

Clinical Development

LCZ696/Sacubitril/Valsartan/Entresto®

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Multicenter, randomized, double-blind, double dummy, parallel group, active-controlled 8-week study and 8-week open label extension to evaluate the effect of initiation of sacubitril/valsartan on objective measures of waking activity and sleep, as health-related quality of life functions in subjects with heart failure and reduced ejection fraction: (AWAKE-HF)

Statistical Analysis Plan (SAP)

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List of abbreviations

AC	Activity Count
ACEi	Angiotensin Converting Enzyme Inhibitor
AE	Adverse Event
AHI	Apnea Hypopnea Index
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ARB	Angiotensin Receptor Blocker
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	bis in diem/twice a day
BMI	Body Mass Index
BPM	Beats Per Minute
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Graft
CKD	Chronic Kidney Disease
CMH	Cochran-Mantel-Haenszel
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
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
H ₀	Null Hypothesis
H _A	Alternative Hypothesis
HF	Heart Failure
██████████	██
ICD	Implantable Cardioverter Defibrillator
IRT	Interactive Response Technology
██████████	██
LOCF	Last Observation Carried Forward
MRI	Magnetic Resonance Imaging
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PD	Pharmacodynamic
PK	Pharmacokinetic
PRO	Patient-reported Outcomes
PT	Preferred Term
RBC	Red Blood Cell

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
■	■
USPI	United States Package Insert
WASO	Wake After Sleep Onset
WBC	White Blood Cell
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 13-Mar-2018 and the data collection tool (DCT) version 3.0 dated 04-May-2017.

1.1 Study design

This study is a multicenter, randomized, double-blind, double dummy, parallel group, active-controlled 8-week study with open-label extension using medical device-grade patient worn sensors to measure waking and sleeping physical activity in the ambulatory outpatient setting. The 18-week study duration will consist of a 2-week baseline observation phase (with patients continuing their current heart failure [HF] drug therapy), followed by an 8-week blinded treatment phase during which approximately 136 patients will be randomized to either initiation of sacubitril/valsartan treatment or enalapril comparator in a 1:1 ratio with no stratification at approximately 25-30 centers in the United States, and finally an 8-week open-label extension phase during which all patients will be treated with sacubitril/valsartan.

Each patient will undergo a 36-hour washout period (during which angiotensin converting enzyme inhibitor [ACEi], or study drug will be withheld) before the start of the randomized, blinded treatment phase, and again before beginning the open-label extension phase to ensure that the blinding of the core study is maintained and to reduce the risk of angioedema.

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). At each subsequent study visit during the double-blind epoch, the study physician will sequentially up-titrate the study drug dose (based on clinical tolerance and the United States Package Insert [USPI]) to achieve the desired 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. Patients not tolerating escalation from Dose Level 1 to Dose Level 2 (or Dose Level 2 to Dose Level 3) can be titrated down to the next lower Dose Level (including active medication and matching placebos), if, in the investigator's judgement, the adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern.

All patients entering the open-label epoch will be given sacubitril/valsartan 49/51 mg BID (Dose Level 2) unless they completed the double-blind treatment epoch on Dose Level 1. Instead, these patients will enter the open-label epoch on sacubitril/valsartan 24/26 mg BID (Dose Level 1). At each subsequent study visit during the open-label epoch, the study physician will sequentially up-titrate the study drug dose (based on clinical tolerance and the USPI) to achieve the targeted desired dose of sacubitril/valsartan 97/103 mg BID (Dose Level 3). Patients not tolerating escalation from Dose Level 1 to Dose Level 2 (or Dose Level 2 to Dose Level 3) can be titrated down to the next lower Dose Level, if, in the investigator's judgement, the adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern.

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).

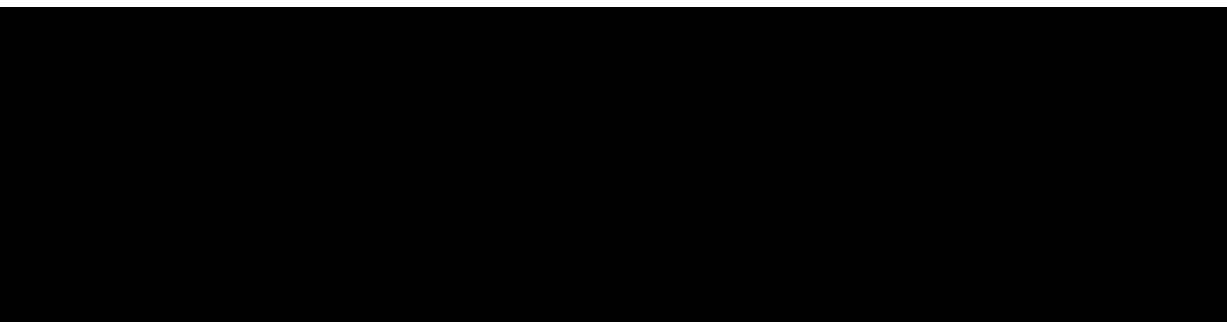
The primary analysis time point will be Week 8 (end of the double-blind period).

There are no interim analyses planned.

1.2 Study objectives and endpoints

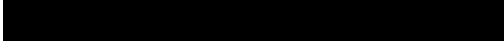
The primary objective is to evaluate the effect of initiation of sacubitril/valsartan treatment versus enalapril on physical activity during the waking hours as an objective measure of physical function.

The secondary objective is to evaluate the effect of initiation of sacubitril/valsartan treatment versus enalapril on patients' sleep as an objective measure of physical function.



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. 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, unless otherwise specified.

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

The last non-missing assessment prior to or on the start date of study treatment (randomization date for patients not treated) will be used as baseline, unless otherwise specified.

Date of first administration of study treatment

Randomized treatment phase: The date of first administration of study treatment in the randomized treatment phase is defined as the first date a dose of study treatment is administered and recorded on the Dosage Administration Record - At Visit (Visit 3) electronic case report form (eCRF).

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

Date of last administration of study treatment

Randomized treatment phase: The date of last administration of study treatment in the randomized treatment phase is defined as the last date a dose of study treatment is administered in the randomized treatment phase and recorded on the Double-Blind Phase Disposition eCRF (for patients continuing into the open-label extension phase) or the Study Completion/Discontinuation eCRF (for patients not continuing into the open-label extension phase).

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

Randomized treatment phase

Assessments performed at Weeks 2, 4, or 8 (e.g., vital signs) are assigned to the randomized treatment phase for summarization purposes. Unscheduled assessments are not assigned to a phase.

For summarization of adverse events [AEs], medications, protocol deviations, and notable vital signs and laboratory abnormalities by treatment phase, an assessment during the randomized treatment 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.

Open-label extension phase

Assessments performed at Weeks 10, 12, or 16 (e.g., vital signs) are assigned to the open-label extension phase for summarization purposes. Unscheduled assessments are not assigned to a study phase.

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

After the date of the Week 8 visit.

Last contact

The date of last contact will be the last visit date for each patient and will be derived by examining all visit data collected in the eCRFs.

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.

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 (<25%, 25% - <35%, ≥35%)
3. Baseline quartiles of mean activity counts during the most active 30 minutes of the patient's day (counts) (mean of data collected each day during Week -1) (based on FAS)
4. New York Heart Association (NYHA) classification [best value during the past month prior to screening visit] (II, III)
5. Prior HF hospitalization (No, Yes)
6. History of diabetes (No, Yes)
7. Baseline body mass index (BMI) categories (<25, 25 - <30, ≥30 kg/m²)
8. Baseline quartiles of mean activity during the daily active period (counts/minute) (mean of data collected each day during Week -1)
9. Baseline sleep efficiency categories (<70%, 70-90%, >90%)
10. Baseline apnea hypopnea index (AHI) 4% categories (<15, ≥15 events/hour)
11. Baseline quartiles of the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score

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
 - Patient/guardian decision

- Number 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 completed study treatment
- 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
 - Patient/guardian decision
- Number and percentage of patients who continued into the open-label phase
- 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 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 treatment phase (see Section 2.1.1 treatment 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

Descriptive summaries and/or listings will be provided for demographics, baseline characteristics and disease history. The number and percentage (categorical variables) and descriptive statistics (continuous data) for the information below will be summarized by treatment group for both the randomized treatment and open-label extension phases.

The RS and 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)
- BMI (kg/m^2) [= *weight (kg)/height (m^2) from Screening Visit 1*]
 - BMI categories (<20, 20 - <25, 25 - 30, >30 kg/m^2)
- Estimated Glomerular Filtration Rate (eGFR) (ml/min/1.73 m^2)
 - eGFR categories (<45, 45 - <60, ≥60 ml/min/1.73 m^2)

Key actigraphy [REDACTED] baseline characteristic variables include:

- Mean activity counts during the most active 30 minutes of the patient's day (counts)
 - Mean activity counts during the most active 6 minutes of the patient's day (counts)
 - Mean activity during sleep (counts/minute)
 - Mean activity during the daily active period (counts/minute)
-



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 HF 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 will be summarized and listed. The summary will be presented by primary system organ class (SOC), preferred term (PT) and treatment group for both the randomized treatment and open-label extension phases. Non-cardiovascular medical history 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. 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 treatment for the randomized treatment phase is defined as:

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

The first date of study treatment is recorded on the Dosage Administration Record - At Visit (Visit 3) eCRF.

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

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

Summary statistics will be displayed for the durations of treatment during the randomized treatment and open-label extension phases.

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 treatment phase.

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

In addition, the number and percentage of patients at each dose level dispensed by visit will be summarized by treatment group for both the randomized treatment and open-label extension phases. The number and percentage of the maximum dose levels dispensed will also be presented by treatment group for both the randomized treatment and open-label extension phases. Similarly, the up-titrated doses, down-titrated doses and unchanged doses will be summarized by visit and treatment group for both the randomized treatment and open-label extension phases.

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 (v15.3 or later). The WHO Drug version will be denoted in the corresponding tables and listings. 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 and treatment group for both the randomized treatment and open-label extension phases. Concomitant medications will be summarized in a similar fashion. Separate summaries of prior ACEi and angiotensin receptor blocker (ARB) will also be produced. 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 mean activity counts collected during the most active 30 minutes of the patient's day between baseline phase (mean of data collected each day during

Week -1) and the final randomized treatment phase measurement (mean of data collected each day during Week 8), as measured by wrist-worn accelerometer collected actigraphy (total counts per 30 minute period collected during the most active 30 minutes of each day). The analysis of the primary endpoint will be based on the FAS.

The following algorithm will be used to exclude “invalid” actigraphy data from analysis of the primary endpoint. Note that AC = activity count.

1. Isolate ‘ACTIVE’ intervals.
2. For each ‘ACTIVE’ interval, use variables [duration] and [%Invalid AC] to create a new variable [duration valid AC]. This new variable reflects the duration of valid activity data within each active period.
3. Find any [duration valid AC] that is <0.5 hours and remove it from the analysis. If an active period contains <30 minutes of valid data, then determining the most active 30 minutes within the period is not possible.
4. For each patient, sum the [duration valid AC] for each unique [Start Date] to create a new variable [all day duration valid AC]. This new variable reflects the total duration of valid activity data for each date. In most cases, each patient will have only one active period per date, but there are cases with two active periods within a single day (e.g., if patient had a nap in the middle of the day).
5. Find any [all day duration valid AC] that is <8 hours and remove all data associated with that [Start Date] from the analysis.
6. In the remaining data for analysis, each patient will have ≥ 8 hours of valid activity data for each date. It might be one long active period, or it might comprise two shorter active periods that add up to ≥ 8 hours.
7. For each patient, find the highest [mostActive30] for each date and use this in the analysis. In most cases, each date will have only one active period and therefore only one [mostActive30] datapoint. On dates that contain more than one active period, select the highest [mostActive30] regardless of the duration of the active period.

As long as for a single date a patient has ≥ 8 hours of valid activity data in total, the 30 minutes with the most activity will be used in the analysis. The 8-hour threshold was selected as this requires each patient to have at least 50% of valid activity data each day, assuming 8 hours of sleep per night.

In order to calculate the mean [mostActive30] across 7 days of data during the given week, the patient must have at least 5 days of data.

2.5.2 Statistical hypothesis, model, and method of analysis

Let μ_j denote the population mean of change in mean activity count from baseline phase to Week 8 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 baseline activity as explanatory variables. The least squares means of the two treatment groups, least squares mean difference of the treatment groups, 95% confidence interval for the difference in the two treatment groups, and p-value based on the fitted linear model will be reported. If the p-value is <0.05 and the least squares mean difference of the treatment groups favors sacubitril/valsartan, statistical significance in favor of sacubitril/valsartan will be declared.

Before performing the above analysis, tests of normality of the variable, change in mean activity counts collected during the most active 30 minutes of the patient's day between baseline and Week 8, and the log of the variable ($\log(\text{Week 8 value}) - \log(\text{baseline value})$) will be performed. In the event the variable is not normally distributed (based on Shapiro-Wilk test p-value <0.05) but the lognormal distribution fits better, the above analysis will be performed using the log transformed data. Anti-log of the least squares mean difference of the treatment groups will be used to report the ratio of the treatment difference in the original scale.

2.5.3 Handling of missing values/censoring/discontinuations

Missing data will be imputed using the last-observation-carried-forward (LOCF) method. If a patient has no post-baseline value, the missing value will not be imputed and the patient will be removed from the analysis. If a patient's data is missing or unevaluable for the week preceding randomization, the data from the previous week will be used as the baseline measurement. If a patient's data is missing or unevaluable for each of these weeks, the patient will be excluded from the analysis.

2.5.4 Supportive analyses

A supportive nonparametric analysis will be performed to examine the consistency of results. For this supportive analysis, the primary endpoint will be analyzed using the Wilcoxon rank-sum test. The probability of one treatment being 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).

In addition, subgroup analyses based on the FAS as described in Section 2.2.1 will be performed.

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

The secondary endpoints include the following:

- Change in mean activity during sleep between baseline phase (mean of data collected during Week -1) and the final randomized treatment phase measurement (mean of data

collected during Week 8), as measured by actigraphy (activity counts per minute during daily sleep period, wrist-worn accelerometer).

- Change in mean activity during sleep between baseline phase (mean of data collected during Week -1) and each randomized treatment and open-label extension phase measurement, as measured by actigraphy (Weeks 1, 9, and 16) (activity counts per minute during daily sleep period, wrist-worn accelerometer).
- Change in mean activity counts during the most active 30 minutes of the patient's day between baseline phase (mean of data collected each day during Week -1) and each randomized treatment and open-label extension phase measurement (Weeks 1, 9, and 16), as measured by wrist worn accelerometer collected actigraphy.

Endpoints will be based on the mean of data collected for at least 5 out of the 7 days during the given week.

2.7.2 Statistical hypothesis, model, and method of analysis

During the randomized treatment phase, change from baseline for each secondary endpoint will be analyzed at each time point using the same ANCOVA model as for the primary endpoint.

During the open-label extension phase, change from baseline (mean of Week -1) for each secondary endpoint will be analyzed at each time point using paired t-tests for the group randomized to sacubitril/valsartan. The analyses will be repeated using the Week 8 measurement as baseline for the group randomized to enalapril.

2.7.3 Handling of missing values/censoring/discontinuations

For the analysis of secondary endpoints during the randomized treatment phase, the same approach for the handling of missing data as for the primary endpoint will be used (see Section 2.5.3).

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

AEs will be 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 treatment 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 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 ($\geq 5\%$) 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
- 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 by primary SOC and PT

2.8.1.4 Adverse events of special interest / grouping of AEs

Separate summaries will be provided for AEs related to 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 treatment phase (see Section 2.1.1 for treatment phase definitions). A patient listing of all deaths with primary and contributing reasons for death will be provided. All patients in the FAS will be included for the above analysis. Deaths will be coded using MedDRA terminology (v19.0 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 treatment phase (see Section 2.1.1 for treatment 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 for both the randomized treatment and open-label extension phases. 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 treatment phase (see Section 2.2.1 for treatment 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).

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.

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 {bpm}], respiration rate [breaths per minute], weight [kg], height [cm], and BMI [kg/m²]) will be descriptively summarized at each visit by treatment group for both the randomized treatment and open-label extension phases. Change from baseline will also be presented. Note that height is only collected at Visit 1.

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 treatment phase (see Section 2.1.1 for treatment phase definitions).

2.8.4.2 Heart Failure (HF) Signs and Symptoms

The number and percentage of patients in the following HF signs and symptoms categories will be summarized by visit and treatment group for both the randomized treatment and open-label extension phases:

- 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

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 and treatment group for both the randomized treatment and open-label extension phases.

- 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)
- 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
 - Shortness of breath/dyspnea (No, Yes, Unknown)
 - Difficulty swallowing/dysphagia (No, Yes, Unknown)
 - Difficulty speaking/dysarthria (No, Yes, Unknown)
 - Pain on swallowing/odynophagia (No, Yes, Unknown)
 - Stridor (No, Yes, Unknown)
 - Abdominal pain (No, Yes, Unknown)
 - Other (No, Yes, Unknown)
- Edema present (No, Yes)
 - Periorbital edema (No, Yes, Unknown)

- Head edema (No, Yes, Unknown)
 - Neck edema (No, Yes, Unknown)
 - Lip edema (No, Yes, Unknown)
 - Tongue edema (No, Yes, Unknown)
 - Throat edema (No, Yes, Unknown)
 - Submandibular edema (No, Yes, Unknown)
 - Genitalia edema (No, Yes, Unknown)
 - Extremities edema (No, Yes, Unknown)
 - Other (No, Yes, Unknown)
- 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 at time of event (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 (other than study medication) (No, Yes)
 - Discontinuation of ARB (other than study medication) (No, Yes)
 - Other (No, Yes)

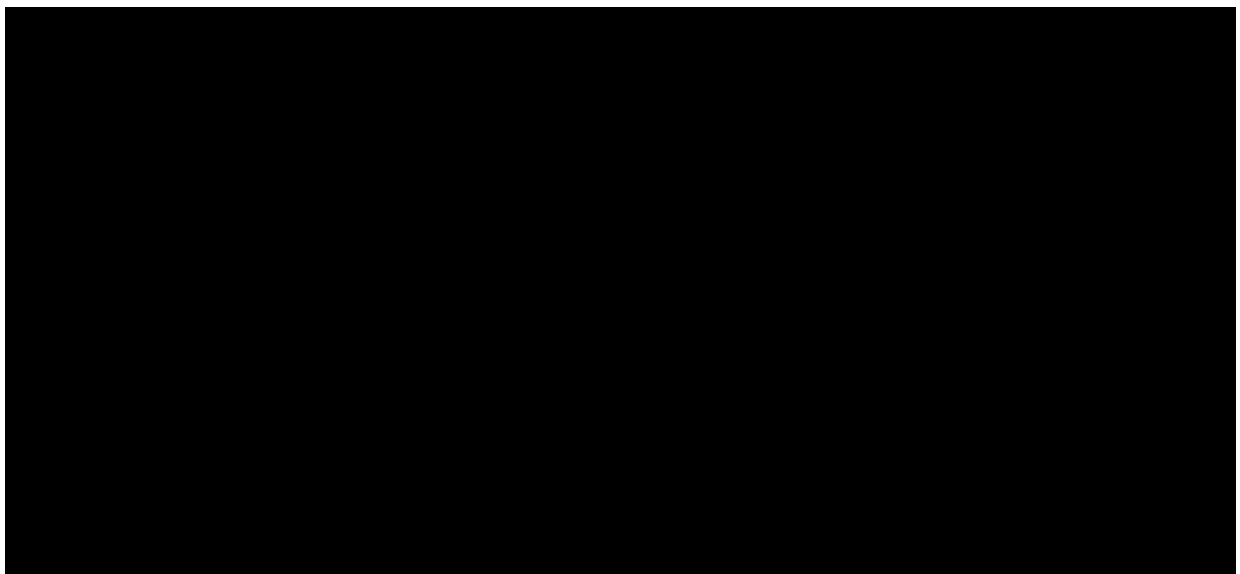
All angioedema assessment data will be listed. Additionally, the adjudicated assessment of the event will be listed separately.

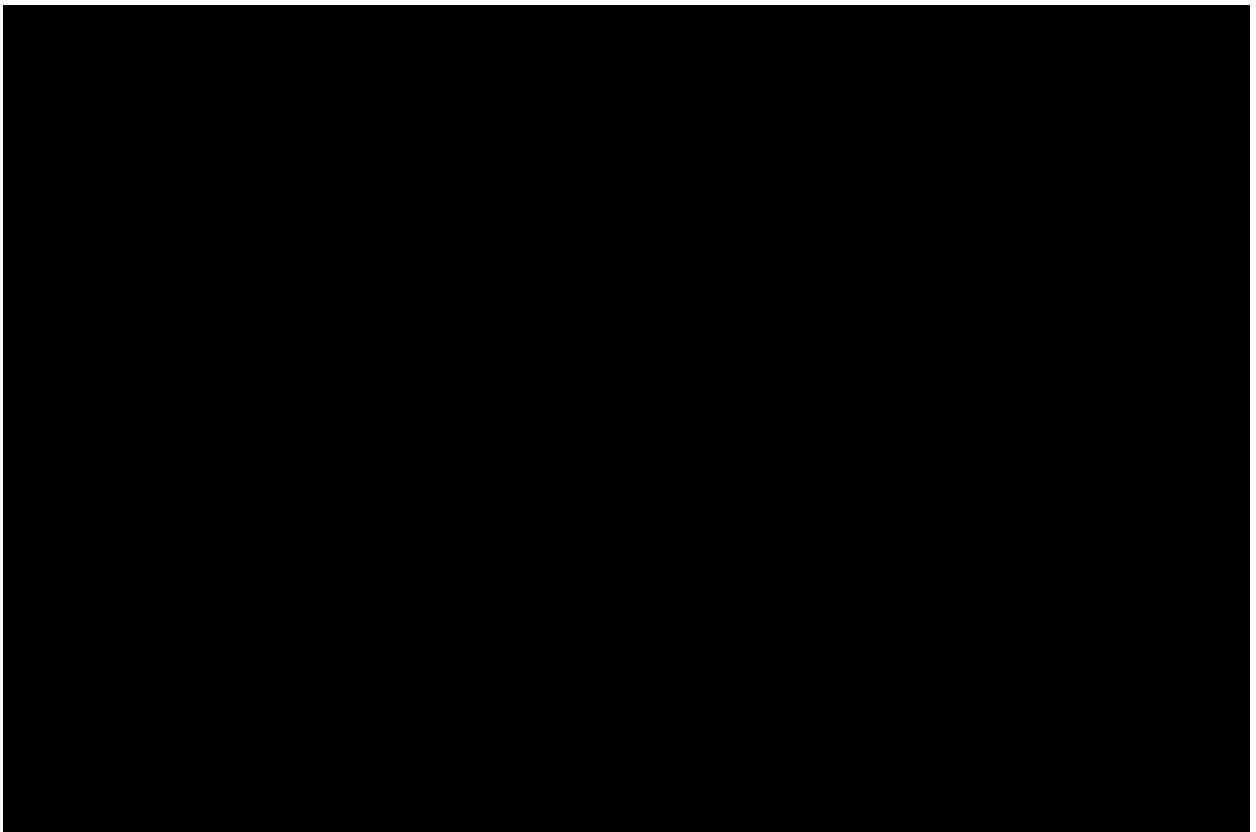
2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

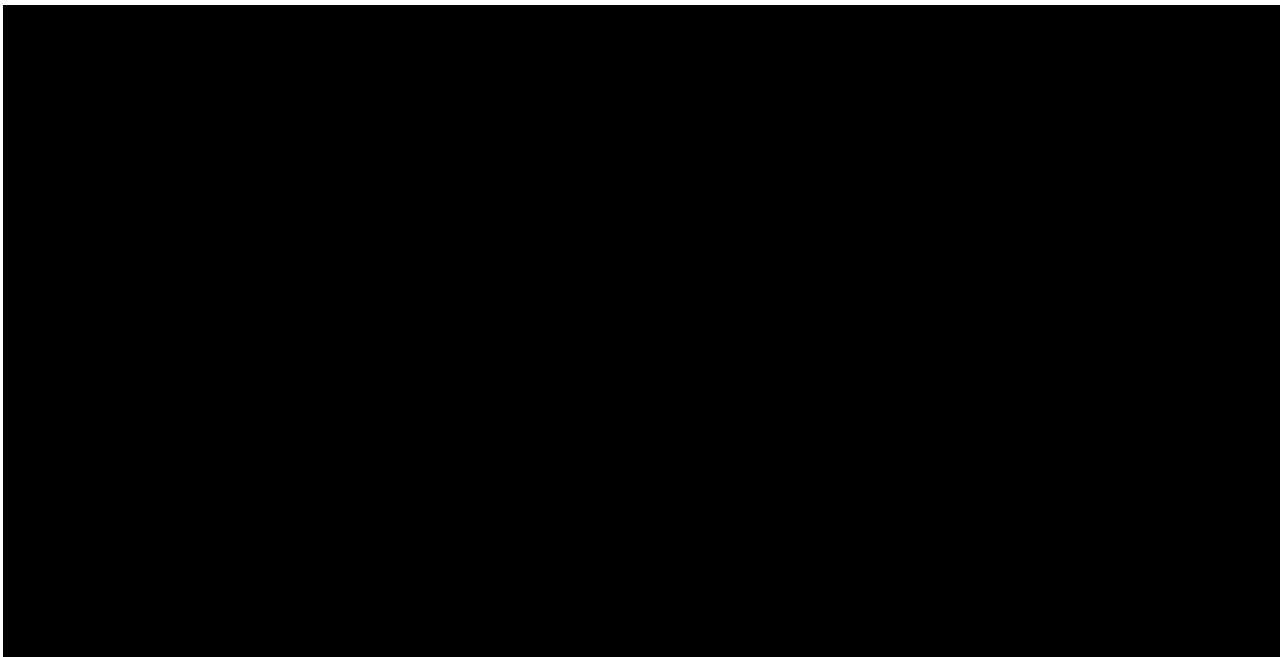
Not applicable.

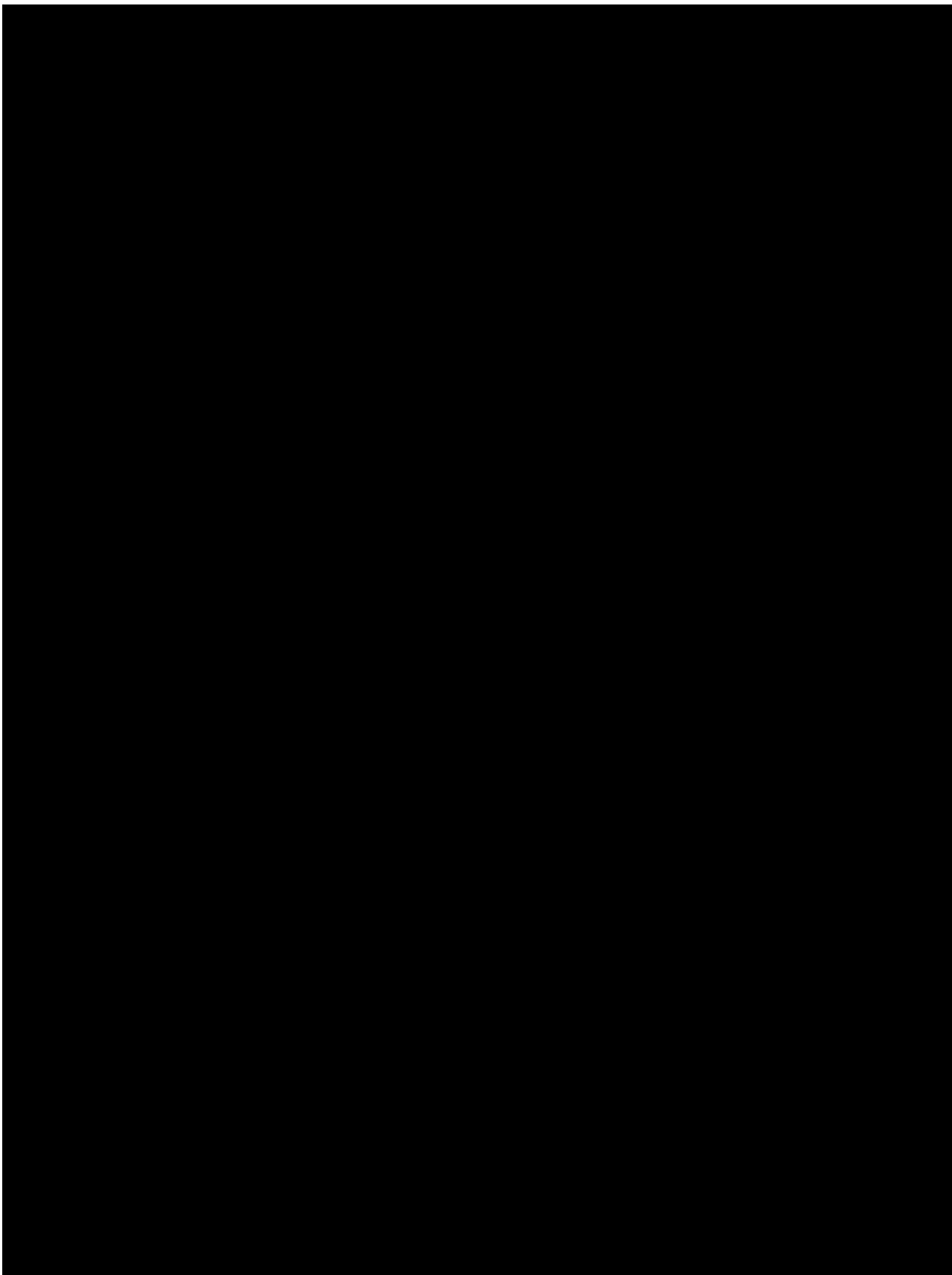


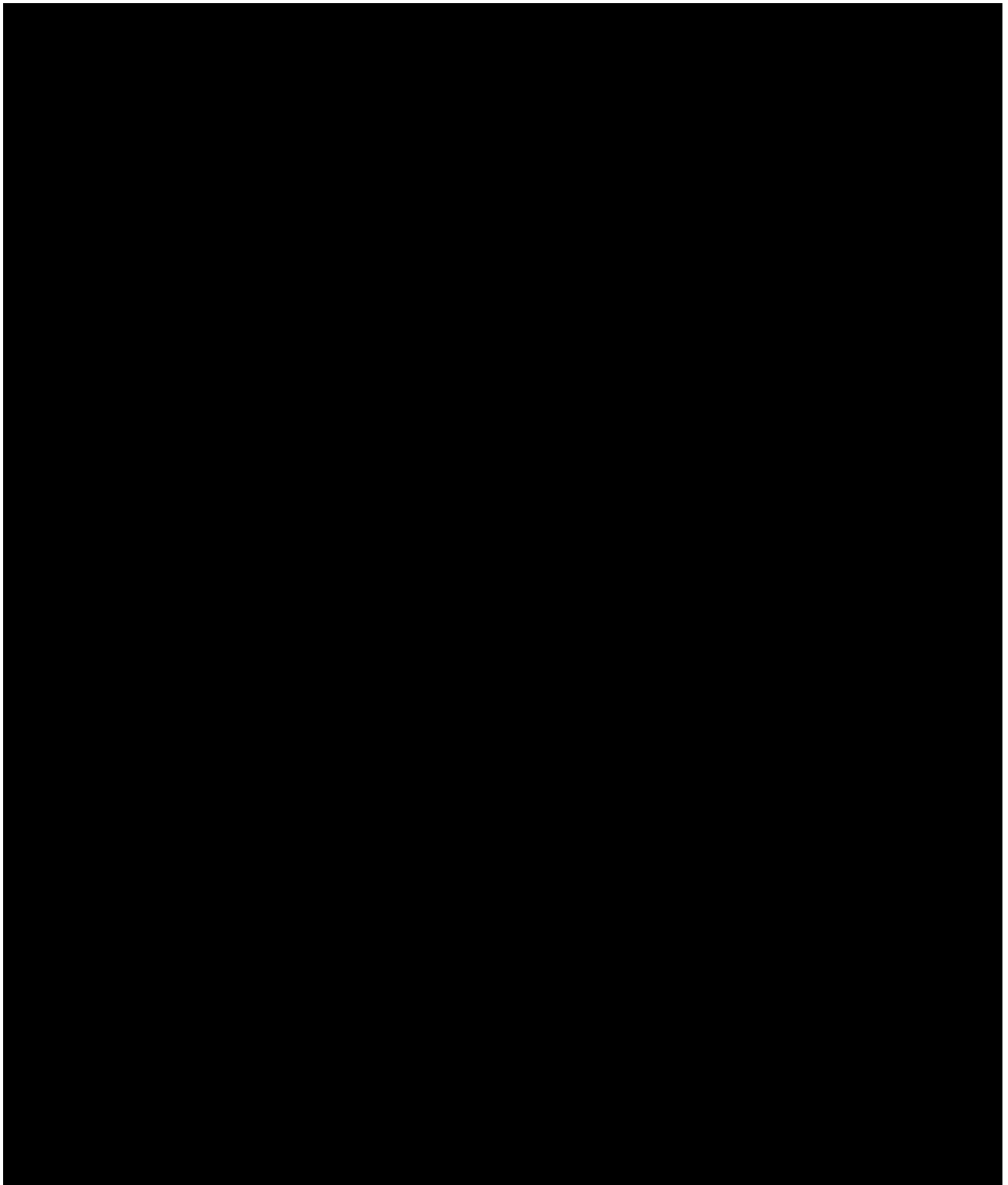


2.12 Biomarkers

Not applicable.







2.14 Interim analysis

No interim analysis is planned.

3 Sample size calculation

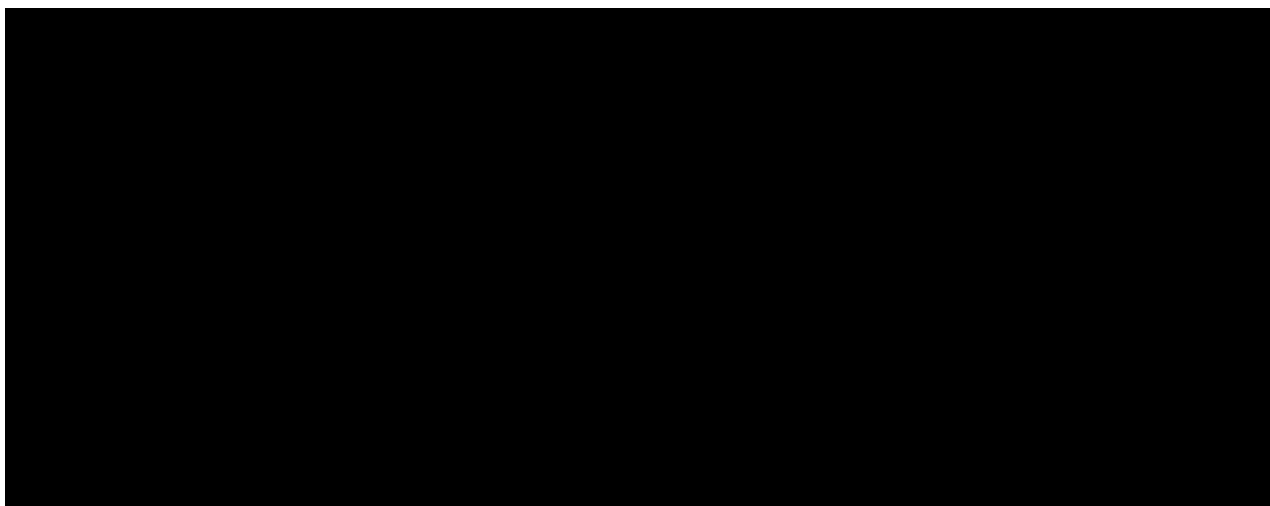
Primary endpoint:

Assuming a significance level of 0.05, a total sample size of 136 patients would provide 90% power to detect a difference of 5000 in the change from baseline in mean activity counts collected during the most active 30 minutes between the sacubitril/valsartan treatment group and the enalapril group during Week 8, assuming a common standard deviation of 7400 (Maurer 2009) and a 20% drop-out rate and a 10% rate of patients with non-evaluable data. The assumed effect size of 68% (5000/7400) will be maintained in the event the log transformation is needed for the primary analysis thus not affecting the sample size calculation and power of the study.

Secondary endpoint:

Assuming a significance level of 0.05, a sample size of 136 patients would provide 93% power to detect a 3.5 point difference in the change from baseline in mean activity value during the sleep (expressed as counts per minute) between the sacubitril/valsartan treatment group and the enalapril group during Week 8, assuming a common standard deviation of 4.9 and a 20% drop-out rate and a 10% rate of patients with non-evaluable data (Peterson 2012).

4 Change to protocol specified analyses



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 UBC coding team will code the AE terms using MedDRA 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

Hematology

Red blood cell (RBC) count >50% increase, >20% decrease

Hemoglobin	>50% increase, >20% decrease
Hematocrit	>50% increase, >20% decrease
White blood cell (WBC) count	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease

Blood Chemistry

Alanine aminotransferase (ALT) (SGPT)	>150% increase
Aspartate aminotransferase (AST) (SGOT)	>150% increase
Blood urea nitrogen (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 mean activity count at Week 8 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 secondary endpoints will use the same approach as described for the analysis of the primary endpoint in Section 5.5.1.

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
NA	NA	NA

Table 2 Patient Classification

Analysis Set	Protocol deviation ID that cause patients to be excluded	Non-protocol deviation criteria that cause patients to be excluded
RS	NA	Not randomized
FAS	NA	Not in RS; Have not received study treatment but inadvertently randomized
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.

[REDACTED]

Maurer M, Cuddihy P, Weisenberg J, Delisle S, Strong BM, Gao Q, Kachnowski S, and Howell J. The Prevalence and Impact of Anergia (Lack of Energy) in Subjects With Heart Failure and its Associations With Actigraphy et al. *Journal of Card Failure* 2009; 15, 145

Peterson B.T, Chiao P, Pickering E, Freeman J, Zammit G.K, Ding Y, and Badura L.L. Comparison of actigraphy and polysomnography to assess effects of zolpidem in a clinical research unit *Sleep Medicine* 13 (2012), pp.419-424