NOVARTIS

Clinical Development

LCZ696

Clinical Trial Protocol CLCZ696BUS01 / NCT02554890

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

[redacted]

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
[redacted]	[redacted]
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

[redacted]

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
[redacted]	[redacted]
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

[redacted]

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

[redacted]

	drug being tested in the study

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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 ep isode 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
[redacted]	

	[redacted]
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

[redacted]

	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.

[redacted]

	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

[redacted]

	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 [redacted]

[redacted]

	[redacted]
Safety assessments	[redacted] 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. [redacted] 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 t he 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

[redacted]

	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.

[redacted]

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 ad ditional 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).

[redacted]

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

[redacted]

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

[redacted]

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.

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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).

[redacted]

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

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 3 rd 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 t o 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.

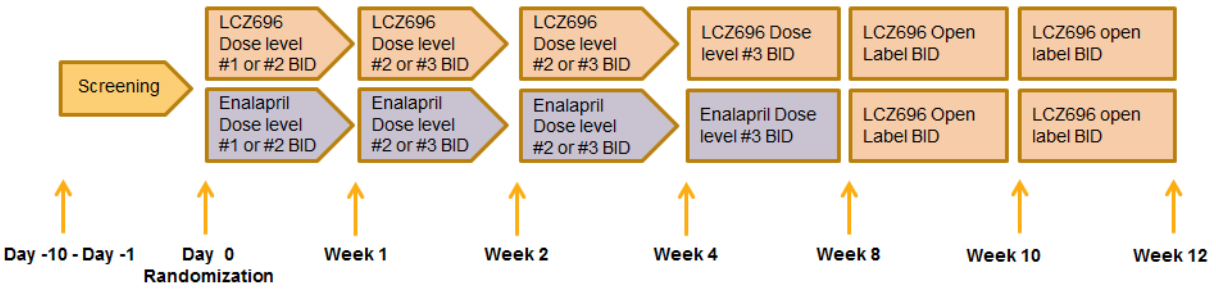
At the end of the 8-week treatment period ALL patients will need to have a 36 hour washout from study treatment prior to starting the open label extension to ensure that the blinding of the core study is maintained. To facilitate this washout, patients should take their final dose of study drug on the 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.

[redacted]

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.

[redacted]

[redacted]

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.

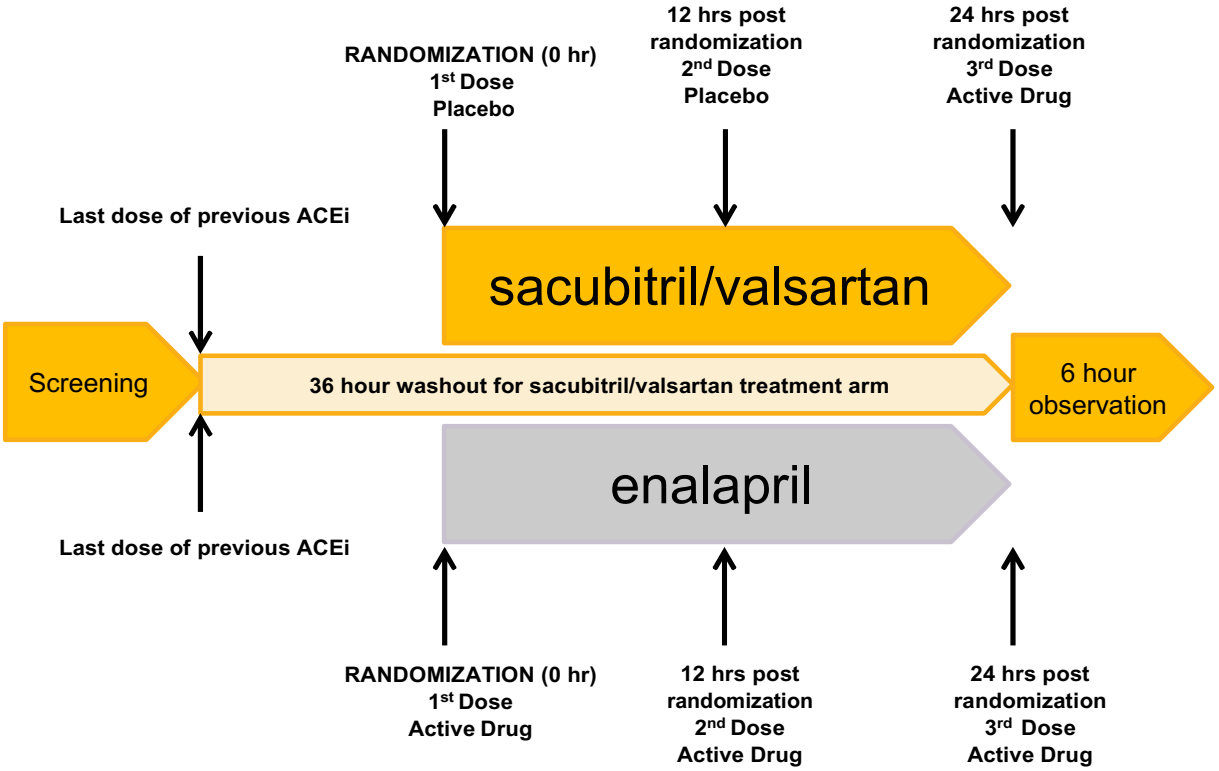
3.6 Risks and benefits

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 hospitalizat ion 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 investi gator, 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.

[redacted]

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

[redacted]

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 Regulation s 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 numbere d 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.

[redacted]

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 D rug 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 ensu re 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 validat ed 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 tim e 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 le vel 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

[redacted]

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

[redacted]

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 o f 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.

[redacted]

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

[redacted]

Visit	Previous dose level	Systolic Blood pressure mm Hg*	Start/remain/tit rate 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.

[redacted]

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 [redacted]

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.

[redacted]

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 t he 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.

[redacted]

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 medicatio n 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

[redacted]

- 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 assessm ents 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

[redacted]

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.

[redacted]

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
[redacted]									
Urinalysis		x							
Chemistry	x	x	x	x	x		x	x[6]	x

[redacted]

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
[redacted]									
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. [redacted]

[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.

[redacted]

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

[redacted]

[redacted]

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.

[redacted]

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)

[redacted]

[redacted]

[redacted]

- urinary cGMP

[redacted]

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

[redacted]

- 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.

[redacted]

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 fr om 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

[redacted]

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

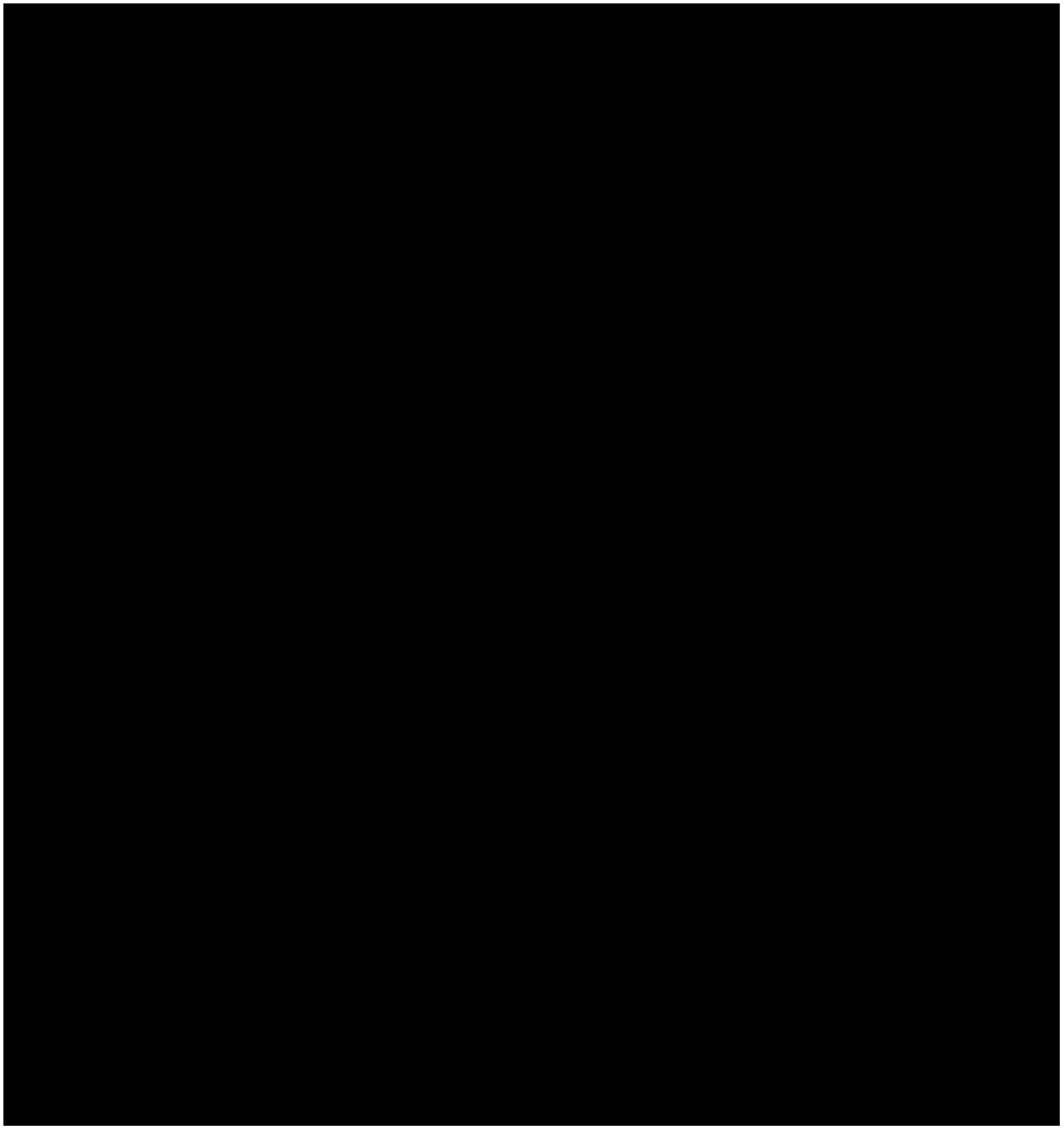
All female patients of childbearing potential will have a serum pregnancy t est (hCG) performed at Visit 1 (local lab) and Visits 5, 7 and 9 (central lab). In addition, these patients will have a urine pregnancy test conducted in the hospital laboratory at Visit 2. If any of these tests are positive at Visits 1 and 2, the patient should not be enrolled in t he 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.

[redacted]

[redacted]



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 sig ns 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, disch arge 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:

[redacted]

- 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 hypothetic ally 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.

[redacted]

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, wheth er 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

[redacted]

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 angioed ema 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 & id entify risks &

[redacted]

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.

[redacted]

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.

[redacted]

Submission of an angioedema report is not a substitution for the submission of a SA E 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

[redacted]

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.

[redacted]

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.

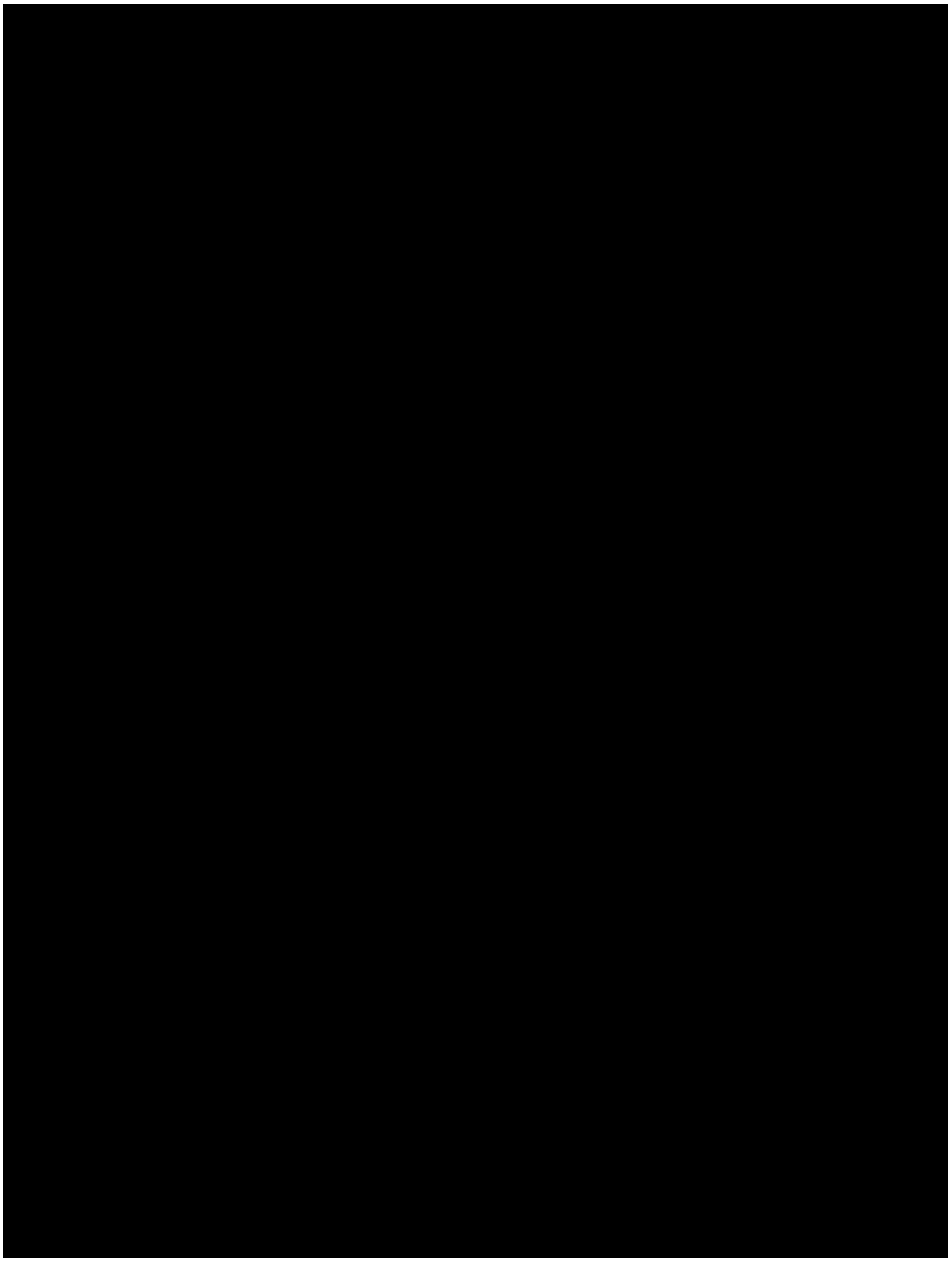
For biomarkers including BNP to NT-proBNP ratio, hs-Troponin, and urinary cGMP, the time-averaged proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model using the data from Weeks 4 and 8 with treatment as a fixed effect factor and the logarithmic baseline biomarker 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.

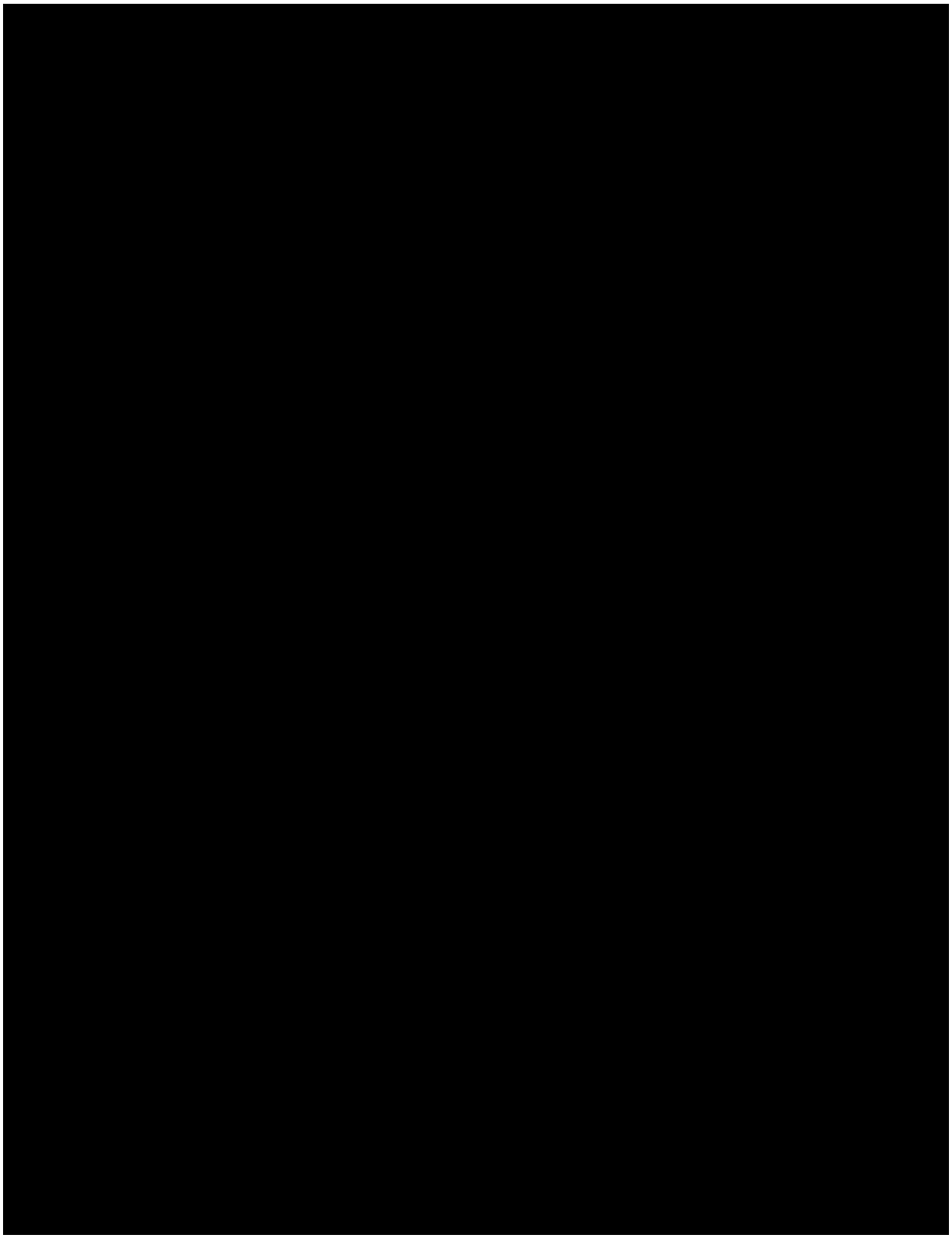
For BNP to NT-proBNP ratio and urinary cGMP at Weeks 1 and 2, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. For each of Weeks 1 and 2 the estimated 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.

[redacted]

[redacted]





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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.

[redacted]

9.5.5 Pharmacokinetics

Not Applicable.

9.5.6 Pharmacogenetics and pharmacogenomics

Not applicable.

[redacted]

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

[redacted]

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 Decla ration 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 t hat 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 sho uld 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

Clinically notable laboratory abnormalities for selected tests based on a percent c hange 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

[redacted]

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)

[redacted]

- 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.

[redacted]

16 Appendix 4: Guidelines for the management of renal dysfunction

General principles:

Glomerular filtration rate in HF patients depends on intrinsic ren al 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

[redacted] 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 value s. If study medication was stopped, every effort will be done to restart it again, according to clinical conditions.

[redacted]