

Clinical Development

LCZ696/Sacubitril/Valsartan/Entresto®

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

Statistical Analysis Plan (SAP)

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26-Mar-2019	Prior to DB Lock	Creation of Amendment 1	<ol style="list-style-type: none"> Updated to align with protocol versions 01 and 02 (amended protocols) dated 10-Jun-2018 and 15-Mar-2019, respectively: escalate the echo endpoints from [REDACTED] secondary objectives; add the echocardiographic parameters of Left Ventricular end systolic and diastolic volume indices, LVESVi and LVEDVi, to the secondary endpoints at 12 weeks [REDACTED] Ensured study objectives wording matched that of protocol Specified that geometric means and confidence intervals will be presented for biomarker data Updated baseline definition Removed “on treatment” terminology and “28 days post last dose of study treatment” lag time (from the open-label phase definition) Clarified definitions for double-blind and open-label phases, and changed terminology from “treatment phase” to “study phase” Clarified definitions for date of last administration of study treatment for double-blind phase and for the study 	<ol style="list-style-type: none"> Section 1 Introduction; Section 1.2 Study Objectives and Endpoints; Section 2.3.3 Demographics and Other Baseline Characteristics; Section 2.7.1 Secondary Endpoints; Section 2.7.2 Statistical Hypothesis, Model, and Method of Analysis; [REDACTED] <i>Section 1.2 Study Objectives and Endpoints</i> Section 2.1 Data analysis general information Section 2.1.1 General Definitions Section 2.1.1 General Definitions Section 2.1.1 General Definitions Section 2.1.1 General Definitions Section 2.1.1 General Definitions Section 2.2 Analysis Sets Section 2.3.3 Demographics and Other Baseline Characteristics; Section 2.4.2 Prior, Concomitant and Post Therapies; Section 2.8.1.1 Coding of AEs; Section 5.2 AEs Coding/Grading

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			8. Clarified definition of date of last contact	11. Section 2.3.3 Demographics and Other Baseline Characteristics
			9. Modified PPS definition to clarify that major protocol deviations will exclude patients from the PPS regardless of the study phase in which they occur	12. Section 2.3.3 Demographics and Other Baseline Characteristics; [REDACTED]
			10. Clarified coding dictionary versions to be utilized	13. Section 2.3.3 Demographics and Other Baseline Characteristics
			11. Clarified that tables summarizing demographics and baseline data will be run only on the FAS	14. Section 2.4.2 Prior, Concomitant and Post Therapies
			12. Indicated that values of the hemodynamic variable carotid-femoral pulse wave velocity will be negative inverse transformed prior to analysis	15. Section 2.5.4 Supportive Analyses 16. Section 2.7.2 Statistical Hypothesis, Model, and Method of Analysis; Section 2.12 Biomarkers;
			13. Removed Chronic Renal Insufficiency from CV history	[REDACTED] 17. Section 2.7.2 Statistical Hypothesis, Model, and Method of Analysis
			14. Added separate summaries of prior and concomitant CV, HF, ACEi and ARB medications	18. Section 2.7.2 Statistical Hypothesis, Model, and Method of Analysis;
			15. Added supportive analyses of the primary endpoint: On-treatment analysis, analysis using the “original” aortic characteristic impedance variable, analysis using the “alternative” aortic characteristic impedance variable	[REDACTED] 19. Section 2.8.1.2 General Rules for AE Reporting; Section 2.8.2 Deaths 20. Section 2.8.1.3 AE Summaries
			16. Removed references to U-creatinine	21. Section 2.8.1.4 Adverse Events of Special Interest/Grouping of AEs; Section 2.8.4.3 Angioedema
			17. Added on-treatment analyses of the secondary endpoints	22. Section 2.8.3 Laboratory data
			18. Clarified correlation analyses of changes from baseline to	

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Week 4 trough, and changes from trough to 4 hours post dose at Week 4	23. Section 2.8.3 Laboratory data
			19. Modified definition of treatment emergent AEs and flagging of deaths in listing to remove “28 days post last dose of study treatment” lag time	24. Section 2.8.4.1 Vital Signs
			20. Added AE overview table (number and percentage of patients in various AE categories), two SAE tables (occurring with frequency $\geq 0.5\%$; by seriousness criteria), and most frequent non-SAEs ($\geq 5\%$) table	25. Section 2.12 Biomarkers
			21. Clarified that separate summaries/analyses of angioedema data, including AEs related to angioedema, will be produced – one based on all angioedema and the other based on positively adjudicated angioedema	
			22. Specified conversion factors for lab values indicated as <x or >	27. Section 5.3.2 Notable Laboratory Analyses
			23. Added separate summaries of the incidence of hyperkalemia and worsening renal function through Week 12 based on central laboratory data	28. Section 5.6 Rule of Exclusion Criteria of Analysis Sets
			24. Added summary of the incidence of hypotension through Week 12	
			25. For biomarkers, specified that values <LOD will be converted to (0.5)(LOD), samples from patients who withdrew consent will not be analyzed by the central laboratory, values indicated as ‘Reported and Unreliable’	

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			will be excluded from analysis, and BNP samples will be reassayed using EDTA tubes for purposes of a side-by-side comparison of results	
			26. Clarified derivation of log(study duration through Week 12) for negative binomial regression analysis	
			27. Removed CPK from the list of notable chemistry abnormalities since this safety lab was not performed for the study	
			28. Updated rules of exclusion criteria of analysis sets based on final review of PDs and associated final PD documentation	

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List of abbreviations

ACEi	Angiotensin Converting Enzyme Inhibitor
AE	Adverse Event
ANCOVA	Analysis of Covariance
ARB	Angiotensin Receptor Blocker
ATC	Anatomical Therapeutic Chemical
BID	bis in diem/twice a day
BMI	Body Mass Index
BNP	B-type Natriuretic Peptide
CABG	Coronary Artery Bypass Graft
CKD	Chronic Kidney Disease
CRO	Contract Research Organization
CRT-P	Cardiac resynchronization therapy – no ICD
CRT-D	Cardiac resynchronization therapy – with ICD
CSR	Clinical Study report
CTCAE	Common Terminology Criteria for Adverse Events
DCT	Data Collection Tool
eCRF	Electronic Case Report Form
ED	Emergency Department
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
H0	Null Hypothesis
HA	Alternative Hypothesis
HF	Heart Failure
hs-TnT	High Sensitivity Troponin
ICD	Implantable Cardioverter Defibrillator
IRT	Interactive Response Technology
LOCF	Last Observation Carried Forward
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MRI	Magnetic Resonance Imaging
MedDRA	Medical Dictionary for Regulatory Activities
NT-proBNP	N-terminal Prohormone of B-type Natriuretic Peptide
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PD	Pharmacodynamic
PK	Pharmacokinetic
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PT	Preferred Term
RS	Randomized Set
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-emergent Adverse Event
TFLs	Tables, Figures, Listings
TIA	Transient Ischemic Attack
█	█
U-cGMP	Urine-cyclic Guanosine Monophosphate
WHO	World Health Organization

1 Introduction

The statistical analysis plan (SAP) will outline in detail the analyses planned in the protocol. The analyses will be used to generate the Clinical Study Report (CSR). The SAP is based on protocol version 02 (amended protocol) dated 15-Mar-2019 and the data collection tool (DCT) version 11.0 dated 23-Jan-2019.

1.1 Study design

This study will use a multicenter, randomized, double-blind, double-dummy, parallel group, active-controlled, forced titration, 12-week design in patients with heart failure and reduced left ventricular ejection fraction (LVEF) $\leq 40\%$. The study duration is a maximum of 30 weeks, including the screening epoch, with 8 scheduled outpatient visits. A total of approximately 432 patients randomized to sacubitril/valsartan or enalapril in a 1:1 ratio is planned with no stratification at approximately 80 centers in the United States.

At the time of randomization, patients will have been on stable treatment with guideline-directed therapy for heart failure with reduced ejection fraction, other than angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), and on an optimal medical regimen to effectively treat co-morbidities such as hypertension, diabetes mellitus and coronary artery disease. All patients will need to meet all other inclusion and none of the exclusion criteria.

Patients will be randomized to either sacubitril/valsartan 24/26 mg bis in diem/twice a day (BID) or enalapril 2.5 mg BID (Dose Level 1), according to the product label(s). Forced titration will occur every 2 weeks to reach the target dose of sacubitril/valsartan 97/103 mg BID or enalapril 10 mg BID (Dose Level 3). Dose level 2 is defined as sacubitril/valsartan 49/51 mg BID or enalapril 5 mg BID. Dose adjustments will only be allowed if indicated per protocol defined safety and tolerability criteria and investigator judgement, or if the investigator believes that adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern. After 12 weeks of double-blind treatment, patients will continue into the 12 week open-label extension.

All patients will need to have a 36-hour washout from study treatment prior to starting the open-label extension to ensure that the blinding of the core study is maintained and to reduce the risk of angioedema. All patients will start open-label treatment on sacubitril/valsartan Dose Level 2, unless they completed double-blind treatment on Dose Level 1. Instead, these patients will enter the open-label extension on sacubitril/valsartan Dose Level 1. Study treatment will be force-titrated every 2 weeks to reach the target dose of sacubitril/valsartan (Dose Level 3).

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 drug to be dispensed to the patient.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient

randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The primary analysis time point will be Week 12.

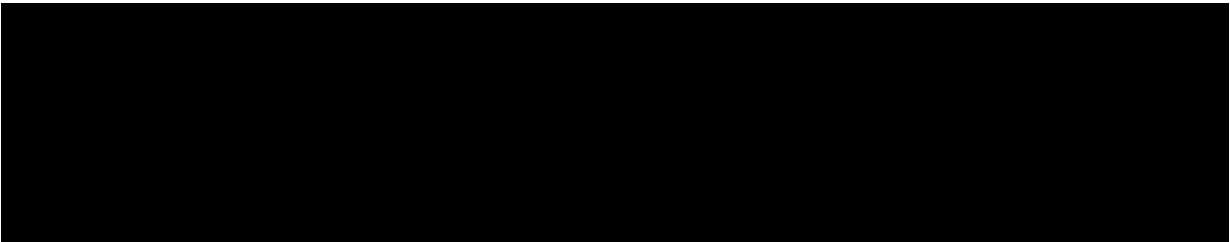
There are no interim analyses planned.

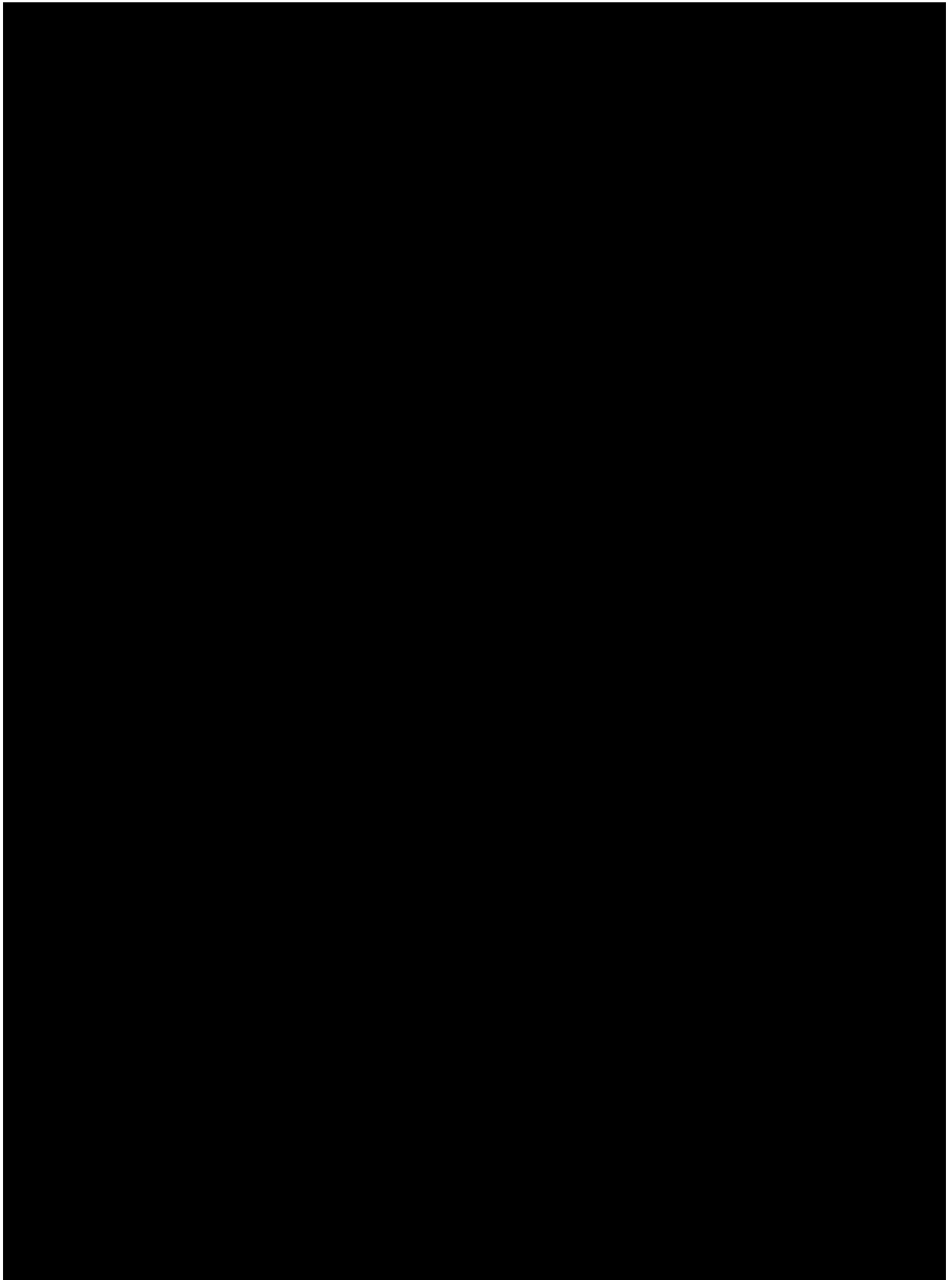
1.2 Study objectives and endpoints

The primary objective is to determine whether treatment with sacubitril/valsartan provides a superior effect on aortic characteristic impedance compared to enalapril in patients with heart failure and reduced ejection fraction (LVEF $\leq 40\%$) after 12 weeks of treatment. The primary endpoint is the change in aortic characteristic impedance ($Z_c = dP/dQ$ in early systole) between baseline and Week 12.

The secondary objectives are:

1. To evaluate the effect of sacubitril/valsartan vs. enalapril after 12 weeks of treatment on change from baseline in N-terminal Prohormone of B-type Natriuretic Peptide (NT-proBNP).
2. To evaluate the effect of sacubitril/valsartan vs. enalapril after 12 weeks of treatment on the changes from baseline in echocardiographic measures including:
 - a. Global longitudinal strain
 - b. Left atrial volume index
 - c. Mitral annular E' velocity (Doppler Tissue Imaging)
 - d. Mitral E/E'
 - e. LVEF
 - f. Ventricular-vascular coupling (Ea/Es)
 - g. LV end systolic and diastolic volume indices
3. To evaluate the effect of sacubitril/valsartan vs. enalapril after 4 weeks of treatment on the relation between the change in aortic characteristic impedance and change in biomarker levels, including B-type Natriuretic Peptide (BNP) and Urine-cyclic Guanosine Monophosphate (U-cGMP)/U-creatinine, during both trough and 4 hours post-dose.








2 Statistical methods

2.1 Data analysis general information

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

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

Unless otherwise specified, for continuous data, the mean, standard deviation, median, first and third quartiles, interquartile range, and minimum and maximum values will be presented. Geometric means and 95% confidence intervals will also be presented for biomarker data. For categorical data, frequencies and percentages will be presented. All statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

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

2.1.1 General definitions

Study treatment

Patients will receive either sacubitril/valsartan or enalapril during the first 12 weeks of the study. Study treatment will refer to either of these two drugs.

Baseline

In general, baseline is defined as the last non-missing assessment prior to or on the start date of study treatment (randomization date for patients not treated). For hemodynamic variables baseline is defined as the assessment with a planned time point value of 'Visit_1_Baseline'.

Unscheduled assessments will be excluded from the determination of baseline.

Date of first administration of study treatment

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

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

Date of last administration of study treatment

Double-blind phase: The date of last administration of study treatment in the double-blind phase is defined as the last date a dose of study treatment is administered in the double-blind phase and recorded on the Dosage Administration Record - At Visit (Visit 6) eCRF. In the event this date is not available from the Dosage Administration Record - At Visit (Visit 6) eCRF, it will

be determined from the End of Study Treatment eCRF or Dosage Administration Record - Summary eCRF.

Open-label phase: The date of last administration of study treatment in the open-label phase is defined as the last date a dose of sacubitril/valsartan is administered in the open-label phase and recorded on the Dosage Administration Record - Summary eCRF.

The date of last administration of study treatment during the study is defined as the last date a dose of study treatment is administered and recorded on the End of Study Treatment eCRF. In the event this date is not available from the End of Study Treatment eCRF, it will be obtained from the Dosage Administration Record - Summary eCRF.

Study day

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

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

Double-blind phase

Assessments performed at Weeks 1, 2, 4, or 12 (including, but not limited to, vital signs) will be assigned to the double-blind phase for summarization purposes. Unscheduled assessments are not assigned to a study phase for purposes of by-visit summaries.

For summarization of adverse events [AEs], medications, protocol deviations, notable vital signs and laboratory abnormalities, angioedema, and hospitalizations/ED visits/unplanned outpatient clinic visits due to worsening HF symptoms by study phase, an assessment during the double-blind phase is defined as any assessment obtained in the following time interval:

Date of randomization (or date of first administration of study treatment, as appropriate) through the date of the Week 12 visit, inclusive. For patients without a Week 12 visit, a projected Week 12 visit date will be derived relative to their randomization date.

Open-label phase

Assessments performed at Weeks 14 or 24 (including, but not limited to, vital signs) are assigned to the open-label phase for summarization purposes. Unscheduled assessments are not assigned to a study phase for purposes of by-visit summaries.

For summarization of AEs, medications, protocol deviations, notable vital signs and laboratory abnormalities, angioedema, and hospitalizations/ED visits/unplanned outpatient clinic visits due to worsening HF symptoms by study phase, an assessment during the open-label phase is defined as any assessment obtained in the following time interval:

After the date of the Week 12 visit. For patients without a Week 12 visit, a projected Week 12 visit date will be derived relative to their randomization date.

Patients who died, withdrew consent, or were lost to follow-up prior to or on their projected Week 12 visit date will be excluded from the open-label phase.

Last contact

The date of last contact will be determined as the later of the following dates:

- The last visit date for each patient derived by examining all visit data collected in the eCRFs
- Date of discontinuation/study phase completion for the double-blind and open-label phases

Year, month and week

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

1 year = 365.25 days

1 month = 30.3475 days

1 week = 7 days

1 day = 24 hours

2.2 Analysis sets

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

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

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

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

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

2.2.1 Subgroup of interest

The following subgroups will be analyzed for the primary objective:

1. Age groups (<65, ≥65 years; and <75, ≥75 years)
2. Baseline ejection fraction categories based on echocardiography (<25%, 25% - <35%, ≥35%)
3. Prior ACEi/ARB exposure groups (never exposed, previously exposed, or currently taking)
4. Prior ACEi/ARB dose groups (low dose, high dose) (e.g., low dose: <10 mg enalapril daily [or equivalent]; high dose: ≥10 mg enalapril daily [or equivalent])

5. Baseline quartiles of aortic characteristic impedance (based on FAS)
6. Baseline estimated glomerular filtration rate (eGFR) categories (<45, 45 - <60, ≥60 ml/min/1.73 m²)
7. Groups defined by quintiles of change from baseline in mean arterial pressure at Week 12 (based on FAS)
8. New York Heart Association (NYHA) classification [best value during the past month prior to screening visit] (I, II, III, IV)
9. Prior heart failure hospitalization (No, Yes)
10. Prior diabetes (No, Yes)
11. Baseline plasma NT-proBNP (pg/mL) categories (≤ median, > median) (based on FAS)

See Section 2.5 for further details on the primary objective.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

All patients will be used for the summary of patient disposition. The following categories will be summarized:

- Number of patients who were screened
- Screening phase disposition
 - Completed
 - Adverse event
 - Death
 - Pregnancy
 - Screen failure
 - Study terminated by sponsor
 - Technical problems
 - Lost to follow-up
 - Physician decision
 - Subject/Guardian decision
- Number of patients who continued into the double-blind phase
- Number and percentage of patients who were randomized
- Number and percentage of patients who were treated
- Number and percentage of patients who achieved dose level 3

- Number and percentage of patients who did not achieve dose level 3
- Reason for not achieving dose level 3
 - Hyperkalemia
 - Symptomatic hypotension
 - Renal dysfunction
 - Angioedema
 - Other adverse event
 - Unrelated to study treatment tolerability
- Number and percentage of patients who prematurely discontinued study treatment during the double-blind phase
 - Treatment unblinded by site (No, Yes)
- Number and percentage of patients who prematurely discontinued study treatment during the open-label phase
- Reason for premature discontinuation of study treatment (during double-blind phase and open-label phase, separately)
 - Adverse event
 - Death
 - Pregnancy
 - Study terminated by sponsor
 - Technical problems
 - Lost to follow-up
 - Physician decision
 - Subject/guardian decision
- Double-blind phase disposition
 - Completed
 - Death
 - Study terminated by sponsor
 - Physician decision
 - Subject/guardian decision
- Number and percentage of patients who continued into the open-label phase
- Open-label phase disposition
 - Completed

- Death
- Study terminated by sponsor
- Lost to follow-up
- Physician decision
- Subject/guardian decision
- Study duration in months [*(date of last contact/death – date of randomization +1)/30.3475*]

Additionally, listings of inclusion/exclusion criteria, screening/double-blind/open-label phase disposition, reason for withdrawal of consent and study treatment disposition will be provided.

2.3.2 Protocol deviations

The number and percentage of patients with protocol deviations by category will be summarized by study phase (see Section 2.1.1 for study phase definitions). Additionally, a listing of protocol deviations during the study will also be presented. The RS will be used.

2.3.3 Demographics and other baseline characteristics

Demographics, baseline characteristics and disease history are collected at the screening visit. Descriptive summaries and/or listings will be provided. The number and percentage (categorical variables) and descriptive statistics (continuous data) for the information below will be summarized by treatment group and open-label sacubitril/valsartan.

The FAS will be used.

Demographics and baseline characteristics

Demographic variables include:

- Age (years), age group (<65, ≥65 years; and <75, ≥75 years)
- Sex (Male, Female)
 - Child bearing status (Able to bear children, Post-menopausal, Sterile)
- Race (Caucasian, Black, Asian, Native American, Pacific Islander, Other, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)

General baseline characteristic variables include:

- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/ m²) [*weight (kg)/height (m²)*]
 - BMI categories (<20, 20 - <25, 25 - 30, >30 kg/m²)
- Smoking history (Never, Current, Former)
- eGFR (ml/min/1.73 m²)

- eGFR categories (<45, 45 - <60, ≥60 ml/min/1.73 m²)
- Plasma NT-proBNP (pg/mL)
 - Plasma NT-proBNP categories (<450, 450 - <900, 900 - <1600, 1600 - <3200, ≥3200 pg/mL)
- PlasmaBNP (pg/mL)
 - Plasma BNP categories (<100, 100 - <225, 225 - <400, 400 - <800, ≥800 pg/mL)

Key hemodynamic baseline characteristic variables include:

- Aortic characteristic impedance (dyne x sec/cm⁵)
- Central (aortic) pulse pressure (mmHg)
- Carotid-femoral pulse wave velocity (m/sec), both untransformed values and negative inverse transformed values (niCFPWV = -1000/CFPWV)
- Augmentation index (%)
- Aorta-carotid reflection coefficient
- Carotid pulsatility index
- Central systolic pressure (mmHg)
- Central diastolic pressure (mmHg)
- Heart rate (bpm)

Key echocardiographic baseline characteristic variables include:

- Global longitudinal strain (%)
- Left atrial volume index (mL/m²)
- Mitral annular E' velocity (cm/sec)
- Mitral E/E'
- LVEF (%)
- Ventricular-vascular coupling (Ea/Ees)
- Left ventricular end systolic volume index (LVESVi) (mL/m²)
- Left ventricular end diastolic volume index (LVEDVi) (mL/m²)

Disease history

Disease history variables, as collected on the Heart Failure History eCRF at screening, include:

- NYHA classification [best value during the past month prior to screening visit] (I, II, III, IV)
- Primary heart failure etiology (Ischemic, Non-ischemic)

- Non-ischemic etiology (Hypertensive [No, Yes], Diabetic [No, Yes], Alcoholic [No, Yes], Myocarditis [No, Yes], Peripartum [No, Yes], Drug induced [non-chemotherapy] [No, Yes], Chemotherapy [No, Yes], Idiopathic Other [No, Yes], Valvular heart disease [No, Yes], Other [No, Yes])
- Myocardial infarction (No, Yes)
- Coronary revascularization (No, Yes)
 - Coronary revascularization type (Percutaneous coronary intervention [PCI], Coronary Artery Bypass Graft [CABG])
- Prior heart failure hospitalization (No, Yes)
 - Number of heart failure hospitalizations in the last 12 months
- Most recent ejection fraction (%)
 - Ejection fraction categories (<25%, 25% - <35%, ≥35%)
 - Method used (Magnetic Resonance Imaging [MRI], Echocardiography, Nuclear [SPECT/PET/MUGA], Ventriculogram, Other)
- ACE inhibitor intolerant (No, Yes)
- Known history of diabetes mellitus (No, Yes)
 - Controlled by: Insulin (No, Yes), Oral anti-diabetic agent (No, Yes), GLP-1 agonist (No, Yes), Diet only (No, Yes)

Cardiovascular history

Cardiovascular history will be summarized. The following disease information will be collected:

- Hypertension (No, Yes, Unknown)
- Transient Ischemic Attack (TIA) (No, Yes, Unknown)
- Stroke (No, Yes, Unknown)
- Peripheral vascular disease (No, Yes, Unknown)
- Chronic Kidney Disease (CKD) stage (CKD stage 1 [eGFR ≥90], CKD stage 2 [eGFR 60 - 89], CKD stage 3 [eGFR 30 - 59], CKD stage 4 [eGFR 15 - 29], CKD stage 5 [eGFR <15 or dialysis], No CKD)
- Arrhythmia (No, Yes, Unknown)
 - Arrhythmia type (Atrial fibrillation, Atrial flutter, Supraventricular tachycardia, Ventricular tachycardia)
- Pacemaker/Implantable Cardioverter Defibrillator (ICD) (No, Yes, Unknown)
 - Device type (Pacemaker, Cardiac resynchronization therapy - no ICD [CRT-P], Cardiac resynchronization therapy - with ICD [CRT-D], ICD only [single/dual chamber], Unknown)
- Moderate to severe valvular heart disease (No, Yes, Unknown)

- Valvular heart disease type (Mitral regurgitation, Aortic regurgitation, Aortic stenosis, Tricuspid regurgitation, Other)
- Prior valvular surgery (No, Yes, Unknown)
 - Valvular surgery type (Mitral, Aortic, Tricuspid, Pulmonic)

Non-cardiovascular medical history

Non-cardiovascular medical history and ongoing conditions will be summarized and listed. The summary will be presented by primary system organ class (SOC), preferred term (PT) and treatment group and open-label sacubitril/valsartan. Non-cardiovascular medical history and ongoing conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology (v21.1 or higher).

Surgeries and Medical Procedures

Surgeries and medical procedures will be listed. Surgeries and medical procedures will be coded using MedDRA terminology (v21.1 or higher).

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

The SS will be used for all analyses associated with study treatment and medications, unless otherwise specified.

2.4.1 Study treatment / compliance

The duration of the double-blind study treatment phase is defined as:

Duration (days) = (date of last study treatment in double-blind study phase – date of first study treatment) +1

The duration of the open-label study treatment phase is defined as:

Duration (days) = (date of last study treatment in open-label study phase – date of first study treatment in open-label study phase) +1

Summary statistics will be displayed for the duration of double-blind study treatment and the duration of open-label study treatment.

The durations will also be categorized into weekly time intervals (<7 days, 7 - <14 days, 14 - <21 days, ..., etc.). The number and percentage of patients in each category will be presented by study phase.

Total patient-days of exposure will also be summarized by study phase.

In addition, the number and percentage of patients at each dose level dispensed by visit will be summarized by treatment group and open-label sacubitril/valsartan. The number and percentage of the maximum dose level dispensed will also be presented by treatment group and open-label sacubitril/valsartan. Similarly, the up-titrated doses, down-titrated doses and unchanged doses will be summarized by visit, treatment group and open-label sacubitril/valsartan.

All information on dose administration will be listed.

2.4.2 Prior, concomitant and post therapies

Prior and concomitant medications will be coded according to the World Health Organization (WHO) Drug Reference List (WHO Drug v2017 Nov or later). Prior and concomitant medications are mutually exclusive, as defined below:

- A prior medication is defined as any medication with an end date prior to the first dose of study treatment.
- A concomitant medication is defined as any medication taken on or after the start of study treatment. A prior medication that is ‘ongoing’ at the time of the first study treatment or whose end date is after first study treatment will be considered a concomitant medication.

The number and percentage of patients with prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) class, preferred term (PT) and treatment group, and open-label sacubitril/valsartan. Separate summaries of prior CV, HF, ACEi and ARB medications will also be produced. Concomitant medications will be summarized in a similar fashion. All medications will be listed.

The number and percentage of patients in the following prior ACEi/ARB exposure categories (assessed at screening) will be summarized:

- ACEi/ARB naïve (never exposed)
- Previously on ACEi/ARB but not currently taking (previously exposed)
- Currently taking

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary endpoint is the change in aortic characteristic impedance ($Z_c = dP/dQ$) between baseline and Week 12. The analysis of the primary endpoint will be based on the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

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

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

$$H_0: \mu_1 - \mu_0 = 0$$

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

The primary endpoint will be analyzed by an analysis of covariance (ANCOVA) model with treatment and Z_c baseline as explanatory variables (Mitchell 2002). The least squares means of the two treatment groups, least squares mean difference of the treatment groups, 95% confidence interval for the difference in the two treatment groups, and p-value based on the fitted linear model will be reported. If the p-value is < 0.05 and the least squares mean difference

of the treatment groups favors sacubitril/valsartan, statistical significance in favor of sacubitril/valsartan is shown.

2.5.3 Handling of missing values/censoring/discontinuations

If a patient has no Week 12 value, the missing value will not be imputed and the patient will be removed from the analysis.

2.5.4 Supportive analyses

A supportive nonparametric analysis will be performed to examine the consistency of results if the assumption of normality for the distribution of the primary endpoint is not tenable. Graphical methods (e.g., normal probability plot and histogram of residuals) and analytical methods (e.g., Shapiro-Wilk test) will be used to assess the assumption of normality. For this supportive analysis, the primary endpoint will be analyzed using the Wilcoxon rank-sum test. The probability of one treatment being the same or better than the other treatment will be estimated (based on the Wilcoxon rank-sum test) and the associated 95% confidence interval will be reported (Chen and Kianifard, 2000).

The following supportive/sensitivity analyses of the primary endpoint will also be performed:

- An analysis based on the FAS using the same analytical approach as described in Section 2.5.2 where missing values at Week 12 are imputed using the Last Observation Carried Forward (LOCF) procedure (only post-baseline trough values will be carried forward).
- An analysis based on the PPS using the same analytical approach as described in Sections 2.5.2 and 2.5.3.
- Change from baseline in aortic characteristic impedance at Weeks 4 and 12 will be analyzed based on a repeated measures ANCOVA model in which treatment, week, and treatment-by-week interaction will be included as fixed-effect factors and the baseline value as a covariate, with a common unstructured covariance for each treatment group. The primary treatment comparison between sacubitril/valsartan and enalapril will be made at Week 12. The analysis will be performed on all available data in the FAS. The estimated treatment effect with the associated two-sided 95% confidence interval at Week 12 will be provided.
- Subgroup analyses based on the FAS as described in Section 2.2.1.
- An on-treatment analysis based on the FAS using the using the same analytical approach as described in Section 2.5.2.
- Analyses of the “original” and “alternative” aortic characteristic impedance variables based on the FAS using the same analytical approach as described in Section 2.5.2.

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary objectives

All analyses will be based on the FAS unless otherwise specified.

2.7.1 Secondary endpoints

Secondary endpoints include the following:

1. Change from baseline in NT-proBNP at Week 12
2. Change from baseline in echocardiographic measures at Week 12 including:
 - Global longitudinal strain
 - Left atrial volume index
 - Mitral annular E' velocity (Doppler Tissue Imaging)
 - Mitral E/E'
 - LVEF
 - Ventricular-vascular coupling (Ea/Ees)
 - LV end systolic and diastolic volume indices
3. Change in aortic characteristic impedance and change in biomarker levels (BNP, UcGMP and UcGMP to Urinary Creatinine ratio) during both trough and 4 hours post-dose at Week 4

2.7.2 Statistical hypothesis, model, and method of analysis

For NT-proBNP a proportional change from baseline at Week 12 in a logarithmic scale will be analyzed using an ANCOVA model with treatment and the logarithmic baseline biomarker value as explanatory variables. The estimated treatment effect in terms of ratios of geometric means, based on the least squares means from the ANCOVA model, the corresponding two-sided 95% confidence intervals and p-values will be provided.

The change from baseline in the echocardiographic measures at Week 12 will be analyzed using an ANCOVA model with treatment and baseline as explanatory variables.

Correlation coefficients between changes from baseline in aortic characteristic impedance and biomarker levels (BNP, UcGMP and UcGMP to Urinary Creatinine ratio) to Week 4 trough will be calculated by treatment and overall. Corresponding two-sided 95% confidence intervals and p-values will be provided. The same analysis will be conducted on changes in aortic characteristic impedance and biomarker levels from trough to 4 hours post dose at Week 4.

On-treatment analyses of all secondary endpoints will be performed using the same analytical approaches described above.

2.7.3 Handling of missing values/censoring/discontinuations

For the analysis of secondary endpoints, if a patient has no post-baseline value at the given time point (Week 4 or Week 12), the missing value will not be imputed and the patient will be removed from the analysis.

2.8 Safety analyses

All safety analyses will be based on the SS unless otherwise specified. There will be no inferential analyses of the safety data.

2.8.1 Adverse events

2.8.1.1 Coding of AEs

Adverse events (AEs) will be coded using MedDRA terminology (v21.1 or later).

2.8.1.2 General rules for AE reporting

AE summaries will include all treatment-emergent AEs (TEAEs). TEAEs are defined as AEs starting on or after the first day of study treatment. All AEs will be listed. AEs starting prior to the first day of study treatment (non-TEAEs) will be flagged in the listings.

All TEAEs will be summarized by study phase as defined in Section 2.1.1.

TEAEs will be summarized by presenting the number and percentage of patients having at least one TEAE, having at least one TEAE in each primary SOC, and for each PT using MedDRA terminology. A patient with multiple occurrences of a TEAE will be counted only once in the AE category.

Separate summaries will be presented by SOC, PT and severity. A patient with multiple severities for an AE will be summarized under the worse severity recorded for the event.

Any information collected will be listed as appropriate.

2.8.1.3 AE summaries

The following summary tables will be provided:

- AEs, regardless of study treatment relationship, by primary SOC, PT and worst severity
- Most frequent ($\geq 5\%$) AEs, regardless of study treatment relationship, by PT
- Most frequent ($\geq 5\%$) non-serious AEs, regardless of study treatment relationship, by PT
- AEs, suspected to be related to study treatment, by primary SOC and PT
- Serious adverse events (SAEs), regardless of study treatment relationship, by primary SOC and PT
- SAEs, suspected to be related to study treatment, by primary SOC and PT
- SAEs occurring with a frequency of $\geq 0.5\%$, regardless of study treatment relationship, by PT
- SAEs, regardless of study treatment relationship, by primary SOC, PT and seriousness criteria
- AEs leading to discontinuation, regardless of study treatment relationship, by primary SOC and PT

- AEs requiring dose adjustment or study treatment interruption, regardless of study treatment relationship, by primary SOC and PT
- AEs requiring additional therapy, regardless of study treatment relationship, by primary SOC and PT
- Death resulting from AEs, regardless of study treatment relationship, by primary SOC and PT

In addition, an overview of TEAEs presenting the number and percentage of patients having at least one TEAE for each of the above categories will be provided.

2.8.1.4 Adverse events of special interest / grouping of AEs

Separate summaries will be provided for AEs related to all angioedema and positively adjudicated angioedema, regardless of study treatment relationship. The summaries will be presented by primary SOC, PT and worst severity.

2.8.2 Deaths

Patient deaths will be summarized by primary SOC, PT and study phase (see Section 2.1.1 for study phase definitions), and whether an autopsy was performed. A patient listing of all deaths with primary and contributing reasons for death will be provided. All patients in FAS will be included for the above analysis. Deaths will be coded using MedDRA terminology (v21.1 or later).

2.8.3 Laboratory data

Laboratory values will be summarized using shift tables (from baseline to most extreme post baseline value) by each laboratory parameter at its worst severity by study phase (see Section 2.1.1 for study phase phase definitions). The number and percentage of patients with laboratory values will be presented by low/normal/high (low and high) classifications to compare baseline to worst post baseline value. Unscheduled assessments will be considered.

In addition, laboratory values and the change from baseline for each parameter by visit will be summarized by treatment group and open-label sacubitril/valsartan. In the event there are multiple laboratory values within a visit, the worst value will be summarized.

A separate summary table will be presented by study phase (see Section 2.2.1 for study phase phase definitions) with the number and percentage of patients having notable lab abnormalities based on percent change from baseline (see Section 5.3 for a list of notable laboratory abnormalities). Unscheduled assessments will be considered.

Listings of all laboratory values will be provided. A separate listing for pregnancy tests will also be provided. Any notable laboratory abnormalities will be flagged.

Laboratory values indicated as $<x$ will be converted to $(0.5)(x)$ for purposes of analysis. Laboratory values indicated as $>x$ will be converted to the values specified in the below table for purposes of analysis.

Laboratory Test	Unconverted Value	Converted Value for Analysis
Red Blood Cell Count	>7.00	7.1
Potassium	>7.0	7.1
Urine Erythrocytes	>182	182.1
Urine Leukocytes	>182	182.1

The incidence of hyperkalemia through Week 12 will be calculated by treatment group. The relative risk (sacubitril/valsartan vs. enalapril) and 95% confidence interval will be presented. Hyperkalemia will be determined from the central laboratory data as potassium >5.3 mEq/L. Unscheduled assessments will be considered.

Similarly, the incidence of worsening renal function through Week 12, relative risk (sacubitril/valsartan vs. enalapril) and 95% confidence interval will be presented. Worsening renal function will be determined from the central laboratory data as a worsening (decrease) in eGFR of $\geq 35\%$ from baseline, or an increase in creatinine of ≥ 0.5 mg/dL from baseline and a worsening (decrease) in eGFR of $\geq 25\%$ from baseline. Unscheduled assessments will be considered.

2.8.4 Other safety data

2.8.4.1 Vital signs

All vital signs (systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute], respiration rate [breaths per minute], weight [kg], height [cm], and BMI [kg/m²]) will be descriptively summarized at each visit by treatment group and open-label sacubitril/valsartan. Change from baseline will also be presented.

A separate summary table will be presented with the number and percentage of patients having notable vital signs based on changes relative to baseline values (see Section 5.4 for a list of notable vital signs) by study phase (see Section 2.1.1 for study phase definitions). Unscheduled assessments will be considered.

The incidence of hypotension through Week 12 will be calculated by treatment group. The relative risk (sacubitril/valsartan vs. enalapril) and 95% confidence interval will be presented. Hypotension will be determined from the vital signs data as systolic blood pressure <90 mmHg. Unscheduled assessments will be considered.

2.8.4.2 Heart Failure (HF) Signs and Symptoms

The number and percentage of patients in the following heart failure signs and symptoms categories will be summarized by visit, treatment group and open-label sacubitril/valsartan:

- Paroxysmal nocturnal dyspnea (Absent, Present)
- Fatigue (Absent, Present)
- Edema (Absent, Trace, Feet and Ankles, Lower Legs or Thighs, Sacrum)
- Peripheral edema (Absent, Present)
- Dyspnea at rest (Absent, Present)

- Dyspnea at upon effort (Absent, Present)
- Orthopnea (Absent, Present)
- Rales (Absent, Basilar only, >1/3 of lung filled)
- Jugular venous distention (Absent, Present)
- Presence of a third heart sound (Absent, Present)
- NYHA classification (Class I, Class II, Class III, Class IV)

2.8.4.3 Angioedema

Data collected from the angioedema assessment and questionnaire will be summarized. Separate summaries will be produced for all angioedema and positively adjudicated angioedema. The number and percentage of patients for categorical variables and summary statistics for continuous variables for the following angioedema assessment data will be presented by study phase (see Section 2.1.1 for study phase definitions).

- Outcome (Not recovered/Not resolved, Recovered/Resolved, Recovering/Resolving, Recovered/Resolved with Sequelae, Fatal, Unknown)
 - Duration of angioedema in days [*end date – start date + 1*]
- Timing of event (After first dose, after multiple doses, dose not given) [not asked for events that occurred during Screening study phase]
 - Study medication discontinued due to event (No, Yes, Unknown)
 - Event occurred within 1 day of dosing (Within 1 day of dose but less than or equal to 1 hour, within 1 day of dose but greater than 1 hour, After 1 day of dosing, Unknown)
- History of prior angioedema or angioedema like event (No, Yes, Unknown)
 - If yes, medications taken at time of previous event:
 - ACE inhibitor
 - ARB
 - Renin inhibitor
 - Other medications
- Presence of hereditary angioedema (No, Yes, Unknown)
- Any family members with history of angioedema-like events (No, Yes, Unknown)
- Signs and symptoms for current event (No, Yes, Unknown)
 - Shortness of breath/dyspnea
 - Difficulty swallowing/dysphagia
 - Difficulty speaking/dysarthria

- Pain on swallowing/odynophagia
 - Stridor
 - Abdominal pain
 - Other
- Edema present (No, Yes)
 - Periorbital edema
 - Head edema
 - Neck edema
 - Lip edema
 - Tongue edema
 - Throat edema
 - Submandibular edema
 - Genitalia edema
 - Extremities edema
 - Other
- Previous edematous episodes (No, Yes, Unknown)
 - Number of previous edematous episodes
- ACEi taken in the past (before screening) (No, Yes, Unknown)
- ACEi taken (other than study medication) during trial participation after screening (No, Yes, Unknown)
 - Dose changed within 2 days of event (No, Yes, Unknown)
- ARB taken in the past (before screening) (No, Yes, Unknown)
- ARB taken (other than study medication) during trial participation after screening (No, Yes, Unknown)
 - Dose changed within 2 days of event (No, Yes, Unknown)
- Patient suffering from influenza, common cold or upper respiratory tract infection? (No, Yes, Unknown)
- Medication allergies (No, Yes, Unknown)
- Food allergies (No, Yes, Unknown)
- Potential causes of angioedema-like event (No, Yes, Unknown)
 - Food
 - Insect bite

- Animal exposure
- Medication
- Dental work
- Pollen
- Dust
- Concomitant disease
- Idiopathic
- Other
- Medical intervention (No, Yes)
 - Administration of H-1 blocker
 - Administration of H-2 blocker
 - Administration of steroids
 - Administration of epinephrine
 - Admission to hospital
 - Admission to ER
 - Endotracheal intubation
 - Tracheostomy
 - Discontinuation of ACE inhibitor (other than study medication)
 - Discontinuation of ARB (other than study medication)
 - Other

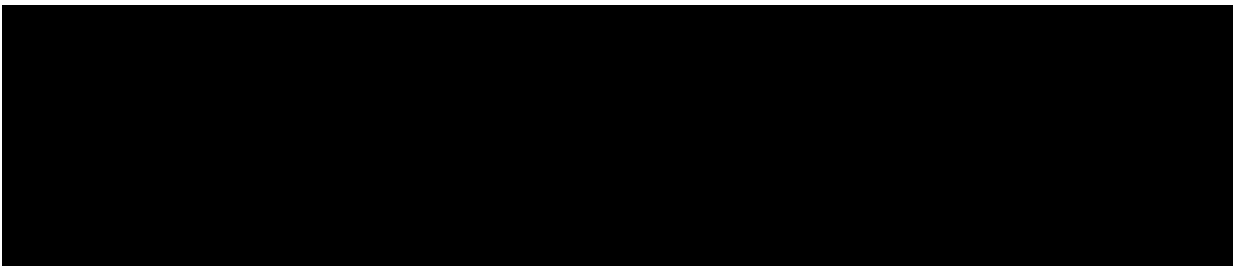
All angioedema assessment data will be listed. Additionally, the adjudicated assessment of the event will be listed separately.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.



2.12 Biomarkers

Biomarkers related to heart failure or mechanism of action (NT-proBNP, BNP, [REDACTED]) and spot urine samples for urinary biomarkers (UcGMP andUcGMP to Urinary Creatinine ratio) will be collected. Values and the change from baseline for each biomarker will be summarized by visit, treatment group and open-label sacubitril/valsartan. Analyses will be based on the FAS.

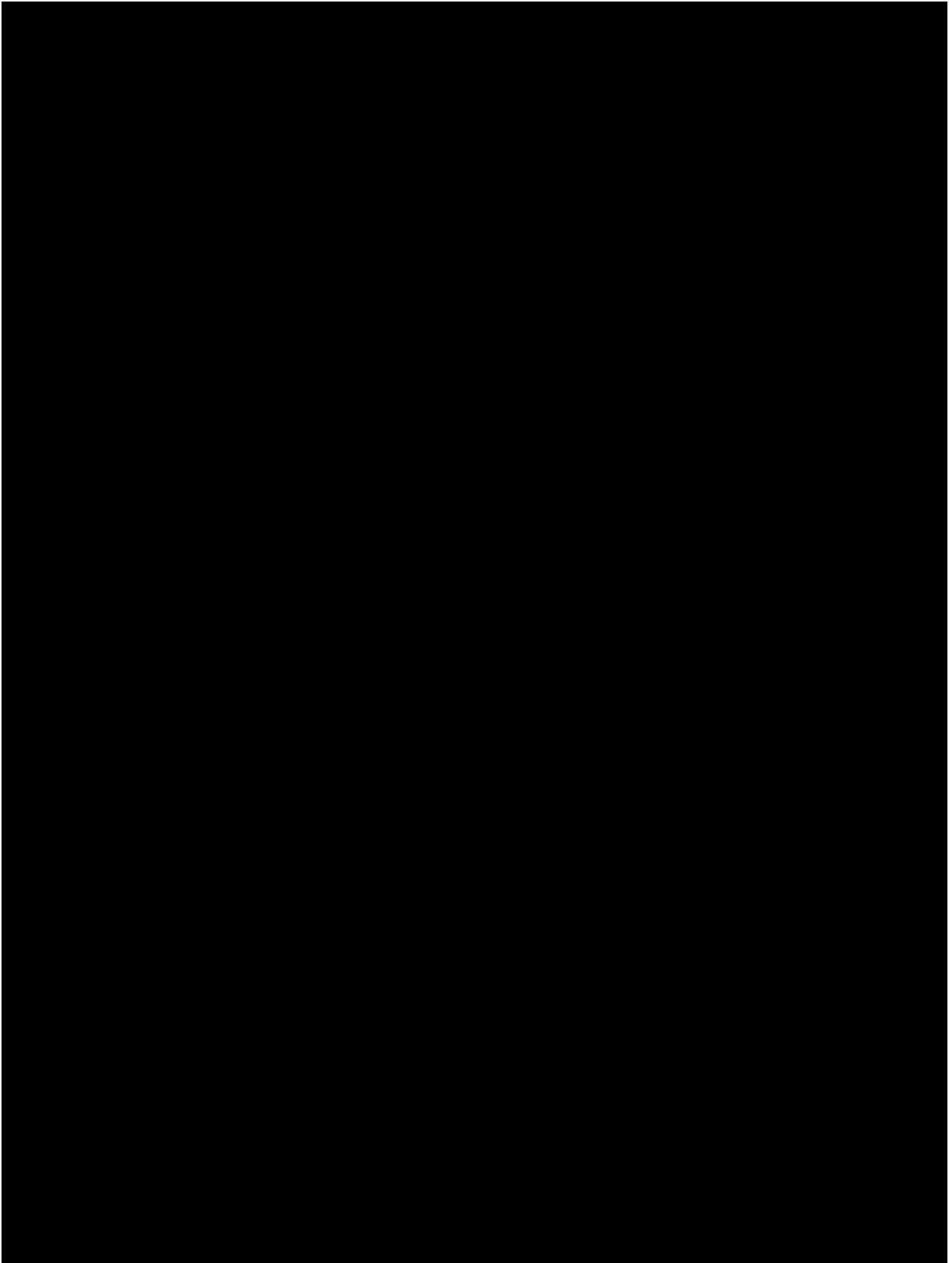
These and other selected biomarkers to be studied will be those believed to be relevant to the pathophysiology of heart failure, including those related to cardio-renal or vascular function, injury and/or fibrosis/remodeling. Biomarkers may include ones assessing cardio-renal or vascular benefit or ones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

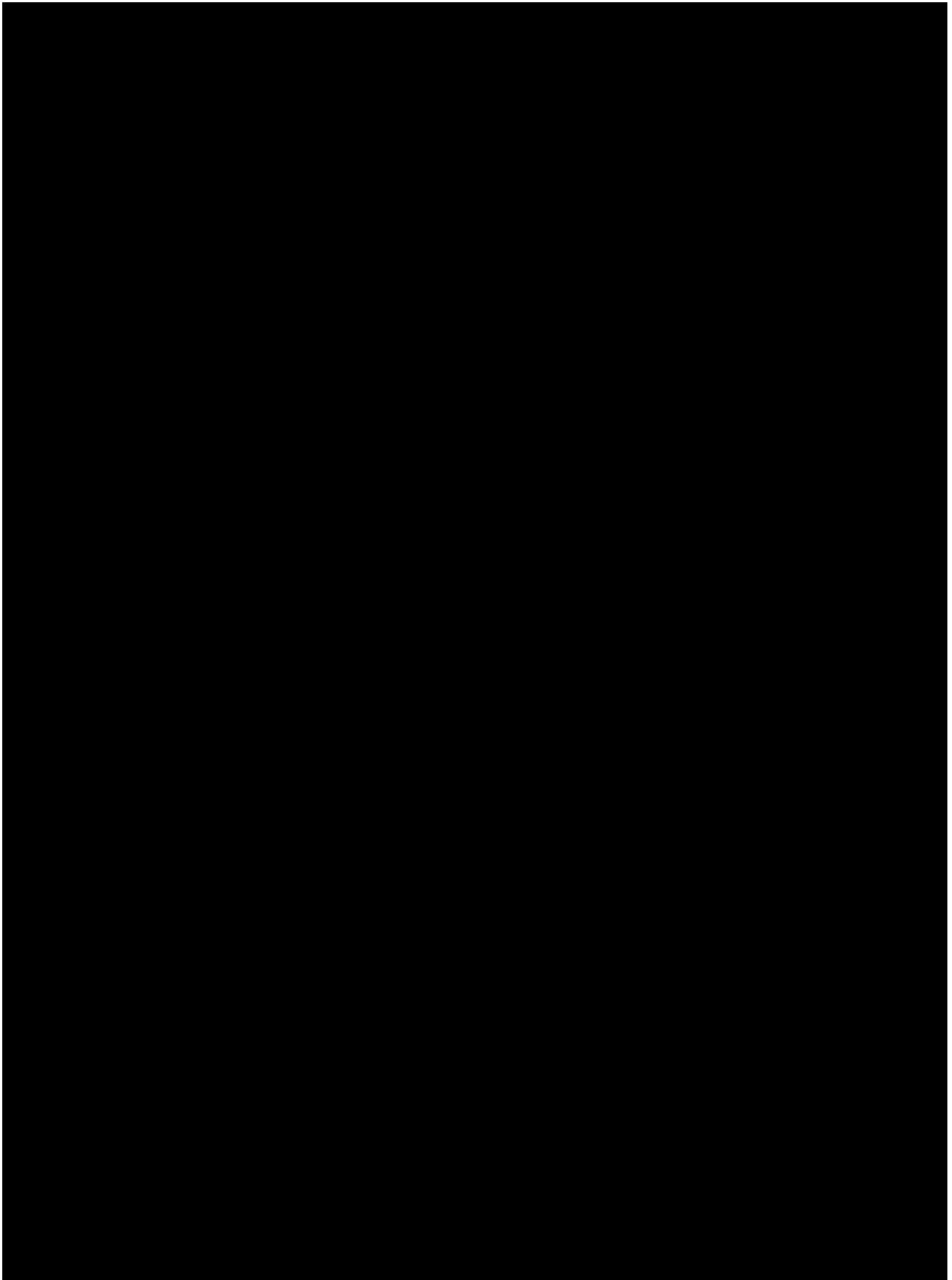
Biomarker values will be based on clinical laboratory samples processed and assessed by the central laboratory. Values below the limit of detection (LOD) (i.e., indicated as <LOD) will be converted to (0.5)(LOD) for purposes of analysis. Values indicated as 'Reported and Unreliable' will be excluded from analysis.

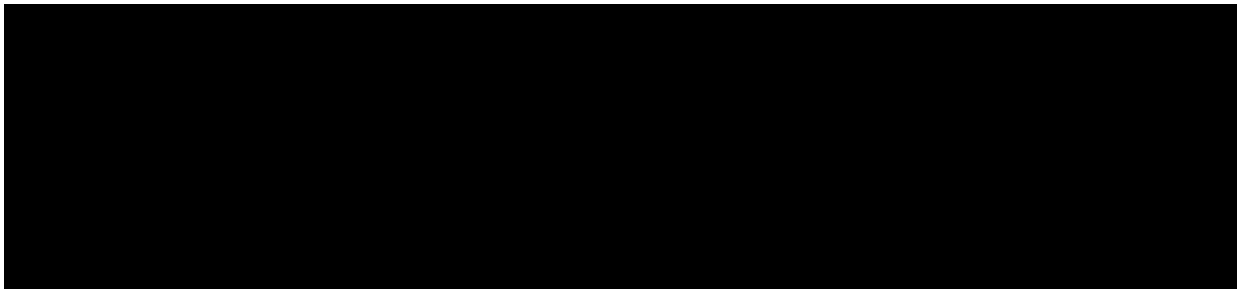
Biomarker samples from patients who withdrew consent will not be analyzed by the central laboratory.

BNP samples, which were originally assayed using P100 tubes, will be re-assayed using EDTA tubes for purposes of a side-by-side comparison of results where the value and change from baseline at each visit will be summarized for the subset of patients who have change from baseline values for the two BNP assays at the given visit.

Additional analysis of biomarkers is discussed in Sections 2.7 and 2.13.







2.14 Interim analysis

No interim analysis is planned.

3 Sample size calculation

In CHOIR (Mitchell 2002), treatment with Omapatrilat was associated with an approximately ~10% reduction in characteristic impedance at 12 weeks, with little or no change seen amongst enalapril- treated patients. Based on a similar study design and population, and accounting for a dropout rate of 20% from first visit to subsequent follow up and a 10% rate of non-evaluable data, assuming a standard deviation of 80 for the primary efficacy variable and 90% power, a sample size of 432 patients (216 per arm) will be necessary to detect a clinically important change of 30 dyne x sec/cm⁵ between the two treatment groups.

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

4 Change to protocol specified analyses

The following changes to protocol specified analyses were made:

- Modified baseline definition as follows:
 - Eliminated requirement that assessment date:time is prior to first dose date:time
 - Clarified how baseline assessments for hemodynamic variables will be identified
- Clarified that tables summarizing demographics and baseline data will be run only on the FAS, and not also on the RS as indicated in the protocol
- Indicated that values of the hemodynamic variable carotid-femoral pulse wave velocity will be negative inverse transformed prior to analysis
- Added separate summaries of prior and concomitant CV, HF, ACEi and ARB medications
- Added the following supportive analyses of the primary endpoint:
 - On-treatment analysis

- Analysis using the “original” aortic characteristic impedance variable
- Analysis using the “alternative” aortic characteristic impedance variable
- Added on-treatment analyses of the secondary endpoints
- Modified the PPS definition to clarify that major protocol deviations will exclude patients from the PPS regardless of the study phase in which they occur
- Added summary of the incidence of hypotension through Week 12
- Added separate summaries of the incidence of hyperkalemia and worsening renal function through Week 12 based on central laboratory data
- Added summary of positively adjudicated angioedema
- Removed CPK from the list of notable chemistry abnormalities since this safety lab was not performed for the study
- Except for the Study Objectives and Endpoints section (to maintain consistency with the corresponding protocol objectives wording), references to "Carotid pressure-flow + pulsatility index" were replaced by "Aorta-carotid reflection coefficient and carotid pulsatility index" as it is a more accurate description
- Clarified that BNP samples will be re-assayed using EDTA tubes for purposes of a side-by-side comparison of results where the value and change from baseline at each visit will be summarized for the subset of patients who have change from baseline values for the 2 BNP assays at the given visit

5 Appendix

5.1 Imputation rules

5.1.1 Study treatment

Full dates for study treatment collected on the eCRF are required; therefore, no imputations will be made.

5.1.2 AE date imputation

The following algorithm should be used to estimate start dates for which only partial information is known:

- Missing day and month
 - If the year is the same as the year of first study treatment, then the day and month of the start date of treatment will be assigned to the missing fields.
 - If the year is prior to the year of first study treatment, then December 31 will be assigned to the missing fields.
 - If the year is after the year of first study treatment, then January 1 will be assigned to the missing fields.

- Missing month only
 - Treat day as missing and replace both month and day according to the above procedure.
- Missing day only
 - If the month and year are the same as the year and month of first study treatment, then the start date of treatment will be assigned to the missing day.
 - If the month and year are before the year and month of first study treatment, then the last day of the month will be assigned to the missing day.
 - If the month and year are after the year and month of first study treatment, then the first day of the month will be assigned to the missing day.

If the imputed start date result is after the stop date (and the stop date is complete), the imputed start date will be reset to the stop date.

The following algorithm should be used to estimate stop dates for which only partial information is known:

- Missing year
 - Date left missing.
- Missing month
 - Impute 'December'.
- Missing day
 - Impute 'last date of that month'.

5.1.3 Concomitant medication date imputation

The following algorithm should be used to estimate start dates for which only partial information is known:

- Missing day and month
 - If the year is the same as the year of first study treatment, then the day and month of the start date of treatment will be assigned to the missing fields.
 - If the year is prior to the year of first study treatment, then December 31 will be assigned to the missing fields.
 - If the year is after the year of first study treatment, then January 1 will be assigned to the missing fields.
- Missing month only
 - Treat day as missing and replace both month and day according to the above procedure.
- Missing day only

- If the month and year are the same as the year and month of first study treatment, then the start date of treatment will be assigned to the missing day.
- If the month and year are before the year and month of first study treatment, then the last day of the month will be assigned to the missing day.
- If the month and year are after the year and month of first study treatment, then the first day of the month will be assigned to the missing day.

If the imputed start date result is after the stop date (and the stop date is complete), the imputed start date will be reset to the stop date.

The following algorithm should be used to estimate stop dates for which only partial information is known:

- Missing year
 - Date left missing. Consider the medication to have been received at all periods after that period determined by the start date.
- Missing month
 - Impute 'December'.
- Missing day
 - Impute 'last date of that month'.

5.2 AEs coding/grading

The [REDACTED] coding team will code the AE terms using MedDRA v21.1 or later. If any terms are not coded, the data management team will issue queries to sites to update the AE term appropriately.

5.3 Laboratory parameters derivations

5.3.1 Laboratory grading

The collected laboratory values will be summarized by severity (low/normal/high) and not converted to Common Terminology Criteria for Adverse Events (CTCAE) grades.

5.3.2 Notable laboratory values

Hematology

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

Blood Chemistry

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

5.4 Vital signs

5.4.1 Notable vital sign values

Systolic blood pressure	<90 mmHg and decrease of >20 mmHg from baseline >180 mmHg and increase of >20 mmHg from baseline
Diastolic blood pressure	<50 mmHg and decrease of >15 mmHg from baseline >105 mmHg and increase of >15 mmHg from baseline
Pulse	<50 bpm and decrease of > 15 bpm from baseline >120 bpm and increase of >15 bpm from baseline
Weight	>7% decrease; >7% increase

5.5 Statistical models

5.5.1 Primary analysis

The null hypothesis for the primary analysis is the difference between the sacubitril/valsartan and enalapril groups in the mean change from baseline in aortic characteristic impedance at Week 12 is equal to zero. An ANCOVA model will be used. The model will have the change from baseline as the dependent variable with treatment as a fixed effect factor and the baseline value as a covariate. The general form for the ANCOVA model is:

$$y_{ij} = \mu + \alpha_i + \beta(x_{ij} - \bar{x}) + \epsilon_{ij}$$

where i indexes treatment group and j indexes patient within treatment group. PROC MIXED in SAS will be used for the analysis (refer to the SAP TFL shells document for additional details).

5.5.2 Key secondary analysis

The analysis of NT-proBNP is similar to the primary analysis, except the null hypothesis is the ratio of the geometric means of NT-proBNP (Week 12/baseline) for the sacubitril/valsartan and enalapril groups are equal. An ANCOVA model will be used. The model will have the proportional change from baseline in a logarithmic scale as the dependent variable with treatment as a fixed effect factor and the logarithmic baseline value as a covariate. The general form for the ANCOVA model is:

$$y_{ij} = \mu + \alpha_i + \beta(x_{ij} - \bar{x}) + \epsilon_{ij}$$

where i indexes treatment group and j indexes patient within treatment group. PROC MIXED in SAS will be used for the analysis (refer to the SAP TFL shells document for additional details).

5.6 Rule of exclusion criteria of analysis sets

Table 1 Protocol deviations that cause patients to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses
I03	Patient did not have history of HTN and one of the following at BOTH screening and pre-randomization: a. SBP > 105 mm Hg on antihypertensive medication b. SBP \geq 140 mm Hg and NOT on antihypertensive medication	Exclusion from PPS
I04	Patient was not diagnosed with heart failure NYHA class I-III and reduced ejection fraction \leq 40%	Exclusion from PPS
E01	Patient has a history of hypersensitivity to any of the study drugs, including history of hypersensitivity to drugs of similar chemical classes, or allergy to ACEis, ARBs, or NEP inhibitors as well as known or suspected contraindications to the study drugs	Exclusion from PPS
E02	Patient has history of intolerance to sacubitril and valsartan, ACEi or ARB standard of care doses	Exclusion from PPS
E03	Patient has history of angioedema	Exclusion from PPS
E04	Patient requires treatment with both ACE inhibitor and ARB	Exclusion from PPS

Deviation ID	Description of Deviation	Exclusion in Analyses
E12	Patient had a persistent or permanent atrial fibrillation at Screening/Baseline (Visit 1)	Exclusion from PPS
E13	Patient had Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid or other major CV surgery, percutaneous coronary intervention (PCI) or carotid angioplasty within the 3 months prior to first Screening/Baseline (Visit 1)	Exclusion from PPS
E14	Patient has an Implantation of a cardiac resynchronization therapy pacemaker (CRT-P) or a cardiac resynchronization therapy defibrillator (CRT-D) or upgrading of an existing conventional pacemaker or an implantable cardioverter defibrillator (ICD) to CRT device within 3 months prior to first visit or intent to implant such a device	Exclusion from PPS
E15	Patient has a heart transplant or ventricular assistance device (VAD) or intent to transplant (on transplant list) or implant a VAD	Exclusion from PPS
E16	Patient has a Coronary or carotid artery disease likely to require surgical or percutaneous intervention within the 6 months after Visit 1	Exclusion from PPS
E17	Patient has a hemodynamically significant aortic stenosis/regurgitation or mitral valve disease other than mitral valve regurgitation related to LV dilation	Exclusion from PPS
E18	Patient has a presence of other hemodynamically significant obstructive lesions of left ventricular outflow tract, including aortic and sub-aortic stenosis	Exclusion from PPS
E28	Patient is unable to secure technically adequate baseline tonometry study	Exclusion from PPS
E29	Patient is pregnant or nursing (lactating)	Exclusion from PPS
O03	Patient randomized in error and not dosed with study drug	Exclusion from FAS and PPS

Table 2 Patient Classification

Analysis Set	PD ID that cause patients to be excluded	Non-PD criteria that cause patients to be excluded
RS	NA	Not randomized
FAS	O03	Not in RS
PPS	I03, I04, E01, E02, E03, E04, E12, E13, E14, E15, E16, E17, E18, E28, E29, O03	Not in FAS
SS	NA	No double-blind study treatment received

6 Reference

Chen M, Kianifard F (2000) A nonparametric procedure associated with a clinically meaningful efficacy measure. *Biostatistics*; 1(3):293-298.

Mitchell GF, Izzo JL, Jr., Lacourciere Y, Ouellet JP, Neutel J, Qian C, Kerwin LJ, Block AJ, Pfeffer MA (2002) Omapatrilat reduces pulse pressure and proximal aortic stiffness in patients with systolic hypertension: results of the conduit hemodynamics of omapatrilat international research study. *Circulation*; 105(25):2955-2961.

