NOVARTIS

Clinical Development

LCZ696/Sacubitril/Valsartan/Entresto®

CLCZ696BUS01 / NCT02554890

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

Statistical Analysis Plan (SAP)

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Document type: SAP Documentation

Document status: Final 2.0, Amendment 1

Release date: 20-Aug-2018

Number of pages: 49

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
27-Sep-2016	Prior to DB Lock	Creation of Final Version	NA – First Version	NA
20-Aug-2018	Prior to DB Lock	Creation of Amendment 1	1. Updated to align with protocol version 02 (amended protocol) dated 05-Oct-2017: sample size increase; addition of secondary endpoint (proportional change in NT-proBNP from baseline to Week 8); █████████████	1. Section 1 Introduction; Section 1.1 Study Design; Section 1.2 Study Objectives and Endpoints; Section 2.7.1 Secondary Endpoints; Section 2.7.2 Statistical Hypothesis, Model, and Method of Analysis; ████████ ████████████
			2. Clarified baseline definition for safety labs and biomarkers █ ████████	
			3. Added sensitivity analysis for primary endpoint based on "strict" baseline definition (i.e., collection date:time < first dose date:time)	2. Section 2.1.1 General Definitions
			4. Modified definition of treatment emergent AEs and flagging of deaths in listing to remove "28 days post last dose of study treatment" lag time	3. Section 2.5.4 Supportive Analyses; Section 4 Change to Protocol Specified Analyses
			████████████████ ████████████████ ██████████	4. Section 2.8.1.2 General Rules for AE Reporting; Section 2.8.2 Deaths
			6. Clarified that biomarker samples from patients who withdraw consent will not be analyzed by the central laboratory	██████████ ███
			7. Removed "on treatment" terminology and "28 days post last dose of study treatment" lag time (from the open-label phase definition)	6. Section 2.12 Biomarkers
				7. Section 2.1.1 General Definitions
			8. Clarified coding dictionary versions to be utilized	8. Section 2.3.4 Demographics and Other Baseline Characteristics;

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			9. Clarified that analyses of BNP and NT-proBNP values will be based on samples processed/assessed by the central laboratory	Section 2.4.2 Prior, Concomitant and Post Therapies; Section 2.8.1.1 Coding of AEs
			10. Clarified definitions for double-blind, open-label, and pooled phases, and changed terminology from "treatment phase" to "study phase"	9. Section 2.1.1 General Definitions; Section 2.12 Biomarkers
			████████████████████ ████████████████████ ████████████████████ ████████████████████	10. Section 2.1.1 General Definitions
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				13. Section 2.1.1 General Definitions
			13. Clarified that date of last contact will be determined from the Date of Last Contact field on the Study Completion/Exit eCRF	████████████████
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			████████████████████ ████████████████████	17. Section 2.7.1 Secondary Endpoints; Section 2.7.2 Statistical Hypothesis, Model, and Method of Analysis; Section 4 Change to Protocol Specified Analyses
			████████████████████ ████████████████████ ████████████████████ ████████████████████ ████████████████████	18. Section 2.5.4 Supportive Analyses; Section 4 Change to Protocol Specified Analyses

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			██████████████	████████████
			17. Specified the following biomarkers as secondary endpoints: UcGMP to urinary creatinine ratio, BNP, and NT-proBNP to BNP ratio	████████████
			18. Replaced supportive analysis of the primary endpoint consisting of summary statistics and t-test p-values for comparing treatment groups on the proportional change from baseline in a logarithmic scale at Weeks 4 and 8 with ANCOVA at Weeks 4 and 8	21. Section 2.2 Analysis Sets; Section 4 Change to Protocol Specified Analyses
			██████████████	22. Section 2.4.1 Study Treatment/Compliance
			██████████████	23. Section 5.6 Rule of Exclusion Criteria of Analysis Sets
			██████████████	24. Section 2.2.1 Subgroup of Interest
			21. Modified the Safety Set definition to remove the word 'active' so that inclusion in the Safety Set is not restricted to patients who received at least one dose of *active* study treatment	25. Section 2.3.1 Patient Disposition
				26. Section 2.3.4 Demographics and Other Baseline Characteristics
				27. Section 2.3.3 Index Hospitalization
			22. Clarified that duration of exposure during the double-blind phase is calculated from the date of first study treatment (not date of first *active* study treatment); added summary of patient dose level and titration data by visit and systolic blood pressure using visit-specific cut-off values from dose titration schedule	28. Section 2.3.4 Demographics and Other Baseline Characteristics
				29. Section 5.4.1 Notable Vital Sign Values
				30. Section 2.8.4.4 HF Signs and Symptoms

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			23. Updated rules of exclusion criteria of analysis sets based on final review of PDs and associated final PD documentation (VAP Module 3 v3.0 dated 15Aug2018)	31. Section 2.7.2 Statistical Hypothesis, Model, and Method of Analysis; Section 2.8.1.4 Adverse Events of Special Interest/Grouping of AEs; Section 2.8.4.6 Angioedema
			24. Combined <30 and 30 – <45 baseline eGFR subgroups into <45 subgroup due to low number of patients in <30 subgroup	
			25. Added disposition categories for patients who prematurely discontinued study treatment during double-blind and open-label phases that exclude deaths; removed disposition categories for patients who completed the double-blind and open-label phases as these are covered in the study completion tables; removed disposition category for patients who were not randomized	32. Section 2.8.1.3 AE Summaries
			26. Added source of patient referral and summary (continuous and categorical) of NT-proBNP and BNP values from local laboratory to demographic and baseline characteristics table; removed Pooled column and broke out Open-Label Sacubitril/Valsartan column by randomized treatment group for all demographic and baseline data tables	
			27. Clarified that summary of index hospitalization data will only be treatment group (and not also by open-label and pooled sacubitril/valsartan)	40. Section 2.5.4 Supportive Analyses
			28. Added categorical summary of number of hospitalizations for HF within past 12 months (excluding index hospitalization)	41. Section 2.4.2 Prior, Concomitant and Post Therapies
			29. Modified notable vital signs criteria	42. Section 2.3.1 Patient Disposition
			30. Clarified that HF Signs and Symptoms will be summarized at	43. Section 2.3.4 Demographics and

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			all visits (not just Randomization and Week 8)	Other Baseline Characteristics
			31. Clarified that separate summaries/analyses of angioedema data, including AEs related to angioedema, will be produced – one based on all angioedema and the other based on positively adjudicated angioedema; added a summary of key characteristics of positively adjudicated angioedema	44. Section 2.3.4 Demographics and Other Baseline Characteristics 45. Section 2.4.1 Study Treatment/Compliance
			32. Added an AE overview table (number and percentage of patients in various AE categories) and two SAE tables (occurring with frequency ≥0.5%; by seriousness criteria)	██████████████
			███████████████	48. Section 2.7.2 Statistical Hypothesis, Model, and Method of Analysis; Section 4 Change to Protocol Specified Analyses
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			███████████████	52. Section 2.2 Analysis Sets; Section 4 Change to Protocol Specified Analyses
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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
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			40. Added a descriptive summary of patient evaluability for primary endpoint analysis based on NT-proBNP values	
			41. Removed reference to diuretics being combined into a single dose equivalent for purposes of the diuretic dose summaries during the index hospitalization and at post-randomization visits	
			42. Modified categories for study completion at Weeks 8 and 12	
			43. Added variable "Time from presentation to randomization (days)" to summary of disease characteristics	
			44. Added variables "ACEi naïve", "ARB naïve", and "ACEi/ARB naïve" to summary of disease characteristics	
			45. Added variable "Dispensed dose level 3 by Week 6" to dose level by visit summary	
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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			████████████████ ██████ ██████	
			48. Added Weeks 4 and 8 to the analysis of change from baseline in biomarkers defined as secondary endpoints; clarified that analysis of hs-Troponin T will not be performed at Week 2 since it is not measured at Week 2	
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			███████████ ████████	
			52. Modified PPS definition to clarify that major protocol deviations will exclude patients from the PPS regardless of the study phase in which they occur	
			██████████████ ███████████████ ███████ ██████	
			54. Implemented various minor clarifications, including those reflected in updated version of DCTs dated 12-Dec-2017	

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List of abbreviations

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

NT-proBNP	N-terminal Prohormone of B-type Natriuretic Peptide
NYHA	New York Heart Association
PD	Pharmacodynamic
PK	Pharmacokinetic
PPS	Per-Protocol Set
PT	Preferred Term
RBB	Right Bundle Branch
RS	Randomized Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-emergent Adverse Event
TFLs	Tables, Figures, Listings
TIA	Transient Ischemic Attack
UcGMP	Urinary cGMP
VAD	Ventricular Assist Device
WHO	World Health Organization

1   Introduction

The statistical analysis plan (SAP) will outline in detail the analyses planned in the protocol. The analyses will be used to generate the Clinical Study Report (CSR). The SAP is based on protocol version 02 (Amended protocol) dated 05-Oct-2017 and the data collection tool (DCT) version 14.0 dated 12-Dec-2017.

1.1   Study design

This study will use a randomized, double-blind, double-dummy, active-controlled, parallel group design. Eligible patients hospitalized for acute decompensated heart failure (ADHF) will be randomized no earlier than 24 hours and up to ten days of presentation while still hospitalized. A total of approximately 882 patients randomized to sacubitril/valsartan or enalapril in a 1:1 ratio is planned with no stratification.

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

- Systolic blood pressure (SBP) $\geq$ 100 mmHg for the preceding 6 hours prior to randomization; no symptomatic hypotension

- No increase (intensification) in intravenous (i.v.) diuretic dose within last 6 hours prior to randomization

- No i.v. inotropic drugs for 24 hours prior to randomization

- No i.v. vasodilators including nitrates within last 6 hours prior to randomization

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

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

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

Eligible patients will be randomized no earlier than 24 hours after presentation at the hospital and no later than within ten days of admission, while still hospitalized, via interactive web

response system (IWRS) to one of the treatment arms. The investigator or his/her delegate will contact the IWRS after confirming that the patient fulfills all of the study entry criteria. The IWRS will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify which bottle from the centralized hospital supply the patient will be dosed for the first day and a unique medication number for the first package of investigational treatment to be dispensed to the patient.

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

The primary time point will be Weeks 4 and 8.

There are no interim analyses planned.

1.2   Study objectives and endpoints

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

The secondary objectives of this study are to examine the effect of sacubitril/valsartan vs. enalapril on:
- The proportional change in NT-proBNP from baseline to Week 8
- Incidence of symptomatic hypotension during 8 weeks of treatment
- Incidence of hyperkalemia (Potassium >5.5 mEq/L) during 8 weeks of treatment
- Incidence of angioedema during 8 weeks of treatment
- Biomarkers: hs-Troponin (high sensitivity), urinary cyclic Guanosine 3',5'-Monophosphate (cGMP) and B-type natriuretic peptide (BNP) to NT-proBNP ratio at 4 and 8 weeks
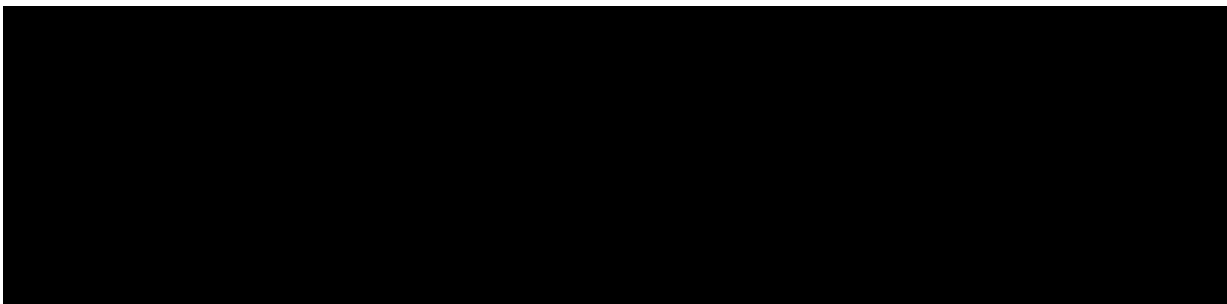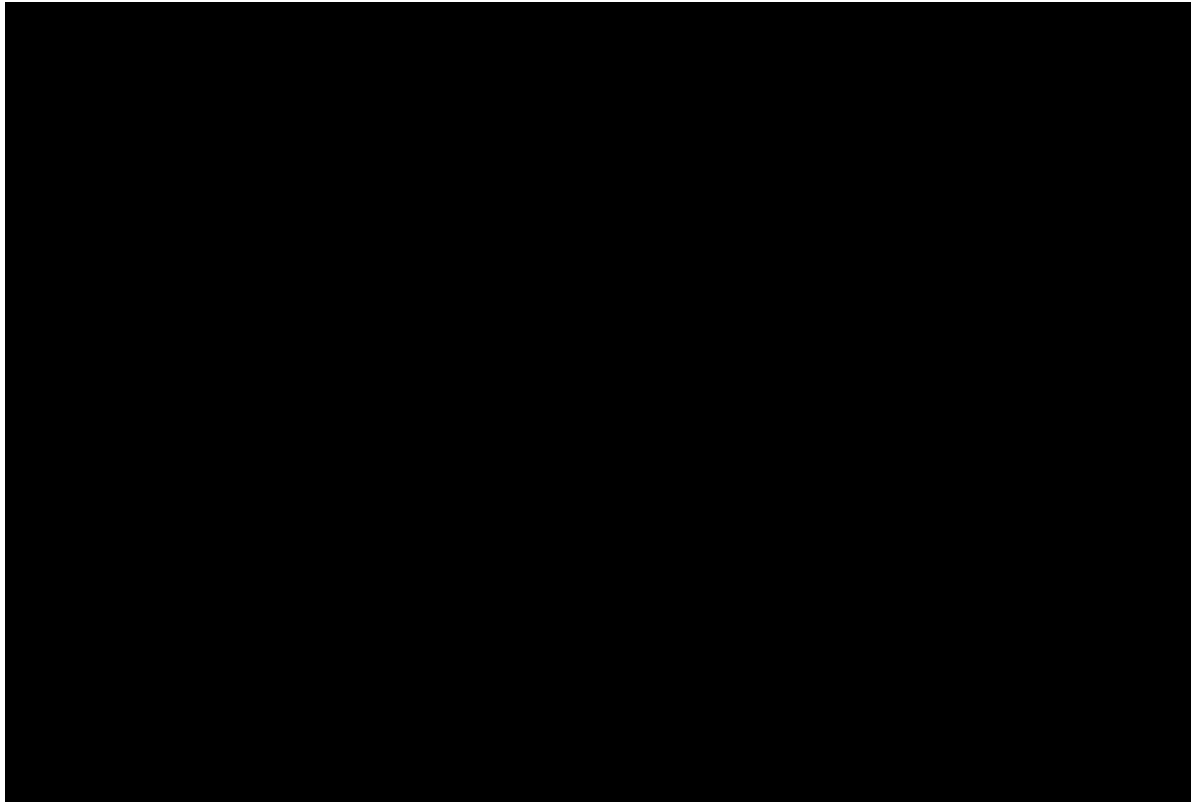
2   Statistical methods

2.1   Data analysis general information

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

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

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

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

2.1.1   General definitions

Study treatment

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

Baseline

For safety labs and biomarkers, baseline is defined as the last non-missing assessment collected <3 hours from the first dose of study treatment, including matching placebos. For patients not treated, baseline is defined as the last non-missing assessment prior to or on the date of randomization. BNP and NT-proBNP values will be based on clinical laboratory samples processed and assessed by the central laboratory.

For other assessments, including those for which assessment time is collected (ECGs, HF Signs and Symptoms, and pregnancy tests), baseline is defined as the last non-missing assessment prior to or on the start date of study treatment (randomization date for patients not treated), including matching placebos.

Date of first administration of study treatment

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

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

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

Date of last administration of study treatment

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

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

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

Study day

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

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

Double-blind phase

Assessments performed at Weeks 1, 2, 4, 6, or 8 (including, but not limited to, vital signs) are assigned to the double-blind phase for summarization purposes. Unscheduled assessments are not assigned to a study phase for purposes of by-visit summaries.

For summarization of adverse events [AEs], medications, protocol deviations, notable vital signs and laboratory abnormalities, and symptomatic hypotension by study phase, an assessment during the double-blind phase is defined as any assessment obtained in the following time interval:

Date of randomization (or date of first administration of study treatment, as appropriate) through the date of the Week 8 visit, inclusive. For patients without a Week 8 visit, a projected Week 8 visit date will be derived relative to their randomization date.

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

Open-label phase

Assessments performed at Weeks 10 or 12 (including, but not limited to, vital signs) are assigned to the open-label phase for summarization purposes. Unscheduled assessments are not assigned to a study phase for purposes of by-visit summaries.

For summarization of AEs, medications, protocol deviations, notable vital signs and laboratory abnormalities, and symptomatic hypotension by study phase, an assessment during the open-label phase is defined as any assessment obtained in the following time interval:

After the date of the Week 8 visit. For patients without a Week 8 visit, a projected Week 8 visit date will be derived relative to their randomization date.

Patients who died, withdrew consent, or were lost to follow-up prior to or on their projected Week 8 visit date will be excluded from the open-label phase.

Pooled phase

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

Last contact

The date of last contact will be determined from the Date of Last Contact field on the Study Completion/Exit eCRF.

Year, month and week

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

1 year = 365.25 days

1 month = 30.3475 days

1 week = 7 days

1 day = 24 hours

2.2 Analysis sets

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

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

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

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

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

2.2.1 Subgroup of interest

The following subgroups will be analyzed for the primary objective and the secondary objective for AEs of special interest:

1. Age group (<65, ≥ 65 years) and (<75, ≥ 75 years)
2. Ejection fraction categories prior to randomization ($>40\%$, $>30\%$ - 40%, $>20\%$ - 30%, $\leq 20\%$)
3. Prior use of ACEi/ARB (at the time of hospitalization)
4. Baseline quartiles of NTproBNP (randomization sample)
5. Baseline eGFR (<45, 45 - <60, ≥ 60 ml/min/1.73 m^2)
6. Systolic blood pressure at randomization (<110, ≥ 110 mm Hg)

See Sections 2.5 and 2.7 for further details on the primary and secondary objectives, respectively.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

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

- Number of patients who were screened
- Primary reason for not continuing to double-blind phase

- o Investigator decision

  o Subject/Guardian decision

  o Screen failure

  o Adverse event

  o Pregnancy

  o Study terminated by sponsor

  o Technical problems

  o Death

- Number of patients who were randomized

- Number and percentage of patients who were treated

- Number and percentage of patients who prematurely discontinued study treatment during double-blind phase

- Number and percentage of patients who prematurely discontinued study treatment during double-blind phase, excluding deaths

- Number and percentage of patients who prematurely discontinued study treatment during open-label phase

- Number and percentage of patients who prematurely discontinued study treatment during open-label phase, excluding deaths

- Reasons for premature discontinuation of study treatment (separately for double-blind phase and open-label phase)

  o Adverse event

  o Death

  o Protocol deviation

  o Investigator decision

  o Subject/Guardian decision

  o Lost to follow-up

  o Technical problems

  o Pregnancy

  o Withdrawal of consent

  o Noncompliance with study treatment

  o Study terminated by sponsor

- Study duration in months [*(date of last contact/death – date of randomization +1)/30.3475*]

A separate summary for study completion will be presented and the FAS will be used. The following categories will be summarized at Week 8 by treatment group, open-label and pooled sacubitril/valsartan:

- Patients who received at least one dose of study treatment

- Patients who did not receive at least one dose of study treatment

- Patients with known vital status at Week 8

    o Dead prior to opening of projected Week 8 visit window

    o Completed Week 8 visit after opening of projected Week 8 visit window

    o Any visit/contact with visit date after opening of projected Week 8 visit window

    o Vital status recorded with last known alive date after opening of projected Week 8 visit window

- Patients with unknown vital status at Week 8

    o Lost to follow-up prior to opening of projected Week 8 visit window

    o Withdrawal of informed consent to any follow-up prior to opening of projected Week 8 visit window

The following categories will be summarized at Week 12 by treatment group, open-label and pooled sacubitril/valsartan:

- Patients who received at least one dose of study treatment

- Patients who did not receive at least one dose of study treatment

- Patients with known vital status at Week 12

    o Dead

    o Visit

        ▪ In person with patient

        ▪ Telephone (or video) contact with patient

        ▪ Known alive through other contact with patient or contact with party other than patient

        ▪ Other contact with patient (mail, email, text, social media, etc.)

- Patients with unknown vital status at Week 12

    o Lost to follow-up

    o Withdrawal of informed consent to any follow-up

Additionally, listings of inclusion/exclusion criteria, screening disposition, reason for withdrawal of consent and study treatment disposition will be provided.

Any visit that did not occur per protocol will be listed with the reason it was not done.

2.3.2   Protocol deviations

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

2.3.3   Index hospitalization

The number and percentages of the following information about patients and their index hospitalization visit will be summarized by treatment group. The RS will be used.

- Patient in shock (No, Yes, Unknown)
- Patients receiving following treatment from index hospitalization to randomization
    - Vasopressor (No, Yes, Unknown)
    - Inotrope (No, Yes, Unknown)
    - Nitroprusside (No, Yes, Unknown)
    - Nesiritide (No, Yes, Unknown)
    - Patient cared for in Intensive Care Unit (ICU) (No, Yes, Unknown)

The number and percentage (categorical variables) and descriptive statistics (continuous data) for information on patient index hospitalization discharge will be summarized by treatment group. The RS will be used.

- Duration of index hospitalization stay in days [(*date:time of discharge – date:time of arrival)/(3600*24)*]
- Discharge disposition (Home or with family/friends, Rehabilitation facility, Skilled nursing facility, Death, Unknown)
- Discharge weight (kg)
- New York Heart Association (NYHA) class (I, II, III, IV, Not done)
- Patient experienced worsening heart failure since randomization (No, Yes, Unknown)
- Patient cared for in ICU (No, Yes, Unknown)
    - Number of nights in ICU since randomization
- Patient treated with any of the following medication classes since randomization (Intravenous inotrope, Intravenous vasopressor, Nitroprusside, No, Unknown)
- Patient took third dose of double-blind study treatment (No, Yes)

All information relating to the index hospitalization will be listed.

2.3.4   Demographics and other baseline characteristics

Demographics, baseline characteristics, and disease history are collected at the screening visit. Descriptive summaries and/or listings will be provided. The number and   percentage

(categorical variables) and descriptive statistics (continuous data) for the information below will be summarized by treatment group for both double-blind and open-label patients.

The FAS will be used.

Demographics and baseline characteristics

Demographic variables include:

- Age (years), age group (<65 years and ≥65 years; <75 years and ≥75 years)
- Sex (Male, Female)
  - Child bearing status (Able to bear children, Premenarche, Post-menopausal [per-protocol >12 months], Sterile-of child bearing age)
- Race (Caucasian, Black, Asian, Native American, Pacific Islander, Unknown, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Source of patient referral (Physician's own practice, Physician referral, Advocacy group, ER or hospital, Friend/family member, Patient database, Unknown, Other)

Baseline characteristic variables include:

- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2) [= *weight (kg)/height (m)^2 from screening visit 1*]
  - BMI categories (<20, 20 - <25, 25 - 30, >30 kg/m^2)
- Smoking history (Former, Current, Never)
- Heart rate (bpm)
- Bundle branch block (or Intraventricular Conduction Delay [IVCD]) present (No, Yes)
  - Bundle branch block type (Left bundle branch [LBB] block, Right bundle branch [RBB block], Non-specific intraventricular conduction delay)
- NT-proBNP (pg/mL), separately for values based on clinical laboratory samples processed and assessed by the central and local laboratories
  - NT-proBNP categories (<450, 450 - <900, 900 - <1600, 1600 - <3200, 3200 - <7400, 7400 - <10000, ≥10000 pg/mL)
- BNP (pg/mL), separately for values based on clinical laboratory samples processed and assessed by the central and local laboratories
  - BNP categories (<100, 100 - <225, 225 - <400, 400 - <800, 800 - <1850, 1850 - <2500, ≥2500 pg/mL)

Disease characteristics

Disease characteristic variables include:

- Category of prior chronic heart failure (CHF) medication (ACEi, Angiotensin Receptor Blocker [ARB], Beta blocker, Aldosterone antagonist, Ivabradine, Hydralazine, Nitrates [long lasting], Digoxin, Diuretic)

- ACEi naïve (No, Yes); ARB naïve (No, Yes); ACEi/ARB naïve (No, Yes)

- History of HF prior to qualifying HF event (No, Yes, Unknown)

- Number of hospitalizations with primary diagnosis of HF within past 12 months not including index hospitalization

  - Number of hospitalizations categories (0, 1, 2, ≥3, Not Applicable)

- Total number of hospitalizations for any reason within past 12 months

- NYHA classification 30 days prior to index hospitalization (I, II, III, IV, Unknown)

- Ejection fraction (%)

  - Ejection fraction categories (>40%, >30% - 40%, >20% - 30%, ≤20%)

- Time from presentation to randomization (days)

Cardiovascular history

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

- Hypertension (No, Yes, Unknown)

- Transient Ischemic Attack (TIA) (No, Yes, Unknown)

- Stroke (No, Yes, Unknown)

- Peripheral vascular disease (No, Yes, Unknown)

- Chronic renal insufficiency [eGFR <60 ml/min/1.73m^2 on testing >30 days prior to index hospitalization] (No, Yes, Unknown)

  - Chronic Kidney Disease (CKD) stage (CKD stage 3 [eGFR 30 - 59], CKD stage 4 [eGFR 15 - 29], CKD stage 5 [eGFR <15 or dialysis])

- Arrhythmia (No, Yes, Unknown)

  - Arrhythmia type (Atrial fibrillation, Atrial flutter, Supraventricular tachycardia, Ventricular tachycardia)

- Pacemaker/Implantable Cardioverter Defibrillator (ICD) (No, Yes, Unknown)

  - Device type (Pacemaker [conventional], Cardiac resynchronization therapy – no ICD [CRT-P], Cardiac resynchronization therapy – with ICD [CRT-D], ICD only [single/dual], Other, Unknown)

- Moderate to severe valvular heart disease (No, Yes, Unknown)

  - Heart disease type (Mitral regurgitation, Aortic regurgitation, Aortic stenosis, Tricuspid regurgitation)

- Prior valvular heart surgery (No, Yes, Unknown)

          o   Valvular surgery type (Mitral, Aortic, Tricuspid, Pulmonic)

Non-Cardiovascular Medical History

Non-cardiovascular medical history and ongoing conditions will be summarized and listed. The summaries will be presented by primary system organ class (SOC), preferred term (PT) and treatment group for both double-blind and open-label patients. Non-cardiovascular medical history and ongoing conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology (v19.0 or later).

Surgeries and Medical Procedures

Surgeries and medical procedures will be listed, including the reason, start date and end date. Surgeries and medical procedures will be coded using MedDRA terminology (v19.0 or later).

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

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

2.4.1 Study treatment / compliance

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

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

The first date of study treatment is recorded on the Dose Administration (Visit 2) eCRF.

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

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

The duration of the pooled phase (sacubitril/valsartan in double-blind phase and/or sacubitril/valsartan in open-label phase) is defined as:

Duration (days) = (date of last study treatment of sacubitril/valsartan [any phase] – date of first study treatment of sacubitril/valsartan [any phase]) +1

Summary statistics will be displayed for the duration of double-blind study treatment, duration of open-label study treatment and duration of pooled sacubitril/valsartan by phase.

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

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

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

and percentage of patients who were dispensed dose level 3 by Week 6 will be summarized by treatment group.

An additional summary of patient dose level and titration data will be generated by visit and systolic blood pressure using the visit-specific systolic blood pressure cut-off values from the dose titration schedule.

All information on dose administration will be listed.

2.4.2 Prior, concomitant and post therapies

Non-HF Medications

Prior and concomitant non-HF medications will be coded according to the World Health Organization (WHO) Drug Reference List (v15.3 or later). Prior and concomitant medications are mutually exclusive, as defined below:

- Prior medications are defined as any medication with an end date prior to the first dose of study treatment

- Concomitant medications are defined as any medications taken on or after the start of study treatment. Prior medications that are 'ongoing' at the time of the first study treatment or whose end date is after first study treatment will be considered a concomitant medication

The number and percentage of patients with concomitant medications that started after study treatment will be summarized by Anatomical Therapeutic Chemical (ATC) class, preferred term and study phase (refer to Section 2.1.1 for study phase definitions). All medications will be listed.

HF Medications

Medication names are provided for ACEi, ARB, beta blocker and other antiplatelets and will be coded using the WHO Drug Reference List (v15.3 or later) and the preferred term will be displayed for these categories.

The number and percentages of prior HF medications at screening will be summarized by treatment group, open-label and pooled sacubitril/valsartan. Similarly, the HF medications collected at randomization will be summarized by treatment group, open-label and pooled sacubitril/valsartan. A descriptive summary for the total daily dose of each medication (for which doses are collected) will also be presented. These summaries will also be presented using the FAS.

The number and percentages of HF medications collected post randomization will be summarized by study phase (see Section 2.1.1 for study phase definitions). The overall summary will be presented. The following medications will be summarized: Beta blocker, Ivabradine, Hydralazine, Nitrites (long acting), Calcium channel blocker, Potassium, Digoxin, Statin, Furosemide, Torsemide, Bumetanide, Hydrochlorothiazide (HCTZ), Diuril (chlorothiazide), Metolazone, Spironolactone and Eplerenone.

Additionally, a descriptive summary for the total daily dose of each diuretic taken post randomization will be presented by visit, treatment group and open-label sacubitril/valsartan;

these include: Furosemide, Torsemide, Bumetanide, HCTZ, Diuril (chlorothiazide), Metolazone, Spironolactone and Eplerenone.

HF Medications at Index Hospitalization Discharge

The number and percentages of HF medications at the index hospitalization discharge will be summarized by treatment group, open-label and pooled sacubitril/valsartan. The following medications will be summarized: Beta blocker, Ivabradine, Hydralazine, Nitrites (long acting), Calcium channel blocker, Potassium, Digoxin and Statin. Additionally, the number and percentages of each daily diuretic and/or potassium taking during the index hospitalization collected at discharge, the route (when applicable) and total daily dose will be summarized by treatment group, open-label and pooled sacubitril/valsartan.

These summaries will also be presented using the FAS.

Post Randomization Non-study Drug ACEi/ARB

Any ACEi and/or ARB taken after randomization will be listed.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary endpoint is the time-averaged proportional change from baseline in NT-proBNP. Weeks 4 and 8 will be included in the analysis (primary analysis time point). The analysis of the primary endpoint will be based on the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

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

For NT-proBNP, the time-averaged proportional change from baseline in a logarithmic scale will be analyzed using an analysis of covariance (ANCOVA) model using data from Weeks 4 and 8 with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate.

The values from Weeks 4 and 8 will be averaged and the change from baseline in log-transformed NT-proBNP will be calculated as follows:

log (average post dose value) – log (baseline value)

The estimated treatment effect in terms of ratios of geometric means, based on the least-squares (LS) means from the model, and the corresponding two-sided 95% confidence intervals will be presented.

The geometric means (presented as a ratio to baseline) will be calculated by exponentially back transforming the LS means based on the ANCOVA model as follows:

exp (LS mean)

2.5.3   Handling of missing values/censoring/discontinuations

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

2.5.4   Supportive analyses

The primary endpoint will be analyzed in the FAS using the same analytical approach as described in Section 2.5.2; however, baseline will be defined as the last non-missing NT-proBNP assessment with collection date:time < first dose date:time.

For NT-proBNP at Weeks 4 and 8, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. For each visit, the estimated treatment effects in terms of ratios of the geometric means based on the LS means from the model and the corresponding two-sided 95% confidence intervals produced from the model will be presented. The geometric mean will be calculated by exponentially back transforming the LS means.

The primary endpoint will also be analyzed in the PPS using the same analytical approach as described in Section 2.5.2.

In addition, a binary outcome variable will be created for patients achieving a 25%, 50% and 75% decline in NT-proBNP (0-no, 1-yes) and a logistic regression model will be fit. The odds ratio, 95% confidence interval and p-value will be provided. The outcome variable will be achieving a decline in NT-proBNP and the predictor of response will be treatment group.

A descriptive summary of patient evaluability for the primary endpoint analysis based on NT-proBNP values will be presented by treatment group.

2.6   Analysis of the key secondary objective

No key secondary objective.

2.7   Analysis of secondary objectives

All analyses will be performed on the FAS, unless otherwise specified.

2.7.1   Secondary endpoints

Secondary endpoints include the following:

- The proportional change in NT-proBNP from baseline to Week 8

- Incidence of symptomatic hypotension during 8 weeks of treatment

- Incidence of hyperkalemia (potassium >5.5 mEq/L) during 8 weeks of treatment

- Incidence of angioedema during 8 weeks of treatment

- Biomarkers: hs-Troponin T (high sensitivity), urinary cGMP (UcGMP), UcGMP to urinary creatinine ratio, BNP, NT-proBNP to BNP ratio, and BNP to NT-proBNP ratio at 4 and 8 weeks

2.7.2   Statistical hypothesis, model, and method of analysis

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

The incidence of symptomatic hypotension up to Week 8 will be calculated by treatment group. The relative risk (sacubitril/valsartan vs. enalapril) and the 95% confidence interval will also be presented. Similarly, the incidence of hyperkalemia, all angioedema, and positively adjudicated angioedema during the 8 week double-blind phase and the relative risk (sacubitril/valsartan vs. enalapril) will be summarized. Additionally, medication change, lowest documented systolic blood pressure and lowest documented diastolic blood pressure will be summarized by treatment group for symptomatic hypotension. The highest potassium value documented for hyperkalemia will also be summarized by treatment group.

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

Similar to the primary endpoint, the values from Weeks 4 and 8 will be averaged and the change from baseline will be calculated.

The estimated treatment effect in terms of ratios of geometric means, based on the LS means from the model, and the corresponding two-sided 95% confidence intervals will be presented. The geometric means (presented as a ratio to baseline) will be calculated by exponentially back transforming the LS means based on the ANCOVA model.

For biomarkers including BNP, BNP to NT-proBNP ratio, NT-proBNP to BNP ratio, UcGMP, and UcGMP to urinary creatinine ratio at Weeks 1, 2, 4 and 8, a proportional change from baseline in a logarithmic scale will be analyzed using an ANCOVA model with treatment as a fixed effect factor and the logarithmic baseline biomarker value as a covariate. For each visit, the estimated treatment effects in terms of ratios of the geometric means based on the LS means from the model, and the corresponding two-sided 95% confidence intervals produced from the model will be presented. Similarly, the geometric mean will be calculated by exponentially back transforming the LS means based on the ANCOVA model. This analysis will also be performed for hs-Troponin T at Weeks 1, 4, and 8 (note that hs-Troponin T is not measured at Week 2).

2.7.3   Handling of missing values/censoring/discontinuations

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

2.8   Safety analyses

All safety analyses will be performed on the SS unless otherwise specified.

2.8.1   Adverse events

2.8.1.1   Coding of AEs

Adverse events are coded using MedDRA terminology (v19.0 or later).

2.8.1.2   General rules for AE reporting

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

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

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

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

Any information collected will be listed as appropriate.

2.8.1.3   AE summaries

The following summary tables will be provided:

- AEs, regardless of study treatment relationship, by primary SOC, PT and worst severity

- Most frequent (≥5%) AEs, regardless of study treatment relationship, by PT

- AEs, suspected to be related to study treatment, by primary SOC and PT

- Serious adverse events (SAE), regardless of study treatment relationship, by primary SOC and PT

- SAEs, suspected to be related to study treatment, by primary SOC and PT

- SAEs occurring with a frequency of ≥0.5%, regardless of study treatment relationship, by PT

- SAEs, regardless of study treatment relationship, by primary SOC, PT and seriousness criteria

- AEs leading to discontinuation, regardless of study treatment relationship, by primary SOC and PT

- AEs requiring dose adjustment or study treatment interruption, regardless of study treatment relationship, by primary SOC and PT

- AEs requiring additional therapy, regardless of study treatment relationship, by primary SOC and PT

- Death resulting from AEs, regardless of study treatment relationship, by primary SOC and PT

2.8.1.4 In addition, an overview of TEAEs presenting the number of percentage of patients having at least one TEAE for each of the above categories will be provided.Adverse events of special interest / grouping of AEs

Separate summaries will be provided for AEs related to all angioedema, positively adjudicated angioedema, elevated creatinine, hyperkalemia and symptomatic hypotension. The summaries will be presented by primary SOC, PT and worst severity.

Additionally, a sensitivity analysis will be performed on the AEs of special interest for patients randomized to sacubitril/valsartan. The number and percentages of AEs of special interest occurring prior to the active dose of sacubitril/valsartan will be presented along with the number and percentages of AEs of special interest occurring on or after the active dose of sacubitril/valsartan during the double-blind phase. The following definition will be used:

Angioedema:

AE prior to active study treatment = if event occurred within 1 day of dosing as recorded on the Angioedema Assessment Visit 2 (randomization)

AE after active study treatment = if event occurred after 1 day of dosing as recorded on the Angioedema Assessment Visit 2 (randomization)

Symptomatic hypotension:

AE prior to active study treatment = First dose date ≤ event < Third dose date of study treatment

AE after active study treatment = Third dose date of study treatment ≤ event ≤ Last dose date of double-blind medication

Elevated creatinine and hyperkalemia:

AE prior to active study treatment = First dose date:time of study treatment ≤ event < Third dose date:time of study treatment

AE after active study treatment = Third dose date:time of study treatment ≤ event ≤ Last dose date:time of double-blind medication

2.8.2 Deaths

Patient deaths will be summarized by total, primary cause of death, type of cardiovascular death and type of non-cardiovascular death and will be presented by study phase (see Section 2.1.1 for study phase definitions). A patient listing of all deaths with recorded principal cause of death will be provided. All patients in the FAS will be included for the above analysis.

2.8.3 Laboratory data

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

will be presented by low/normal/high (low and high) classifications to compare baseline to worst post baseline value.

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

A separate summary table will be presented by study phase (see Section 2.1.1 for study phase definitions) with the number and percentage of patients having notable lab abnormalities based on percent change from baseline (see Section 5.3 for a list of notable laboratory abnormalities).

A summary of hyperkalemia labs by visit will also be presented by treatment group and open-label sacubitril/valsartan. The highest potassium value for the event and any potassium re-test results will be descriptively summarized. Similarly, creatinine labs will also be presented by visit, treatment group and open-label sacubitril/valsartan. The highest creatinine value for the event and any creatinine re-test results will be descriptively summarized.

Listings of all laboratory values will be provided. Separate listings for hyperkalemia labs, creatinine labs and pregnancy tests will also be provided. Any notable laboratory abnormalities will also be flagged.

2.8.4   Other safety data

2.8.4.1   ECG and cardiac imaging data

ECG data will be collected at screening and all data, including unscheduled visits, will be listed.

2.8.4.2   Vital signs

All vital signs (systolic and diastolic blood pressure [mmHg], pulse rate [sitting/beats per minute], weight [kg], height [cm], BMI [kg/m^2] and waist/hip circumference) will be descriptively summarized at each visit by treatment group and open-label sacubitril/valsartan. Change from baseline will also be presented.

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

The number and percentages of patients having symptomatic hypotension will also be summarized by study phase. The following variables associated with symptomatic hypotension will also be presented: symptoms occurring while standing, any treatment or medication change as a result of episode, lowest documented systolic blood pressure, systolic blood pressure position, lowest documented diastolic blood pressure and diastolic blood pressure position. A listing for symptomatic hypotension will also be presented.

2.8.4.3   Heart Failure Event

Any new heart failure event information will be collected and listed. The following will be presented:

- Type of event (HF hospitalization [hospital stay ≥24 hours], Heart failure emergency department visit, Urgent/unplanned heart failure office visit, Worsening heart   failure

during the index hospitalization [qualifying heart failure event], None of the aforementioned types occurred with, or apply to, this HF event)

- Symptoms of worsening HF (Dyspnea – [Dyspnea at rest, Dyspnea on exertion, Orthopnea, Paroxysmal nocturnal dyspnea, Tachypnea], Decreased exercise tolerance [reduced ability to perform activities that induce physical exertion due to dyspnea or fatigue], Fatigue [lack of energy, extreme tiredness, inability to complete usual activities], Worsening end-organ perfusion – [Confusion (thought to be from low cardiac output), Reduced urine output], Symptoms of volume overload – [Lower extremity swelling, Increased abdominal distension)], Other)

- Physical exam signs of worsening HF (Peripheral edema, Increased abdominal distension or ascites [in the absence of hepatic disease], Pulmonary rales/crackles, Elevated jugular venous pressure and/or hepatojugular reflux, New or worsening 3rd heart sound, Clinically significant weight gain thought to be related to fluid retention [>3 - 4 lbs. in 3 to 4 days], Other)

- Laboratory evidence of worsening HF (Increased NT-proBNP [>2,000 pg/mL], Radiographic evidence of pulmonary congestion, Right heart catheterization with pulmonary capillary wedge pressure $\geq$18 mmHg, central venous pressure $\geq$12 mmHg, or a cardiac index of <2.2 L/min/m^2, Other)

- Increased or additional therapy (No, Yes, Unknown)
  - Therapy type (Augmentation of oral diuretic therapy with additional diuretic, Initiation of intravenous diuretic, Uptitration of intravenous therapy, if already on therapy, Initiation of inotrope, or vasodilator therapy, Initiation of percutaneous mechanical circulatory support, Initiation of temporary surgical support [ECMO or temporary surgical ventricular assist device (VAD) i.e. centrimag], Implantation of durable LVAD, Listed for heart transplantation)

- Evidence of cardiogenic shock (No, Yes, Unknown)

- Blood sample collected for BNP or NT-proBNP (No, Yes, Unknown)
  - BNP result (pg/mL)
  - NT-proBNP result (mg/mL)

- Contributors/precipitants of worsening heart failure (Medication nonadherence, Dietary indiscretion, Acute coronary syndrome, Other systemic illness – [Respiratory infection, Urinary tract infection, Other])

2.8.4.4   HF Signs and Symptoms

Heart failure signs and symptoms will be collected at screening, randomization and at post randomization visits. The number and percentage of the following parameters will be summarized at each visit by treatment group and open-label sacubitril/valsartan:

- Heart failure signs or symptoms within the past 24 hours prior to this visit (No, Yes)

- Rales (Not present, Basilar only, >1/3 of lung filled, Not done)

- Peripheral edema (Absent, Trace, Feet and ankles, Lower legs or thighs, Sacrum, Not done)

- Current NYHA heart failure classification (Class I, Class II, Class III, Class IV, Not done)

- Fatigue (Not present, Seldom, Frequent, Continuous, Not done)

- Dyspnea (Not present, Seldom, Frequent, Continuous, Not done)

- Orthopnea (Not present, Seldom, Frequent, Continuous, Not done)

2.8.4.5   Hospitalization

Information related to hospitalization will be listed. The following will be presented:

- Type of hospitalization (Elective, Planned, Unplanned)

- Reason for hospitalization (refer to eCRF for list of reasons)

- Patient discharged (No, Yes, Unknown)

  o Duration of hospitalization in days [*date of discharge – date of admission + 1*]

- Patient admitted to ICU or Coronary Care Unit (CCU) (No, Yes, Unknown)

  o Number of days in ICU or CCU

- Discharge disposition (Home or with family/friends, Rehabilitation facility, Skilled nursing facility, Death, Unknown)

2.8.4.6   Angioedema

Data collected from the angioedema assessment and questionnaire at screening, randomization and follow-up visits will be summarized. Separate summaries will be produced for all angioedema and positively adjudicated angioedema. The number and percentage for categorical variables and summary statistics for continuous variables of the following will be presented by visit, treatment group and open-label sacubitril/valsartan:

- Outcome (Not recovered/Not resolved, Recovered/Resolved, Recovering/Resolving, Recovered/Resolved with Sequelae, Fatal, Unknown)\

  o Duration of angioedema in days [*end date – start date + 1*]

- Timing of event (After first dose, after multiple doses, dose not given) [not asked at screening]

  o Study medication discontinued due to event (No, Yes, Unknown)

  o 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)

  o If yes, medications taken at time of previous event:

- ▪ ACE inhibitor (No, Yes, Unknown)
- ▪ ARB (No, Yes, Unknown)
- ▪ Renin inhibitor (No, Yes, Unknown)
- ▪ Other medications (No, Yes, Unknown)
- Presence of hereditary angioedema (No, Yes, Unknown)
- Any family members with history of angioedema-like events (No, Yes, Unknown)
- Signs and symptoms for current event
  - o Shortness of breath/dyspnea (No, Yes, Unknown)
  - o Difficulty swallowing/dysphagia (No, Yes, Unknown)
  - o Difficulty speaking/dysarthria (No, Yes, Unknown)
  - o Pain on swallowing/odynophagia (No, Yes, Unknown)
  - o Stridor (No, Yes, Unknown)
  - o Abdominal pain (No, Yes, Unknown)
  - o Other (No, Yes, Unknown)
- Edema present (No, Yes)
  - o Periorbital edema (No, Yes, Unknown)
  - o Head edema (No, Yes, Unknown)
  - o Neck edema (No, Yes, Unknown)
  - o Lip edema (No, Yes, Unknown)
  - o Tongue edema (No, Yes, Unknown)
  - o Throat edema (No, Yes, Unknown)
  - o Submandibular edema (No, Yes, Unknown)
  - o Genitalia edema (No, Yes, Unknown)
  - o Extremities edema (No, Yes, Unknown)
  - o Other (No, Yes, Unknown)
- Previous edematous episodes (No, Yes, Unknown)
  - o Number of previous edematous episodes
- ACEi taken in the past (No, Yes, Unknown)
- ACEi taken during trial participation after screening (No, Yes, Unknown) [not asked at screening]
  - o Dose changed within 2 days of event (No, Yes, Unknown)
- ARB taken in the past (No, Yes, Unknown)

- ARB taken during trial participation after screening (No, Yes, Unknown) [not asked at screening]
    - Dose changed within 2 days of event (No, Yes, Unknown)
- Patient suffering from influenza, common cold or upper respiratory tract infection (No, Yes, Unknown)
- Medication allergies (No, Yes, Unknown)
- Food allergies (No, Yes, Unknown)
- Potential causes of angioedema-like event
    - Food (No, Yes, Unknown)
    - Insect bite (No, Yes, Unknown)
    - Animal exposure (No, Yes, Unknown)
    - Medication (No, Yes, Unknown)
    - Dental work (No, Yes, Unknown)
    - Pollen (No, Yes, Unknown)
    - Dust (No, Yes, Unknown)
    - Concomitant disease (No, Yes, Unknown)
    - Idiopathic (No, Yes, Unknown)
    - Other (No, Yes, Unknown)
- Medical intervention (No, Yes)
    - Administration of H-1 blocker (No, Yes)
    - Administration of H-2 blocker (No, Yes)
    - Administration of steroids (No, Yes)
    - Administration of epinephrine (No, Yes)
    - Admission to hospital (No, Yes)
    - Admission to ER (No, Yes)
    - Endotracheal intubation (No, Yes)
    - Tracheostomy (No, Yes)
    - Discontinuation of ACE inhibitor (No, Yes)
    - Discontinuation of ARB (No, Yes)
    - Other

All assessment data will be listed. The adjudicated assessment of the event will be listed separately.
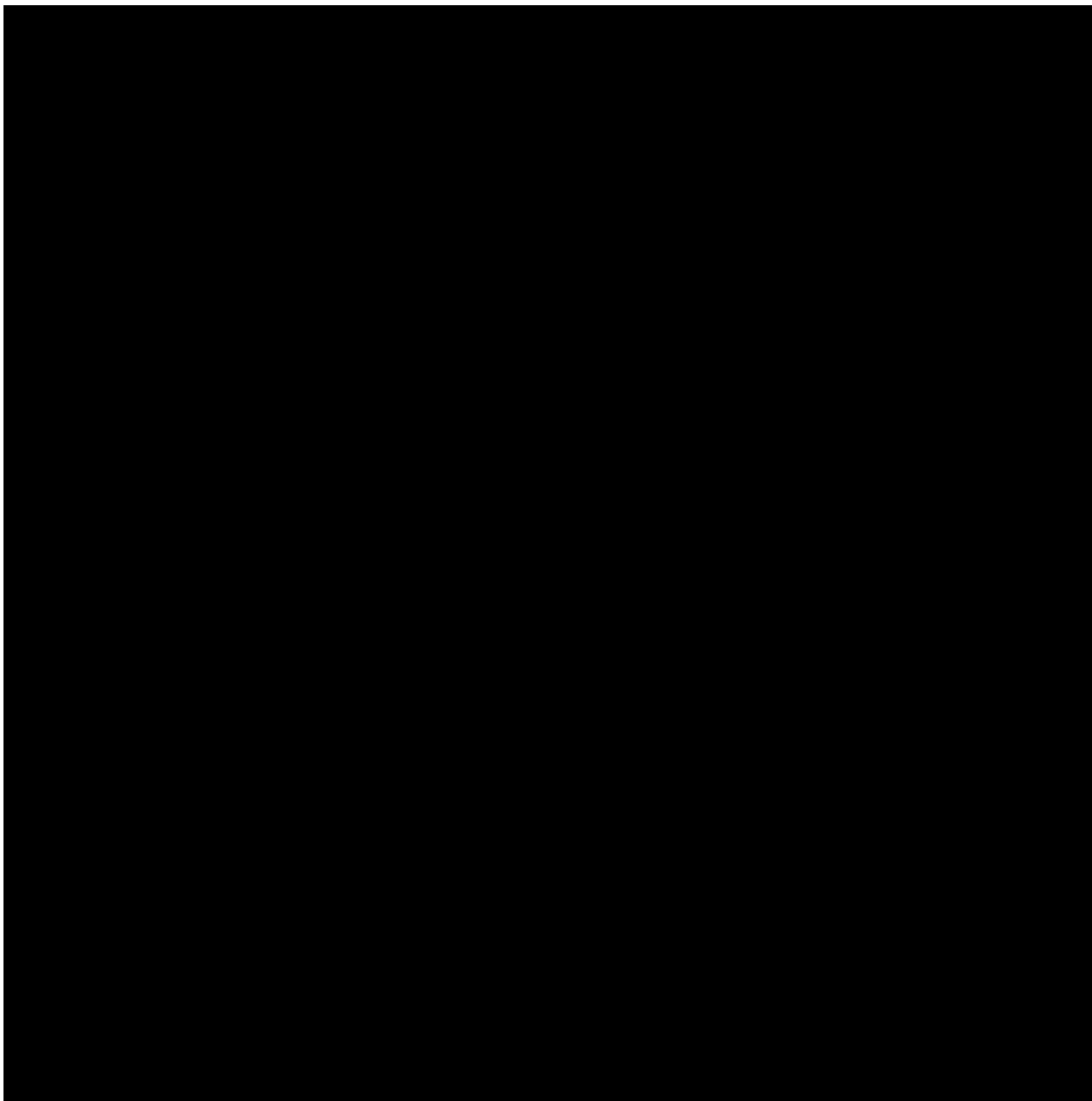
In addition, key characteristics of positively adjudicated angioedema will be summarized with descriptive statistics by study phase as defined in Section 2.1.1.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.12   Biomarkers

BNP and NT-proBNP will be collected and descriptively summarized by visit, treatment group and open-label sacubitril/valsartan. Values and the change from baseline for each parameter will be summarized by visit, treatment group and open-label sacubitril/valsartan. Analyses will be based on the FAS. BNP and NT-proBNP values will be based on clinical laboratory samples processed and assessed by the central laboratory.

Additional biomarker measurements believed to be relevant to the pathophysiology of the disease processes of heart failure and dysfunction will also be collected and summarized by visit, treatment group and total. These may include, but no limited to those assessing cardiac and renal benefit or biomarkers related to the study treatment mechanism of action such as:

- Neurohormones BNP and NT-proBNP

- hs-Troponin T

- █████████

- ████████████

- ██

- urinary cGMP

- ██

Additional analysis of biomarkers is discussed in Sections 2.5, 2.7 and 2.13.

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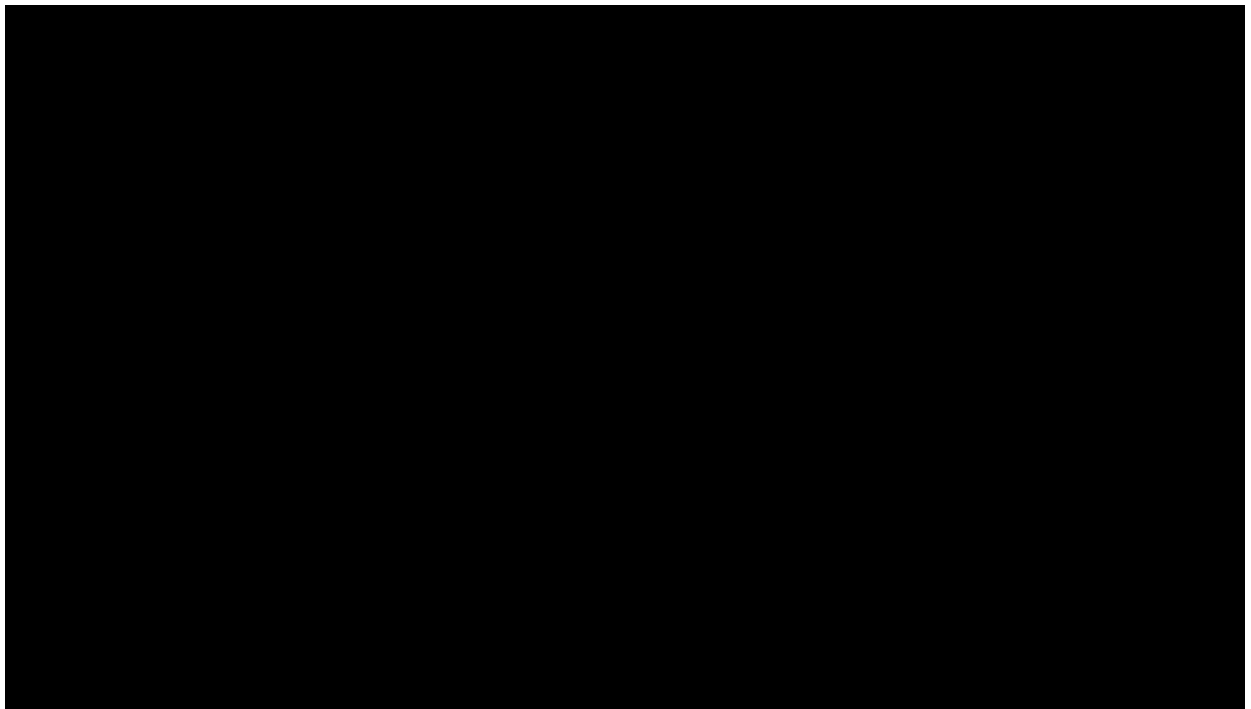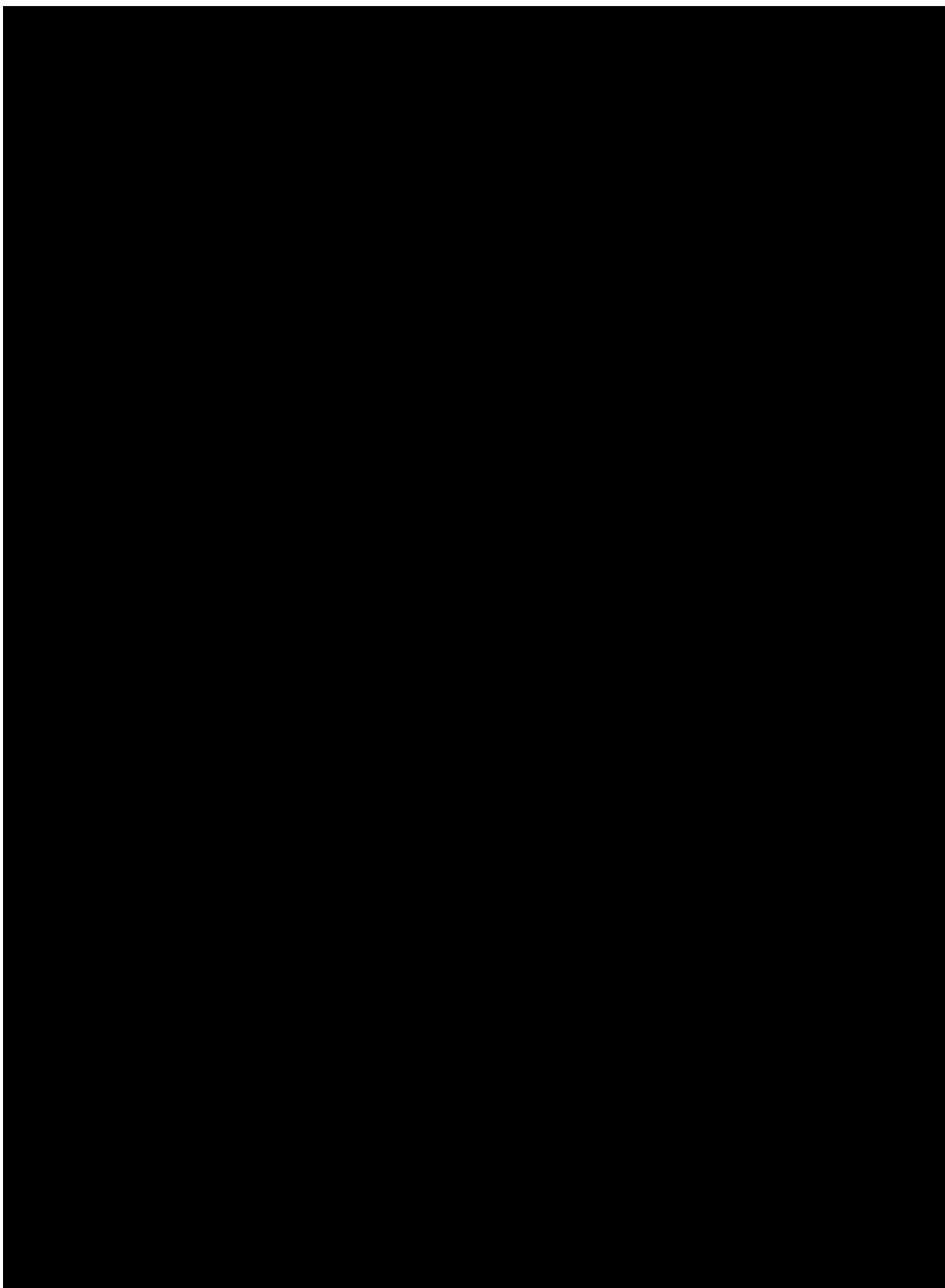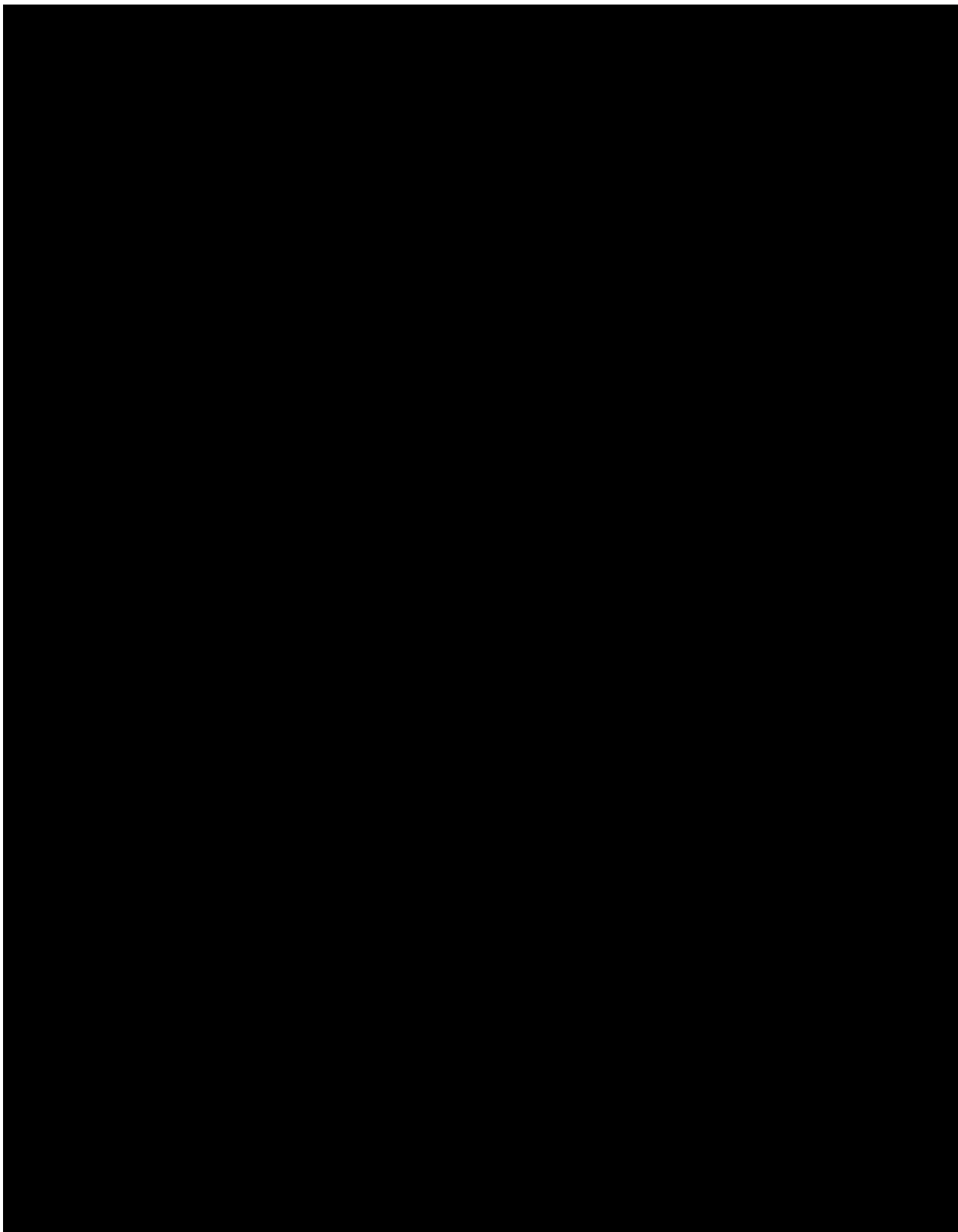
2.14   Interim analysis

No interim analysis is planned.

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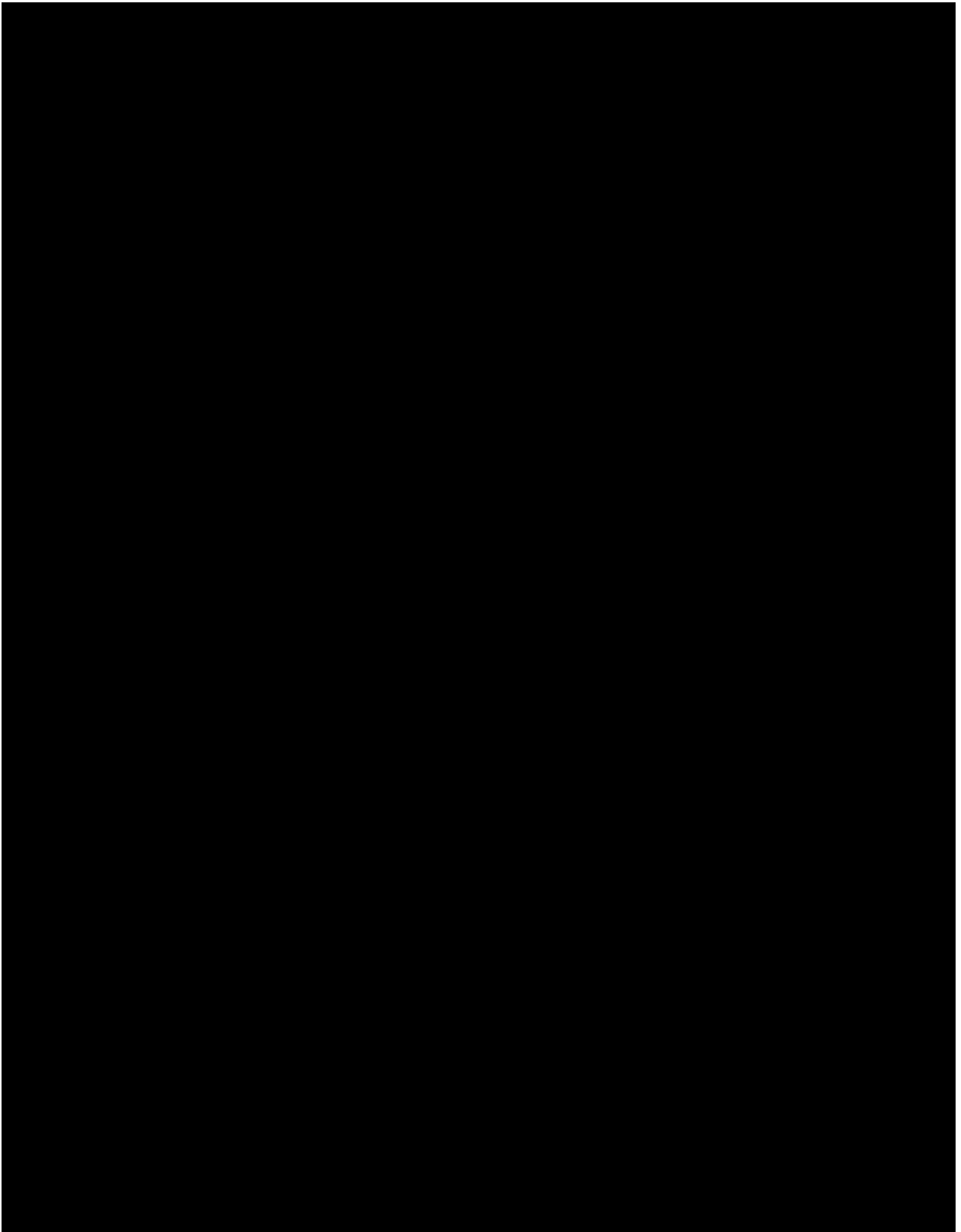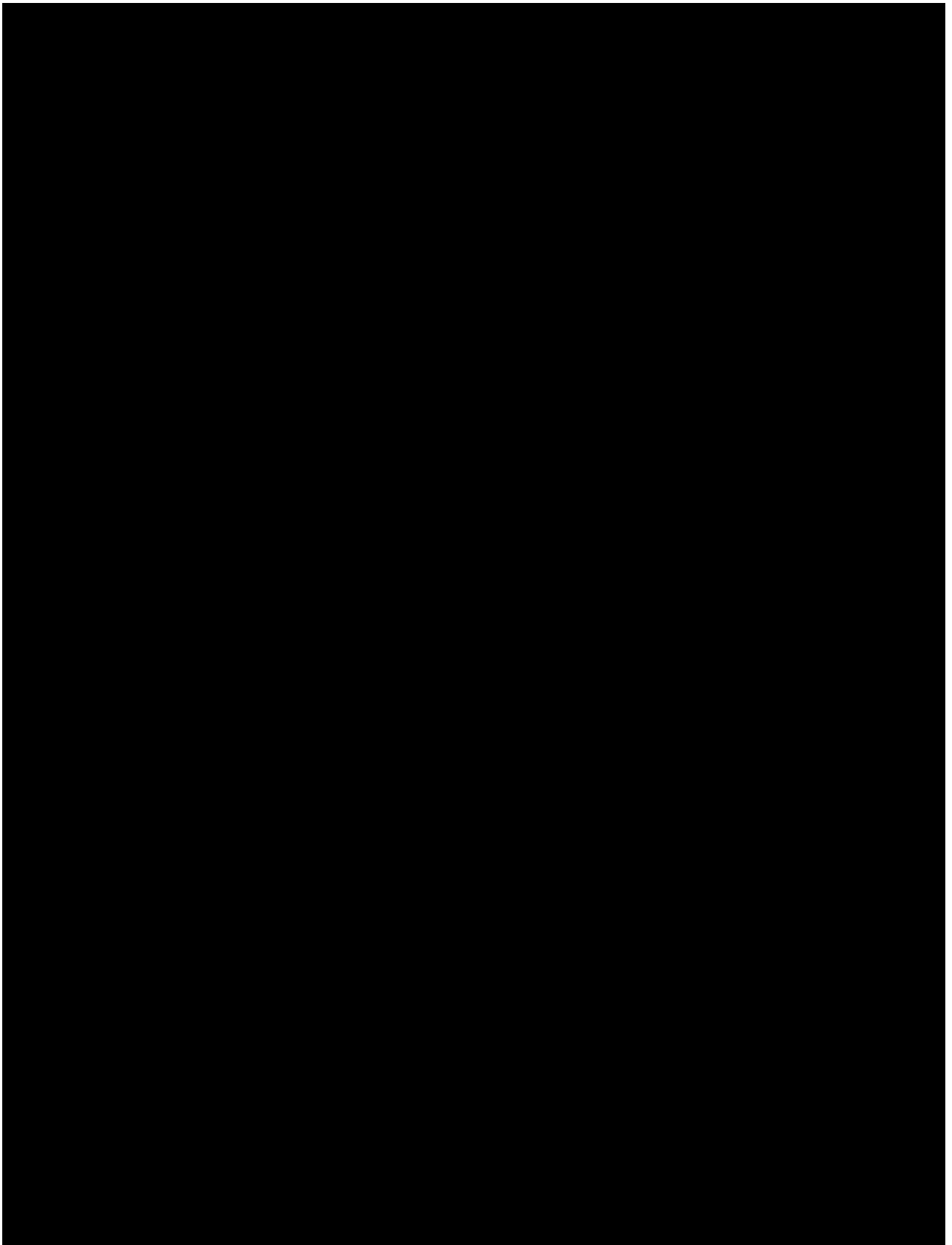
Assuming a significance level of 0.05 and 85% power, a sample size of 882 patients would be needed to detect an 18% reduction in the geometric mean of the time-averaged proportional change from baseline (average of Weeks 4 and 8) in NT-proBNP for the sacubitril/valsartan treatment group assuming a value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

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

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

4   Change to protocol specified analyses

The following changes to protocol specified analyses were made:

- Specified the following additional biomarkers as secondary endpoints:
    - o UcGMP to urinary creatinine ratio
    - o BNP
    - o NT-proBNP to BNP ratio

- Added sensitivity analyses for the following endpoints using the "strict" baseline definition (i.e., collection date:time < first dose date:time):

    o Primary endpoint

    ▮ ██

    ▮ ██

- Clarified that tables summarizing demographics and baseline data will be run only on the FAS, and not also on the RS as indicated in the protocol

- Replaced supportive analysis of the primary endpoint consisting of summary statistics and t-test p-values for comparing treatment groups on the proportional change from baseline in a logarithmic scale at Weeks 4 and 8 with ANCOVA at Weeks 4 and 8

    ▮ ██

    ▮ ██

- Modified the Safety Set definition to remove the word 'active' so that inclusion in the Safety Set is not restricted to patients who received at least one dose of *active* study treatment

    ▮ ████████████████████████████████████

    ▮ ██

    ▮ ██

- Added Weeks 4 and 8 to the analysis of change from baseline in biomarkers defined as 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

    ▮ ██

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 <u>start dates</u> 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 <u>stop dates</u> 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 <u>start dates</u> for which only partial information is known:

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

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

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

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

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

5.1.3.1   Prior therapies date imputation

The same imputation as concomitant medication will be used. See Section 5.1.3.

5.1.3.2   Post therapies date imputation

The same imputation as concomitant medication will be used. See Section 5.1.3.

5.2   AEs coding/grading

The ████ coding team will code the AE terms using MedDRA terminology (v19.0 or later). If any terms are not coded, the data management team will issue queries to sites to update the AE term appropriately.

5.3   Laboratory parameters derivations

5.3.1   Laboratory grading

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

5.3.2   Notable laboratory values

<u>Hematology</u>

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

<u>Blood Chemistry</u>

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

5.4   Vital signs

5.4.1   Notable vital sign values

Systolic blood pressure	<90 mmHg and decrease of >20 mmHg from baseline
	>140 mmHg and increase of >20 mmHg from baseline
	>160 mmHg and increase of >20 mmHg from baseline
	<90 mmHg
	>140 mmHg
	>160 mmHg
	Decrease of >20 mmHg from baseline
	Increase of >20 mmHg from baseline
Diastolic blood pressure	<50 mmHg and decrease of >15 mmHg from baseline
	>100 mmHg and increase of >15 mmHg from baseline

<50 mmHg

>100 mmHg

Decrease of >15 mmHg from baseline

Increase of >15 mmHg from baseline

Pulse   <50 bpm and decrease of >15 bpm from baseline

>120 bpm and increase of >15 bpm from baseline

<50 bmp

>120 bpm

Decrease of >15 bpm from baseline

Increase of >15 bpm from baseline

Weight   >7% decrease; >7% increase

5.5   Statistical models

5.5.1   Primary analysis

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

$$y_{ij} = \mu + T_i + B(x_{ij} - \overline{x_i}) + E_{ij}$$

PROC MIXED in SAS will be used for the analysis. The LSMEANS option will be used with options of CL to output the confidence limits.

5.5.2   Key secondary analysis

Similar to the primary analysis, the null hypothesis for the secondary analysis is the ratio of the geometric means of different biomarkers (BNP to NT-proBNP ratio, hs-Troponin and urinary cGMP) for the sacubitril/valsartan and enalapril group are equal. An ANCOVA model will be used. The model will have the time-averaged proportional change from baseline in a logarithmic scale be the dependent variable with treatment as a fixed effect factor and the logarithmic baseline value as a covariate. The general form for the ANCOVA model is:

$$y_{ij} = \mu + T_i + B(x_{ij} - \overline{x_i}) + E_{ij}$$

PROC MIXED in SAS will be used for the analysis. The LSMEANS option will be used with options of CL to output the confidence limits.

5.6   Rule of exclusion criteria of analysis sets

Table 1   Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses
D01	Patient met one or more of the Discontinuation of Study Drug criteria but study drug was not discontinued	Exclusion from PPS
E02	Patient is enrolled in another clinical trial involving an investigational agent or investigational device	Exclusion from PPS
E03	Patients has a history of hypersensitivity, known or suspected contraindications, or intolerance to the study drugs, including ACEIs, ARBs, or Sacubitril (NEP inhibitor)	Exclusion from PPS
E04	Patient has a history of angioedema related to previous ACE inhibitor or ARB therapy	Exclusion from PPS
E11	The patient had implantation of a cardiac resynchronization therapy device (CRTD) within the prior 3 months from Visit 1, the patient intends to have implantation of a cardiac resynchronization therapy device (CRTD)	Exclusion from PPS
E19	Patient is a pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test	Exclusion from PPS
I07	LVEF was not ≤ 40% within the past 6 months (including current hospitalization) using echocardiography, multi gated acquisition scan (MUGA), CT scanning	Exclusion from PPS
I09	Patient did not have an elevated NT-proBNP ≥ 1600pg/mL or BNP ≥ 400 pg/mL during current hospitalization	Exclusion from PPS

Deviation ID	Description of Deviation	Exclusion in Analyses
M01	Patient had concomitant intake of a prohibited medication as outlined in the protocol	Exclusion from PPS
O04	Patient randomized in error and not dosed with study drug	Exclusion from FAS and PPS
O05	Missing NT-ProBNP sample at either baseline, week 4 or week 8	Exclusion from PPS
O06	Patient took first dose of study drug before baseline NT-proBNP sample was drawn	Exclusion from PPS
O07	Patient missed 1 or more consecutive dose(s) of study drug immediately or prior to visit 5 or visit 7	Exclusion from PPS

Table 2   Patient Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
RS	NA	Not randomized
FAS	O04	Not in RS
PPS	D01, E02, E03, E04, E11, E19, I07, I09, M01, O04, O05, O06, O07	Not in FAS
SS	NA	No double-blind study treatment received

6   Reference