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LCZ696

Clinical Trial Protocol CLCZ696DUS01 / NCT03988634

A multicenter, randomized, double-blind, double-dummy, parallel group, active controlled study to evaluate the effect of sacubitril/valsartan (LCZ696) versus valsartan on changes in NT-proBNP, safety, and tolerability in HFpEF patients with a WHF event (HFpEF decompensation) who have been stabilized and initiated at the time of or within 30 days post-decompensation (PARAGLIDE-HF)

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List of abbreviations

AC	Adjudication committee
ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ADHF	acute decompensated heart failure
AE	adverse event
AF	atrial fibrillation
AHF	acute heart failure
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANP	atrial natriuretic peptide
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
AST	aspartate aminotransferase
AT1	angiotensin type 1
ATC	Anatomical Therapeutic Chemical
BID	twice a day
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
bpm	beats per minute
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CCB	Calcium channel blocker
cGMP	Cyclic guanosine monophosphate
CHF	chronic heart failure
CFR	US Code of Federal Regulations
CMO&PS	Chief Medical Office and Patient Safety
COPD	Chronic obstructive pulmonary disease
COVID-19	COronaVIrus Disease 2019
COX-2	cyclo-oxygenase-2
CPK	creatine phosphokinase
CRA	clinical research associate (site monitor)
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRT	Cardiac resynchronization therapy
CTT	Clinical trial team
CV	cardiovascular
DBP	diastolic blood pressure
DM	diabetes mellitus
DMC	Data Monitoring Committee

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EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
Echo	echocardiogram
eCRF	electronic case report form
ED	Emergency Department
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
cGMP	cyclic guanosine monophosphate
EMA	European Medicines Agency
ER	emergency room
EU	European
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCS	Global Clinical Supply
[redacted]	[redacted]
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
Hgb	hemoglobin
hs-Troponin	high sensitivity troponin
HTN	hypertension
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	investigator notification
IV	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
LS	least squared
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
MI	myocardial infarction
mm Hg	millimeters of mercury
NEP	neutral endopeptidase

[redacted]

NSAID	non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
QMS	Quality Management System
RAN	Randomized Analysis Set
RAS	renin angiotensin system; randomize analysis set (statistics)
RASi	Renin angiotensin system inhibition
RBC	red blood cell
RR	relative risk
SAE	serious adverse event
SAF	safety set
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	Standard Deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
USPI	United States prescribing information/package insert
WBC	white blood cell(s)
WHF	Worsening heart failure
WHO	World Health Organization

[redacted]

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study patient
Cohort	A specific group of patients fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) 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
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
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)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last patient or at a later point in time as defined by the protocol
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication bottles
Mis-randomized patients	Mis-randomized patients are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease
Patient	An individual with the condition of interest for the study
Patient number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug
Personal data	Patient information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes patient identifier information, study information and biological samples.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient

[redacted]

Screen Failure	A patient who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first patient
Study treatment	Any single drug or combination of drugs or intervention administered to the patient as part of the required study procedures
Study treatment discontinuation	When the patient permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Subject	A trial participant (can be a healthy volunteer or a patient)
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer and does not allow any further collection of personal data

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Protocol summary

Protocol number	CLCZ696DUS01
Full Title	A multicenter, randomized, double-blind, double-dummy, parallel group, active controlled study to evaluate the effect of sacubitril/valsartan (LCZ696) versus valsartan on changes in NT-proBNP, safety, and tolerability in HFpEF patients with a WHF event (HFpEF decompensation) who have been stabilized and initiated at the time of or within 30 days post-decompensation (PARAGLIDE-HF)
Brief title	Prospective comparison of ARNI with ARB Given following stabiLization In DEcompensated HFpEF (PARAGLIDE-HF)
Sponsor and Clinical Phase	Novartis, Phase IIIB
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to assess the effect of sacubitril/valsartan vs. valsartan on changes in NT-proBNP, safety, and tolerability in HFpEF patients with a WHF event (HFpEF decompensation) who have been stabilized and initiated at the time of or within 30 days post-decompensation
Primary Objective(s)	To demonstrate the effect of sacubitril/valsartan vs. valsartan on time-averaged proportional change in NT-proBNP from baseline to Weeks 4 and 8 in HFpEF patients with a WHF event (HFpEF decompensation) who have been stabilized for and initiated at the time of or within 30 days post-decompensation
Secondary Objectives	• To determine the effect of sacubitril/valsartan vs. valsartan on the composite hierarchical outcome consisting of: a) time to CV death, b) total HF hospitalizations, c) total urgent HF visits, and d) time-averaged proportional change in NT-proBNP (from baseline to Weeks 4 and 8) using win ratio methodology • To assess the effect of sacubitril/valsartan vs. valsartan on total composite events based on CV death, HF hospitalizations, and urgent HF visits • To assess the effect of sacubitril/valsartan vs. valsartan on the incidences of a composite endpoint of worsening renal function (renal death, reaching ESRD, or $\geq$ 50% decline in eGFR relative to baseline • To assess the effect of sacubitril/valsartan vs. valsartan on change in NT-proBNP from baseline to Week 8 • To assess the effect of sacubitril/valsartan vs. valsartan on change from baseline in hs-Troponin (high sensitivity) at Weeks 4 and 8 • To assess the effect of sacubitril/valsartan vs. valsartan on tolerability and the incidence of adverse events of special interest during treatment
Study design	This study will use a randomized, double-blind, double-dummy, active-controlled, parallel group design. Eligible patients will be randomized either during hospitalization for, or within 30 days of, a WHF event

[redacted]

	(HFpEF decompensation). A WHF event (HFpEF decompensation) is defined as a hospitalization, emergency department (ED) visit or out-of-hospital urgent HF visit, all requiring IV diuretics. Randomized patients will have been hemodynamically stabilized, defined in this study as: • SBP ≥100mmHg for the preceding 6 hours prior to randomization; no symptomatic hypotension • No increase (intensification) in IV diuretic dose within last 6 hours prior to randomization • No IV inotropic drugs for 24 hours prior to randomization • No IV vasodilators including nitrates within last 6 hours prior to randomization All patients will need to meet all inclusion and none of the exclusion criteria. Patients will be randomized 1:1 to sacubitril/valsartan or valsartan. Initial dose at randomization will be determined based on the patient's previous dose of or lack of ACEi/ARB immediately prior to current WHF event (HFpEF decompensation), or at the time of post-decompensation randomization. Patients currently or recently taking ACEi: In order to provide for a necessary 36-hour washout of prior ACEi treatment before receiving sacubitril/valsartan, eligible patients will be randomized no earlier than 36 hours from their last ACEi dose). Hospital medication administration and medication reconciliation records should be reviewed to confirm that eligible patients have not received ACEi for at least 36 hours prior to randomization and the first dose of study medication. The maximum duration of study for the first patient randomized after amendment 1 is approximately 20 months; the anticipated minimum follow-up would be for 8 weeks.
Population	The study population will consist of male and female patients, ≥ 18 years of age, currently hospitalized for or within 30 days of a WHF event (HFpEF decompensation). A WHF event (HFpEF decompensation) is defined as a hospitalization, emergency department (ED) visit or out-of-hospital urgent HF visit, all requiring IV diuretics. A total of approximately 450 patients will be randomized to sacubitril/valsartan or valsartan in a 1:1 ratio at approximately 130 centers in the United States and Canada. Randomized patients will have been hemodynamically stabilized defined in this study as: • SBP ≥100mmHg for the preceding 6 hours prior to randomization; no symptomatic hypotension • No increase (intensification) in IV diuretic dose within last 6 hours prior to randomization • No IV inotropic drugs for 24 hours prior to randomization • No IV vasodilators including nitrates within last 6 hours prior to randomization

[redacted]

	All patients will need to meet all other inclusion and none of the exclusion criteria.
Key Inclusion criteria	1. Signed informed consent must be obtained prior to participation in the study 2. Patients ≥18 years of age, male or female 3. Current hospitalization for WHF (HFpEF decompensation), or within 30 days of discharge following a WHF event (defined as hospitalization, emergency department (ED) visit or out-of-hospital urgent HF visit, all requiring IV diuretics). Patients with a diagnosis of acute heart failure had to have symptoms and signs of fluid overload (i.e. jugular venous distention, edema or rales on auscultation or pulmonary congestion on chest x-ray). Eligible patients will be randomized after IV diuresis for HFpEF is given (and no earlier than 36 hours from their last ACEi dose if applicable) and within 30 days post-decompensation after presentation with acute HFpEF decompensation and meeting the following definitions of hemodynamic stability: Randomized patients will have been hemodynamically stable defined in this study as: a. SBP ≥100mmHg for the preceding 6 hours prior to randomization; no symptomatic hypotension b. No increase (intensification) in IV diuretic dose within last 6 hours prior to randomization c. No IV inotropic drugs for 24 hours prior to randomization d. No IV vasodilators including nitrates within last 6 hours prior to randomization 4. HFpEF with most recent LVEF >40% (within past 3 months) 5. Elevated NT-proBNP or BNP at the time of acute HFpEF decompensation or post-decompensation screening (and within 72 hours for out-of-hospital randomization, if applicable): a. Patients not in AF at the time of biomarker assessment: NT-proBNP ≥ 500pg/mL or BNP ≥ 150 pg/mL; patients in AF at the time of biomarker assessment: NT-proBNP ≥ 1000pg/mL or BNP ≥ 300 pg/mL b. Patients recruited in-hospital will be randomized based on the qualifying local lab value in-hospital NT-proBNP or BNP value. c. Patients enrolled post-decompensation can be randomized based on their NT-proBNP or BNP value in the following way: i. if enrolling in post-decompensation setting then need eligible screening/local NT-proBNP/BNP within 72 hours of randomization. The test value could be from recent hospitalization if within 72 hours or ii. would require (re)drawing NT-proBNP or BNP labs in post-decompensation setting if the lab value is not already available within the last 72 hours).

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	6. Has not taken an ACEi for 36 hours prior to randomization
Key Exclusion criteria	1) Any clinical event within the 90 days prior to randomization that could have reduced the LVEF (i.e., MI, CABG), unless an echo measurement was performed after the event confirming the LVEF to be >40% 2) Entresto™ (sacubitril/valsartan) usage within the past 60 days 3) eGFR < 20ml/min/1.73 m2 as measured by the simplified Modification of Diet in Renal Disease (MDRD) formula at most recent assessment prior to randomization and within 24 hours prior to inpatient randomization or 72 hours prior to outpatient randomization 4) Serum potassium > 5.2 mEq/L at most recent assessment prior to randomization and within 24 hours prior to inpatient randomization or 72 hours prior to outpatient randomization 5) Acute coronary syndrome, stroke, transient ischemic attack; cardiac, carotid or other major CV surgery; percutaneous coronary intervention (PCI) or carotid angioplasty, within 30 days prior to randomization 6) Probable alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms (i.e. dyspnea, fatigue) such as significant pulmonary disease (including primary pulmonary HTN), anemia or obesity. 7) Isolated right HF in the absence of left-sided structural heart disease 8) History of hypersensitivity (i.e. including angioedema), known or suspected contraindications, or intolerance to any of the study drugs including ARNIs (i.e. sacubitril/valsartan), and/or ARBs 9) Patients with a known history of angioedema due to any etiology 10) Patients with a history of heart transplant or LVAD, currently on the transplant list, or with planned intent to implant LVAD or CRT device within the initial three months of enrollment during the trial 11) A cardiac or non-cardiac medical condition other than HF with an estimated life expectancy of < 6 months 12) Known pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy including suspected or confirmed amyloid heart disease (amyloidosis) 13) Life-threatening or uncontrolled dysrhythmia, including symptomatic or sustained ventricular tachycardia and atrial fibrillation or flutter with a resting ventricular rate >110 bpm 14) Clinically significant congenital heart disease felt to be the cause of the patient's symptoms and signs of HF 15) Coronary or carotid artery disease or valvular heart disease likely to require surgical or percutaneous intervention within the duration of the trial 16) Any surgical or medical condition, which in the opinion of the investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study 17) 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

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<table>
<tr><td></td><td>18) Participation in any other clinical trial involving investigational agents or devices within the past 30 days
19) Current confirmed COVID19 infection
20) Past COVID19 infection with persistent symptom burden suspected due to COVID19 (further defined in Section 5.2).
21) 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.
22) Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of investigational drug and for 7 days off of study drug. Highly effective contraception methods are defined in Section 5.2.</td></tr>
<tr><td>Study treatment</td><td>All eligible patients will be randomized to receive either sacubitril/valsartan or valsartan. The following treatment will be provided (double-blind, double dummy) until the last patient randomized is followed for 8 weeks:

<table><tr><th>Dose Level</th><th>Sacubitril/valsartan</th><th>Valsartan</th></tr><tr><td>1</td><td>24/26 mg [50mg] BID</td><td>40 mg BID</td></tr><tr><td>2</td><td>49/51 mg [100mg] BID</td><td>80 mg BID</td></tr><tr><td>3</td><td>97/103 mg [200 mg] BID</td><td>160 mg BID</td></tr></table>
Sacubitril/valsartan with matching placebo and valsartan with matching placebo will be provided for the double-blind treatment period.

Initial dose at randomization will be determined based on the patient’s previous dose of or lack of ACEi/ARB immediately prior to current WHF event (HFpEF decompensation), or at the time of post-decompensation randomization.. Every attempt should be made to titrate to and maintain patients on target study drug Dose Level 3 for as long as possible throughout the study.</td></tr>
<tr><td>Key safety assessments</td><td>• Incidence of worsening renal function, defined as an increase in serum creatinine of ≥0.5mg/dl and worsening of the eGFR by at least 25%
• Incidence of symptomatic hypotension
• Incidence of hyperkalemia (potassium >5.5 mEq/l)
• Incidence of angioedema

Safety assessments will consist of monitoring and recording of all adverse events and serious adverse events, evaluation of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations.</td></tr>
<tr><td>Sample Size and power</td><td>The target sample size for this study is approximately 450 total patients, randomized in the two treatment groups in 1:1 ratio. The maximum planned duration of follow-up after randomization (for patients enrolled under Amendment 1 or later) is approximately 20 months; the anticipated minimum follow-up would be for 8 weeks. The</td></tr>
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	power of the study is determined based on these 450 patients for the primary endpoint. **Power for the primary endpoint** This sample size of 450 patients would have 85% power to detect a 23% reduction in the geometric mean of the proportional change from baseline to an average of Weeks 4 and 8 in NT-proBNP for the sacubitril/valsartan treatment group. The power is estimated assuming a two-sided significance level of 0.05, a common standard deviation of 0.85 for change in log transformed NT-proBNP and a 15% rate of missingness of NT-proBNP at baseline or both Week 4 and Week 8. nQuery Version 8.4.1.0 (2019) software package is used in calculating the power of the test.
Data analysis	The Full Analysis Set (FAS) comprises all participants to whom study treatment has been assigned by randomization. According to the intent-to-treat principle, participants will be included for analysis according to the treatment they have been assigned to during the randomization procedure. The patients in this trial are divided in two groups, (1) Those who are randomized under Protocol Version 00 (Original Protocol patients) and (2) Those who are randomized under Protocol Version 01 or later. FAS includes patients from both groups. See Section 3 for details. **Analysis of the primary endpoint** The primary null hypothesis (H_{10}) to be tested is that the ratio of the geometric means of NT-proBNP (average of Weeks 4 and 8) divided by baseline for the sacubitril/valsartan and valsartan groups are equal versus the alternative hypothesis (H_{1a}) that the ratio of the geometric means of NT-proBNP are not equal. First, the arithmetic mean of NT-proBNP at Weeks 4 and 8 will be calculated, then the change from baseline in natural log-transformed NT-proBNP will be calculated as follows: *ln(mean post dose value) – ln(baseline value).* The natural logarithm will be used in all these calculations. This log-transformed value will be used as the dependent variable in the analysis of covariance (ANCOVA) model described below. This dependent variable is called, the time-averaged proportional change from baseline in logarithmic scale. The dependent variable will be analyzed using an ANCOVA model with treatment in-/out-of-hospital randomization, gender, race, baseline LVEF (<=57%, >57%) as fixed effect factors, age and the logarithmic baseline NT-proBNP as covariates. The treatment effect in terms of ratios of geometric means is estimated based on the least-squared means (LS-means) from the ANCOVA model and the corresponding two-sided 95% confidence interval will be provided. Geometric means will be calculated by exponentially back transforming the LS-means based on the fitted ANCOVA model.

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	Interim analysis: There is no planned interim analysis for efficacy in the study. An independent Data Monitoring Committee (DMC) will be responsible for performing interim safety assessment using independent statistician and programmer who will not be involved in the trial conduct. The DMC charter will contain the committee's responsibilities regarding the interim safety assessment. Details of this safety assessment will be included in the Statistical Analysis Plan. Interim safety assessments are planned to be performed during the study and results will be provided to DMC for their review and recommendation. The number and/or timing of these safety assessments will be mentioned in the Data Monitoring Committee Charter. No adjustment of the level of significance will be made for these interim safety assessments. See Section 12 for additional information on planned data analyses.
Key words	Heart failure with preserved ejection fraction, HFpEF, heart failure hospitalization, NYHA, NT-proBNP, win ratio, acute decompensated heart failure, sacubitril/valsartan, [redacted] Worsening heart failure (WHF), heart failure decompensation

[redacted]

1 Introduction

1.1 Background

Sacubitril/valsartan is a first-in-class angiotensin receptor-neprilysin inhibitor (ARNI). The PARAMOUNT and PARAGON-HF trials provided information regarding the effect of sacubitril/valsartan compared with valsartan on clinical outcomes in patients with chronic heart failure with preserved ejection fraction (HFpEF), initiating treatment in the outpatient setting (Solomon et al 2012; Solomon et al 2019). Further data are needed regarding the use of sacubitril/valsartan in patients hospitalized due to acute decompensated HFpEF and in key populations not broadly represented in PARAGON-HF, including newly diagnosed, morbidly obese, recently hospitalized, and Black patients. PARAGLIDE-HF will provide important information regarding the efficacy, safety, and tolerability of initiating sacubitril/valsartan therapy in patients with a WHF event (HFpEF decompensation) who have been hemodynamically stabilized during a hospitalization or WHF event requiring IV diuretics.

Sacubitril/valsartan has been evaluated for efficacy and safety in ambulatory patients with chronic HFpEF. The PARAMOUNT study was a randomized, double-blind, active-controlled phase 2 trial of 308 patients with HFpEF (Left ventricular ejection fraction (LVEF) ≥45%) (Solomon et al 2012). Patients enrolled in the study received sacubitril/valsartan titrated to 97/103 mg twice daily or valsartan titrated to 160 mg twice daily. The primary end point, change in NT-proBNP levels from baseline to 12 weeks, was significantly reduced in the sacubitril/valsartan group compared with the valsartan group (sacubitril/valsartan: baseline, 783 pg/mL [95% CI 670-914], 12 weeks 605 pg/mL [95% CI512-714]; valsartan: baseline, 862 pg/mL [95% CI 733-1012], 12 weeks 835 pg/mL [95% CI 710-981]; ratio of change from baseline: sacubitril/valsartan / valsartan, 0.77, 95% CI 0.64-0.92, p=0.005. Sacubitril/valsartan was well tolerated and had a similar adverse effect profile compared to valsartan.

In PARAGON-HF, a randomized, double-blind, active-controlled phase 3 trial with 4822 ambulatory chronic HFpEF patients, the primary endpoint was a composite of total hospitalizations for heart failure and death from cardiovascular causes. After a single blind run-in period, patients were randomized to either sacubitril/valsartan or valsartan at target doses of 97/103mg or 160mg twice daily, respectively, and were followed for a median duration of 35 months. There were 894 (12.8 per 100 patient-years) primary composite events (CEC-confirmed total heart failure hospitalizations and CV deaths) in the sacubitril/valsartan group compared to 1009 (14.6 per 100 patient-years) in the valsartan group, indicating a 13% relative rate reduction in the primary composite endpoint, a treatment effect that narrowly missed statistical significance (RR=0.87; 95% CI: 0.75-1.01; p=0.0587) (Solomon et al 2019). No new safety signals were seen in PARAGON-HF, and safety assessments were consistent with PARADIGM-HF, a HF with reduced ejection fraction study comparing sacubitril/valsartan to enalapril (McMurray et al 2014).

It has been reported that the period subsequent to a worsening heart failure event is when the patients are most vulnerable for hospitalization, re-hospitalizations, and increased mortality. In a post-hoc analysis of PARAGON-HF, those HFpEF patients who were recently hospitalized had a 2-3 fold higher risk of rehospitalization and cardiovascular death. Of the 4796 patients

[redacted]

randomized and included in the full analysis set (FAS), 48% had a hospitalization prior to the index hospitalization in PARAGON-HF. Moreover, 622 (13% of the total randomized) patients had had at least one hospitalization within 30 days of trial screening. The event rate was 26.7 (≤30 days) vs. 7.9 (not previously hospitalized) per 100 patient-years in the valsartan group. In comparison, the absolute risk reduction for patients enrolled at ≤ 30 days after hospitalization was 6.4% in the group receiving sacubitril/valsartan compared to valsartan and this effect decreased as time from hospitalization increased (Vaduganathan et al 2019).

HFpEF patients with ADHF are known to have markedly elevated levels of BNP and NT-proBNP, which are reduced following adequate treatment and normalization of their cardiac decompensation. In the I-PRESERVE trial, patients with both a recent hospitalization and elevated NT-ProBNP (> 360 pg/mL) had a greater risk of cardiovascular death and subsequent heart failure hospitalization (Kristensen et al 2015). Therefore, it is important to evaluate therapeutic strategies that can lead to superior reductions in NT-proBNP in patients hospitalized due to acute decompensation.

The PIONEER-HF trial evaluated the effect of in-hospital initiation of sacubitril/valsartan vs. enalapril in patients with heart failure with reduced ejection fraction (HFrEF) who had been stabilized during hospitalization for acute decompensated heart failure. PIONEER-HF demonstrated greater reduction with sacubitril/valsartan vs. enalapril in time-averaged proportional change in NT-ProBNP from baseline to weeks 4 and 8 (percent change, -46.7% vs. -25.3%; ratio of change with sacubitril/valsartan vs. enalapril 0.71 [0.63 – 0.81], p<0.001) and a decrease in the exploratory clinical composite outcome of death, re-hospitalization for heart failure, LVAD implantation, or listing for cardiac transplant (Velazquez et al 2018).

Based on the above, PARAGLIDE-HF is designed to assess the efficacy, safety and tolerability of sacubitril/valsartan in HFpEF patients with a WHF event (HFpEF decompensation) who have been stabilized and initiated at the time of or within 30 days post-decompensation.

These data from PARAGLIDE-HF will complement TRANSITION and PIONEER-HF, where both examined the safety and efficacy of sacubitril/valsartan in hospitalized patients hemodynamically stabilized after an acute decompensated HFrEF event (Wachter R et al 2018, Velazquez et al 2018).

1.2 Rationale for Protocol Amendments

Amendment 1 (January 2020)

PARAGLIDE-HF amendment 1 reflects learnings from the PARAGON-HF trial, which was completed 3 months into PARAGLIDE-HF trial enrollment. From PARAGON-HF, learnings about hospitalized HF with preserved ejection fraction (HFpEF) patients helped guide additional key endpoints as well as sample size, timeline, and duration of treatment changes.

Amendment 2 (September 2020)

Based on technology advancements, site-level changes, and regulatory adjustments during the COVID-19 pandemic, Amendment 2 reflects allowances for virtual visits, per patient stability and Investigator discretion, at time points defined in Section 8.

[redacted]

Amendment 3 (October 2020)

Amendment 3 corrects an administrative error identified within Amendment 2. As described in Amendment 2, Visit 14, based on patient stability and Investigator discretion, can be conducted virtually. [redacted]

Amendment 4 (December 2021)

Amendment 4 adjusts the protocol to adapt to recruitment challenges experienced during the COVID19 pandemic which have affected patients and research sites and negatively impacted study timelines. This amendment decreases the sample size (from 800 to 450 patients) to focus on the primary endpoint of changes from baseline in NT-proBNP and moves the key (clinical) secondary endpoints to traditional secondary endpoints due to the key secondary endpoints having reduced statistical power. Inclusion and exclusion criteria were adjusted based on a thorough examination of screening logs and discussions with investigators who noted that many patients with bona fide HFpEF were being excluded due to the stringent exclusion language (example, prior exclusion #6a, b, and c). These changes aim to increase the generalizability of the trial population to real world patients. In addition, a HFpEF patient with a WHF event (including a HF hospitalization, ED visit, or urgent HF visit, all requiring IV diuretics) within 30 days would now qualify for enrollment, versus the prior criteria requiring hospitalization within 30 days. Patients with WHF events have a similar risk of future cardiovascular events to those hospitalized for HF and remain understudied.

1.3 Changes to Protocol

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

Amendment 1: Significant changes from Protocol Version 00 include:

- Addition of two key secondary endpoints that will assess clinical outcomes
- Increased sample size from 616 to approximately 800 patients (with increased study sites from 100 to approximately 130)
- Extended duration of treatment from 12 weeks (Original Protocol) to maximum of approximately 20 months and an average duration of study for all patients is anticipated to be approximately 11 months.
- Extended trial recruitment period extending to within 30 days post-discharge
- Some of the inclusion and exclusion criteria were changed/modified based on additional data from other analyses/publications or input from the Steering Committee/external experts.
- Based on safety data from a randomized trial including 414 subjects with estimated GFR of 20-60 mL/min/1.73 m2 comparing sacubitril/valsartan to irbesartan, the exclusion criteria was lowered to allow subjects with an estimated GFR of 20 mL/min/1.73 m2 and higher (Haynes R et al 2018)

[redacted]

Amendment 2: Significant changes from Protocol Version 01 include:

- Covid-19 exclusion criteria language was added
- Allowance for virtual visits at visits 10, 12, 14, and 16, based on patient stability and Investigator discretion
- Updated dosing table 6-5 and Section 6.6.2 to initiate study drug at Dose Level 1 if the patient's estimated GFR is <30mL/min/1.73 m^2

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

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

Amendment 3: Significant changes from Protocol Version 02 include:

[redacted]

Amendment 4: Significant changes from Protocol Version 03 include:

- Inclusion of patients with a WHF event (HFpEF decompensation), defined as a hospitalization, emergency department (ED) visit or out-of-hospital urgent HF visit, all requiring IV diuretics
- Qualifying age changed from >=40 to >=18 years old
- Sample size reduced to 450 patients (from 800 patients)
- Key secondary endpoints (the win ratio endpoint and the triple composite endpoint) were moved to a secondary position, with the trial power shifting to the NTproBNP primary endpoint
- Exclusion 2 modified to allow prior Entresto usage if >60 days
- Exclusion 6 modified to allow PI discretion on other reasons for HF-like symptoms (COPD, Hgb, Obesity)
- Altered the visit schedule (see Section 8) reducing total visits from 15 to 10 visits
- Updated language for contraception (exclusion 22)

1.4 Purpose

The purpose of this study is to assess the effect of sacubitril/valsartan vs. valsartan on changes in NT-proBNP, safety, and tolerability in HFpEF patients with a WHF event (HFpEF decompensation) who have been stabilized and initiated at the time of or within 30 days post decompensation.

[redacted]

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate the effect of sacubitril/valsartan vs. valsartan on time-averaged proportional change in NT-proBNP from baseline to weeks 4 and 8 in HFpEF patients with a WHF event (HFpEF decompensation) who have been stabilized for and initiated at the time of or within 30 days post-decompensation	• The time averaged proportional change in NT-proBNP from Baseline to Weeks 4 and 8.
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To determine the effect of sacubitril/valsartan vs. valsartan on the composite hierarchical outcome consisting of: a) time to CV death, b) total HF hospitalizations, c) total urgent HF visits, and d) time-averaged proportional change in NT-proBNP (from baseline to weeks 4 and 8) using win ratio methodology	• The composite hierarchical outcome consisting of: a) time to CV death, b) number and times of HF hospitalizations during follow-up, c) number and times of urgent HF visits during follow-up, and d) time averaged proportional change in NT-proBNP (from baseline to Weeks 4 and 8)
• To assess the effect of sacubitril/valsartan vs. valsartan on total composite events based on CV death, HF hospitalizations, and urgent HF visits	• The cumulative number of recurrent composite events overtime, i.e., the total number of composite events of HF hospitalizations, urgent HF visits, and CV death.
• To assess the effect of sacubitril/valsartan vs. valsartan on the incidences of a composite endpoint of worsening renal function (renal death, reaching ESRD, or decline in eGFR >/= 50%)	• The incidences of a composite endpoint of worsening renal function, defined as: o renal death o reaching end-stage renal disease (ESRD) o ≥ 50% decline in estimated glomerular filtration rate (eGFR) relative to baseline
• To assess the effect of sacubitril/valsartan vs. valsartan on	• Proportional change in NT-proBNP from baseline to Week 8

[redacted]

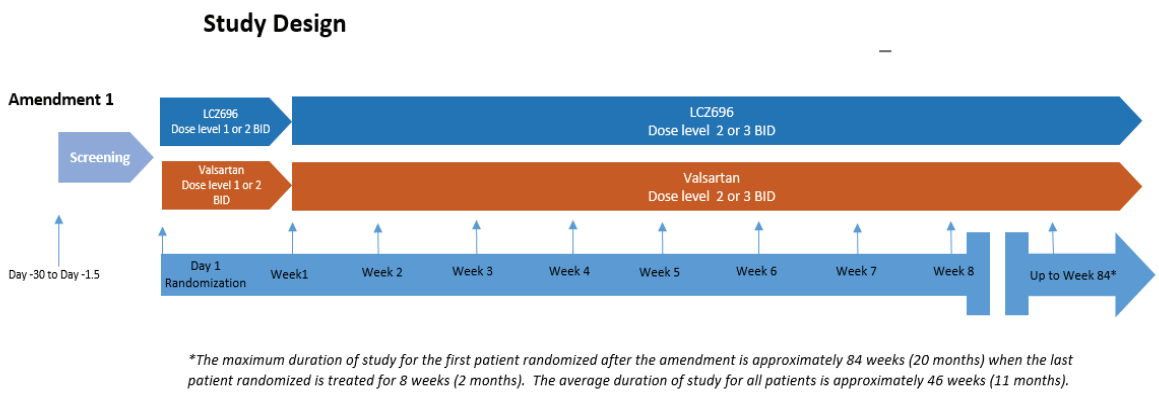
Objective(s)	Endpoint(s)
change in NT-proBNP from baseline to Week 8	
• To assess the effect of sacubitril/valsartan vs. valsartan on change from baseline in hs-Troponin (high sensitivity) at Weeks 4 and 8	• Proportional change from baseline in hs-Troponin (high sensitivity) at Weeks 4 and 8
• To assess the effect of sacubitril/valsartan vs. valsartan on tolerability and the incidence of adverse events of special interest during treatment	• Dosing levels and discontinuations • Incidence of symptomatic hypotension during treatment • • Incidence of hyperkalemia (potassium >5.5 mEq/L) • Incidence of angioedema • Incidence of worsening renal function, defined as an increase in serum creatinine of ≥0.5mg/dl and worsening of the eGFR by at least 25%

[redacted]

[redacted]

3 Study design

Figure 3-1 Study Design



**The maximum duration of study for the first patient randomized after the amendment is approximately 84 weeks (20 months) when the last patient randomized is treated for 8 weeks (2 months). The average duration of study for all patients is approximately 46 weeks (11 months).*

This study will use a randomized, double-blind, double-dummy, active-controlled, parallelgroup design. Eligible patients will be randomized either during hospitalization for, or within 30 days of, a WHF event (HFpEF decompensation). A WHF event (HFpEF decompensation) is defined as a hospitalization, emergency department (ED) visit or out-of-hospital urgent HF visit, all requiring IV diuretics.

[redacted]

Randomized patients will have been hemodynamically stabilized defined in this study as:

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

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

Patients will be randomized 1:1 to sacubitril/valsartan or valsartan. Initial dose at randomization will be determined based on the patient's previous dose of or lack of ACEi/ARB immediately prior to current WHF event (HFpEF decompensation), or at the time of post-decompensation randomization.

Patients currently or recently taking ACEi: In order to provide for a necessary 36-hour washout of prior ACEi treatment before receiving sacubitril/valsartan, eligible patients will be randomized no earlier than 36 hours from their last ACEi dose. Hospital medication administration and medication reconciliation records should be reviewed to confirm that eligible patients have not received ACEi for at least 36 hours prior to randomization and the first dose of study medication.

The maximum duration of study for the first patient randomized after the amendment is approximately 20 months; the anticipated minimum follow-up would be for 8 weeks.

4 Rationale

4.1 Rationale for study design

Hospitalization for ADHF identifies patients at increased risk of death and re-hospitalization following discharge. This increased risk justifies intervention with novel treatment strategies initiated prior to hospital discharge to improve patient outcomes.

The PARADIGM-HF and PARAMOUNT trials demonstrated reductions in NT-proBNP compared to the comparator enalapril and valsartan, respectively, in patients with chronic reduced ejection fraction and preserved ejection fraction heart failure (McMurray et al 2014; Packer et al 2015; Solomon et al 2012).

PARAGON-HF demonstrated increased risk of events in HFpEF patients who were recently hospitalized and the benefit from sacubitril/valsartan appeared greater in those patients hospitalized within 30 days of screening, compared to those hospitalized greater than 30 days or never previously hospitalized (Vaduganathan et al 2019).

The PIONEER-HF trial evaluated the effect of in-hospital initiation of sacubitril/valsartan vs. enalapril in patients with HFrEF who had been stabilized during hospitalization for ADHF. PIONEER-HF demonstrated greater reduction in NT-proBNP with sacubitril/valsartan vs. enalapril in time-averaged proportional change in NT-proBNP from baseline to weeks 4 and 8

[redacted]

(percent change, -46.7% vs. -25.3%; ratio of change with sacubitril/valsartan vs. enalapril 0.71 [0.63 – 0.81], p<0.001) and a decrease in the pre-specified, exploratory, serious clinical composite outcome of death, re-hospitalization for heart failure, LVAD implantation, or listing for cardiac transplant (Velazquez et al 2018). This current trial (PARAGLIDE-HF) will build upon the data generated through the PIONEER-HF trial by specifically studying patients with HFpEF and ADHF. PARAGLIDE-HF will have a similar primary end-point of NT-proBNP to PIONEER-HF, but will also include patients randomization during a WHF event (requiring IV diuretics) and within thirty days post-decompensation. The duration of PARAGLIDE-HF will be up to 20 months to account for accrual of the secondary outcome events.

The need for a 36-hour wash-out period is required per the FDA approved USPI label because there is a potential for increased risk for angioedema in patients who receive both an ACE inhibitor and the combination of sacubitril/valsartan. The requirement to stop the ARB is because there is an ARB contained within sacubitril/valsartan combination.

4.2 Rationale for dose/regimen and duration of treatment

Sacubitril/valsartan 97/103 mg BID was selected as the target dose. This is the USPI approved target dose of sacubitril/valsartan in patients with HFrEF and is the target dose studied in the phase III PARAGON-HF trial in patients with HFpEF (Solomon et al 2019). This dose of sacubitril/valsartan delivers similar exposures of valsartan as Diovan 160 mg BID, the maximal approved Diovan dose for heart failure and the dose recommended in international guidelines for the treatment of heart failure. In addition, biomarker analysis (increase in ANP and cGMP) indicates that this sacubitril dose delivers approximately 90% of its maximal neutral endopeptidase (NEP) inhibition Dosing with 97/103 mg twice daily is to ensure sustained NEP inhibition over 24 hours, which is thought to be critical for patients with heart failure. Both the PIONEER-HF and TRANSITION studies demonstrated that patients with heart failure with reduced ejection fraction could be safely initiated on sacubitril/valsartan in the hospital after stabilization of an ADHF episode (Velazquez et al 2018, Wachter et al 2018).

In PARAGON-HF, HFpEF patients were followed for a median time of 35 months (interquartile range, 30 to 41) with no new safety signal seen, and consistent safety to PARADIGM-HF. In this study, the duration of treatment will be from 8 weeks (minimum) to approximately 20 months (maximum). The longer duration of follow-up allows for more events to occur, facilitating more accurate assessment of the clinical outcome secondary endpoints..

4.3 Rationale for choice of comparator

To date, there is no evidence-based, guideline-recommended, pharmacologic therapy for HFpEF patients that has been proven to reduce morbidity and mortality (Yancy et al 2013). Valsartan is being given to treat the comorbidities that are prevalent in HFpEF, such as HTN, DM, and coronary artery disease where there is an indication for RAS blocking therapy (McMurray et al 2012). For the same reason, background ACEIs or ARBs were permitted in other outcomes studies in HFpEF for treating comorbidities, including TOPCAT, where a RAS blocker was used in 85% of patients at baseline (Desai et al 2011).

[redacted]

Valsartan was chosen as the RAS blocker comparator because it is a commonly prescribed ARB and the target dose of sacubitril/valsartan (LCZ696) delivers systemic exposure similar to the target dose of valsartan for heart failure. It was also the comparator used in both the PARAMOUNT study as well as in the PARAGON-HF study in patients with HFpEF.

A placebo comparator is not considered appropriate in this trial, as the comorbidities commonly present in HFpEF patients require RAS inhibition (i.e., ACEI or ARB). RAS inhibition should not be used concomitantly with LCZ696 due to the potential increased risk of angioedema (ACEI), and because LCZ696 already provides AT1 blockade (ARB).

4.4 Purpose and timing of interim analyses/design adaptations

There is no planned interim analysis for efficacy in the study. See Section 12.8 for sample size calculation for the primary endpoint. See Section 10.2.2 and Section 12.7 for descriptions of the Data Monitoring Committee and interim safety assessments.

4.5 Risks and benefits

In order to minimize the interaction between an ACEi and sacubitril in potentiating the development of angioedema, patients cannot receive ACEi for 36 hours prior to the first dose of study medication. To help ensure this documented washout, patients currently or recently taking ACEi will not be eligible for randomization until at least 36 hours from their last ACEi dose. Medication administration records should be reviewed to insure no ACEi was administered for at least 36 hours prior to the first dose of study medication.

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

Women of child bearing potential and sexually active males 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 highly effective contraception requirements outlined in the exclusion criteria. If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

Participating patients will benefit from careful monitoring and follow-up during the entire study duration regardless of whether they are receiving study medication.

5 Population

The study population will consist of male and female patients, ≥ 18 years of age, currently hospitalized for or within 30 days of a WHF event (HFpEF decompensation). A WHF event (HFpEF decompensation) is defined as a hospitalization, emergency department (ED) visit or out-of-hospital urgent HF visit, all requiring IV diuretics. A total of approximately 450 patients

[redacted]

will be randomized to sacubitril/valsartan or valsartan in a 1:1 ratio at approximately 130 centers in the United States and Canada

Patients are defined as, (1) those randomized and completing the trial according to the Original Protocol Version 00, and (2) those randomized (or eligible and re-consented Original protocol patients) based on Amendment 1, which will be pooled for the final analysis (including a sensitivity analysis to ensure consistency (see Section 12.4.3).

A total of approximately 450 patients will be randomized to sacubitril/valsartan or valsartan in a 1:1 ratio at approximately 130 centers.

Randomized patients will have been hemodynamically stabilized defined in this study as:

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

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

5.1 Inclusion criteria

Patients eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Patients ≥18 years of age, male or female
3. Current hospitalization for WHF (HFpEF decompensation), or within 30 days of discharge following a WHF event (defined as hospitalization, emergency department (ED) visit or out-of-hospital urgent HF visit, all requiring IV diuretics). Patients with a diagnosis of acute heart failure had to have symptoms and signs of fluid overload (i.e. jugular venous distention, edema or rales on auscultation or pulmonary congestion on chest x-ray). Eligible patients will be randomized after IV diuresis for HFpEF is given (and no earlier than 36 hours from their last ACEi dose if applicable) and within 30 days post-decompensation after presentation with acute HFpEF decompensation and meeting the following definitions of hemodynamic stability:

   Randomized patients will have been hemodynamically stable defined in this study as:

   a. SBP≥100mmHg for the preceding 6 hours prior to randomization; no symptomatic hypotension
   b. No increase (intensification) in IV diuretic dose within last 6 hours prior to randomization
   c. No IV inotropic drugs for 24 hours prior to randomization
   d. No IV vasodilators including nitrates within last 6 hours prior to randomization

4. HFpEF with most recent LVEF >40% (within past 3 months)

[redacted]

5. Elevated NT-proBNP or BNP at the time of acute HFpEF decompensation or post-decompensation screening (and within 72 hours for post-decompensation randomization, if applicable):Patients not in AF at the time of biomarker assessment: NT-proBNP ≥ 500pg/mL or BNP ≥ 150 pg/mL; patients in AF at the time of biomarker assessment: NT-proBNP ≥ 1000pg/mL or BNP ≥ 300 pg/mL
   a. Patients recruited in-hospital will be randomized based on the qualifying local lab value in-hospital NT-proBNP or BNP value.
   b. Patients enrolled post-decompensation can be randomized based on their NT-proBNP or BNP value in the following way:
      - if enrolling in post-decompensation setting then need eligible screening/local NT-proBNP/BNP within 72 hours of randomization. The test value could be from recent hospitalization if within 72 hours or
      - would require (re)drawing NT-proBNP or BNP labs in post-decompensation setting if the lab value is not already available within the last 72 hours
6. Has not taken an ACEi for 36 hours prior to randomization

5.2 Exclusion criteria

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

1. Any clinical event within the 90 days prior to randomization that could have reduced the LVEF (i.e., MI, CABG), unless an echo measurement was performed after the event confirming the LVEF to be >40%
2. Entresto™ (sacubitril/valsartan) usage within the past 60 days
3. eGFR < 20ml/min/1.73 m2 as measured by the simplified Modification of Diet in Renal Disease (MDRD) formula at most recent assessment prior to randomization and within 24 hours prior to inpatient randomization or 72 hours prior to outpatient randomization
4. Serum potassium > 5.2 mEq/L at most recent assessment prior to randomization and within 24 hours prior to inpatient randomization or 72 hours prior to outpatient randomization
5. Acute coronary syndrome, stroke, transient ischemic attack; cardiac, carotid or other major CV surgery; percutaneous coronary intervention (PCI) or carotid angioplasty, within 30 days prior to randomization
6. Probable alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms (i.e. dyspnea, fatigue) such as significant pulmonary disease (including primary pulmonary HTN), anemia or obesity.
7. Isolated right HF in the absence of left-sided structural heart disease
8. History of hypersensitivity (i.e. including angioedema), known or suspected contraindications, or intolerance to any of the study drugs including ARNIs (i.e. sacubitril/valsartan), and/or ARBs

[redacted]

9. Patients with a known history of angioedema due to any etiology
10. Patients with a history of heart transplant or LVAD, currently on the transplant list, or with planned intent to implant LVAD or CRT device within the initial three months of enrollment during the trial
11. A cardiac or non-cardiac medical condition other than HF with an estimated life expectancy of < 6 months
12. Known pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy including suspected or confirmed amyloid heart disease (amyloidosis)
13. Life-threatening or uncontrolled dysrhythmia, including symptomatic or sustained ventricular tachycardia and atrial fibrillation or flutter with a resting ventricular rate >110 bpm
14. Clinically significant congenital heart disease felt to be the cause of the patient's symptoms and signs of HF
15. Coronary or carotid artery disease or valvular heart disease likely to require surgical or percutaneous intervention within the duration of the trial
16. Any surgical or medical condition, which in the opinion of the investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study
17. 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
18. Participation in any other clinical trial involving investigational agents or devices within the past 30 days
19. Current confirmed COVID19 infection
20. Past COVID19 infection with persistent symptom burden suspected due to COVID19
    - Persistent symptoms may include, but are not limited to, continued cough, breathing difficulty, muscle/joint aches, and gastrointestinal symptoms from the time of COVID19 infection onward.
21. 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.
22. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of investigational drug and for 7 days off of study drug. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment

[redacted]

- Male sterilization (at least 6 months prior to Visit 1). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
- 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

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment

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) 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.

In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the ICF.

6 Treatment

6.1 Study treatment Investigational and control drugs

The study treatment in Table 6-1 will be provided until the last patient appropriately randomized has had the opportunity of at least eight (8) weeks of follow-up in accordance to the protocol.

Novartis will supply the investigators with all study medications required for the course of the study. Patients will be provided with study drug corresponding to their assigned treatment arm and dose level, sufficient to last until the next scheduled visit.

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.

Both sacubitril/valsartan and valsartan 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.

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Sacubitril/valsartan 24/26mg BID	Tablet	Oral use	Double Blind supply; bottles	Sponsor (global)

[redacted]

Sacubitril/valsartan 49/51mg BID	Tablet	Oral use	Double Blind supply; bottles	Sponsor (global)
Sacubitril/valsartan 97/103mg BID	Tablet	Oral use	Double Blind supply; bottles	Sponsor (global)
Sacubitril/valsartan matching placebo	Tablet	Oral use	Double Blind supply; bottles	Sponsor (global)
Valsartan 40mg BID	Tablet	Oral use	Double Blind supply; bottles	Sponsor (global)
Valsartan 80mg BID	Tablet	Oral use	Double Blind supply; bottles	Sponsor (global)
Valsartan 160mg BID	Tablet	Oral use	Double Blind supply; bottles	Sponsor (global)
Valsartan matching placebo	Tablet	Oral use	Double Blind supply; bottles	Sponsor (global)

Table 6-2 Treatment Dose Levels

Dose Level	Sacubitril/valsartan	Valsartan
1	24/26 mg [50mg] BID	40 mg BID
2	49/51 mg [100mg] BID	80 mg BID
3	97/103 mg [200 mg] BID	160 mg BID

Each participating hospital will be provided with the patient's initial supply of study medication. Bottles will be numbered and assigned via an Interactive Response Technology (IRT).

Sacubitril/valsartan dose or valsartan dose levels may be increased to the targeted desired dose of 97/103 mg twice daily or valsartan 160 BID on an every 2-week basis or earlier if based on clinical need and investigator judgment. Every effort should be made to titrate to and maintain patients on the target dose level, as tolerated by the patient.

Patients not tolerating the target dose of sacubitril/valsartan 97/103 mg BID or valsartan 160 mg BID will be titrated down to the lower dose level (including active medication and matching placebos), at the investigator's discretion, based on the defined safety and tolerability criteria. Per the guidance in Section 6.4.1, every attempt should be made to uptitrate again is the patient's status allows.

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

[redacted]

6.1.1 Treatment arms/group

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

6.1.2 Treatment duration

The planned duration of treatment is up to approximately 20 months of double-blind treatment and the last patient randomized will be followed for a minimum of 8 weeks. Patients may be discontinued from treatment earlier due to unacceptable toxicity, disease progression and/or if treatment is discontinued at the discretion of the investigator or the patient. Every attempt should be made to maintain patients on the target study drug dose level for as long as possible throughout the study.

6.1.3 Concomitant therapy

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

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. If the patient is already enrolled, contact Novartis to determine if the patient should continue participation in the study.

6.1.3.1 Permitted concomitant therapy requiring caution and/or action

Other heart failure and cardiovascular medication

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

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

Medications known to raise potassium levels

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

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

Phosphodiesterase-5 (PDE-5) inhibitors

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

[redacted]

6.1.4 Prohibited medication

Use of the treatments displayed in the table below is NOT allowed after the baseline phase. Please note the list of prohibited medication is not exhaustive. If you have any questions, the medical monitor should be contacted.

Table 6-3 Prohibited medication

Medication	Prohibition period	Action taken
Any ACEIs Inhibitor	Duration of study	Discontinue study drug. The open label ACEI must be stopped for ≥36 hours prior to re-initiation of study drug
Any Angiotensin Receptor Blocker	Duration of study	Discontinue study drug. The open label ARB must be stopped prior to re-initiation of study drug
Aliskiren (in patients with concurrent diabetes or those with renal impairment [eGFR < 60 mL/min/1.73 m²])	Duration of study	Discontinue study drug. The open label renin inhibitor must be stopped prior to re-initiation of study drug
Nesiritide and intravenous nitrates	Duration of study	Do not randomize. If hospitalized, either interrupt or discontinue study treatment. Concomitant administration of sacubitril/valsartan with nesiritide and intravenous nitrates has not been studied. Oral, topical and sublingual nitrates are permissible.
Bile acid sequestering agents (such as cholestyramine or colestipol)	Duration of study	Switch to alternate agent to avoid interference with study drug absorption. If use of alternate agent is not appropriate, do not randomize or discontinue study drug treatment.

ACEIs and ARBs

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

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

Nesiritide and intravenous nitrates

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

Other medications

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

[redacted]

6.1.5 Rescue medication

At any time during the study investigators have the option to discontinue 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.
- **Patients CANNOT receive ACEIs and/or ARBs 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.**
- If the investigator has not made the decision to permanently discontinue study treatment, then the patient can resume study treatment as long as the 36-hours ACEI washout was observed.
- **A 36-hour wash-out period is required if the investigator chooses to withdraw the patient from study treatment and switch to ACEI due to symptoms of worsening heart failure.**
- Use of rescue medication must be recorded on the appropriate Concomitant Medications eCRF.

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

6.2 Patient numbering, treatment assignment, randomization

6.2.1 Patient numbering

Each patient is uniquely identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient No. available 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).

6.2.2 Treatment assignment, randomization

At randomization visit, all eligible patients 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 treatment to be dispensed to the patient.

[redacted]

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the 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 Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to bottles containing the study treatment.

The randomization scheme for patients will be reviewed and approved by Novartis.

Initial dose at randomization will be determined based on the patient's previous dose of or lack of ACEi/ARB immediately prior to current WHF event (HFpEF decompensation), or at the time of post-decompensation randomization. Dose adjustments to lower dose levels may be made at any time at both scheduled and unscheduled visit only if clinically indicated for blood pressure control or tolerability reasons. Dose adjustments to increase dose levels may be made at any time at both scheduled and unscheduled visits based on clinical need or investigator judgment.

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

6.3 Treatment blinding

Patients, investigator staff, persons performing the assessments, and 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, members of the Data Monitoring Committee (DMC) and the independent biostatistician and programmer assigned to the DMC. (2) The identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

Unblinding may be considered in the case of patient emergencies. It is highly recommended that the investigator/site coordinator contact the Novartis Medical Monitor to discuss any unblinding concerns, as most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study person who presents with an

[redacted]

emergency condition. Full unblinding will occur at the conclusion of the study, after database lock.

6.4 Dose modification

6.4.1 Dose modifications

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or mandated in order to allow patients to continue the study treatment.

Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent treatment discontinuation is mandatory for specific events listed in Section 9.1.1.

These dose changes must be recorded on the appropriate case report form (CRF).

Every attempt should be made to maintain patients on the target study drug dose level for as long as possible throughout the study. If, however, in the opinion of the investigator, a patient is unable to tolerate the protocol-specified target dose, the investigator should consider whether dose adjustments of concomitant medications may rectify the situation before reducing the dose of study treatment. If adjustment of the concomitant medications is not possible or does not alleviate the side effects of concern, the investigator may down-titrate the dose of the study drug to the previous dose level. If needed, the study drug may be stopped completely, if this occurs, the patient should return to the clinic as soon as possible, after discontinuation of study drug, for an end of study visit. Patients may restart their current dose of study drug following an interruption of treatment, based on investigator judgment.

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

- Hyperkalemia
- Symptomatic hypotension
- Clinically significant decrease in eGFR/increase in serum creatinine (defined as a serum creatinine of $\geq$ 0.5mg/dl with at least a 25% decrease in eGFR)
- Angioedema

These changes must be recorded on the appropriate CRF. Every attempt should be made to titrate to and maintain patients on target study drug Dose Level 3 for as long 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:

Steps:

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;

[redacted]

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 1 to a maximum of 4 weeks. 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, every effort must be made to complete an end of study visit and obtain follow up health status information and NT-proBNP for any patient that withdraws from the study.

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 appropriate eCRF.

[redacted]

Study visits should occur as close as possible to the pre-defined visit and time schedule described in Table 8-1. 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.

6.4.2 Follow-up for 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.

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

The investigator may be also contacted by Novartis regarding AEs that may resemble an angioedema-like event. A list of terms that are considered 'angioedema-like' will be provided to sites in a manual.

Details on the procedures for reporting angioedema events will be provided to investigators in a manual.

6.5 Additional treatment guidance

6.5.1 Treatment compliance

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

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

6.5.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. 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

[redacted]

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 that the code has been broken.

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

- protocol number
- patient number

In addition, oral and written information to the patient 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.

6.6 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

A unique medication number is printed on the study medication label. Investigator staff will identify the study medication bottles to dispense to the patient by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication bottle to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

During the COVID-19 pandemic that limits or prevents on-site study visits, delivery of IP directly to a participant's home is generally permitted in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. Implementation will need to be discussed with Novartis. The dispatch of IP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 4-months supply. In this case, regular phone calls or virtual contacts are suggested per Investigator discretion based on patient stability and status until the participants can again visit the site.

6.6.1 Handling of study treatment and additional treatment

6.6.1.1 Handling of study treatment

Study 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 designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis US Quality Assurance.

[redacted]

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.

6.6.2 Instruction for prescribing and taking study treatment

All medication for the duration of the study will be provided by Novartis. Eligible patients will be randomized via IRT to either sacubitril/valsartan or valsartan.

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

Initial dose at randomization will be determined based on the patient's previous dose of or lack of ACEi/ARB immediately prior to current WHF event (HFpEF decompensation), or at the time of post-decompensation randomization.

- For patients who were not being treated with ACEi/ARB at the time of presentation to hospital, or at the time of post-decompensation randomization, the starting dose should be dose level 1.
- For patients with an estimated GFR of ≥20 to <30 mL/min/1.73 m2, regardless of ACEi/ARB dose at the time of presentation to hospital or post-decompensation randomization, should be initiated at dose level 1.
- Those patients previously treated with low dose of ACEi/ARB (Table 6-4) should be initiated at dose level 1.
- For patients previously treated with high dose ACEi/ARB (Table 6-4), the starting dose is dose level 2.

Table 6-5 summarizes the starting dose of study medication based on RASi stratum at time of patient presentation to the hospital, or at the time of post-decompensation randomization.

The target dose for sacubitril/valsartan is 97/103 mg BID and for valsartan is 160 mg BID (dose level 3). Every attempt should be made to titrate to and maintain patients on the target study drug dose level for as long as possible throughout the study. However, maximal doses for study medication will be determined by the investigator based upon the patient's clinical status. It is recommended that patients remain at each dose level during up-titration for 1 to 2 weeks such that patients initiated at dose level 1 reach target dose in 2 to 4 weeks and those patients initiated at dose level 2 reach target dose in 1 to 2 weeks. In certain circumstances, longer up-titration periods may be required as deemed necessary by the investigator.

[redacted]

If patients cannot tolerate the target dose of study medication (dose level 3), down titration to a lower dose is allowed (see Section 6.4). Patients should be re-challenged to the target dose of study medication when their condition permits up-titration based on their systolic blood pressure (SBP), eGFR, potassium values, and at the investigator's discretion. However, patients can remain at low doses (level 1 or 2), based on their tolerability and clinical judgment of the investigator.

Up titration may be done prior to the week 1 visit at the investigator's discretion i.e., if concerned about managing hypertension.

Table 6-4 Definition of low and high total daily doses for commonly used ACEIs and ARBs

ACEi/ARB	Low RASi stratum (total daily dose)	High RASi stratum (total daily dose)
ACEis		
Enalapril	≤ 10 mg	> 10 mg
Benazepril	≤ 20 mg	> 20 mg
Captopril	≤ 100 mg	> 100 mg
Fosinopril	≤ 20 mg	> 20 mg
Lisinopril	≤ 10 mg	> 10 mg
Moexipril	≤ 7.5 mg	> 7.5 mg
Perindopril	≤ 4 mg	> 4 mg
Quinapril	≤ 20 mg	> 20 mg
Ramipril	≤ 5 mg	> 5 mg
Trandolapril	≤ 2 mg	> 2 mg
ARBs		
Candesartan	≤ 16 mg	> 16 mg
Eprosartan	≤ 400 mg	> 400 mg
Irbesartan	≤ 150 mg	> 150 mg
Losartan	≤ 50 mg	> 50 mg
Olmesartan	≤ 10 mg	> 10 mg
Telmisartan	≤ 40 mg	> 40 mg
Valsartan	≤ 160 mg	> 160 mg

Table 6-5 Starting dose of study medication

RASi stratum at time of presentation to hospital or at the time of post-decompensation randomization*	Starting dose level of study medication
Patients not being treated with ACEi/ARB at the time of presentation to hospital or at the time of out-of-hospital randomization	Dose level 1

[redacted]

Estimated GFR ≥20 and <30 mL/min/1.73 m2, regardless of ACEi/ARB dose at the time of presentation to hospital or post-decompensation randomization	Dose level 1
Low dose ACEi/ARB	Dose level 1
High dose ACEi/ARB	Dose level 2

* A 36-hour washout of prior ACEi treatment is required before administering sacubitril/valsartan. Eligible patients hospitalized for ADHF will be randomized no earlier than 36 hours after presentation with acute decompensated heart failure while still hospitalized and no later than 30 days post-decompensation (with a 36 hour-washout period from their last outpatient ACEi dose).

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

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

All bottles of study treatment assigned by the IRT will be recorded in the IRT system.

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

7 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the patient's representative(s) gives consent (if allowed according to local requirements), 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 agreement by personally signing and dating the written informed consent document.

During the COVID-19 pandemic that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference). Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc).

For continuity of trial procedures, the Investigator may continue to conduct the informed consent discussion remotely as described above for the remainder of the trial, or as otherwise described by local regulatory bodies.

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.

[redacted]

Eligible patients enrolled in the Original Protocol (Version 00) must sign a new informed consent form to participate in Amendment 1 (Protocol Version 01). Eligible patients are defined as those currently enrolled in the double-blind treatment period of the Original Protocol at the time of each site's Amendment 1 IRB approval.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's 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 investigational drug 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 then must be discussed with the patient.

Women of childbearing 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 requirements.

Male patients must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments and when they are performed for participants consented to Protocol Amendment V04. See Section 16.5 Appendix 5 for Expanded Assessment Schedule, which includes visit assessments for Protocol Amendment V04 and previous protocol amendment versions. All data obtained from these assessments must be supported in the patient's source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. 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 the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

If the COVID-19 pandemic limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Virtual visits [e.g. phone calls, video visits (preferred)] or visits by site staff/home nursing service to the participant´s home

[redacted]

depending on local regulations and capabilities, can replace on-site study visits, for the duration of the pandemic until it is safe for the participant to visit the site again.

[redacted]

Table 8-1 Assessment Schedule

Period	**Screening**	**Double-Blind Treatment (84 week)**								
Visit Name	**Screening**	**Randomization/Baseline**								**Study Completion/ End of Study**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 5**	**Visit 7**	**Visit 11**	**Visit 13**	**Visit 15**	**Visit 16**	**Visit 17**
Week (Day)	**[Day -30 to -1.5 (36hours)]**	**0 (Day 1)**	**1 (Day 7)**	**4 (Day 28)**	**8 (Day 56)**	**24 (Day 168)**	**40 (Day 280)**	**56 (Day 392)**	**68 (Day 476)**	**84 (Day 588)**
Information and informed consent	S									
Inclusion/exclusion criteria	X	X								
Demography / Medical history	X									
Heart failure and CV disease history	X									
ECG	X									
Physical Exam	S			S	S	S	S	S	S	S
Height	X	X								
Weight	X	X	X	X	X	X	X	X	X	X
Waist/hip circumference	X									
Vital Signs	X	X	X	X	X	X	X	X	X	X
HF signs and symptoms and NYHA classification	X	X	X	X	X	X	X	X	X	X
Heart failure and CV medications	X	X[4]	X	X	X	X	X	X	X	X

[redacted]

Period	**Screening**	**Double-Blind Treatment (84 week)**								
Visit Name	**Screening**	**Randomization/Baseline**								**Study Completion/ End of Study**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 5**	**Visit 7**	**Visit 11**	**Visit 13**	**Visit 15**	**Visit 16**	**Visit 17**
Week (Day)	**[Day -30 to -1.5 (36hours)]**	**0 (Day 1)**	**1 (Day 7)**	**4 (Day 28)**	**8 (Day 56)**	**24 (Day 168)**	**40 (Day 280)**	**56 (Day 392)**	**68 (Day 476)**	**84 (Day 588)**
Chemistry labs	X	X	X	X	X	X	X	X	X	X
Hematology labs	X	X			X	X	X	X	X	X
Hemoglobin A1C		X								X
eGFR	X	X	X	X	X	X	X	X	X	X
Urinalysis		X								
Pregnancy Test[2]	X	X		X	X	X	X	X	X	X
IRT	X	X	X	X	X	X	X	X	X	X
Randomization		X								
Plasma NT-proBNP or BNP	X[5]	X	X	X	X					
hs-Troponin		X		X	X					
[redacted]										
Drug accountability			X	X	X	X	X	X	X	X
Dispense study treatment		X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X

[redacted]

Period	**Screening**	**Double-Blind Treatment (84 week)**								
Visit Name	**Screening**	**Randomization/Baseline**								**Study Completion/ End of Study**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 5**	**Visit 7**	**Visit 11**	**Visit 13**	**Visit 15**	**Visit 16**	**Visit 17**
Week (Day)	**[Day -30 to -1.5 (36hours)]**	**0 (Day 1)**	**1 (Day 7)**	**4 (Day 28)**	**8 (Day 56)**	**24 (Day 168)**	**40 (Day 280)**	**56 (Day 392)**	**68 (Day 476)**	**84 (Day 588)**
Adverse events / Serious Adverse events	X	X	X	X	X	X	X	X	X	X
Angioedema assessment	X	X	X	X	X	X	X	X	X	X
Thank You letter		X								X
[redacted]										
Study completion – randomized treatment										X
Post study completion follow up										S[6]

[redacted]

Period	Screening	Double-Blind Treatment (84 week)								
Visit Name	Screening	Randomization/Baseline								Study Completion/ End of Study
Visit Number	Visit 1	Visit 2	Visit 3	Visit 5	Visit 7	Visit 11	Visit 13	Visit 15	Visit 16	Visit 17
Week (Day)	[Day -30 to -1.5 (36hours)]	0 (Day 1)	1 (Day 7)	4 (Day 28)	8 (Day 56)	24 (Day 168)	40 (Day 280)	56 (Day 392)	68 (Day 476)	84 (Day 588)

X = assessment to be recorded in the clinical database or received electronically from a vendor
S = assessment to be recorded in the source documentation and in the database
[redacted]
[2] All female patients of childbearing potential will have a serum pregnancy test (hCG) performed at Visit 1 (local lab). A urine pregnancy test will be conducted in the local laboratory for remaining visits
[4] CV medications will be recorded at time of hospital discharge.
[5] BNP or NT-proBNP will be assessed at Visit 1 via local laboratory. Only NT-proBNP will be assessed via central laboratory for Visits 2, 3, 5 and 7.
[6] Health status phone call 4 weeks after study completion.

[redacted]

8.1 Screening

A patient who enters screening but is determined not to be eligible will be considered a screen failure. The investigator may consider re-screening the patient at a later time if he/she believes that the patient's condition has changed and they may potentially be eligible. In this case, a new patient number will be allocated to the subject and he/she will need to re-perform all Visit 1 procedures. A patient may be re-screened once. A minimum of 24 hours must elapse between screen failure and re-screening. The patient must provide new written informed consent before they are re-screened.

8.1.1 Information to be collected on screening failures

Patients who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, Inclusion/Exclusion pages and Protocol Amendment Log must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a serious adverse event during the screening phase (see SAE section for reporting details). If the patient fails to be randomized, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

Patients who are randomized and fail to start treatment, e.g. patients randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Patient demographics/other baseline characteristics

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

8.3 Efficacy

The efficacy endpoints are:

Primary variable:

- Time averaged proportional change in NT-proBNP from baseline to Weeks 4 and 8

Secondary variables:

- The composite hierarchical outcome consisting of: a) time to CV death, b) number and times of HF hospitalizations during follow-up, c) number and times of urgent HF visits during follow-up, and d) time averaged proportional change in NT-proBNP (from baseline to Weeks 4 and 8) using win ratio analysis of composite hierarchical outcome

[redacted]

- The cumulative number of composite events, i.e., the composite events of CV death, total HF hospitalizations, and total urgent HF visits for a given subject, over time.
- The incidences of a composite endpoint of worsening renal function (renal death, reaching ESRD, or > 50% decline in eGFR relative to baseline)
- Change in NT-proBNP from baseline to Week 8
- Change from baseline in hs-Troponin (high sensitivity) at Weeks 4 and 8
- Dosing levels, discontinuations, and the incidence of adverse events of special interest during treatment

[redacted]

8.3.1 Heart failure signs and symptoms

Signs and symptoms of heart failure will be reviewed by the investigator at all in-person 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 documented at each visit.

8.3.2 Estimated glomerular filtration rate (eGFR)

The eGFR to determine eligibility of the patient for screening into the trial will be calculated at Visit 1 from the serum creatinine concentration measured at the local laboratory. The eGFR will be further calculated from creatinine concentration measured at Visits 2, 3, 5, 7, 11, 13, 15, and 16 (randomization, Weeks 1, 4, 8, 24, 40, 56, and 68), and end of study (Week 84) at the central laboratory. The eGFR calculation will be based on the Abbreviated Modification of Diet in Renal Disease (MDRD) study equation (Levey, et al 2007).

[redacted]

8.3.3 Biomarkers

BNP or NT-proBNP will be measured in all patients by using the local laboratory at Visit 1 to determine eligibility. NT-proBNP will be measured in all patients using the central laboratory at Visits 2 (randomization), 3, 5, and 7 (Weeks 0, 1, 4, and 8 respectively).

[redacted]

During the COVID-19 pandemic that limits or prevents on-site study visits, or if visits by site staff to a participant's home are not feasible, the collection of standard chemistry and hematology samples may be modified by Novartis and will be communicated to the Investigator. For the primary endpoint biomarkers (Weeks 4 and 8), alternative methods of collecting and ensuring shipment of biomarkers to the central laboratory should be implemented. Alternative methods must comply with guidance issued by local regulatory bodies and be discussed with Novartis.

[redacted]

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

8.3.4 Appropriateness of efficacy assessments

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

8.4 Safety

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

[redacted]

- Incidence of angioedema

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

During the COVID-19 pandemic that limits or prevents on-site study visits, regular phone or virtual calls should occur for safety monitoring and discussion of the participant´s health status until the participant can again visit the site. If a participant cannot visit the site to have pregnancy tests done, a home urine pregnancy or central lab pregnancy test kit may be used. Relevant participants can perform the urine pregnancy test at home at the time of the scheduled visit and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the site is informed of the pregnancy test results.

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

Table 8-2 Assessments & Specifications

Assessment	Specification
Physical examination	A complete physical exam will be performed at Visits 1, 5, 7, 11, 13, 15, 16 and 17 (physical exam at visit 2 to be performed only if randomization visit is done on a different calendar date than screening). 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. Information for all physical examinations must be included in the source documentation at the study site (with the exceptions of pandemic-related virtual visits mentioned above). Significant findings that are present prior to the informed consent must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's eCRF. Significant findings made after informed consent which meet the definition of an adverse event must be recorded on the Adverse Event eCRF.
Vital signs	Vital signs will be assessed at every in-person visit, and in cases where the COVID-19 pandemic limits or prevents on-site study visits,. This will include blood pressure and pulse measurements. BP will be measured using a standard sphygmomanometer with an appropriately sized cuff and the non-dominant arm in the sitting position after 5 minutes of rest. Every effort should be made to use the same arm for the patient for all vital signs assessments and where possible, the same person doing the assessment. For virtual visits, documentation of any vital signs available (e.g. home BP cuff results) should be recorded in the eCRF.
Height and weight	Height in centimeters if possible will be measured at Visits 1 and 2. Body weight to the nearest 0.1 kg without shoes, will be measured at Visits 1, 2, 3, 5, 7, 11, 13, 15, 16 and 17.

[redacted]

Assessment	Specification
Waist/hip circumference	Waist/hip circumference to the nearest centimeter will be measured at Visit 1.
Angioedema	Angioedema is a type of abrupt swelling that occurs under the skin and/or mucous membranes and is often localized to the head, neck, throat, and/or tongue, but may occur elsewhere, including the genitalia and intestines. Severe cases may be associated with airway compromise. Although, the mechanism is not fully understood, bradykinin has been implicated as the putative mediator. Therefore, medications that raise the levels of endogenous bradykinin by inhibiting the enzymes responsible for its breakdown, such as ACE, aminopeptidase P, and NEP, may result in this potentially dangerous side effect. All suspected cases of angioedema, regardless of suspected causality, must be reported. The Angioedema Questionnaire must be completed and the Clinical Trial Lead or their designee must be notified. If the angioedema event meets SAE criteria, the investigator must ensure that an SAE form is completed and submitted to Novartis Drug Safety and Epidemiology.

8.4.1 Laboratory evaluations

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

Clinically notable laboratory findings are defined in Appendix 1.

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

[redacted]

Table 8-3 Laboratory Assessments

Test Category	Test Name
Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other (absolute value preferred , %s are acceptable), and platelet count will be measured at Visits 1 (local lab), 2, 7, 11, 13, 15, 16, and 17 (central lab). Hemoglobin A1c will be measured at Visits 2 and 17 (central lab).
Chemistry	Assessments required for eligibility that need to be measured at Visit 1 include creatinine, potassium, and total bilirubin. Blood urea nitrogen (BUN), glucose, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), alkaline phosphatase, sodium, potassium, chloride, calcium , total protein, albumin, uric acid, and lipid profile be measured at Visits 1 (local lab), 2, 3, 5, 7, 9, 11, 13, 15, 16, and 17 (central lab).
Urinalysis	Dipstick-test determination of specific gravity, pH, blood, total protein, bilirubin, ketones, and leukocytes will be measured at Visit 2 (central lab). If dipstick is positive, a qualitative microscopic determination, including white blood cells high power field (WBCs/HPF) and red blood cells high power field (RBCs/HPF) will be performed.
Pregnancy Test	All female patients of childbearing potential will have a serum pregnancy test (hCG) performed at Visit 1 (local lab). In addition, these patients will have a urine pregnancy test conducted in the local laboratory at Visits 2, 5, 7, 11, 13, 15, 16 and 17. If any of these tests are positive at Visits 1 and 2, the patient should not be enrolled in the trial. If a patient should become pregnant during the trial, the patient may remain in the trial for follow-up visits but must discontinue study drug.

8.4.2 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed at Visit 1. Interpretation of the tracing must be made by a qualified physician and documented on the ECG section of the CRF. Each ECG tracing should be labeled with the study, subject number and date and kept in the source documents at the study site.

Clinically significant abnormalities must be recorded on the CRF as either medical history and/or adverse events as appropriate.

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum pregnancy test (hCG) performed at Visit 1 (local lab). In addition, these patients will have a urine pregnancy test conducted in the local laboratory at Visits 2, 5, 7, 11, 13, 15, 16 and 17. . If any of these tests are positive at Visits 1 and 2, the patient should not be enrolled in the trial. If a patient should become pregnant during the trial, the patient may remain in the trial for follow-up visits but must discontinue study drug.

8.4.4 Appropriateness of safety measurements

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

[redacted]

8.5 Additional assessments

Not applicable.

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study treatment 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 he/she believes that continuation would negatively impact the patient's well-being.

Study treatment must be discontinued under the following circumstances:

- Patient/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the patient
- Following emergency unblinding
- Any severe suspected drug related AE at the investigator’s discretion

[redacted]

- Suspected occurrence of angioedema. A patient with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator to determine if it constitutes a reason for discontinuation of study medication.
- Depending on the serum potassium, blood pressure, or eGFR, patient 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 investigator should make a reasonable effort to understand the primary reason for the patient's premature discontinuation of study treatment and record this information.

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section,). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the patient/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

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.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

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

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

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

9.1.2 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

Every effort should be made to encourage trial continuation to collect information regarding the secondary clinical endpoints (CV Death, HF Hospitalization, and Urgent HF Visits) during the longer term follow-up (Amendment 1 and subsequent versions).

[redacted]

In the situation the patient still wants to withdraw, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent and record this information.

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 the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a patient's samples until the time of withdrawal) according to applicable law.

For US: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

9.1.3 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" 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 considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination can include:

- Unexpected, significant, or unacceptable safety risk to patients enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider patient welfare and safety. Should early termination be necessary, patients 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 or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

[redacted]

9.2 Study completion and post-study treatment

At the study completion/end of study visit, patients will be asked to return all remaining study drug. The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. When the patient has completed all scheduled study assessments, the investigator must call the IRT to record the patient completion in the IRT.

Study completion is defined as when the last patient finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision (e.g. Each patient will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them).

The PARAGON-HF Post Trial Access Program (PTA) was stopped after the results of PARAGON-HF became known. The primary endpoint was not met; therefore this met the pre-specified stopping rule for the program. In view of the discontinuation of the PTA program for PARAGON-HF, the company, after careful deliberation, decided to close the PTA for all Entresto HFpEF trials, including PARAGLIDE-HF. This means that the PTA for PARAGLIDE-HF, as documented in the Original Protocol Version 00, will no longer be offered to patients enrolled in PARAGLIDE-HF.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 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 patient or clinical investigation patient after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual patient and identifying adverse events.

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

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 they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

[redacted]

1. The severity grade:

   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 treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment

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

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

6. its outcome (i.e. recovery status or whether it was fatal)

Conditions that were already present at the time of informed consent should be recorded in medical history of the patient.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

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

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

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

[redacted]

- 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 patients with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

10.1.2 Serious adverse events

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:

- fatal
- life-threatening

  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 (please refer to the ICH-E2D Guidelines).
- 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
  - 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
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
  - 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
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

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. Such events should be considered as "medically significant". 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 (please refer to the ICH-E2D Guidelines).

[redacted]

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 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 must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

SAEs occurring after the patient has provided informed consent until the time the patient is deemed a Screen Failure must be reported to Novartis.

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.

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 CMO & PS 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 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.

Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

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.

[redacted]

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 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 recorded on the appropriate CRF 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 within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Study Treatment 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

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Reporting angioedema-like events

It is important that the investigator pays special attention to any swelling or edema that may resemble angioedema or angioedema-like events that may be reported by patients, including during pandemic-related virtual visits when video allows assessment (video is the preferred method for virtual visits). If such an event occurs, the investigator will complete a 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.

Occasionally, the investigator may be contacted by the Novartis regarding AEs that were reported on behalf of patients that may resemble an angioedema-like event. The investigator or his/her delegated staff must complete the required report forms and supply the required medical

[redacted]

records for such events, regardless of whether the investigator views the event in question as angioedema or not.

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 Questionnaire for an Angioedema-like Event.

10.2.2 Data Monitoring Committee

An external data monitoring committee (DMC) independent of Novartis will be appointed to review the incidence of the pre-specified clinical events including major cardiac events, serious adverse events, the rate and distribution of adverse events, and relevant laboratory findings on an ongoing basis.

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

The DMC will review and make recommendations to the sponsor on whether and how to continue the protocol.

10.2.3 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating in the trial, i.e. not being members of the DMC and Novartis/sponsor representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the 'Steering Committee Charter'.

10.2.4 Adjudication committees

Endpoint Adjudication Committee: The role of the Endpoint Adjudication Committee (EAC) is to ensure that all clinical outcomes are judged uniformly, using standard criteria and processes. The EAC will be composed of independent clinical experts to evaluate disease progression and harmonize endpoint assessment criteria using data provided by the sponsor.

All deaths, (re-)hospitalizations, and urgent HF visits will be adjudicated.

All personnel involved in the adjudication process will remain blinded to treatment allocation throughout the trial. Specific details regarding endpoint definitions can be found in the adjudication charter.

[redacted]

11 Data collection and database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs will be built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

Data not requiring a separate written record will be defined in the protocol and the Assessment Schedule (Table 8-1) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

The investigator/designee is responsible for assuring that the data entered into eCRFs are complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Randomization codes and data about all study treatment (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 data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

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.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis/moved to restricted area to be accessed by independent programmer

[redacted]

and statistician. Any changes to the database after that time can only be made after written agreement by Novartis management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis and UBC representative will review the protocol and data capture requirements (i.e. eCRFs) 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 data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized UBC CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. 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 will be disclosed.

12 Data analysis and statistical methods

It is planned that the data from all centers that participate in this study will be combined, so that an adequate number of patients will be available for analysis. Unless otherwise specified, all statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

The final analysis will be conducted on all participant data at the end of the study.

Details on data analysis will be included in the Statistical Analysis Plan (SAP) and will be finalized before the database lock.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

[redacted]

12.1 Analysis sets

The Randomized Analysis Set (RAN) consists of all randomized participants.

The Full Analysis Set (FAS) comprises all participants to whom study treatment has been assigned by randomization. According to the intent-to-treat principle, participants will be included for analysis according to the treatment they have been assigned to during the randomization procedure.

The Safety Set (SAF) includes all participants who received at least one dose of study treatment. Participants will be included for analysis according to the study treatment they received, where treatment received is defined as the randomized treatment if the participant took at least one dose of that treatment or the first study treatment received if the randomized treatment was never received.

The patients in this trial are divided in two groups, (1) Those who are randomized under Protocol Version 00 (Original Protocol patients) and (2) Those who are randomized after site execution of Protocol Version 01 (Amendment 1 and subsequent amendment patients). FAS includes patients from both groups. See Section 3 for details.

12.2 Patient demographics and other baseline characteristics

Baseline value is the last non-missing assessment before the first administration of study drug, unless specified otherwise. Baseline is labeled as Week 0. Summary statistics will be provided by treatment group and baseline classification of in/out-of-hospital randomization.

Continuous variables will be summarized using n, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency and percentage. Additionally, summary statistics will be provided by treatment group and in/out-of-hospital randomization group. Geometric means will be used to summarize the NT-proBNP [redacted].

Relevant medical history and current medical conditions at Baseline will be summarized by system organ class and preferred term, by treatment group.

The FAS will be the population for the above analyses. Summary statistics will be provided for Original Protocol patients, Amendment 1 patients, and all patients in FAS.

12.3 Treatments

The overall duration of treatment by study drug will be summarized by treatment group and in/out-of-hospital randomization category using mean, standard deviation, median, minimum, and maximum. Additionally, the number and percentage of participants will be summarized by treatment group and in/out-of-hospital randomization for duration category. Concomitant medications and significant non-drug therapies, prior to and after the randomization, will be summarized by therapeutic class, preferred term, treatment group, and in/out-of-hospital randomization category. The number and percentage of participants on different HFpEF

[redacted]

background medications (e.g., aldosterone antagonists, β-blockers, diuretics, digoxin) will be tabulated by treatment and in/out-of-hospital randomization category at Baseline and post randomization period. The SAF population will be used for the above analyses.

12.4 Analysis of the primary endpoint

There is one primary endpoint.

Definition of primary endpoint

The primary endpoint is the time averaged proportional change in NT-proBNP from Baseline to Weeks 4 and 8.

12.4.1 Analysis of the primary endpoint

The primary null hypothesis (H_{10}) to be tested is that the ratio of the geometric means of NT-proBNP (average of Weeks 4 and 8) divided by baseline for the sacubitril/valsartan and valsartan groups are equal versus the alternative hypothesis (H_{1a}) that the ratio of the geometric means of NT-proBNP are not equal.

First, the arithmetic mean of NT-proBNP at Weeks 4 and 8 will be calculated, then the change from baseline in log-transformed NT-proBNP will be calculated as follows: *ln (mean post dose value) – ln (baseline value)*. The natural logarithm will be used in all these calculations. This log-transformed value will be used as the dependent variable in the analysis of covariance (ANCOVA) model described below. This dependent variable is called, the time-averaged proportional change from baseline in logarithmic scale. The dependent variable will be analyzed using an ANCOVA model with treatment, in-/out-of-hospital randomization, gender, and baseline LVEF (<= 57%, > 57%) as fixed effect factors, age and the logarithmic baseline NT-proBNP as covariates.

The treatment effect in terms of ratios of geometric means is estimated based on the least-squared means (LS-means) from the ANCOVA model and the corresponding 95% two-sided confidence interval will be provided. Geometric means will be calculated by exponentially back transforming the LS-means based on the fitted ANCOVA model.

The FAS will be used in the main analysis of the primary endpoint.

12.4.2 Handling of missing values/censoring/discontinuations

The analysis will be performed based on all available data in the FAS. Missing values caused due to unevaluable samples or early discontinuations will not be imputed. If either the baseline value or both Weeks 4 and 8 are missing, then the patient will not be included in the analysis.

12.4.3 Sensitivity and Supplementary Analyses

Sensitivity analysis

Robustness of the primary efficacy results will be explored by developing an algorithm to impute missing values in the primary analysis, except the baseline value. Baseline value will

[redacted]

not be imputed. When applicable, multiple imputations technique will be considered for replacing the missing values. Data will be analyzed using the same ANCOVA model used in the primary analysis.

A second sensitivity analysis will be performed based on the Amendment 1 patients only. The analysis will be performed like the main analysis of the primary endpoint.

Additional sensitivity analysis will be performed by excluding assessments after COVID-19 positive status (during the study) at the patient level.

Supplemental analysis

In this supplementary analysis the variable to be analyzed is: Achieving a pre-specified percent change from baseline in NT-proBNP (binary). Three binary outcome variables will be created for patients achieving a 25%, 50% and 75% decline in NT-proBNP (0-no, 1-yes). The dataset used in the primary analysis will be used to define these categorical variables. Also, like the primary analysis, the missing values will not be imputed for this analysis. Logistic regression model will be fitted. The odds ratio, confidence interval and p-value will be provided for each analysis. The dependent variable will be achieving a target decline in NT-proBNP and the predictor of response will be treatment group and in-/out-of-hospital randomization category.

In addition, analysis of the primary endpoint will be performed with patients randomized after Amendment 4 (yes, no) as an additional factor to the model mentioned in Section 12.4.1.

Subgroup analyses

A set of pre-specified subgroups will be defined in the Statistical Analysis Plan to assess consistency of the primary efficacy result and effect of these subgroups on NT-proBNP.

12.5 Analysis of Secondary Endpoints

12.5.1 Secondary endpoints

1. The composite hierarchical outcome consisting of: a) time to CV death, b) number and times of HF hospitalizations during follow-up, c) number and times of urgent HF visits during follow-up, and d) time averaged proportional change in NT-proBNP (from baseline to Weeks 4 and 8)
2. The cumulative number of recurrent composite events overtime, i.e., the total number of composite events of HF hospitalizations, urgent HF visits, and CV death.
3. Incidences of a composite endpoint of worsening renal function defined as:
   - renal death
   - reaching end-stage renal disease (ESRD)
   - ≥ 50% decline in estimated glomerular filtration rate (eGFR) relative to baseline
4. Proportional change in NT-proBNP from Baseline to Week 8
5. Proportional change in hs-Troponin (high sensitivity) from baseline to Weeks 4 and 8
6. Dosing levels and discontinuations
7. Incidence of adverse events of special interest during treatment

[redacted]

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

Analysis of secondary endpoint 1

This secondary endpoint will be analyzed estimating the unmatched **win ratio** by comparing every participant in the sacubitril/valsartan arm to every participant in the valsartan arm to determine a winner (unmatched pairing method). The estimated win ratio (the total number of wins in the sacubitril/valsartan arm divided by the total number of wins in the valsartan arm) will be calculated. The corresponding null and alternative hypotheses are:

H_{20}: Win ratio is equal to 1, versus

H_{2a}: Win ratio is not equal to 1.

A win ratio greater than 1 will be in favor of sacubitril/valsartan arm. This test will be performed only if the primary null hypothesis (H_{10}) is rejected. The testing of hypothesis H_{20} and calculation of the corresponding two-sided 95% confidence intervals will be performed.

A component will only be used as tie-breaker in the pairwise comparison between two patients if the comparison of components with a higher priority resulted in a tie. For component a) the patient with the later time to death in the common follow-up period is the winner. For component b) the patient with the smaller number of HF hospitalizations in the common follow-up period is the winner. If the number of HF hospitalizations in the common follow-up period is tied, the patient with the later time of the last HF hospitalization in the common follow-up period is the winner. For component c) the same algorithm is applied as for component b). For component d), the patient with the larger decrease or smaller increase in the proportional change is considered a winner; if the ratio of the proportional changes from two patients is between 0.75 and 1/0.75, then the pairwise comparison of the change in NT-proBNP is considered tied.

The analysis will be performed using the unmatched pair win ratio approach (Pocock et al 2012). Contributions of each component of the composite endpoint to total number of winners used in estimation of the win ratio will be reported.

Handling of missing values/censoring/discontinuations

Time to CV death

The time from randomization to CV death will be considered as censored for analysis for participants who have not experienced a CV death and for whom at least one of the following applies at or prior to the analysis time point:

- withdrawal of informed consent
- loss to follow up
- death from non-CV causes

[redacted]

The censoring date for those participants without CV death prior to the analysis time point will be whichever occurs first of the following:

- date of withdrawal of informed consent
- date of last visit (End of Study visit)
- date of death from non-CV causes

NT-proBNP measurement at Weeks 4 and 8

Cardiovascular death, HF hospitalization, and urgent HF visit are at a higher hierarchy level than NT-proBNP in the composite endpoint for win ratio analysis. Therefore, missing values due to CV death or after HF hospitalization or urgent HF visit do not affect the analysis. Missing NT-proBNP measurements at Weeks 4 and 8 due to other reasons (e.g., non-CV death) are expected to be infrequent; they may result in more ties with minimal impact on the power. No imputation will be done for missing NT-proBNP measurement at Weeks 4 and 8.

Analysis of secondary endpoint 2

The cumulative number of composite events, i.e., the total number of composite events of CV death, recurrent HF hospitalizations, and recurrent urgent HF visits for a patient over time will be calculated. The time to these recurrent events will be analyzed using the semi-parametric proportional rates model (abbreviated as LWYY model) (Lin et al 2000). The hypotheses of interest are:

H_{30}: Rate ratio of sacubitril/valsartan arm over valsartan arm equal to 1, versus

H_{3a}: Rate ratio of sacubitril/valsartan arm over valsartan arm not equal 1.

A rate ratio < 1 indicates an effect in favor of sacubitril/valsartan arm.

The FAS will be used in the main analysis of the second key secondary endpoint.

The hypothesis (H_{30}) will be tested and 95% confidence interval will be provided. The rate ratio will be estimated from the above proportional rates model through maximization of a partial likelihood score function and the confidence intervals will be based on the robust estimate of the standard errors. The number and percentage of CV events by event type will be summarized.

The CV death will not be considered as a censoring variable, but as a composite endpoint event and a conditional factor in this analysis. Time to non-CV death will be considered as a censoring variable. Any censoring due to non-CV death is assumed to be non-dependent in the analysis.

Analysis of secondary endpoint 3

The total number of composite events will be analyzed using a negative binomial regression model with the count data as the dependent variable. Treatment group and in/out-of-hospital randomization as a fixed-effect factors and log (follow-up duration) as the off-set. The model will be used to estimate event rates and their 95% confidence intervals by treatment group.

The time to the first composite event will be analyzed using Cox's proportional hazard model with factors treatment and in/out-of-hospital randomization. Hazard ratio for treatment and its 95% confidence interval will be reported.

[redacted]

Analysis of secondary endpoint 4

The proportional change in NT-proBNP from Baseline to Week 8 will be analyzed using an ANCOVA model similar to that of the primary efficacy analysis.

Analysis of secondary endpoint 5

The proportional change in hs-Troponin (high sensitivity) from baseline to Week 4 will be analyzed using an ANCOVA model similar to that of the primary efficacy analysis. Log-transformed hs-Troponin will be used for analysis. The analysis will be repeated for Week 8.

Analysis of secondary endpoint 6

The dosing level will be summarized by treatment group and in-/out-of-hospital randomization status. Incidence of discontinuations (all causes) will be summarized by treatment group and in-/out-of-hospital randomization status.

Analysis of secondary endpoint 7

Incidence of event will be analyzed using logistic regression model with treatment and in/out-of-hospital randomization as fixed factors. The model will be used to estimate the odds ratio for treatment and its 95% confidence interval.

The number (and proportion) of patients with adverse events of special interest will be summarized by treatment, primary system organ class and preferred term. All these secondary endpoints will be analyzed using FAS and nominal p-values will be reported. There will be no adjustment for multiplicity.

12.5.2 Safety endpoints

For all safety analyses, the safety set (SAF) will be used. All listings and tables will be presented by treatment group and in/out-of-hospital randomization category.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of Baseline data, will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate listing for death including on-treatment and post-treatment deaths will be provided. In particular, summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to the last study visit.

Adverse events

All information obtained on adverse events will be displayed by treatment group and patient. The number (and percentage) of patients with treatment emergent adverse events (events started after the first dose of study medication, or events present prior to start of double-masked treatment but increased in severity based on preferred term) will be summarized in the following ways:

[redacted]

- By treatment, primary system organ class and preferred term.
- By treatment, primary system organ class, preferred term and maximum severity.
- By treatment, pre-defined topic of interest, primary system organ class and preferred term.

Separate summaries will be provided for study medication related adverse events, serious adverse events, and other significant adverse events leading to discontinuation.

A patient with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment group, in/out-of-hospital randomization, patient, and visit/time and if ranges are available, abnormalities will be flagged. Descriptive statistics will be provided by treatment, and visit/time and will be presented graphically.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, in/out-of-hospital randomization, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment, in/out-of-hospital randomization, and visit/time. Shift tables using the low/normal/high/ classification will be used to compare baseline to the worst on-treatment value.

12.5.3 Biomarkers

See Sections 12.4 and 12.5 for a description of the methods used to analyze the biomarkers.

[redacted]

[redacted]

[redacted]

12.7 Interim analysis

There is no planned interim analysis for efficacy in the study.

An independent Data Monitoring Committee (DMC) will be responsible for performing interim safety assessment using independent statistician and programmer who will not be involved in the trial conduct. The DMC charter will contain the committee's responsibilities regarding the interim safety assessment. Details of this safety assessment will be included in the Statistical Analysis Plan.

Interim safety assessments are planned to be performed and results will be provided to DMC for their review and recommendation. The number and/or timing of these safety assessments will be mentioned in the Data Monitoring Committee Charter. No adjustment of the level of significance will be made for these interim safety assessments.

12.8 Sample size and Power

The target sample size for this study is approximately 450 total patients (including original protocol and all Amendment patients), randomized in the two treatment groups in 1:1 ratio. The maximum planned duration of follow-up after randomization of these patients is approximately 20 months and the planned duration of follow-up for the last patient in the group is 2 months. The power of the study is determined based on these 450 patients for the primary endpoint.

Sample size for the primary endpoint

This sample size of 450 patients would have 85% power to detect a 23% reduction in the geometric mean of the proportional change from baseline to an average of Weeks 4 and 8 in NT-proBNP for the sacubitril/valsartan treatment group. This 23% reduction in geometric mean is equivalent to -0.2614 in natural log scale (*=ln(0.77)*). The power is estimated assuming a two-sided significance level of 0.05, a common standard deviation of 0.85 for change in log transformed NT-proBNP and a 15% rate of missingness in NT-proBNP at both Week4 and Week8. nQuery Version 8.4.1.0 (2019) software package is used in calculating the power of the test.

13 Ethical considerations and administrative procedures

13.1 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 with the ethical principles laid down in the Declaration of Helsinki.

[redacted]

13.2 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, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients (e.g., patient materials and thank you letters). 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.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.) .

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, 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

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information,

[redacted]

observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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.

14.1 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 required for patient safety 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, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

[redacted]

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

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

Hematology

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

Blood Chemistry

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

[redacted]

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

General principles

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

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

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

Recommended corrective action for management of hyperkalemia

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

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

[redacted]

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

Serum potassium > 5.5 and < 6.0 mEq/L

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

Serum potassium greater than or equal to 6.0 mEq/L

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

[redacted]

16.3 Appendix 3: Guidelines for the management of blood pressure

Guidelines

1. Investigator should monitor blood pressure closely
2. If symptomatic hypotension occurs:
    a. Correct any treatable cause, e.g. hypovolemia
    b. If hypotension persists, any antihypertensive drug and non-disease-modifying drugs, such as diuretics, CCBs, nitrates, and α-blockers, should be down-titrated or stopped first before down-titration of the study drug is considered
3. If hypotension persists, the study drug should be down-titrated or even temporarily withdrawn. The dose re-challenge and medication adjustment guidelines described in Section 6.4.1 should be adhered to as much as possible.

16.4 Appendix 4: Guidelines for the management of renal dysfunction

General principles:

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

Two types of response to serum creatinine increase are described:

Surveillance situation

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

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

Action situation

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

[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.

[redacted]

16.5 Appendix 5: Expanded Assessment Schedule

Period	**Screening**	**Double-Blind Treatment (84 week)**															
Visit Name	**Screening**	**Randomization/Baseline**															**Study Completion/ End of Study**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4[8]**	**Visit 5**	**Visit 6[7]**	**Visit 7**	**Visit 8[7]**	**Visit 9[8]**	**Visit 10[8]**	**Visit 11**	**Visit 12[8]**	**Visit 13**	**Visit 14[8]**	**Visit 15**	**Visit 16**	**Visit 17**
Week (Day)	**[Day -30 to -1.5 (36hours)]**	**0 (Day 1)**	**1 (Day 7)**	**2 (Day 14)**	**4 (Day 28)**	**6 (Day 42)**	**8 (Day 56)**	**10 (Day 70)**	**12 (Day 84)**	**16 (Day 112)**	**24 (Day 168)**	**32 (Day 224)**	**40 (Day 280)**	**48 (Day 336)**	**56 (Day 392)**	**68 (Day 476)**	**84 (Day 588)**
Information and informed consent	S																
Inclusion/exclusion criteria	X	X															
Demography / Medical history	X																
Heart failure and CV disease history	X																
ECG	X																
Physical Exam	S				S		S		S	S	S	S	S	S	S	S	S
Height	X	X															
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist/hip circumference	X																
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HF signs and symptoms and NYHA classification	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

Period	Screening	Double-Blind Treatment (84 week)															
Visit Name	**Screening**	**Randomization/Baseline**															**Study Completion/ End of Study**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4[8]**	**Visit 5**	**Visit 6[7]**	**Visit 7**	**Visit 8[7]**	**Visit 9[8]**	**Visit 10[8]**	**Visit 11**	**Visit 12[8]**	**Visit 13**	**Visit 14[8]**	**Visit 15**	**Visit 16**	**Visit 17**
Week (Day)	**[Day -30 to -1.5 (36hours)]**	**0 (Day 1)**	**1 (Day 7)**	**2 (Day 14)**	**4 (Day 28)**	**6 (Day 42)**	**8 (Day 56)**	**10 (Day 70)**	**12 (Day 84)**	**16 (Day 112)**	**24 (Day 168)**	**32 (Day 224)**	**40 (Day 280)**	**48 (Day 336)**	**56 (Day 392)**	**68 (Day 476)**	**84 (Day 588)**
Heart failure and CV medications	X	X[4]	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Chemistry labs	X	X	X	X	X		X	X[3]	X		X		X		X	X	X
Hematology labs	X	X		X			X				X		X		X	X	X
Hemoglobin A1C		X															X
eGFR	X	X	X	X	X		X	X[3]	X		X		X		X	X	X
Urinalysis		X															
Pregnancy Test[2]	X	X			X		X		X	X	X	X	X	X	X	X	X
IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X															
Plasma NT-proBNP or BNP	X[5]	X	X		X		X										
hs-Troponin		X			X		X										
[redacted]																	
Drug accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study treatment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

Period	**Screening**	**Double-Blind Treatment (84 week)**															
Visit Name	**Screening**	**Randomization/Baseline**															**Study Completion/ End of Study**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4[8]**	**Visit 5**	**Visit 6[7]**	**Visit 7**	**Visit 8[7]**	**Visit 9[8]**	**Visit 10[8]**	**Visit 11**	**Visit 12[8]**	**Visit 13**	**Visit 14[8]**	**Visit 15**	**Visit 16**	**Visit 17**
Week (Day)	**[Day -30 to -1.5 (36hours)]**	**0 (Day 1)**	**1 (Day 7)**	**2 (Day 14)**	**4 (Day 28)**	**6 (Day 42)**	**8 (Day 56)**	**10 (Day 70)**	**12 (Day 84)**	**16 (Day 112)**	**24 (Day 168)**	**32 (Day 224)**	**40 (Day 280)**	**48 (Day 336)**	**56 (Day 392)**	**68 (Day 476)**	**84 (Day 588)**
Adverse events / Serious Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Angioedema assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Thank You letter		X															X
[redacted]																	
Study completion – randomized treatment																	X
Post study completion follow up																	S[6]

[redacted]

Period	Screening	Double-Blind Treatment (84 week)															
Visit Name	Screening	Randomization/Baseline															Study Completion/ End of Study
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4[8]	Visit 5	Visit 6[7]	Visit 7	Visit 8[7]	Visit 9[8]	Visit 10[8]	Visit 11	Visit 12[8]	Visit 13	Visit 14[8]	Visit 15	Visit 16	Visit 17
Week (Day)	[Day -30 to -1.5 (36hours)]	0 (Day 1)	1 (Day 7)	2 (Day 14)	4 (Day 28)	6 (Day 42)	8 (Day 56)	10 (Day 70)	12 (Day 84)	16 (Day 112)	24 (Day 168)	32 (Day 224)	40 (Day 280)	48 (Day 336)	56 (Day 392)	68 (Day 476)	84 (Day 588)

X = assessment to be recorded in the clinical database or received electronically from a vendor
S = assessment to be recorded in the source documentation and in the database
[redacted]
[2] All female patients of childbearing potential will have a serum pregnancy test (hCG) performed at Visit 1 (local lab). A urine pregnancy test will be conducted in the local laboratory for remaining visits.
[3] Limited chemistry panel. eGFR will be calculated from creatinine concentration.
[4] CV medications will be recorded at time of hospital discharge.
[5] BNP or NT-proBNP will be assessed at Visit 1 via local laboratory. Only NT-proBNP will be assessed via central laboratory for Visits 2, 3, 5 and 7.
[6] Health status phone call 4 weeks after study completion.
[7] Visits are applicable to Original Protocol Version 00, but are not applicable for patients following Amended Protocol Version 01 and all subsequent amendments.
[8] Visits are applicable to Amended Protocol Version 03, but are not applicable for patients following Amended Protocol Version 04 and all subsequent amendments.

[redacted]