Official Title:	**A Randomized, Double-blind, Active-controlled Study to Assess the Effect of Sacubitril/Valsartan Compared With Enalapril to Improve Erectile Function in Patients With Heart Failure With Reduced Ejection Fraction and Erectile Dysfunction**
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NOVARTIS

Clinical Development

LCZ696/Sacubitril/Valsartan

CLCZ696BDE03

A randomized, double-blind, active-controlled study to assess the effect of sacubitril/valsartan compared with enalapril to improve erectile function in patients with heart failure with reduced ejection fraction (HFrEF) and erectile dysfunction (ED)

Statistical Analysis Plan (SAP)

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29-Sep-2021	Between Dry run & DB lock	Amendment 02	Imputation rule for AE for start date added	Section 5.1.2 AE date imputations
			Imputation rule for CM start date added	Section 5.1.3 Concomitant medication date imputation
			Objectives for endpoints updated to remove text "Mean"	Section1.2 Study objectives and endpoints
			SAS mock code updated	Section 5.4 Statistical models
			Removed all severity codes except code 03 as per communication from ML	Section 5.5 Rule of exclusion criteria of analysis sets
			[redacted]	
			Question 6 responses added manually	Section 2.11.2 IIEF-15
			SAD score added manually,	Section 2.7 Analysis of secondary

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				efficacy objectives (s)
			Patient reported sexual activity updated.	Section 2.7.2
			Added summary of CFB for SAD and NT-proBNP.	Statistical hypothesis, model, and method of analysis
			Laboratory data for HbA1c absolute removed	Section 2.8.3 Laboratory data
			[redacted]	

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List of abbreviations

AE	Adverse event
ACE	Angiotensin-converting-enzyme
ACEI	Angiotensin-converting-enzyme inhibitor
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
CHF	Chronic heart failure
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ED	Erectile dysfunction
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
HF	Heart Failure
HFrEF	Heart failure with reduced ejection fraction
IVR	Interactive Voice Response
IWR	Interactive Web Response
IRB	Institutional Review Board
IRT	Interactive Response Technology
LFT	Liver function test
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mmHg	Millimeter mercury
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SmPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This SAP module describes the planned statistical methods for all safety and efficacy analyses. Any changes made to the statistical plan and methodology after the clinical database lock will be documented as an addendum.

The main purpose of this document is to provide summary of the statistical methodology that will be used for this clinical study; this includes a detailed description of data summaries. Analyses plan in this document refers to the related statistical analysis sections in clinical study report.

Data will be analyzed by Novartis according to the data analysis section 9 of the clinical study protocol. That statistical methodology is described below and any deviations from the protocol are documented. Additional detailed information regarding the analysis methodology is contained in the Appendix section.

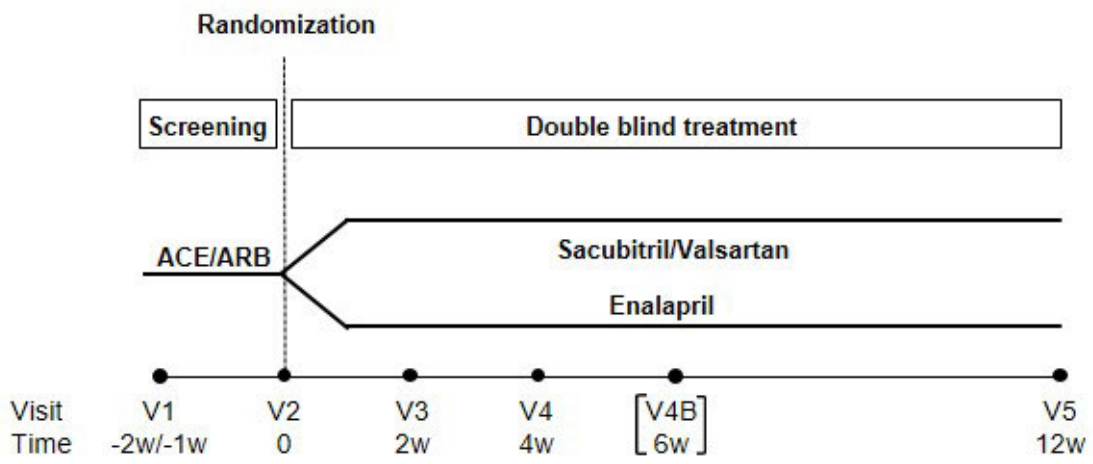
1.1 Study design

This is a randomized, double-blind, double-dummy, multi-center, active-controlled, interventional study to compare sacubitril/valsartan to enalapril in improving erectile function in male patients with chronic heart failure (NYHA II) with reduced ejection fraction (HFrEF) and erectile dysfunction (ED).

The study comprises five obligatory and one optional visit over a period of approximately 14 weeks. Once patients' eligibility has been ascertained at Visit 1 (Screening), patients will be randomized at Visit 2 (Randomization) to receive either sacubitril/valsartan or enalapril in a 1:1 allocation during the double-blind period. At Visit 2, all efficacy assessments will be collected and used as baseline values. Double-blind treatment will be initiated with 5 mg bid enalapril or 49 mg/51 mg bid sacubitril/valsartan and up-titrated after 2 weeks to the final dose of 10mg bid enalapril or 97 mg/103 mg bid sacubitril/valsartan. According to the sacubitril/valsartan SmPC, initiation of treatment is recommended with the 24 mg/26 mg bid sacubitril/valsartan or 2.5 mg bid enalapril dose for certain patients. For these patients, an optional visit 4B after achieving the target dose of 97 mg /103 mg bid sacubitril/valsartan or 10 mg bid enalapril is mandatory. For the detailed understanding of study design and allowed investigational treatment dose adjustments during double-blind period refer Section 3.1 and Section 5.5.4 of the protocol.

The study design is shown in the below figure.

Figure 1.1-1 Study design



There are 200 patients planned to be randomized in 1:1 allocation to receive either sacubitril/valsartan or enalapril.

There will be no stratification at randomization in this study. The primary analysis will be done based on the erectile function score of the questionnaire International Index of Erectile Function (IIEF-15) at the end of the study i.e. at visit 5 (Week 12).

There is no interim analysis planned for this study.

1.2 Study objectives and endpoints

Table 1.2-1 Study objectives and related endpoints

Primary Objective(s)	**Endpoint(s) for primary objective(s)**
To demonstrate the superiority of sacubitril/valsartan compared to enalapril regarding improvement in erectile function and ability in male patients with chronic heart failure and erectile dysfunction using the questionnaire International Index of Erectile Function (IIEF-15) at the end of the study	Erectile function score using IIEF-15 at Week 12.
Secondary objective(s)	**Endpoint(s) for Secondary objective(s)**
To assess the early-onset effect as well as the effect at the end of the study of sacubitril/valsartan versus enalapril regarding improvement in sexual activity	Self-reported sexual activity per week at week 4 and week 12

assessed using patient's self-reported sexual activity per week	
To assess the early-onset effect as well as the effect at the end of the study of sacubitril/valsartan versus enalapril regarding NT-proBNP levels	NT-proBNP levels at week 4 and week 12

[redacted]

2 Statistical methods

2.1 Data analysis general information

The data analysis will be conducted by Novartis on all patient data after database lock for the respective trial periods. Analysis datasets and statistical outputs will be produced using the most recent SAS® Version 9.4 or higher (SAS Institute Inc., Cary, NC, USA), and stored in Novartis global programming & statistical environment (GPS).

Continuous variables will be summarized by number of patients, mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum. Categorical variables will be summarized by absolute frequencies. Summary statistics will also be presented graphically wherever applicable.

p-value and 95% confidence interval will be provided wherever applicable. Unless otherwise stated, the level of significance will be set to 5% (two-sided, family-wise type-I-error).

For categorical data, percentages will be rounded up to 1 decimal place. For continuous data, mean, median and quartiles will be rounded up to 1 additional decimal place compared to the original data. Standard deviation will be rounded up to 2 additional decimal places. Minimum and maximum will be displayed with the same accuracy as in the original data. Wherever changes from baseline will be used, change will be calculated as "post-baseline value – baseline value". The number of decimal places for the "change from baseline" variables will be the same as for the original measurement.

2.1.1 General definitions

Study treatment: Study treatment refers to

Sacubitril/valsartan bid and placebo matching enalapril bid

Enalapril bid and placebo matching sacubitril/valsartan bid.

Study treatment start and end date: Study treatment start date is defined as the first date when a non-zero dose of study drug is administered and recorded on the Drug Administration Record (DAR) CRF page. Similarly, study drug end date is defined as the last date when a non-zero dose of study drug is administered and recorded on the DAR CRF page of the study.

Study day: Study day will be calculated as (event date – study drug start date + 1 day) for events that occurred on or after study drug start date (e.g., visit, lab samples, AEs). For events prior to study drug start date (e.g., time of diagnosis), study day will be negative and calculated as (event date – study drug start date). Note that study drug start date is study day 1 and the day before study drug start date is study day -1 (i.e. not study day 0).

Note that, the first dose day is Day 1, and the day before the first dose day is counted as day -1 (not day 0).

Baseline and post-baseline: Baseline value is defined as the last non-missing assessment prior to the first dose of randomized study medication. A post-baseline value refers to a measurement taken after the first dose of study treatment.

Lost to follow up: Subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw. A patient cannot be considered as lost to follow-up until the time point of his planned end of study visit has passed.

Study completion: A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol.

2.2 Analysis sets

The following analysis sets will be used for the statistical analyses:

Full Analysis Set (FAS): The full analysis set (FAS) will consist of all randomized patients who received at least one dose of study drug. Following the intent-to-treat principle, patients will be analyzed according to the treatment which they were assigned to at randomization. Efficacy variables will be analyzed based on the FAS.

Safety Set (SAF): The safety set (SAF) will consist of all randomized patients who received at least one dose of study drug. Patients will be analyzed according to the treatment actually received. The SAF will be used for the analyses of safety variables.

2.2.1 Subgroup of interest

Not applicable.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number and percentage of patients screened, completed the screening and randomized will be presented. In addition, the reasons for screen failures will be provided.

The number and percentage of patients who completed the study and/or discontinued the study prematurely (including the primary reason for discontinuation) will be presented, if appropriate, for each treatment group and all randomized patients.

The number and percentage of patients who took rescue medication will be presented. For each protocol deviation (PD), the number and percentage of patients for whom the PD applies will be tabulated for all the patients in FAS.

2.3.2 Patient demographics and other baseline characteristics

Summary statistics will be provided by treatment group for demographics and baseline characteristics, including age, age group (<65 years vs. >= 65 years and <= 75 years), sex, race, weight, height, body mass index (BMI), category of prior CHF medication, prior HF hospitalization, NYHA class, score of short International Index of Erectile Function (IIEF-5), and vital signs.

BMI will be calculated as weight (kg) / height^2 (m^2) from the collected height and weight at Visit 1 (Screening).

Continuous variables will be summarized using n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency and percentage.

The full analysis set (FAS) will be used for the above analyses.

2.3.3 Medical history

Any condition entered on the relevant medical history / current medical conditions CRF will be coded using the MedDRA dictionary. They will be summarized by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary. Summaries for cardiovascular and heart failure medical history will be reported separately. Smoking history (baseline) will be summarized and listed.

Apart from summarizing medical history, Cardiovascular history, and Heart failure history will also be listed. Analyses will be based on the full analysis set.

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

2.4.1 Study treatment / compliance

The summaries by treatment will be performed by the actual treatment received as follows:

- Sacubitril/Valsartan
- Enalapril

The analysis of study treatment data will be based on Safety analysis set (SAF).

Duration of exposure

The duration of exposure to study treatment will also be summarized by treatment group using mean, standard deviation, median, minimum and maximum. In addition, the number and percentage of patients with cumulative exposure levels (e.g. any exposure, ≥ 2 weeks, ≥4 weeks, ≥ 6 weeks, ≥8 weeks, ≥ 12 weeks, etc.) will be presented.

Duration of exposure for study treatment will be defined as the time from first dose of study treatment to the time of treatment end for each treatment.

The analyses of duration of exposure described above will be done for the entire study treatment periods.

Compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient.

2.4.2 Prior, concomitant and post therapies

Prior and concomitant medications will be summarized in separate tables by treatment group based on safety set.

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and the date of the last study visit will be a concomitant medication, including those, which were started pre-baseline and continued into the period where study treatment is administered.

Concomitant medications and significant non-drug therapies, prior to and after the randomization date respectively, will be summarized by therapeutic class, preferred term, and treatment group according to the WHO-DRL dictionary.

The number and percentage of patients on different CHF background medications (β-blockers, diuretics) will be tabulated by treatment at baseline and during the treatment period.

2.5 Analysis of the primary objective

The primary objective is to demonstrate the superiority of sacubitril/valsartan compared to enalapril regarding improvement in erectile function and ability in male patients with chronic heart failure and erectile dysfunction using the questionnaire International Index of Erectile Function (IIEF-15) at the end of the study.

2.5.1 Primary endpoint

The primary endpoint is the erectile function score IIEF-15 at week 12. The trial aims to estimate the effect of the treatment policy, irrespective of intercurrent events such as dose changes or adherence to randomized treatment.

The following estimand will be used:

Population – Full Analysis Set (FAS)

Variable of Interest – Erectile function score IIEF-15 at week 12

Intervention effect – effect between sacubitril/valsartan versus enalapril at week 12 regardless of adherence to randomized treatment.

Summary measure – difference in means.

For patients who permanently discontinue study treatment, values collected after study drug discontinuation will generally be included in the primary analysis.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary variable will be analyzed using a mixed model for repeated measures (MMRM), The response variable will be the Erectile function score IIEF-15 and change from baseline. Treatment (sacubitril/valsartan versus enalapril), visit and treatment-by-visit interaction will be included as fixed-effect factors; baseline IIEF-15 will be included as a covariate; the within-patient covariance will be modeled using an unstructured covariance matrix (a common matrix for the two treatment groups). The analysis will include all (two) scheduled post-baseline visits and will be performed based on the likelihood method with an assumption of missing at random (MAR) for missing data.

The null-hypothesis to be rejected is that there is no difference in mean IIEF-15 erectile function score at week 12 between the two treatment arms.

In mathematical terms:

$$H_0: \mu_1 = \mu_2$$

vs. H_a: $\mu_1 \neq \mu_2$

where μ_1 and μ_2 are mean erectile function IIEF-15 scores at week 12 for the treatment groups of sacubitril/valsartan versus enalapril, respectively.

The statistical test will be performed at the two-sided significance level of 0.05 based on the MMRM model. The estimates and the corresponding 95% confidence intervals will be provided for the difference in adjusted means at month 3 between the two treatment groups based on the MMRM model. Although this test is defined as two-sided, superiority of sacubitril/valsartan versus enalapril will be claimed only, if the difference is in favor of sacubitril/ valsartan.

The FAS will be used for the above primary analyses.

2.5.3 Handling of missing values/censoring/discontinuations

Patients will be followed up and all scheduled visits should be performed, even if study drug is discontinued for that respective patient prematurely. Therefore, missing values should only occur in case of death, withdrawal of informed consent or loss to follow up. In these cases, patients will be included with their available values into the statistical MMRM model.

2.5.4 Sensitivity analyses

A 'while on treatment' estimand might be meaningful to explore the effect of drop-outs on the primary estimand. This estimand will include drop-outs with their last observed value and will not (like the MMRM model of the primary estimand) extrapolate a possible improvent that might have been observed if the patient had continued. The following estimand will be used:

Population – Full Analysis Set (FAS)

Variable of Interest – Erectile function score IIEF-15 at last observed visit.

Intervention effect – effect between sacubitril/valsartan versus enalapril at last observed visit regardless of adherence to randomized treatment.

Summary measure – difference in means.

For patients for whom an IIEF-15 at week 12 is available, this value will be used, regardless of adherence to treatment. Analysis will be performed using an Analysis of Covariance model for IIEF-15 at last observed visit with factor treatment group and covariate baseline IIEF-15.

2.6 Analysis of the key secondary objective

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

All the secondary efficacy evaluation will be performed on FAS population.

Following are the secondary objectives need to be assessed in this trial:

- To assess the early-onset effect as well as the effect at the end of the study of sacubitril/valsartan versus enalapril regarding improvement in sexual activity assessed using patient's self-reported sexual activity per week

Sexual activity diary contains seven questions. Six questions have 5 response options (scored from 1 to 5) and one question (Question no. 5) has 2 response options (yes or no). Descriptive summary for total score of Self-reported sexual activity (Except question no. 5) will be provided per week (i.e at week 4 and week 12). For question no. 5, only frequency distribution for each category (yes and no) will be provided at week 4 and week 12.

Q1-Q2	Score
Not at all (no attempt to masturbate within the past 7 days)	1
Not at all (no attempted sexual intercourse within the past 7 days)	1
Once	2
Twice	3
Three times	4
More than three times	5
Q3-Q4	Score
Not at all (no erection at night or in the morning)	1
Not at all (no other sexual activity)	1
Once	2
2-3 times	3
4-5 times	4
More than 5 times	5
Q6	Score
Non existent	1
Little	2
Satisfactory	3
Strong	4
Very strong	5
Q7	Score
Very negatively affected	1
Negatively affected	2
Not affected	3
Positively affected	4
Very positively affected	5

- To assess the early-onset effect as well as the effect at the end of the study of sacubitril/valsartan versus enalapril regarding NT-proBNP levels

2.7.1 Secondary endpoints

The following secondary variables will be analyzed:

- Self-reported sexual activity per week at week 4 and week 12
- NT-proBNP levels at week 4 and week 12

2.7.2 Statistical hypothesis, model, and method of analysis

Not applicable

Patient-reported sexual activity

Sexual activity diary contains seven questions. Six questions have 5 response options (scored from 1 to 5) and one question (Question no. 5) has 2 response options (yes or no). Descriptive summary for total score and change from baseline of Self-reported sexual activity (Except question no. 5) will be provided per week (i.e at week 4 and week 12). For question no. 5, only frequency distribution for each category (yes and no) will be provided at week 4 and week 12.

NT-proBNP

Raw & Change from basline NT-proBNP levels at week 4 and week 12 will be summarized descriptively using n, mean, standard deviation, median, minimum and maximum.

NT-proBNP data will remain blinded till data base lock.

2.7.3 Handling of missing values/censoring/discontinuations

No missing data imputation will be used for secondary variables.

2.8 Safety analyses

Safety set will be used for the safety analyses.

2.8.1 Adverse events (AEs)

Adverse events will be coded by primary system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA).

The crude incidence of treatment emergent adverse events (i.e. events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized by primary system organ class and preferred term.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having at least one AE, having an AE in each primary system organ class and having each individual AE (preferred term).

Summaries will also be presented for AEs by severity and for study treatment related AEs. If a particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity and drug relationship will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

Separate summaries will be provided for

- All adverse events
- Adverse events suspected to be related to study drug by the investigator
- Deaths
- Serious adverse events
- Adverse events leading to discontinuation
- Adverse events requiring dose adjustment or study-drug interruption

In the data listings of adverse events, the severity of an AE, whether or not an AE is study drug related, and whether or not it is a serious AE, will be indicated.

2.8.1.1 Adverse events of special interest / grouping of AEs

The following event will be considered as adverse event of special interest.

- Angioedema

Adverse events of special interest will be coded by primary system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events of special interest will be summarized by presenting, for each treatment group, the number and percentage of patients having at least one AE, having an AE in each primary system organ class and having each individual AE (preferred term).

2.8.2 Deaths

Separate summaries and listings will be provided for deaths. Death information will be summarized based on safety set.

2.8.3 Laboratory data

The laboratory analysis will be carried out on safety set.

Laboratory data will be summarized by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges) to each visit. The summary of laboratory evaluations will be presented for hematology and blood chemistry parameters seperately.

The following laboratory variables will be presented for all visits:

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential counts, and platelet count.

Biochemistry

Glucose, blood urea nitrogen (BUN), Blood urea, creatinine, creatinine kinase, total bilirubin, AST, ALT, alkaline phosphatase, INR, GFR, HbA1c relative, sodium, potassium, chloride, calcium, total protein, albumin, HDL, LDL, triglycerides, and uric acid The number and percentage of subjects with clinically notable laboratory results after baseline will be presented. Clinically notable laboratory results, for those parameters where ranges are available, are given in Table 2.8.3-1 below. For the calculation the denominator are based on the evaluable post-baseline subjects who did not have the notable abnormality at baseline.

For all laboratory evaluation scheduled and unscheduled laboratory measurements will be taken into account.

Table 2.8.3-1 Clinically notable laboratory values

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

Hematology	
RBC count	>50% increase, >20% decrease
Hemoglobin	>50% increase, >20% decrease
Hematocrit	>50% increase, >20% decrease
WBC count	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease
Blood Chemistry	
ALT (SGPT)	>150% increase
AST (SGOT)	>150% increase
BUN	>50% increase
Creatinine	>50% increase
Total bilirubin	>100% increase
CPK	>300% increase
Alkaline phosphatase	>100% increase
Potassium	>20% increase, >20% decrease
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease

Uric acid	>50% increase

2.8.3.1 Urine analysis

Not Applicable

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Not applicable.

2.8.4.2 Vital signs

Vital signs include blood pressure and pulse measurements. These parameters will be summarized by visit with standard summary statistics (mean, median, standard deviation, and ranges), including change from baseline. Change from baseline will only be summarized for subjects with both baseline and post-baseline values.

The number and percentage of patients with newly occurring notable vital signs will be presented. Criteria for notable vital sign abnormalities are provided in Table 2.8.4-1 below.

2.8.4.3 Height and weight

Height and weight collected will be listed based on safety set.

2.8.4.4 Physical examination

Collected physical examination parameters on CRF will be listed based on safety set.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

The following Patient reported outcomes (PROs) will be analyzed in the study:

2.11.1 IIEF-5

The IIEF-5 score will be used in male patients with heart failure with reduced ejection fraction to determine the patients'/subjects' eligibility for study participation. The IIEF-5 consists of 5 items. For every item, 5 possible response options are available (score 1-5) adding up to a maximum total score of 25. Erectile function will be determined by study personnel by adding individual scores to a total score.

22-25: No erectile dysfunction

17-21: Mild erectile dysfunction

12-16: Mild to moderate erectile dysfunction

8-11 : Moderate erectile dysfunction

5-7 : Severe erectile dysfunction.

The number and percentage of patients in each category based on total score will be summarized for FAS population.

2.11.2 IIEF-15

The IIEF-15 score will be used in male patients with heart failure with reduced ejection fraction. The IIEF-15 is a validated, multi-dimensional, self-administered questionnaire for the assessment of erectile function. The questionnaire of 15 items organized in 5 domains. The respective domains are:

• Erectile function

• Orgasmic function

• Sexual desire

• Intercourse satisfaction

• Overall satisfaction

For every item 5 possible response options are available (score 1-5) resulting in a maximum score of 75. Each domain will be determined by study personnel by adding individual scores to a total score based on the following consideration.

For each question, 0-5 points can be achieved with 5 being the best outcome (Rosen et al., 1997). In this study, the IIEF-15 will be completed by patients at baseline (Visit 2), as well as at 2 weeks (Visit 3), at 1 month (Visit 4) and at 3 months (Visit 5) and all categories will be evaluated separately: erectile function (questions 1-5; 15), orgasmic function (questions 9-10), sexual desire (questions 11-12), intercourse satisfaction (questions 6-8) and overall satisfaction (questions 13-14). Among 15 questions except question 6 all the questions are scored properly. For question 6 score value (range) will be changed manually based on below considerations for analysis.

How many times have you attempted sexual intercourse ?	Score value
No attempt	0
One to two attempts	1
Three to four attempts	2
Five to six attempts	3
Seven to ten attempts	4
Eleven and more attempts	5

The IIEF-15 will be assessed at Week 0 (Randomization) for baseline and at week 2, 4, 12 (end of study) and in case of PD or TSD.

Summary of IIEF-15 score will be presented for each IIEF-15 domain with exception of Orgasmic function.

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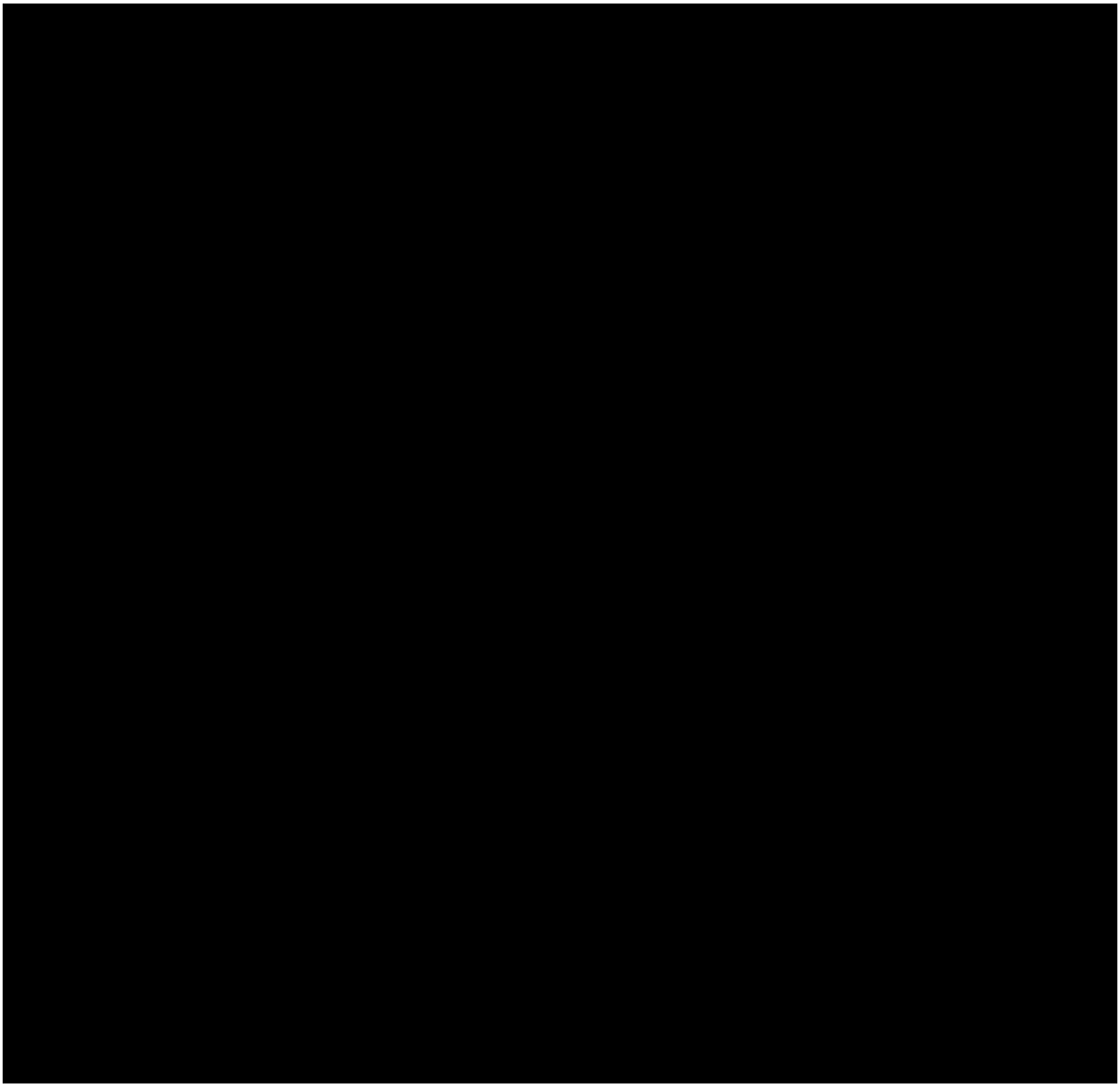
[redacted]

2.11.4 Patient-reported sexual activity

Please refer to the Section 2.7.2 for analysis of Patient-reported sexual activity.

[redacted]



2.14 Interim analysis

No interim analysis will be performed.

3 Sample size calculation

For the IIEF-15 domain “erectile function”, the treatment effect and SD of sacubitril/valsartan compared to enalapril was estimated based on the previous VALED study, which demonstrated that valsartan showed a highly significant increase in erectile function from 16.54±8.27 to 23.14±6.49 IIEF units in hypertensive males (Dusing, 2003). VALED was an open-label study comparing 6 months treatment with valsartan to baseline. CONFIDENCE on the other hand is a double-blind randomized trial and the beneficial effect of sacubitril/valsartan will likely be driven not by valsartan but by the neprilysin inhibition introduced by sacubitril. For sample size

calculation the shorter study period, differing patient population (heart failure versus hypertension) as well as the use of bisoprolol/metoprolol have to be taken into account. Beta-blocker have differing effects on erectile function. While propranolol and atenolol are well-known to reduce sexual function, nebivolol has vasodilating effects, which may even be beneficial in erectile dysfuntion (Baumhakel et al., 2011). Bisoprolol/metoprolol have been suggested to have a neutral effect on erectile dysfunction (Baumhakel et al., 2011) and were thus chosen as the allowed concomitant beta-blockers within the study.

Therefore, a treatment effect of sacubitril/valsartan compared to enalapril of 3.5 IIEF units was estimated. Assuming a standard deviation of 7 IIEF units and a two-sided alpha of 0.05, 86 patients per arm would confer a 90% power to detect a conservative treatment difference of 3.5 IIEF units. This is in accordance with the minimal clinically important difference of the erectile function domain of IIEF-15 of 2 and 5 IIEF units in patients with mild and moderate erectile dysfunction, respectively (Rosen et al., 2011).

To compensate for some drop-out and other protocol deviations, 100 patients/arm (200 in total) should be randomized into this trial. There will be no additional recruitment in case some patients will not be able to achieve the target dose since based on PARADIGM-HF and a shorter trial duration, no substantial influence on the power of the trial is expected.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

AE date imputation is based only on a comparison of the partial AE start date to the treatment start date as mentioned in the Table 5.1.2-1 below.

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If the AE year is less than the treatment year and the AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Else if the AE year is less than the treatment year and the AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).

3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE year is greater than the treatment year and the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. Else if the AE year is greater than the treatment year and the AE month is not missing, the imputed AE start date is set to the month start point (01MONYYYY).
4. If the AE start date year value is equal to the treatment start date year value:
    a. And the AE month is missing or the AE month is equal to the treatment start month, the imputed AE start date is set to one day after treatment start.
    b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
    c. Else if the AE month is greater than the treatment start month, the imputed AE start date is set to the start month point (01MONYYYY).

Table 5.1.2-1: AE start date imputation

	MON / **MISSING**	**MON < CFM**	**MON = CFM**	**MON > CFM**
YYYY MISSING	NULL	NULL	NULL	NULL
	Uncertain	Uncertain	Uncertain	Uncertain
YYYY < CFY	(D) = 01JULYYYY	(C)= 15MONYYYY	(C)= 15MONYYYY	(C)= 15MONYYYY
	Before Treatment Start	Before Treatment Start	Before Treatment Start	Before Treatment Start
YYYY = CFY	(B)= TRTSTD+1	(C)= 15MONYYYY	(A)= TRTSTD+1	(A)= 01MONYYYY
	Uncertain	Before Treatment Start	Uncertain	After Treatment Start
YYYY > CFY	(E)= 01JANYYYY	(A)= 01MONYYYY	(A)= 01MONYYYY	(A)= 01MONYYYY
	After Treatment Start	After Treatment Start	After Treatment Start	After Treatment Start

Before Treatment Start	Partial indicates date prior to Treatment Start Date
After Treatment Start	Partial indicates date after Treatment Start Date
Uncertain	Partial insufficient to determine relationship to Treatment Start Date
LEGEND:	
(A)	MAX(01MONYYYY,TRTSTD+1)
(B)	TRTSTD+1

	MON MISSING	MON < CFM	MON = CFM	MON > CFM
(C)		15MONYYYY		
(D)		01JULYYYY		
(E)		01JANYYYY		

Adverse Event End Date Imputation

For the purpose of date imputation, the study treatment follow-up period date is defined as the last available visit date, i.e. including unscheduled visits after the end of study visit.

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (study treatment follow-up period date, 31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (study treatment follow-up period date, last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.

If the imputed AE end date is less than the existing AE start date then use AE start date as AE end date.

5.1.3 Concomitant medication date imputation

Concomitant medication (CMD) date imputation uses both a comparison of the partial CMD start date to the treatment start date, and the value of the CMDTYP1C flag (1, 2, or 3). Event date comparisons to treatment start date are made based on the year and month values only (any day values are ignored) in Table 5.1.3-1 below.

1. If the CMD start date year value is missing, the date will be imputed based on the CMDTYP1C flag value. If the flag value is 1 or 3, the imputed CMD start date is set to one day before the treatment start date. Else, if the flag value is missing or 2, the imputed CMD start date is set to one day after the treatment start date. (Note that for some legacy data, the CMDTYP1C variable may not exist in the data. When this happens and the CMD start date year value is missing, the imputed date value will be NULL.)
2. If the CMD start date year value is less than the treatment start date year value, the CMD started before treatment. Therefore:
    a. if the CMD year is less than the treatment year and the CMD month is missing, the imputed CMD start date is set to the mid-year point (01JulYYYY).
    b. Else if the CMD year is less than the treatment year and the CMD month is not missing, the imputed CMD start date is set to the mid-month point (15MONYYYY).
3. If the CMD start date year value is greater than the treatment start date year value, the CMD started after treatment. Therefore:

a. If the CMD year is greater than the treatment year and the CMD month is missing, the imputed CMD start date is set to the year start point (01JanYYYY).

b. Else if the CMD year is greater than the treatment year and the CMD month is not missing, the imputed CMD start date is set to the month start point (01MONYYYY).

4. If the CMD start date year value is equal to the treatment start date year value:

   a. and the CMD month is missing or the CMD month is equal to the treatment start month,

      i. If the flag value is 1 or 3, the imputed CMD start date is set to one day before the treatment start date.

      ii. Else, if the flag value is missing or 2, the imputed CMD start date is set to one day after the treatment start date.

   b. Else if the CMD month is less than the treatment start month, the imputed CMD start date is set to the mid-month point (15MONYYYY).

Else if the CMD month is greater than the treatment start month, the imputed CMD start date is set to the start month point (01MONYYYY).

Table 5.1.3-1: CMD date imputation

	MON MISSING	**MON < CFM**	**MON = CFM**	**MON > CFM**
YYYY MISSING	**(F)**	**(F)**	**(F)**	**(F)**
	Uncertain	Uncertain	Uncertain	Uncertain
YYYY < CFY	**(D)=01JULYYYY**	**(C)=15MONYY**	**(C)=15MONYY**	**(C)=15MONYY**
	Before Treatment Start	Before Treatment Start	Before Treatment Start	Before Treatment Start
YYYY = CFY	**(B)**	**(C)=15MONYY**	**(B)**	**(A)=01MONYYYY**
	Uncertain	Before Treatment Start	Uncertain	After Treatment Start
YYYY > CFY	**(E)= 01JANYYYY**	**(A)=01MONYYYY**	**(A)=01MONYYYY**	**(A)=01MONYYYY**
	After Treatment Start	After Treatment Start	After Treatment Start	After Treatment Start

Before Treatment Start	Partial indicates date prior to Treatment Start Date
After Treatment Start	Partial indicates date after Treatment Start Date
Uncertain	Partial insufficient to determine relationship to Treatment Start Date
LEGEND:	
(A)	MAX (01MONYYYY,TRTSTD+1)
(B)	IF CMDTYP1C IN (1,3) THEN TRTSTD-1 ELSE IF CMDTYP1C in (. , 2) THEN TRTSTD+1

	MON MISSING	MON < CFM	MON = CFM	MON > CFM
(C)		15MONYYYY		
(D)		01JULYYYY		
(E)		01JANYYYY		
(F)		IF CMDTYP1C IN (1,3) THEN TRTSTD-1 ELSE IF CMDTYP1C in (. , 2) THEN TRTSTD+1		

Concomitant Medication End Date Imputation

1. If the CM end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the CM end year value is missing or ongoing, the imputed CM end date will be set to NULL.
2. Else, if the CM end date month is missing, the imputed end date will be set to the earliest of the (Last contact date of subject in study, 31DECYYYY, date of death).
3. If the CM end date day is missing, the imputed end date will be set to the earliest of the (Last contact date of subject in study, last day of the month, date of death).
4. If the imputed CM end date is less than the existing CM start date, the CM start date will be used as the imputed CM end date.

5.1.3.1 Prior therapies date imputation

Not applicable.

5.1.3.2 Post therapies date imputation

Not applicable.

5.1.3.3 Other imputations

5.2 AEs coding/grading

The verbatim term recorded on CRF will be identified as adverse event and will be coded by primary system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 and above.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

5.4.1 Primary analysis

SAS code for mixed model:

```
proc mixed data=aaa;
        class TRT USUBJID AVISITN;
        model AVAL/CHG=TRT AVISITN BASE TRT*AVISITN
/  ddfm=kr; lsmeans TRT*AVISITN / diff cl;
repeated AVISITN / type=un subject=USUBJID;
Run;
```

In case the MMRM model does not converge the following sequential steps will be used:

1. change ddfm=kr to ddfm=bw. If still no convergence, perform step 2.

2. change type=un to type=cs. If still no convergence, perform step 3.

3. remove covariates in the following order until convergence: BASE*AVISITN,

5.4.2 STRATA.Key secondary analysis

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

Table 5-1 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
INCL01	Signed informed consent was not obtained prior to initiation of any study-related procedure.	EXCLUDE FROM FAS AND SAF	3

Table 5-2 Analysis set exclusions based on population codes

Analysis set	Population codes that cause a subject to be excluded
SAF	3
FAS	3

Table 5-3 Population code text

Population Code	Population code text
3	EXCLUDE FROM FAS AND SAF

Unless otherwise stated, summary tables, figures and listings will be on all subjects included in the analysis set under consideration.

6 Reference