NOVARTIS

US Clinical Development and Medical Affairs - General Medicine

LCZ696B

sacubitril/valsartan

Clinical Trial Protocol CLCZ696BUS08 / NCT02874794

A multicenter, randomized, double-blind, double-dummy, parallel group, active-controlled, forced-titration, 12-week comparison of combined angiotensin-neprilysin inhibition with sacubitril/valsartan versus enalapril on changes in central aortic stiffness in patients with heart failure and reduced ejection fraction (HFrEF): EVALUATE-HF

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Table of contents

[redacted]

[redacted]

[redacted]

[redacted]

List of tables

[redacted]

List of figures

[redacted]

List of abbreviations

ACE	angiotensin converting enzyme
ACEi	angiotensin converting enzyme inhibitor
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	analysis of covariance model
ARNi	angiotensin receptor neprilysin inhibitor
AST	Aspartate Aminotransferase
BID	twice a day
BNP	B-type natriuretic peptide
CFR	US Code of Federal Regulations
CDS	Core Data Sheet (for marketed drugs)
CRF/eCRF	(electronic) Case Report/Record Form
CPO	Country Pharma Organization
CRO	Contract Research Organization
CTC	Common Terminology Criteria
CTRD	Clinical Trial Results Database
CV	Cardiovascular
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
Echo	Echocardiogram
ED	Emergency Department
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
EOS	End of Study
EOT	End of Treatment
FAS	Full analysis set
GCP	Good Clinical Practice
HF	heart failure
HFrEF	Heart failure with reduced ejection fraction
hs-Troponin	high sensitivity troponin
HTN	Hypertension
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
[redacted]	[redacted]
LFT	Liver function test
MAP	Mean arterial pressure
MedDRA	Medical dictionary for regulatory activities

[redacted]

mm Hg	millimeter mercury
MoA	Mechanism of action
NEP	Neutral endopeptidase
NEPi	Neutral endopeptidase inhibitor
NPO	Nothing by mouth
NP	Natriuretic peptide
NT-proBNP	N-terminal pro-brain natriuretic peptide
o.d.	once a day
p.o.	oral(ly)
RAAS	Renin angiotensin aldosterone system
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TD	Study Treatment Discontinuation
UNL	Upper limit of normal
USPI	United States prescribing information/package insert
WHO	World Health Organization
WoC	Withdrawal of Consent
Zc	Characteristic impedance

[redacted]

Glossary of terms

Cohort	A specific group of patients/subjects fulfilling certain criteria
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study, which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
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."
Medication pack number	A unique identifier on the label of each investigational drug package
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/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
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), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Amendment 2

Rationale for amendment

The purpose for Amendment 2 is to add the echocardiographic parameters of Left Ventricular end systolic and diastolic volume indices, LVESVi and LVEDVi, to the secondary endpoints at 12 weeks [redacted] in the Protocol summary, Sections: 2.2, [redacted] 6.4, 9.5.1, 9.6, and a few other editorial changes.

[redacted]

Protocol summary

Protocol number	CLCZ696BUS08
Title	A multicenter, randomized, double-blind, double-dummy, parallel group, active-controlled, forced-titration, 12-week comparison of combined angiotensin-neprilysin inhibition with sacubitril/valsartan versus enalapril on changes in central aortic stiffness in patients with heart failure and reduced ejection fraction (HFrEF)
Brief title	A study of the effects of sacubitril/valsartan vs. enalapril, on aortic stiffness, in patients with mild to moderate heart failure and reduced pumping ability.
Sponsor and Clinical Phase	Novartis Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine the effect of sacubitril/valsartan compared to enalapril on reducing aortic stiffness in patients with mild to moderate heart failure with reduced ejection fraction
Primary Objective(s)	The primary objective is to determine whether treatment with sacubitril/valsartan provides a superior effect on aortic characteristic impedance compared to enalapril in patients with heart failure and reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤ 40%) after 12 weeks of treatment. The primary endpoint is the change in aortic characteristic impedance (Zc = dP/dQ in early systole) between baseline and Week 12.
Secondary Objectives	1. To evaluate the effect of sacubitril/valsartan vs. enalapril after 12 weeks of treatment on change from baseline in NT-proBNP. 2. To explore the effect of sacubitril/valsartan vs. enalapril after 12 weeks of treatment on the changes from baseline in echocardiographic measures including: • Global longitudinal strain • Left atrial volume index • Mitral annular E' velocity (Doppler Tissue Imaging) • Mitral E/E' • Left ventricular ejection fraction • Ventricular-vascular coupling (Ea/Ees) • LV end systolic and diastolic volume indices 3. To evaluate the effect of sacubitril/valsartan vs. enalapril after 4 weeks of treatment on the relation between the change in aortic characteristic impedance and change in biomarker levels, including BNP, U-cGMP/U-creatinine, during both trough and 4 hours post-dose.
Study design	This study will use a multicenter, randomized, double-blind, double-dummy, parallel group, active-controlled, forced - titration, 12-week design in patients with heart failure and reduced ejection fraction (HFrEF) ≤ 40%. The study duration is a maximum of 30 weeks with 8 scheduled outpatient visits. Patients will enter a screening epoch up to 6 weeks to assess eligibility requirements and to confirm patients are on stable treatment with guideline-directed therapy for HFrEF, other than ACEis and ARBs. Patients will then be randomized to either sacubitril/valsartan

	or to enalapril starting doses (Dose Level 1), according to the product label(s). Forced titration will occur every 2 weeks to reach the target dose of sacubitril valsartan or enalapril (Dose Level 3). Dose adjustments will only be allowed if indicated per protocol defined safety and tolerability criteria and investigator judgement, or if the investigator believes that adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern. After 12 weeks of double-blind treatment, patients will continue into the 12-week open-label extension epoch.
Population	The study population will consist of male and female patients, ≥ 50 years of age with a history of hypertension (HTN) and heart failure (NYHA Class I-III) with a reduced ejection fraction (HFrEF) ≤ 40%. The goal is to randomize a total of approximately 432 patients in a 1:1 ratio (216 per arm) to sacubitril/valsartan or enalapril in approximately 80 centers in the United States. It is estimated that approximately 575 patients will be screened because a screen failure rate of approximately 25% is anticipated based on previous experience.
Key Inclusion criteria	1. Men and women ≥ 50 years of age. 2. History of HTN and one of the following at BOTH screening and pre-randomization: a. SBP > 105 mm Hg on antihypertensive medication. b. SBP ≥ 140 mm Hg and NOT on antihypertensive medication. 3. NYHA class I-III heart failure and with a reduced ejection fraction ≤ 40%. 4. On stable doses of treatment with guideline-directed therapy, other than ACEis and ARBs prior to randomization. 5. On an optimal medical regimen of diuretics and background medications to effectively treat co-morbidities such as HTN, DM, and coronary artery disease
Key Exclusion criteria	1. History of hypersensitivity to any of the study drugs, including history of hypersensitivity to drugs of similar chemical classes, or allergy to ACEis, ARBs, or NEP inhibitors as well as known or suspected contraindications to the study drugs. 2. Previous history of intolerance to sacubitril/valsartan, ACEi or ARB standard of care doses despite appropriate and gradual up-titration. 3. History of angioedema, drug-related or otherwise. 4. Requirement of treatment with both ACE inhibitor and ARB. 5. Current or prior treatment with sacubitril/valsartan
Study treatment	All eligible patients will be randomized to receive either sacubitril/valsartan or enalapril. The following study treatment will be provided for the 12-week double blind double dummy treatment epoch: • sacubitril/valsartan tablets + matching placebo, or; • enalapril tablets + matching placebo. All patients will begin on Dose Level 1 and will be titrated every 2 weeks to target Dose Level 3. Safety and tolerability is monitored. Down-titration to temporary withdrawal of study treatment is permitted. Rescue option is available for worsening heart failure. Sacubitril/valsartan tablets will be provided for the 12-week open label extension. All dose levels are available. Target is Dose Level 3.
Efficacy assessments	**Primary (Week 12)**

	• Change in aortic characteristic impedance (Zc = dP/dQ) between baseline and Week 12. **Secondary** 1. Change from baseline in NT-proBNP at Week 12. 2. Changes from baseline in echocardiographic measures at week 12 including: • Global longitudinal strain • Left atrial volume index • Mitral annular E' velocity (Doppler Tissue Imaging) • Mitral E/E' • Left ventricular ejection fraction • Ventricular-vascular coupling (Ea/Ees) • LV end systolic and diastolic volume indices 3. The change in aortic characteristic impedance and change in biomarker levels, including BNP, U-cGMP/U-creatinine, during both trough and 4 hours post-dose at Week 4.
Key safety assessments	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. The safety and tolerability assessments are listed below: • AEs and SAEs • Sitting systolic, diastolic BP, and pulse pressure • Heart rate • Laboratory values

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Data analysis	**Primary** The primary efficacy variable will be analyzed by an analysis of covariance (ANCOVA) model with treatment and baseline as explanatory variables. The least squares means of the two treatment groups, least squares mean difference of the treatment groups, 95% confidence interval for the difference in the two treatment groups, and p-value based on the fitted linear model will be reported. If the p-value is < 0.05 and the least squares mean difference of the treatment groups favors sacubitril/valsartan, statistical significance in favor of sacubitril/valsartan is shown. The primary analysis of the primary efficacy variable will be based on the Full Analysis Set. **Secondary** For NT-proBNP, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment and the logarithmic baseline (Day 1) biomarker value as explanatory variables. The estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, the corresponding two-sided 95% confidence intervals and p-values will be provided. The change from baseline in the echocardiographic measures will be analyzed using an ANCOVA model with treatment and baseline as explanatory variables. Correlation coefficients between changes from baseline in aortic characteristic impedance and biomarker levels (markers such as BNP, U- cGMP/U-creatinine) during both trough and 4 hours post-dose at Week 4 will be calculated by treatment and overall. Analyses of the secondary efficacy 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. Other safety data will be summarized as appropriate.

[redacted]

	In CHOIR, treatment with Omapatrilat was associated with an approximately ~10% reduction in characteristic impedance at 12 weeks, with little or no change seen amongst enalapril- treated patients. Based on a similar study design and population, and accounting for a dropout rate of 20% from first visit to subsequent follow up and a 10% rate of non-evaluable data, assuming a standard deviation of 80 for the primary efficacy variable and 90% power, a sample size of 432 subjects (216 per arm) will be necessary to detect a clinically important change of 30 dyne x sec/cm5 between the two treatment groups.
Key words	aortic characteristic impedance, heart failure, increased pulsatile load, reduced ejection fraction, hypertension, angiotensin receptor-neprilysin Inhibition, ventricular-vascular coupling (Ea/Ees)

[redacted]

1 Introduction

1.1 Background

Central Aortic Stiffening May be an Important Mediator of Heart Failure Progression

Higher pulse pressure, an indirect measure of proximal aortic stiffness, is an independent predictor of cardiovascular events in the general population and in those with hypertension. Aortic stiffening enhances the amplitude of incident pressure waves leaving the heart, which increases load on the heart. Aortic stiffening also reduces the amount of protective wave reflection that normally occurs at the interface between a compliant aorta and stiff muscular arteries (Mitchell 2008). The resulting enhanced pulse wave transmission into the periphery due to stiffening of the proximal aorta and reduced wave reflection is associated with excessive energy transmission into the microcirculation. Excessive energy dissipation in the microcirculation is associated with microvascular damage and greater risk for end-organ damage, particularly in high flow organs like the brain (Mitchell 2011) and kidneys (Woodard 2015). Increased pulsatile load has been associated with several deleterious consequences including accelerated vascular and ventricular hypertrophy and fibrosis, endothelial dysfunction, atherogenesis, cognitive impairment and kidney dysfunction, which may explain the association between pulse pressure and various clinical events including incident myocardial infarction and heart failure. In addition, because of direct mechanical coupling between LV and aorta, stiffening of the proximal aortic increases systolic longitudinal load on the left ventricle (LV) and reduces early diastolic filling (Bell 2015). These features suggest that proximal aortic stiffening may play an important role in mediating the development and progression of heart failure.

While pulse pressure is an important cardiovascular disease risk factor and a rough surrogate for central arterial stiffening, it is an imprecise measure of load because it is flow-dependent and therefore highly variable. Thus, pulse pressure can be shown to predict risk in large observational studies, but in smaller, mechanistic studies, pulse pressure cannot be used as a robust measure of load. Some have argued that central pressure is a more precise measure of load on the LV and various devices have been developed that purport to measure central pressure. However, central pressure is confounded by the same dependency on flow as peripheral pressure. Furthermore, central pressure is not independently related to events in models that account for peripheral pressure. Thus central pressure alone, without concurrent assessment of flow, provides limited additional information as compared to peripheral pressure. Aortic characteristic impedance, Zc, is the ratio of the change in pressure (dP) produced by a given change in flow (dQ) in early systole, i.e., Zc = dP/dQ. Zc is related directly to aortic wall stiffness and inversely to lumen area and accurately summarizes the initial load that the heart encounters in early systole. The importance of forward wave amplitude, Zc and pulsatile load was highlighted in a recent paper from the Framingham Heart Study (FHS), which showed that higher forward wave amplitude and Zc were associated with increased risk for a first major cardiovascular disease event during 7 years of follow-up (Cooper 2015). These relations persisted in models that adjusted for standard cardiovascular disease risk factors, including systolic blood pressure and carotid-femoral pulse wave velocity.

As the forward wave travels down the aorta, it encounters regions of impedance mismatch that give rise to wave reflection. Although often portrayed as unfavorable, wave reflection plays a

[redacted]

critical role in normal function of the arterial system because it limits the amount of pulsatile energy that is transmitted distally into the microvasculature. Wave reflection has been maligned because of the perceived increase in late systolic load on the heart that results from a premature reflected wave that produces pressure augmentation in late systole, as often assessed by measuring augmentation index (AI) on a central pressure waveform. However, recent studies have shown that much of the apparent increase in wave reflection with advancing age, as assessed by AI, is not attributable to an increase in wave reflection or early arrival of the reflected wave, but is rather a result of alterations in the ejection pattern of the LV (Fok 2014, Torjesen 2014). Importantly, measures of wave reflection were not independently related to events in the FHS analysis of components of pulsatile load, where central aortic pressure and flow were measured in order to assess load comprehensively (Cooper 2015). In patients with heart failure and reduced LV function, Zc is elevated and measures of apparent wave reflection, such as AI, are actually reduced (Mitchell 2001). Thus, Zc is a major contributor to abnormal hemodynamic load in patients with heart failure.

The LV must interact directly with Zc in order to deliver pulsatile flow. When LV function is preserved, an increase in hemodynamic demand leads to an increase in forward wave amplitude and pulse pressure. However, an impaired LV has a limited ability to increase pressure and hence higher Zc will limit flow in patients with reduced LV function. The load imposed by Zc is present throughout systole, including early systole when flow is high and LV geometry in unfavorable (large chamber volume and thin wall). As a result, Zc is the principal determinant of peak wall stress in the LV (Chirinos 2012). In contrast, wave reflection has a limited effect on wall stress because late systolic geometry (smaller chamber, thicker wall) protects the heart from external pressure load. It is likely, therefore, that changes in Zc, more than changes in wave reflection or central pressure, may adversely impact ventricular-vascular coupling and promote heart failure progression in patients with reduced ejection fraction.

Composite Angiotensin Receptor-Neprilysin Inhibition may reduce Central Aortic Stiffness in Heart Failure and Improve Ventricular-Vascular Coupling

Traditional afterload reduction with peripheral vasodilator drugs reduces peripheral resistance, MAP and wave reflection, but does not reduce Zc. If cardiac output increases because of the reduction in peripheral resistance, pulsatile overhead will paradoxically increase because the additional flow must be transferred through Zc, which remains high. In addition, even more pulsatile energy will be transmitted to the periphery because of the reduction in wave reflection. Thus, traditional vasodilator drugs reduce MAP, which is often already either normal or low in patients with heart failure, yet increase pulsatile stress on the LV and arterial system.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARB) may reduce aortic stiffness by opposing vasoconstrictive, hypertrophic, and profibrotic effects of angiotensin II on the vessel wall. Neprilysin or neutral endopeptidase (NEP) is an enzyme that inactivates several vasodilatory peptides including the natriuretic peptides that are thought to play a role in the body's defense against hypertension. Data from experimental models suggests that natriuretic peptides may have favorable effects on the aorta. Combined

ACE/NEP inhibition with omapatrilat 80 mg was associated with greater reductions in pulse pressure and Zc than enalapril 40 mg in the Conduit Hemodynamics of Omapatrilat International Research Study (CHOIR), but was associated with an unacceptable risk of

[redacted]

angioedema. The novel Angiotensin Receptor-Neprilysin inhibitor sacubitril/valsartan is associated with similar hemodynamic and antihypertensive benefits to omapatrilat, but does not carry the same risks of angioedema. The PARAMOUNT study of sacubitril/valsartan versus valsartan in subjects with heart failure and preserved ejection fraction suggested significant reductions in natriuretic peptide levels and left atrial remodeling that may be mediated in part through impacts on pulsatile load. More recently the PARADIGM-HF study identified a 20% reduction in the primary composite outcome of cardiovascular death or heart failure hospitalization as well as a 20% reduction in cardiovascular death associated with sacubitril/valsartan treatment relative to enalapril in patients with heart failure and reduced ejection fraction (McMurray 2014). The mechanism of sacubitril/valsartan benefit in heart failure patients remains unclear. We propose a study to examine the effects of sacubitril/valsartan relative to enalapril on aortic stiffness and ventricular-vascular coupling in heart failure patients.

We further propose to explore the effects of sacubitril/valsartan on carotid pressure-flow relations in order to gather preliminary support for the hypothesis that a reduction in Zc will reduce pressure and flow pulsatility transmitted into the cerebrovasculature. Data from the AGES-Reykjavik Study has demonstrated that higher aortic Zc is associated with reduced wave reflection at the interface with the common carotid arteries, resulting in greater transmission of pressure and flow pulsatility into the cerebral microcirculation, which is associated with cerebral small vessel disease and lower performance on cognitive testing (Mitchell 2011). Carotid flow pulsatility was strongly related to various magnetic resonance imaging measures of cerebral small vessel disease as well as performance in all 3 major cognitive domains (memory, processing speed and executive function). Some have expressed concern that NEP inhibition may reduce clearance of amyloid from the brain. However, recent evidence suggests that amyloid deposition may be increased or clearance decreased by exposure of the cerebrovasculature to excessive pulsatility (Hughes 2015). By measuring pressure and flow in the common carotids, we can examine the effective reflection coefficient, which should be increased, as well as the carotid flow pulsatility, which should be reduced, by a treatment-related reduction in Zc. If sacubitril/valsartan reduces Zc, and thereby reduces transmission of pressure and flow pulsatility into the cerebrovasculature, there may be a net beneficial effect of treatment on amyloid deposition and cognitive performance—a hypothesis that could be tested in an adequately powered follow-up study.

Please refer to the Clinical Data Sheet for further information on sacubitril/valsartan.

1.2 Purpose

The purpose of this study is to determine the effect of sacubitril/valsartan compared to enalapril on reducing aortic stiffness in patients with mild to moderate HFrEF. Results from this study may be used to support the mechanism of benefit for sacubitril/valsartan and to subsequently explore if heart failure progression may be slowed down or mitigated by treatment.

[redacted]

2 Study objectives and endpoints

2.1 Primary objective(s)

The primary objective is to determine whether treatment with sacubitril/valsartan provides a superior effect on aortic characteristic impedance compared to enalapril in patients with heart failure and reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤ 40%) after 12 weeks of treatment.

The primary endpoint is the change in aortic characteristic impedance (Zc = dP/dQ in early systole) between baseline and Week 12.

2.2 Secondary objective(s)

1. To evaluate the effect of sacubitril/valsartan vs. enalapril after 12 weeks of treatment on change from baseline in NT-proBNP.
2. To evaluate the effect of sacubitril/valsartan vs. enalapril after 12 weeks of treatment on the changes from baseline in echocardiographic measures including:
   - Global longitudinal strain
   - Left atrial volume index
   - Mitral annular E' velocity (Doppler Tissue Imaging)
   - Mitral E/E'
   - Left ventricular ejection fraction
   - Ventricular-vascular coupling (Ea/Ees)
   - LV end systolic and diastolic volume indices
3. To evaluate the effect of sacubitril/valsartan vs. enalapril after 4 weeks of treatment on the relation between the change in aortic characteristic impedance and change in biomarker levels, including BNP, U-cGMP/U-creatinine, during both trough and 4 hours post-dose.

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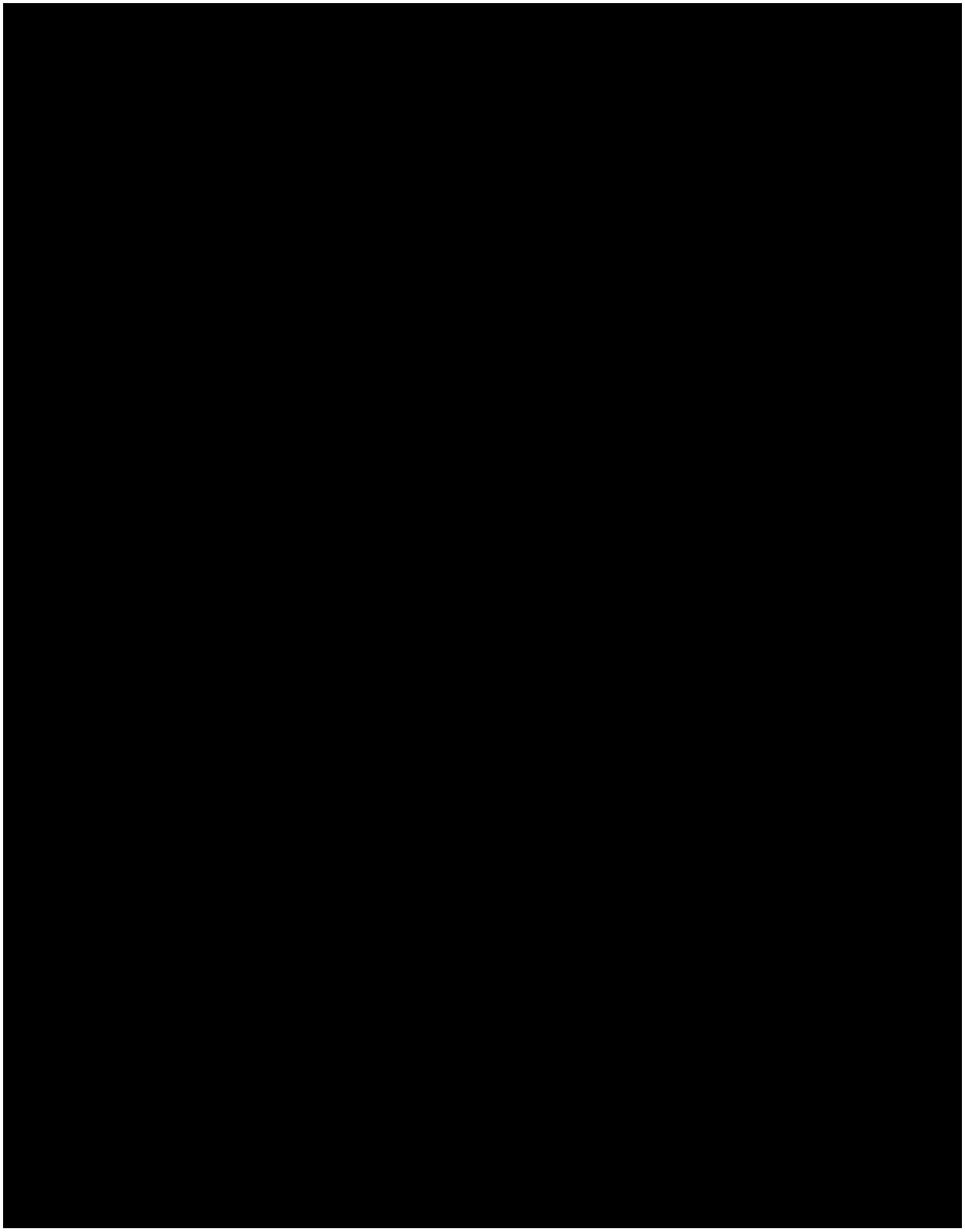

3 Investigational plan

3.1 Study design

This study will use a multicenter, randomized, double-blind, double-dummy, parallel group, active-controlled, forced titration, 12-week design in patients with heart failure and reduced left ventricular ejection fraction (LVEF) ≤ 40%. The study duration is a maximum of 30 weeks, including the screening epoch, with 8 scheduled outpatient visits.

Screening epoch

Patients will enter a screening epoch up to 6 weeks, beginning with Baseline (Visit 1) at - 42 to -1 day(s) prior to randomization to assess eligibility requirements and to confirm patients are on stable treatment with guideline-directed therapy for HFrEF, other than ACEis and ARBs.

- Screening/Baseline echocardiography (echo), ECG and safety labs will be obtained.
- Non-invasive arterial hemodynamics assessments will be obtained specifically within the window of study day -7 to -2 prior to randomization on Day 1 (Visit 2) to ensure quality control and to allow for a repeat study on day -1, if necessary.
- Biomarkers [redacted] will be obtained on Day 1 (Visit 2), pre-randomization.
- If the patient is currently taking an ACEi, a 36-hour washout is required prior to randomization (Visit 2).
- If the patient is currently taking an ARB, they must discontinue the ARB before initiation of study treatment however, washout is not required.

Note: Baseline for this study includes assessments performed during Screening and through Day 1 (Visit 2) pre-randomization.

Patients can be randomized as soon as screening criteria are met.

Double-blind, randomized treatment epoch

- On Day 1 (Visit 2), patients will be randomized to either sacubitril/valsartan 24/26 mg BID or enalapril 2.5 mg BID (Dose Level 1), according to the product label(s) and will return for a safety assessment at Week 1 (Visit 3).
- Study treatment will be force-titrated every 2 weeks to reach the target dose of sacubitril/valsartan 97/103 mg BID and enalapril 10 mg BID (Dose Level 3).

Deviation from the titration schedule or dose adjustments will only be allowed if indicated per protocol defined safety and tolerability criteria (See Section 5.5.5, Table 5-7) and investigator judgement, if the investigator believes that adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern.

At any time during the 12 week randomized, double-blind treatment epoch, investigators have the option to withdraw patients from study treatment if they develop signs and symptoms of worsening heart failure for which the investigator would like to administer appropriate therapy. (See Section 5.5.5 and Section 5.5.6)

[redacted]

Open-label extension epoch

The purpose of this open-label period is to observe the additional vascular effects of sacubitril/valsartan that occur beyond 12 weeks of treatment.

After 12 weeks of successful double-blind, active treatment, patients will continue into the 12 week open-label extension epoch. Patients will have received the final dose of double-blind treatment medication in the clinic at Week 12 (Visit 6).

- 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 and to reduce the risk of angioedema.
- To facilitate this washout, patients will be instructed NOT to start their open-label treatment until the evening of the following day.
- All patients will start open-label treatment on sacubitril/valsartan 49/51 mg BID (Dose level 2), unless they completed the double-blind treatment epoch on Dose Level 1. Instead, these patients will enter the open-label epoch on sacubitril/valsartan 24/26 mg BID dose (Dose level 1).
- Study treatment will be force-titrated every 2 weeks to reach the target dose of sacubitril/valsartan 97/103 mg BID (Dose Level 3).

Deviation from the titration schedule or dose adjustments will only be allowed if indicated per protocol defined safety and tolerability criteria (See Section 5.5.5, Table 5-7), and investigator judgement, if the investigator believes that adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern.

Follow-up safety visits will occur throughout the study at Weeks 1, 2, 4, 12, 14 and 24 (Visits 3, 4, 5, 6, 7, and 8).

Primary efficacy assessments will be conducted at Screening/Baseline, Day 1 (Visit 2) pre-randomization, and Week 12 (Visit 6).

[redacted]

Patients will be contacted by phone at approximately 30 days following the last administration of study treatment at Week 24 (Visit 8), or early withdrawal, in order to determine if any SAE(s) occurred during this time period. These SAEs will be recorded in the source document only and must be reported to Novartis. Attempts to contact the patient should also be recorded in the source document.

Every SAE occurring after the patient has provided informed consent and until 30 days following the last administration of study treatment must be reported directly to the Novartis Drug Safety and Epidemiology Department within 24 hours of learning of its occurrence.

No interim analysis is planned. If it is deemed necessary for internal decision making, due to patient safety, an interim analysis will be conducted by an independent statistical group.

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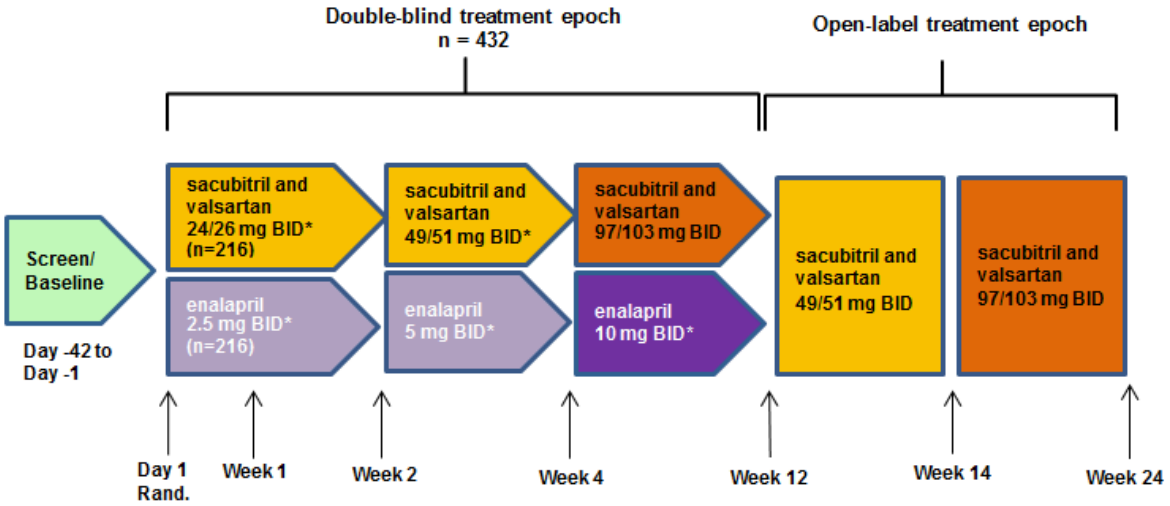
Figure 3-1 Study design



*Patients who are currently taking ACEi must undergo a 36 hour washout from these prior to Day 1 randomization.
^Patients who completed the double-blind treatment epoch on Dose Level 1 will enter the open-label epoch on Dose Level 1.
Note: Down-titration is available at any time during the study based on the investigator's clinical judgement. Rechallenge is required.

3.2 Rationale for study design

The Evaluate-HF study is designed to provide a definitive assessment of the hemodynamic mechanism of action of sacubitril/valsartan in HFrEF.

In the CHOIR study, ACE/NEP inhibition with omapatrilat was associated with greater reductions in pulse pressure and Zc than enalapril after 12 weeks of treatment. Based on this, the double-blind treatment epoch of this study was designed to be 12 weeks. Additionally, given the superior results obtained with sacubitril/valsartan in the PARADIGM-HF trial, the duration of the double-blind period also limits the patients' exposure to the current standard of care, enalapril.

Prior to the double-blind treatment epoch, we wanted to ensure that patients had the opportunity to be optimized on treatment with guideline-directed therapy for HFrEF, other than ACEi and ARBs. As many patients are able to be up-titrated on medications in a 4 to 6 week period, we have allowed up to 6 weeks for the screening epoch.

We wanted the ability to assess the vascular effects of patients who switch from enalapril to sacubitril/valsartan as well as to understand if there are additional vascular effects in patients who have extended treatment with sacubitril/valsartan. We believe that 12 weeks of open-label treatment was enough time to evaluate both of these measures.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

Sacubitril/valsartan 97/103 mg BID was selected as the target dose because it was the dose used in the PARADIGM-HF study where it was shown to have superior results versus enalapril in reducing CV death and heart failure hospitalizations. This is also the USPI approved target dose.

In addition, this dose delivers similar exposures of valsartan as Diovan 160 mg BID, the maximal approved Diovan dose for heart failure and the dose recommended in international guidelines for the treatment of heart failure and biomarker analysis (increase in ANP and cGMP) indicates that this sacubitril dose delivers approximately 90% of its maximal neutral endopeptidase (NEP) inhibition. Dosing with 97/103 mg twice daily ensures sustained NEP inhibition over 24 hours, which is thought to be critical for patients with heart failure.

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. Additionally, ACEi may reduce aortic stiffness by opposing vasoconstrictive, hypertrophic, and profibrotic effects of angiotensin II on the vessel wall.

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. The same dose will be used in this study so that we can appropriately assess the hemodynamic benefits of the drug and whether it supports the clinical outcomes that were seen in both trials.

3.5 Purpose and timing of interim analyses/design adaptations

Not Applicable

3.6 Risks and benefits

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, and the provision of rescue options.

3.6.1 Risks

Experience in the PARADIGM-HF trial, both in the run-in period as well as the double-blind randomization period, indicated that the major risks associated with the treatment of sacubitril/valsartan are renal dysfunction, [426 (10.14%) in 4203 patients in the double-blind treatment period], hyperkalemia, [488 (11.61%) in 4203 patients in the double-blind treatment period], and hypotension [740 (17.61%) in 4203 patients in the double-blind treatment period].

In PARADIGM-HF, patients treated with enalapril experienced these events at a similar rate with the exception of hypotension; renal dysfunction, [487 (11.52%) in 4229 patients in the double-blind treatment period]; hyperkalemia, [592 (14%) in 4229 patients in the double-blind treatment period]; and hypotension, [506 (11.97%) in 4229 patients in the double-blind treatment period]. Results from the TITRATION study indicated that patients whom are ACE or ARB naïve are at an increased risk of experiencing these adverse events.

In this study, the risk of experiencing renal dysfunction, hyperkalemia, and hypotension are mitigated by appropriate up-titration of the drug every two weeks. The risks are further mitigated by appropriate inclusion and exclusion criteria. Patients entering into the study must have an SBP of at least 140 mmHg if not treated for hypertension or a SBP of >105 mmHg if

they are currently on treatment. Additionally, patients are excluded if they have an eGFR < 30 ml/min/1.73 m^2 or a potassium > 5.2 mEq/L at screening.

Drug to drug interactions are known to occur with concomitant use of ACE/ARB/NEP and renin inhibitors. See Section 5.5.8 for prohibited medications. Patient will be provided with study treatment instructions and their medication histories will be reviewed at Screening and all subsequent visits.

Sacubitril/valsartan, [19 (0.5%) in 4203 patients in the double-blind treatment period of PARADIGM-HF] and enalapril 10 (0.2%) in 4229 patients in the double-blind treatment period of PARADIGM-HF] may also cause angioedema. The risk of developing angioedema is increased if patients take both an ACEi and sacubitril/valsartan. To decrease this risk, patients will be required to undergo a 36-hour washout prior to randomization as well as the open-label treatment epoch to minimize the interaction between an ACEi and sacubitril/valsartan in potentiating the development ofangioedema.

In the PARADIGM-HF study, sacubitril/valsartan reduced the risk of CV death and HF hospitalization versus enalapril. In the US, sacubitril/valsartan is approved and indicated to reduce these risks in patients with chronic heart failure (NYHA class II-IV) and reduced ejection fraction. Due to this, the double-blind treatment epoch is limited to 12 weeks to minimize the chance of exposure to standard treatment with enalapril. Thereafter, all patients will have the opportunity to receive 12 weeks of open-label sacubitril/valsartan. It should be noted that the population of patients studied in PARADIGM-HF included NYHA class II-IV patients that were all on either ACEi or ARBs prior to study enrollment. The population of patients included in this study is different than that of PARADIGM-HF.

There is a chance a patient may develop signs and symptoms of worsening heart failure for which the investigator would like to administer appropriate therapy. Appropriate adjustments, intensifications, or additions to concomitant medications should be considered. If needed, the investigator can choose to withdraw the patient from the study to initiate treatment with sacubitril/valsartan, ACEi, or ARBs if the investigator believes this to be appropriate treatment. Rescue options are provided in Section 5.5.6.

In addition to investigational treatment, all patients will be allowed to continue receiving the rest of their background cardiovascular (CV) medications throughout the study. Patients will be randomized to study treatment only after the investigator has confirmed the patient is on stable treatment with guideline-directed therapy for HFrEF, other than ACEis and ARBs, which will ensure that patients are receiving appropriate treatment for their heart failure.

The study procedures and assessments for this study are either non-invasive or minimally invasive (venipuncture for blood draws) and are considered low risk.

3.6.2 Benefits

All patients will receive active treatment for heart failure that reduces the risk of mortality and hospitalizations. After completion of the double-blind treatment epoch, all patients will have the opportunity to receive 12 weeks of open-label sacubitril/valsartan, a drug which has been proven to reduce the risks of CV death and HF hospitalization versus enalapril.

[redacted]

This study is the first clinical trial to treat NYHA Class I asymptomatic heart failure patients with sacubitril/valsartan. Data collected may determine if heart failure progression can be prevented. Additionally, patients with NYHA Class I heart failure wouldn't otherwise have access to sacubitril/valsartan as the drug is not approved for use in these patients.

Study assessments and frequent visits will provide close monitoring of patients' conditions and may provide information that may benefit heart failure patients in the future.

4 Population

The study population will consist of out-patient male and female patients, ≥ 50 years of age with HFrEF ≤ 40% who have a history of hypertension. The goal is to randomize a total of approximately 432 patients to sacubitril/valsartan or enalapril in a 1:1 ratio at approximately 80 centers in the United States. The estimated screen failure rate is 25%. Approximately 575 patients will be screened.

At the time of randomization, patients will have been on stable treatment with guideline-directed therapy for HFrEF, other than ACEis and ARBs, and on an optimal medical regimen to effectively treat co-morbidities such as HTN, DM and coronary artery disease. Patients will have met all other inclusion and none of the exclusion criteria.

4.1 Inclusion criteria

Patients/subjects eligible for inclusion in this study must fulfill all of the following criteria at screening and randomization:

1. Written informed consent must be obtained before any assessment is performed.
2. Men and women ≥ 50 years of age.
3. History of HTN and one of the following at BOTH screening and pre-randomization:
   a. SBP > 105 mm Hg on antihypertensive medication.
   b. SBP ≥ 140 mm Hg and NOT on antihypertensive medication.
4. Patients diagnosed with heart failure NYHA class I-III and reduced ejection fraction ≤ 40% as determined by any local measurement made within the past 12 months using echocardiography, MUGA, CT scanning, MRI, ventricular angiography or single-photon emission computed tomography (*SPECT*), provided no subsequent measurement above 40%. Patients who have had an intervening medical event (e.g. myocardial infarction) or procedure (e.g. revascularization, cardiac resynchronization), must have a reassessment of EF ≥ 3 months following the event to ensure that eligibility criteria are still met.
5. On stable doses of treatment with guideline-directed therapy, other than ACEis and ARBs, prior to randomization.
   a. If the patient is currently taking an ACEi, a 36-hour washout is required prior to randomization (Visit 2).
   b. If the patient is currently taking an ARB, they must discontinue the ARB before initiation of study treatment however, washout is not required.
6. On an optimal medical regimen to effectively treat co-morbidities such as HTN, DM, and coronary artery disease. Investigators should make every effort to control a patient's BP in accordance with local treatment guidelines and investigator judgment.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria, at screening and prior to randomization, are not eligible for inclusion in this study for purposes of safety measures. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients/subjects.

1. History of hypersensitivity to any of the study drugs, including history of hypersensitivity to drugs of similar chemical classes, or allergy to ACEis, ARBs, or NEP inhibitors as well as known or suspected contraindications to the study drugs.
2. Previous history of intolerance to sacubitril/valsartan, ACEi or ARB standard of care doses despite appropriate and gradual up-titration.
3. History of angioedema, drug-related or otherwise.
4. Requirement of treatment with both ACE inhibitor and ARB.
5. Current or prior treatment with sacubitril/valsartan.

Patients/subjects taking medications prohibited by the protocol (see Section 5.5.8, Table 5-9).

6. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
7. Currently enrolled in any other clinical trial involving any investigational agent or investigational device.
8. DBP > 100 mm Hg at screening or at randomization.
9. eGFR < 30 ml/min/1.73 m2 (calculated by the Modification of Diet in Renal Disease formula) at screening.
10. Potassium > 5.2 mEq/L at screening.
11. Documented or untreated ventricular arrhythmia with syncopal episodes within the 3 months prior to Screening/Baseline (Visit 1).
12. Persistent or permanent atrial fibrillation at Screening/Baseline (Visit 1).
13. Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid or other major CV surgery, percutaneous coronary intervention (PCI) or carotid angioplasty within the 3 months prior to first Screening/Baseline (Visit 1).
14. Implantation of a cardiac resynchronization therapy pacemaker (CRT-P) or a cardiac resynchronization therapy defibrillator (CRT-D) or upgrading of an existing conventional pacemaker or an implantable cardioverter defibrillator (ICD) to CRT device within 3 months prior to first visit or intent to implant such a device.
15. Heart transplant or ventricular assistance device (VAD) or intent to transplant (on transplant list) or implant a VAD.
16. Coronary or carotid artery disease likely to require surgical or percutaneous intervention within the 6 months after Visit 1.
17. Hemodynamically significant aortic stenosis/regurgitation or mitral valve disease other than mitral valve regurgitation related to LV dilation.
18. Presence of other hemodynamically significant obstructive lesions of left ventricular outflow tract, including aortic and sub-aortic stenosis.
19. Isolated right HF due to severe pulmonary disease.

[redacted]

20. Diagnosis of peripartum or chemotherapy induced cardiomyopathy within the 12 months prior to Screening/Baseline (Visit 1).
21. Treatment with Vaughn Williams Type Ic anti-arrhythmic agents (e.g., Flecainide, propafenone, moricizine).
22. Symptomatic bradycardia or second or third degree heart block without a pacemaker.
23. History of familial long QT syndrome or known family history of Torsades de Pointes
24. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past year with a life expectancy of less than 1 year.
25. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or extraction of study drug, including but not limited to any of the following:
    a. History of active inflammatory bowel disease during the 12 months prior to Screening/Baseline (Visit 1)
    b. History of peptic ulcer disease without successful eradication of H. pylori.
    c. Gastrointestinal/rectal bleeding during the 3 months prior to Screening/Baseline (Visit 1).
    d. Current treatment with cholestyramine of colestipol resins.
26. Known hepatic impairment (as evidenced by total bilirubin > 3 mg/dL, or increased ammonia levels, if performed), or history of cirrhosis with evidence of portal hypertension such as varices.
27. Bilateral renal artery stenosis.
28. Inability to secure technically adequate baseline tonometry study.
29. 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.
30. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 7 days after stopping of study medication. Highly effective contraception methods include:
    a. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    c. Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    d. Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

[redacted]

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

31. 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 have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation 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 is she considered not of child-bearing potential.
32. Sexually active males must use a condom during intercourse while taking drug and for 7 days after stopping study medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

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

Table 5-1 Investigational and comparator treatment during the double-blind epoch

Treatment Arm	Number of Patients	Minimum dose	Maximum dose	Frequency	Formulation	Administration Route
sacubitril/valsartan*	216	24/26 mg	97/103 mg	BID	tablet	oral
sacubitril/valsartan matching placebo						oral
enalapril	216	2.5 mg	10 mg	BID	tablet	oral
enalapril matching placebo						oral

*Investigational product labeling for sacubitril/valsartan dose levels is based on the total contribution of both components of sacubitril/valsartan and reads, 50 mg, 100 mg and 200 mg. This is equivalent to the sacubitril/valsartan dose levels 24/26 mg, 49/51 mg and 97/103 mg, respectively.

Table 5-2 Treatment dose level during the double-blind epoch

Dose Level	Sacubitril/valsartan*	Enalapril
1	24/26 mg or matching placebo BID	2.5 mg or matching placebo BID
2	49/51 mg or matching placebo BID	5 mg or matching placebo BID
3	97/103 mg or matching placebo BID	10 mg or matching placebo BID

*Investigational product labeling for sacubitril/valsartan dose levels is based on the total contribution of both components of sacubitril/valsartan and reads, 50 mg, 100 mg and 200 mg. This is equivalent to the sacubitril/valsartan dose levels 24/26 mg, 49/51 mg and 97/103 mg, respectively.

[redacted]

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

Sacubitril/valsartan and enalapril will be packaged separately to limit the number of pack types, which will allow more flexibility in the drug supply process to cover all the different treatment possibilities (treatment arm and medication dose level), see Table 5-2 and Table 5-4. Packaging type is described below:

- sacubitril/valsartan and its matching placebo will be provided in HDPE bottles.
- enalapril 2.5 mg and its matching placebo will be provided in HDPE bottles.
- enalapril 5 mg and 10 mg and its matching placebo will be provided in blister packs.

Each participating site will be provided with an investigational drug supply containing Dose Levels 1, 2, and 3 and their matching placebos. Bottles and blister packs will be numbered and assigned via an interactive voice response system (IRT). Treatment for the day of randomization and all visits forward will be assigned via IRT. All patients will begin the study on Dose Level 1. Then:

- Sacubitril/valsartan or enalapril dose levels will be force-titrated to achieve the targeted desired dose of 97/103 mg BID or 10 mg BID (Dose Level 3).
- Patients not tolerating the target dose of sacubitril/valsartan 97/103 mg BID or enalapril 10 mg BID (Dose Level 3) can be titrated down to Dose Level 2 (including active medication and matching placebos), if, in the investigator's judgement, the adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern. See Section 5.5.5.

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.

Table 5-3 Investigational treatment during the open label epoch

Treatment	Number of patients	Minimum dose*	Maximum dose	Frequency	Formulation	Route
Open-label sacubitril/valsartan**	~346	49/51 mg	97/103 mg	BID	tablet	oral

*sacubitril/valsartan 24/26 mg BID (Dose Level 1) will be given to patients who completed the double-blind treatment epoch on Dose Level 1 and is available if down-titration is required.

**Investigational product labeling for sacubitril/valsartan dose levels is based on the total contribution of both components of sacubitril/valsartan and reads, 50 mg, 100 mg and 200 mg. This is equivalent to the sacubitril/valsartan dose levels 24/26 mg, 49/51 mg and 97/103 mg, respectively.

Table 5-4 Treatment Dose Levels during the open-label epoch

Dose Level*	Sacubitril/valsartan**
2	49/51 mg BID
3	97/103 mg BID

*Sacubitril/valsartan 24/26 mg BID (Dose Level 1) will be given to patients who completed the double-blind treatment epoch on Dose Level 1. It is also available if down-titration is required.

**Investigational product labeling for sacubitril/valsartan dose levels is based on the total contribution of both components of sacubitril/valsartan and reads, 50 mg, 100 mg and 200 mg. This

Dose Level*	Sacubitril/valsartan**

is equivalent to the sacubitril/valsartan dose levels 24/26 mg, 49/51 mg and 97/103 mg, respectively.

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 12-weeks.

- Patients entering the open label-treatment epoch will be given sacubitril/valsartan 49/51 mg BID (Dose Level 2) unless they completed the double-blind treatment epoch on Dose Level 1. Instead, these patients will enter the open-label epoch on sacubitril/valsartan 24/26 mg BID dose (Dose Level 1).
- Study treatment will be force-titrated every 2 weeks to reach the target dose of sacubitril/valsartan 97/103 mg BID (Dose Level 3).

Schedule and dose adjustments will only be allowed if, in the investigator's judgement, the adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern. See Section 5.5.5.

5.1.2 Additional treatment

The protocol requires patients to be on stable treatment with guideline-directed therapy for HFrEF, other than ACEis and ARBs, and on an optimal medical regimen to effectively treat co-morbidities such as HTN, DM and coronary artery disease.

5.2 Treatment arms

Patients/subjects will be assigned at Visit 2 to one of the following two treatment arms in a 1:1 ratio:

- sacubitril/valsartan; or,
- enalapril

5.3 Treatment assignment and randomization

At Visit 2, all eligible patients/subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient.

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

[redacted]

The randomization scheme for patients/subjects will be reviewed and approved by a member of the Novartis Biostatistics Group.

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, data analysts and the Clinical Trial Team (CTT) 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 IRT provider generating the randomization code. (2) The identity of the treatments will be concealed by the use of investigational treatments that are identical in packaging, labeling, and schedule of administration, appearance, taste and odor.

A double-dummy design is used because the identity of the study drug cannot be disguised, as the drug products are visibly different. To maintain the blinding, patients will be required to take their assigned active treatment tablet along with placebo matching the opposite treatment twice daily.

Unblinding will only occur in the case of patient emergencies see Section 5.6 and at the conclusion of the study.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

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 3-digit sequential number assigned by the investigator (e.g., 001, 002, etc.). Hence, a 7-digit study patient identification number, e.g., 0501-001. 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 IRT and provide the assigned patient study identification number along with the requested identifying information for the patient to register them into the IRT. 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 study drug

Each study site will be supplied by Novartis with investigational and comparator treatment in packaging of identical appearance.

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 IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will

[redacted]

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 study treatment must be stored according to the instructions specified on the labels. Medication labels will include storage conditions but no information about the patient except for the medication number. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

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

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

Medication labels will be in the local language and comply with the legal requirements of the country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

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

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of other study treatment

Each study site will be supplied, by Novartis, with open-label sacubitril/valsartan for the 12-week open-label treatment epoch. The IRT 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 IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient,

[redacted]

investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

Open-label sacubitril/valsartan treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all open-label sacubitril/valsartan treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Medication labels will include storage conditions but no information about the patient except for the medication number. The investigator must maintain an accurate record of the shipment and dispensing of open-label sacubitril/valsartan treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site visits or remotely and at the completion of the study. Patients will be asked to return all unused open-label treatment and packaging at the end of the study or at the time of discontinuation of treatment.

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

5.5.3.3 Handling of non-study treatment

The following non-study treatment has to be monitored specifically and recorded in the CRF:

- ACEi/ARB treatment prior to randomization and/or after early discontinuation of study treatment.
- All protocol required background therapy.
- Rescue treatment.

5.5.4 Instructions for prescribing and taking study treatment

Novartis will supply the investigators with all medications sufficient for the course of the study. Patients will be provided with medication packs containing study drug corresponding to their assigned treatment arm and dose level, sufficient to last until the next scheduled visit. Patients will be instructed to hold their morning study medication dose on the day of study visits. Study drug will be administered at the site after pre-dose vital signs, blood samples and assessments are performed. Vital signs will include blood pressure, pulse and respiration measurements. BP will be measured using a standard sphygmomanometer with an appropriate sized cuff and the non-dominant arm in the seated position after 5 minutes of rest, with back supported and both feet placed flat on the floor. 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.

In order to adequately blind the study, patients will be required to take their assigned active treatment tablet along with placebo matching the opposite treatment twice daily. Patients will be instructed to take a total of two tablets by mouth twice a day for the duration of the double-blind treatment epoch, as follows:

- one tablet from the sacubitril/valsartan/sacubitril/valsartan matching placebo pack, and;
- one tablet from the enalapril/enalapril matching placebo pack

Table 5-5 summarizes the study drug that will be taken during the double-blind treatment epoch by visit and Table 5-6 summarizes the study drug that will be taken during the open-label treatment epoch.

Forced-titration will proceed according to the following table:

Table 5-5 Study drug dispense during double-blind treatment epoch

Visit	Dose Level	Sacubitril/valsartan**	Enalapril	Route	Timing
Rando/Visit 2	1[a,b]	24/26 mg or matching placebo BID	2.5 mg or matching placebo BID	Oral	AM & PM
Week 2/Visit 4	2[ce]	49/51 mg or matching placebo BID	5 mg or matching placebo BID	Oral	AM & PM
Week 4/Visit 5	3[d]	97/103 mg or matching placebo BID	10 mg or matching placebo BID	Oral	AM & PM

**Investigational product labeling for sacubitril/valsartan dose levels is based on the total contribution of both components of sacubitril/valsartan and reads, 50 mg, 100 mg and 200 mg. This is equivalent to the sacubitril/valsartan dose levels 24/26 mg, 49/51 mg and 97/103 mg, respectively.

a. Initial starting dose (Level 1) Eligible patients will be randomized via IRT to either sacubitril/valsartan or enalapril, Dose Level 1.

b. Available after Rando/Visit 2 to end of double-blind treatment epoch only if Dose Levels 2 and 3 are not tolerated despite modification of other non-disease-modifying HF medications and re-challenge.

c. Only if Dose Level 3 is not tolerated despite modification of other non-disease-modifying HF medications and re-challenge.

d. This target Dose Level must be maintained for as long a duration as possible. If down-titration is necessary due to side effects, the patient should be re-challenged as soon as medically possible per the investigator's judgment.

e. The evening dose of study medication prior to Week 4/Visit 5 must be taken no less than 12 hours before the hemodynamic assessment time scheduled for Week 4/Visit 5. See Section 6.4.1.

- At Randomization on Day 1 (Visit 2), eligible patients will be randomized via IRT to either sacubitril/valsartan or enalapril. All patients will start at Dose Level 1 (2.5 mg enalapril or 24/26 mg sacubitril/valsartan, BID).
- At Week 1 (Visit 3), patients will return to the study center for a safety assessment only. Study medication will not be up-titrated.
- At Week 2 (Visit 4), patients will be force-titrated to Dose Level 2 (5 mg enalapril or 49/51 mg sacubitril/valsartan.
- At Week 4 (Visit 5), patients will be force-titrated to the target dose, Dose Level 3 (10 mg enalapril or 97/100 mg sacubitril/valsartan and remain on this target dose for 8 weeks through the evening dose prior to Week 12 (Visit 6).
- At Week 12 (Visit 6), patients will have the final dose of double-blind treatment medication administered in the clinic after pre-dose assessments have been completed. Drug accountability will be performed and all double-bind treatment medication will be returned to the site.
- All patients that complete the 12 week (Visit 6) double-blind treatment epoch will proceed into the 12-week open-label epoch on sacubitril/valsartan.
- Open-label sacubitril/valsartan will be dispensed at Week 12 (Visit 6) with patient instructions **NOT** to start their open label-treatment until the evening after completing a 36-hour wash out. All patients will have the wash out in order to maintain the blinding of the core study.

[redacted]

All dose levels will be available throughout the study. 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.

All study treatment assigned by the IRT will be recorded/databased in the IRT.

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

Study medication should be taken twice daily with a glass of water with or without food. Prior to scheduled study visit days, instruct the patient to have nothing by mouth after midnight and to take study medication after vital signs and study assessments are taken by the study coordinator at the investigator site.

If the patient misses taking any study drug dose, he/she should take it as soon as possible and within 4 hours of the scheduled dose time. If the patient is unable to take the missed dose within 4 hours of the scheduled dose time, he/she should skip the missed dose and return to his/her regular study drug administration schedule.

The investigator must 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 must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

Table 5-6 Study drug dispense during open-label treatment epoch

Dose Level	Visit	Sacubitril/valsartan**	Route	Timing
2[a]	Week 12/Visit 6	49/51 mg	Oral	AM & PM
3	Week 14/Visit 7	97/103 mg	Oral	AM & PM

**Investigational product labeling for sacubitril/valsartan dose levels is based on the total contribution of both components of sacubitril/valsartan and reads, 50 mg, 100 mg and 200 mg. This is equivalent to the sacubitril/valsartan dose levels 24/26 mg, 49/51 mg and 97/103 mg, respectively.

- All patients entering the open-label treatment epoch will start open-label treatment on sacubitril/valsartan 49/51 mg BID (Dose Level 2) unless they completed the double-blind treatment epoch on Dose Level 1. Instead, these patients will enter the open-label epoch on sacubitril/valsartan 24/26 mg BID dose (Dose Level 1).
- Study treatment will be force-titrated every 2 weeks to reach the target dose of sacubitril/valsartan 97/103 mg BID (Dose Level 3).

Schedule and dose adjustments will only be allowed if, in the investigator's judgement, the adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern. See Section 5.5.5.

5.5.5 Permitted dose adjustments and interruptions of study treatment based on safety and tolerability

Study drug dose level adjustments should be mainly based on overall safety and tolerability and investigator judgement, with a special focus on:

[redacted]

- hyperkalemia;
- clinically significant decreases in eGFR/increase in serum creatinine; and,
- symptomatic hypotension

Table 5-7 Safety and tolerability guidance for dose adjustments

Parameter	Criteria
Potassium level	K > 5.3 mEq/L
Kidney function	• eGFR reduction ≥ 35% compared to baseline; OR, serum creatinine of ≥0.5mg/dl with at least a 25% decrease in eGFR
Blood pressure	• No symptomatic hypotension or SBP < 90 mmHg
Adverse events (AEs) or conditions	• No postural symptoms or any conditions that preclude continuation according to the investigator's judgment

Every attempt should be made to maintain patients on target study drug Dose Level 3 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 will manage the patient's treatment according to the below guidelines:

1. Adjust Concomitant Medications

- Dose adjustments/elimination of concomitant medications may remedy 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, THEN;

2. Adjust Study Treatment Dose Level

- Down-titrate study treatment to the previous dose level. The patient may continue receiving the lower dose level for a recommended period of 1 to a maximum of 4 weeks.
- A re-challenge to titrate back up to the target dose level should be attempted at 2 weeks, or when patient is deemed stable. THEN:

3. Further Adjust Study Treatment Dose Level

- If tolerability issues are not alleviated despite down-titration by one dose level, the investigator may down-titrate further to the next lower study treatment dose level. The patient may continue receiving the lower dose level for a recommended period of one to a maximum of 4 weeks, up to a temporary withdrawal of study treatment. See Step 5.
- Again, once stable, the patient should be re-challenged with up-titration to the next higher dose level in an attempt to gradually bring the patient back to the target study treatment 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.

4. Stopping Study Treatment

If needed, the study treatment may be stopped completely, however, the patient should continue to attend all study visits and be followed until the completion of the study. See Section 5.5.6.

[redacted]

5. Study drug restart after temporary treatment interruption

- Once the investigator considers the patient's condition appropriate for receiving the study drug, the investigator should re-start the patient on study treatment at the most appropriate and allowable dose level per his/her medical judgment.
- If tolerated, the patient should be titrated up to the next dose level every 1 to 4 weeks, as per the investigator's judgment.
- In some instances, Dose Level 1 or 2 could be maintained if the investigator 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 2, whichever is the higher and tolerated dose level by the patient, but reasons for not getting to Dose Level 3 need to be captured in the eCRF.
- Should the patient not tolerate the re-start study drug dose level, he/she may be down-titrated again (if appropriate) or discontinued from study treatment.

Patients re-started on the study drug will retain their original randomization and study identification numbers.

The IRT must be contacted to register any changes in the patient's study treatment dose level, including in cases of temporary and permanent withdrawal or re-start of the study drug, and to obtain the medication numbers of the study drug supplies required for the new study treatment dose level. All dose changes and interruptions must also be recorded on the Dosage Administration Record eCRF.

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

In case of pregnancy discovered during the study, the patient should be instructed to stop taking the study drug immediately. (See Section 6.5.6 and Section 7.6)

5.5.6 Rescue medication for worsening heart failure

At any time during the 12 week randomized, double-blind treatment epoch, investigators have the option to withdraw patients from study treatment if they develop signs and symptoms of worsening heart failure for which the investigator would like to administer appropriate therapy.

- Appropriate adjustments, intensifications, or additions to concomitant medications should be considered before deciding to withdraw the patient from study treatment.
- **Other than their study treatment, patients CANNOT receive ACEis, ARBs, or sacubitril/valsartan during the study. These medications can ONLY be administered if the investigator believes that the patient needs to be withdrawn from study treatment so that they may be treated with these therapies due to signs and symptoms of worsening heart failure.**
- **A 36 hour wash-out period is required if the investigator chooses to withdraw the patient from double-blind treatment and switch to sacubitril/valsartan or ACEi due to symptoms of worsening heart failure.**

[redacted]

- Use of rescue medication must be recorded on the Concomitant medications eCRF.

Investigators will use clinical judgement to determine if patient condition requires closer monitoring. Unscheduled visits are permitted as needed.

Guidance on handling hyperkalemia, hypotension, and renal dysfunction are provided to investigators in the appendices.

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All new medications, administered after the patient signs the study informed consent, must be recorded on the concomitant medications eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

ACEis and ARBs:

Patients taking an ACEi at screening must undergo a 36-hour washout prior to randomization (Visit 2). Patients taking an ARB must discontinue the ARB prior to initiating treatment with study medication however, a washout is not necessary.

The concomitant use of ACEis or ARBs is strictly prohibited while the patient is receiving study medication. Adjustment, intensification, or addition of concomitant medications should be considered first before the decision is made to treat the patient with an ACEi or ARB. **If the investigator believes that the patient needs to be withdrawn from the study medication so that they may be treated with either an ACEi or ARB, the study medication must first be stopped and a 36-hour washout period will be required for patients being switched to an ACEi.**

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.

Table 5-8 Concomitant medications to be used with caution

Classification	Caution	Action
1. Potassium sparing diuretics; 2. Potassium supplements; 3. Aldosterone antagonists; and, 4. Any other medication known to raise potassium levels.	Increased possibility of hyperkalemia.	Monitor potassium levels regularly, especially after dose initiation and up-titration.
Phosphodiesterase-5 (PDE-5) inhibitors	Increased possibility of occurrence of hypotension.	Monitor for symptomatic hypotension.

[redacted]

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-9 is NOT allowed after the screening epoch.

Table 5-9 Prohibited medication

Medication	Prohibition period	Action taken
ACEis/ARBs/NEPs	ACEi 36 hour prior to study treatment, ACEi, ARB, NEP during study treatment, ACEi and NEP within 36 hours post double-blind randomization.	If the investigator believes that addition of an ACEi ARB or sacubitril/valsartan is necessary, then study drug must be discontinued, while monitoring renal function. ACEi or sacubitril/valsartan must not be started until 36 hours after discontinuing study drug to reduce the risk of angioedema.
Renin inhibitors (Aliskerin)	During study treatment.	Do not randomize, or, use alternate treatment.
Bile acid sequestering agents (such as cholestyramine or colestipol)	During study treatment.	Switch to alternate agent to avoid interference with study drug absorption. If use of alternate agent is not allowed, do not randomize or discontinue study drug treatment.
Nesiritide and intravenous nitrates	During study treatment.	Do not randomize. If hospitalized, either interrupt or discontinue study treatment. Nesiritide and intravenous nitrates have not been studied. Oral, topical and sublingual nitrates are permissible.

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

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

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number

[redacted]

- study drug name (if available)
- patient number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol, Week 24 (Visit 8).

- Week 12 (Visit 6), completes the end of double-blind treatment epoch
- Week 24 (Visit 8) completes the end of open-label treatment epoch and the end of study

At the end of study visit, investigational product will be returned and reconciled. Concomitant medications and adverse events will be reconciled. Continuing care should be provided by investigator and/or referring physician based on patient availability for follow-up. The following recommendations for initiating other treatment outside the study include:

- Continue on commercially available sacubitril/valsartan
- Return to treatment regimen prior to study

Patients will be contacted by phone at approximately 30 days following the last administration of study treatment (Week 24), or early withdrawal, in order to determine if any SAE(s) occurred during this time period. These SAEs will be recorded in the source document only and must be reported to Novartis. Attempts to contact the patient should also be recorded in the source document.

Every SAE occurring after the patient has provided informed consent and until 30 days following the last administration of study treatment must be reported directly to the Novartis Drug Safety and Epidemiology Department within 24 hours of learning of its occurrence.

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

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

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Withdrawal of consent
- Pregnancy (see Section 6.5.8 and Section 7.6)
- Use of prohibited treatment as per recommendations in Table 5-9
- Any protocol deviation that constitutes a risk to the patient

[redacted]

- Any situation in which study participation might result in a safety risk to the patient
- Unresolved worsening HF

Study medication may be discontinued at the investigator's discretion if any of the following serious suspected drug-related AEs occur:

- Symptomatic hypotension
- 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.
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study.

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.

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on End of Study Treatment eCRF. After study treatment discontinuation, the patient should attend the regularly scheduled visits and have all study assessments performed.

Investigator judgement will determine if the patient should return to the clinic for an earlier unscheduled visit. If discontinuation of study treatment occurred due to a significant adverse event, an unscheduled visit should occur to assess the patient and obtain laboratories as needed. See Table 6-1 for Unscheduled Visit assessments. At a minimum, in abbreviated visits, the following data should to be collected at clinic visits or via telephone visits:

- new / concomitant treatments
- adverse events/Serious Adverse Events

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9.

5.6.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore

And

[redacted]

- Does not want any further visits or assessments

And

- Does not want any further study related contacts

And

- Does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information in the eCRF.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in Table 6-1, End of Treatment Visit 6 assessments or End of Study Visit 8 assessments, based on the treatment epoch from which the patient discontinues.

5.6.4 Loss 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.

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

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.

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrollment). Should this be necessary, the patient must 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

Table 6-1 lists all of the assessments and indicates with an "X" when the visits are performed. Assessments that will only be reported in the source documentation are marked with an 'S'.

Patients must be seen for all visits on the designated day, or as close to it as possible, including those on dose interruptions or discontinued treatment. A visit window of +/- 3 days is allowed. Every effort should be made to respect the time frame for the primary efficacy endpoint at Week 12 (Visit 6) visit.

Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for Visit 6 (End of Treatment) or Visit 8 (End of Study) will be performed, depending on the epoch from which the patient prematurely discontinues from the study. See Section 5.6.3. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the eCRF.

Patients will be contacted by phone at approximately 30 days following the last administration of study treatment, Week 24 (Visit 8), or early study discontinuation, in order to determine if any SAE(s) occurred during this time period. These SAE(s) will be recorded in the source document only and must be reported to Novartis. Attempts to contact the patient should be recorded within the source document.

Every SAE occurring after the patient has provided informed consent and until 30 days following the last administration of study treatment must be reported directly to the Novartis Drug Safety and Epidemiology Department within 24 hours of learning of its occurrence.

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

[redacted]

Table 6-1 Assessment schedule

Epoch		**Screening/ Baseline****	**Double-Blind Treatment**					**Open Label Treatment**		**Unsched. Visit◊**
Visit number	**D/S***	**1**	**2**	**3**	**4**	**5**	**6/EOT***	**7**	**8/EOS****	
Week		**-6 to -1**		**1†**	**2**	**4**	**12**	14	24	
Day		**-42 to – 1**	**1**	**7**	**14**	**28**	**84**	98	168	
Obtain informed consent[1]	S	X								
Inclusion/Exclusion	S	X	X							
Demography/ medical history	D	X								
HF and CV disease history	D	X								
ECG[2]	S	X								
Full Physical Exam	S	X					X		X	X
Cardiac Exam[3]	S		X	X	X	X		X		X
Height	D	X								
Weight	D	X	X	X	X	X	X	X	X	X
Vital signs[4]	D	X	X	X	X	X	X	X	X	X
NYHA Classification (HF signs and symptoms)	D	X	X			X	X	X	X	X
HF and CV medications	D	X*	X	X	X	X	X	X	X	X

[redacted]

Epoch		Screening/ Baseline**	Double-Blind Treatment					Open Label Treatment		Unsched. Visit◊
Visit number	**D/S***	**1**	**2**	**3**	**4**	**5**	**6/EOT***	**7**	**8/EOS****	
Week		**-6 to -1**		**1†**	**2**	**4**	**12**	14	24	
Day		**-42 to – 1**	**1**	**7**	**14**	**28**	**84**	98	168	
Concomitant medication	D	X	X	X	X	X	X	X	X	X
Adverse events/SAEs	D	X	X	X	X	X	X	X	X	X
Angioedema assessment	D	X	X	X	X	X	X	X	X	X
[redacted]										
Serum pregnancy[5]	D	X					X		X	X
Dipstick urinalysis[6]	D	X	X		X	X	X			X
Hematology	D	X					X		X	X
Full chemistry profile[7]	D	X		X	X		X		X	X
Abbreviated chemistry panel[7]	D		X			X		X		X
Cardiac Biomarkers: NT-proBNP, BNP, [redacted] (pre-dose)[8]	D		X		X	X	X		X	
Additional Cardiac plasma/serum biomarkers for bio-banking (pre-dose)[8,9]	D		X		X	X	X		X	
Spot urine biomarkers (pre-dose)[8,10]	D		X		X	X	X		X	
BNP and spot urine biomarkers @ 4 hours post-dose[8,10,19]	D					X				
Echocardiography[11]	D	X[12]				X	X		X	
Hemodynamic assessment trough study with limited echo[13]	D	X[14]				X	X		X	

[redacted]

Epoch		Screening/ Baseline**	Double-Blind Treatment					Open Label Treatment		Unsched. Visit◊
Visit number	**D/S***	**1**	**2**	**3**	**4**	**5**	**6/EOT***	**7**	**8/EOS****	
Week		**-6 to -1**		**1†**	**2**	**4**	**12**	14	24	
Day		**-42 to – 1**	**1**	**7**	**14**	**28**	**84**	98	168	
Hemodynamic assessment 4 hours post-dose with limited echo[15,19]	D					X	X		X	
Contact IRT	D		X		X	X	X	X	X	X
Randomize	D		X							
Dispense treatment	D		X		X	X	X	X		X
Dosage Administration Record[16]	D		X	X	X	X	X	X	X	
Drug accountability	S		X	X	X	X	X	X	X	X
Titration	D				X	X		X		X
Screening Disposition	D	X								
Study phase completion – randomized double-blind treatment	D						X			
36 hour study drug wash-out[17]	D						X		X	
Study completion - open-label treatment and end of study[18]	D								X[18]	

* D: to be documented in the clinical database; S: in the source data.

** Baseline is defined as assessments occurring any time prior to randomization. In this study, some of the baseline assessments are performed during the Screening period and some are performed on Day 1 prior to Randomization.

***** End of Treatment Visit: Visit 6 (Week 12) assessments must be performed for subjects who discontinue from the study prematurely during the double-blind treatment period, as well as all subjects who complete the double-blind treatment period.

****** End of Study Visit: Visit 8 (Week 24) assessments must be performed for subjects who discontinue the study prematurely during the open label phase, as well as all study completers.

◊ Unscheduled Visit Assessments marked with (X) are optional procedures that may be performed at the investigator's discretion.

†. Safety visit post-dose initiation. No titration. Perform Drug Accountability, administer dose in clinic and return study medication to patient.

[redacted]

Epoch		Screening/ Baseline**	Double-Blind Treatment					Open Label Treatment		Unsched. Visit◊
Visit number	**D/S***	**1**	**2**	**3**	**4**	**5**	**6/EOT***	**7**	**8/EOS****	
Week		**-6 to -1**		**1†**	**2**	**4**	**12**	14	24	
Day		**-42 to – 1**	**1**	**7**	**14**	**28**	**84**	98	168	

1. ICF includes 24 week study and hemodynamic assessments using arterial tonometry (trough and 4-hrs post-dose)
2. ECG to be performed locally.
3. Cardiac exam to be completed on Day 1 pre-randomization (Visit 2) and at Weeks 1 2, 4, and 14 (Visits 3, 4, 5 and 7). Document in Source.
4. Vital signs include blood pressure, pulse and respiratory rate 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, with back supported and both feet placed flat on the floor. 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.
5. A serum pregnancy test is not required for a woman who is sterile or who is post-menopausal. All serum pregnancy tests will be sent to the central laboratory.
6. Urine dipstick. If positive, send full urinalysis to central laboratory.
7. Clinical Chemistry: Repeat Full Chemistry Profile if Randomization (Visit 2) occurs greater than 2 weeks from Screening (Visit 1). Abbreviated Chemistry Panel (electrolytes and creatinine) is measured for safety at visits not requiring full chemistry profile. Hemoglobin A1c is measured at Screening and at Weeks 12 and 24 (Visits 6 and 8).
8. Must be strictly processed and stored according lab manual instructions and timelines.
9. Includes cardiac, renal, and drug mechanism of action biomarkers.
10. Includes urinary biomarkers such as U-cGMP/U-creatinine.
11. Echocardiography is completed simultaneously with hemodynamic assessments.
12. Screening echocardiography can be performed any time during the Screening/Baseline epoch, but should be performed before the hemodynamic assessment to ensure inclusion criterion is met first.
13. Fasting required after midnight prior to hemodynamics trough studies. Instruct and remind patient to take study medication the evening before the actual visit and no less than 12-hrs prior to the scheduled assessment time.
14. Screening hemodynamic assessment can be done within the window of day -7 to day -2 to allow sufficient time for a repeat test, if quality is not good.
15. Patient to remain at clinic for 4-hr post-dose hemodynamic assessment.
16. Instruct patient to take morning dose of study treatment in the clinic on the day of visit, after all pre-dose assessments have been completed.

[redacted]

Epoch		**Screening/ Baseline****	**Double-Blind Treatment**					**Open Label Treatment**		**Unsched. Visit◊**
Visit number	**D/S***	**1**	**2**	**3**	**4**	**5**	**6/EOT***	**7**	**8/EOS****	
Week		**-6 to -1**		**1†**	**2**	**4**	**12**	14	24	
Day		**-42 to – 1**	**1**	**7**	**14**	**28**	**84**	98	168	

17. 36-hr washout required post-dose at Week 12 to avoid drug-drug interaction between ACEis and NEPi. Also, post-dose at Week 24 after open-label epoch is completed, if ACEi is to be initiated post-study.

18. Patients will be contacted by phone approximately 30 days following the last administration of study treatment (Week 24*),* or early study discontinuation, in order to determine if any SAE(s) occurred during this time period. Document in source. Every SAE occurring after the patient has provided informed consent and until 30 days following the last administration of study treatment must be reported to the Novartis Drug Safety and Epidemiology Department within 24 hours of learning of its occurrence.

19. Window for 4 hrs. post-dose assessments is ± 0.5 hrs.

[redacted]

6.1 Information to be collected on screening failures

All patients/subjects who have signed informed consent but not entered into the next epoch will have screening disposition, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race, and ethnicity. Relevant medical history/current medical condition data includes data until the subject provides written informed consent for the study. Where possible, diagnoses and not symptoms will be recorded. HF medications and other CV medications will also be recorded in Concomitant Medications eCRF. 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 patient. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Record.

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 end dates recorded in the Dosage Administration Record eCRF.

6.4 Efficacy

The efficacy variables are:

Primary:

- Change in aortic characteristic impedance (Zc = dP/dQ) between baseline and Week 12

Secondary variables are:

1. Change from baseline NT-proBNP after 12 weeks of treatment
2. Changes from baseline in echocardiographic measures at week 12 including:
    - Global longitudinal strain
    - Left atrial volume index
    - Mitral annular E' velocity (Doppler Tissue Imaging)
    - Mitral E/E'
    - Left ventricular ejection fraction
    - Ventricular-vascular coupling (Ea/Ees)

[redacted]

- LV end systolic and diastolic volume indices

3. The change in aortic characteristic impedance and change in biomarker levels such as, BNP , U-cGMP/U-creatinine during both trough and 4 hours post-dose at Week 4

[redacted]

[redacted]

6.4.1 Hemodynamic Assessments using arterial tonometry

Hemodynamic assessment of arterial parameters during trough and 4 hours post-dose will be obtained using the methods, custom instrumentation and software reported by (Mitchell, et al. 2008, 2010, and 2011). Auscultatory brachial blood pressure will be assessed by using the computer-controlled NIHem device, which is capable of digitizing the cuff pressure, electrocardiogram (1000 Hz) and a cuff microphone channel (12 kHz) throughout the inflation and deflation sequence in order to allow for over-read of all blood pressure acquisitions by the Hemodynamic Core Lab. A detailed manual with instructions on performing hemodynamic assessments using arterial tonometry will be provided to all sites.

Hemodynamic trough assessments will be performed at approximately 08:00 hrs., prior to administration of study drug. A time window between 07:00 and 11:00 hrs. Is permitted to accommodate patient schedules while still allowing for the 4-hr post-dose assessment to be completed the same day. The Screening/Baseline assessment will be obtained between day -7 to day -2 window to allow for a repeat test for quality assurance, if necessary, prior to Randomization on Day 1 (Visit 2).

During treatment with study medication, hemodynamic trough and 4-hr.,, post-dose assessments will be performed at Weeks 4, 12 and 24 (Visits, 5, 6 and 8). The patient will be provided with the following instructions:

- Take study medication the evening before the actual visit and no less than 12 hrs. prior to the scheduled assessment time.
- No cigarettes or caffeinated beverages within 6 hrs. before (or between) studies.
- Remain NPO after 12MN until after the 0:8:00 hemodynamic trough.

  Note: Patients may eat a light snack or breakfast after the 08:00 hemodynamic trough assessment. This would include a low glycemic energy bar or something that most people, including diabetic, would be able to tolerate. The meal time will be recorded in the source document.
- Patients will then remain in or near the clinic until the hemodynamic assessment at 4-hrs post-dose (± 0.5 hrs.) is performed at 12:00.
- Dress in comfortable clothing, preferably shorts, to allow access to anatomical pulse recording sites. A patient gown may also be provided.
- Arrive at the clinic one-half hour before the hemodynamic assessment, which will take approximately 1 hour.
- Rest in a comfortably supported supine posture for 15–20 minutes.

A qualified echocardiographer and a trained site professional will obtain the following hemodynamic measurements using arterial tonometry with electrocardiogram, using a custom transducer from the Cardiovascular Engineering, Inc. core lab.

1. brachial, radial, femoral and carotid pulsatile pressures
2. body surface measurements from suprasternal notch to pulse recording sites, using a fiberglass tape measure for carotid, brachial and radial sites and a caliper for the femoral site.

[redacted]

All blood pressure acquisitions and tonometry waveforms will be transmitted to the Hemodynamic Core Lab at Cardiovascular Engineering, Inc. for overreads. Tonometry waveforms will be signal-averaged using the electrocardiogram R-wave as a fiducial point. Carotid-femoral pulse wave velocity (CFPWV) will be calculated from ECG-gated carotid and femoral arterial waveforms and body surface measurements. Doppler audio signals recorded in the left ventricular outflow tract will be analyzed and signal averaged using custom software. The resulting high resolution flow waveform will be extracted and paired with the calibrated pressure waveform in order to perform central pressure-flow analysis. Characteristic impedance will be computed as the ratio of change in pressure divided by change in flow as assessed from the foot of the respective waveforms to the time when flow reaches 95% of peak flow. Joint analysis of pressure and flow waveforms will be used to separate forward, reflected waves, and measure their amplitudes. Augmentation index will be assessed from the carotid pressure waveform.

Carotid artery flows will be analyzed from digitized Doppler audio data using a semi-automated signal-averaging approach as detailed previously by (Mitchell, et al. 2004, 2011). Flow spectra are signal-averaged (1000 Hz resolution) using the electrocardiogram as a fiducial point. Flow velocities are multiplied by carotid artery cross-sectional area to obtain volume flows. Carotid volume flows will be paired with the carotid pressure waveform to perform carotid artery pressure-flow analysis and to model transmission of pulsatility into the carotid circulation (Mitchell 2011). Carotid pulsatility index will be computed for each carotid by dividing the flow pulse amplitude (peak flow minus flow at the onset of the systolic upstroke) by mean flow. Values for the right and left carotid will be averaged.

6.4.2 Echocardiography

Echocardiograms will be performed at the sites by qualified echocardiographic personnel (technicians or physicians) in accordance with standard echocardiographic clinical practice. The baseline echocardiogram will be performed before administration of study medication. The echocardiographic examination required will be a modification of the standard echocardiographic examination, and will include the majority of standard echocardiographic views normally obtained for clinical practice, in addition to specific echocardiographic assessments designed to assess LV mass, LA volume, and diastolic function (Table 6-2).

1. LV mass index, left atrial volume index
2. Diastolic function (lateral E' velocity, E/E')
3. Systolic function (ejection fraction, S' velocity)

Table 6-2 Echocardiographic Assessment Obtained at Sites

Echocardiographic view	Images obtained
• Parasternal long axis view	• 2-D image for septal and posterior wall thickness • M-Mode Images • Color flow Doppler

[redacted]

• Parasternal Short axis view, papillary muscle level	• 2-D images for Septal and posterior wall thickness
• Apical 4-chamber View	• 2-D images for volume and ejection fraction measures, LA size and RV function • Color flow Doppler for assessment of mitral regurgitation • Doppler Tissue Imaging of Mitral annular velocities • Mitral Inflow Pulsed Doppler
• Apical 5-chamber View	• Apical 5 chamber view with LVOT PW Doppler and AV CW Doppler

Echocardiograms will be recorded to digital media in DICOM format (CD, or Magneto-Optical Disc) and sent to the core laboratory for analysis. All echocardiographic measurements will be made at the core laboratory [redacted], [redacted]

Ventricular-vascular coupling will be assessed noninvasively as the ratio (Ea/Ees) using the single-beat estimation formula proposed by Chen, et al. This method requires the measurement of systolic and diastolic BPs, ejection fraction (EF), and SV, pre-ejection period, and total systolic ejection period on Doppler echocardiography. This single-beat elastance approach has been validated against invasively measured E_{LV} with a correlation coefficient of 0.81 ($P < 0.001$) [single-beat $E_{LV} = 0.78 \times E_{LV}$(invasive) + 0.55, SE of estimate = 0.6].

The echo data obtained during Baseline/Screening (Visit 1), pre-dose at Weeks 4, 12 and 24 (Visits 5, 6 and 8) and the limited echo data obtained post-dose at Weeks 4, 12 and 24 will be sent to a core laboratory for evaluations and analysis. A detailed manual of all echo procedures will be provided to all sites.

6.4.3 Biomarkers

Blood samples for biomarkers related to heart failure or mechanism of action such as NT-proBNP, BNP, [redacted] and spot urine samples for urinary biomarkers U-cGMP/U-creatinine, will be obtained pre-dose in all patients on Day 1 pre-randomization (Visit 2) and at Weeks 2, 4 12 and 24 (Visits 4, 5, 6 and 8). BNP, U-cGMP/U-creatinine will also be collected in all patients at 4 hours post-dose (± 0.5 hrs.) at Week 4 (Visit 5). Specimens will be processed at a central laboratory. Details on sample collection, handling and shipment of biomarker samples will be provided to investigators in a laboratory manual.

These and other selected biomarkers to be studied will be those believed to be relevant to the pathophysiology of heart failure, including those related to cardio-renal or vascular function, injury and/or fibrosis/remodeling. Biomarkers may include ones assessing cardio-renal or vascular benefit or ones related to the study drug mechanism of action. The list of blood and/or urine biomarkers may change during the course of the study, as new or more relevant biomarkers are determined. Biomarker analysis may also occur retrospectively after study close with biomarker decisions dependent on study outcome and/or new biomarkers relevant to this heart failure patient population.

[redacted]

6.4.4 Appropriateness of efficacy assessments

An assessment of aortic input impedance fully characterizes load on the left ventricle. Zc represents the contribution of proximal aortic properties to the aortic input impedance spectrum. Prior work has demonstrated that pulsatile hemodynamic load, as assessed by Zc, is increased in patients with heart failure (Mitchell 2001). Zc represents pulsatile load at the point of coupling between heart and arterial system. As a result, Zc represents a noncircumventable load on the left ventricle. Standard approaches to afterload reduction in heart failure, by using peripheral vasodilating drugs, will paradoxically increase pulsatile load on the heart in patients with elevated Zc, potentially attenuating favorable effects of vasodilation. Zc is the main hemodynamic determinant of peak left ventricular wall stress, which is particularly important in the presence of reduced left ventricular systolic function and enhanced load sensitivity. Zc has been shown to predict incident major CVD events in the Framingham Offspring cohort. Thus, Zc represents a critical component of pulsatile hemodynamic load that is abnormal in patients with heart failure and is associated with adverse outcomes. It stands to reason that therapy that specifically reduces Zc would be expected to have a favorable effect on left ventricular function and outcomes in patients with HFrEF.

6.5 Safety

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 Required sequence of cardiovascular data collection

The sequential order of cardiovascular data collection during study visits is:

1. ECG
2. Physical exam/cardiac exam
3. Vital signs
4. Hemodynamic assessments
5. Echo
6. Blood sampling

This sequence is important to minimize the impact of ECHO or blood sampling on hemodynamic assessments.

6.5.2 Physical examination

A complete physical exam will be performed at Screening/Baseline and, Weeks 12 and 24 (Visits 1, 6, and 8). 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.

A cardiac exam will be performed at all visits starting at Visit 3, except where a complete physical examination is required (see above), and will include the examination of vital signs

[redacted]

(systolic and diastolic blood pressure, pulse and respiration rate), heart and lung sounds, jugular venous distension, and extremities.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that were present prior to the subject providing written informed consent for the study must be included in the Relevant Medical History/Current Medical Conditions eCRF. Significant findings made after the subject provides written informed consent for the study, which meet the definition of an adverse event, must be recorded on the Adverse Event eCRF.

6.5.3 Heart failure signs and symptoms

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

6.5.4 Vital signs

Vital signs will be assessed at every visit. This will include blood pressure, pulse and respiration 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, with back supported and both feet placed flat on the floor. 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.

Clinically notable vital signs are defined in Appendix 1.

6.5.5 Height and weight

Height in centimeters (cm) will be measured once at Screening/Baseline (Visit 1). Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at every visit.

6.5.6 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 Adverse Event and angioedema eCRFs must be completed and the Novartis Medical Monitor must be notified.

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

[redacted]

6.5.7 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1. Clinically significant abnormalities must be recorded on the AE e(CRF) page as appropriate.

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 AE eCRF. If the laboratory abnormality is the primary reason for an unforeseen hospitalization or otherwise fulfills the seriousness criteria of an SAE, 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 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, or designee.

6.5.7.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential counts, and platelet count will be measured at Screening/Baseline, Weeks 12 and Week 24 (Visits 1, 6, and 8).

6.5.7.2 Clinical chemistry

Blood urea nitrogen (BUN), creatinine, total bilirubin, AST (SGOT), ALT (SGPT), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALT), sodium, potassium, chloride, calcium, magnesium, phosphorous, total protein, albumin, uric acid and glucose will be measured at Screening/Baseline (Visit 1) and at Weeks 1, 2, 12 and Week 24 (Visits 3, 4, 6, and 8).

If Randomization occurs greater than 2 weeks from Screening (Visit 1), clinical chemistries will be repeated at pre-randomization (Visit 2).

Hemoglobin A1c will be measured at Screening/Baseline (Visit 1) and at Weeks 12 and 24 (Visits 6 and 8).

6.5.7.3 Abbreviated chemistry panel

Electrolytes and creatinine will be measured pre-dose on Day 1 pre-randomization (Visit 2) and at Weeks 4, and 14 (Visits 2, 5 and 7)

6.5.8 Urinalysis

Dipstick urine measurements Screening/Baseline (Visit 1) and at Weeks 0, 2, 4, and 12 (Visits 2, 4, 5 and 6) for specific gravity, pH, albumin, total protein, bilirubin, glucose ketones, blood and leukocytes will be performed. Microscopy and WBC and RBC sediments will also be assessed in case of an abnormal dipstick test. If dipstick is positive, a qualitative microscopic

[redacted]

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

6.5.9 Electrocardiogram (ECG)

In the event that a clinically significant ECG abnormality is identified at the site (e.g. severe arrhythmia, conduction abnormality of QTcF > 500 ms), a copy of the assessment is sent to the study medical monitor for expedited review and reported to Novartis Drug Safety and Epidemiology, if applicable, and the ECG is repeated to confirm the diagnosis. If the patient is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

For this study, a Screening/Baseline ECG will be performed only. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12 lead ECGs are collected. The original ECGs *on non-heat-sensitive paper* appropriately, signed by the investigator, must be collected and archived at the study site.

Each ECG tracing must be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs must be performed to confirm the safety finding. Clinically significant ECG findings at baseline must be discussed with the sponsor or designee before administration of study treatment.

Clinically significant abnormalities must be recorded on the AE eCRF page as appropriate. Any SAE will be reported to Novartis Drug Safety and Epidemiology.

6.5.10 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. A serum pregnancy test (hCG) will be performed by the central lab at Screening/Baseline, Weeks 12 and 24 (Visits 1, 6, 8) and early withdrawal. If any of these tests are positive, the patient must be discontinued from the study.

6.5.11 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population. They include the 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.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when the patient volunteers them during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values, which are considered to be non-typical in patient with

underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

1. the severity grade [mild, moderate, severe]
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
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)

CTCAE Grade 5 (death) is not used, but is collected in other CRFs (Study Completion).

There may be cases where a CTCAE with a grade of 4 (life-threatening) may not necessarily be an SAE (e.g. certain laboratory abnormalities in the absence of meeting other serious criteria).

- Its relationship to the study treatment and other investigational treatment
- "No Relationship to study treatment or other investigational treatment" or
- "Relationship to study treatment" or
- "Relationship to other investigational treatment" or
- "Relationship to both study treatment and other investigational treatment or indistinguishable"
- Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- Whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding [investigational] treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- study treatment dosage increased/reduced
- study treatment dosage interrupted/withdrawn
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of

[redacted]

any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

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

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

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

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (see Annex IV, ICH-E2D Guideline).

[redacted]

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 (see Annex IV, ICH-E2D Guideline).

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

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days [after the last study visit/ following the last administration of study treatment if there are post-treatment follow-up visits with no required procedures] *(please select as appropriate, see comment below)* must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30-day period [after the last study visit/ following the last administration of study treatment if there are post-treatment follow-up visits with no required procedures] should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to *each specific component of study treatment (if study treatment consists of several components)* complete the SAE Report Form in English, and submit the completed within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and

[redacted]

reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

Not applicable.

7.4 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum event:
  - confirmed (after ≥24h) increase in serum creatinine of ≥25% compared to baseline during normal hydration status
- Urine event
  - new onset (≥1+) proteinuria; confirmed by doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable)
  - new onset (≥1+), hematuria or glycosuria

Every renal laboratory alert or renal event, as defined in Table 17-1 in Appendix 5, should be followed up by the investigator or designated personnel, at the trial site, as summarized in Appendix 5.

7.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

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

[redacted]

7.6 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

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

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

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 CRO representative will review the protocol and 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. 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 CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients/subjects will be disclosed.

[redacted]

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to US CFR 21Part 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 transfer of the data to the CRO working on behalf of Novartis. 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 copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

CRO 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.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events 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 a designated CRO.

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

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared 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 after written agreement by Novartis Medical Affairs management.

8.4 Data monitoring committee

Not applicable.

[redacted]

8.5 Angioedema Adjudication Committee

8.5.1 Composition and purpose

The Angioedema Adjudication Committee (AAC) consists of a group of experts in clinical angioedema who have been selected according to their educational, clinical, and research experience and are independent from Novartis. The purpose of the AAC is to review and to adjudicate all suspected angioedema events, in a uniform and consistent manner, and to assign severity for each confirmed case for the project wide sacubitril/valsartan program. The AAC will remain blinded to treatment allocation during the adjudication process whenever possible and necessary.

8.5.2 Overview of site responsibility

An overview of site responsibility for reporting angioedema is described below.

At each study visit, it is important for the investigator to pay 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 Novartis, or designee, regarding AEs that were reported on behalf of patients that may resemble an angioedema-like event. The investigator or his/her delegated staff must complete the required report forms and supply the required medical records for such events, regardless of whether the investigator views the event in question as angioedema or not.

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

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

Please refer to the Angioedema Adjudication Site Manual for additional details regarding the process for documenting and reporting angioedema-like events.

9 Data analysis

The analysis will be conducted on all patient data at the time the trial ends, defined as when the last patient enrolled completes the Week 24 visit. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

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.

[redacted]

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. Discrete variables will be summarized by frequencies and percentages.

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 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, unless specified otherwise in the protocol.

Summary statistics will be provided, by treatment group, for demographics and baseline characteristics. Geometric means will be used to summarize the cardiac biomarkers results including NT-proBNP. 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 (frequency and percent) by therapeutic class, preferred term, and treatment group.

[redacted]

9.4 Analysis of the primary variable(s)

9.4.1 Variable(s)

Change in aortic characteristic impedance (Zc = dP/dQ) between baseline and Week 12.

9.4.2 Statistical model, hypothesis, and method of analysis

Let μ_j denote the population mean of change from baseline in the aortic characteristic impedance at Week 12 for treatment group j, j = 0, 1, where 0 corresponds to enalapril and 1 corresponds to sacubitril/valsartan.

The following null hypothesis (H_0) will be tested against the alternative hypothesis (H_A):

H_0: $\mu_1 - \mu_0 = 0$

H_A: $\mu_1 - \mu_0 \neq 0$

The primary efficacy variable will be analyzed by an analysis of covariance (ANCOVA) model with treatment and Zc baseline as explanatory variables (Mitchell 2002). The least squares means of the two treatment groups, least squares mean difference of the treatment groups, 95% confidence interval for the difference in the two treatment groups, and p-value based on the fitted linear model will be reported. If the p-value is < 0.05 and the least squares mean difference of the treatment groups favors sacubitril/valsartan, statistical significance in favor of sacubitril/valsartan is shown.

The primary analysis of the primary efficacy variable will be based on the Full Analysis Set.

9.4.3 Handling of missing values/censoring/discontinuations

If a subject has no post-baseline value, the missing value will not be imputed and the subject will be removed from the analysis.

9.4.4 Sensitivity analyses

A supportive nonparametric analysis will be performed to examine the consistency of results if the assumption of normality for the distribution of the primary efficacy variable is not tenable. For this supportive analysis, the primary efficacy variable will be analyzed using the Wilcoxon rank-sum test. The probability of one treatment being the same or better than the other treatment will be estimated (based on the Wilcoxon rank-sum test) and the associated 95% confidence interval will be reported (Chen and Kianifard, 2000).

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

1. Change from baseline in NT-proBNP at Week 12
2. Changes from baseline in echocardiographic measures at week 12 including:
   - Global longitudinal strain
   - Left atrial volume index
   - Mitral annular E' velocity (Doppler Tissue Imaging)

[redacted]

- Mitral E/E'
- Left ventricular ejection fraction
- Ventricular-vascular coupling (Ea/Ees)
- LV end systolic and diastolic volume indices

3. The change in aortic characteristic impedance and change in biomarker levels such as BNP, U-cGMP/U-creatinine, during both trough and 4 hours post-dose at Week 4

For NT-proBNP, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment and the logarithmic baseline biomarker value as a covariate and baseline (Day 1) as explanatory variables. The estimated treatment effects in terms of ratios of geometric means, based on the least-squared means from the ANCOVA model, the corresponding two-sided 95% confidence intervals and p-values will be provided.

The change from baseline in the echocardiographic measures will be analyzed using an ANCOVA model with treatment and baseline as explanatory variables.

Correlation coefficients between changes from baseline in aortic characteristic impedance and biomarker levels (BNP, U-cGMP/U-creatinine) during both trough and 4 hours post-dose at Week 4 will be calculated by treatment and overall.

For the analysis of secondary efficacy variables, if a subject has no post-baseline value, the missing value will not be imputed and the subject will be removed from the analysis.

Analyses of the secondary efficacy variables will be based on the Full Analysis Set.

9.5.2 Safety variables

The safety and tolerability assessments are listed below:

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

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

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

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

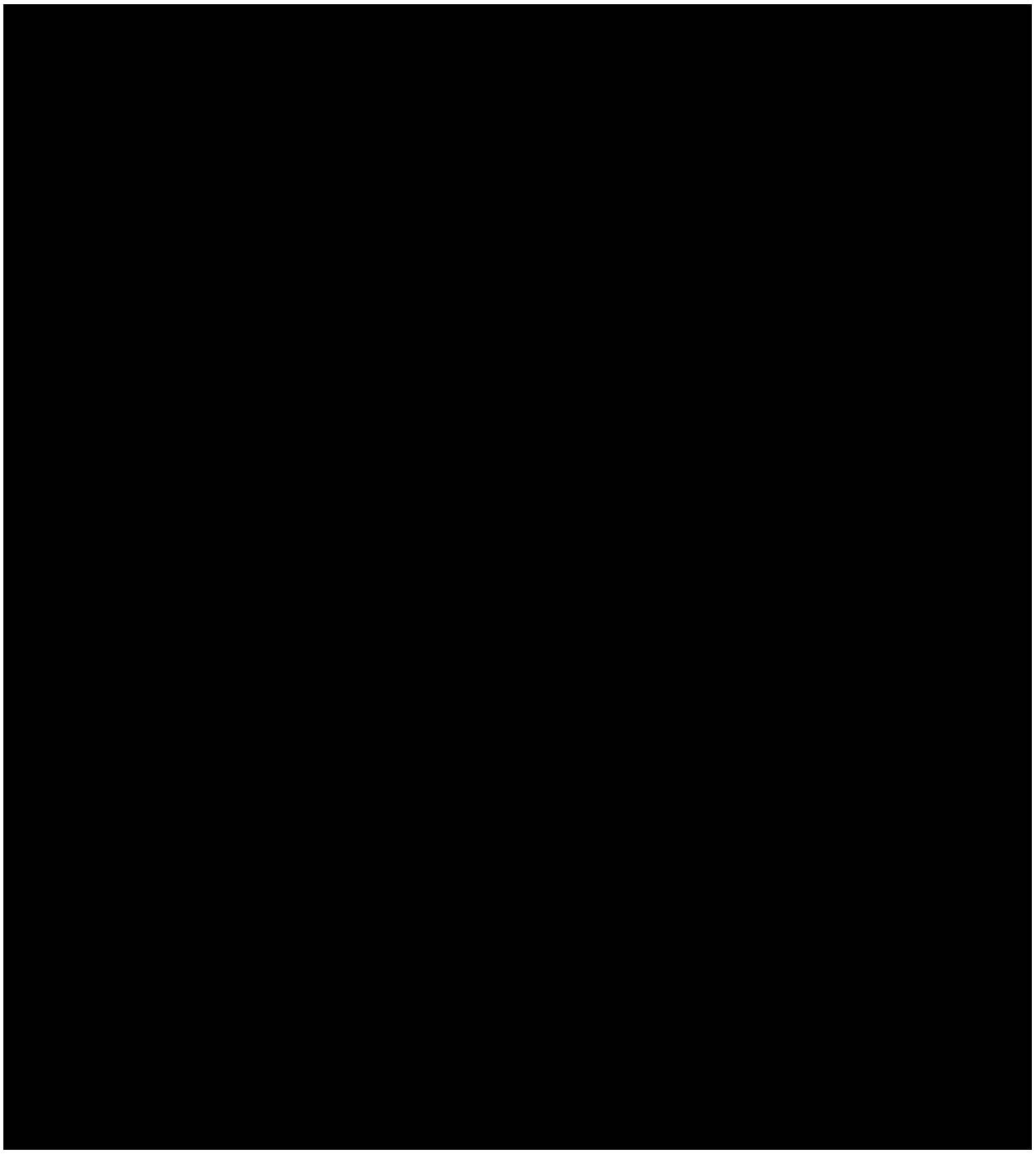
[redacted]

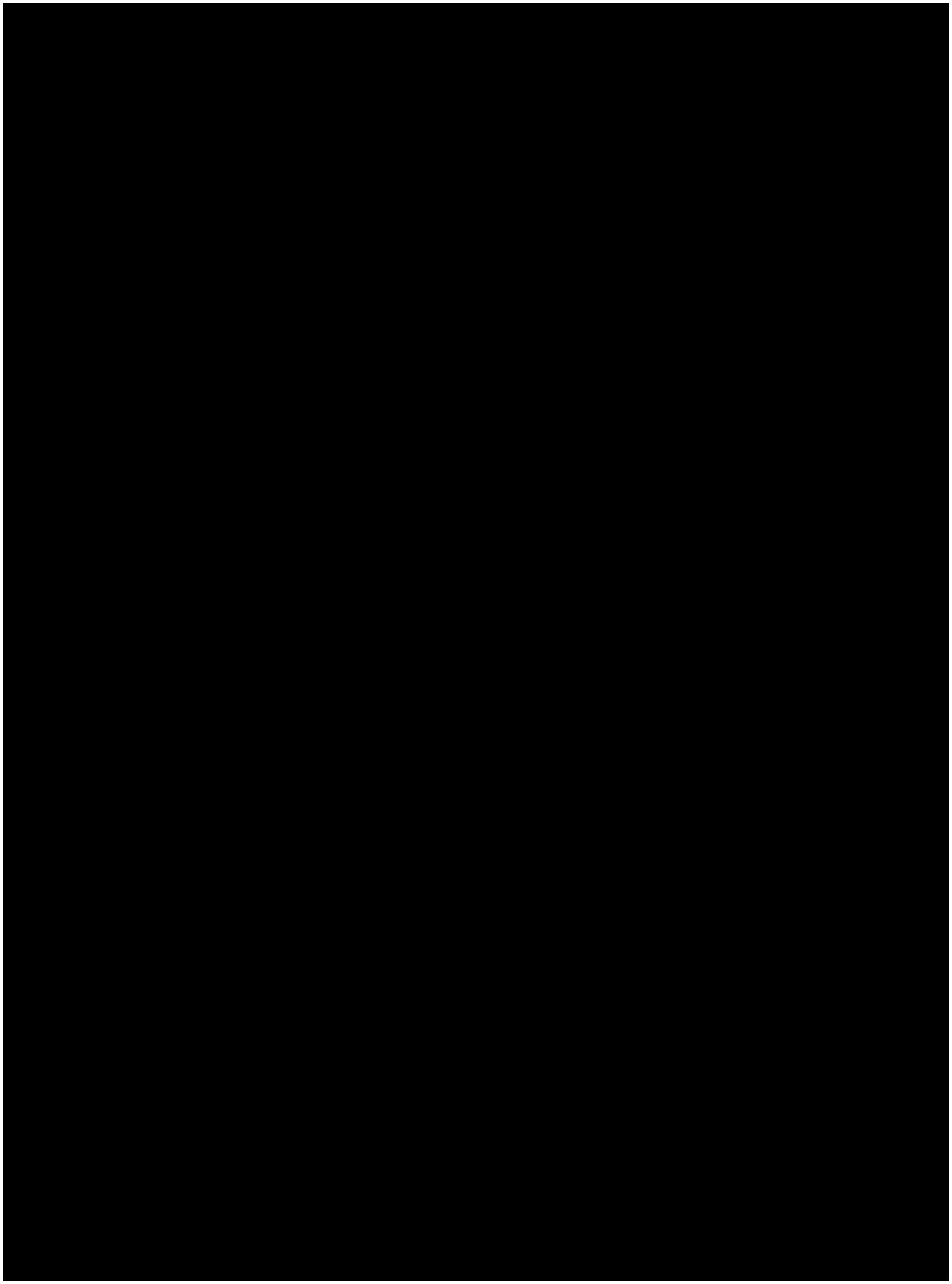
Data from other tests (e.g., vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

Safety analyses will be performed based on the Safety Set. There will be no inferential analyses of the safety data. See Section 9.5.1.

9.5.3 Biomarkers

See Section 9.5.1.





9.7 Interim analyses

No interim analysis is planned.

9.8 Sample size calculation

In CHOIR (Mitchell 2002), treatment with Omapatrilat was associated with an approximately ~10% reduction in characteristic impedance at 12 weeks, with little or no change seen amongst enalapril- treated patients. Based on a similar study design and population, and accounting for a dropout rate of 20% from first visit to subsequent follow up and a 10% rate of non-evaluable data, assuming a standard deviation of 80 for the primary efficacy variable and 90% power, a sample size of 432 subjects (216 per arm) will be necessary to detect a clinically important change of 30 dyne x sec/cm^5 between the two treatment groups.

Assuming a significance level of 0.05, a sample size 432 patients would provide 88% power to detect a 25% reduction in the geometric mean of the proportional change from baseline to Week 12 in NT-proBNP for the sacubitril/valsartan treatment group assuming a value of 0.95 for the enalapril group, a value of 0.7125 for the sacubitril/valsartan group (25% reduction), a common standard deviation of 0.85 and a 20% drop-out rate. The difference between the logs for the two treatment groups is therefore assumed to be 0.288.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must 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 (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must 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 must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must 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/subjects. 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

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.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance (CQA), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

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/subjects should be administered as deemed necessary on a case-by-case basis. Under no circumstances is an

investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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.

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/subjects 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 must be followed.

[redacted]

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[redacted]

13 Appendix 1: Clinically notable laboratory values and vital signs

Clinically notable vital signs will be defined in this study as a SBP < 90 mmHg. The study treatment shall be interrupted or stopped based on investigator judgement.

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

Hematology

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

Blood Chemistry

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

[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)
- Consider down-titration of study medication, according to investigator medical judgment if he/she believes that adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern medical judgment.

[redacted]

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

[redacted]

15 Appendix 3: Guidelines for the management of blood pressure

Guidelines

- Investigator should monitor blood pressure closely
- If symptomatic hypotension occurs:
- Correct any treatable cause, e.g. hypovolemia
- 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
- If hypotension persists, the study drug should be down titrated or even temporarily withdrawn. The dose re-challenge and medication adjustment guidelines described in Section 5.5.5 should be adhered to as much as possible.

16 Appendix 4: Guidelines for the management of renal dysfunction

General principles:

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

Two types of response to serum creatinine increase are described:

Surveillance situation

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

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

Action situation

If a patient's 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).

[redacted]

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

17 Appendix 5: Specific Renal Alert Criteria and Actions

Table 17-1 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥1+ Albumin- or Protein-creatinine ratio increase ≥2-fold Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥3 mg/mmol; Protein-creatinine ratio (PCR)≥150 mg/g or >15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick glycosuria ≥1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.