	Clinical Study Report
CTL	Clinical Trial Leader
CV	cardiovascular

DBP	diastolic blood pressure
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
Echo	echocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
eGFR	estimated glomerular filtration rate
cGMP	cyclic guanosine monophosphate
EOS	end of study
ER	emergency room
HF	heart failure
HfrEF	heart failure with reduced ejection fraction
hs-Troponin	high sensitivity troponin
HTN	hypertension
IA	interim analysis
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	investigator notification
i.v.	intravenous
IRB	Institutional Review Board
IWRS	Interactive Web Response System
KCCQ	Kansas City Cardiomyopathy Questionnaire
LFT	Liver function test (raised serum transaminases and/or bilirubin levels)
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
LVESV	left ventricular end systolic volume
LVH	left ventricular hypertrophy

MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
mm Hg	millimeter mercury
MUGA	multi gated acquisition scan
NEP	neutral endopeptidase
NEPi	neutral endopeptidase inhibitor
NP	natriuretic peptide
NT-proBNP	N-terminal pro-brain natriuretic peptide
PCI	percutaneous coronary intervention
PGA	Patient Global Assessment
QoL	Quality of Life
RAAS	renin angiotensin aldosterone system
SAE	serious adverse event
SBP	systolic blood pressure
SUSAR	Suspected Unexpected Serious Adverse Reactions
ULN	upper limit of normal
USPI	United States prescribing information/package insert

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Period	A subdivision of a cross-over study
Premature subject/patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the

	drug being tested in the study

Protocol summary

Protocol number	CLCZ696BUS01
Title	A multicenter, randomized, double-blind, double-dummy, parallel group, active-controlled 8-week study to evaluate the effect of sacubitril/valsartan (LCZ696) versus enalapril on changes in NT-proBNP and safety and tolerability of in-hospital initiation of sacubitril/valsartan compared to enalapril in HFrEF patients who have been stabilized following hospitalization for acute decompensated heart failure (ADHF)
Brief title	In-hospital initiation of sacubitril/valsartan vs. enalapril to assess changes in NT-proBNP through 8 weeks of treatment following an episode of acute decompensated heart failure.
Sponsor and Clinical Phase	Novartis Phase IIIb/IV
Investigation type	Interventional
Study type	Multicenter, randomized, double-blind, parallel group, active-controlled
Purpose and rationale	The purpose of this study is to assess the effect of in-hospital initiation of sacubitril/valsartan tablets vs. enalapril on time averaged proportional change in NT-proBNP in patients hospitalized for acute decompensated heart failure (ADHF) and reduced ejection fraction (left ventricular ejection fraction (LVEF) ≤ 40%). Hospitalization for acute decompensated heart failure identifies patients at increased risk of death and re-hospitalization following discharge. This increased risk justifies intervention with novel treatment strategies initiated prior to hospital discharge to improve patient outcomes.
Primary Objective(s)	The primary objective of this study is to assess the effect of in-hospital initiation of sacubitril/valsartan tablets vs. enalapril on the time-averaged proportional change of NT-proBNP from baseline in patients who have been stabilized following hospitalization for acute decompensated heart failure and reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤ 40%). Weeks 4 and 8 will be included in the analysis (primary analysis time point).
Secondary Objectives	To examine the effect of sacubitril/valsartan tablets vs. enalapril on change in: • The proportional change in NT-proBNP from baseline to Week 8 • Incidence of symptomatic hypotension during 8 weeks of treatment • Incidence of hyperkalemia (Potassium >5.5 mEq/L) during 8 weeks of treatment • Incidence of angioedema during 8 weeks of treatment • Biomarkers: high sensitivity-Troponin (hs-Troponin), urinary cGMP at 4 and 8 weeks; and BNP:NT-proBNP ratio
Exploratory Objectives	• Time to first occurrence of composite clinical endpoint that includes death, heart failure re-hospitalization, requirement of LVAD, listed for cardiac transplantation, unplanned acute HF visits requiring i.v. diuretics,

	additional heart failure drug or increase in >50% of the diuretic dose. • Change from baseline at Weeks 1 and 2 in NT-proBNP • Incidence of re-hospitalization, ED visit or unplanned outpatient clinic visits due to worsening HF symptoms • Re-hospitalization through Day 30 • Need for advanced heart failure therapies (including but not limited to i.v. inotropes, LVAD, transplantation) • Patient centered outcomes including the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Patient Global Assessment (PGA) at 4 weeks and 8 weeks post randomization • Change in biomarkers related to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury, and renal function, including estimated glomerular filtration rate (eGFR) • Change from Week 8 in NT-proBNP in the enalapril arm during the 4 week open label period • Medical resource utilization • Incidence of worsening renal function during 8 weeks of treatment, defined as an increase in serum creatinine of ≥0.5mg/dl from the values measured at baseline
Study design	This study will use a randomized, double-blind, double-dummy, active-controlled, parallel group design. Eligible patients hospitalized for ADHF will be randomized no earlier than 24 hours and up to ten days of presentation, while still hospitalized. At the time of randomization, patients will have been stabilized, defined for this study as: • SBP ≥100mm Hg for the preceding 6 hours prior to randomization; no symptomatic hypotension; • No increase (intensification) in i.v. diuretic dose within the last 6 hours prior to randomization; • No i.v. inotropic drugs for 24 hours prior to randomization; • No i.v. vasodilators including nitrates within the last 6 hours prior to randomization All patients will need to meet all other inclusion and none of the exclusion criteria. Patients will be randomized to sacubitril/valsartan or enalapril. All patients randomized to sacubitril/valsartan will require a 36-hour wash-out from previous ACEi treatment prior to first dose of active study treatment. All randomized patients in the trial will remain hospitalized for observation for 6 hours following the third dose of study medication. See section 3.1 for more details. At the end of the 8-week treatment period, all patients will enter a 4-week follow up period on open label sacubitril/valsartan.
Population	The study population will consist of male and female patients, ≥ 18 years of age, admitted to hospital for acute decompensated heart failure. The goal is to randomize a total of approximately 882 patients to sacubitril/valsartan or

	enalapril in a 1:1 ratio in approximately 170 centers in the United States. At the time of randomization, patients will have been stabilized, defined for this study as: • SBP ≥100mm Hg for the preceding 6 hours prior to randomization; no symptomatic hypotension • No increase (intensification) in i.v. diuretic dose within last 6 hours prior to randomization • No i.v. inotropic drugs for 24 hours prior to randomization • No i.v. vasodilators including nitrates within last 6 hours prior to randomization; All patients will need to meet all other inclusion and none of the exclusion criteria.
Inclusion criteria	Patients eligible for inclusion in this study have to fulfill all of the following criteria: 1. Possess the capacity to provide written informed consent which must be obtained before any assessment is performed. 2. Patients ≥ 18 years of age, male or female. 3. Currently hospitalized for ADHF. Patients with a diagnosis of acute heart failure had to have symptoms and signs of fluid overload (i.e. jugular venous distention, edema or rales on auscultation or pulmonary congestion on chest x-ray) at time of hospitalization. 4. Eligible patients will be randomized no earlier than 24 hours and up to ten days after presentation while still hospitalized as long as meet the following definition of stable status: • SBP ≥100mm Hg for the preceding 6 hours prior to randomization; no symptomatic hypotension • No increase (intensification) in i.v. diuretic dose within last 6 hours prior to randomization • No i.v. inotropic drugs for 24 hours prior to randomization • No i.v. vasodilators including nitrates within last 6 hours prior to randomization 5. LVEF ≤40% within the past 6 months (including current hospitalization) using echocardiography, multi gated acquisition scan (MUGA), CT scanning, MRI or ventricular angiography provided no subsequent study documented an EF of >40%. 6. Elevated NT-proBNP ≥ 1600pg/mL OR BNP ≥400 pg/mL during current hospitalization
Exclusion criteria	Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients. 1. Currently taking sacubitril/valsartan tablets or any use within the past 30 days.

	2. Enrollment in any other clinical trial involving an investigational agent or investigational device. 3. History of hypersensitivity, known or suspected contraindications, or intolerance to any of the study drugs, including ACEIs, ARBs, or Sacubitril (NEP inhibitor) 4. Patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy. 5. Requirement of treatment with both ACE inhibitor and ARB. 6. eGFR < 30 ml/min/1.73 m2 as measured by the simplified Modification of Diet in Renal Disease (MDRD) formula at screening. 7. Serum potassium > 5.2 mEq/L at screening. 8. Acute coronary syndrome, stroke, transient ischemic attack; cardiac, carotid or other major CV surgery; percutaneous coronary intervention (PCI) or carotid angioplasty, within one month prior to Visit 1. 9. Primary cause of dyspnea due to non-cardiac, non-heart failure causes such as acute or chronic respiratory disorders 10. Intended coronary or carotid artery disease revascularization within the 6 months after Visit 1. 11. Implantation of a cardiac resynchronization therapy device (CRTD) within the prior 3 months from Visit 1or intent to implant a CRTD. 12. History of heart transplant or patients who are on a transplant list or with left ventricular assistance device (LVAD). 13. Isolated right HF due to severe pulmonary disease. 14. Documented untreated ventricular arrhythmia with syncopal episodes within the 3 months prior to Visit 1. 15. Symptomatic bradycardia or second or third degree heart block without a pacemaker. 16. Presence of hemodynamically significant mitral, aortic, or hypertrophic cardiomyopathy. 17. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past year with a life expectancy of less than 1 year. 18. Known hepatic impairment (as evidenced by total bilirubin > 3 mg/dL, or increased ammonia levels, if performed), or history of cirrhosis with evidence of portal hypertension such as varices. 19. 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 hCG laboratory test. 20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they are using two birth control methods. The two methods can be a double barrier method (if accepted by the local regulatory authority and ethics committee) or a barrier method plus a hormonal method • Adequate barrier methods of contraception include: diaphragm, condom (by the partner), intrauterine device (copper or hormonal), sponge or spermicide. Hormonal contraceptives include any

	marketed contraceptive agent that includes an estrogen and/or a progesterone agent. • Reliable contraception should be maintained throughout the study and for 7 days after study drug discontinuation. • Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL and estradiol < 20 pg/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
Investigational and reference therapy	All eligible patients will be randomized to receive either sacubitril/valsartan or enalapril. The following study treatment will be provided for the 8-week double blind double dummy treatment period: • sacubitril/valsartan tablets + matching placebo or enalapril tablets + matching placebo. Open-label, sponsor-provided sacubitril/valsartan tablets will be provided for the open label extension.
Efficacy assessments	Primary: Time-averaged proportional change from baseline in NT-proBNP. Weeks 4 and 8 will be included in the analysis. Secondary: Proportional change in NT-proBNP from baseline to Week 8 Biomarkers: hs-Troponin, urinary cGMP and BNP to NT-proBNP ratio Exploratory: Time to first occurrence of composite clinical endpoint that includes death, heart failure re-hospitalization, requirement of LVAD, listed for cardiac transplantation, unplanned acute HF visits requiring i.v. diuretics, additional heart failure drug or increase in >50% of the diuretic dose. Change from baseline at Weeks 1 and 2 in NT-proBNP Incidence of re-hospitalization or unplanned heart failure visits Re-hospitalization through Day 30 Need for advanced heart failure therapies (including but not limited to i.v. inotropes, LVAD, transplantation) Patient centered outcomes including the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Patient Global Assessment (PGA) at 4 weeks and 8 weeks post randomization. Change in biomarkers related to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury, and renal function, including estimated glomerular filtration rate (eGFR). Change in NT-proBNP in the enalapril arm during the 4 week open label

	period Medical resource utilization Incidence of worsening renal function during 8 weeks of treatment, defined as an increase in serum creatinine of ≥ 0.5 mg/dl from the values measured at baseline
Safety assessments	Change from baseline in serum creatinine of ≥0.5mg/dl with at least a 25% decrease in eGFR Incidence of symptomatic hypotension Incidence of hyperkalemia (serum potassium ≥5.5 mEq/l) Incidence of angioedema In addition, safety will be assessed through physical exam, vital signs, laboratory evaluations, other adverse events and serious adverse events. The Data Monitoring Committee (DMC) will monitor safety.
Data analysis	The primary hypothesis to be tested is that the ratio of the geometric means of NT-Pro BNP (average of Weeks 4 and 8/baseline) for the sacubitril/valsartan tablets and enalapril groups are equal (H0) versus the ratio of the geometric means of NT-Pro BNP are not equal (Ha). For NT-proBNP, the time-averaged proportional change from baseline in a logarithmic scale will be analyzed using an analysis of covariance (ANCOVA) model using data from Weeks 4 and 8 with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. The estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0. For NT-proBNP at Week 8, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. The estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0. Week 4 will be used if the Week 8 value is missing. For worsening renal function, a logistic regression model with treatment and baseline value as covariates having fixed effects will be run. Incidences of symptomatic hypotension, hyperkalemia and angioedema will be calculated, along with relative risk of sacubitril/valsartan vs. enalapril and 95% confidence intervals of the relative risk. For biomarkers including BNP to NT-proBNP ratio, hs-Troponin, and urinary cGMP, the time-averaged proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model using the data from Weeks 4 and 8 with treatment as a fixed effect factors and the logarithmic baseline biomarker value as a covariate For each of Weeks 4 and 8 the estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0. For BNP to NT-proBNP ratio and urinary cGMP at Weeks 1 and 2, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the

	logarithmic baseline biomarker value as a covariate, using observed data. For each of Weeks 1 and 2 the estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0. Analyses of the secondary variables will be based on the full analysis set. The assessment of safety will be based primarily on the frequency of adverse events, SAEs, and laboratory abnormalities. Safety analyses will be performed based on the Safety Set. There will be no inferential analyses of the safety data. Assuming a significance level of 0.05 and 85% power, a sample size of 882 patients would be needed to detect an 18% reduction in the geometric mean of the time-averaged proportional change from baseline (average of Weeks 4 and 8) in NT-proBNP for the sacubitril/valsartan treatment group assuming a value of 0.95 for the enalapril group, a common standard deviation of 0.85 and a 25% rate of missing/non-evaluable samples.

1 Introduction

1.1 Background

Heart failure is a major public health issue. More than 5 million Americans have heart failure (HF) and treatment costs for HF are approximately $31 billion annually (Go et al 2014). Outcomes for patients after a hospitalization for HF remain disappointingly poor. The 1-year mortality rate after a HF hospitalization is 20-30%, and this number has been relatively unchanged over the past decade (Chen et al 2011, Loehr et al 2008).

The current state of treatments for patients hospitalized with acute heart failure (AHF) is focused around maintaining previously established guideline directed medical therapy, optimizing volume status, and initiating beta-blockers if indicated (Yancy et al 2013, Gattis et al 2004). Unfortunately, recent clinical trials employing a variety of additional in-hospital interventions have failed to improve post-discharge outcomes (Binanany et al 2005, Konstam et al 2007, Massie et al 2010, O'Connor et al 2011). Thus, therapeutic options to improve post-discharge survival free of recurrent HF hospitalizations for patients hospitalized for AHF are limited.

In addition, while intravenous diuretics are nearly universally required for symptom relief during a HF hospitalization (Gheorghiade et al 2005), they activate the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system and may provoke renal dysfunction (Felker et al 2012). Activation of the RAAS plays a fundamental role in the pathophysiology of HF (Braunwald 2013, Givertz 2001), and although therapies to block adverse neurohormonal activation are well established and improve clinical outcomes in chronic HF with reduced ejection fraction (Yancy et al 2013, McMurray et al 2012), they have not been extensively tested among patients hospitalized with AHF. Further reducing RAAS activation during the period following a HF hospitalization may hold promise to change the trajectory of poor post-discharge outcomes for patients with HF.

Volume expansion and congestion during AHF leads to the synthesis and release of counter-regulatory natriuretic peptides from the myocardium: A-type natriuretic peptide (ANP) responding predominantly to atrial distention and B-type natriuretic peptide (BNP) to ventricular wall stress. The precursor molecule of BNP is a propeptide (proBNP108) that when cleaved, results in the generation of the biologically active BNP and the release in the circulation of a biologically inert aminoterminal fragment called N-terminal prohormone of Brain Natriuretic Peptide (NT-proBNP). This fragment is a largely stable peptide that can be measured in serum. Both BNP and NT-proBNP are useful to aid the diagnosis or exclusion of HF (Yancy et al 2013). The PROTECT study was a small study (N=151) that demonstrated that NT-proBNP guided therapy was superior to standard of care in reducing total cardiovascular events, improved quality of life and impact on cardiac remodeling in patients with chronic reduced ejection fraction (Januzzi 2011). A larger on-going study is looking to evaluate whether treatment directed therapy based on NT-proBNP levels will provide benefit to patients compared to standard of care in patients with reduced ejection fraction (Felker 2014).

Patients developing an AHF episode are known to have markedly elevated levels of BNP and NT-proBNP, which are reduced following adequate treatment and normalization of their cardiac decompensation. In the RELAX AHF trial, it was shown that patients that have a higher NT-proBNP level during an AHF hospitalization have a worse prognosis (Metra et al. 2013). Therefore, it is important to evaluate therapeutic strategies that can lead to superior reductions in NT-proBNP in patients hospitalized due to an AHF episode.

Sacubitril/valsartan combination tablet is an orally available, first in class, combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin receptor blocker that targets complementary pathways, RAAS inhibition via an Angiotensin II receptor blockade and natriuretic peptide augmentation via neprilysin inhibition. This novel agent may also hold promise in modifying the poor outcomes currently observed after a hospitalization for AHF, especially in the initial high-risk post-hospitalization period.

Preliminary studies

Sacubitril/valsartan, which is known in prior trials as LCZ696, has been evaluated for safety and efficacy in patients with chronic heart failure. The PARAMOUNT study was a randomized, double-blind, active-controlled phase 2 trial of 308 patients with HF with preserved ejection fraction (Left ventricular ejection fraction (LVEF) ≥45%) (Solomon et al 2012). Patients enrolled in the study received sacubitril/valsartan tablets titrated to 97/103 mg twice daily or valsartan titrated to 160 mg twice daily. The primary end point of the study was change in NT-proBNP levels from baseline to 12 weeks. NT-proBNP levels were significantly reduced at 12 weeks in the sacubitril/valsartan group compared with the valsartan group (sacubitril/valsartan: baseline, 783 pg/mL [95% CI 670 to 914], 12 weeks 605 pg/mL [95% CI512-714]; valsartan: baseline, 862 pg/mL [95% CI 733-1012], 12 weeks 835 pg/mL [95% CI 710-981]; ratio: sacubitril/valsartan /valsartan, 0.77, 95% CI 0.64 to 0.92, p=0.005. The sacubitril/valsartan combination was well tolerated and had a similar adverse effect profile to valsartan. The PARAGON-HF trial is now enrolling 4300 similar patients with chronic HF with preserved ejection fraction (LVEF ≥ 45%) to test whether the favorable effect of sacubitril/valsartan combination tablet in reducing NT-proBNP seen in PARAMOUNT translates into a reduction in the composite end point of cardiovascular morbidity and total (first and recurrent) HF hospitalizations.

The PARADIGM-HF study was a large randomized, double-blind, active-controlled trial of 8442 patients with symptomatic, chronic HF with reduced ejection fraction (LVEF ≤ 40%) (McMurray et al 2013, McMurray et al 2014). Patients enrolled in the study started in a single blind sequential run-in phase with enalapril 10 mg twice daily and after a washout period of 36 hours, went on to sacubitril/valsartan combination tablet at 97/103 mg daily to assess for safety and tolerability. Those patients who completed the run-in phase were then randomized and received sacubitril/valsartan combination tablet titrated to 97/103 mg twice daily or enalapril 10 mg twice daily. The trial was stopped prematurely after a median follow-up of 27 months upon the recommendation of the data safety monitoring board due to compelling evidence in favor of sacubitril/valsartan. Patients receiving sacubitril/valsartan combination tablet, compared to enalapril, were noted to have reduced risk of the primary outcome of composite of death from cardiovascular causes or hospitalization for HF (HR0.80, 95% CI 0.73-0.87). The hazard ratio for all-cause mortality was 0.84 (95% CI, 0.76-0.93) and for

hospitalization for HF was 0.79 (95% CI 0.71-0.89) (McMurray et al 2014). In PARADIGM-HF, 8385 patients had a baseline NT-proBNP obtained. Results were consistent with the primary composite endpoint regardless of whether the NT-proBNP was less than or equal to the median values compared to higher than median values (USPI Entresto, figure 4). Additionally, a subset of patients had biomarkers obtained at baseline, visit 3 (end of enalapril run-in), visit 5 (end of sacubitril/valsartan combination tablet run-in), 4 weeks after randomization, and at 8 months after randomization. The ratio of NT-proBNP to baseline levels was 25% lower in the sacubitril/valsartan combination tablet group compared to the enalapril group at 4 weeks and 8 months post-randomization (both $p<0.0001$). Conversely, BNP levels were approximately 23% higher in the sacubitril/valsartan combination tablet group compared to the enalapril group at 4 weeks and 8 months post-randomization (both $p<0.0001$). These findings are consistent with NT-proBNP not being a substrate of neprilysin, whereas BNP is a substrate of neprilysin; levels of BNP reflect the action of the drug whereas NT-proBNP levels reflect the effect of the sacubitril/valsartan combination on the heart [PARADIGM-HF data on file, [Packer 2014]].

Table 1-1 Adverse reactions occurring at an incidence of >5% of patients in the double-blind period of PARADIGM-HF were as follows:

	Sacubitril/valsartan (N=4203) %	Enalapril (N=4220) %
Hypotension	18	12
Hyperkalemia	12	14
Cough	9	13
Dizziness	6	5
Renal failure/acute renal failure	5	5

Angioedema occurred at rate of 0.5% in the sacubitril/valsartan arm compared to 0.2% in the enalapril arm (ENTRESTO USPI).

The combination of sacubitril/valsartan was evaluated in a multicenter, randomized, double-blind, and parallel group design in heart failure patients with reduced ejection fraction to assess the safety and tolerability of two different titration regimens (NCT01922089). Patients were stratified on low RAAS inhibition (whether they were ACEi/ARB naïve or receiving ≤10 mg daily of enalapril or ≤ 160 mg daily of valsartan (or equivalent doses of other ACEi/ARBs)) or high RAAS inhibition stratum. This high RAAS inhibition stratum was defined as receiving > 10 mg daily of enalapril or > 160 mg daily of valsartan (or equivalent doses of other ACEi or ARBs). The patients underwent dosing with 50 mg BID during the open-label run-in period of 5 days, and then were randomized to titration of the target dose of 97/103 mg twice daily over 6 weeks (conservative up-titration) compared to three weeks (condensed up-titration). 540 patients entered the run-in period and 498 were randomized. The primary endpoint was the proportion of patients experiencing pre-specified adverse events (AEs) and pre-specified laboratory assessment outcomes. The results were presented at the European Society of Cardiology Heart Failure meeting in 2015. The combination of sacubitril/valsartan demonstrated an acceptable safety and tolerability profile regardless of the

up-titration regimen. After excluding non-adverse events discontinuations or death-related discontinuations, >76% of patients achieved and maintained the target dose of 97/103 twice daily for 12 weeks. Achievement of target dose was possible even in patients who required dose interruption or down-titration during the study period, and rates of AEs were generally lower than in the PARADIGM-HF trial. Hypotension occurred in 9.7% of the condensed regimen compared to 8.4% in the conservative regimen; renal dysfunction occurred in 7.3% of condensed compared to 7.6% in the conservative regimen, hyperkalemia occurred in 7.7% in the condensed regimen compared to 4.4% in the conservative regimen and angioedema occurred in 0.0% in the condensed regimen compared to 0.8% in the conservative regimen.

ENTRESTO™ (sacubitril/valsartan) received FDA approval on 07July2015. It is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA class II-IV) and reduced ejection fraction. It is usually administered in conjunction with other heart failure therapies in place of an ACE inhibitor or other ARB. The approved dosages are 24/26 mg, 49/51 mg, and 97/103 mg twice daily. During the prior clinical studies 24/26 mg, 49/51 mg, and 97/103 mg were referred to as 50 mg, 100 mg and 200 mg, respectively.

The present study will be the first study to examine sacubitril/valsartan combination tablet administration during ADHF and whether it can safely mitigate the adverse neuro-hormonal activation that persists and contributes to the unacceptably high adverse event rate currently observed in the first months after hospitalization for ADHF as determined by the effect on NT-proBNP in this patient population. Importantly, although it is likely that clinical events (i.e., death, hospitalizations, etc.) will occur in the patients randomized in the present study, there is not enough statistical power to assess the effect on these hard clinical outcomes and therefore this trial will not include differences in the rate of mortality or HF hospitalizations as part of the primary or secondary endpoints. These endpoints will only be analyzed for the purpose of safety evaluation.

1.2 Rationale for protocol amendment

Amendment 2 (05Oct2017)

On the basis of blinded review of the projected aggregated (enalapril and sacubitril/valsartan treatment groups combined) rate of missing samples for NTproBNP, this rate exceeds the initial trial assumption of 10%. The sample size has been increased to 882 patients in order to preserve the originally intended power.

Given interest in the effect of sacubitril/valsartan on NTproBNP after titration to dose level 3, a secondary endpoint has been added.

The exploratory endpoint of re-hospitalization through Day 30 is added due to the interest in decreasing hospital readmissions in view of the significant financial penalties that institutions can incur for these readmissions.

Amendment 1 (28Jul2016)

The protocol inclusion criteria have been modified to be more closely aligned with clinical practice in the United States where patients with acute decompensated heart failure are often rapidly stabilized and transitioned from intravenous to oral diuretic therapy so as to move efficiently to outpatient care, with close follow-up. The protocol has been modified to include patients who are at least 24 hours from hospital presentation versus 48 hours. This change was instituted to allow sites to randomize stabilized patients who otherwise might be discharged earlier than 48 hours. In addition, the window of eligibility, which had been set at 5 days, has been extended to 10 days to permit inclusion of patients who have longer hospitalizations (e.g. due to initial diagnostic uncertainty).

Because a substantial proportion of patients who are stabilized with medical therapy for acute decompensation heart failure are asymptomatic with a systolic blood pressure that remains predominantly within the range of 100 – 110 mm Hg, the inclusion criterion regarding systolic blood pressure has been lowered to ≥100 mmHg. The SBP stabilization period was also changed from 24 hours to 6 hours because a 6 hour window is considered an adequate period of time to establish stability.

1.3 Changes to protocol

Changes to specific sections in the protocol are shown in the track changes version of the protocol using the strike through font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and Health Authorities.

The changes described in this amendment require IRB/IEC approval prior to implementation. In addition, since the changes herein do affect the informed consent, sites will be required to update and submit for approval a revised informed consent that takes into account the changes.

1.4 Purpose

The purpose of this study is to assess the effect of in-hospital initiation of sacubitril/valsartan vs. enalapril on time averaged proportional change in NT-proBNP in patients who have been stabilized following hospitalization for acute decompensated heart failure (ADHF) and reduced ejection fraction (left ventricular ejection fraction (LVEF) ≤ 40%).

2 Study objectives

2.1 Primary objective(s)

The primary objective of this study is to assess the effect of in-hospital initiation of sacubitril/valsartan vs. enalapril on the time-averaged proportional change of NT-proBNP from baseline in patients who have been stabilized following hospitalization for ADHF and reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤ 40%). Weeks 4 and 8 will be included in the analysis (primary analysis time point).

2.2 Secondary objectives

To examine the effect of sacubitril/valsartan vs. enalapril on:

- The proportional change in NT-proBNP from baseline to Week 8
- Incidence of symptomatic hypotension during 8 weeks of treatment
- Incidence of hyperkalemia (Potassium >5.5 mEq/L) during 8 weeks of treatment
- Incidence of angioedema during 8 weeks of treatment
- Biomarkers: hs-Troponin (high sensitivity), urinary cGMP and BNP to NT-proBNP ratio at 4 and 8 weeks

2.3 Exploratory objectives

- To examine the effect of sacubitril/valsartan vs. enalapril on time to first occurrence of composite clinical endpoint that includes death, heart failure re-hospitalization, requirement of LVAD, listed for cardiac transplantation, unplanned acute HF visits requiring i.v. diuretics, additional heart failure drug or increase in >50% of the diuretic dose.
- To examine the effect of sacubitril/valsartan vs. enalapril on change from baseline at Weeks 1 and 2 in NT-proBNP
- To examine the effect of sacubitril/valsartan vs. enalapril on incidence of re-hospitalization, ED visit or unplanned outpatient clinic visits due to worsening HF symptoms
- To examine the effect of sacubitril/valsartan vs. enalapril on incidence of re-hospitalization through Day 30
- To examine the effect of sacubitril/valsartan vs. enalapril on the need for advanced heart failure therapies (including but not limited to i.v. inotropes, LVAD, transplantation)
- To examine the effect of sacubitril/valsartan vs. enalapril on patient centered outcomes including the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Patient Global Assessment (PGA) at 4 weeks and 8 weeks post randomization.
- To examine the effect of sacubitril/valsartan vs. enalapril on change in biomarkers related to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury, and renal function, including estimated glomerular filtration rate (eGFR).
- Change in NT-proBNP in the enalapril arm during the 4 week open label period
- To examine the effect of sacubitril/valsartan vs. enalapril on medical resource utilization
- To examine the effect of sacubitril/valsartan vs. enalapril on incidence of worsening renal function during 8 weeks of treatment, defined as an increase in serum creatinine of ≥0.5mg/dl

3 Investigational plan

3.1 Study design

This study will use a randomized, double-blind, double-dummy, active-controlled, parallel group design. Eligible patients hospitalized for ADHF will be randomized no earlier than 24 hours and up to ten days of presentation while still hospitalized.

At the time of randomization, patients will have been stabilized, defined for this study as:

- SBP ≥100mm Hg for the preceding 6 hours prior to randomization; no symptomatic hypotension
- No increase (intensification) in i.v. diuretic dose within last 6 hours prior to randomization
- No i.v. inotropic drugs for 24 hours prior to randomization
- No i.v. vasodilators including nitrates within last 6 hours prior to randomization

All patients will need to meet all other inclusion and none of the exclusion criteria.

In order to provide for a necessary 36 hour washout of prior ACEi treatment prior to receiving sacubitril/valsartan (known as LCZ696 in prior trials), the supplied blinded study drug for those allocated to sacubitril/valsartan will be placebo only until the 3rd dose. Because the study is blinded, ALL patients, regardless of randomization arm, need to remain in the hospital for six hours after they have received their 3rd dose of study medication. Please see Figure 3-2.

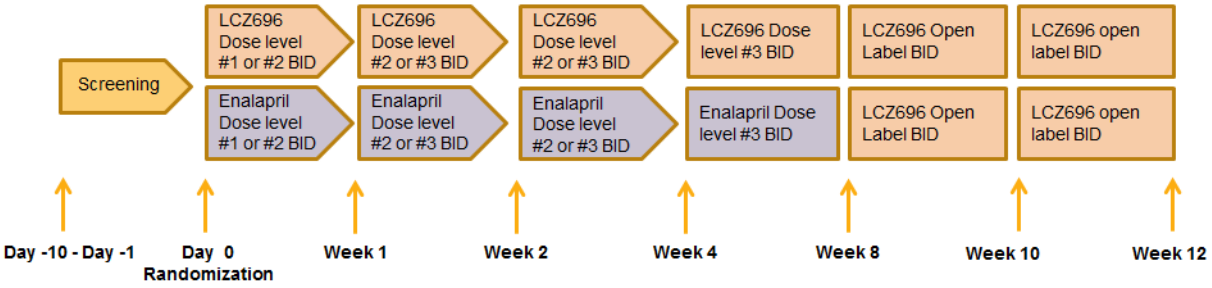
Patients will be randomized to sacubitril/valsartan or enalapril. Initial dose will be determined by the blood pressure at the time of randomization. Study treatment will be titrated to the Level #3 target doses of sacubitril/valsartan 97/103 mg bid and enalapril 10 mg bid. Titration will be based on blood pressure at the time of the visit. Dose adjustments will only be allowed if indicated per protocol defined safety and tolerability criteria and investigator judgement.

At the end of the 8-week treatment period ALL patients will need to have a 36 hour washout from study treatment prior to starting the open label extension to ensure that the blinding of the core study is maintained. To facilitate this washout, patients should take their final dose of study drug on the morning of their week 8 visit and then begin open label sacubitril/valsartan after 36 hours in the evening of week 8 visit + one day.

All patients will start open label treatment on sacubitril/valsartan at their final dosing level during double blind treatment. However, at an investigator's judgement, starting dose may be adjusted by one dose level up or down.

The intent of the open-label phase is to have the patients up-titrated to the desired dose level #3 (97/103 mg sacubitril/valsartan) based on clinical need and investigator judgement.

Figure 3-1 Study Design



3.2 Rationale of study design

Hospitalization for ADHF identifies patients at increased risk of death and re-hospitalization following discharge. This increased risk justifies intervention with novel treatment strategies initiated prior to hospital discharge to improve patient outcomes. Both the PARAMOUNT and PARADIGM-HF trials demonstrated reductions in the NT-proBNP compared to the comparator enalapril and valsartan, respectively, in both the chronic reduced ejection fraction and preserved ejection fraction heart failure patients. PARADIGM-HF demonstrated reductions in the NT-proBNP values seen at both 4 weeks and 8 months post randomization in the arm receiving the combination of the sacubitril/valsartan compared to the enalapril arm. In the current protocol, the primary endpoint of NT-proBNP will be evaluated at both the 4 and 8 week intervals to better assess the short-term benefit/risk ratio of sacubitril/valsartan compared to enalapril in patients who have been stabilized from an ADFH hospitalization in the setting of reduced ejection fraction.

The need for a 36-hour wash-out period is required per the FDA approved USPI label because there is a potential for increased risk for angioedema in patients who receive both an ACE inhibitor and the combination of sacubitril/valsartan. The requirement to stop the ARB is because there is an ARB contained within sacubitril/valsartan combination. The open-label period of 4 weeks provides the opportunity for every patient to receive sacubitril/valsartan and evaluate the change in NT-proBNP and other biomarkers in patients who had been previously receiving enalapril, while still being monitored for safety outcomes.

3.3 Rationale of dose/regimen and duration of treatment

Sacubitril/valsartan 97/103 mg BID was selected as the target dose and is the USPI approved target dose. This dose of sacubitril/valsartan delivers similar exposures of valsartan as Diovan 160 mg BID, the maximal approved Diovan dose for heart failure and the dose recommended in international guidelines for the treatment of heart failure. In addition, biomarker analysis (increase in ANP and cGMP) indicates that this sacubitril dose delivers approximately 90% of its maximal neutral endopeptidase (NEP) inhibition. Dosing with 97/103 mg twice daily is to ensure sustained NEP inhibition over 24 hours, which is thought to be critical for patients with heart failure. The PARADIGM-HF study had a median duration of 27 months with patients treated up to 4.3 years. In the PARADIGM-HF study, patients could have been hospitalized within the past year, but 37% never had a prior hospitalization. However, there is no data on

the short-term benefit/risk ratio of starting sacubitril/valsartan while in the hospital after a patient has been stabilized after an ADHF episode.

Additionally, the duration of the double-blind period also limits the patients' exposure to the current standard of care, enalapril, based on the superior results obtained with sacubitril/valsartan in the PARADIGM-HF trial. Sacubitril/valsartan (Entresto™) is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction and this is usually administered in conjunction with other heart failure therapies in place of an ACE inhibitor or other ARB.

3.4 Rationale for choice of comparator

Treatment with ACEI has been well established as the standard of care for RAAS blockade and is recommended by treatment guidelines as a 1A recommendation for all patients with CHF and reduced LVEF, unless ACEI-intolerant. As a well-studied ACEI in heart failure, enalapril has been selected as the comparator for this study with a target dose of 10 mg BID The 10 mg BID dose was the same target dosage studied in the SOLVD study and is the dose that was chosen in the PARADIGM-HF trial.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

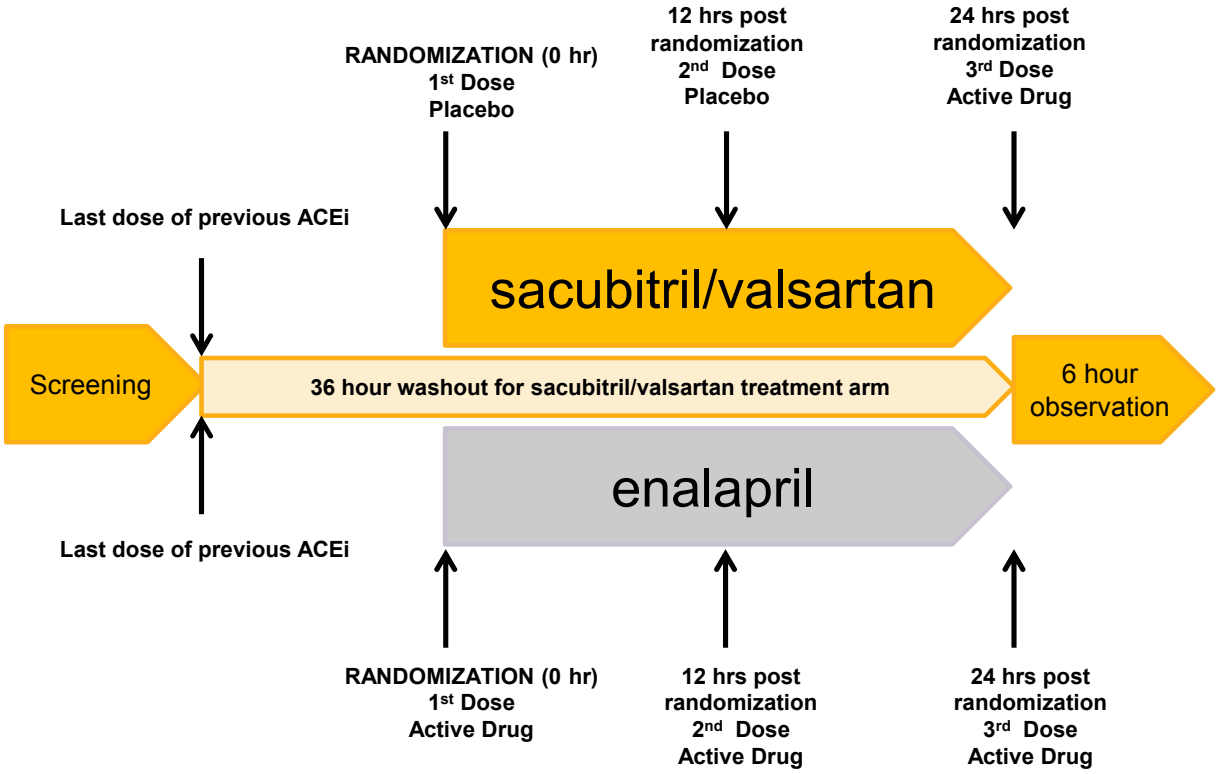
3.6 Risks and benefits

All patients randomized to the sacubitril/valsartan treatment arm will be given matching placebo doses of both sacubitril/valsartan and enalapril on the day of randomization to fulfill the requirement for a 36 hour washout prior to sacubitril/valsartan treatment initiation. The first active dose of sacubitril/valsartan treatment will be the third dose of study drug received after randomization. The 36 hour wash out period is required to minimize the interaction between an ACEi and sacubitril in potentiating the development of angioedema. Patients randomized to the enalapril treatment arm do not require a washout, but will receive sacubitril/valsartan matching placebo in addition to active enalapril starting on the day of randomization.

Since this is a double blind study, **all** study patients must remain in the hospital for at least 6 hours following the third dose of study medication even though the 36 hour wash out is only required for patients randomized to sacubitril/valsartan. This will allow for the first dose of active sacubitril/valsartan (third dose of study medication) to be administered in the hospital and will ensure that the blind is maintained.

All patients will be allowed to continue receiving the rest of their background cardiovascular (CV) medications. The risk to patients in this trial will be minimized by compliance with the eligibility criteria and close clinical monitoring. A Data Monitoring Committee (DMC) will also monitor the study for all safety considerations, since this population represents a patient population who are being initiated on study drug during the same hospitalization for admission for acute decompensated heart failure.

Figure 3-2 36 hour washout design



All patients will be allowed to continue receiving the rest of their background cardiovascular (CV) medications. The risk to patients in this trial will be minimized by compliance with the eligibility criteria and close clinical monitoring. A Data Monitoring Committee (DMC) will also monitor the study for all safety considerations, since this population represents a patient population who are being initiated on study drug during the same hospitalization for admission for acute decompensated heart failure.

4 Population

The study population will consist of male and female patients, ≥ 18 years of age, presenting to the hospital for acute decompensated heart failure. The goal is to randomize a total of approximately 882 patients to sacubitril/valsartan or enalapril in a 1:1 ratio in approximately 170 centers in the United States. At the time of randomization, patients will have been stabilized, defined for this study as:

- SBP ≥100mm Hg for the preceding 6 hours prior to randomization; no symptomatic hypotension
- No increase (intensification) in i.v. diuretic dose within last 6 hours prior to randomization
- No i.v. inotropic drugs for 24 hours prior to randomization
- No i.v. vasodilators including nitrates within last 6 hours prior to randomization;

All patients will need to meet all other inclusion and none of the exclusion criteria.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Possess the capacity to provide written informed consent which must be obtained before any assessment is performed.
2. Patients ≥ 18 years of age, male or female.
3. Currently hospitalized for ADHF. Patients with a diagnosis of acute heart failure had to have symptoms and signs of fluid overload (i.e. jugular venous distention, edema or rales on auscultation or pulmonary congestion on chest x-ray) at time of hospitalization.
4. Eligible patients will be randomized no earlier than 24 hours and up to ten days after presentation while still hospitalized as long as meet the following definition of stable status:
    - SBP ≥100mm Hg for the preceding 6 hours prior to randomization; no symptomatic hypotension
    - No increase (intensification) in i.v. diuretic dose within last 6 hours prior to randomization
    - No i.v. inotropic drugs for 24 hours prior to randomization
    - No i.v. vasodilators including nitrates within last 6 hours prior to randomization
5. LVEF ≤40% within the past 6 months (including current hospitalization) using echocardiography, multi gated acquisition scan (MUGA), CT scanning, MRI or ventricular angiography, provided no subsequent study documented an EF of >40%.
6. Elevated NT-proBNP ≥ 1600pg/mL OR BNP ≥400 pg/mL during current hospitalization.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Currently taking sacubitril/valsartan tablets or any use within the past 30 days.
2. Enrollment in any other clinical trial involving an investigational agent or investigational device.
3. History of hypersensitivity, known or suspected contraindications, or intolerance to any of the study drugs, including ACEIs, ARBs, or Sacubitril (NEP inhibitor).
4. Patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy.
5. Requirement of treatment with both ACE inhibitor and ARB.
6. eGFR < 30 ml/min/1.73 m2 as measured by the simplified Modification of Diet in Renal Disease (MDRD) formula at screening.
7. Serum potassium > 5.2 mEq/L at screening.

8. Acute coronary syndrome, stroke, transient ischemic attack; cardiac, carotid or other major CV surgery; percutaneous coronary intervention (PCI) or carotid angioplasty, within one month prior to Visit 1.
9. Primary cause of dyspnea due to non-cardiac, non-heart failure causes such as acute or chronic respiratory disorders.
10. Intended coronary or carotid artery revascularization within the 6 months after Visit 1.
11. Implantation of a cardiac resynchronization therapy device (CRTD) within the prior 3 months from Visit 1or intent to implant a CRTD.
12. History of heart transplant or patients who are on a transplant list or with left ventricular assistance device (LVAD).
13. Isolated right HF due to severe pulmonary disease.
14. Documented untreated ventricular arrhythmia with syncopal episodes within the 3 months prior to Visit 1.
15. Symptomatic bradycardia or second or third degree heart block without a pacemaker.
16. Presence of hemodynamically significant mitral, aortic or hypertrophic obstructive cardiomyopathy.
17. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past year with a life expectancy of less than 1 year.
18. Known hepatic impairment (as evidenced by total bilirubin > 3 mg/dL, or increased ammonia levels, if performed), or history of cirrhosis with evidence of portal hypertension such as varices.
19. 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 hCG laboratory test.
20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they are using two birth control methods. The two methods can be a double barrier method (if accepted by the local regulatory authority and ethics committee) or a barrier method plus a hormonal method.
    - Adequate barrier methods of contraception include: diaphragm, condom (by the partner), intrauterine device (copper or hormonal), sponge or spermicide. Hormonal contraceptives include any marketed contraceptive agent that includes an estrogen and/or a progesterone agent.
    - Reliable contraception should be maintained throughout the study and for 7 days after study drug discontinuation.
    - Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL and estradiol < 20 pg/mL or have had surgical bilateral oophorectomy (with or

without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational and control treatment

Table 5-1 Investigational and comparator treatment

All eligible patients will be randomized to receive either sacubitril/valsartan or enalapril. The following study treatment will be provided:

Treatment	Minimum dose	Maximum dose	Frequency	Admin. Route
sacubitril/valsartan	24/26 mg	97/103 mg	BID	oral
sacubitril/valsartan matching placebo				oral
Enalapril	2.5 mg	10 mg	BID	oral
Enalapril matching placebo				oral

Table 5-2 Treatment Dose Levels

Dose Level	sacubitril/valsartan	Enalapril
1	24/26 mg BID	2.5 mg BID
2	49/51 mg BID	5.0 mg BID
3	97/103 mg BID	10 mg BID

Both sacubitril/valsartan and enalapril and their matching placebos will be packaged and labeled by the sponsor in accordance with the US Code of Federal Regulations governing handling of investigational treatments, and will be dispensed by the study physician.

Matching placebo will also be needed for sacubitril/valsartan combination tablet and matching placebo for the enalapril for the first day of treatment to allow for the 36-hour washout required for patients randomized to the sacubitril/valsartan treatment arm.

Each participating hospital will be provided with a central supply kit containing dose levels 1 and 2 and their matching placebos. Bottles will be numbered and assigned via an Interactive Web Response System (IWRS). On the day of randomization (visit 2), the IWRS system will assign both a hospital kit and a patient kit.

Treatment for the day of randomization will be provided to the patients from the hospital kit.

Treatment for the second day of dosing onward will be provided from the patient kit which patients will take home upon discharge.

Patients not tolerating the target dose of sacubitril/valsartan 97/103 mg bid or enalapril 10 mg bid will be titrated down to the lower dose level (including active medication and matching placebos), at the investigator's discretion, based on the defined safety and tolerability criteria.

Sacubitril/valsartan dose or enalapril dose levels may be increased to the targeted desired dose level #3 of 97/103mg twice daily or enalapril 10 BID on an every 2 week basis or earlier if based on clinical need and investigator judgement.

Patients not tolerating the target dose level #3 of sacubitril/valsartan 200 mg BID or enalapril 10 mg BID will be titrated down to the lower dose level (including active medication and matching placebos), at the investigator's discretion, based on the defined safety and tolerability criteria.

This study is designed as a double-blind, double-dummy trial to ensure the blinding during the entire course of the study. To maintain the blinding, patients will be required to take their assigned active treatment tablet along with placebo matching the opposite treatment twice daily.

All study sites will be provided with a Treatment Manual describing the treatment packaging and treatment instructions.

5.1.2 Additional study treatment

Treatment	# of patients	Minimum dose	Maximum dose	Frequency	Admin. Route
Open-label sacubitril/valsartan	882	Dose level #1 (24/26 mg)	Dose level #3 (97/103 mg)	BID	oral

Open-label sacubitril/valsartan will be packaged and labeled by the sponsor in accordance with the US Code of Federal Regulation governing handling of investigational treatments, and will be dispensed by the study physician. Open-label treatment will be provided for a 4-week follow up.

All patients will start open label treatment on sacubitril/valsartan at their final dosing level during double blind treatment. However, at an investigator's judgement, starting dose may be adjusted by one dose level up or down.

The intent of the open-label phase is to have the patients up-titrated to the desired dose level #3 (200 mg sacubitril/valsartan) based on clinical need and investigator judgement.

5.2 Treatment arms

Patients will be randomized in a 1:1 ratio to either sacubitril/valsartan or enalapril.

5.3 Treatment assignment, randomization

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A randomization list will be produced by or under the responsibility of Novartis Drug Supply

Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio.

Eligible patients will be randomized no earlier than 24 hours after presentation at the hospital and no later than within ten days of admission, while still hospitalized, via IWRS to one of the treatment arms. The investigator or his/her delegate will contact the IWRS after confirming that the patient fulfills all the study entry criteria. The IWRS will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify which bottle from the centralized hospital supply the patient will be dosed for the first day and a unique medication number for the first package of investigational treatment to be dispensed to the patient. The initial dose will be determined by the patient's blood pressure at the time of the call to the IWRS.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IWRS provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Initial dose at randomization will be determined by systolic blood pressure (SBP). See Table 5-3.

Dose adjustments to lower dose levels may be made at any time at both scheduled and unscheduled visit only if clinically indicated for blood pressure control/tolerability reasons. Dose adjustments to increase dose levels may be made at any time at both scheduled and unscheduled visits based on clinical need or investigator judgement.

Subsequent supplies of study drug will be assigned in the following manner. The investigator or his or her delegate will call the IWRS and provide the patient's number. The IWRS will ask the caller whether there is a change in the dose level of the study drug. If the caller indicates that there is no change in the dose level, the IWRS will provide the unique medication numbers of the study drug with the same dose level that was dispensed at the previous dispensing. If the caller indicates that the dose level has changed since the last dispensing, the IWRS will ask the caller which dose level should be dispensed. The caller will enter the dose level to dispense or whether no study drug should be dispensed (in case of study drug withdrawal). If applicable, the IWRS will provide the unique medication numbers for the study drug supplies that should be dispensed at the new dose level.

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the exception of the IWRS provider generating the randomization code, members of the DMC and the independent biostatistician assigned to the DMC. (2) The identity of the treatments will be

concealed by the use of investigational treatments that are identical in packaging, labeling, and schedule of administration, appearance, taste and odor.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.11) and at the conclusion of the study.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed by the 4-digit site number (e.g., 0501, 0502 etc.) assigned by Novartis and a 5-digist sequential number assigned by the investigator (e.g., 00001, 00002, etc.). Hence a 9-digit study patient identification number, e.g., 050100001. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IWRS and provide the assigned patient study identification number along with the requested identifying information for the patient to register them into the IWRS. The site will enter this number on the electronic case report form (eCRF) in the electronic data capture system (EDC).

5.5.2 Dispensing the investigational and comparator treatment

Each study site will be supplied by Novartis with investigational and comparator treatment in packaging of identical appearance. Each hospital will be provided a kit for Day 1 of treatment, from which all patients will be provided their first 2 doses. This kit will include dose levels 1 and 2 and their matching placebos. Since the first day of treatment is placebo only for patients randomized to the sacubitril/valsartan arm in order to facilitate the required 36-hour washout, the bottles assigned for the sacubitril/valsartan treatment arm will all contain placebos. Patients will receive their first 2 doses from the centralized hospital supply. The third dose of treatment will be provided from the patient supply that will be sent home with the patient upon discharge.

The investigational and control treatment packaging will have a 2-part label. A unique randomization number is printed on each part of this label which corresponds to one of the 2 treatment arms and a dose level. Investigator staff will identify the investigational treatment package(s) to dispense to the patient by contacting the IWRS and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational and comparator treatment

Investigational and comparator treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all investigational and comparator treatment should be stored according to the instructions specified on the labels. Clinical

supplies are to be dispensed only in accordance with the protocol. Medication labels will include storage conditions but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of investigational and comparator treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused investigational or comparator treatment and packaging at the end of the study or at the time of discontinuation of treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational and comparator treatment, packaging, drug labels, and a copy of the completed drug accountability log according to the instructions provided by Novartis or its agents.

5.5.3.2 Handling of other study treatment

Each study site will be supplied by Novartis with open-label sacubitril/valsartan for the 4-week open-label follow up period. The IWRS will need to be called to receive drug shipments prior to dispensing.

The open-label sacubitril/valsartan packaging will have a 2-part label. Investigator staff will identify the treatment package(s) to dispense to the patient by contacting the IWRS and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

Open-label sacubitril/valsartan treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all open-label sacubitril/valsartan treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Medication labels will include storage conditions but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of open-label sacubitril/valsartan treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site visits or remotely and at the completion of the study. Patients will be asked to return all unused open-label treatment and packaging at the end of the study or at the time of discontinuation of treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused open-label treatment, packaging, drug labels, and a copy of the completed drug accountability log according to the instructions provided by Novartis or its agents.

5.5.4 Instructions for prescribing and taking study treatment

All medication for the duration of the study will be provided by Novartis. Eligible patients will be randomized via IWRS to either sacubitril/valsartan or enalapril. Patients randomized to the sacubitril/valsartan arm will receive sacubitril/valsartan matching placebo for the first day of treatment to fulfill the required 36-hour wash-out period (in addition to enalapril matching placebo). Patients randomized to enalapril will not require a washout and will receive active treatment on the first day of treatment, in addition to sacubitril/valsartan matching placebo. The first day of dosing will be provided from a centralized hospital supply containing dose levels 1 and 2 and matching placebos.

From the second day of treatment (third dose), patients will be provided with sufficient medication to last until the next scheduled visit. In order to adequately blind the study, patients will be required to take a total of two tablets (one tablet from the sacubitril/valsartan / sacubitril/valsartan matching placebo pack and one tablet from the enalapril/enalapril matching placebo pack) twice a day for the duration of the study.

Initial dose at randomization will be determined by systolic blood pressure (SBP).

- All patients with a systolic blood pressure (SBP) of ≥100 to ≤120 mm Hg will start at Dose level #1 (2.5 mg Enalapril or 24/26 mg sacubitril/valsartan, BID).
- Patients with a SBP ≥ 120 mm Hg will start at dose level #2 (5 mg enalapril or 49/51 mg sacubitril/valsartan, BID).
- Patients will be titrated to the next dose level at Weeks 1 and 2 (Visits 3 and 4) with the goal of reaching the target dose for dose level #3 (10 mg enalapril or 97/103 mg sacubitril/valsartan, BID) by week 2 (Visit 4).
- Patients should be titrated to the next dose level at week 1 only if their SBP is >110 mm Hg and at week 2 if their SBP is > 100 mm Hg.

Dose titration will proceed according to the following table:

Table 5-3 Dose titration schedule based on SBP

Visit	Previous dose level	Systolic Blood pressure mm Hg*	Start/remain/titrate to: Dose level #
Baseline (Visit 2)	N/A	≥ 100	1
	N/A	≥120	2
1 Week (Visit 3)**	1	<110	1
	1	≥110	2
	2	<110	2
	2	≥110	3
2 weeks (Visit 4)	1	<100	1
	1	≥100	2
	2	<100	2
	2	≥100	3

Visit	Previous dose level	Systolic Blood pressure mm Hg*	Start/remain/titrate to: Dose level #
4 Weeks (Visit 5)	1	<100	1
	1	≥100	2
	2	<100	2
	2	≥100	3
6 Weeks (Visit 6)	1	<100	1
	1	≥100	2
	2	<100	2
	2	≥100	3

**Up titration may be done prior to the week 1 visit for patients who were started at dose level 1 who were previously on high dose RAS blockade (>10 mg enalapril total daily dose or > 160 mg valsartan total daily dose or equivalent doses of other ACEi or ARB).

Dose adjustments to lower dose levels may be made at any time at both scheduled and unscheduled visits only if indicated for blood pressure control/tolerability reasons.

Study medication should be taken with a glass of water with or without food. If the patient misses taking any study drug dose, he/she should take it as soon as possible, unless it is almost time for the following scheduled dose. In this case, the patient should skip the missed dose and return back to his/her regular study drug administration schedule.

All dosage prescribed and dispensed to the patient and all dose changes during the study must be recorded in the IWRS and on the Dosage Administration Record eCRF.

The investigator should promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable to take the study treatment as prescribed for any reason.

All patients that complete 8 weeks of treatment will proceed with a 4-week follow up on open-label sacubitril/valsartan. All patients will have the wash out in order to maintain the blinding of the core study. To facilitate this washout, patients should take their final dose of study drug on the morning of their week 8 visit and then begin open label sacubitril/valsartan after 36 hours in the evening of week 8 visit + one day. All patients will start open label treatment on sacubitril/valsartan at their final dosing level during double blind treatment. However, at an investigator's judgement, starting dose may be adjusted by one dose level up or down.

The intent of the open-label phase is to have the patients up-titrated to the desired dose level #3 (200 mg sacubitril/valsartan) based on clinical need and investigator judgement.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Every attempt should be made to maintain patients on the target study drug dose level for as long a duration as possible throughout the study. If, however, in the opinion of the investigator, a patient is unable to tolerate the protocol-specified target dose, the investigator should consider whether dose adjustments of concomitant medications may rectify the situation before reducing the dose of study treatment. If adjustment of the concomitant medications is not possible or does not alleviate the side effects of concern, the investigator may down-titrate the dose of the study drug to the previous dose level. If needed, the study drug may be stopped completely, but the patient should continue to attend the study visits and be followed until the completion of the study. Patients may restart their current dose of study drug following an interruption of treatment, based on investigator judgment.

Study drug dose level adjustments should be mainly based on overall safety and tolerability with special focus on hyperkalemia, symptomatic hypotension and clinically significant decrease in eGFR/increase in serum creatinine (defined as a serum creatinine of ≥0.5mg/dl with at least a 25% decrease in eGFR).

Adjustment of study drug dose level

If necessary, the patient may be down-titrated to the next lower dose level. The patient may continue receiving the lower dose level for a recommended period of 1 to a maximum of 4 weeks. Re-challenge to titrate back up to the target dose level should be attempted at 2 weeks. It must be noted that the desired dose of study medication is the highest dose (dose level #3), but patient tolerability and safety must be taken into account.

If the tolerability issues are not alleviated despite down-titration by one dose level, the investigator may lower the study drug dose further to the next lower level for 1 to a maximum of 4 weeks, up to temporary withdrawal of the study drug. Again, once stable, the patient should be re-challenged with up-titration to the next higher dose level in an attempt to bring back the patient gradually to the target study drug dose level (dose level #3). The investigator may choose the next dose level for down- or up-titration according to his or her clinical judgment. The IWRS should be contacted to register any changes in the patient's study drug dose level, including in cases of temporary and permanent withdrawal of the study drug, and to obtain the medication numbers of the study drug supplies required for the new study drug dose level.

In some instances, according to the safety and tolerability criteria and the investigator's judgment, dose level 1 or 2 could be maintained if he/she considers that the patient's condition would not allow any further up-titration to the target dose of study medication (dose level #3). In this case it would be acceptable to maintain the patient at dose level #1 or level #2, whichever is the higher and tolerated dose level by the patient, but reasons for not getting to dose level #3 need to be clearly described in the eCRF.

Study drug restart after temporary treatment interruption

Study drug should be reintroduced in those who temporarily discontinue it as soon as medically justified in the opinion of the investigator.

Once the investigator considers the patient's condition appropriate for receiving the study drug, the investigator should re-start the patient on the study drug at the most appropriate and allowable dose level per his/her medical judgment. If tolerated, the patient should be up-titrated up to dose level 3 every 1 to 4 weeks, as per the investigator's judgment. Patients re-started on the study drug will retain their original randomization and study identification numbers. Should the patient not tolerate the re-start study drug dose level, he/she may be down-titrated again (if appropriate) or discontinue the study medication.

Study visits should occur as close as possible to the pre-defined visit schedule. The timeframe between the regular visits should be maintained as scheduled, irrespective of the number of unscheduled visits that may be performed in between, according to the visit and time schedule described in Table 6-1.

Any changes in the study drug dose level, including temporary/permanent withdrawal or re-start of the study drug, must be recorded on the Dosage Administration Record eCRF and registered in the IWRS.

In case of pregnancy discovered during the study, the patient should be instructed to stop taking the study drug immediately.

5.5.6 Rescue medication

Guidance on handling hyperkalemia, hypotension, and renal dysfunction are provided to investigators in the appendices. Patients may receive open-label (non-study medications) ACEIs and/or ARBs during the study **ONLY** if the study medication has been discontinued either temporarily or permanently. A 36 hour wash-out period is required when switching from or to an ACE inhibitor. Use of rescue medication must be recorded in the eCRF.

5.5.7 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after informed consent must be recorded on the Concomitant medications or Surgeries and Medical Procedures eCRF.

ACEIs and ARBs:

Patients' pre-study ACEIs/ARBs will be replaced with the study medication.

The concomitant use of open-label ACEIs or ARBs is strictly prohibited while the patient is receiving study medication. If the investigator believes that addition of an ACEI or ARB is necessary, then study drug must be discontinued. Study medication should be stopped 36 hours prior to addition of open-label ACEI. If not already treated with aldosterone antagonist, consideration should be given to adding this therapy rather than an ACEI or and ARB, while monitoring renal function.

Other heart failure and cardiovascular medication

If a patient's condition warrants any change in concomitant heart failure or cardiovascular medications, changes may be made at the investigator's discretion.

Oral diuretics may be used and may be adjusted throughout the study duration at the discretion of the investigator.

Medications known to raise potassium levels

Potassium sparing diuretics, potassium supplements, aldosterone antagonists, and any other medications known to raise potassium levels should be used with caution while the patient is receiving study medication due to the increased possibility of occurrence of hyperkalemia. Potassium levels should be monitored regularly especially in those who are receiving these medications.

Concomitant administration of renin inhibitors, such as aliskiren, is prohibited.

Phosphodiesterase-5 (PDE-5) inhibitors

PDE-5 inhibitors should be used with caution while the patient is receiving study medication due to the increased possibility of occurrence of hypotension.

Nesiritide and intravenous nitrates

The concomitant admission of sacubitril/valsartan with nesiritide and intravenous nitrates has not been studied. Concomitant use of nesiritide will not be permitted during the study.

Other medications

Bile acid sequestering agents such as cholestyramine or colestipol are prohibited to avoid interference with study drug absorption.

5.5.8 Discontinuation of study drug

Patients may voluntarily discontinue the study drug for any reason at any time.

Study drug must be discontinued under the following circumstances:

- Withdrawal of consent
- Pregnancy
- Use of prohibited concomitant medication
- Any protocol deviation that constitutes a risk to the patient
- Investigator believes that continuation of study drug may be detrimental to the patient's well-being

Study medication may be discontinued at the investigator's discretion if any of the following occur:

- Any severe suspected drug related AE

- Suspected occurrence of angioedema. A patient with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator to determine if it constitutes a reason for discontinuation of study medication.
- Depending on the serum potassium, blood pressure, or eGFR, patients may need to have their study drug dose or the dose of another concomitant medication reduced or discontinued; or, if appropriate, have potentially contributing agents adjusted. Refer to appendices for treatment guidelines for hyperkalemia, hypotension or renal dysfunction, respectively.

In the case of study drug discontinuation, patients should remain in the trial and attend follow-up visits. If the patient refuses, he/she should be contacted by telephone to obtain follow-up health status information in place of protocol-specified visits unless the patient expressly refuses such contacts.

The investigator must notify the IWRS of any study drug discontinuation and record it on the drug administration eCRF.

5.5.9 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a patient does not want to participate in the study anymore and does not want any further visits or assessments and does not want any further study related contacts and does not allow analysis of already obtained biologic material. If a patient withdraws consent, the sites must request permission from patients who withdraw consent for a final telephone contact for patient health status.

At the time a patient withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information. Study drug must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

5.5.10 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

5.5.11 Emergency breaking of assigned treatment code

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IWRS. When the investigator contacts the system to break a treatment code for a patient, he/she must

provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Clinical Trial Lead (CTL) that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place in case of an emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, study treatment name if available, patient number, and instructions for contacting Novartis Country Pharma Organization CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case an emergency treatment code break is required at a time when the investigator and backup are unavailable.

5.5.12 Study completion and post-study treatment

At the end of study visit, patients will be asked to return all remaining study drug. The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

When the patient has completed all scheduled study assessments, the investigator must call the IWRS to record the patient completion in the IWRS.

5.5.13 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

All assessments are listed in Table 6-1. Assessments that are to be reported in the clinical database are marked with an 'x'. Assessments that will only be reported in the source documentation are marked with a 's'. Patients should be seen for all visits on the designated day or as close to it as possible.

The screening period may begin following an admission to hospital for ADHF. Clinical assessments performed during a patient's hospitalization, prior to signing of informed consent, may be used for Visit 1/Screening. Eligible patients may be randomized once it is confirmed that they meet all inclusion criteria and none of the exclusion criteria.

Patients may be contacted for safety evaluations for 30 days after the last dose of the 4-week open-label follow-up period. Documentation of attempts to contact the patient should be recorded in the source documentation.

Unscheduled visits for safety/medication evaluation/unscheduled assessments are permitted at any time during the study.

Table 6-1 Assessment schedule

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Phase	**screening**	**Treatment**						**4 week f/u-titration**	**4 week f/u**
Week			**1**	**2**	**4**	**6**	**8**	**10**	**~12**
Day	**-10 to -1**	**1**	**7**	**14**	**28**	**42**	**56**	**70**	**84**
Informed consent	s								
Inclusion/exclusion criteria	x	x							
Demography/ medical history	x								
Heart failure and CV disease history	x								
ECG	x								
Physical exam	s			s (cardiac related only)			s		s
Height	x	x							
Weight	x	x	x	x	x	x	x	x	x
Vital signs	x	x	x	x	x	x	x	x	x
Waist/hip circumference	x								
HF signs and symptoms and NYHA	x	x	x	x	x	x	x	x	x
HF and CV medications	x	x[8]	x	x	x	x	x		x
Conmeds	x	x	x	x	x	x	x	x	x
AE/SAE	x	x	x	x	x	x	x	x	x
Pregnancy test	x	x[4]			x		x		x
Plasma BNP or NT-proBNP	x[9]	x	x	x	x		x		x
Plasma/serum biomarkers[1]		x	x	x	x		x		x
Spot urine biomarkers[2]		x	x	x	x		x		x
eGFR	x	x	x	x	x		x	x[6]	x
Urinalysis		x							
Chemistry	x	x	x	x	x		x	x[6]	x

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Phase	**screening**	**Treatment**						**4 week f/u-titration**	**4 week f/u**
Week			**1**	**2**	**4**	**6**	**8**	**10**	**~12**
Day	**-10 to -1**	**1**	**7**	**14**	**28**	**42**	**56**	**70**	**84**
Hematology	x	x					x		
Hemoglobin A1C		x							
IWRS call	x	x	x	x	x	x	x	x	x
Randomization		x							
Dispense treatment		x	x	x	x	x	x[5]	x	
Drug accountability			x	x	x	x	x	x	x
Angioedema assessment	x	x	x	x	x	x	x	x	x
PRO (KCCQ, PGA)		x[7]			x		x		x
Medical Resource utilization									x
Study completion – randomized treatment							x		
Study completion – open label period									x
Post study completion follow up[3]									s[3]

[1] includes cardiac, renal, and drug mechanism of action biomarkers

[2] include urinary markers such as cGMP.

[3]Health status phone call 4 weeks after study completion (16 weeks).

[4]Urine pregnancy test will be done at Visit 2 at the local laboratory.

[5]At week 8, patients will receive open label sacubitril/valsartan and be instructed to not take study medication on the day of the final visit in order to fulfill the washout requirement

[6]Limited chemistry panel. eGFR will be calculated from creatinine concentration.

[7]Patient Global Assessment is not completed at Visit 2. Patients should be asked to remember how he/she feels at Visit 2. Throughout the study the patient will be asked to rate how he/she presently feels compared to how he/she felt at the randomization visit (Visit 2).

[8]CV medications will be recorded at time of hospital discharge.

[9] BNP or NT-proBNP will be assessed at Visit 1 via local laboratory. NT-proBNP will be assessed via central laboratory for Visits 2-9.

6.1 Information to be collected on screening failures

All patients who have signed informed consent but are not randomized will have the study completion page for the screening visit, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race, ethnicity and source of patient referral. Relevant medical history/current medical condition data includes data collected up to the point in which informed consent is signed. Where possible, diagnoses and not symptoms, will be recorded. HF medications will be recorded in eCRFs separately from other medications. Likewise, detailed HF history and other relevant CV medical history will be recorded on eCRFs separately from other medical history.

6.3 Treatment exposure and compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the care giver. This information should be captured in the source document at each visit. Patient compliance should be at least 80% during the double-blind treatment period. The investigator and/or study personnel will counsel the patient if compliance is below 80%. Study drug accountability will also be determined by the site monitor while performing routine site visits and at the completion of the study.

Duration of double-blind study drug exposure will be calculated based upon the start and stop dates recorded in the eCRF.

6.4 Efficacy

The efficacy end points are:

Primary:

Time-averaged proportional change from baseline in NT-proBNP. Weeks 4 and 8 will be included in the analysis.

Secondary:

- The proportional change in NT-proBNP from baseline to Week 8
- Biomarkers: hs-Troponin, urinary cGMP and BNP to NT-proBNP ratio

Exploratory:

- Time to first occurrence of composite clinical endpoint that includes death, heart failure re-hospitalization, requirement of LVAD, listed for cardiac transplantation, unplanned acute HF visits requiring i.v. diuretics, additional heart failure drug or increase in >50% of the diuretic dose.
- Change in NT-proBNP at Weeks 1 and 2
- Incidence of re-hospitalization or unplanned heart failure visits
- Re-hospitalization through Day 30
- Need for advanced heart failure therapies (including but not limited to i.v. inotropes, LVAD, transplantation)
- Patient centered outcomes including the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Patient Global Assessment (PGA) at 4 weeks and 8 weeks post randomization.

- Change in biomarkers related to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury, and renal function, including estimated glomerular filtration rate.
- Change in NT-proBNP in the enalapril arm during the 4 week open label period
- Medical resource utilization
- Incidence of worsening renal function during 8 weeks of treatment, defined as an increase in serum creatinine of ≥0.5mg/dl from the values measured at baseline

6.4.1 Heart failure signs and symptoms

Signs and symptoms of heart failure will be reviewed by the investigator at all visits during the study. The signs and symptoms evaluation may include, but are not limited to, paroxysmal nocturnal dyspnea, fatigue, edema, dyspnea at rest, dyspnea upon effort, orthopnea, rales, jugular venous distention, presence of a third heart sound. NYHA classification will be assessed and scored at each visit.

6.4.2 Estimated glomerular filtration rate (eGFR)

The eGFR to determine eligibility of the patient for screening into the trial will be calculated at Visit 1 from the serum creatinine concentration measured at the local laboratory. The eGFR will be further calculated from creatinine concentration measured at Visits 2, 3, 4, 5, and 7 (randomization, weeks 1, 2, 4, 8/end of study), visit 8 and 9, titration visit (Week 10) and end of extension (Week 12) at the central laboratory. The eGFR calculation will be based on the Abbreviated Modification of Diet in Renal Disease (MDRD) study equation [Levey, et al 2007].

6.4.3 Biomarkers

BNP or NT-proBNP will be obtained in all patients by using the local laboratory at Visit 1 to determine eligibility. NT-proBNP will be obtained in all patients using the central laboratory at Visits 2, 3, 4, 5 and 7 (randomization, weeks 1, 2, 4, and 8), and at the end of the open label extension, Visit 9 (Week 12).

In addition, biomarker measurements will be obtained from serum and plasma samples at Visits 2, 3, 4, 5, 7 and 9 (randomization, 2, 4, 8 and 12 weeks), to determine effects of treatment on biomarkers of CV, CHF or renal risk. Spot urine will be collected at Visits 2, 3, 4, 5, 7 and 9 (randomization, weeks 1, 2, 4, 8 and 12) to measure urinary cGMP.

The selected biomarkers to be studied will be those believed to be relevant to the pathophysiology of the disease processes of heart failure and renal dysfunction. Biomarkers studies may include, but are not limited to those accessing cardiac and renal benefit or biomarkers related to the study drug mechanism of action such as:

- Neurohormones BNP and NT-proBNP
- hs-Troponin (will not be measured at Week 2)
- Cystatin c
- ST2

- eGFR (MDRD calculation)
- urinary cGMP
- other biomarkers related to cardiac fibrosis/remodelling, tissue perfusion/injury, renal function/injury or other pathophysiologies involved in ADHF

Evaluation of Neprilysin measurement at baseline as a predictor of clinical outcome may be added depending on availability of a validated assay and sample handling requirements. The list may be changed or expanded further as new relevant biomarkers may be discovered during this study and after its completion. As such, serum and plasma will be bio-banked for analysis of yet to be identified diagnostic biomarkers. Details of sample collection, handling and shipment will be provided to investigators in the laboratory manual.

6.4.4 Appropriateness of efficacy measurements

The selected efficacy variables for this study including changes in NT-proBNP and other biomarkers concentrations, as well as heart failure signs and symptoms are standard for the evaluation of therapeutic agents in a heart failure population.

6.5 Safety

- Incidence of worsening renal function, defined as an increase in serum creatinine of ≥0.5mg/dl and worsening of the eGFR by at least 25%
- Incidence of symptomatic hypotension
- Incidence of hyperkalemia (Potassium >5.5 meq/l)
- Incidence of angioedema

Safety assessments will consist of monitoring and recording of all adverse events and serious adverse events, evaluation of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations.

6.5.1 Physical examination

A complete physical exam will be performed at Visits 1, 7 and 9 (screening, weeks 8 and 12). It will include the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and vascular and neurological examinations. If indicated based on medical history, and/or symptoms, rectal, external genitalia, breast and pelvic exams will be performed. The Visit 4 (Week 2) physical exam will only be a cardiac care exam.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the start of the study drug must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's eCRF. Significant findings made after informed consent which meet the definition of an adverse event must be recorded on the Adverse Event eCRF.

6.5.2 Vital signs

Vital signs will be assessed at every visit. This will include blood pressure and pulse measurements. BP will be measured using a standard sphygmomanometer with an appropriate sized cuff and the non-dominant arm in the sitting position after 5 minutes of rest. Every effort should be made to use the same arm for the patient for all vital signs assessments and where possible, the same person doing the assessment.

6.5.3 Height, weight and waist/hip circumference

Height in centimeters if possible will be measured at Visits 1 and 2. Body weight to the nearest 0.1 kg without shoes, will be measured at all visits. Waist/hip circumference to the nearest centimeter will be measured at Visit 1.

6.5.4 Angioedema

Angioedema is a type of abrupt swelling that occurs under the skin and/or mucous membranes and is often localized to the head, neck, throat, and/or tongue, but may occur elsewhere, including the genitalia and intestines. Severe cases may be associated with airway compromise. Although, the mechanism is not fully understood, bradykinin has been implicated as the putative mediator. Therefore, medications that raise the levels of endogenous bradykinin by inhibiting the enzymes responsible for its breakdown, such as ACE, aminopeptidase P, and NEP, may result in this potentially dangerous side effect. All suspected cases of angioedema, regardless of suspected causality, must be reported. The Angioedema Assessment forms must be completed and the Clinical Trial Lead or their designee must be notified.

If the angioedema event meets SAE criteria, the investigator must ensure that an SAE form is completed and submitted to Novartis Drug Safety and Epidemiology.

6.5.5 Laboratory evaluations

The local hospital laboratory will be used for all laboratory evaluations required to determine eligibility. If eligibility laboratory assessments were not done during the patient's hospitalization, samples should be collected and sent to the local laboratory. A central laboratory will be used for analysis of all collected specimens from baseline through the final visit. Details on the collections, shipment of samples and reporting of results by the central laboratory will be provided to investigators in the laboratory manual. Results from the local hospital laboratory will be recorded in the laboratory evaluations eCRF.

Clinically notable laboratory findings are defined in Appendix 1.

Local laboratory assessments may be performed on an as-needed basis for unscheduled visits.

Laboratory values that exceed the boundaries of a notable laboratory abnormality must be commented on by the investigator in the Comments screen of the patient's eCRF and additional laboratory evaluations should be performed, as judged appropriate by the investigator. If the laboratory abnormality induces clinical signs or symptoms, or requires therapeutic intervention, then the diagnosis or medical condition must be entered on the AEs screen of the patient's eCRF. If the laboratory abnormality is the primary reason for an

unforeseen hospitalization or otherwise fulfills the seriousness category of an AE, then the procedure for rapid notification of SAEs must be followed. Likewise, if the laboratory abnormality leads to discontinuation from the study drug (temporarily or permanently), the patient must be followed until the abnormality resolves or until it is judged to be permanent. This investigation may include continued monitoring by repeat laboratory testing or by performing additional laboratory tests as deemed necessary by the investigator or the Novartis medical monitor.

6.5.5.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured at Visits 1 (local lab), 2 and 7 (central lab). Hemoglobin A1c will be measured at Visit 2 (central lab).

6.5.5.2 Clinical chemistry

Assessments required for eligibility that need to be measured at Visit 1 include creatinine, potassium, and total bilirubin. Blood urea nitrogen (BUN), glucose, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), alkaline phosphatase, sodium, potassium, chloride, calcium , total protein, albumin, uric acid, and lipid profile will be measured at Visits 2, 3, 4, 5, 7 and 9 (central lab).

6.5.5.3 Urinalysis

Dipstick-test determination of specific gravity, pH, blood, total protein, bilirubin, ketones, and leukocytes will be measured at Visit 2 (central lab). If dipstick is positive, a qualitative microscopic determination, including white blood cells high power field (WBCs/HPF) and red blood cells high power field (RBCs/HPF) will be performed.

6.5.6 Pregnancy and assessments of fertility

All female patients of childbearing potential will have a serum pregnancy test (hCG) performed at Visit 1 (local lab) and Visits 5, 7 and 9 (central lab). In addition, these patients will have a urine pregnancy test conducted in the hospital laboratory at Visit 2. If any of these tests are positive at Visits 1 and 2, the patient should not be enrolled in the trial. If a patient should become pregnant during the trial, the patient may remain in the trial for follow-up visits but must discontinue study drug.

6.5.7 Appropriateness of safety measurements

The majority of safety assessments selected for this study are standard for the evaluation of patients with heart failure.

6.6 Other assessments

6.6.1 The Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Patient Global Assessment (PGA)

The KCCQ is a self-administered questionnaire and requires, on average, 4-6 minutes to complete. It contains 23 items, covering physical function, clinical symptoms, social function,

self-efficacy and knowledge, and Quality of Life (QoL), each with different Likert scaling wording, including limitations, frequency, bother, change in condition, understanding, levels of enjoyment and satisfaction. A change of 5 points on the scale scores, either as a group mean difference or an intra-individual change appears to be clinically significant, based on comparisons of changes in the scale scores to clinical indicators and patient global reports of change. The KCCQ is a valid, reliable and responsive health status measure for patients with CHF and may serve as a clinically meaningful outcome in CV clinical research, patient management and quality assessment [Green et al 2000].

The HF symptoms and physical limitation domains scores show the best correlation for improvements following a CHF exacerbation [Green et al 2000]. Thus, one of the secondary endpoints is a clinical summary score based on the HF symptoms and physical limitation domains scores of the KCCQ. All other domains will be analyzed as exploratory endpoints, as the instruments will be administered as a whole.

The KCCQ questionnaire will be completed at Visits 2, 5, 7 and 9.

The KCCQ is available in a number of validated translations. However, patients in whose language a validated translation of the KCCQ is not available will be exempt from completing this instrument.

The patient global assessment (PGA) is a seven-point patient self-evaluation scale. At Visit 2 (randomization), the investigator should call the patient's attention to how he/she feels about his/her condition at that time and to explain that periodically the patient will be asked to rate how he/she feels at this point in the study. Subsequently, patients will be asked to rate how well they feel compared to Visit 2 (randomization/baseline) [COPERNICUS Investigators 2002]. This evaluation is combined with the NYHA functional class, one of the most reliable instruments for rating HF patients' functionality, and with occurrence of death and hospitalization for heart failure to arrive at an overall evaluation of whether a patient is considered to have improved, worsened, or unchanged after a pre-specified period of time [Packer 2001].

The PGA will be conducted at Visits 2, 5, 7 and 9.

6.6.2 Medical resource utilization

The effect of treatment on medical resource utilization will be assessed during the 4-week open-label period. This will include doctor visits, hospitalizations including any procedures during hospitalization, and changes in treatment (addition of medication, dose adjustments).

7 Safety monitoring

7.1 Adverse events

Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during any phase of the study. Medical conditions/diseases present before informed consent are only considered AEs if they worsen after informed consent. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. AEs also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All AEs must be recorded on the Adverse Events CRF with the following information.

1. the severity grade [mild, moderate, severe]
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.2**.**

All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this AE; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the AE should be recorded on the Adverse Event CRF.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Novartis may request additional information on specific adverse events of interest and may make requests to perform additional diagnostic tests to further assess the safety profile of the study medications. Such information may include diagnostic procedure reports, discharge summaries, autopsy reports, and other relevant information that may help in assessing the reported adverse event. All additional information will be de-identified prior to collection by Novartis or its agents.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe .

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse .

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to DS&E as per section 7.2.2.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

In addition if required by the local health authority or ethics committee, the investigator should report all expected and unexpected serious adverse events to these authorities and also inform the institutional review board at the study institution.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety and Epidemiology (DS&E) Department. The telephone number of the contact persons in the local department of DS&E, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If a SAE is unexpected, i.e., the event is not previously documented in the Investigator's Brochure (new occurrence) and is suspected to be related to the Novartis study drug, **this event is considered a Suspected Unexpected Serious Adverse Reaction (SUSAR)**. A DS&E associate may urgently require further information from the investigator for Health Authority reporting purposes. **In general, it is Novartis policy to unblind SUSARs for regulatory reporting. If the unblinding shows that the Novartis drug is involved,** Novartis will issue an Investigator Notification (IN) to inform all investigators participating in any study with the same drug that this SUSAR has been reported. In addition, SUSARs will be collected and reported to the competent authorities and relevant ethics committees as per United States regulatory requirements in the USA.

An external independent DMC will be appointed and will review efficacy and safety data of the ongoing trial on a regular basis. DMC opinion and recommendations will be notified by Novartis as soon as possible to the competent authorities and the ECs where they qualify for expedited reporting.

7.3 Reporting of study treatment errors including misuse/abuse

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

7.4 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of

the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

7.5 Reporting angioedema-like events

It is important that the investigator pays special attention to any swelling or edema that may resemble angioedema or angioedema-like events that may be reported by patients. If such an event occurs, the investigator will complete an Adjudication Questionnaire for an Angioedema-like Event form (provided by Novartis) to summarize the event, its treatment, and its ultimate outcome and communicate this report to Novartis as soon as possible. Follow-up reports must be communicated to Novartis as soon as new information regarding the event becomes available. All hospital records related to the event must be communicated to Novartis.

Occasionally, the investigator may be contacted by the Novartis regarding AEs that were reported on behalf of patients that may resemble an angioedema-like event. The investigator or his/her delegated staff must complete the required report forms and supply the required medical records for such events, regardless of whether the investigator views the event in question as angioedema or not.

All angioedema reports will be forwarded to an angioedema adjudication committee by Novartis for assessment.

Submission of an angioedema report is not a substitution for the submission of a SAE report. If an angioedema-like event satisfies the definition of a SAE, the investigator must submit a SAE report in addition to the Adjudication Questionnaire for an Angioedema-like Event.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and (e)CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized monitor. Additionally, a central analytics organization may analyze data & identify risks &

trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the (e)CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRFs) using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before review of the data by the CRO working on behalf of Novartis. Prior to database lock, the Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

CRO staff working on behalf of Novartis, review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to CRO staff who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to the designated CRO.

Randomization codes and data about all study drug dispensed to the patient and all dosage changes will be tracked using an Interactive Voice Response System (IWRS). The system will be supplied by a vendor, who will also manage the IWRS database. The IWRS database will be sent electronically to the designated CRO.

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis. The occurrence of reportable protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Head of Biometrics and the Medical Unit Head.

8.4 Data Monitoring Committee

An external data monitoring committee (DMC) independent of Novartis will be appointed to review the incidence of the pre-specified clinical events including major cardiac events, serious adverse events, the rate and distribution of adverse events, and relevant laboratory findings on an ongoing basis. If it is deemed necessary for internal decision making due to patient safety, an interim analysis will be conducted by an independent statistical group.

The membership of the DMC and the responsibilities of the DMC and Novartis will be defined in a separate document entitled 'Data Monitoring Committee Charter'. The DMC Charter will include information about data flow, purpose and timing of DMC meetings, guidance in the decision making process, communication strategy, procedures for ensuring confidentiality, procedure to address conflicts of interest and statistical monitoring guidelines.

8.5 Adjudication Committee

It is important that the investigator pays special attention to any swelling or edema that may resemble angioedema or angioedema-like events that may be reported by patients. There will be a separate eCRF for angioedema events. If such an event occurs, the investigator will complete an Adjudication Questionnaire for an Angioedema-like Event form (provided by Novartis) to summarize the event, its treatment, and its ultimate outcome and communicate this report to Novartis as soon as possible. Follow-up reports must be communicated to Novartis as soon as new information regarding the event becomes available. All hospital records related to the event must be communicated to Novartis.

Occasionally, the investigator may be contacted by the Novartis regarding AEs that were reported on behalf of patients that may resemble an angioedema-like event. The investigator or his/her delegated staff must complete the required report forms and supply the required medical records for such events, regardless of whether the investigator views the event in question as angioedema or not.

All angioedema reports will be forwarded to an angioedema adjudication committee by Novartis for assessment.

Submission of an angioedema report is not a substitution for the submission of a SAE report. If an angioedema-like event satisfies the definition of a SAE, the investigator must submit a SAE report in addition to the Adjudication Questionnaire for an Angioedema-like Event.

9 Data analysis

A designated Contract Research Organization will perform the statistical analysis.

It is planned that the data from all centers that participate in this protocol will be combined, so that an adequate number of subjects will be available for analysis.

Unless otherwise specified, all statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

Efficacy, safety, and other data will be summarized. For continuous variables, summary statistics (mean, standard deviation, median, 25th and 75th percentiles, interquartile range, minimum, and maximum) at each time point and for change from baseline to each time point will be reported by treatment group.

9.1 Analysis sets

The following patient sets will be used for the statistical reporting and analyses:

The Randomized Set will consist of all randomized patients.

The Full Analysis Set (FAS) will consist of all randomized patients with the exception for those patients who have not been qualified for randomization and have not received study drug, but have been inadvertently randomized into the study. Following the intent-to-treat principle, patients will be analyzed according to the treatment to which they were assigned at randomization. Efficacy variables will be analyzed based on the FAS as the primary set.

The Safety Set (SAF) will consist of all randomized patients who received at least one dose of study drug. Patients will be included in the analysis according to the treatment actually received. The Safety Set will be used for the analyses of safety variables.

The Per-Protocol (PP) set will be a subset of the FAS which will consist of the patients who do not have major deviations from the protocol procedures in the double-blind study stage. Major protocol deviations will be pre-specified prior to unblinding treatment codes for analyses. This supplemental efficacy set will be used to support the primary analysis results.

9.2 Patient demographics and other baseline characteristics

Baseline value is defined as the last non-missing assessment prior to the first dose of randomized study medication, including the matching placebos, unless specified otherwise in the protocol.

Summary statistics will be provided by treatment group for demographics and baseline characteristics, including age, age group (<65 years vs. ≥65 years; <75 years vs. ≥75 years), sex, race, ethnicity, weight, height, body mass index (BMI), category of prior CHF medication, prior HF hospitalization, NYHA class, NT-proBNP, BNP, and vital signs. BMI

will be calculated as weight (kg) / height^2 (m^2) from the collected height and weight at Visit 1 (Screening Visit). Continuous variables will be summarized using n, mean, standard deviation, median, 25th and 75th percentiles, interquartile range, minimum, and maximum. Geometric means will be used to summarize the NT-proBNP results. Categorical variables will be summarized using frequency and percentage.

The Randomized Set and FAS will be the patient sets for the above analyses.

9.3 Treatments

The overall duration on the double-blind study drug will be summarized by treatment group using mean, standard deviation, median, 25th and 75th percentiles, interquartile range, minimum, and maximum. Additionally, the number and percentage of patients will be summarized by treatment group for duration category.

Concomitant medications and significant non-drug therapies, prior to and after the randomization date will be summarized by therapeutic class, preferred term, and treatment group.

The number and percentage of patients on different HF background medications will be tabulated by treatment at baseline and during the double-blind stage.

The Safety Set will be used for the above analyses.

9.4 Analysis of the primary variable(s)

9.4.1 Variables

The primary efficacy variable is the time-averaged proportional change from baseline in NT-proBNP. Weeks 4 and 8 will be included in the analysis (primary analysis time point).

9.4.2 Statistical model, hypothesis, and method of analysis

The primary hypothesis to be tested is that the ratio of the geometric means of NT-proBNP (average of Weeks 4 and 8/baseline) for the sacubitril/valsartan and enalapril groups are equal (H0) versus the ratio of the geometric means of NT-proBNP are not equal (Ha).

For NT-proBNP, the time-averaged proportional change from baseline in a logarithmic scale will be analyzed using an analysis of covariance (ANCOVA) model using data from Weeks 4 and 8 with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate The estimated treatment effect in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0.

The change from baseline log-transformed NT-proBNP will be calculated as log (post-dose value) – log (baseline value). Geometric means (presented as a ratio to baseline) will be calculated by exponentially back-transforming the LS means based on the ANCOVA model.

9.4.3 Handling of missing values/censoring/discontinuations

The analysis will be performed based on all available data in the FAS and based on likelihood method with an assumption of missing at random for missing data.

9.4.4 Supportive analyses

T-tests comparing treatment groups using change from log (baseline) to log (Week 8) values and log (Week 4) values will be performed.

In addition to the primary analysis, the primary efficacy variable will also be analyzed using the same analysis model in the PP Set as supportive.

9.5 Analysis of secondary and exploratory variables

9.5.1 Secondary variables

For NT-proBNP at Week 8, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. The estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0. Week 4 will be used if the Week 8 value is missing.

Incidences of symptomatic hypotension, hyperkalemia and angioedema will be calculated, along with the relative risk of sacubitril/valsartan vs. enalapril and 95% confidence intervals of the relative risk.

For biomarkers including BNP to NT-proBNP ratio, hs-Troponin, and urinary cGMP, the time-averaged proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model using the data from Weeks 4 and 8 with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. The estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0.

For BNP to NT-proBNP ratio and urinary cGMP at Weeks 1 and 2, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. For each of Weeks 1 and 2 the estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0.

Analyses of the secondary variables will be based on the FAS.

9.5.2 Exploratory variables

Exploratory variables:

1. Time to first occurrence of composite clinical endpoint that includes death, heart failure re-hospitalization, requirement of LVAD, listed for cardiac transplantation, unplanned

acute HF visits requiring i.v. diuretics, additional heart failure drug or increase in >50% of the diuretic dose

2. Change from baseline at Weeks 1 and 2 in NT-proBNP
3. Need for re-hospitalization, ED visit, or unplanned outpatient clinic visits due to worsening HF symptoms
4. Re-hospitalization through Day 30
5. Need for advanced heart failure therapies (including but not limited to i.v. inotropes, LVAD, transplantation)
6. Patient centered outcomes including the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Patient Global Assessment (PGA) at 4 weeks and 8 weeks post randomization
7. Change in biomarkers related to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury, and renal function, including estimated glomerular filtration rate (eGFR)
8. Change from Week 8 in NT-proBNP in the enalapril arm during the 4 week open label period
9. Medical resource utilization
10. Incidence of worsening renal function during 8 weeks of treatment, defined as an increase in serum creatinine of ≥0.5 mg/dl from the value measured at baseline

For the composite variable (exploratory variable 1), Kaplan-Meier estimates of the rates of the composite event will be presented, and treatment groups will be compared using a log- rank test. Kaplan-Meier plots will be presented. Hazard ratios and 95% CIs will be estimated from a Cox proportional hazard regression model with treatment as a factor.

For NT-proBNP at Weeks 1 and 2, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. For each of Weeks 1 and 2 the estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0.

Within exploratory variable 3, the time to first hospitalization will be analyzed presenting Kaplan-Meier estimates and testing with the log rank test.

Exploratory variable 4 will be analyzed presenting Kaplan-Meier estimates and testing with the log rank test. Patients without an event will be censored at the earlier of the last contact date or Day 30.

Within exploratory variables 3 and 5, categorical variables will be analyzed using a logistic regression model with treatment as a factor.

Within exploratory variable 3, the number of re-hospitalizations and number of heart failure visits requiring diuretics will be analyzed using a negative binomial regression model with the count data as the dependent variable and treatment group as a fixed-effect factors and log(follow-up duration) as the off-set. The model will estimate event rates (intensities/risks)

and their 95% confidence intervals will be provided by treatment group. The treatment comparison will be performed through the estimated ratio and its 95% confidence interval.

Within exploratory variables 3 and 5, for variables representing a number of days, the mean differences between treatment groups will be compared using an analysis of variance model with treatment group as a factor. The estimated treatment difference and its 95% confidence interval will be provided.

Analysis of KCCQ clinical summary score as continuous variable

The KCCQ instrument includes several domains. Only the domains that address HF symptoms and physical limitations will be analyzed. The clinical summary score of KCCQ is computed as the mean of the following available domain scores:

- Physical limitation score
- Total HF symptom score

The clinical summary score at weeks 4 and 8 of KCCQ will be analyzed based on a repeated measures ANCOVA model in which treatment, visit, and treatment-by-visit interaction will be included as fixed-effect factors and baseline value as a covariate, with a common unstructured covariance for each treatment group. The primary treatment comparison between sacubitril/valsartan and enalapril is to be made at Week 8. The analysis will be performed based on all available data in the FAS and based on likelihood method. The estimated treatment effect with the associated confidence interval at Week 8 will be provided.

Responder analyses based on the number of patients with at least 5 points improvement or deterioration of the KCCQ clinical summary score will be performed using logistic regression models. The list of explanatory variables in the logistic regression model will be determined when the Statistical Analysis Plan is prepared prior to database lock.

The Physician's Global Assessment will be analyzed at Weeks 4 and 8, using Cochran-Mantel-Haenszel (CMH) test for different row (treatment) means based on the modified ridit scores.

For biomarkers related to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury, and renal function, a proportional change from baseline in a logarithmic scale will be analyzed using a repeated measures ANCOVA model using the data from Weeks 2, 4 and 8 with treatment, week and treatment-by-week interaction as fixed effect factors and the logarithmic baseline biomarker value as a covariate, using observed data. The unstructured working correlation matrix will be used. For each of Weeks 2, 4 and 8 the estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0.

For NT-pro BNP, change from Week 8 to Week 12 in a logarithmic scale will be summarized by treatment group.

The medical resource utilization data analysis is described in Section 9.5.4.

For worsening renal function, a logistic regression model with treatment and baseline creatinine value as covariates having fixed effects will be run.

Analyses of the exploratory variables will be based on the FAS.

9.5.3 Other safety variables

The safety and tolerability assessments are listed below:

- AEs and SAEs
- Sitting systolic, diastolic BP, and pulse pressure
- Heart rate
- Laboratory values

The assessment of safety will be based primarily on the frequency of adverse events, SAEs, and laboratory abnormalities. Other safety data will be summarized as appropriate.

The incidence of treatment-emergent adverse events (new or worsened) will be summarized by primary system organ class, preferred term, severity, and relationship to study drug. In addition, the incidence of death, SAEs, and AEs leading to discontinuation will be summarized separately by primary system organ class and preferred term.

Laboratory data will be summarized by presenting shift tables using extended reference ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (mean, median, standard deviation, 25th and 75^{th} percentiles, interquartile range, minimum and maximum) and by the flagging of notable values in data listings.

Data from other tests (e.g., ECG or vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

Safety analyses will be performed based on the Safety Set. There will be no inferential analyses of the safety data.

9.5.4 Resource utilization

Data relating to resource utilization will be used to describe medical resources used by the study participants. Only descriptive statistics of resources utilization data will be provided by treatment group.

9.5.5 Pharmacokinetics

Not Applicable.

9.5.6 Pharmacogenetics and pharmacogenomics

Not applicable.

9.5.7 Biomarkers

See Sections 9.4 and Section 9.5 for a description of the methods used to analyze the biomarkers. Any other biomarkers collected but not specifically mentioned in Sections 9.4 or 9.5 will be analyzed in the same manner.

9.5.8 PK/PD

Not applicable.

9.6 Interim analyses

No interim analysis is planned.

9.7 Sample size calculation

Assuming a significance level of 0.05 and 85% power, a sample size of 882 patients would be needed to detect an 18% reduction in the geometric mean of the time-averaged proportional change from baseline (average of Weeks 4 and 8) in NT-proBNP for the sacubitril/valsartan treatment group assuming a value of 0.95 for the enalapril group, a common standard deviation of 0.85 and a 25% rate of missing/non-evaluable samples. The estimates are based on the day 5 to day 14 data from the RELAX-AHF study. The standard deviation estimate is supported by data from PARADIGM.

The assumption of a 18% reduction in the geometric mean for NT-proBNP for the sacubitril/valsartan treatment group vs. the enalapril group is consistent with NT-proBNP results seen in PARADIGM (26% and 25% relative reduction of sacubitril/valsartan vs. enalapril at Week 4 and Month 8 respectively), PARAMOUNT (23% relative of sacubitril/valsartan vs. valsartan at Week 12) and RELAX-AHF (19% relative reduction of serelaxin vs. placebo at Day 2).

Table 9-1 Sample size and power for various rate of reduction in sacubitril/valsartan group given alpha =0.05:

Change in GM for enalapril	Common SD	Relative reduction in GM for sacubitril/valsartan group compared to enalapril group	Change in GM for sacubitril/valsartan group	Power	Non-evaluable rate	Total sample size after adjusting for non-evaluable rate
.95	.85	15%	.81	85%	10%	1096
.95	.85	15%	.81	90%	10%	1280
.95	.85	18%	.78	85%	10%	736
.95	.85	18%	.78	90%	10%	860
.95	.85	18%	.78	85%	25%	882
.95	.85	20%	.76	85%	10%	582
.95	.85	20%	.76	90%	10%	680

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated

agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in section 7 Safety Monitoring should be followed.

12 References

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13 Appendix 1: Clinically notable laboratory values

Clinically notable laboratory abnormalities for selected tests based on a percent change from baseline:

Hematology

RBC count	>50% increase, >20% decrease
Hemoglobin	>50% increase, >20% decrease
Hematocrit	>50% increase, >20% decrease
WBC count	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease

Blood Chemistry

ALT (SGPT)	>150% increase
AST (SGOT)	>150% increase
BUN	>50% increase
Creatinine	>50% increase
Total bilirubin	>100% increase
CPK	>300% increase
Alkaline phosphatase	>100% increase
Potassium	>20% increase, >20% decrease
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease
Uric acid	>50% increase

14 Appendix 2: Treatment guidelines for hyperkalemia (serum potassium greater than or equal to 5.5 mEq/L)

General principles

Elevation of potassium levels above the predefined values should be repeated and confirmed before any action is taken.

Any patient who experiences a potassium level ≥ 5.5 mEq/L confirmed by repeated testing after randomization requires regular, repeated checks of potassium concentration (beyond that prescribed in the protocol) until it is clear that the potassium concentration is stable and not rising into the range of concern (≥ 5.5 mEq/L).

Patients with elevated potassium value will be managed according to the corrective actions outlined below and the investigator's clinical judgement. Hyperkalemia should be followed until resolution.

Recommended corrective action for management of hyperkalemia

Serum potassium > 5.3 and less than or equal to 5.5 mEq/L

- Confirm potassium concentration in a non-hemolyzed sample
- Reinforce low potassium diet and restriction of food/drinks with high potassium content (e.g. orange juice, melon, bananas, low-salt substitutes etc.)
- Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia. Consider reduction in dose or discontinuation of these agents:
- Aldosterone antagonists (if they are believed to be the most likely cause of hyperkalemia)
- Potassium-sparing diuretics (e.g. amiloride and triamterene) including in combination products with thiazide or loop diuretics
- Potassium supplements, e.g., potassium chloride
- Salt substitutes
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Cyclo-oxygenase-2 (COX-2) inhibitors
- Trimethoprim and trimethoprim-containing combination products, such as Bactrim® and Septra® (trimethoprim/sulfamethoxazole fixed combination)
- Herbal Supplements:
- For example, Noni juice, alfalfa (*Medicago sativa*), dandelion (*Taraxacum officinale*), horsetail (*Equisetum arvense*), nettle (*Urtica dioica*), milkweed, lily of the valley, Siberian ginseng, hawthorn berries
- Repeat serum potassium measurement within 3 to 5 days
- If serum potassium remains > 5.3 and ≤ 5.5 mEq/L, regularly monitor serum potassium levels to ensure stability (suggested once monthly)

- Consider down-titration of study medication, according to investigator's medical judgment.

Serum potassium > 5.5 and < 6.0 mEq/L

- Confirm potassium concentration in a non-hemolyzed sample
- Consider down-titration or temporarily discontinue study drug according to investigator medical judgment.
- Apply all measures outlined for serum potassium > 5.3 and ≤ 5.5 mEq/L
- Repeat serum potassium measurement after 2-3 days
- If serum potassium < 5.5 mEq/L, consider resumption of study drug at lower dose with repeat potassium within 5 days

Serum potassium greater than or equal to 6.0 mEq/L

- Immediately discontinue study drug
- Confirm potassium concentration in a non-hemolyzed sample
- Urgently evaluate patient and treat hyperkalemia as clinically indicated
- Apply all measures outlined for serum potassium > 5.3 and < 6.0 mEq/L
- If serum potassium < 5.5 mEq/L, consider resumption of study drug at lower dose with repeat potassium within 5 days

15 Appendix 3: Guidelines for the management of blood pressure

Guidelines

1. Investigator should monitor blood pressure closely
2. If symptomatic hypotension occurs:
    a. Correct any treatable cause, e.g. hypovolemia
    b. If hypotension persists, any antihypertensive drug and non-disease-modifying drugs, such as diuretics, CCBs, nitrates, and α-blockers, should be down-titrated or stopped first before down-titration of the study drug is considered
3. If hypotension persists, the study drug should be down-titrated or even temporarily withdrawn. The dose re-challenge and medication adjustment guidelines described in Section 5.5.5 should be adhered to as much as possible.

16 Appendix 4: Guidelines for the management of renal dysfunction

General principles:

Glomerular filtration rate in HF patients depends on intrinsic renal function and on a balance between afferent and efferent glomerular arterial tonicity. This tonicity is partly regulated by a stimulation of angiotensin II and could be affected by either study medication. Moreover, renal dysfunction may develop or may deteriorate in some patients after study drug administration. These recommendations have been developed to guide the investigators in managing patients with renal dysfunction after randomization.

Two types of response to serum creatinine increase are described:

Surveillance situation

If, at any time after randomization, eGFR decreases by ≥ 25% from baseline (or if serum creatinine concentration increase to 2.5 mg/dL [221 μmol/L]), the investigator will check for potentially reversible causes of renal dysfunction such as:

- Non-steroidal anti-inflammatory drug intake, antibiotics, or other treatments known to affect creatininemia
- Volume decrease, including that resulting from excessive dosing of diuretics
- Urinary infection
- Urinary tract obstruction
- Study medication

Action situation

If a patient eGFR decreases by ≥ 40% from baseline (or if serum creatinine concentration rises above 3 mg/dL (265 μmol/L), the investigator will check for potentially reversible causes of renal dysfunction (see above).

If the investigator judges that study medication has to be stopped, he/she will have to contact the Novartis medical monitor or his/her designee. Thereafter, serum creatinine assessments will have to be repeated at least each week until levels return to acceptable values. If study medication was stopped, every effort will be done to restart it again, according to clinical conditions.

17 Appendix 5: Kansas City Cardiomyopathy Questionnaire

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Showering/Bathing	☐	☐	☐	☐	☐	☐
Walking 1 block on level ground	☐	☐	☐	☐	☐	☐
Doing yardwork, housework or carrying groceries	☐	☐	☐	☐	☐	☐
Climbing a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Hurrying or jogging (as if to catch a bus)	☐	☐	☐	☐	☐	☐

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
☐	☐	☐	☐	☐	☐

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
☐	☐	☐	☐	☐	☐

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
☐	☐	☐	☐	☐	☐

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
☐	☐	☐	☐	☐	☐

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
☐	☐	☐	☐	☐

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
☐	☐	☐	☐	☐

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
☐	☐	☐	☐	☐

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I felt that way **all of the time**	I felt that way **most of the time**	I **occasionally** felt that way	I **rarely** felt that way	I **never** felt that way
☐	☐	☐	☐	☐

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please place an **X** in one box on each line

Activity	**Severely** limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	☐	☐	☐	☐	☐	☐
Working or doing household chores	☐	☐	☐	☐	☐	☐
Visiting family or friends out of your home	☐	☐	☐	☐	☐	☐
Intimate relationships with loved ones	☐	☐	☐	☐	☐	☐

PIONEER-HF Protocol – Summary of Changes

Amendment 1 (28Jul2016)
The protocol inclusion criteria have been modified to be more closely aligned with clinical practice in the United States where patients with acute decompensated heart failure are often rapidly stabilized and transitioned from intravenous to oral diuretic therapy so as to move efficiently to outpatient care, with close follow-up. The protocol has been modified to include patients who are at least 24 hours from hospital presentation versus 48 hours. This change was instituted to allow sites to randomize stabilized patients who otherwise might be discharged earlier than 48 hours. In addition, the window of eligibility, which had been set at 5 days, has been extended to 10 days to permit inclusion of patients who have longer hospitalizations (e.g. due to initial diagnostic uncertainty). Because a substantial proportion of patients who are stabilized with medical therapy for acute decompensation heart failure are asymptomatic with a systolic blood pressure that remains predominantly within the range of 100 – 110 mm Hg, the inclusion criterion regarding systolic blood pressure has been lowered to ≥100 mmHg. The SBP stabilization period was also changed from 24 hours to 6 hours because a 6 hour window is considered an adequate period of time to establish stability.

Summary of Changes

Location of change in original protocol	**Change**
Throughout	'sacubitril and valsartan' changed to 'sacubitril/valsartan'
Throughout	'in hospital' changed to 'in-hospital'
Page 7, List of abbreviations	'IVRS' corrected to 'IWRS'
Page 12. Protocol summary, Study design	Randomization window changed to 'no earlier than 24 hours and up to ten days of presentation, while still hospitalized' Deleted: 'Patients randomized to sacubitril and valsartan will require a 36-hour wash-out from prior ACEi/ARB treatment prior to first dose of active study treatment.' Stabilization criteria changed to: • 'SBP ≥100mm Hg for the preceding 6 hours prior to randomization; • no symptomatic hypotension; • no increase (intensification) in i.v. diuretic dose for within the last 6 hours prior to randomization; • no i.v. inotropic drugs for 24 hours prior to randomization; • no i.v. vasodilators including nitrates within the last 6 hours prior to randomization;' Text added: 'All patients randomized to sacubitril/valsartan will require a 36-hour wash-out from previous ACEi treatment prior to first dose of active study treatment. All randomized patients in the trial will remain hospitalized for observation for 6 hours following the third dose of study medication. See section 3.1 for more details.' Text deleted: 'Initial dose will be determined by the blood pressure at the time of randomization. Study treatment will be titrated to the target dose of sacubitril and valsartan 97/103 mg bid and enalapril 10 mg bid. Titration will be based on blood pressure at the time of

	the visit. Dose adjustments will be allowed per protocol defined safety and tolerability criteria.'
Page 12. Protocol summary, Population	Stabilization criteria amended as in 'study design' section
Page 13, Protocol summary, Inclusion criteria	Written informed consent criterion edited to read: 'Possess the capacity to provide written informed consent which must be obtained before any assessment is performed.' Criterion 4 replaced with: 'Eligible patients will be randomized no earlier than 24 hours and up to ten days after presentation while still hospitalized as long as meet the following definition of stable status: □□SBP ≥100mm Hg for the preceding 6 hours prior to randomization; no symptomatic hypotension □□No increase (intensification) in i.v. diuretic dose within last 6 hours prior to randomization □□No i.v. inotropic drugs for 24 hours prior to randomization □□No i.v. vasodilators including nitrates within last 6 hours prior to randomization' Criterion 5 deleted 'via any local measurement', added '(including current hospitalization)' Criterion 6 added 'during current hospitalization'
Page 14, Protocol summary, Exclusion criteria	Replaced criterion 3 with: 'History of hypersensitivity, known or suspected contraindications, or intolerance to any of the study drugs, including ACEIs, ARBs, or Sacubitril (NEP inhibitor)' Deleted criteria 4 and 7 Changed criterion 10 from 3 months prior to Visit 1 to one month prior to Visit 1 Replaced criterion 11 with 'Primary cause of dyspnea due to non-cardiac, non-heart failure causes such as acute or chronic respiratory disorders' Deleted criterion12 Edited criterion 13 to read: 'Intended coronary or carotid artery disease revascularization within the 6 months after Visit 1.' Deleted criteria 17, 18, 21, 22 Edited criterion 23 to read: 'Presence of hemodynamically significant mitral, aortic, or hypertrophic cardiomyopathy.' Deleted criteria 25-29 Added text: 'Adequate barrier methods of contraception include: diaphragm, condom (by the partner), intrauterine device (copper or hormonal), sponge or spermicide. Hormonal contraceptives include any marketed contraceptive agent that includes an estrogen and/or a progesterone agent.

	□□Reliable contraception should be maintained throughout the study and for 7 days after study drug discontinuation. □□Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL and estradiol <20 pg/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.'
Page 20, Preliminary studies	Replaced first sentence with: 'Sacubitril/valsartan, which is known in prior trials as LCZ696, has been evaluated for safety and efficacy in patients with chronic heart failure.'
Page 22, Preliminary studies	Replaced 'AHF' with 'ADHF'
Page 22	Added: '**1.2 Rationale for protocol amendment** The protocol inclusion criteria have been modified to be more closely aligned with clinical practice in the United States where patients with acute decompensated heart failure are often rapidly stabilized and transitioned from intravenous to oral diuretic therapy so as to move efficiently to outpatient care, with close follow-up. The protocol has been modified to include patients who are at least 24 hours from hospital presentation versus 48 hours. This change was instituted to allow sites to randomize stabilized patients who otherwise might be discharged earlier than 48 hours. In addition, the window of eligibility, which had been set at 5 days, has been extended to 10 days to permit inclusion of patients who have longer hospitalizations (e.g. due to initial diagnostic uncertainty). Because a substantial proportion of patients who are stabilized with medical therapy for acute decompensation heart failure are asymptomatic with a systolic blood pressure that remains predominantly within the range of 100 – 110 mm Hg, the inclusion criterion regarding systolic blood pressure has been lowered to ≥100 mmHg. The SBP stabilization period was also changed from 24 hours to 6 hours because a 6 hour window is considered an adequate period of time to establish stability.
Page 23	Added: '**1.3 Changes to protocol** Changes to specific sections in the protocol are shown in the track changes version of the protocol using the strike through font for deletions and red underlined for insertions. A copy of this amended protocol will be sent to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and Health Authorities. The changes described in this amendment require IRB/IEC approval prior to implementation. In addition, since the changes herein do affect the informed consent, sites will be required to update and submit for approval a revised informed consent that takes into account the changes
Page 25, 3.1 Study design	Edited to read:

	‘This study will use a randomized, double-blind, double-dummy, active-controlled, parallel group design. Eligible patients hospitalized for ADHF will be randomized no earlier than 24 hours and up to ten days of presentation while still hospitalized. At the time of randomization, patients will have been stabilized, defined for this study as: □□SBP ≥100mm Hg for the preceding 6 hours prior to randomization; no symptomatic hypotension □□No increase (intensification) in i.v. diuretic dose within last 6 hours prior to randomization □□No i.v. inotropic drugs for 24 hours prior to randomization □□No i.v. vasodilators including nitrates within last 6 hours prior to randomization All patients will need to meet all other inclusion and none of the exclusion criteria. In order to provide for a necessary 36 hour washout of prior ACEi treatment prior to receiving sacubitril/valsartan (known as LCZ696 in prior trials), the supplied blinded study drug for those allocated to sacubitril/valsartan will be placebo only until the 3rd dose. Because the study is blinded, ALL patients, regardless of randomization arm, need to remain in the hospital for six hours after they have received their 3rd dose of study medication. Please see Figure 3-2. Patients will be randomized to sacubitril/valsartan or enalapril. Initial dose will be determined by the blood pressure at the time of randomization. Study treatment will be titrated to the Level #3 target doses of sacubitril/valsartan 97/103 mg bid and enalapril 10 mg bid. Titration will be based on blood pressure at the time of the visit. Dose adjustments will only be allowed if indicated per protocol defined safety and tolerability criteria and investigator judgement. At the end of the 8-week treatment period ALL patients will need to have a 36 hour washout from study treatment prior to starting the open label extension to ensure that the blinding of the core study is maintained. To facilitate this washout, patients should take their final dose of study drug on the morning of their week 8 visit and then begin open label sacubitril/valsartan after 36 hours in the evening of week 8 visit + one day. All patients will start open label treatment on sacubitril/valsartan at their final dosing level during double blind treatment. However, at an investigator’s judgement, starting dose may be adjusted by one dose level up or down. The intent of the open-label phase is to have the patients up-titrated to the desired dose level #3 (97/103 mg sacubitril/valsartan) based on clinical need and investigator judgement.
Page 28, 3.6 Risks and benefits	Edited to read: All patients randomized to the sacubitril/valsartan treatment arm will be given matching placebo doses of both sacubitril/valsartan and enalapril on the day of randomization to fulfill the requirement for a 36 hour washout prior to sacubitril/valsartan treatment initiation. The first active dose of sacubitril/valsartan treatment will be the third dose of study drug received after randomization. The 36 hour wash out period is required to minimize the interaction between an ACEi and sacubitril in potentiating the development of angioedema. Patients randomized to the enalapril treatment arm do not require a washout, but will receive sacubitril/valsartan

	matching placebo in addition to active enalapril starting on the day of randomization. Since this is a double blind study, **all** study patients must remain in the hospital for at least 6 hours following the third dose of study medication even though the 36 hour wash out is only required for patients randomized to sacubitril/valsartan. This will allow for the first dose of active sacubitril/valsartan (third dose of study medication) to be administered in the hospital and will ensure that the blind is maintained.
Page 29, 4 Population	Edited to read: 'The study population will consist of male and female patients, ≥ 18 years of age, presenting to the hospital for acute decompensated heart failure. The goal is to randomize a total of approximately 736 patients to sacubitril/valsartan or enalapril in a 1:1 ratio in approximately 140 centers in the United States. At the time of randomization, patients will have been stabilized, defined for this study as: □□SBP ≥100mm Hg for the preceding 6 hours prior to randomization; no symptomatic hypotension □No increase (intensification) in i.v. diuretic dose within last 6 hours prior to randomization □□No i.v. inotropic drugs for 24 hours prior to randomization □□No i.v. vasodilators including nitrates within last 6 hours prior to randomization; All patients will need to meet all other inclusion and none of the exclusion criteria.
Page 30, 4.1 Inclusion criteria	Replaced with: 1. Possess the capacity to provide written informed consent which must be obtained before any assessment is performed. 2. Patients ≥ 18 years of age, male or female. 3. Currently hospitalized for ADHF. Patients with a diagnosis of acute heart failure had to have symptoms and signs of fluid overload (i.e. jugular venous distention, edema or rales on auscultation or pulmonary congestion on chest x-ray) at time of hospitalization. 4. Eligible patients will be randomized no earlier than 24 hours and up to ten days after presentation while still hospitalized as long as meet the following definition of stable status: □□SBP ≥100mm Hg for the preceding 6 hours prior to randomization; no symptomatic hypotension □□No increase (intensification) in i.v. diuretic dose within last 6 hours prior to randomization □□No i.v. inotropic drugs for 24 hours prior to randomization □□No i.v. vasodilators including nitrates within last 6 hours prior to randomization 5. LVEF ≤40% within the past 6 months (including current hospitalization) using echocardiography, multi gated acquisition scan (MUGA), CT scanning, MRI or ventricular angiography, provided no subsequent study documented an EF of >40%. 6. Elevated NT-proBNP ≥ 1600pg/mL OR BNP ≥400 pg/mL during current hospitalization.
Page 31, Exclusion criteria	Replaced with: 1. Currently taking sacubitril/valsartan tablets or any use within the past 30 days. 2. Enrollment in any other clinical trial involving an investigational agent or investigational device.

	3. History of hypersensitivity, known or suspected contraindications, or intolerance to any of the study drugs, including ACEIs, ARBs, or Sacubitril (NEP inhibitor). 4. Patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy. 5. Requirement of treatment with both ACE inhibitor and ARB. 6. eGFR < 30 ml/min/1.73 m2 as measured by the simplified Modification of Diet in Renal Disease (MDRD) formula at screening. 7. Serum potassium > 5.2 mEq/L at screening. 8. Acute coronary syndrome, stroke, transient ischemic attack; cardiac, carotid or other major CV surgery; percutaneous coronary intervention (PCI) or carotid angioplasty, within one month prior to Visit 1. 9. Primary cause of dyspnea due to non-cardiac, non-heart failure causes such as acute or chronic respiratory disorders. 10. Intended coronary or carotid artery revascularization within the 6 months after Visit 1. 11. Implantation of a cardiac resynchronization therapy device (CRTD) within the prior 3 months from Visit 1or intent to implant a CRTD. 12. History of heart transplant or patients who are on a transplant list or with left ventricular assistance device (LVAD). 13. Isolated right HF due to severe pulmonary disease. 14. Documented untreated ventricular arrhythmia with syncopal episodes within the 3 months prior to Visit 1. 15. Symptomatic bradycardia or second or third degree heart block without a pacemaker. 16. Presence of hemodynamically significant mitral, aortic or hypertrophic obstructive cardiomyopathy. 17. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past year with a life expectancy of less than 1 year. 18. Known hepatic impairment (as evidenced by total bilirubin > 3 mg/dL, or increased ammonia levels, if performed), or history of cirrhosis with evidence of portal hypertension such as varices. 19. 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 hCG laboratory test. 20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they are using two birth control methods. The two methods can be a double barrier method (if accepted by the local regulatory authority and ethics committee) or a barrier method plus a hormonal method. □□Adequate barrier methods of contraception include: diaphragm, condom (by the partner), intrauterine device (copper or hormonal), sponge or spermicide. Hormonal contraceptives include any marketed contraceptive agent that includes an estrogen and/or a progesterone agent. □□Reliable contraception should be maintained throughout the study and for 7 days after study drug discontinuation.

	□□Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL and estradiol < 20 pg/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
Page 35, 5.1.1 Investigational and control treatment	'Bottles will be numbered and assigned via an interactive voice response system (IVRS)' replaced with: 'Bottles will be numbered and assigned via an Interactive Web Response System (IWRS). On the day of randomization (visit 2), the IWRS system will assign both a hospital kit and a patient kit.' 'Treatment for the second day of dosing onwards, also assigned via IVRS, will be provided in bottles and or blister packs for the patients to take home upon discharge.' replaced with: 'Treatment for the second day of dosing onward will be provided from the patient kit which patients will take home upon discharge.'
Page 36, 5.1.1 Investigational and control treatment	Added: 'Patients not tolerating the target dose level #3 of sacubitril/valsartan 200 mg BID or enalapril 10 mg BID will be titrated down to the lower dose level (including active medication and matching placebos), at the investigator's discretion, based on the defined safety and tolerability criteria.'
Page 36, 5.1.2 Additional study treatment	Replaced: 'Patients entering the open label phase will be given dose level 2 and titrated according to the USPI. Adjustment of the sacubitril and valsartan or enalapril dose levels may be increased on an every 2 -4 week basis per USPI to the desired target maintenance dose of 97/103 mg or increased within a 1-2 week time period based on clinical need and/or investigator judgement.' With: 'All patients will start open label treatment on sacubitril/valsartan at their final dosing level during double blind treatment. However, at an investigator's judgement, starting dose may be adjusted by one dose level up or down. The intent of the open-label phase is to have the patients up-titrated to the desired dose level #3 (200 mg sacubitril/valsartan) based on clinical need and investigator judgement.
Page 37, 5.3 Treatment assignment, randomization	Randomization time changed from: 'no earlier than 48 hours after presentation at the hospital and no later than within 5 days of admission' to: 'no earlier than 24 hours after presentation at the hospital and no later than within ten days of admission'
Page 38, 5.5.1 Patient numbering	Deleted: 'The Screen Failure eCRF which includes demographic information must be completed for patients who fail to be randomized.'
Page 41, Table 5-3, first row	Replaced Systolic Blood pressure '<120' with '≥100'

Page 42, 5.5.4 Instructions for prescribing and taking study treatment	Edited text to read: 'All patients that complete 8 weeks of treatment will proceed with a 4 -week follow up on open-label sacubitril/valsartan. All patients will have the wash out in order to maintain the blinding of the core study. To facilitate this washout, patients should take their final dose of study drug on the morning of their week 8 visit and then begin open label sacubitril/valsartan after 36 hours in the evening of week 8 visit + one day. All patients will start open label treatment on sacubitril/valsartan at their final dosing level during double blind treatment. However, at an investigator's judgement, starting dose may be adjusted by one dose level up or down. The intent of the open-label phase is to have the patients up-titrated to the desired dose level #3 (200 mg sacubitril/valsartan) based on clinical need and investigator judgement.
Page 43, 5.5.6 Rescue medication	Inserted '(non-study medications)'
Page 44, 5.5.7 Concomitant treatment	Replaced: 'the patient was enrolled into the study must be recorded on the Concomitant medications/Significant non-drug therapies eCRF.' With: 'informed consent must be recorded on the Concomitant medications or Surgeries and Medical Procedures eCRF.'
Page 45, 5.5.8 Discontinuation of study drug	Replaced: 'In the case of study drug discontinuation, every effort must be made to complete an end of study visit and obtain follow up health status information for any patients that withdraw from the study. If the patient refuses, he/she should be contacted by telephone in place of protocol-specified visits unless the patient expressly refuses such contacts.' With: 'In the case of study drug discontinuation, patients should remain in the trial and attend followup visits. If the patient refuses, he/she should be contacted by telephone to obtain follow-up health status information in place of protocol-specified visits unless the patient expressly refuses such contacts.'
Page 46, 6 Visit schedule and assessments	Deleted: 'with an allowed visit window of ± 3 days for post baseline visits.' Inserted: 'Clinical assessments performed during a patient's hospitalization, prior to signing of informed consent, may be used for Visit 1/Screening.'
Page 50, 6.2 Patient demographics/other baseline characteristics	Replaced: 'Relevant medical history/current medical condition data includes data until the start of study drug. Where possible, diagnoses and not symptoms, will be recorded. HF medications and other CV medications will be recorded in eCRFs separately from other medications.' With: 'Relevant medical history/current medical condition data includes data collected up to the point in which informed consent is signed. Where possible, diagnoses and not symptoms, will be recorded. HF medications will be recorded in eCRFs separately from other medications.'
Page 52, 6.4.3 Biomarkers	Replaced:

	"BNP and NT-proBNP will be obtained in all patients by using the local laboratory at Visit 1 to determine eligibility; and using the central laboratory at Visits 2, 3, 4, 5 and 7 (randomization, weeks 1, 2, 4, and 8), and at the end of the open label extension, Visit 9 (Week 12).' With: 'BNP or NT-proBNP will be obtained in all patients by using the local laboratory at Visit1 to determine eligibility. NT-proBNP will be obtained in all patients using the central laboratory at Visits 2, 3, 4, 5 and 7 (randomization, weeks 1, 2, 4, and 8), and at the end of the open label extension, Visit 9 (Week 12).' Replaced: 'In addition, biomarker measurements will be obtained from serum and plasma samples at Visits 2, 4, 5, and 7 (randomization, 2, 4, and 8 weeks)' With: 'In addition, biomarker measurements will be obtained from serum and plasma samples at Visits 2, 3, 4, 5, 7 and 9 (randomization, 2, 4, 8 and 12 weeks)
Page 53, 6.5.1 Physical examination	Replaced: 'Significant findings made after the start of study drug which meet the definition of an adverse event must be recorded on the Adverse Event screen of the eCRF.' With: 'Significant findings made after informed consent which meet the definition of an adverse event must be recorded on the Adverse Event eCRF.'
Page 53, 6.5.3 Height, weight and waist/hip circumference	Replaced: 'Height in centimeters if possible, body weight to the nearest 0.1 kg without shoes, will be measured at all visits. Waist/hip circumference to the nearest centimeter will be measured at Visits 1, 2, 5 and 7.' With: 'Height in centimeters if possible will be measured at Visits 1 and 2. Body weight to the nearest 0.1 kg without shoes, will be measured at all visits. Waist/hip circumference to the nearest centimeter will be measured at Visit 1.'
Page 53, 6.5.4 Angioedema	Replaced: 'The angioedema eCRF must be completed and the Novartis Medical Monitor must be notified.' With: 'The Angioedema Assessment forms must be completed and the Clinical Trial Lead or their designee must be notified.'
Page 53, 6.5.5 Laboratory evaluations	Added: 'If eligibility laboratory assessments were not done during the patient's hospitalization, samples should be collected and sent to the local laboratory.'
Page 54, 6.5.5.1 Hematology	Added 'Hemoglobin A1c will be measured at Visit 2 (central lab).'
Page 54, 6.5.5.2 Clinical chemistry	Added 'Assessments required for eligibility that need to be measured at Visit 1 include creatinine, potassium, and total bilirubin.' Deleted 'hemoglobin A1C'
Page 54, 6.5.5.3 Urinalysis	Replaced:

	'Dipstick-test determination of specific gravity, pH, blood, total protein, bilirubin, ketones, and leukocytes will be measured at Visits 1 (local lab) 2, 4, 5 and 7 (central lab).' With: 'Dipstick-test determination of specific gravity, pH, blood, total protein, bilirubin, ketones, and leukocytes will be measured at Visit 2 (central lab).'
Page 54, 6.5.6 Pregnancy and assessments of fertility	Replaced: 'If any of these tests are positive, the patient must be discontinued from the study.' With 'If any of these tests are positive at Visits 1 and 2, the patient should not be enrolled in the trial. If a patient should become pregnant during the trial, the patient may remain in the trial for follow-up visits but must discontinue study drug.'
Page 56, 7.1 Adverse events	Replaced 'starting study drug' with 'informed consent'
Page 59	Added new section 7.3 Reporting of study treatment errors including misuse/abuse:
Page 59, 7.4 Pregnancy reporting	Text replaced with: 'To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment. Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.'
Page 74, Appendix 1	Deleted 'and vital Signs' from section title

Amendment 2 (05Oct2017)
On the basis of blinded review of the projected aggregated (enalapril and sacubitril/valsartan treatment groups combined) rate of missing samples for NTproBNP, this rate exceeds the initial trial assumption of 10%. The sample size has been increased to 882 patients in order to preserve the originally intended power.
Given interest in the effect of sacubitril/valsartan on NTproBNP after titration to dose level 3, a secondary endpoint has been added.
The exploratory endpoint of re-hospitalization through Day 30 is added due to the interest in decreasing hospital readmissions in view of the significant financial penalties that institutions can incur for these readmissions.

Summary of Changes

Location of change in original protocol	**Change**

Page 11, Protocol Summary, Secondary Objectives	Objective added: The proportional change in NT-proBNP from baseline to Week 8
Page 12, Protocol Summary, Exploratory objectives	Objective added: Re-hospitalization through Day 30
Page 12, Protocol Summary, Population	Randomization goal changed from 736 to 882 patients
Page 13, Protocol Summary, Population	Number of centers changed from approximately 140 to approximately 170
Page 15, Protocol Summary, Efficacy Assessments	Secondary assessment added: Proportional change in NT-proBNP from baseline to Week 8 Exploratory assessment added: Re-hospitalization through Day 30
Page 16, Protocol Summary, Data analysis	Text added: For NT-proBNP at Week 8, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. The estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0. Week 4 will be used if the Week 8 value is missing.
Page 17, Protocol Summary, Data analysis	Text changed: Assuming a significance level of 0.05 and 85% power, a sample size of ~~736~~ 882 patients would be needed to detect an 18% reduction in the geometric mean of the time-averaged proportional change from baseline (average of Weeks 4 and 8) in NT-proBNP for the sacubitril/valsartan treatment group assuming a value of 0.95 for the enalapril group, a common standard deviation of 0.85 and a ~~10~~25% rate of missing/non-evaluable samples~~loss to follow-up rate~~.
Page 21, 1.2 Rationale for protocol amendment	Text added: Amendment 2 (05Oct2017) On the basis of blinded review of the projected aggregated (enalapril and sacubitril/valsartan treatment groups combined) rate of missing samples for NTproBNP, this rate exceeds the initial trial assumption of 10%. The sample size has been increased to 882 patients in order to preserve the originally intended power. Given interest in the effect of sacubitril/valsartan on NTproBNP after titration to dose level 3, a secondary endpoint has been added. The exploratory endpoint of re-hospitalization through Day 30 is added due to the interest in decreasing hospital readmissions in view of the significant financial penalties that institutions can incur for these readmissions.
Page 23, 2.2 Secondary objectives	Objective added: □□The proportional change in NT-proBNP from baseline to Week 8
Page 23, 2.3 Exploratory objectives	Objective added: To examine the effect of sacubitril/valsartan vs. enalapril on incidence of rehospitalization through Day 30
Page 27, 4 Population	Number of patients changed from 736 to 882 Number of centers changed from 140 to 170

Page 31, Table 5.1.2	Number of patients changed from 736 to 882
Page 44, 6.4 Efficacy	Secondary end point added: The proportional change in NT-proBNP from baseline to Week 8
Page 45, 6.4 Efficacy	Exploratory end point added: Re-hospitalization through Day 30
Page 58, 9.5.1 Secondary variables	Text added: For NT-proBNP at Week 8, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. The estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0. Week 4 will be used if the Week 8 value is missing.
Page 59, 9.5.2, Exploratory variables	Variable added: Re-hospitalization through Day 30
Page 60, 9.5.2, Exploratory variables	Text added: Exploratory variable 4 will be analyzed presenting Kaplan-Meier estimates and testing with the log rank test. Patients without an event will be censored at the earlier of the last contact date or Day 30.
Page 62, 9.7 Sample size calculation	First paragraph edited: Assuming a significance level of 0.05 and 85% power, a sample size of ~~736~~ 882 patients would be needed to detect an 18% reduction in the geometric mean of the time –averaged proportional change from baseline (average of Weeks 4 and 8) in NT-proBNP for the sacubitril/valsartan treatment group assuming a value of 0.95 for the enalapril group, a common standard deviation of 0.85 and a ~~10~~25% ~~loss to follow up~~ rate of missing/nonevaluable samples. The estimates are based on the day 5 to day 14 data from the RELAX -AHF study. The standard deviation estimate is supported by data from PARADIGM.
Page 62, Table 9-1	New column added: 'Non-evaluable rate' New row added: Non-evaluable rate 25%

NOVARTIS

Clinical Development

LCZ696/Sacubitril/Valsartan/Entresto®

CLCZ696BUS01

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

Statistical Analysis Plan (SAP)

Author:	CRO Statistician, UBC, McBride, Scott

Document type:	SAP Documentation
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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
27-Sep-2016	Prior to DB Lock	Creation of Final Version	NA – First Version	NA

Table of contents

List of abbreviations

ACEi	Angiotensin Converting Enzyme Inhibitors
ADHF	Acute Decompensated Heart Failure
AE	Adverse Event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ARB	Angiotensin Receptor Blocker
ATC	Anatomical Therapeutic Chemical
bid	bis in diem/twice a day
BMI	Body Mass Index
BNP	B-type Natriuretic Peptide
CCU	Coronary Care Unit
cGMP	cyclic Guanosine 3',5'-Monophosphate
CHF	Chronic Heart Failure
CKD	Chronic Kidney Disease
CMH	Cochran-Mantel-Haenszel
CRO	Contract Research Organization
CRT-P	Cardiac resynchronization therapy – no ICD
CRT-D	Cardiac resynchronization therapy – with ICD
CSR	Clinical Study report
CTCAE	Common Terminology Criteria for Adverse Events
DCT	Data Collection Tool
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Emergency Department
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
HCTZ	Hydrochlorothiazide
HF	Heart Failure
HS	High Sensitivity
ICD	Implantable Cardioverter Defibrillator
ICU	Intensive Care Unit
i.v.	Intravenous
IVCD	Intraventricular Conduction Delay
IWRS	Interactive Web Response System
KCCQ	Kansas City Cardiomyopathy Questionnaire
KM	Kaplan Meier
LBB	Left Bundle Branch
LCZ696	Sacubitril/Valsartan
LS	Least squares
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities

MRU	Medical Resource Utilization
NT-proBNP	N-terminal Prohormone of B-type Natriuretic Peptide
NYHA	New York Heart Association
PD	Pharmacodynamic
PGA	Patient Global Assessment
PK	Pharmacokinetic
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PT	Preferred Term
RBB	Right Bundle Branch
RS	Randomized Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-emergent Adverse Event
TFLs	Tables, Figures, Listings
TIA	Transient Ischemic Attack
UBC	United BioSource Corporation
VAD	Ventricular Assist Device
WHO	World Health Organization

1 Introduction

The statistical analysis plan (SAP) will outline in detail the analyses planned in the protocol. The analyses will be used to generate the Clinical Study Report (CSR). The SAP is based on protocol version 01 (Amended protocol) dated 28Jul2016 and the data collection tool (DCT) version 4.0 dated 14Jul2016.

1.1 Study design

This study will use a randomized, double-blind, double-dummy, active-controlled, parallel group design. Eligible patients hospitalized for acute decompensated heart failure (ADHF) will be randomized no earlier than 24 hours and up to ten days of presentation while still hospitalized. A total of approximately 736 patients randomized to sacubitril/valsartan or enalapril in a 1:1 ratio is planned with no stratification.

At the time of randomization, patients will have been stabilized, defined for this study as:

- Systolic blood pressure (SBP) $\geq$ 100 mmHg for the preceding 6 hours prior to randomization; no symptomatic hypotension
- No increase (intensification) in intravenous (i.v.) diuretic dose within last 6 hours prior to randomization
- No i.v. inotropic drugs for 24 hours prior to randomization
- No i.v. vasodilators including nitrates within last 6 hours prior to randomization

All patients will need to meet all other inclusion and none of the exclusion criteria.

In order to provide for a necessary 36 hour washout of prior angiotensin converting enzyme inhibitors (ACEi) treatment prior to receiving sacubitril/valsartan (known as LCZ696 in prior trials), the supplied blinded study drug for those allocated to sacubitril/valsartan will be placebo only until the 3rd dose. Because the study is blinded, all patients, regardless of randomization arm, need to remain in the hospital for six hours after they have received their 3rd dose of study medication.

Initial dose will be determined by the blood pressure at the time of randomization. Study treatment will be titrated to the Level #3 target doses of sacubitril/valsartan 97/103 mg (bis in diem/twice a day) bid and enalapril 10 mg bid. Titration will be based on blood pressure at the time of the visit. Dose adjustments will only be allowed if indicated per protocol defined safety/tolerability criteria and investigator judgement. At the end of the 8-week treatment period all patients will need to have a 36 hour washout from study treatment prior to starting the open-label extension to ensure that the blinding of the core study is maintained. To facilitate this washout, patients should take their final dose of study drug on the morning of their week 8 visit and then begin open label sacubitril/valsartan after 36 hours in the evening of week 8 visit + one day. All patients will start open label treatment on sacubitril/valsartan at their final dosing level during double blind treatment. However, at an investigator's judgement, starting dose may be adjusted by one dose level up or down.

Eligible patients will be randomized no earlier than 24 hours after presentation at the hospital and no later than within ten days of admission, while still hospitalized, via interactive web response system (IWRS) to one of the treatment arms. The investigator or his/her delegate will contact the IWRS after confirming that the patient fulfills all of the study entry criteria. The IWRS will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify which bottle from the centralized hospital supply the patient will be dosed for the first day and a unique medication number for the first package of investigational treatment to be dispensed to the patient.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IWRS provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The primary time point will be weeks 4 and 8.

There are no interim analyses planned.

1.2 Study objectives and endpoints

The primary objective of this study is to assess the effect of in hospital initiation of sacubitril/valsartan vs. enalapril on the time-averaged proportional change of N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) from baseline in patients who have been stabilized following hospitalization for ADHF and reduced ejection fraction (left ventricular ejection fraction [LVEF] $\leq$ 40%). Weeks 4 and 8 will be included in the analysis (primary analysis time point).

The secondary objectives of this study are to examine the effect of sacubitril/valsartan vs. enalapril on:

- Incidence of symptomatic hypotension during 8 weeks of treatment
- Incidence of hyperkalemia (Potassium >5.5 mEq/L) during 8 weeks of treatment
- Incidence of angioedema during 8 weeks of treatment
- Biomarkers: hs-Troponin (high sensitivity), urinary cyclic Guanosine 3',5'-Monophosphate (cGMP) and B-type natriuretic peptide (BNP) to NT-proBNP ratio at 4 and 8 weeks

In addition, the exploratory objectives are:

- To examine the effect of sacubitril/valsartan vs. enalapril on time to first occurrence of composite clinical endpoint that includes death, heart failure re-hospitalization, requirement of left ventricular assist device (LVAD), listed for cardiac transplantation, unplanned acute heart failure (HF) visits requiring i.v. diuretics, additional heart failure drug or increase in >50% of the diuretic dose.

- To examine the effect of sacubitril/valsartan vs. enalapril on change from baseline at Weeks 1 and 2 in NT-proBNP.
- To examine the effect of sacubitril/valsartan vs. enalapril on incidence of re-hospitalization, emergency department (ED) visit or unplanned outpatient clinic visits due to worsening HF symptoms.
- To examine the effect of sacubitril/valsartan vs. enalapril on the need for advanced heart failure therapies (including but not limited to i.v. inotropes, LVAD, transplantation).
- To examine the effect of sacubitril/valsartan vs. enalapril on patient centered outcomes including the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Patient Global Assessment (PGA) at 4 and 8 weeks post randomization.
- To examine the effect of sacubitril/valsartan vs. enalapril on change in biomarkers related to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury, and renal function, including estimated glomerular filtration rate (eGFR).
- To examine change in NT-proBNP in the enalapril arm during the 4 week open label period.
- To examine the effect of sacubitril/valsartan vs. enalapril on medical resource utilization (MRU).
- To examine the effect of sacubitril/valsartan vs. enalapril on incidence of worsening renal function during 8 weeks of treatment, defined as an increase in serum creatinine of $\geq$ 0.5 mg/dL from the value measured at baseline.

2 Statistical methods

2.1 Data analysis general information

United BioSource Corporation (UBC), a Novartis-designated Contract Research Organization (CRO) will be performing all analyses outlined in this SAP. SAS® version 9.3 (or higher) will be used for all analyses.

Data from all centers that participate in this protocol will be combined, so that an adequate number of patients will be available for analysis.

Unless otherwise specified, for continuous data, the mean, standard deviation, median, first and third quartile, interquartile range, and minimum and maximum values will be presented. For categorical data, frequencies and percentages will be presented. All statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

All data will be provided in listings in addition to summaries described below.

2.1.1 General definitions

Study treatment

Patients will receive either sacubitril/valsartan or enalapril during the first 8 weeks of the study. Study treatment will refer to either of these two drugs.

Baseline

In general, the last non-missing assessment prior to the start of study treatment, including matching placebos, will be used as the baseline assessment. If time is available for the assessment, it should be used to determine the last non-missing assessment prior to start date:time of study treatment. If time is not available, the last non-missing assessment prior to or on the start date of study treatment will be used.

Date of first administration of study treatment

Double-blind phase: The date of first administration of study treatment in the double-blind phase is defined as the first date a dose of study treatment is administered and recorded on the dose administration (randomization/visit 2) electronic case report form (eCRF).

Open-label phase: The date of first administration of study treatment in the open-label phase is defined as the first date a dose of sacubitril/valsartan is administered in the open-label phase and recorded on the dose administration (week 8/visit 7) eCRF.

Pooled phase: The date of first administration of study treatment in the pooled phase is defined as the first date a dose of sacubitril/valsartan is administered either in the double-blind phase or open-label phase.

Date of last administration of study treatment

Double-blind phase: The date of last administration of study treatment in the double-blind phase is defined as the last date a dose of study treatment is administered in the double-blind phase and recorded on the dose administration (week 8/visit 7) eCRF, or earlier if prematurely discontinued and recorded on the Early Investigational Product Permanent Discontinuation eCRF.

Open-label phase: The date of last administration of study treatment in the open-label phase is defined as the last date of sacubitril/valsartan is administered in the open-label phase and recorded on the drug administration eCRF.

Pooled phase: The date of last administration of study treatment in the pooled phase is defined as the last date of sacubitril/valsartan administered either in double-blind phase or open-label phase.

Study day

The study day describes the day of the assessment relative to the date of randomization.

The study day will be calculated as the difference between the date of assessment and the date of randomization plus 1. If the date of assessment is prior to the date of randomization, the study day will be negative and will be calculated as the difference between the date of the assessment and the date of randomization.

On-treatment assessment (double-blind phase)

An on-treatment assessment during the double-blind phase is defined as any assessment obtained in the following time intervals:

Date of first administration of study treatment through the date of the last administration of study treatment in the double-blind phase, inclusive.

This will also be referred to as the double-blind phase.

An 'active treatment' assessment is also defined for the purpose of sensitivity analyses starting with the first dose of study treatment in patients randomized to enalapril and the third dose of study treatment in patients randomized to sacubitril/valsartan.

On-treatment assessment (open-label phase)

An on-treatment assessment during the open-label phase is defined as any assessment obtained in the following time interval: Date of first administration of study treatment in open-label phase through the date of the last administration of study treatment + 28 days, inclusive.

This will also be referred to as the open-label phase.

On-treatment assessment (pooled phase)

An on-treatment assessment during the pooled phase is defined as any on-treatment assessment obtained in the double-blind phase for patients randomized to sacubitril/valsartan or any on-treatment assessment obtained in the open-label phase, regardless of randomized treatment arm.

This will also be referred to as the pooled phase.

Last contact

The date of last contact will be the last date at which vital status can be ascertained for each patient and will be derived by examining all data collected in the eCRFs. Details are described in the separate programming specifications.

Year, month and week

For reporting purposes, the rules below will be followed to convert a year, month and week to days.

1 year = 365.25 days

1 month = 30.3475 days

1 week = 7 days

1 day = 24 hours

2.2 Analysis sets

The following analysis data sets will be used in the analyses:

Randomized Set (RS): The RS will consist of all randomized patients.

Full Analysis Set (FAS): The FAS will consist of all randomized patients with the exception for those patients who have not been qualified for randomization and have not received study treatment, but have been inadvertently randomized into the study. Following the intent-to-treat principle, patients will be analyzed according to the treatment to which they were assigned at randomization. Efficacy variables will be analyzed based on the FAS as the primary set.

Safety Set (SS): The SS will consist of all randomized patients who have received at least one dose of active study treatment. Patients will be included in the analysis according to the treatment actually received. The SS will be used for the analyses of safety variables.

Per-Protocol Set (PPS): The PPS will be a subset of the FAS which will consist of the patients who do not have a major deviations from the protocol procedures in the double-blind study phase. Major protocol deviations will be pre-specified prior to unblinding treatment code for analysis. This supplemental efficacy set will be used to support the primary analysis results.

2.2.1 Subgroup of interest

The following subgroups will be analyzed for the primary objective and the secondary objective for adverse events (AEs) of special interest:

1. Age group (<65, ≥65 years) and (<75, ≥ 75 years)
2. Ejection fraction categories prior to randomization (>40%, >30%-40%, >20%-30%, ≤20%)
3. Prior use of ACEi/ARB (at the time of hospitalization)
4. Baseline quartiles of NTproBNP (randomization sample)
5. Baseline eGFR (<30, 30 - <45, 45-<60, ≥60 ml/min/1.73 m^2)
6. Systolic blood pressure at randomization (<110, ≥110 mm Hg)

See sections 2.5 and 2.7 for further details on the primary and secondary objectives, respectively.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

All patients will be used for the summary of patient disposition. The following categories will be summarized:

- Number of patients who were screened
- Number of patients who were not randomized
- Primary reason for not continuing to double-blind phase
    - Investigator decision
    - Subject/Guardian decision
    - Screen failure
    - Adverse event
    - Pregnancy
    - Study terminated by sponsor
    - Technical problems

  - Death
- Number of patients who were randomized
- Number and percentage of patients who were treated
- Number and percentage of patients who prematurely discontinued study treatment during double-blind phase
- Number and percentage of patients who prematurely discontinued study treatment during open-label phase
- Reasons for premature discontinuation of study treatment (during double-blind phase and open-label phase)
  - Adverse event
  - Death
  - Protocol deviation
  - Investigator decision
  - Subject/Guardian decision
  - Lost to follow-up
  - Technical problems
  - Pregnancy
  - Withdrawal of consent
  - Noncompliance with study treatment
  - Study terminated by sponsor
- Number and percentages of patients who completed the double-blind phase
- Number and percentages of patients who completed the open-label phase
- Study duration in months [*(date of last contact/death – date of randomization +1)/30.3475*]

A separate summary for study completion will be presented and the FAS will be used. The following categories will be summarized at week 8 and week 12, unless otherwise specified, by treatment group, open-label and pooled sacubitril/valsartan with all information presented in a listing:

- Randomized patients (Received medication, did not receive medication)
- Patients complete (week 8 or week 12)
- Patient deaths (prior to week 8, prior to week 12)
- Patients with known vital status (In person or death, telephone contact, other contact)
- Patients with unknown vital status (Withdrawal of informed consent, potential lost to follow-up)

- Patients with clinical event assessment (In person or death, telephone contact, other contact)
- Patients with vital status only
- Patients with NT-proBNP assessment (week 4, week 8)

Additionally, listings of inclusion/exclusion criteria, screening disposition, reason for withdrawal of consent and study treatment disposition will be provided.

Any visit that did not occur per protocol will be listed with the reason it was not done.

2.3.2 Protocol deviations

The number and percentages of protocol deviations by category will be summarized by treatment phase (see section 2.1.1 for on-treatment assessment phase definitions). Additionally, a listing of deviations during the study will also be presented. The RS will be used.

2.3.3 Index hospitalization

The number and percentages of the following information about patients and their index hospitalization visit will be summarized by treatment group, open-label and pooled sacubitril/valsartan. The RS will be used.

- Patient in shock (No, Yes, Unknown)
- Patients receiving following treatment from index hospitalization to randomization
    - Vasopressor (No, Yes, Unknown)
    - Inotrope (No, Yes, Unknown)
    - Nitroprusside (No, Yes, Unknown)
    - Nesiritide (No, Yes, Unknown)
    - Patient in Intensive Care Unit (ICU) (No, Yes, Unknown)

The number and percentages (categorical variables) and descriptive statistics (continuous data) for information on patient index hospitalization discharge will be summarized by treatment group, open-label and pooled sacubitril/valsartan. The RS will be used.

- Duration of index hospitalization stay in days [(*date:time of discharge – date:time of arrival)/(3600*24)*]
- Discharge disposition (Home or with family/friends, Rehabilitation facility, Skilled nursing facility, Death, Unknown)
- Discharge weight (kg)
- New York Heart Association (NYHA) class (I, II, III, IV, Not done)
- Experience of worsening heart failure after randomization (No, Yes, Unknown)
- Patient in ICU (No, Yes, Unknown)

- Number of nights in ICU since randomization

- Since randomization, patient treated with the following medication classes? (Intravenous inotrope, Intravenous vasopressor, Nitroprusside, No, Unknown)
- Patient took third dose of double-blind study treatment (No, Yes)

All information relating to the index hospitalization will be listed.

2.3.4 Demographics and other baseline characteristics

Demographics and baseline characteristics and disease history are collected at the screening visit. Descriptive summaries and/or listings will be provided. The number and percentages (categorical variables) and descriptive statistics (continuous data) for the information below will be summarized by treatment group, open-label and pooled sacubitril/valsartan.

The FAS will be used.

Demographics and baseline characteristics

Demographic variables include:

- Age (years), age group (<65 years and ≥ 65 years; < 75 years and ≥ 75 years)
- Sex (Male, Female)
    - Child bearing status (Able to bear children, Premenarche, Post-menopausal [per-protocol > 12 months], Sterile-of child bearing age)
- Race (Caucasian, Black, Asian, Native American, Pacific Islander, Unknown, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

Baseline characteristic variables include:

- Height (cm)
- Weight (kg)
- Body mass index (BMI) [= *weight (kg)/height (m)^2 from screening visit 1*]
    - BMI categories (<20, 20-25, 25-30, >30)
- Smoking history (Former, Current, Never)
- Heart rate (bpm)
- Bundle branch block (or Intraventricular Conduction Delay [IVCD]) present? (No, Yes)
    - Bundle branch block type (Left bundle branch [LBB] block, Right bundle branch [RBB block], Non-specific intraventricular conduction delay)
- NT-proBNP (pg/mL)
    - NT-proBNP (pg/mL) categories (<450, 450 - <900, 900 - <1600, 1600 - <3200, 3200 - <7400, 7400 - <10000, ≥10,000)

- BNP (pg/mL)
    - BNP (pg/mL) categories (<100, 100 – <225, 225 – <400, 400 - <800, 800 - <1850, 1850 - < 2500, ≥2500)

Disease characteristics

Disease characteristic variables include:

- Category of prior chronic heart failure (CHF) medication (ACEi, Angiotensin Receptor Blocker [ARB], Beta blocker, Aldosterone antagonist, Ivabradine, Hydralazine, Nitrates [long lasting], Digoxin, Diuretic)
- History of HF prior to qualifying event (No, Yes, Unknown)
- Number of prior HF hospitalization within past 12 months
- Number of any prior hospitalizations within past 12 months
- NYHA classification (I, II, III, IV, Unknown)
- Ejection fraction (%)
    - Ejection fraction (%) categories (>40%, >30%-40%, >20%-30%, ≤20%)

Cardiovascular history

Cardiovascular history will be summarized. The following disease information will be collected:

- Hypertension (No, Yes, Unknown)
- Transient Ischemic Attack (TIA) (No, Yes, Unknown)
- Stroke (No, Yes, Unknown)
- Peripheral vascular disease (No, Yes, Unknown)
- Chronic renal insufficiency [eGFR < 60 ml/min/1.73m^2 on testing >30 days prior to index hospitalization] (No, Yes, Unknown)
    - Chronic Kidney Disease (CKD) stage (CKD stage 3 [eGFR 30-59], CKD stage 4 [eGFR 15-29], CKD stage 5 [eGFR <15 or dialysis])
- Arrhythmia (No, Yes, Unknown)
    - Arrhythmia type (Atrial fibrillation, Atrial flutter, Supraventricular tachycardia, Ventricular tachycardia)
- Pacemaker/Implantable Cardioverter Defibrillator (ICD) (No, Yes, Unknown)
    - Device type (Pacemaker [conventional], Cardiac resynchronization therapy – no ICD [CRT-P], Cardiac resynchronization therapy – with ICD [CRT-D], ICD only [single/dual], Other, Unknown)
- Moderate to severe valvular heart disease (No, Yes, Unknown)

- Heart disease type (Mitral regurgitation, Aortic regurgitation, Aortic stenosis, Tricuspid regurgitation)

Non-Cardiovascular Medical History

Non-cardiovascular medical history and ongoing conditions, will be summarized and listed. The summaries will be presented by primary system organ class, preferred term and treatment group, open-label and pooled sacubitril/valsartan Medical history and ongoing conditions are coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology (v19.0).

Surgeries and Medical Procedures

Any surgeries and/or medical procedures will be listed including the reason, start date and end date.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

The SS will be used for all analyses associated with study treatment and medications, unless otherwise specified.

2.4.1 Study treatment / compliance

The duration of double-blind study treatment phase is defined as:

Duration (days) = (date of last study treatment in double-blind study phase – date of first active study treatment) +1

The first date of active study treatment is recorded on the dose administration (randomization/visit 2) eCRF for enalapril and the third dose on Discharge from Index Hospitalization eCRF for sacubitril/valsartan. It is therefore expected that the duration of active study treatment will differ between randomized treatment groups.

The duration of the open-label study treatment phase is defined as:

Duration (days) = (date of last study treatment in open-label study phase – date of first study treatment in open-label phase) +1

The duration of the pooled phase (sacubitril/valsartan in double-blind phase and/or sacubitril/valsartan in open-label phase) is defined as:

Duration (days) = (date of last study treatment of sacubitril/valsartan [any phase] – date of first study treatment of sacubitril/valsartan [any phase]) +1

Summary statistics will be displayed for the duration of double-blind study treatment, duration of open-label study treatment and duration of pooled sacubitril/valsartan by phase.

The durations will also be categorized into weekly time intervals (< 7 days, 7 - < 14 days, 14 - < 21 days, …, etc.). The number and percentage of patients in each category will be presented by phase.

Total patient-days of exposure will also be summarized by phase.

In addition, the number and percentages of each dose level by visit will be summarized by treatment group and open-label sacubitril/valsartan. The number and percentage of the

maximum dose levels achieved will also be presented by treatment group and open-label sacubitril/valsartan. Similarly, the up-titrated doses, down-titrated doses and unchanged doses will be summarized by visit, treatment group and open-label sacubitril/valsartan.

All information on dose administration will be listed.

2.4.2 Prior, concomitant and post therapies

Non-HF Medications

Prior and concomitant non-HF medications will be coded according to the World Health Organization (WHO) Drug Reference List. The WHO Drug version will be denoted in the corresponding tables and listings. Prior and concomitant medications are mutually exclusive, as defined below:

- Prior medications are defined as any medication with an end date prior to the first dose of study treatment
- Concomitant medications are defined as any medications taken on or after the start of study treatment. Prior medications that are 'ongoing' at the time of the first study treatment or whose end date is after first study treatment will be considered a concomitant medication

The number and percentage of patients with concomitant medications that started after study treatment will be summarized by Anatomical Therapeutic Chemical (ATC) class, preferred term and treatment phase (refer to section 2.1.1 for on-treatment assessment phase definitions). All medications will be listed.

HF Medications

Medication names are provided for ACEi, ARB, Beta blocker and other antiplatelets and will be coded using the WHO Drug Reference List and the preferred term will be displayed for these categories.

The number and percentages of prior HF medications at screening will be summarized by treatment group, open-label and pooled sacubitril/valsartan. Similarly, the HF medications collected at randomization will be summarized by treatment group, open-label and pooled sacubitril/valsartan. A descriptive summary for the total daily dose of each medication (for which doses are collected) will also be presented. These summaries will also be presented using the FAS.

The number and percentages of HF medications collected post randomization will be summarized by treatment phase (see section 2.1.1 for on-treatment assessment phase definitions). The overall summary will be presented. The following medications will be summarized: Beta blocker, Ivabradine, Nitrites (long acting), Calcium channel blocker, Potassium, Digoxin, Statin, Furosemide, Torsemide, Bumetanide, Hydrochlorothiazide (HCTZ), Diuril (chlorothiazide), Metolazone, Spironolactone and Eplerenone.

Additionally, a descriptive summary for the total daily dose of each diuretic taken post randomization will be presented by visit, treatment group and open-label sacubitril/valsartan. These include: Furosemide, Torsemide, Bumetanide, HCTZ, Diuril (chlorothiazide), Metolazone, Spironolactone and Eplerenone. Additionally, the diuretics will be combined into

a single dose equivalent and the total daily dose will be summarized. The derivation of the combined diuretic dose will be defined in the programming specifications section of the SAP TFL mock-ups document.

HF Medications at Index Hospitalization Discharge

The number and percentages of HF medication at the index hospitalization discharge will be summarized by treatment group, open-label and pooled sacubitril/valsartan. The following medications will be summarized: Beta blocker, Ivabradine, Hydralazine, Nitrites (long acting), Calcium channel blocker, Potassium, Digoxin and Statin. Additionally, the number and percentages of each daily diuretic and/or potassium taking during the index hospitalization collected at discharge, the route (when applicable) and total daily dose will be summarized by treatment group, open-label and pooled sacubitril/valsartan. Additionally, the diuretics will be combined into a single dose equivalent and the total daily dose will be summarized. The derivation of the combined diuretic dose will be defined in the programming specifications section of the SAP TFL mock-ups document.

These summaries will also be presented using the FAS.

Post Randomization Non-study Drug ACEi/ARB

Any ACEi and/or ARB taken after randomization will be listed.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary endpoint is the time-averaged proportional change from baseline in NT-proBNP. Weeks 4 and 8 will be included in the analysis (primary analysis time point). The analysis of the primary endpoint will be based on the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary hypothesis to be tested is the ratio of the geometric means of NT-proBNP (average of Weeks 4 and 8/baseline) for the sacubitril/valsartan and enalapril treatment groups are equal (H0) versus the ratio of the geometric means of NT-proBNP are not equal (Ha).

For NT-proBNP, the time-averaged proportional change from baseline in a logarithmic scale will be analyzed using an analysis of covariance (ANCOVA) model using data from Weeks 4 and 8 with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate.

The values from Weeks 4 and 8 will be averaged and the change from baseline in log-transformed NT-proBNP will be calculated as follows:

log (average post dose value) – log (baseline value)

The estimated treatment effect in terms of ratios of geometric means, based on the least-squares (LS) means from the model, and the corresponding two-sided 95% confidence intervals will be presented.

The geometric means (presented as a ratio to baseline) will be calculated by exponentially back transforming the LS means based on the ANCOVA model as follows:

exp (LS mean)

2.5.3 Handling of missing values/censoring/discontinuations

The analysis will be performed based on all available data in the FAS and based on likelihood method with an assumption of missing at random for missing data.

2.5.4 Supportive analyses

Summary statistics showing the log-transformed change from baseline values for NT-proBNP at Weeks 4 and 8 will be presented. T-tests comparing treatment groups using change from (log) baseline to log (Week 4) and log (Week 8) values will be performed.

The primary endpoint will also be analyzed in the PPS using the same analytical approach as described in Section 2.5.2.

In addition, a binary outcome variable will be created for patients achieving a 25%, 50% and 75% decline in NT-proBNP (0-no, 1-yes) and a logistic regression model will be fit. The odds ratio, 95% confidence interval and p-value will be provided. The outcome variable will be achieving a decline in NT-proBNP and the predictor of response will be treatment group.

2.6 Analysis of the key secondary objective

No key secondary objective.

2.7 Analysis of secondary objectives

All analyses will be performed on the FAS, unless otherwise specified.

2.7.1 Secondary endpoints

Secondary endpoints include the following:

- Incidence of symptomatic hypotension during 8 weeks of treatment
- Incidence of hyperkalemia (potassium >5.5 mEq/L) during 8 weeks of treatment
- Incidence of angioedema during 8 weeks of treatment
- Biomarkers: hs-Troponin (high sensitivity), urinary cGMP and BNP to NT-proBNP ratio at 4 and 8 weeks

2.7.2 Statistical hypothesis, model, and method of analysis

The incidence of symptomatic hypotension up to week 8 will be calculated by treatment group. The relative risk (sacubitril/valsartan vs. enalapril) and the 95% confidence interval will also be presented. Similarly, the incidence of hyperkalemia and angioedema during the 8 week double-blind phase and the relative risk (sacubitril/valsartan vs. enalapril) will be summarized. Additionally, medication change, lowest documented systolic blood pressure and lowest documented diastolic blood pressure will be summarized by treatment group for symptomatic

hypotension. The highest potassium value documented for hyperkalemia will also be summarized by treatment group.

For biomarkers including BNP to NT-proBNP ratio, hs-Troponin, and urinary cGMP, the time-averaged proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model using data from Weeks 4 and 8 with treatment group as a fixed effect factor and the logarithmic baseline biomarker value as a covariate.

Similar to the primary endpoint, the values from Weeks 4 and 8 will be averaged and the change from baseline will be calculated.

The estimated treatment effect in terms of ratios of geometric means, based on the LS means from the model, and the corresponding two-sided 95% confidence intervals will be presented. The geometric means (presented as a ratio to baseline) will be calculated by exponentially back transforming the LS means based on the ANCOVA model.

For biomarkers BNP to NT-proBNP ratio and urinary cGMP at weeks 1 and 2, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. For each visit, the estimated treatment effects in terms of ratios of the geometric means based on the LS means from the model, and the corresponding two-sided 95% confidence intervals produced from the model will be presented. Similarly, the geometric mean will be calculated by exponentially back transforming the LS means based on the ANCOVA model.

2.7.3 Handling of missing values/censoring/discontinuations

The analysis will be performed based on all available data in the FAS and based on likelihood method with an assumption of missing at random for missing data.

2.8 Safety analyses

All safety analyses will be performed on the SS unless otherwise specified.

2.8.1 Adverse events

2.8.1.1 Coding of AEs

Adverse events are coded using the MedDRA (v19.0).

2.8.1.2 General rules for AE reporting

AE summaries will include all treatment-emergent AEs (TEAEs). TEAEs are defined as AEs starting on or after study day 1 (i.e., on or after the first day of study treatment) and starting no later than 28 days after the last day of study treatment (depending on treatment phase). All AEs will be listed. AEs starting prior to study day 1 and AEs starting later than 28 days after the last day of treatment will be flagged in the listings.

All TEAEs will be summarized by treatment phase as defined in Section 2.1.1.

TEAEs will be summarized by presenting the number and percentage of patients having at least one TEAE, having at least one TEAE in each primary system organ class (SOC), and for

each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of a TEAE will be counted only once in the AE category.

Separate summaries will be presented by SOC, PT and severity. A patient with multiple severities for an AE will be summarized under the worse severity recorded for the event.

Any information collected will be listed as appropriate.

2.8.1.3 AE summaries

The following summary tables will be provided by:

- AEs, regardless of study treatment relationship by primary SOC, PT and worst severity
- Most frequent (≥5%) AEs, regardless of study treatment relationship by PT
- AEs suspected to be related to study treatment by primary SOC and PT
- Serious adverse events (SAE), regardless of study treatment relationship, by primary SOC and PT
- SAEs suspected to be related to study treatment by primary SOC and PT
- AEs leading to discontinuation, regardless of study treatment relationship, by primary SOC and PT
- AEs requiring dose adjustment or study treatment interruption, regardless of study treatment relationship, by primary SOC and PT
- AEs requiring additional therapy, regardless of study treatment relationship, by primary SOC and PT
- Death resulting from AEs by primary SOC and PT

2.8.1.4 Adverse events of special interest / grouping of AEs

Separate summaries will be provided for AEs related to angioedema, elevated creatinine, hyperkalemia and symptomatic hypotension. The summaries will be presented by primary SOC, PT and maximum severity.

Additionally, a sensitivity analysis will be performed on the AEs of special interest for patients randomized to sacubitril/valsartan. The number and percentages of AEs of special interest occurring prior to the active dose of sacubitril/valsartan will be presented along with the number and percentages of AEs of special interest occurring on or after the active dose of sacubitril/valsartan during the double-blind phase. The following definition will be used:

Angioedema:

AE prior to active study treatment = if event occurred within 1 day of dosing as recorded on the Angioedema Assessment Visit 2 (randomization)

AE after active study treatment = if event occurred after 1 day of dosing as recorded on the Angioedema Assessment Visit 2 (randomization)

Symptomatic hypotension:

AE prior to active study treatment = First dose date ≤ event < Third dose date of study treatment

AE after active study treatment = Third dose date of study treatment ≤ event ≤ Last dose date of double-blind medication

Elevated creatinine and hyperkalemia:

AE prior to active study treatment = First dose date:time of study treatment ≤ event < Third dose date:time of study treatment

AE after active study treatment = Third dose date:time of study treatment ≤ event ≤ Last dose date:time of double-blind medication

2.8.2 Deaths

Patient deaths will be summarized by total, primary cause of death, type of cardiovascular death and type of non-cardiovascular death and will be presented by treatment phase (see section 2.1.1 for on-treatment assessment phase definitions). A patient listing of all deaths with recorded principal cause of death will be provided. All patients in FAS will be included for the above analysis and deaths that are after 28 days of last dose of treatment will be flagged in the listing.

2.8.3 Laboratory data

Laboratory values will be summarized using shift tables (from baseline to most extreme post baseline value) by each laboratory parameter at its worst severity by treatment phase (see section 2.1.1 for on-treatment assessment phase definitions). The number and percentage of patients with laboratory values will be presented by low/normal/high (low and high) classifications to compare baseline to worst post baseline value.

In addition, laboratory values and the change from baseline for each parameter by visit will be summarized by treatment group and open-label sacubitril/valsartan. In the event that there are multiple laboratory values within a visit, the worst value will be summarized.

A separate summary table will be presented with the number and percentage of patients having notable lab abnormalities based on percent change from baseline (see section 5.3 for a list of notable laboratory abnormalities). Summary table will be presented by treatment phase (see section 2.2.1 for on-treatment assessment phase definitions).

A summary of hyperkalemia labs by visit will also be presented by treatment group and open-label sacubitril/valsartan. The highest potassium value for the event and any potassium re-test results will be descriptively summarized. Similarly, creatinine labs will also be presented by visit, treatment group and open-label sacubitril/valsartan. The highest creatinine value for the event and any creatinine re-test results will be descriptively summarized.

Listings of all laboratory values will be provided. Separate listings for hyperkalemia labs, creatinine labs and pregnancy tests will also be provided. Any notable laboratory abnormalities will also be flagged.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

ECG data will be collected at screening and all data, including unscheduled visits, will be listed.

2.8.4.2 Vital signs

All vital signs (systolic and diastolic blood pressure [mmHg], pulse rate [sitting/beats per minute], weight [kg], height [cm], BMI [kg/m^2] and waist/hip circumference) will be descriptively summarized at each visit by treatment group and open-label sacubitril/valsartan. Change from baseline will also be presented.

A separate summary table will be presented with the number and percentages of patients having notable vital signs based on changes relative to baseline values (see section 5.4 for a list of notable vital signs) by treatment phase (see section 2.1.1 for on-treatment assessment phase definitions).

The number and percentages of patients having symptomatic hypotension will also be summarized by treatment phase. The following variables associated with symptomatic hypotension will also be presented: symptoms occurring while standing, any treatment or medication change as a result of episode, lowest documented systolic blood pressure, systolic blood pressure position, lowest documented diastolic blood pressure and diastolic blood pressure position. A listing for symptomatic hypotension will also be presented.

2.8.4.3 Heart Failure Event

Any new heart failure event information will be collected and listed. The following will be presented:

- Type of event (HF hospitalization [hospital stay ≥ 24 hours], Heart failure emergency department visit, Urgent/unplanned heart failure office visit, Worsening heart failure during the index hospitalization [qualifying heart failure event])
- Symptoms of worsening HF (Dyspnea – [Dyspnea at rest, Dyspnea on exertion, Orthopnea, Paroxysmal nocturnal dyspnea, Tachypnea], Decreased exercise tolerance [reduced ability to perform activities that induce physical exertion due to dyspnea or fatigue], Fatigue [lack of energy, extreme tiredness, inability to complete usual activities], Worsening end-organ perfusion – [Confusion (thought to be from low cardiac output), Reduced urine output], Symptoms of volume overload – [Lower extremity swelling, Increased abdominal distension)], Other)
- Physical exam signs of worsening HF (Peripheral edema, Increased abdominal distension or ascites [in the absence of hepatic disease], Pulmonary rales/crackles, Elevated jugular venous pressure and/or hepatojugular reflux, New or worsening 3rd heart sound, Clinically significant weight gain throught to be related to fluid retention [> 3-4 lbs. in 3 to 4 days], Other)
- Laboratory evidence of worsening HF (Increased NT-proBNP [>2,000 pg/mL], Radiographic evidence of pulmonary congestion, Right heart catheterization with

pulmonary capillary wedge pressure ≥ 18mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index of < 2.2 L/min/m^2, Other)

- Increase/addition of therapy (No, Yes, Unknown)
    - Therapy type (Augmentation of oral diuretic therapy with additional diuretic, Initiation of intravenous diuretic, Uptitration of intravenous therapy, if already on therapy, Initiation of inotrope, or vasodilator therapy, Initiation of percutaneous mechanical circulatory support, Initiation of temporary surgical support [ECMO or temporary surgical ventricular assist device (VAD) i.e. centrimag], Implantation of durable LVAD, Listed for heart transplantation)
- Evidence of cardiogenic shock (No, Yes, Unknown)
- Blood sample collected for BNP/NT-proBNP (No, Yes, Unknown)
    - BNP, pg/mL
    - NT-proBNP, mg/mL
- Contributors/precipitants of worsening heart failure (Medication nonadherence, Dietary indiscretion, Acute coronary syndrome, Other systemic illness – [Respiratory infection, Urinary tract infection, Other])

2.8.4.4 HF Signs and Symptoms

Heart failure signs and symptoms will be collected at screening, randomization and at post randomization visits. The number and percentage of the following parameters will be summarized by visit (at randomization and Week 8), treatment group and open-label sacubitril/valsartan:

- Rales (Not present, Basilar only, > 1/3 of lung filled, Not done)
- Peripheral edema (Absent, Trace, Feet and ankles, Lower legs or thighs, Sacrum, Not done)
- Current NYHA heart failure classification (Class I, Class II, Class III, Class IV, Not done)
- Fatigue (Not present, Seldom, Frequent, Continuous, Not done)
- Dyspnea (Not present, Seldom, Frequent, Continuous, Not done)
- Orthopnea (Not present, Seldom, Frequent, Continuous, Not done)

2.8.4.5 Hospitalization

Information related to hospitalization will be listed. The following will be presented:

- Type of hospitalization (Elective, Planned, Unplanned)
- Reason for hospitalization
- Patient discharged (No, Yes, Unknown)
    - Duration of hospitalization in days [*date of discharge – date of admission + 1*]

- Patient admittance to ICU or Coronary Care Unit (CCU) (No, Yes, Unknown)
    - Number of days in ICU or CCU
- Discharge disposition (Home or with family/friends, Rehabilitation facility, Skilled nursing facility, Death, Unknown)

2.8.4.6 Angioedema

Data collected from the angioedema assessment and questionnaire at screening, randomization and follow-up visits will be summarized. The number and percentage for categorical variables and summary statistics for continuous variables of the following will be presented by visit, treatment group and open-label sacubitril:

- Outcome (Not recovered/Not resolved, Recovered/Resolved, Recovering/Resolving, Recovered/Resolved with Sequelae, Fatal, Unknown)\
    - Duration of angioedema in days [*end date – start date + 1*]
- Timing of event (After first dose, after multiple doses, dose not given) [not asked at screening]
    - Study medication discontinued due to event (No, Yes, Unknown)
    - Event occurred within 1 day of dosing (Within 1 day of dose but less than or equal to 1 hour, within 1 day of dose but greater than 1 hour, After 1 day of dosing, Unknown)
- History of prior angioedema or angioedema like event (No, Yes, Unknown)
    - If yes, medications taken at time of previous event:
        - ACE inhibitor
        - ARB
        - Renin inhibitor
        - Other medications
- Presence of hereditary angioedema (No, Yes, Unknown)
- Any family members with history of angioedema-like events (No, Yes, Unknown)
- Signs and symptoms for current event
    - Shortness of breath/dyspnea
    - Difficulty swallowing/dysphagia
    - Difficulty speaking/dysarthria
    - Pain on swallowing/odynophagia
    - Stridor
    - Abdominal pain
    - Other

- Edema present (No, Yes)
    - Periorbital edema
    - Head edema
    - Neck edema
    - Lip edema
    - Tongue edema
    - Throat edema
    - Submandibular edema
    - Genitalia edema
    - Extremities edema
    - Other
- Previous edematous episodes (No, Yes, Unknown)
    - Number of previous edematous episodes
- ACEi taken in the past (No, Yes, Unknown)
- ACEi taken during trial participation after screening (No, Yes, Unknown) [not asked at screening]
    - Dose changed within 2 days of event (No, Yes, Unknown)
- ARB taken in the past (No, Yes, Unknown)
- ARB taken during trial participation after screening (No, Yes, Unknown) [not asked at screening]
    - Dose changed within 2 days of event (No, Yes, Unknown)
- Patient suffering from influenza, common cold or upper respiratory tract infection? (No, Yes, Unknown)
- Medication allergies (No, Yes, Unknown)
- Food allergies (No, Yes, Unknown)
- Potential causes of angioedema-like event
    - Food
    - Insect bite
    - Animal exposure
    - Medication
    - Dental work
    - Pollen

- Dust
- Concomitant disease
- Idiopathic
- Other

- Medical intervention (No, Yes)
  - Administration of H-1 blocker
  - Administration of H-2 blocker
  - Administration of steroids
  - Administration of epinephrine
  - Admission to hospital
  - Admission to ER
  - Endotracheal intubation
  - Tracheostomy
  - Discontinuation of ACE inhibitor
  - Discontinuation of ARB
  - Other

All assessment data will be listed. Additionally, the adjudicated assessment of the event will be listed separately.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes (PRO)

All analyses will be performed on the FAS.

2.11.1 Kansas City Cardiomyopathy Questionnaire[1]

The KCCQ is a 23-item self-administered instrument that quantifies physical limitations (question 1a – 1f), symptoms (questions 2 through 9), self-efficacy and knowledge (questions 10 and 11), social limitation (question 15a – 15d) and quality of life (questions 12 through 14). A likert-type scale is used with the higher values representing better outcomes.

Missing values within each domain will be imputed using the average of the answered items within the same domain. Scale scores will be transformed into values of 0 to 100 by subtracting the lowest possible scale score, dividing by the range of the scale and multiplying by 100. Further details on calculation of the transformed scores are available in the

programming specifications section of the SAP tables, figures, listing (TFL) mock-ups document. If a patient has died, each question for the last KCCQ assessment prior to death will be imputed as the worse response (coded as 1) prior to transformation and flagged in the listing. All analysis will be based on the transformed score.

The composite score for each domain, clinical summary score and an overall score will be summarized by visit and treatment group and open-label sacubitril/valsartan. The clinical summary score is the composite of the symptoms and social limitation domains.

Additional KCCQ analysis will be described in Section 2.13.

2.11.2 Patient Global Assessment

The PGA is a seven-point patient self-evaluation scale. At randomization, the patient will take note of how he/she feels about his/her condition and will be asked how they feel compared to randomization at follow-up visits.

The PGA will be summarized by visit, treatment group and open-label sacubitril/valsartan.

Additional PGA analysis will be described in Section 2.13.

2.12 Biomarkers

BNP and NT-proBNP will be collected and descriptively summarized by visit, treatment group and total. Values and the change from baseline for each parameter will be summarized by treatment group and total. Analyses will be based on the FAS.

Additional biomarker measurements believed to be relevant to the pathophysiology of the disease processes of heart failure and dysfunction will also be collected and summarized by visit, treatment group and total. These may include, but no limited to those assessing cardiac and renal benefit or biomarkers related to the study treatment mechanism of action such as:

- Neurohormones BNP and NT-proBNP
- hs-Troponin
- Cystatin c
- ST2
- eGFR
- urinary cGMP
- other biomarkers related to cardiac fibrosis/remodeling, tissue perfusion/injury, renal function/injury or other pathophysiologies involved in ADHF

Additional analysis of biomarkers is discussed in sections 2.5, 2.7 and 2.13.

2.13 Other Exploratory analyses

All analyses will be based on the FAS, unless otherwise specified.

Time to first occurrence of composite clinical endpoint

The composite clinical endpoint includes death, heart failure re-hospitalization, requirement of LVAD, listed for cardiac transplantation, unplanned acute HF visits requiring i.v. diuretics, additional heart failure drug or increase in >50% of the diuretic dose. Further details on derivation of the composite clinical endpoint are available in the programming specifications section of the SAP TFL mock-ups document. Individual elements of the composite will also be reported.

Time to first occurrence will be calculated in days as *date of first occurrence – start date of study treatment + 1*. Distribution of time to first occurrence will be estimated using the Kaplan-Meier (KM) method. The 25th percentile, median and the 75th percentile will be presented by treatment group along with the 95% confidence intervals and failure probabilities will be presented at 1 week, 2 weeks, etc., until 8 weeks along with the corresponding 95% confidence interval. Patients not having any of the endpoints described above will be censored at the date of last contact. The treatment groups will be compared using a log-rank test and the p-value will be presented. The number and percentages of each component of the clinical endpoint will also be presented.

In addition to the KM method, the time to first occurrence will also be analyzed using a Cox proportional hazards regression model with treatment as a factor. The hazard ratio with 95% confidence interval will be presented.

Change from baseline at Weeks 1 and 2 in NT-proBNP

For NT-proBNP at weeks 1 and 2, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. For each visit, the estimated treatment effects in terms of ratios of the geometric means based on the LS means from the model and the corresponding two-sided 95% confidence intervals produced from the model will be presented. The geometric mean will be calculated by exponentially back transforming the LS means.

Time to first hospitalization

The time to first hospitalization (re-hospitalization, ED and/or unplanned outpatient clinic visits due to worsening HF symptoms) after index hospitalization will be calculated in days as *date of first hospitalization – start date of study treatment + 1*. Further details on derivation of first hospitalization are available in the programming specifications section of the SAP TFL mock-ups document. Distribution of time to first hospitalization will be estimated using the KM method. The 25th percentile, median and the 75th percentile will be presented by treatment group along with the 95% confidence intervals and failure probabilities will be presented at 1 week, 2 weeks, etc., until 8 weeks along with the corresponding 95% confidence interval. Patients not having any of the endpoints described above will be censored at the date of last contact. The treatment groups will be compared using a log-rank test and the p-value will be presented. The number and percentages of each component of hospitalizations (re-hospitalization, ED and unplanned outpatient clinic visit due to worsening HF symptoms) will also be presented.

In addition, a binary outcome variable will be created for hospitalization within 30 days after index hospitalization discharge (0-no, 1-yes) and a logistic regression model will be fit. The

odds ratio, 95% confidence interval and p-value will be provided. The outcome variable will be hospitalization and the predictor of response will be treatment group. Similarly, a logistic regression model will be fit for each component hospitalization within 30 days after index hospitalization discharge – re-hospitalizations, ED visit and unplanned outpatient clinic visit due to worsening HF symptoms. The odds ratio, 95% confidence interval and p-value will be provided. The outcome variable will be each component of the hospitalizations and predictor response will be treatment group.

A negative binomial regression model will also be fit with the outcome variable being the number of re-hospitalizations and the predictor of response will be treatment group. To reduce bias, the model will use an offset option for the log of exposure duration to adjust the estimates. The log of exposure duration will be calculated in days by *log (date of last study treatment – start date of study treatment + 1).* The estimated event rates by treatment group and the 95% confidence intervals will be presented. In addition, the treatment comparison estimated ratio and the 95% confidence interval will also be presented. Similarly, a negative binomial regression mode will also be fit with the outcome variable as the number of heart failure visits requiring diuretics using the same approach discussed above. The estimated event rates by treatment group and the 95% confidence intervals will be presented. In addition, the treatment comparison estimated ratio and the 95% confidence interval will also be presented.

The following days summaries will also be presented:

- Days alive after index hospitalization not including re-hospitalization
- Days in the ICU/CCU
- Days on LVAD

An analysis of variance (ANOVA) model will be fit for each of these days variables as the dependent variable and the treatment group as an independent variable. The estimated difference in means between the treatment groups will be presented with 95% confidence intervals.

Need for advanced heart failure therapies

The need for advanced heart failure therapies including but not limited to i.v. inotropes, LVAD and/or transplantation will be analyzed. A binary outcome variable will be created (0-advanced heart failure therapies not needed, 1-advanced heart failure therapies needed) and a logistic regression model will be fit. The odds ratio, 95% confidence interval and p-value will be provided. The outcome variable will be advanced heart failure therapies and the predictor of response will be treatment group.

Patient centered outcomes at 4 weeks and 8 weeks post randomization

The clinical summary score at weeks 4 and 8 of the KCCQ will be analyzed using a repeated measures ANCOVA model with treatment, visit and treatment by visit interaction as fixed effect factors and the baseline value as a covariate. A common unstructured covariance for each treatment group will be used. The primary treatment comparison will be made at week 8. The analysis will be performed on all available data and based on the likelihood method. The

estimates of the treatment effects with the associated confidence intervals at week 8 will be provided by treatment group.

Additional analyses will be performed to determine characteristics that could affect improvement or deterioration of the KCCQ clinical summary score. A responder analysis having at least a 5 point improvement in the clinical summary score and a responder analysis having at least a 5 point deterioration in the clinical summary score from baseline will be performed. A logistic regression model will be fit with a binary outcome variable (0-no improvement/deterioration, 1-improvement/deterioration) and the predictors of response are age group, sex and race. The odds ratio, 95% confidence interval and p-value will be provided.

The PGA will be analyzed at week 4 and 8 using a Cochran-Mantel-Haenszel (CMH) test for comparison of the different treatment means based on modified ridit scores. P-values will be presented.

Change in biomarkers

For biomarkers relating to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury and/or renal function a proportional change from baseline in a logarithmic scale at weeks 2, 4 and 8 will be analyzed using a repeated measures ANCOVA model with treatment, visit and treatment by visit interaction as a fixed effect factors and the logarithmic baseline biomarker value as a covariate. The unstructured working correlation matrix will be used.

For each visit, the estimated treatment effects in terms of ratios of the geometric means based on the LS means from the model, and the corresponding two-sided 95% confidence intervals produced from the model will be presented. The geometric mean will be calculated by exponentially back transforming the LS mean.

Change in NT-proBNP during the 4 week open label period

The change from week 8 to week 12 for NT-proBNP will be descriptively summarized including p-values using a t-test comparing time point values by treatment group and total in a logarithmic scale.

Medical resource utilization

Medical resource utilization will be summarized by treatment group, open-label and pooled sacubitril/valsartan. The following will be presented:

- Unplanned doctor visits (No, Yes, Unknown)
    - Reason for visit (Cardiovascular, Non-cardiovascular, Unknown)
        - Visit heart failure related? (No, Yes, Unknown)
- Any hospitalizations? (No, Yes, Unknown)
- Patient initiated on dialysis or ultrafiltration? (No, Yes, Unknown)
    - Dialysis or ultrafiltration initiated for worsening heart failure? (No, Yes, Unknown)
- Pacemaker/ICD (No, Yes, Unknown)

- Pacemaker/ICD type (Pacemaker [conventional], cardiac resynchronization therapy-no ICD [CRT-P], cardiac resynchronization therapy-ICD [CRT-D], ICD only (single/dual), Unknown)

- Patient undergo placement of a cardioMEMS? (No, Yes, Unknown)

Incidence of worsening renal function during 8 weeks of treatment

Worsening renal function during 8 weeks of treatment is defined as an increase in serum creatinine of $\geq$ 0.5 mg/dL from the value measured at baseline. A logistic regression model will be fit with a binary outcome variable (0-no worsening renal function, 1-worsening renal function) and the predictors of response are treatment and baseline creatinine value. The odds ratio, 95% confidence interval and p-value will be provided.

2.14 Interim analysis

No interim analysis is planned.

3 Sample size calculation

Assuming a significance level of 0.05 and 85% power, a sample size of 736 patients would be needed to detect an 18% reduction in the geometric mean of the time-averaged proportional change from baseline (average of Weeks 4 and 8) in NT-proBNP for the sacubitril/valsartan treatment group assuming a value of 0.95 for the enalapril group, a common standard deviation of 0.85 and a 10% loss to follow-up rate. The estimates are based on the day 5 to day 14 data from the RELAX-AHF study. The standard deviation estimate is supported by data from PARADIGM.

The assumption of a 18% reduction in the geometric mean for NT-proBNP for the sacubitril/valsartan treatment group vs. the enalapril group is consistent with NT-proBNP results seen in PARADIGM (26% and 25% relative reduction of sacubitril/valsartan vs. enalapril at Week 4 and Month 8 respectively), PARAMOUNT (23% relative of sacubitril/valsartan vs. valsartan at Week 12) and RELAX-AHF (19% relative reduction of serelaxin vs. placebo at Day 2).

Sample size and power for various rate of reduction in sacubitril/valsartan group given alpha = 0.05 and 10% drop out rate are given in Table 9-1 in the protocol.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

5.1.1 Study treatment

Full dates for study treatment collected on the eCRF are required; therefore, no imputations will be made.

5.1.2 AE date imputation

The following algorithm should be used to estimate start dates for which only partial information is known:

- Missing day and month
  - If the year is the same as the year of first study treatment, then the day and month of the start date of treatment will be assigned to the missing fields.
  - If the year is prior to the year of first study treatment, then December 31 will be assigned to the missing fields.
  - If the year is after the year of first study treatment, then January 1 will be assigned to the missing fields.
- Missing month only
  - Treat day as missing and replace both month and day according to the above procedure.
- Missing day only
  - If the month and year are the same as the year and month of first study treatment, then the start date of treatment will be assigned to the missing day.
  - If the month and year are before the year and month of first study treatment, then the last day of the month will be assigned to the missing day.
  - If the month and year are after the year and month of first study treatment, then the first day of the month will be assigned to the missing day.

If the imputed start date result is after the stop date (and the stop date is complete), the imputed start date will be reset to the stop date.

The following algorithm should be used to estimate stop dates for which only partial information is known:

- Missing year
  - Date left missing.
- Missing month
  - Impute ‘December’.
- Missing day
  - Impute ‘last date of that month’.

5.1.3 Concomitant medication date imputation

The following algorithm should be used to estimate start dates for which only partial information is known:

- Missing day and month
  - If the year is the same as the year of first study treatment, then the day and month of the start date of treatment will be assigned to the missing fields.
  - If the year is prior to the year of first study treatment, then December 31 will be assigned to the missing fields.
  - If the year is after the year of first study treatment, then January 1 will be assigned to the missing fields.
- Missing month only
  - Treat day as missing and replace both month and day according to the above procedure.
- Missing day only

- If the month and year are the same as the year and month of first study treatment, then the start date of treatment will be assigned to the missing day.
- If the month and year are before the year and month of first study treatment, then the last day of the month will be assigned to the missing day.
- If the month and year are after the year and month of first study treatment, then the first day of the month will be assigned to the missing day.

If the imputed start date result is after the stop date (and the stop date is complete), the imputed start date will be reset to the stop date.

The following algorithm should be used to estimate stop dates for which only partial information is known:

- Missing year
  - Date left missing. Consider the medication to have been received at all periods after that period determined by the start date.
- Missing month
  - Impute 'December'.
- Missing day
  - Impute 'last date of that month'.

5.1.3.1 Prior therapies date imputation

The same imputation as concomitant medication will be used. See section 5.1.3.

5.1.3.2 Post therapies date imputation

The same imputation as concomitant medication will be used. See section 5.1.3.

5.2 AEs coding/grading

The UBC coding team will code the AE terms using MedDRA v19.0. If any terms are not coded, the data management team will issue queries to sites to update the AE term appropriately.

5.3 Laboratory parameters derivations

5.3.1 Laboratory grading

The collected laboratory values will be summarized by severity (low/normal/high) and not converted to Common Terminology Criteria for Adverse Events (CTCAE) grades.

5.3.2 Notable laboratory values

Hematology

RBC count	>50% increase, >20% decrease
Hemoglobin	>50% increase, >20% decrease
Hematocrit	>50% increase, >20% decrease
WBC count	>50% increase, >50% decrease

Platelet count	>75% increase, >50% decrease

Blood Chemistry

ALT (SGPT)	>150% increase
AST (SGOT)	>150% increase
BUN	>50% increase
Creatinine	>50% increase
Total bilirubin	>100% increase
CPK	>300% increase
Alkaline phosphatase	>100% increase
Potassium	>20% increase, >20% decrease
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease
Uric acid	>50% increase

5.4 Vital signs

5.4.1 Notable vital sign values

Systolic blood pressure	<90 mmHg and decrease of >20 mmHg from baseline
	>180 mmHg and increase of >20 mmHg from baseline
Diastolic blood pressure	<50 mmHg and decrease of >15 mmHg from baseline
	>105 mmHg and increase of >15 mmHg from baseline
Pulse	<50 bpm and decrease of > 15 bpm from baseline
	>120 bpm and increase of >15 bpm from baseline
Weight	>7% decrease; >7% increase

5.5 Statistical models

5.5.1 Primary analysis

The null hypothesis for the primary analysis is the ratio of the geometric means of NT-proBNP for the sacubitril/valsartan and enalapril group are equal. An ANCOVA model will be used. The model will have the time-averaged proportional change from baseline in a logarithmic scale be the dependent variable with treatment as a fixed effect factor and the logarithmic baseline value as a covariate. The general form for the ANCOVA model is:

$$y_{ij} = \mu + \tau_i + B\left(x_{ij} - \overline{x_i}\right) + \epsilon_{ij}$$

PROC MIXED in SAS will be used for the analysis. The LSMEANS option will be used with options of CL to output the confidence limits.

5.5.2 Key secondary analysis

Similarly to the primary analysis, the null hypothesis for the secondary analysis is the ratio of the geometric means of different biomarkers (BNP to NT-proBNP ratio, hs-Troponin and urinary cGMP) for the sacubitril/valsartan and enalapril group are equal. An ANCOVA model will be used. The model will have the time-averaged proportional change from baseline in a logarithmic scale be the dependent variable with treatment as a fixed effect factor and the logarithmic baseline value as a covariate. The general form for the ANCOVA model is:

$$y_{ij} = \mu + \tau_i + B\left(x_{ij} - \overline{x_i}\right) + \epsilon_{ij}$$

PROC MIXED in SAS will be used for the analysis. The LSMEANS option will be used with options of CL to output the confidence limits.

5.6 Rule of exclusion criteria of analysis sets

Table 1 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses
I05	Patient was not randomized between 24 hours and ten days after presentation while still hospitalized	Exclusion from PPS
I06	Patient was randomized between 24 hours and ten days after presentation while still hospitalized, however they did not meet the following definition of stable status	Exclusion from PPS
I07	LVEF was not ≤40% within past 6 months	Exclusion from PPS
E01	Patient is currently taking sacubitril/valsartan tablets or used within the past 30 days	Exclusion from PPS
M01	Patient had concomitant intake of a prohibited medication as outlined in the protocol	Exclusion from PPS
D01	Patient met one or more of the Discontinuation of Study Drug criteria but study drug was not discontinued.	Exclusion from PPS
D02	Patient did not complete required 36-hour washout period	Exclusion from PPS

Table 2 Patient Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
RS	NA	Not randomized
FAS	NA	Not in RS; Have not received study treatment but inadvertently randomized
PPS	I06, I07, E01, M01, D01, D02	Not in FAS;
SS	NA	No double-blind study treatment received

6 Reference

1 Green, CP, Porter, CB, Bresnaham, DR, & Spertus, JA 2000, 'Development and evaluation of the kansas city cardiomyopathy questionnaire: a new health status measure for heart failure', *Journal of the American College of Cardiology,* vol. 35, no. 5, pp. 1245-1255

NOVARTIS

Clinical Development

LCZ696/Sacubitril/Valsartan/Entresto®

CLCZ696BUS01

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

Statistical Analysis Plan (SAP)

Author:	CRO Statistician, UBC, McBride, Scott Statistician, Novartis, McCague, Kevin

Document type:	SAP Documentation
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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
27-Sep-2016	Prior to DB Lock	Creation of Final Version	NA – First Version	NA
20-Aug-2018	Prior to DB Lock	Creation of Amendment 1	1. Updated to align with protocol version 02 (amended protocol) dated 05-Oct-2017: sample size increase; addition of secondary endpoint (proportional change in NT-proBNP from baseline to Week 8); addition of exploratory endpoint (re-hospitalization through Day 30) 2. Clarified baseline definition for safety labs and biomarkers vs. other assessments 3. Added sensitivity analysis for primary endpoint based on "strict" baseline definition (i.e., collection date:time < first dose date:time) 4. Modified definition of treatment emergent AEs and flagging of deaths in listing to remove "28 days post last dose of study treatment" lag time 5. Clarified imputation rule for KCCQ domain/clinical/overall summary scores for patients who died 6. Clarified that biomarker samples from patients who withdraw consent will not be analyzed by the central laboratory 7. Removed "on treatment" terminology and "28 days post last dose of study treatment" lag time (from the open-label phase definition) 8. Clarified coding dictionary versions to be utilized	1. Section 1 Introduction; Section 1.1 Study Design; Section 1.2 Study Objectives and Endpoints; Section 2.7.1 Secondary Endpoints; Section 2.7.2 Statistical Hypothesis, Model, and Method of Analysis; Section 2.13 Other Exploratory Analyses; Section 3 Sample Size Calculation 2. Section 2.1.1 General Definitions 3. Section 2.5.4 Supportive Analyses; Section 4 Change to Protocol Specified Analyses 4. Section 2.8.1.2 General Rules for AE Reporting; Section 2.8.2 Deaths 5. Section 2.11.1 KCCQ 6. Section 2.12 Biomarkers 7. Section 2.1.1 General Definitions 8. Section 2.3.4 Demographics and Other Baseline Characteristics;

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			9. Clarified that analyses of BNP and NT-proBNP values will be based on samples processed/assessed by the central laboratory	Section 2.4.2 Prior, Concomitant and Post Therapies; Section 2.8.1.1 Coding of AEs
			10. Clarified definitions for double-blind, open-label, and pooled phases, and changed terminology from "treatment phase" to "study phase"	9. Section 2.1.1 General Definitions; Section 2.12 Biomarkers
			11. Clarified that time to first occurrence of composite clinical endpoint and its components will be will be assessed from date of randomization rather than start date of study treatment	10. Section 2.1.1 General Definitions
			12. Clarified that censoring will account for deaths (ie, date of last contact/death) for endpoints of time to first hospitalization and re-hospitalization through Day 30	11. Section 2.13 Other Exploratory Analyses
			13. Clarified that date of last contact will be determined from the Date of Last Contact field on the Study Completion/Exit eCRF	12. Section 2.13 Other Exploratory Analyses
			14. Co-located text for KM and logistic regression analyses of re-hospitalization through Day 30	13. Section 2.1.1 General Definitions
			15. Added sensitivity analysis for incidence of worsening renal function based on "strict" baseline definition (i.e., serum creatinine collection date:time < first dose date:time)	14. Section 2.13 Other Exploratory Analyses
			16. Added sensitivity analysis for biomarkers relating to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury and/or renal function (eGFR) based on "strict" baseline definition (i.e., biomarker collection date:time < first dose date:time); clarified that a common unstructured covariance will be specified as part of the repeated	15. Section 2.13 Other Exploratory Analyses; Section 4 Change to Protocol Specified Analyses 16. Section 2.13 Other Exploratory Analyses; Section 4 Change to Protocol Specified Analyses 17. Section 2.7.1 Secondary Endpoints; Section 2.7.2 Statistical Hypothesis, Model, and Method of Analysis; Section 4 Change to Protocol Specified Analyses 18. Section 2.5.4 Supportive Analyses; Section 4 Change to Protocol Specified Analyses

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			measures analysis of biomarkers at Weeks 2, 4 and 8 (using the MIXED procedure) to align with the repeated measures analysis approach for KCCQ clinical summary score at Weeks 4 and 8 17. Specified the following biomarkers as secondary endpoints: UcGMP to urinary creatinine ratio, BNP, and NT-proBNP to BNP ratio 18. Replaced supportive analysis of the primary endpoint consisting of summary statistics and t-test p-values for comparing treatment groups on the proportional change from baseline in a logarithmic scale at Weeks 4 and 8 with ANCOVA at Weeks 4 and 8 19. Added the change from baseline to Week 12 for sacubitril/valsartan to the assessment of NT-proBNP during the open-label period 20. Clarified that KCCQ data will be summarized by randomized treatment group during the open-label phase, and that changes during the open-label phase for patients randomized to enalapril will be assessed relative to Week 8 21. Modified the Safety Set definition to remove the word 'active' so that inclusion in the Safety Set is not restricted to patients who received at least one dose of *active* study treatment 22. Clarified that duration of exposure during the double-blind phase is calculated from the date of first study treatment (not date of first *active* study treatment); added summary of patient dose level and titration data by visit and systolic blood pressure using visit-specific cut-off values from dose titration schedule	19. Section 2.13 Other Exploratory Analyses; Section 4 Change to Protocol Specified Analyses 20. Section 2.11.1 Kansas City Cardiomyopathy Questionnaire; Section 4 Change to Protocol Specified Analyses 21. Section 2.2 Analysis Sets; Section 4 Change to Protocol Specified Analyses 22. Section 2.4.1 Study Treatment/Compliance 23. Section 5.6 Rule of Exclusion Criteria of Analysis Sets 24. Section 2.2.1 Subgroup of Interest 25. Section 2.3.1 Patient Disposition 26. Section 2.3.4 Demographics and Other Baseline Characteristics 27. Section 2.3.3 Index Hospitalization 28. Section 2.3.4 Demographics and Other Baseline Characteristics 29. Section 5.4.1 Notable Vital Sign Values 30. Section 2.8.4.4 HF Signs and Symptoms

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			23. Updated rules of exclusion criteria of analysis sets based on final review of PDs and associated final PD documentation (VAP Module 3 v3.0 dated 15Aug2018) 24. Combined <30 and 30 – <45 baseline eGFR subgroups into <45 subgroup due to low number of patients in <30 subgroup 25. Added disposition categories for patients who prematurely discontinued study treatment during double-blind and open-label phases that exclude deaths; removed disposition categories for patients who completed the double-blind and open-label phases as these are covered in the study completion tables; removed disposition category for patients who were not randomized 26. Added source of patient referral and summary (continuous and categorical) of NT-proBNP and BNP values from local laboratory to demographic and baseline characteristics table; removed Pooled column and broke out Open-Label Sacubitril/Valsartan column by randomized treatment group for all demographic and baseline data tables 27. Clarified that summary of index hospitalization data will only be treatment group (and not also by open-label and pooled sacubitril/valsartan) 28. Added categorical summary of number of hospitalizations for HF within past 12 months (excluding index hospitalization) 29. Modified notable vital signs criteria 30. Clarified that HF Signs and Symptoms will be summarized at	31. Section 2.7.2 Statistical Hypothesis, Model, and Method of Analysis; Section 2.8.1.4 Adverse Events of Special Interest/Grouping of AEs; Section 2.8.4.6 Angioedema 32. Section 2.8.1.3 AE Summaries 33. Section 2.13 Other Exploratory Analyses; Section 4 Change to Protocol Specified Analyses 34. Section 2.13 Other Exploratory Analyses 35. Section 2.13 Other Exploratory Analyses 36. Section 2.13 Other Exploratory Analyses 37. Section 2.13 Other Exploratory Analyses; Section 4 Change to Protocol Specified Analyses 38. Section 2.13 Other Exploratory Analyses 39. Section 2.13 Other Exploratory Analyses 40. Section 2.5.4 Supportive Analyses 41. Section 2.4.2 Prior, Concomitant and Post Therapies 42. Section 2.3.1 Patient Disposition 43. Section 2.3.4 Demographics and

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			all visits (not just Randomization and Week 8)	Other Baseline Characteristics
			31. Clarified that separate summaries/analyses of angioedema data, including AEs related to angioedema, will be produced – one based on all angioedema and the other based on positively adjudicated angioedema; added a summary of key characteristics of positively adjudicated angioedema	44. Section 2.3.4 Demographics and Other Baseline Characteristics 45. Section 2.4.1 Study Treatment/Compliance 46. Section 2.13 Other Exploratory Analyses; Section 4 Change to Protocol Specified Analyses
			32. Added an AE overview table (number and percentage of patients in various AE categories) and two SAE tables (occurring with frequency ≥0.5%; by seriousness criteria)	47. Section 2.13 Other Exploratory Analyses
			33. Replaced CMH test with an exact Mantel-Haenszel Chi-Square test for analysis of PGA values	48. Section 2.7.2 Statistical Hypothesis, Model, and Method of Analysis; Section 4 Change to Protocol Specified Analyses
			34. Indicated that missing data at Week 8 will be imputed using the LOCF method for logistic regression analysis of KCCQ clinical summary score improvement/deterioration	49. Section 2.13 Other Exploratory Analyses; Section 4 Change to Protocol Specified Analyses
			35. For the negative binomial regression analyses, modified the offset to be the log of study duration through Week 8; clarified that re-hospitalizations are HF hospital stays ≥24 hours; clarified that the determination of HF visits requiring diuretics involves i.v. diuretics; clarified that analysis will be focused on the double-blind phase (ie, through Day 56/Week 8)	50. Section 2.13 Other Exploratory Analyses; Section 4 Change to Protocol Specified Analyses 51. Section 2.13 Other Exploratory Analyses; Section 4 Change to Protocol Specified Analyses
			36. Clarified that analysis of time to first occurrence of composite clinical endpoint, and its individual components, will be focused on the double-blind phase (ie, through Day 56)	52. Section 2.2 Analysis Sets; Section 4 Change to Protocol Specified Analyses 53. Section 2.13 Other Exploratory Analyses;

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			37. Added analysis of time to first occurrence of 'serious' composite clinical endpoint consisting of death, HF re-hospitalization, requirement of LVAD, and listed for cardiac transplantation	Section 4 Change to Protocol Specified Analyses 54. Various sections
			38. Clarified that analysis of time to first hospitalization will be focused on the double-blind phase (ie, through Day 56/Week 8) starting from the date of index hospitalization discharge	
			39. Clarified that "days" variables analyses will be focused on the double-blind phase (ie, through Day 56/Week 8)	
			40. Added a descriptive summary of patient evaluability for primary endpoint analysis based on NT-proBNP values	
			41. Removed reference to diuretics being combined into a single dose equivalent for purposes of the diuretic dose summaries during the index hospitalization and at post-randomization visits	
			42. Modified categories for study completion at Weeks 8 and 12	
			43. Added variable "Time from presentation to randomization (days)" to summary of disease characteristics	
			44. Added variables "ACEi naïve", "ARB naïve", and "ACEi/ARB naïve" to summary of disease characteristics	
			45. Added variable "Dispensed dose level 3 by Week 6" to dose level by visit summary	
			46. Added analysis of time-averaged proportional change in NT-proBNP and other biomarkers from Week 1 to Weeks 4 and 8	

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			47. Removed hs-Troponin T from repeated measures analysis of Weeks 2, 4, and 8 since it is not measured at Week 2	
			48. Added Weeks 4 and 8 to the analysis of change from baseline in biomarkers defined as secondary endpoints; clarified that analysis of hs-Troponin T will not be performed at Week 2 since it is not measured at Week 2	
			49. Added analysis of change from baseline in sST2 to Week 4/Week 8 and Weeks 1, 2, 4, and 8	
			50. Added assessment of demographics, baseline characteristics, disease history, and primary and secondary endpoints in "early" (1st half) vs. "late" (2nd half) enrollers	
			51. Added recurrent event analysis of the composite clinical endpoint	
			52. Modified PPS definition to clarify that major protocol deviations will exclude patients from the PPS regardless of the study phase in which they occur	
			53. Added a repeat analysis of the time to first occurrence of composite clinical endpoint based on all data through the double-blind study phase	
			54. Implemented various minor clarifications, including those reflected in updated version of DCTs dated 12-Dec-2017	

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List of abbreviations

ACEi	Angiotensin Converting Enzyme Inhibitors
ADHF	Acute Decompensated Heart Failure
AE	Adverse Event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ARB	Angiotensin Receptor Blocker
ATC	Anatomical Therapeutic Chemical
bid	bis in diem/twice a day
BMI	Body Mass Index
BNP	B-type Natriuretic Peptide
CCU	Coronary Care Unit
cGMP	cyclic Guanosine 3',5'-Monophosphate
CHF	Chronic Heart Failure
CKD	Chronic Kidney Disease
CRO	Contract Research Organization
CRT-P	Cardiac resynchronization therapy – no ICD
CRT-D	Cardiac resynchronization therapy – with ICD
CSR	Clinical Study report
CTCAE	Common Terminology Criteria for Adverse Events
DCT	Data Collection Tool
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Emergency Department
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
HCTZ	Hydrochlorothiazide
HF	Heart Failure
HS	High Sensitivity
ICD	Implantable Cardioverter Defibrillator
ICU	Intensive Care Unit
i.v.	Intravenous
IVCD	Intraventricular Conduction Delay
IWRS	Interactive Web Response System
KCCQ	Kansas City Cardiomyopathy Questionnaire
KM	Kaplan Meier
LBB	Left Bundle Branch
LCZ696	Sacubitril/Valsartan
LS	Least squares
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities

MRU	Medical Resource Utilization
NT-proBNP	N-terminal Prohormone of B-type Natriuretic Peptide
NYHA	New York Heart Association
PD	Pharmacodynamic
PGA	Patient Global Assessment
PK	Pharmacokinetic
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PT	Preferred Term
RBB	Right Bundle Branch
RS	Randomized Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SOC	System Organ Class
SS	Safety Set
sST2	Soluble ST2
TEAE	Treatment-emergent Adverse Event
TFLs	Tables, Figures, Listings
TIA	Transient Ischemic Attack
UBC	United BioSource Corporation
UcGMP	Urinary cGMP
VAD	Ventricular Assist Device
WHO	World Health Organization

1 Introduction

The statistical analysis plan (SAP) will outline in detail the analyses planned in the protocol. The analyses will be used to generate the Clinical Study Report (CSR). The SAP is based on protocol version 02 (Amended protocol) dated 05-Oct-2017 and the data collection tool (DCT) version 14.0 dated 12-Dec-2017.

1.1 Study design

This study will use a randomized, double-blind, double-dummy, active-controlled, parallel group design. Eligible patients hospitalized for acute decompensated heart failure (ADHF) will be randomized no earlier than 24 hours and up to ten days of presentation while still hospitalized. A total of approximately 882 patients randomized to sacubitril/valsartan or enalapril in a 1:1 ratio is planned with no stratification.

At the time of randomization, patients will have been stabilized, defined for this study as:

- Systolic blood pressure (SBP) $\geq$ 100 mmHg for the preceding 6 hours prior to randomization; no symptomatic hypotension
- No increase (intensification) in intravenous (i.v.) diuretic dose within last 6 hours prior to randomization
- No i.v. inotropic drugs for 24 hours prior to randomization
- No i.v. vasodilators including nitrates within last 6 hours prior to randomization

All patients will need to meet all other inclusion and none of the exclusion criteria.

In order to provide for a necessary 36 hour washout of prior angiotensin converting enzyme inhibitors (ACEi) treatment prior to receiving sacubitril/valsartan (known as LCZ696 in prior trials), the supplied blinded study drug for those allocated to sacubitril/valsartan will be placebo only until the 3rd dose. Because the study is blinded, all patients, regardless of randomization arm, need to remain in the hospital for six hours after they have received their 3rd dose of study medication.

Initial dose will be determined by the blood pressure at the time of randomization. Study treatment will be titrated to the Level #3 target doses of sacubitril/valsartan 97/103 mg (bis in diem/twice a day) bid and enalapril 10 mg bid. Titration will be based on blood pressure at the time of the visit. Dose adjustments will only be allowed if indicated per protocol defined safety/tolerability criteria and investigator judgement. At the end of the 8-week treatment period, all patients will need to have a 36 hour washout from study treatment prior to starting the open-label extension to ensure that the blinding of the core study is maintained. To facilitate this washout, patients should take their final dose of study drug on the morning of their week 8 visit and then begin open label sacubitril/valsartan after 36 hours in the evening of week 8 visit + one day. All patients will start open label treatment on sacubitril/valsartan at their final dosing level during double blind treatment. However, at an investigator's judgement, starting dose may be adjusted by one dose level up or down.

Eligible patients will be randomized no earlier than 24 hours after presentation at the hospital and no later than within ten days of admission, while still hospitalized, via interactive web

response system (IWRS) to one of the treatment arms. The investigator or his/her delegate will contact the IWRS after confirming that the patient fulfills all of the study entry criteria. The IWRS will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify which bottle from the centralized hospital supply the patient will be dosed for the first day and a unique medication number for the first package of investigational treatment to be dispensed to the patient.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IWRS provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The primary time point will be Weeks 4 and 8.

There are no interim analyses planned.

1.2 Study objectives and endpoints

The primary objective of this study is to assess the effect of in hospital initiation of sacubitril/valsartan vs. enalapril on the time-averaged proportional change of N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) from baseline in patients who have been stabilized following hospitalization for ADHF and reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤ 40%). Weeks 4 and 8 will be included in the analysis (primary analysis time point).

The secondary objectives of this study are to examine the effect of sacubitril/valsartan vs. enalapril on:

- The proportional change in NT-proBNP from baseline to Week 8
- Incidence of symptomatic hypotension during 8 weeks of treatment
- Incidence of hyperkalemia (Potassium >5.5 mEq/L) during 8 weeks of treatment
- Incidence of angioedema during 8 weeks of treatment
- Biomarkers: hs-Troponin (high sensitivity), urinary cyclic Guanosine 3',5'-Monophosphate (cGMP) and B-type natriuretic peptide (BNP) to NT-proBNP ratio at 4 and 8 weeks

In addition, the exploratory objectives are:

- To examine the effect of sacubitril/valsartan vs. enalapril on time to first occurrence of composite clinical endpoint that includes death, heart failure re-hospitalization, requirement of left ventricular assist device (LVAD), listed for cardiac transplantation, unplanned acute heart failure (HF) visits requiring i.v. diuretics, additional heart failure drug or increase in >50% of the diuretic dose.
- To examine the effect of sacubitril/valsartan vs. enalapril on change from baseline at Weeks 1 and 2 in NT-proBNP.

- To examine the effect of sacubitril/valsartan vs. enalapril on incidence of re-hospitalization, emergency department (ED) visit or unplanned outpatient clinic visits due to worsening HF symptoms.
- To examine the effect of sacubitril/valsartan vs. enalapril on incidence of re-hospitalization through Day 30.
- To examine the effect of sacubitril/valsartan vs. enalapril on the need for advanced heart failure therapies (including but not limited to i.v. inotropes, LVAD, transplantation).
- To examine the effect of sacubitril/valsartan vs. enalapril on patient centered outcomes including the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Patient Global Assessment (PGA) at 4 and 8 weeks post randomization.
- To examine the effect of sacubitril/valsartan vs. enalapril on change in biomarkers related to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury, and renal function, including estimated glomerular filtration rate (eGFR).
- To examine change in NT-proBNP in the enalapril arm during the 4 week open label period.
- To examine the effect of sacubitril/valsartan vs. enalapril on medical resource utilization (MRU).
- To examine the effect of sacubitril/valsartan vs. enalapril on incidence of worsening renal function during 8 weeks of treatment, defined as an increase in serum creatinine of $\geq$ 0.5 mg/dL from the value measured at baseline.

2 Statistical methods

2.1 Data analysis general information

United BioSource Corporation (UBC), a Novartis-designated Contract Research Organization (CRO) will be performing all analyses outlined in this SAP. SAS® version 9.3 (or higher) will be used for all analyses.

Data from all centers that participate in this protocol will be combined, so that an adequate number of patients will be available for analysis.

Unless otherwise specified, for continuous data, the mean, standard deviation, median, first and third quartile, interquartile range, and minimum and maximum values will be presented. For categorical data, frequencies and percentages will be presented. All statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

All data will be provided in listings in addition to summaries described below.

2.1.1 General definitions

Study treatment

Patients will receive either sacubitril/valsartan or enalapril during the first 8 weeks of the study. Study treatment will refer to either of these two drugs.

Baseline

For safety labs and biomarkers, baseline is defined as the last non-missing assessment collected <3 hours from the first dose of study treatment, including matching placebos. For patients not treated, baseline is defined as the last non-missing assessment prior to or on the date of randomization. BNP and NT-proBNP values will be based on clinical laboratory samples processed and assessed by the central laboratory.

For other assessments, including those for which assessment time is collected (ECGs, HF Signs and Symptoms, and pregnancy tests), baseline is defined as the last non-missing assessment prior to or on the start date of study treatment (randomization date for patients not treated), including matching placebos.

Date of first administration of study treatment

Double-blind phase: The date of first administration of study treatment in the double-blind phase is defined as the first date a dose of study treatment is administered and recorded on the Dose Administration (Visit 2) electronic case report form (eCRF).

Open-label phase: The date of first administration of study treatment in the open-label phase is defined as the first date a dose of sacubitril/valsartan is administered in the open-label phase and recorded on the Dose Administration (Visit 7) eCRF.

Pooled phase: The date of first administration of study treatment in the pooled phase is defined as the first date a dose of sacubitril/valsartan is administered either in the double-blind phase or open-label phase.

Date of last administration of study treatment

Double-blind phase: The date of last administration of study treatment in the double-blind phase is defined as the last date a dose of study treatment is administered in the double-blind phase and recorded on the Dose Administration (Visit 7) eCRF, or earlier if prematurely discontinued and recorded on the Early Investigational Product Permanent Discontinuation eCRF.

Open-label phase: The date of last administration of study treatment in the open-label phase is defined as the last date of sacubitril/valsartan is administered in the open-label phase and recorded on the Drug Administration eCRF.

Pooled phase: The date of last administration of study treatment in the pooled phase is defined as the last date of sacubitril/valsartan administered either in double-blind phase or open-label phase.

Study day

The study day describes the day of the assessment relative to the date of randomization.

The study day will be calculated as the difference between the date of assessment and the date of randomization plus 1. If the date of assessment is prior to the date of randomization, the study day will be negative and will be calculated as the difference between the date of the assessment and the date of randomization.

Double-blind phase

Assessments performed at Weeks 1, 2, 4, 6, or 8 (including, but not limited to, vital signs) are assigned to the double-blind phase for summarization purposes. Unscheduled assessments are not assigned to a study phase for purposes of by-visit summaries.

For summarization of adverse events [AEs], medications, protocol deviations, notable vital signs and laboratory abnormalities, and symptomatic hypotension by study phase, an assessment during the double-blind phase is defined as any assessment obtained in the following time interval:

Date of randomization (or date of first administration of study treatment, as appropriate) through the date of the Week 8 visit, inclusive. For patients without a Week 8 visit, a projected Week 8 visit date will be derived relative to their randomization date.

An 'active treatment' assessment is defined for sensitivity analyses starting with the first dose of study treatment in patients randomized to enalapril and the third dose of study treatment in patients randomized to sacubitril/valsartan.

Open-label phase

Assessments performed at Weeks 10 or 12 (including, but not limited to, vital signs) are assigned to the open-label phase for summarization purposes. Unscheduled assessments are not assigned to a study phase for purposes of by-visit summaries.

For summarization of AEs, medications, protocol deviations, notable vital signs and laboratory abnormalities, and symptomatic hypotension by study phase, an assessment during the open-label phase is defined as any assessment obtained in the following time interval:

After the date of the Week 8 visit. For patients without a Week 8 visit, a projected Week 8 visit date will be derived relative to their randomization date.

Patients who died, withdrew consent, or were lost to follow-up prior to or on their projected Week 8 visit date will be excluded from the open-label phase.

Pooled phase

An assessment during the pooled phase is defined as any assessment obtained in the double-blind phase for patients randomized to sacubitril/valsartan, or any assessment obtained in the open-label phase regardless of randomized treatment arm.

Last contact

The date of last contact will be determined from the Date of Last Contact field on the Study Completion/Exit eCRF.

Year, month and week

For reporting purposes, the rules below will be followed to convert a year, month and week to days.

1 year = 365.25 days

1 month = 30.3475 days

1 week = 7 days

1 day = 24 hours

2.2 Analysis sets

The following analysis data sets will be used in the analyses:

Randomized Set (RS): The RS will consist of all randomized patients.

Full Analysis Set (FAS): The FAS will consist of all randomized patients with the exception for those patients who have not been qualified for randomization and have not received study treatment, but have been inadvertently randomized into the study. Following the intent-to-treat principle, patients will be analyzed according to the treatment to which they were assigned at randomization. Efficacy variables will be analyzed based on the FAS as the primary set.

Safety Set (SS): The SS will consist of all randomized patients who have received at least one dose of study treatment. Patients will be included in the analysis according to the treatment actually received. The SS will be used for the analyses of safety variables.

Per-Protocol Set (PPS): The PPS will be a subset of the FAS, which will consist of the patients who do not have major deviations from the protocol procedures. Major protocol deviations will be pre-specified prior to unblinding treatment code for analysis. This supplemental analysis set will be used to support the primary analysis results.

2.2.1 Subgroup of interest

The following subgroups will be analyzed for the primary objective and the secondary objective for AEs of special interest:

1. Age group (<65, ≥65 years) and (<75, ≥75 years)
2. Ejection fraction categories prior to randomization (>40%, >30% - 40%, >20% - 30%, ≤20%)
3. Prior use of ACEi/ARB (at the time of hospitalization)
4. Baseline quartiles of NTproBNP (randomization sample)
5. Baseline eGFR (<45, 45 - <60, ≥60 ml/min/1.73 m^2)
6. Systolic blood pressure at randomization (<110, ≥110 mm Hg)

See Sections 2.5 and 2.7 for further details on the primary and secondary objectives, respectively.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

All patients will be used for the summary of patient disposition. The following categories will be summarized:

- Number of patients who were screened
- Primary reason for not continuing to double-blind phase

  - Investigator decision
  - Subject/Guardian decision
  - Screen failure
  - Adverse event
  - Pregnancy
  - Study terminated by sponsor
  - Technical problems
  - Death
- Number of patients who were randomized
- Number and percentage of patients who were treated
- Number and percentage of patients who prematurely discontinued study treatment during double-blind phase
- Number and percentage of patients who prematurely discontinued study treatment during double-blind phase, excluding deaths
- Number and percentage of patients who prematurely discontinued study treatment during open-label phase
- Number and percentage of patients who prematurely discontinued study treatment during open-label phase, excluding deaths
- Reasons for premature discontinuation of study treatment (separately for double-blind phase and open-label phase)
  - Adverse event
  - Death
  - Protocol deviation
  - Investigator decision
  - Subject/Guardian decision
  - Lost to follow-up
  - Technical problems
  - Pregnancy
  - Withdrawal of consent
  - Noncompliance with study treatment
  - Study terminated by sponsor
- Study duration in months [*(date of last contact/death – date of randomization +1)/30.3475*]

A separate summary for study completion will be presented and the FAS will be used. The following categories will be summarized at Week 8 by treatment group, open-label and pooled sacubitril/valsartan:

- Patients who received at least one dose of study treatment
- Patients who did not receive at least one dose of study treatment
- Patients with known vital status at Week 8
    - Dead prior to opening of projected Week 8 visit window
    - Completed Week 8 visit after opening of projected Week 8 visit window
    - Any visit/contact with visit date after opening of projected Week 8 visit window
    - Vital status recorded with last known alive date after opening of projected Week 8 visit window
- Patients with unknown vital status at Week 8
    - Lost to follow-up prior to opening of projected Week 8 visit window
    - Withdrawal of informed consent to any follow-up prior to opening of projected Week 8 visit window

The following categories will be summarized at Week 12 by treatment group, open-label and pooled sacubitril/valsartan:

- Patients who received at least one dose of study treatment
- Patients who did not receive at least one dose of study treatment
- Patients with known vital status at Week 12
    - Dead
    - Visit
        - In person with patient
        - Telephone (or video) contact with patient
        - Known alive through other contact with patient or contact with party other than patient
        - Other contact with patient (mail, email, text, social media, etc.)
- Patients with unknown vital status at Week 12
    - Lost to follow-up
    - Withdrawal of informed consent to any follow-up

Additionally, listings of inclusion/exclusion criteria, screening disposition, reason for withdrawal of consent and study treatment disposition will be provided.

Any visit that did not occur per protocol will be listed with the reason it was not done.

2.3.2 Protocol deviations

The number and percentages of protocol deviations by category will be summarized by study phase (see Section 2.1.1 for study phase definitions). Additionally, a listing of protocol deviations during the study will also be presented. The RS will be used.

2.3.3 Index hospitalization

The number and percentages of the following information about patients and their index hospitalization visit will be summarized by treatment group. The RS will be used.

- Patient in shock (No, Yes, Unknown)
- Patients receiving following treatment from index hospitalization to randomization
    - Vasopressor (No, Yes, Unknown)
    - Inotrope (No, Yes, Unknown)
    - Nitroprusside (No, Yes, Unknown)
    - Nesiritide (No, Yes, Unknown)
    - Patient cared for in Intensive Care Unit (ICU) (No, Yes, Unknown)

The number and percentage (categorical variables) and descriptive statistics (continuous data) for information on patient index hospitalization discharge will be summarized by treatment group. The RS will be used.

- Duration of index hospitalization stay in days [(*date:time of discharge – date:time of arrival)/(3600*24)*]
- Discharge disposition (Home or with family/friends, Rehabilitation facility, Skilled nursing facility, Death, Unknown)
- Discharge weight (kg)
- New York Heart Association (NYHA) class (I, II, III, IV, Not done)
- Patient experienced worsening heart failure since randomization (No, Yes, Unknown)
- Patient cared for in ICU (No, Yes, Unknown)
    - Number of nights in ICU since randomization
- Patient treated with any of the following medication classes since randomization (Intravenous inotrope, Intravenous vasopressor, Nitroprusside, No, Unknown)
- Patient took third dose of double-blind study treatment (No, Yes)

All information relating to the index hospitalization will be listed.

2.3.4 Demographics and other baseline characteristics

Demographics, baseline characteristics, and disease history are collected at the screening visit. Descriptive summaries and/or listings will be provided. The number and percentage

(categorical variables) and descriptive statistics (continuous data) for the information below will be summarized by treatment group for both double-blind and open-label patients.

The FAS will be used.

Demographics and baseline characteristics

Demographic variables include:

- Age (years), age group (<65 years and ≥65 years; <75 years and ≥75 years)
- Sex (Male, Female)
    - Child bearing status (Able to bear children, Premenarche, Post-menopausal [per-protocol >12 months], Sterile-of child bearing age)
- Race (Caucasian, Black, Asian, Native American, Pacific Islander, Unknown, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Source of patient referral (Physician's own practice, Physician referral, Advocacy group, ER or hospital, Friend/family member, Patient database, Unknown, Other)

Baseline characteristic variables include:

- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2) [= *weight (kg)/height (m)^2 from screening visit 1*]
    - BMI categories (<20, 20 - <25, 25 - 30, >30 kg/m^2)
- Smoking history (Former, Current, Never)
- Heart rate (bpm)
- Bundle branch block (or Intraventricular Conduction Delay [IVCD]) present (No, Yes)
    - Bundle branch block type (Left bundle branch [LBB] block, Right bundle branch [RBB block], Non-specific intraventricular conduction delay)
- NT-proBNP (pg/mL), separately for values based on clinical laboratory samples processed and assessed by the central and local laboratories
    - NT-proBNP categories (<450, 450 - <900, 900 - <1600, 1600 - <3200, 3200 - <7400, 7400 - <10000, ≥10000 pg/mL)
- BNP (pg/mL), separately for values based on clinical laboratory samples processed and assessed by the central and local laboratories
    - BNP categories (<100, 100 - <225, 225 - <400, 400 - <800, 800 - <1850, 1850 - <2500, ≥2500 pg/mL)

Disease characteristics

Disease characteristic variables include:

- Category of prior chronic heart failure (CHF) medication (ACEi, Angiotensin Receptor Blocker [ARB], Beta blocker, Aldosterone antagonist, Ivabradine, Hydralazine, Nitrates [long lasting], Digoxin, Diuretic)
- ACEi naïve (No, Yes); ARB naïve (No, Yes); ACEi/ARB naïve (No, Yes)
- History of HF prior to qualifying HF event (No, Yes, Unknown)
- Number of hospitalizations with primary diagnosis of HF within past 12 months not including index hospitalization
    - Number of hospitalizations categories (0, 1, 2, ≥3, Not Applicable)
- Total number of hospitalizations for any reason within past 12 months
- NYHA classification 30 days prior to index hospitalization (I, II, III, IV, Unknown)
- Ejection fraction (%)
    - Ejection fraction categories (>40%, >30% - 40%, >20% - 30%, ≤20%)
- Time from presentation to randomization (days)

Cardiovascular history

Cardiovascular history will be summarized. The following disease information will be collected:

- Hypertension (No, Yes, Unknown)
- Transient Ischemic Attack (TIA) (No, Yes, Unknown)
- Stroke (No, Yes, Unknown)
- Peripheral vascular disease (No, Yes, Unknown)
- Chronic renal insufficiency [eGFR <60 ml/min/1.73m^2 on testing >30 days prior to index hospitalization] (No, Yes, Unknown)
    - Chronic Kidney Disease (CKD) stage (CKD stage 3 [eGFR 30 - 59], CKD stage 4 [eGFR 15 - 29], CKD stage 5 [eGFR <15 or dialysis])
- Arrhythmia (No, Yes, Unknown)
    - Arrhythmia type (Atrial fibrillation, Atrial flutter, Supraventricular tachycardia, Ventricular tachycardia)
- Pacemaker/Implantable Cardioverter Defibrillator (ICD) (No, Yes, Unknown)
    - Device type (Pacemaker [conventional], Cardiac resynchronization therapy – no ICD [CRT-P], Cardiac resynchronization therapy – with ICD [CRT-D], ICD only [single/dual], Other, Unknown)
- Moderate to severe valvular heart disease (No, Yes, Unknown)
    - Heart disease type (Mitral regurgitation, Aortic regurgitation, Aortic stenosis, Tricuspid regurgitation)
- Prior valvular heart surgery (No, Yes, Unknown)

- Valvular surgery type (Mitral, Aortic, Tricuspid, Pulmonic)

Non-Cardiovascular Medical History

Non-cardiovascular medical history and ongoing conditions will be summarized and listed. The summaries will be presented by primary system organ class (SOC), preferred term (PT) and treatment group for both double-blind and open-label patients. Non-cardiovascular medical history and ongoing conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology (v19.0 or later).

Surgeries and Medical Procedures

Surgeries and medical procedures will be listed, including the reason, start date and end date. Surgeries and medical procedures will be coded using MedDRA terminology (v19.0 or later).

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

The SS will be used for all analyses associated with study treatment and medications, unless otherwise specified.

2.4.1 Study treatment / compliance

The duration of double-blind study treatment phase is defined as:

Duration (days) = (date of last study treatment in double-blind study phase – date of first study treatment) +1

The first date of study treatment is recorded on the Dose Administration (Visit 2) eCRF.

The duration of the open-label study treatment phase is defined as:

Duration (days) = (date of last study treatment in open-label study phase – date of first study treatment in open-label phase) +1

The duration of the pooled phase (sacubitril/valsartan in double-blind phase and/or sacubitril/valsartan in open-label phase) is defined as:

Duration (days) = (date of last study treatment of sacubitril/valsartan [any phase] – date of first study treatment of sacubitril/valsartan [any phase]) +1

Summary statistics will be displayed for the duration of double-blind study treatment, duration of open-label study treatment and duration of pooled sacubitril/valsartan by phase.

The durations will also be categorized into weekly time intervals (<7 days, 7 - <14 days, 14 - <21 days, …, etc.). The number and percentage of patients in each category will be presented by phase.

Total patient-days of exposure will also be summarized by phase.

In addition, the number and percentages of each dose level dispensed by visit will be summarized by treatment group and open-label sacubitril/valsartan. The number and percentage of the maximum dose levels dispensed will also be presented by treatment group and open-label sacubitril/valsartan. Similarly, the up-titrated doses, down-titrated doses and unchanged doses will be summarized by visit, treatment group and open-label sacubitril/valsartan. The number

and percentage of patients who were dispensed dose level 3 by Week 6 will be summarized by treatment group.

An additional summary of patient dose level and titration data will be generated by visit and systolic blood pressure using the visit-specific systolic blood pressure cut-off values from the dose titration schedule.

All information on dose administration will be listed.

2.4.2 Prior, concomitant and post therapies

Non-HF Medications

Prior and concomitant non-HF medications will be coded according to the World Health Organization (WHO) Drug Reference List (v15.3 or later). Prior and concomitant medications are mutually exclusive, as defined below:

- Prior medications are defined as any medication with an end date prior to the first dose of study treatment
- Concomitant medications are defined as any medications taken on or after the start of study treatment. Prior medications that are 'ongoing' at the time of the first study treatment or whose end date is after first study treatment will be considered a concomitant medication

The number and percentage of patients with concomitant medications that started after study treatment will be summarized by Anatomical Therapeutic Chemical (ATC) class, preferred term and study phase (refer to Section 2.1.1 for study phase definitions). All medications will be listed.

HF Medications

Medication names are provided for ACEi, ARB, beta blocker and other antiplatelets and will be coded using the WHO Drug Reference List (v15.3 or later) and the preferred term will be displayed for these categories.

The number and percentages of prior HF medications at screening will be summarized by treatment group, open-label and pooled sacubitril/valsartan. Similarly, the HF medications collected at randomization will be summarized by treatment group, open-label and pooled sacubitril/valsartan. A descriptive summary for the total daily dose of each medication (for which doses are collected) will also be presented. These summaries will also be presented using the FAS.

The number and percentages of HF medications collected post randomization will be summarized by study phase (see Section 2.1.1 for study phase definitions). The overall summary will be presented. The following medications will be summarized: Beta blocker, Ivabradine, Hydralazine, Nitrites (long acting), Calcium channel blocker, Potassium, Digoxin, Statin, Furosemide, Torsemide, Bumetanide, Hydrochlorothiazide (HCTZ), Diuril (chlorothiazide), Metolazone, Spironolactone and Eplerenone.

Additionally, a descriptive summary for the total daily dose of each diuretic taken post randomization will be presented by visit, treatment group and open-label sacubitril/valsartan;

these include: Furosemide, Torsemide, Bumetanide, HCTZ, Diuril (chlorothiazide), Metolazone, Spironolactone and Eplerenone.

HF Medications at Index Hospitalization Discharge

The number and percentages of HF medications at the index hospitalization discharge will be summarized by treatment group, open-label and pooled sacubitril/valsartan. The following medications will be summarized: Beta blocker, Ivabradine, Hydralazine, Nitrites (long acting), Calcium channel blocker, Potassium, Digoxin and Statin. Additionally, the number and percentages of each daily diuretic and/or potassium taking during the index hospitalization collected at discharge, the route (when applicable) and total daily dose will be summarized by treatment group, open-label and pooled sacubitril/valsartan.

These summaries will also be presented using the FAS.

Post Randomization Non-study Drug ACEi/ARB

Any ACEi and/or ARB taken after randomization will be listed.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary endpoint is the time-averaged proportional change from baseline in NT-proBNP. Weeks 4 and 8 will be included in the analysis (primary analysis time point). The analysis of the primary endpoint will be based on the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary hypothesis to be tested is the ratio of the geometric means of NT-proBNP (average of Weeks 4 and 8/baseline) for the sacubitril/valsartan and enalapril treatment groups are equal (H0) versus the ratio of the geometric means of NT-proBNP are not equal (Ha).

For NT-proBNP, the time-averaged proportional change from baseline in a logarithmic scale will be analyzed using an analysis of covariance (ANCOVA) model using data from Weeks 4 and 8 with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate.

The values from Weeks 4 and 8 will be averaged and the change from baseline in log-transformed NT-proBNP will be calculated as follows:

log (average post dose value) – log (baseline value)

The estimated treatment effect in terms of ratios of geometric means, based on the least-squares (LS) means from the model, and the corresponding two-sided 95% confidence intervals will be presented.

The geometric means (presented as a ratio to baseline) will be calculated by exponentially back transforming the LS means based on the ANCOVA model as follows:

exp (LS mean)

2.5.3 Handling of missing values/censoring/discontinuations

The analysis will be performed based on all available data in the FAS and based on likelihood method with an assumption of missing at random for missing data.

2.5.4 Supportive analyses

The primary endpoint will be analyzed in the FAS using the same analytical approach as described in Section 2.5.2; however, baseline will be defined as the last non-missing NT-proBNP assessment with collection date:time < first dose date:time.

For NT-proBNP at Weeks 4 and 8, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. For each visit, the estimated treatment effects in terms of ratios of the geometric means based on the LS means from the model and the corresponding two-sided 95% confidence intervals produced from the model will be presented. The geometric mean will be calculated by exponentially back transforming the LS means.

The primary endpoint will also be analyzed in the PPS using the same analytical approach as described in Section 2.5.2.

In addition, a binary outcome variable will be created for patients achieving a 25%, 50% and 75% decline in NT-proBNP (0-no, 1-yes) and a logistic regression model will be fit. The odds ratio, 95% confidence interval and p-value will be provided. The outcome variable will be achieving a decline in NT-proBNP and the predictor of response will be treatment group.

A descriptive summary of patient evaluability for the primary endpoint analysis based on NT-proBNP values will be presented by treatment group.

2.6 Analysis of the key secondary objective

No key secondary objective.

2.7 Analysis of secondary objectives

All analyses will be performed on the FAS, unless otherwise specified.

2.7.1 Secondary endpoints

Secondary endpoints include the following:

- The proportional change in NT-proBNP from baseline to Week 8
- Incidence of symptomatic hypotension during 8 weeks of treatment
- Incidence of hyperkalemia (potassium >5.5 mEq/L) during 8 weeks of treatment
- Incidence of angioedema during 8 weeks of treatment
- Biomarkers: hs-Troponin T (high sensitivity), urinary cGMP (UcGMP), UcGMP to urinary creatinine ratio, BNP, NT-proBNP to BNP ratio, and BNP to NT-proBNP ratio at 4 and 8 weeks

2.7.2 Statistical hypothesis, model, and method of analysis

For NT-proBNP at Week 8, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker as a covariate. The estimated treatment effects in terms of ratios of geometric means, based on the LS means from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. Baseline is Week 0. Week 4 will be used if the Week 8 value is missing.

The incidence of symptomatic hypotension up to Week 8 will be calculated by treatment group. The relative risk (sacubitril/valsartan vs. enalapril) and the 95% confidence interval will also be presented. Similarly, the incidence of hyperkalemia, all angioedema, and positively adjudicated angioedema during the 8 week double-blind phase and the relative risk (sacubitril/valsartan vs. enalapril) will be summarized. Additionally, medication change, lowest documented systolic blood pressure and lowest documented diastolic blood pressure will be summarized by treatment group for symptomatic hypotension. The highest potassium value documented for hyperkalemia will also be summarized by treatment group.

For biomarkers including BNP, BNP to NT-proBNP ratio, NT-proBNP to BNP ratio, hs-Troponin T, UcGMP, and UcGMP to urinary creatinine ratio, the time-averaged proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model using data from Weeks 4 and 8 with treatment group as a fixed effect factor and the logarithmic baseline biomarker value as a covariate.

Similar to the primary endpoint, the values from Weeks 4 and 8 will be averaged and the change from baseline will be calculated.

The estimated treatment effect in terms of ratios of geometric means, based on the LS means from the model, and the corresponding two-sided 95% confidence intervals will be presented. The geometric means (presented as a ratio to baseline) will be calculated by exponentially back transforming the LS means based on the ANCOVA model.

For biomarkers including BNP, BNP to NT-proBNP ratio, NT-proBNP to BNP ratio, UcGMP, and UcGMP to urinary creatinine ratio at Weeks 1, 2, 4 and 8, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. For each visit, the estimated treatment effects in terms of ratios of the geometric means based on the LS means from the model, and the corresponding two-sided 95% confidence intervals produced from the model will be presented. Similarly, the geometric mean will be calculated by exponentially back transforming the LS means based on the ANCOVA model. This analysis will also be performed for hs-Troponin T at Weeks 1, 4, and 8 (note that hs-Troponin T is not measured at Week 2).

2.7.3 Handling of missing values/censoring/discontinuations

The analysis will be performed based on all available data in the FAS and based on likelihood method with an assumption of missing at random for missing data.

2.8 Safety analyses

All safety analyses will be performed on the SS unless otherwise specified.

2.8.1 Adverse events

2.8.1.1 Coding of AEs

Adverse events are coded using MedDRA terminology (v19.0 or later).

2.8.1.2 General rules for AE reporting

AE summaries will include all treatment-emergent AEs (TEAEs). TEAEs are defined as AEs starting on or after the first day of study treatment. All AEs will be listed. AEs starting prior to the first day of study treatment (non-TEAEs) will be flagged in the listings.

All TEAEs will be summarized by study phase as defined in Section 2.1.1.

TEAEs will be summarized by presenting the number and percentage of patients having at least one TEAE, having at least one TEAE in each primary SOC, and for each PT using MedDRA coding. A patient with multiple occurrences of a TEAE will be counted only once in the AE category.

Separate summaries will be presented by SOC, PT and severity. A patient with multiple severities for an AE will be summarized under the worst severity recorded for the event.

Any information collected will be listed as appropriate.

2.8.1.3 AE summaries

The following summary tables will be provided:

- AEs, regardless of study treatment relationship, by primary SOC, PT and worst severity
- Most frequent (≥5%) AEs, regardless of study treatment relationship, by PT
- AEs, suspected to be related to study treatment, by primary SOC and PT
- Serious adverse events (SAE), regardless of study treatment relationship, by primary SOC and PT
- SAEs, suspected to be related to study treatment, by primary SOC and PT
- SAEs occurring with a frequency of ≥0.5%, regardless of study treatment relationship, by PT
- SAEs, regardless of study treatment relationship, by primary SOC, PT and seriousness criteria
- AEs leading to discontinuation, regardless of study treatment relationship, by primary SOC and PT
- AEs requiring dose adjustment or study treatment interruption, regardless of study treatment relationship, by primary SOC and PT
- AEs requiring additional therapy, regardless of study treatment relationship, by primary SOC and PT

- Death resulting from AEs, regardless of study treatment relationship, by primary SOC and PT

2.8.1.4 In addition, an overview of TEAEs presenting the number of percentage of patients having at least one TEAE for each of the above categories will be provided.Adverse events of special interest / grouping of AEs

Separate summaries will be provided for AEs related to all angioedema, positively adjudicated angioedema, elevated creatinine, hyperkalemia and symptomatic hypotension. The summaries will be presented by primary SOC, PT and worst severity.

Additionally, a sensitivity analysis will be performed on the AEs of special interest for patients randomized to sacubitril/valsartan. The number and percentages of AEs of special interest occurring prior to the active dose of sacubitril/valsartan will be presented along with the number and percentages of AEs of special interest occurring on or after the active dose of sacubitril/valsartan during the double-blind phase. The following definition will be used:

Angioedema:

AE prior to active study treatment = if event occurred within 1 day of dosing as recorded on the Angioedema Assessment Visit 2 (randomization)

AE after active study treatment = if event occurred after 1 day of dosing as recorded on the Angioedema Assessment Visit 2 (randomization)

Symptomatic hypotension:

AE prior to active study treatment = First dose date ≤ event < Third dose date of study treatment

AE after active study treatment = Third dose date of study treatment ≤ event ≤ Last dose date of double-blind medication

Elevated creatinine and hyperkalemia:

AE prior to active study treatment = First dose date:time of study treatment ≤ event < Third dose date:time of study treatment

AE after active study treatment = Third dose date:time of study treatment ≤ event ≤ Last dose date:time of double-blind medication

2.8.2 Deaths

Patient deaths will be summarized by total, primary cause of death, type of cardiovascular death and type of non-cardiovascular death and will be presented by study phase (see Section 2.1.1 for study phase definitions). A patient listing of all deaths with recorded principal cause of death will be provided. All patients in the FAS will be included for the above analysis.

2.8.3 Laboratory data

Laboratory values will be summarized using shift tables (from baseline to most extreme post baseline value) by each laboratory parameter at its worst severity by study phase (see Section 2.1.1 for study phase definitions). The number and percentage of patients with laboratory values

will be presented by low/normal/high (low and high) classifications to compare baseline to worst post baseline value.

In addition, laboratory values and the change from baseline for each parameter by visit will be summarized by treatment group and open-label sacubitril/valsartan. In the event that there are multiple laboratory values within a visit, the worst value will be summarized.

A separate summary table will be presented by study phase (see Section 2.1.1 for study phase definitions) with the number and percentage of patients having notable lab abnormalities based on percent change from baseline (see Section 5.3 for a list of notable laboratory abnormalities).

A summary of hyperkalemia labs by visit will also be presented by treatment group and open-label sacubitril/valsartan. The highest potassium value for the event and any potassium re-test results will be descriptively summarized. Similarly, creatinine labs will also be presented by visit, treatment group and open-label sacubitril/valsartan. The highest creatinine value for the event and any creatinine re-test results will be descriptively summarized.

Listings of all laboratory values will be provided. Separate listings for hyperkalemia labs, creatinine labs and pregnancy tests will also be provided. Any notable laboratory abnormalities will also be flagged.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

ECG data will be collected at screening and all data, including unscheduled visits, will be listed.

2.8.4.2 Vital signs

All vital signs (systolic and diastolic blood pressure [mmHg], pulse rate [sitting/beats per minute], weight [kg], height [cm], BMI [kg/m^2] and waist/hip circumference) will be descriptively summarized at each visit by treatment group and open-label sacubitril/valsartan. Change from baseline will also be presented.

A separate summary table will be presented with the number and percentages of patients having notable vital signs based on changes relative to baseline values (see Section 5.4 for a list of notable vital signs) by study phase (see Section 2.1.1 for study phase definitions).

The number and percentages of patients having symptomatic hypotension will also be summarized by study phase. The following variables associated with symptomatic hypotension will also be presented: symptoms occurring while standing, any treatment or medication change as a result of episode, lowest documented systolic blood pressure, systolic blood pressure position, lowest documented diastolic blood pressure and diastolic blood pressure position. A listing for symptomatic hypotension will also be presented.

2.8.4.3 Heart Failure Event

Any new heart failure event information will be collected and listed. The following will be presented:

- Type of event (HF hospitalization [hospital stay ≥24 hours], Heart failure emergency department visit, Urgent/unplanned heart failure office visit, Worsening heart failure

during the index hospitalization [qualifying heart failure event], None of the aforementioned types occurred with, or apply to, this HF event)

- Symptoms of worsening HF (Dyspnea – [Dyspnea at rest, Dyspnea on exertion, Orthopnea, Paroxysmal nocturnal dyspnea, Tachypnea], Decreased exercise tolerance [reduced ability to perform activities that induce physical exertion due to dyspnea or fatigue], Fatigue [lack of energy, extreme tiredness, inability to complete usual activities], Worsening end-organ perfusion – [Confusion (thought to be from low cardiac output), Reduced urine output], Symptoms of volume overload – [Lower extremity swelling, Increased abdominal distension)], Other)
- Physical exam signs of worsening HF (Peripheral edema, Increased abdominal distension or ascites [in the absence of hepatic disease], Pulmonary rales/crackles, Elevated jugular venous pressure and/or hepatojugular reflux, New or worsening 3rd heart sound, Clinically significant weight gain thought to be related to fluid retention [>3 - 4 lbs. in 3 to 4 days], Other)
- Laboratory evidence of worsening HF (Increased NT-proBNP [>2,000 pg/mL], Radiographic evidence of pulmonary congestion, Right heart catheterization with pulmonary capillary wedge pressure ≥18 mmHg, central venous pressure ≥12 mmHg, or a cardiac index of <2.2 L/min/m^2, Other)
- Increased or additional therapy (No, Yes, Unknown)
    - Therapy type (Augmentation of oral diuretic therapy with additional diuretic, Initiation of intravenous diuretic, Uptitration of intravenous therapy, if already on therapy, Initiation of inotrope, or vasodilator therapy, Initiation of percutaneous mechanical circulatory support, Initiation of temporary surgical support [ECMO or temporary surgical ventricular assist device (VAD) i.e. centrimag], Implantation of durable LVAD, Listed for heart transplantation)
- Evidence of cardiogenic shock (No, Yes, Unknown)
- Blood sample collected for BNP or NT-proBNP (No, Yes, Unknown)
    - BNP result (pg/mL)
    - NT-proBNP result (mg/mL)
- Contributors/precipitants of worsening heart failure (Medication nonadherence, Dietary indiscretion, Acute coronary syndrome, Other systemic illness – [Respiratory infection, Urinary tract infection, Other])

2.8.4.4 HF Signs and Symptoms

Heart failure signs and symptoms will be collected at screening, randomization and at post randomization visits. The number and percentage of the following parameters will be summarized at each visit by treatment group and open-label sacubitril/valsartan:

- Heart failure signs or symptoms within the past 24 hours prior to this visit (No, Yes)
- Rales (Not present, Basilar only, >1/3 of lung filled, Not done)

- Peripheral edema (Absent, Trace, Feet and ankles, Lower legs or thighs, Sacrum, Not done)
- Current NYHA heart failure classification (Class I, Class II, Class III, Class IV, Not done)
- Fatigue (Not present, Seldom, Frequent, Continuous, Not done)
- Dyspnea (Not present, Seldom, Frequent, Continuous, Not done)
- Orthopnea (Not present, Seldom, Frequent, Continuous, Not done)

2.8.4.5 Hospitalization

Information related to hospitalization will be listed. The following will be presented:

- Type of hospitalization (Elective, Planned, Unplanned)
- Reason for hospitalization (refer to eCRF for list of reasons)
- Patient discharged (No, Yes, Unknown)
    - Duration of hospitalization in days [*date of discharge – date of admission + 1*]
- Patient admitted to ICU or Coronary Care Unit (CCU) (No, Yes, Unknown)
    - Number of days in ICU or CCU
- Discharge disposition (Home or with family/friends, Rehabilitation facility, Skilled nursing facility, Death, Unknown)

2.8.4.6 Angioedema

Data collected from the angioedema assessment and questionnaire at screening, randomization and follow-up visits will be summarized. Separate summaries will be produced for all angioedema and positively adjudicated angioedema. The number and percentage for categorical variables and summary statistics for continuous variables of the following will be presented by visit, treatment group and open-label sacubitril/valsartan:

- Outcome (Not recovered/Not resolved, Recovered/Resolved, Recovering/Resolving, Recovered/Resolved with Sequelae, Fatal, Unknown)\
    - Duration of angioedema in days [*end date – start date + 1*]
- Timing of event (After first dose, after multiple doses, dose not given) [not asked at screening]
    - Study medication discontinued due to event (No, Yes, Unknown)
    - Event occurred within 1 day of dosing (Within 1 day of dose but less than or equal to 1 hour, within 1 day of dose but greater than 1 hour, After 1 day of dosing, Unknown)
- History of prior angioedema or angioedema like event (No, Yes, Unknown)
    - If yes, medications taken at time of previous event:

        - ACE inhibitor (No, Yes, Unknown)
        - ARB (No, Yes, Unknown)
        - Renin inhibitor (No, Yes, Unknown)
        - Other medications (No, Yes, Unknown)
- Presence of hereditary angioedema (No, Yes, Unknown)
- Any family members with history of angioedema-like events (No, Yes, Unknown)
- Signs and symptoms for current event
    - Shortness of breath/dyspnea (No, Yes, Unknown)
    - Difficulty swallowing/dysphagia (No, Yes, Unknown)
    - Difficulty speaking/dysarthria (No, Yes, Unknown)
    - Pain on swallowing/odynophagia (No, Yes, Unknown)
    - Stridor (No, Yes, Unknown)
    - Abdominal pain (No, Yes, Unknown)
    - Other (No, Yes, Unknown)
- Edema present (No, Yes)
    - Periorbital edema (No, Yes, Unknown)
    - Head edema (No, Yes, Unknown)
    - Neck edema (No, Yes, Unknown)
    - Lip edema (No, Yes, Unknown)
    - Tongue edema (No, Yes, Unknown)
    - Throat edema (No, Yes, Unknown)
    - Submandibular edema (No, Yes, Unknown)
    - Genitalia edema (No, Yes, Unknown)
    - Extremities edema (No, Yes, Unknown)
    - Other (No, Yes, Unknown)
- Previous edematous episodes (No, Yes, Unknown)
    - Number of previous edematous episodes
- ACEi taken in the past (No, Yes, Unknown)
- ACEi taken during trial participation after screening (No, Yes, Unknown) [not asked at screening]
    - Dose changed within 2 days of event (No, Yes, Unknown)
- ARB taken in the past (No, Yes, Unknown)

- ARB taken during trial participation after screening (No, Yes, Unknown) [not asked at screening]
    - Dose changed within 2 days of event (No, Yes, Unknown)
- Patient suffering from influenza, common cold or upper respiratory tract infection (No, Yes, Unknown)
- Medication allergies (No, Yes, Unknown)
- Food allergies (No, Yes, Unknown)
- Potential causes of angioedema-like event
    - Food (No, Yes, Unknown)
    - Insect bite (No, Yes, Unknown)
    - Animal exposure (No, Yes, Unknown)
    - Medication (No, Yes, Unknown)
    - Dental work (No, Yes, Unknown)
    - Pollen (No, Yes, Unknown)
    - Dust (No, Yes, Unknown)
    - Concomitant disease (No, Yes, Unknown)
    - Idiopathic (No, Yes, Unknown)
    - Other (No, Yes, Unknown)
- Medical intervention (No, Yes)
    - Administration of H-1 blocker (No, Yes)
    - Administration of H-2 blocker (No, Yes)
    - Administration of steroids (No, Yes)
    - Administration of epinephrine (No, Yes)
    - Admission to hospital (No, Yes)
    - Admission to ER (No, Yes)
    - Endotracheal intubation (No, Yes)
    - Tracheostomy (No, Yes)
    - Discontinuation of ACE inhibitor (No, Yes)
    - Discontinuation of ARB (No, Yes)
    - Other

All assessment data will be listed. The adjudicated assessment of the event will be listed separately.

In addition, key characteristics of positively adjudicated angioedema will be summarized with descriptive statistics by study phase as defined in Section 2.1.1.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes (PRO)

All analyses will be performed on the FAS.

2.11.1 Kansas City Cardiomyopathy Questionnaire[1]

The KCCQ is a 23-item self-administered instrument that quantifies physical limitations (question 1a – 1f), symptoms (questions 2 through 9), self-efficacy and knowledge (questions 10 and 11), social limitation (question 15a – 15d) and quality of life (questions 12 through 14). A likert-type scale is used with the higher values representing better outcomes.

Missing values within each domain will be imputed using the average of the answered items within the same domain. Scale scores will be transformed into values of 0 to 100 by subtracting the lowest possible scale score, dividing by the range of the scale and multiplying by 100. Further details on calculation of the transformed scores are available in the programming specifications section of the SAP TFL Shells document. All analysis will be based on the transformed score.

Actual values and changes from baseline in the composite score for each domain, clinical summary score and an overall score will be summarized by visit and treatment group for the double-blind and open-label phases. Changes during the open-label phase for patients randomized to enalapril will be assessed relative to Week 8. The clinical summary score is the composite of the symptoms and social limitation domains. For patients who die, a worst score (score of 0) will be imputed for the domain scores and clinical and overall summary scores at all subsequent scheduled visits after the date of death where these scores would have been assessed.

Additional KCCQ analysis is described in Section 2.13.

2.11.2 Patient Global Assessment

The PGA is a seven-point patient self-evaluation scale. At randomization, the patient will take note of how he/she feels about his/her condition and will be asked how they feel compared to randomization at follow-up visits.

The PGA will be summarized by visit, treatment group and open-label sacubitril/valsartan.

Additional PGA analysis is described in Section 2.13.

2.12 Biomarkers

BNP and NT-proBNP will be collected and descriptively summarized by visit, treatment group and open-label sacubitril/valsartan. Values and the change from baseline for each parameter will be summarized by visit, treatment group and open-label sacubitril/valsartan. Analyses will be based on the FAS. BNP and NT-proBNP values will be based on clinical laboratory samples processed and assessed by the central laboratory.

Additional biomarker measurements believed to be relevant to the pathophysiology of the disease processes of heart failure and dysfunction will also be collected and summarized by visit, treatment group and total. These may include, but no limited to those assessing cardiac and renal benefit or biomarkers related to the study treatment mechanism of action such as:

- Neurohormones BNP and NT-proBNP
- hs-Troponin T
- Cystatin C
- soluble ST2 (sST2)
- eGFR (based on abbreviated Modification of Diet in Renal Disease [MDRD] calculation)
- urinary cGMP
- other biomarkers related to cardiac fibrosis/remodeling, tissue perfusion/injury, renal function/injury or other pathophysiologies involved in ADHF

Additional analysis of biomarkers is discussed in Sections 2.5, 2.7 and 2.13.

Biomarker samples from patients who withdrew consent will not be analyzed by the central laboratory.

2.13 Other Exploratory analyses

All analyses will be based on the FAS, unless otherwise specified.

Time to first occurrence of composite clinical endpoint through Week 8

The composite clinical endpoint includes death, heart failure re-hospitalization, requirement of LVAD, listed for cardiac transplantation, unplanned acute HF visits requiring i.v. diuretics, additional heart failure drug, or increase in >50% of the diuretic dose. Further details on derivation of the composite clinical endpoint are available in the programming specifications section of the SAP TFL Shells document. Individual elements of the composite, as well as a 'serious' composite clinical endpoint (consisting of death, heart failure re-hospitalization, requirement of LVAD, or listed for cardiac transplantation), will also be reported.

Time to first occurrence through Week 8 will be calculated in days as *date of first occurrence through Day 56 – date of randomization + 1*. Distribution of time to first occurrence will be estimated using the Kaplan-Meier (KM) method. The 25th percentile, median and the 75th percentile will be presented by treatment group along with the 95% confidence intervals and failure probabilities will be presented at 1 week, 2 weeks, etc., until 8 weeks along with the corresponding 95% confidence interval. Patients not having any of the endpoints described above will be censored at the earlier of the date of last contact or Day 56. The treatment groups

will be compared using a log-rank test and the p-value will be presented. The number and percentages of each component of the clinical endpoint will also be presented.

In addition to the KM method, the time to first occurrence will also be analyzed using a Cox proportional hazards regression model with treatment as a factor. The hazard ratio with 95% confidence interval will be presented.

The above analysis will be repeated using all data through the double-blind study phase.

The number of the composite clinical endpoint recurrent events through Week 8 will be summarized and analyzed using appropriate statistical methods.

Change from baseline at Weeks 1 and 2 in NT-proBNP

For NT-proBNP at Weeks 1 and 2, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. For each visit, the estimated treatment effects in terms of ratios of the geometric means based on the LS means from the model and the corresponding two-sided 95% confidence intervals produced from the model will be presented. The geometric means will be calculated by exponentially back transforming the LS means.

Time to first hospitalization through Week 8

The time to first hospitalization (re-hospitalization, ED visit or unplanned outpatient clinic visit due to worsening HF symptoms) after index hospitalization through Week 8 will be calculated for patients discharged from their index hospitalization in days as *date of first hospitalization through Day 56 – date of index hospitalization discharge + 1.* Further details on derivation of first hospitalization are available in the programming specifications section of the SAP TFL Shells document. Distribution of time to first hospitalization will be estimated using the KM method. The 25th percentile, median and the 75th percentile will be presented by treatment group along with the 95% confidence intervals and failure probabilities will be presented at 1 week, 2 weeks, etc., until 8 weeks along with the corresponding 95% confidence interval. Patients not having any of the endpoints described above will be censored at the earlier of the date of last contact/death or Day 56. The treatment groups will be compared using a log-rank test and the p-value will be presented. The number and percentages of each component of hospitalization (re-hospitalization, ED visit and unplanned outpatient clinic visit due to worsening HF symptoms) will also be presented.

A negative binomial regression model will also be fit with the outcome variable being the number of re-hospitalizations through Week 8 and the predictor of response will be treatment group. Re-hospitalizations are defined as HF hospital stays ≥24 hours. To reduce bias, the model will use an offset option for the log of study duration to adjust the estimates. The log of study duration through Week 8 will be calculated in days by *log(earlier of the date of last contact/death or Day 56 – date of index hospitalization discharge + 1).* The estimated event rates by treatment group and the 95% confidence intervals will be presented. In addition, the treatment comparison estimated ratio and the 95% confidence interval will also be presented. Similarly, a negative binomial regression mode will also be fit with the outcome variable as the number of heart failure visits requiring i.v. diuretics through Week 8 using the same approach discussed above. The estimated event rates by treatment group and the 95% confidence intervals

will be presented. In addition, the treatment comparison estimated ratio and the 95% confidence interval will also be presented. Further details on derivation of heart failure visits requiring i.v. diuretics are available in the programming specifications section of the SAP TFL Shells document.

The following days summaries will also be presented:

- Days alive after index hospitalization, not including re-hospitalization, through Week 8
- Days in the ICU/CCU through Week 8
- Days on LVAD through Week 8

An analysis of variance (ANOVA) model will be fit for each of these days variables as the dependent variable and treatment group as an independent variable. The estimated difference in means between the treatment groups will be presented with a 95% confidence interval.

Re-hospitalization through Day 30

Time to first re-hospitalization (re-hospitalization, ED visit or unplanned outpatient clinic visit due to worsening HF symptoms) through Day 30 will be calculated for patients discharged from their index hospitalization in days as *date of first re-hospitalization through Day 30 – date of index hospitalization discharge + 1*. Further details on derivation of re-hospitalization through Day 30 are available in the programming specifications section of the SAP TFL Shells document. Distribution of time to first re-hospitalization through Day 30 will be estimated using the KM method. The 25th percentile, median and the 75th percentile will be presented by treatment group along with the 95% confidence intervals. Patients without an event will be censored at the earlier of the date of last contact/death or Day 30. The treatment groups will be compared using a log-rank test and the p-value will be presented.

In addition, a binary outcome variable will be created for re-hospitalization within 30 days after index hospitalization discharge (0-no, 1-yes) and a logistic regression model will be fit. The outcome variable will be re-hospitalization within 30 days after index hospitalization discharge and the predictor of response will be treatment group. The odds ratio, 95% confidence interval and p-value will be provided. Similarly, a logistic regression model will be fit for each component hospitalization within 30 days after index hospitalization discharge – re-hospitalization, ED visit and unplanned outpatient clinic visit due to worsening HF symptoms. The odds ratio, 95% confidence interval and p-value will be provided. The outcome variable will be each component of the hospitalizations and the predictor of response will be treatment group.

Need for advanced heart failure therapies through Week 8

The need for advanced heart failure therapies through Week 8 including but not limited to i.v. inotropes, LVAD and/or transplantation will be analyzed. A binary outcome variable will be created (0-advanced heart failure therapies not needed, 1-advanced heart failure therapies needed) and a logistic regression model will be fit. The outcome variable will be advanced heart failure therapies and the predictor of response will be treatment group. The odds ratio, 95% confidence interval and p-value will be provided.

Patient centered outcomes at 4 weeks and 8 weeks post randomization

The clinical summary score at Weeks 4 and 8 of the KCCQ will be analyzed using a repeated measures ANCOVA model with treatment, visit and treatment by visit interaction as fixed effect factors and the baseline value as a covariate. A common unstructured covariance for each treatment group will be used. The primary treatment comparison will be made at Week 8. The analysis will be performed on all available data and based on the likelihood method. The estimates of the treatment effects with the associated confidence intervals at Week 8 will be provided by treatment group.

Additional analyses will be performed to determine characteristics that could affect improvement or deterioration in the Week 8 KCCQ clinical summary score relative to baseline. Missing data at Week 8 will be imputed using the last-observation-carried-forward method. A responder analysis having at least a 5 point improvement in the clinical summary score and a responder analysis having at least a 5 point deterioration in the clinical summary score from baseline will be performed. A logistic regression model will be fit with a binary outcome variable (0-no improvement/deterioration, 1-improvement/deterioration) and the predictors of response will be treatment group, age group, sex and race. The odds ratio, 95% confidence interval and p-value will be provided.

The PGA will be analyzed at Weeks 4 and 8 using an exact Mantel-Haenszel Chi-Square test for comparison of the different treatment means based on modified ridit scores. P-values will be presented.

Change in biomarkers

For biomarkers relating to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury and/or renal function, a proportional change from baseline in a logarithmic scale at Weeks 2, 4 and 8 will be analyzed using a repeated measures ANCOVA model with treatment, visit and treatment by visit interaction as fixed effect factors and the logarithmic baseline biomarker value as a covariate. A common unstructured covariance for each treatment group will be used. Note that hs-Troponin T will not be analyzed since it is not measured at Week 2.

For each visit, the estimated treatment effects in terms of ratios of the geometric means based on the LS means from the model, and the corresponding two-sided 95% confidence intervals produced from the model will be presented. The geometric mean will be calculated by exponentially back transforming the LS mean.

A sensitivity analysis will be performed with baseline defined as the last non-missing biomarker assessment with collection date:time < first dose date:time.

Change in NT-proBNP during the 4 week open-label period

The change from Week 8 to Week 12 in NT-proBNP will be descriptively summarized based on untransformed values and analyzed using a paired t-test in a logarithmic scale for each treatment group. The same analysis will be conducted for sacubitril/valsartan on the change from baseline to Week 12.

Medical resource utilization

Medical resource utilization will be summarized by treatment group, open-label and pooled sacubitril/valsartan. The following will be presented:

- Unplanned doctor visits (No, Yes, Unknown)
    - Reason for visit (Cardiovascular, Non-cardiovascular, Unknown)
        - Visit heart failure related (No, Yes, Unknown)
- Any hospitalizations (No, Yes, Unknown)
- Patient initiated on dialysis or ultrafiltration (No, Yes, Unknown)
    - Dialysis or ultrafiltration initiated for worsening heart failure (No, Yes, Unknown)
- Pacemaker/ICD (No, Yes, Unknown)
    - Pacemaker/ICD type (Pacemaker [conventional], cardiac resynchronization therapy-no ICD [CRT-P], cardiac resynchronization therapy-with ICD [CRT-D], ICD only (single/dual), Unknown)
- Patient undergo placement of a cardioMEMS (No, Yes, Unknown)

Incidence of worsening renal function during 8 weeks of treatment

Worsening renal function during 8 weeks of treatment is defined as an increase in serum creatinine of ≥0.5 mg/dL from the value measured at baseline. A logistic regression model will be fit with a binary outcome variable (0-no worsening renal function, 1-worsening renal function) and the predictors of response will be treatment group and baseline creatinine value. The odds ratio, 95% confidence interval and p-value will be provided.

A sensitivity analysis will be performed with baseline defined as the last non-missing serum creatinine assessment with collection date:time < first dose date:time.

Change from Week 1 to Weeks 4 and 8 in biomarkers

For NT-proBNP, hs-Troponin T, sST2, UcGMP and BNP to NT-proBNP, the time-averaged proportional change from Week 1 to Weeks 4 and 8 in a logarithmic scale will be analyzed using the same approach described for the primary endpoint in Section 2.5.2. The values from Weeks 4 and 8 will be averaged and the change from Week 1 will be calculated.

Change from baseline to Week 4/Week 8 and Weeks 1, 2, 4, and 8 in sST2

For sST2, the time-averaged proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model using data from Weeks 4 and 8 with treatment group as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. Similar to the primary endpoint, the values from Weeks 4 and 8 will be averaged and the change from baseline will be calculated.

For Weeks 1, 2, 4, and 8, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate.

The estimated treatment effects in terms of ratios of the geometric means based on the LS means from the model, and the corresponding two-sided 95% confidence intervals produced from the model will be presented. The geometric means will be calculated by exponentially back transforming the LS means based on the ANCOVA model.

Assessment of "early" (1st half) vs. "late" (2nd half) enrollers

Demographics, baseline characteristics, disease history, and primary and secondary endpoint analyses will be generated for the following subgroups:

- First half of randomized patients ("early" enrollers)
- Second half of randomized patients ("late" enrollers)

The first and second halves of randomized patients will be identified according to their randomization date and time.

2.14 Interim analysis

No interim analysis is planned.

3 Sample size calculation

Assuming a significance level of 0.05 and 85% power, a sample size of 882 patients would be needed to detect an 18% reduction in the geometric mean of the time-averaged proportional change from baseline (average of Weeks 4 and 8) in NT-proBNP for the sacubitril/valsartan treatment group assuming a value of 0.95 for the enalapril group, a common standard deviation of 0.85 and a 25% rate of missing/non-evaluable samples. The estimates are based on the day 5 to day 14 data from the RELAX-AHF study. The standard deviation estimate is supported by data from PARADIGM.

The assumption of a 18% reduction in the geometric mean for NT-proBNP for the sacubitril/valsartan treatment group vs. the enalapril group is consistent with NT-proBNP results seen in PARADIGM (26% and 25% relative reduction of sacubitril/valsartan vs. enalapril at Week 4 and Month 8 respectively), PARAMOUNT (23% relative of sacubitril/valsartan vs. valsartan at Week 12) and RELAX-AHF (19% relative reduction of serelaxin vs. placebo at Day 2).

Sample size and power for various rate of reduction in sacubitril/valsartan group given alpha = 0.05 are given in Table 9-1 in the protocol.

4 Change to protocol specified analyses

The following changes to protocol specified analyses were made:

- Specified the following additional biomarkers as secondary endpoints:
    - UcGMP to urinary creatinine ratio
    - BNP
    - NT-proBNP to BNP ratio

- Added sensitivity analyses for the following endpoints using the "strict" baseline definition (i.e., collection date:time < first dose date:time):
    - Primary endpoint
    - Incidence of worsening renal function during 8 weeks of treatment
    - Biomarkers related to cardiac fibrosis/remodeling, myocardial stress, inflammation, tissue perfusion/injury and/or renal function (eGFR)
- Clarified that tables summarizing demographics and baseline data will be run only on the FAS, and not also on the RS as indicated in the protocol
- Replaced supportive analysis of the primary endpoint consisting of summary statistics and t-test p-values for comparing treatment groups on the proportional change from baseline in a logarithmic scale at Weeks 4 and 8 with ANCOVA at Weeks 4 and 8
- Added the change from baseline to Week 12 for sacubitril/valsartan to the assessment of NT-proBNP during the open-label period
- Clarified that KCCQ data will be summarized by randomized treatment group during the open-label phase, and that changes during the open-label phase for patients randomized to enalapril will be assessed relative to Week 8
- Modified the Safety Set definition to remove the word 'active' so that inclusion in the Safety Set is not restricted to patients who received at least one dose of *active* study treatment
- Replaced CMH test with an exact Mantel-Haenszel Chi-Square test for analysis of PGA values at Weeks 4 and 8
- Added analysis of time to first occurrence of 'serious' composite clinical endpoint consisting of death, HF re-hospitalization, requirement of LVAD, and listed for cardiac transplantation
- Added analysis of time-averaged proportional change in NT-proBNP and other biomarkers from Week 1 to Weeks 4 and 8
- Added Weeks 4 and 8 to the analysis of change from baseline in biomarkers defined as secondary endpoints
- Added analysis of change from baseline in sST2 to Week 4/Week 8 and Weeks 1, 2, 4, and 8
- Added assessment of demographics, baseline characteristics, disease history, and primary and secondary endpoints in "early" (1st half) vs. "late" (2nd half) enrollers
- Added recurrent event analysis of the composite clinical endpoint
- Modified the PPS definition to clarify that major protocol deviations will exclude patients from the PPS regardless of the study phase in which they occur
- Added a repeat analysis of the time to first occurrence of composite clinical endpoint based on all data through the double-blind study phase

5 Appendix

5.1 Imputation rules

5.1.1 Study treatment

Full dates for study treatment collected on the eCRF are required; therefore, no imputations will be made.

5.1.2 AE date imputation

The following algorithm should be used to estimate start dates for which only partial information is known:

- Missing day and month
  - If the year is the same as the year of first study treatment, then the day and month of the start date of treatment will be assigned to the missing fields.
  - If the year is prior to the year of first study treatment, then December 31 will be assigned to the missing fields.
  - If the year is after the year of first study treatment, then January 1 will be assigned to the missing fields.
- Missing month only
  - Treat day as missing and replace both month and day according to the above procedure.
- Missing day only
  - If the month and year are the same as the year and month of first study treatment, then the start date of treatment will be assigned to the missing day.
  - If the month and year are before the year and month of first study treatment, then the last day of the month will be assigned to the missing day.
  - If the month and year are after the year and month of first study treatment, then the first day of the month will be assigned to the missing day.

If the imputed start date result is after the stop date (and the stop date is complete), the imputed start date will be reset to the stop date.

The following algorithm should be used to estimate stop dates for which only partial information is known:

- Missing year
  - Date left missing.
- Missing month
  - Impute ‘December’.
- Missing day
  - Impute ‘last date of that month’.

5.1.3 Concomitant medication date imputation

The following algorithm should be used to estimate start dates for which only partial information is known:

- Missing day and month
  - If the year is the same as the year of first study treatment, then the day and month of the start date of treatment will be assigned to the missing fields.

- If the year is prior to the year of first study treatment, then December 31 will be assigned to the missing fields.
- If the year is after the year of first study treatment, then January 1 will be assigned to the missing fields.

- Missing month only
  - Treat day as missing and replace both month and day according to the above procedure.
- Missing day only
  - If the month and year are the same as the year and month of first study treatment, then the start date of treatment will be assigned to the missing day.
  - If the month and year are before the year and month of first study treatment, then the last day of the month will be assigned to the missing day.
  - If the month and year are after the year and month of first study treatment, then the first day of the month will be assigned to the missing day.

If the imputed start date result is after the stop date (and the stop date is complete), the imputed start date will be reset to the stop date.

The following algorithm should be used to estimate stop dates for which only partial information is known:

- Missing year
  - Date left missing. Consider the medication to have been received at all periods after that period determined by the start date.
- Missing month
  - Impute 'December'.
- Missing day
  - Impute 'last date of that month'.

5.1.3.1 Prior therapies date imputation

The same imputation as concomitant medication will be used. See Section 5.1.3.

5.1.3.2 Post therapies date imputation

The same imputation as concomitant medication will be used. See Section 5.1.3.

5.2 AEs coding/grading

The UBC coding team will code the AE terms using MedDRA terminology (v19.0 or later). If any terms are not coded, the data management team will issue queries to sites to update the AE term appropriately.

5.3 Laboratory parameters derivations

5.3.1 Laboratory grading

The collected laboratory values will be summarized by severity (low/normal/high) and not converted to Common Terminology Criteria for Adverse Events (CTCAE) grades.

5.3.2 Notable laboratory values

Hematology

RBC count	>50% increase, >20% decrease
Hemoglobin	>50% increase, >20% decrease
Hematocrit	>50% increase, >20% decrease
WBC count	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease

Blood Chemistry

ALT (SGPT)	>150% increase
AST (SGOT)	>150% increase
BUN	>50% increase
Creatinine	>50% increase
Total bilirubin	>100% increase
CPK	>300% increase
Alkaline phosphatase	>100% increase
Potassium	>20% increase, >20% decrease
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease
Uric acid	>50% increase

5.4 Vital signs

5.4.1 Notable vital sign values

Systolic blood pressure	<90 mmHg and decrease of >20 mmHg from baseline
	>140 mmHg and increase of >20 mmHg from baseline
	>160 mmHg and increase of >20 mmHg from baseline
	<90 mmHg
	>140 mmHg
	>160 mmHg
	Decrease of >20 mmHg from baseline
	Increase of >20 mmHg from baseline
Diastolic blood pressure	<50 mmHg and decrease of >15 mmHg from baseline
	>100 mmHg and increase of >15 mmHg from baseline

	<50 mmHg
	>100 mmHg
	Decrease of >15 mmHg from baseline
	Increase of >15 mmHg from baseline
Pulse	<50 bpm and decrease of >15 bpm from baseline
	>120 bpm and increase of >15 bpm from baseline
	<50 bmp
	>120 bpm
	Decrease of >15 bpm from baseline
	Increase of >15 bpm from baseline
Weight	>7% decrease; >7% increase

5.5 Statistical models

5.5.1 Primary analysis

The null hypothesis for the primary analysis is the ratio of the geometric means of NT-proBNP for the sacubitril/valsartan and enalapril group are equal. An ANCOVA model will be used. The model will have the time-averaged proportional change from baseline in a logarithmic scale be the dependent variable with treatment as a fixed effect factor and the logarithmic baseline value as a covariate. The general form for the ANCOVA model is:

$$y_{ij} = \mu + \tau_i + B\left(x_{ij} - \overline{x_i}\right) + \epsilon_{ij}$$

PROC MIXED in SAS will be used for the analysis. The LSMEANS option will be used with options of CL to output the confidence limits.

5.5.2 Key secondary analysis

Similar to the primary analysis, the null hypothesis for the secondary analysis is the ratio of the geometric means of different biomarkers (BNP to NT-proBNP ratio, hs-Troponin and urinary cGMP) for the sacubitril/valsartan and enalapril group are equal. An ANCOVA model will be used. The model will have the time-averaged proportional change from baseline in a logarithmic scale be the dependent variable with treatment as a fixed effect factor and the logarithmic baseline value as a covariate. The general form for the ANCOVA model is:

$$y_{ij} = \mu + \tau_i + B\left(x_{ij} - \overline{x_i}\right) + \epsilon_{ij}$$

PROC MIXED in SAS will be used for the analysis. The LSMEANS option will be used with options of CL to output the confidence limits.

5.6 Rule of exclusion criteria of analysis sets

Table 1 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses
D01	Patient met one or more of the Discontinuation of Study Drug criteria but study drug was not discontinued	Exclusion from PPS
E02	Patient is enrolled in another clinical trial involving an investigational agent or investigational device	Exclusion from PPS
E03	Patients has a history of hypersensitivity, known or suspected contraindications, or intolerance to the study drugs, including ACEIs, ARBs, or Sacubitril (NEP inhibitor)	Exclusion from PPS
E04	Patient has a history of angioedema related to previous ACE inhibitor or ARB therapy	Exclusion from PPS
E11	The patient had implantation of a cardiac resynchronization therapy device (CRTD) within the prior 3 months from Visit 1, the patient intends to have implantation of a cardiac resynchronization therapy device (CRTD)	Exclusion from PPS
E19	Patient is a 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 hCG laboratory test	Exclusion from PPS
I07	LVEF was not ≤ 40% within the past 6 months (including current hospitalization) using echocardiography, multi gated acquisition scan (MUGA), CT scanning	Exclusion from PPS
I09	Patient did not have an elevated NT-proBNP ≥ 1600pg/mL or BNP ≥ 400 pg/mL during current hospitalization	Exclusion from PPS

Deviation ID	Description of Deviation	Exclusion in Analyses
M01	Patient had concomitant intake of a prohibited medication as outlined in the protocol	Exclusion from PPS
O04	Patient randomized in error and not dosed with study drug	Exclusion from FAS and PPS
O05	Missing NT-ProBNP sample at either baseline, week 4 or week 8	Exclusion from PPS
O06	Patient took first dose of study drug before baseline NT-proBNP sample was drawn	Exclusion from PPS
O07	Patient missed 1 or more consecutive dose(s) of study drug immediately or prior to visit 5 or visit 7	Exclusion from PPS

Table 2 Patient Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
RS	NA	Not randomized
FAS	O04	Not in RS
PPS	D01, E02, E03, E04, E11, E19, I07, I09, M01, O04, O05, O06, O07	Not in FAS
SS	NA	No double-blind study treatment received

6 Reference

1 Green, CP, Porter, CB, Bresnaham, DR, & Spertus, JA 2000, 'Development and evaluation of the kansas city cardiomyopathy questionnaire: a new health status measure for heart failure', *Journal of the American College of Cardiology,* vol. 35, no. 5, pp. 1245-1255