NOVARTIS

Clinical Development

Sacubitril/Valsartan (Entresto™).

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Controlled trial on the short-term effects of sacubitril/valsartan therapy on cardiac oxygen consumption and efficiency of cardiac work in patients with NYHA II-III heart failure and reduced systolic function using ^{11}C-acetate positron emission tomography and echocardiography

Statistical Analysis Plan (SAP)

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List of abbreviations

AE	Adverse Event
ACEI	Angiotensin Converting Enzyme Inhibitor
ARB	Angiotensin II type‑1 Receptor Blocker
ATC	Anatomical Therapeutic Chemical
BID	Twice a Day
CRF	Case Report Form
CSR	Clinical Study Report
DMS	Document Management System
DTS	Data Transfer Specification
EDC	Electronic Data Capture
FAS	Full Analysis Set
HF	Heart Failure
HR	Heart Rate
IA	Interim Analyses
IMP	Investigational Medicinal Product
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PT	Preferred Term
RAAS	renin‑angiotensin‑aldosterone system
RAP	Reporting & Analysis Process
SAE	Serious Adverse Event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The statistical aspects of this study is briefely described in the protocol. The purpose of this Statistical Analysis Plan (SAP) is ot provide a more detailed description of the analyses to be conducted in this study. This SAP is based on:

- Clinical Study Protocol, Version 3, dated 24 June 2020
- CRF version: [redacted]_PET_CR5 (ver 1), dated 21 Sep 2020

1.1 Study design

This is a phase IV, prospective, randomized, double-blind, double-dummy, parallel group study, performed at a single center that is formed by [redacted]. The subjects enrolled into this study are subjects with chronic heart failure (HF) who fulfill all of the inclusion criteria and none of the exclusion criteria.

This study consists of two parts, a screening/run-in period (up to 6 weeks) and a treatment period (approximately 8 weeks). The subjects who sign the ICF entered the screening/run-in period of the study.

During the screening/run-in period the subject will be switched to valsartan treatment and this will replace his/her previously used ACEI or ARB treatment. The starting dose of valsartan will be 80 mg BID or if the dose of previous RAAS blockage medication has been higher, the valsartan dose will be 160 mg BID. Approximately one week after the screening visit 1, screening visit 2 will be scheduled in order to evaluate the safety and efficacy of the ongoing valsartan treatment. Only subjects who tolerate 80 mg BID or 160 mg BID of valsartan and can maintain a stable dose for at least 4 weeks will be eligible to enter into the treatment period.

After the screening evaluations and confirmation of eligibility, the subjects will be randomized into the following two treatment arms in a 1:1 ratio:

- the sacubitril/valsartan treatment arm
- the valsartan treatment arm

The randomization is generated by an independent statistician at [redacted] using SAS®.

Study drugs will be dispensed by an unblinded member of the study team during the treatment period while the study personnel directly involved in the clinical assessments will remain blinded throughout the study. The starting dose for each subject in the sacubitril/valsartan arm

will be 100 mg BID and in the valsartan arm 80 mg BID or 160 mg BID. The study subjects will return to the study center 2-3 times during the treatment period at approximately 2 weeks (visit 1), 3 weeks (visit 2) and 8 weeks (visit 3) after the start of the treatment period.

During visit 1, possible dose up-titration will be considered. Every subject should be attempted to be up-titrated to the next dose level (sacubitril/valsartan 200 mg or valsartan 160 mg, if the latter needed), if clinically possible. If up-titration is not possible, the starting dose should be maintained. After visit 2, if clinically indicated, the dose of the study treatment may be modified (up- or down-titrated) up to week 4.

During the treatment period, the subjects will self-administer two tablets from two study drug packages BID (one tablet from the study drug package containing the active treatment and one tablet from the study drug package containing the placebo). The last study visit will include the final efficacy assessments.

No more than 50% of the study subjects are allowed to have diabetes. To achieve similar groups randomization was stratified by:

- renal insufficiency (GFR 45-60 or >60 mL/min/1.73m^2) and/or
- diabetes mellitus (on insulin or oral glucose-lowering therapy)
- baseline HF therapy (valsartan 160 mg BID at the time of randomization)

The general study design is presented in Figure 1, and the titration patterns according to treatment arms are presented in Figure 2 and 3.

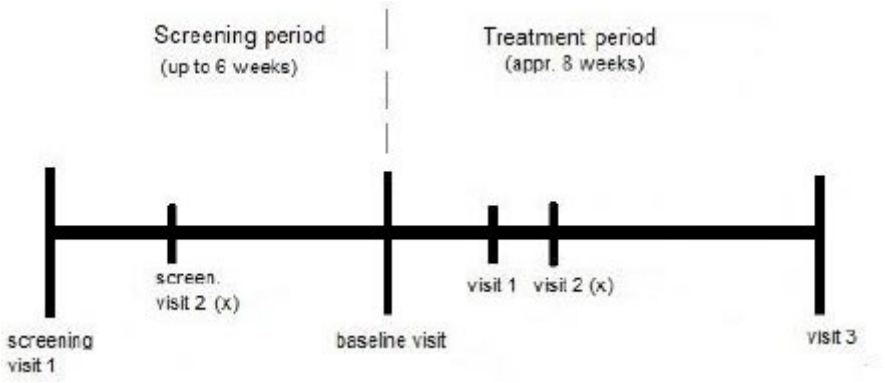

Figure 1 Study design

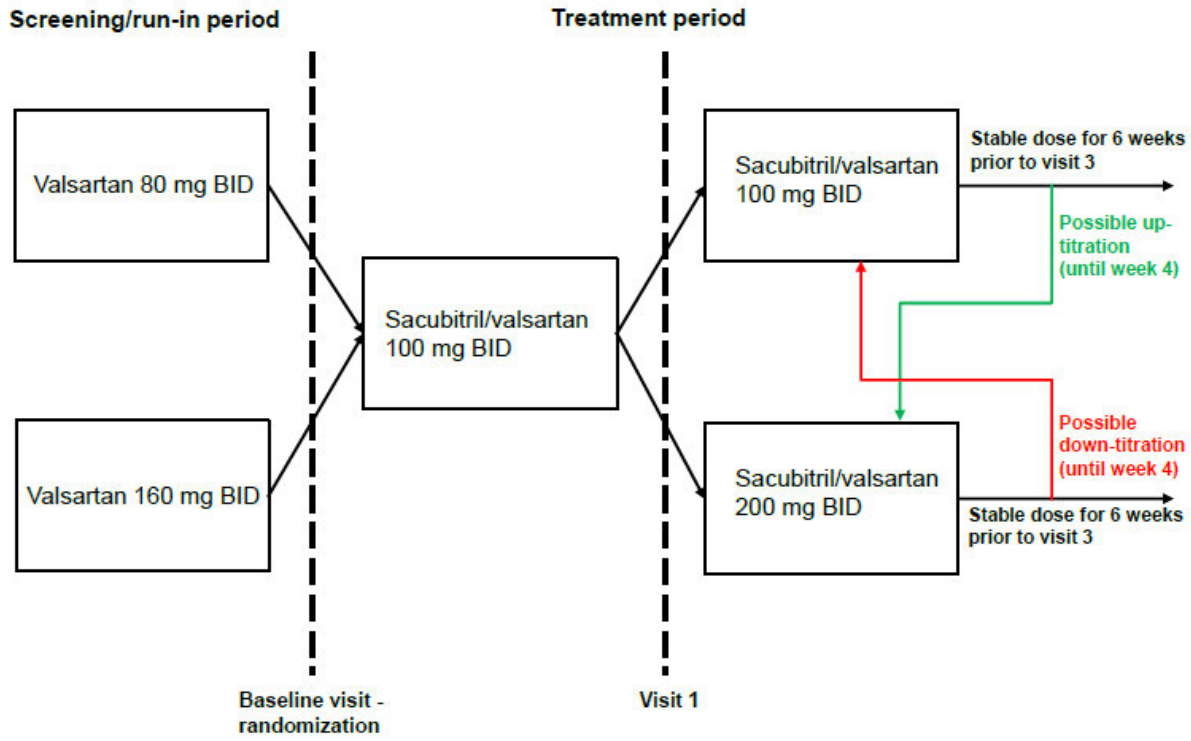

Figure 2. Study treatment during the double-blind treatment period with sacubitril/valsartan.

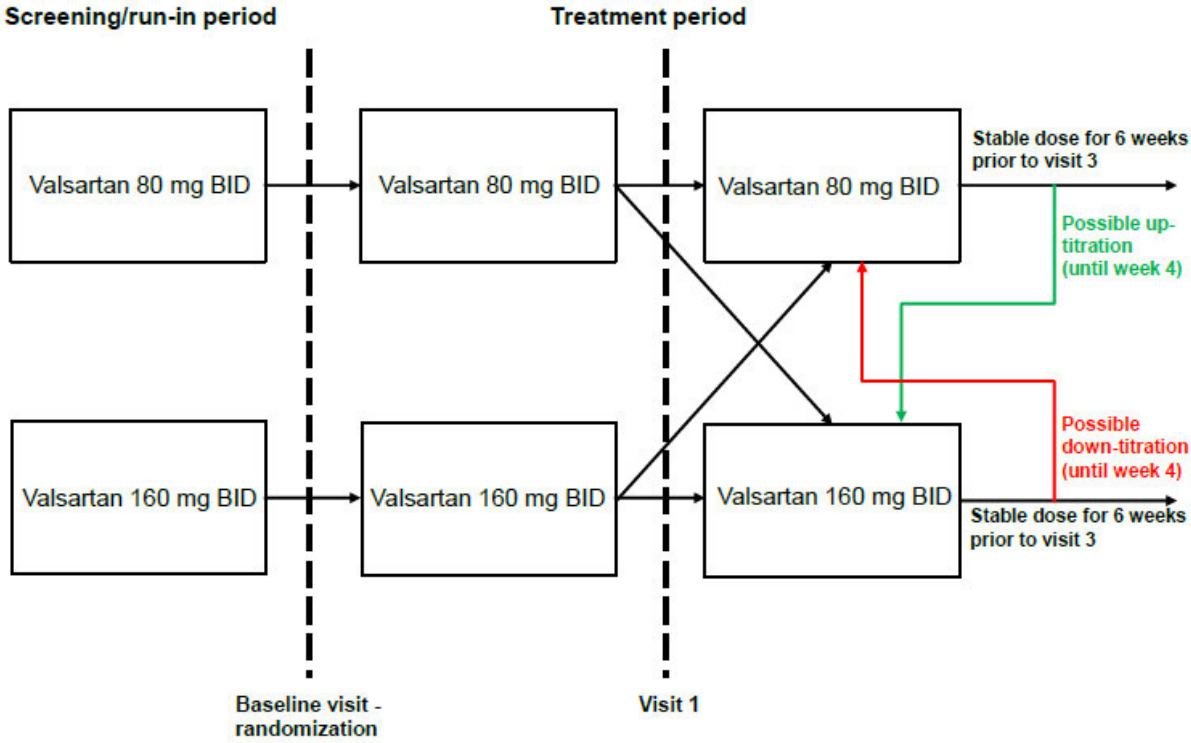

Figure 3. Study treatment during the double-blind treatment period with valsartan.

1.2 Study objectives, endpoints and estimands

This study was not designed with the estimand framework according to ICH E9(R1) taken into consideration. The primary analysis is based on FAS and the intention is to strive to correspond to a Treatment Policy approach to analysis of data based on this population. However, as intercurrent events may have lead to withdrawal of subjects from the study that would otherwise not have been withdrawn, had the treatment policy estimand framework been taken into consideration, the interpretation of the results may not fully correspond to a treatment policy approach.

Primary objective

The primary objective of the study is to evaluate the effects of 6 weeks of stable sacubitril/valsartan therapy, as compared with valsartan therapy, on the efficiency of cardiac work in subjects with NYHA II-III HF and reduced systolic function using ^{11}C-acetate and echocardiography.

Exploratory objectives and endpoints

The exploratory objective of the study is to evaluate the effects of 6 weeks of stable sacubitril/valsartan therapy, as compared with valsartan therapy, on myocardial oxygen consumption and cardiac and systemic hemodynamics.

1.2.1 Primary Endpoint

Difference in cardiac efficiency will be evaluated by comparing the results obtained after 6 weeks of stable treatment to the results from the baseline visit.

1.2.2 Secondary Endpoints

Difference in the following cardiac and systemic hemodynamic parameters will be evaluated as exploratory endpoints:

- Ejection fraction (EF)
- N-terminal prohormone brain natriuretic peptide (NT-proBNP),
- Systemic BP,
- Systemic vascular resistance (SVR),
- Coronary Cascular Resistance
- Cardiac Oxygen Consumption.

2 Statistical methods

2.1 Data analysis general information

The statistical analyses in this study will be conducted by the CRO [redacted] using SAS 9.4M3. At [redacted] the raw data generated by electronic data capture (EDC) system will be combined to applicable analysis data sets, as required, and statistical output will be generated based on these aggregated data sets.

All data will be tabulated using summary statistics and/or listed. For continuous data both absolute values and the corresponding changes form baseline will be presented, and the following summary statistics will be included; number of observations, mean, standard deviation, minimum, first quartile, median, third quartile and maximum. In addition gemetric mean and coefficient of variation may be provided in the summaries of efficacy endpoints, as applicable.

Categorical data will be presented as counts and percentages, i.e., n (xx.x%). Changes form baseline in categtorical data will be displayed in shift tables. Percentages will be based on the number of subjects in the analysis data set used.

Summary statistics will be presented by randomized treatment group and in total, and by visit and assessment time, as applicable. In addition, summary statistics may be presented by final titrated dose group during run-in period and other stratification factor levels as described in the each section of this document.

2.1.1 General definitions

Baseline	Generally, a baseline measurement refers to the last non-missing assessment made before the first administration of randomized treatment (baseline visit). This is valid for, for example, vital signs and laboratory data, where a difference from baseline is derived.
Relative day	The relative day of an event with a start date is derived as: Relative day = (Start date) - (Baseline date) + 1 For events occurring or starting before baseline the relative day is derived as: Relative day = (Start date) - (Baseline date) In this way, there will be no Day 0. Day 1 is the same day as baseline, and Day -1 is the day before.
Date format	All dates in analysis datasets and tables, listings and figures will be in the format YYYY-MM-DD

Treatment Emergent	All Adverse Events occurring on, or after the day of randomization will be considered Treatment Emergent (TE)
First drug date	The first administration of randomized treatment is assumed to be on the same day as randomization
Last drug date	The last day of randomized treatment (treatment end date) is stated on the study termination page in CRF.
By dose level	In all cases where summaries are stated to be by dose level, then data will be summarized by the final titrated dose level during the run-in period, ie the stratification by dose.

2.2 Analysis sets

The following analysis sets will be used for the statistical analysis and presentation of data:

- **The safety analysis set (SAF)** will consist of all randomised subjects who received at least one dose of the study medication in the treatment period, provided that there was at least one safety follow-up performed for the subject.

- **The full analysis set (FAS)** will consist of all randomised subjects who have received at least one dose of study medication in the treatment period and have at least one post-baseline assessment of any efficacy endpoints.

- **The per protocol set (PPS)** will consist of all subjects in the FAS who received at least 75% of the study drug doses, and do not have any other major protocol violations which will affect the assessment of efficacy. Major/important protocol violations may include, but are not limited to, the following:
    - Non-fulfillment of all inclusion criteria
    - Fulfillment of at least one exclusion criteria
    - Use of certain concomitant medications (this will be judged on a case to case basis, depending on extent of treatment)

The final criteria for PPS, regarding which protocol deviations that warrant exclusions, will be determined when all data on protocol violations/deviations are available and before breaking the blind. The decision of what protocol violations/deviations will lead to exclusion as well as the final classification of subjects according to analysis sets will be documented and signed off before breaking the blind. These decisions will be documented in a separate Pre-Analysis Review document.

The FAS is considered as the primary analysis dataset, and will be used for all primary and secondary efficacy analyses. The primary efficacy analysis will be repeated using the PPS.

Any significant discrepancy between the results from the FAS and the PPS will be analysed and discussed.

Baseline presentations will be based on the safety set.

Safety presentations will be based on the safety set.

2.2.1 Subgroup of interest

The study is stratified by :

- renal insufficiency (GFR 45-60 or >60 mL/min/1.73m^2) and/or
- diabetes mellitus (on insulin or oral glucose-lowering therapy)
- baseline HF therapy (valsartan 160 mg BID at the time of randomization)

The number of subjects per stratum and combination of strata will be summarized. An analysis for primary endpoint, including the interaction between stratum and treatment will be conducted in order to estimate the stratum related treatment effects.

2.3 Subject disposition, demographics and other baseline characteristics

2.3.1 Subject disposition

A subject disposition will be created including the total number of subjects screened, the number of subjects entering the run-in period, number of subjects completing and not completing the run-in period, the No. of subjects randomized and exposed in total and per treatment group, the No. of subjects completing not completing the treatment period in total and per treatment group. The subject disposition will also include the number of subjects included in each of the analysis sets, in total and by treatment group. In addition, a table will be created listing the number of subjects per reason for discontinuation.

The number and reasons for withdrawals and discontinuations will be listed and tabulated by treatment. Separate listings will be provided for subjects screened but not included in the study (screening failures).

A table will be made displaying the number of subjects by visit.

2.3.2 Demographics and other baseline characteristics

The collected demographics include Age, Sex, and Race. These demographics will be summarized using descriptive statistics and will be listed.

Medical history will be coded using MedDRA version 20.1 and will be summarized by system organ class (SOC) and preferred term (PT). All Medical history will also be listed.

2.3.3 Study treatment / compliance

Study drug compliance is assessed at site and recorded in the eCRF. This information will be used to evaluate the criterion of "at least 75% of the study drug doses received" for inclusion of subjects in the PPS as described in Section 2.2. The inclusion of subjects in PPS based on this criterion and other important criteria will be decided and documented as part of the pre-analysis-review, prior to unblinding of data.

The prescribed dose levels and titrated dose levels for both screening/run-in period and randomized treatment groups are captured in the eCRF. The number of subjects according to dose level will be summarized by visit.

All drug accountability data will be listed.

2.3.4 Prior, concomitant and post therapies

All concomitant treatments administered during the study must be recorded on the CRF page for concomitant treatments. No other investigational treatment is allowed to be used during the study. A study subject must not participate concurrently or have participated in any other clinical drug study within 3 months prior to the first study treatment administration of this study.

All concomitant medications/therapies will be classified according to ATC level 3 group text and World Health Organization (WHO) Drug Dictionary preferred name. The medications will be classified into categories Prior, Concomitant and Post IMP based on start date and end date in relation to IMP exposure (randomized double-blinded treatment).

- Prior medications are those were end dates of the medication/therapy are strictly before date of first administration of IMP.
- Concomitant medications are those for which the period between their start dates and end dates coincide with exposure to study drug and can be further classified into:
    - Concomitant medications starting prior to first exposure of IMP having start dates strictly before first exposure of IMP and end dates on same date or after date of first administration of IMP or are ongoing.
    - Concomitant medications starting on the date of first administration of IMP or after but before or on the date of last administration of IMP
- Post medications are those for which the start dates are strictly after date of last administration of IMP

The concomitant medications will be presented in a summary table broken down on timing in relation to IMP (i.e., Prior, Concomitant and Post). Each subject will only be counted once for each medication and timing category, on a preferred name level in each period.

2.4 Analysis supporting primary objective(s)

2.4.1 Primary endpoint(s)

The primary endpoint is this study is change from baseline in cardiac efficiency at visit 3, after 6 weeks of stable sacubitril/valsartan or valsartan treatment.

The definition of cardiac efficiency is (LV work/gram of tissue) / Oxygen consumtption. Where LV work/gram of tissue is obtained by Echocardiography as (SBP x SV x HR) / LV mass, and Oxygen consumtption is obtained by ^{11}Cacetate PET as tracer as a mono exponential clearance rate of ^{11}Cacetate (k_{mono})

So, cardiac efficiency is calculated based on the following formula:

$$\text{Myocardial efficiency} = ((\text{SBP} \times \text{SV} \times \text{HR})/\text{LV mass})/K_{mono}$$

Where

- SBP : Systolic blood pressure during PET
- SV : Stroke volume (Echocardiography)
- HR : Heart rate
- Kmono: Mono-exponential clearance rate (11C-acetate PET- scan)
- LV mass: Left ventricular mass

2.4.2 Statistical hypothesis, model, and method of analysis

The study hypothesis is that short-term therapy with sacubitril/valsartan added on standard HF therapy improves cardiac efficiency in subjects with systolic HF. In order to test this, the null hypothesis is formulated as follows:

$$H_0 : \mu_1 = \mu_2$$

which will be tested against the alternative hypothesis:

$$H_A : \mu_1 \neq \mu_2$$

where μ_1 and μ_2 are the mean values of change in cardiac efficiency in the two treatment arms, as measured by PET and echocardiography at visit 3. The null hypothesis will be tested based on a two-sided test and a significance level of 0.05.

The primary endpoint, change from baseline in cardiac efficiency after 6 weeks on stable sacubitril/valsartan or valsartan therapy, will be analyzed by an ANCOVA including treatment and stratification as independent factors and covariate adjustment for baseline

cardiac efficiency. From this model, the within treatment group changes from baseline will be estimated using least square means, and contrasts will be set up to estimate the corresponding treatment difference (sacubitril/valsartan-valsartan) with a 95% confidence interval and p-value.

Summary statistics will be prepared for the derived Myocardial energetic efficiency by visit and its change from baseline, using discriptive statistics. In addition, Box-plots will be constructed showing the distribution of changes from baseline by treatment group.

2.4.3 Handling of intercurrent events

The protocol for this study did not define a primary estimand of interest and thus the implication for interpretation of study results related to the occurrence and type of intercurrent events was not considered prior to design of this study.

Section 5.8 in the CSP describes criteria for withdrawal of subjects from the study. It is stated that subject may be withdrawn from the study if his/her adherence to the study protocol is not acceptable and the following situations should result in the withdrawal of the subject, unless the investigator considers it safe for the subject to continue in the study, possibly after dose modifications of the study drug or other concomitant medication:

- persistent symptomatic hypotension after randomization;

- serum potassium > 5.2 mmol/l after randomization;

- serum creatinine > 1.5 x ULN after randomization.

The CSP does not distinguish between withdrawal from study and withdrawal from treatment which would have been important for a strict treatment policy approach.

However, the number of subjects actually withdrawing from the study is expected to be very limited, which would allow a treatment policy estimand interpreation to still be applicable.

2.4.4 Handling of missing values not related to intercurrent event

In case of any missing response data for the primary analysis, then the missing data will be imputed using Multiple Imputation (MI). The missing data will be imputed based on the factors (treatment and stratification) and baseline as covariate as applied in the ANCOVA for the primary analysis.

2.4.5 Sensitivity analyses

In addition to the derivation of the primary endpoint as stated in Section 2.4.1, an alternative formula will be used, where the viable myocardium energetic efficiency will be derived as:

$$\text{Viable myocardial energetic efficiency} = ((\text{SBP} \times \text{SV} \times \text{HR})/\text{LV mass}) / vK_{mono}$$

Where

- vK_{mono} : Viable myocardium clearance rate

This alternative parameter is included as a sensitivity analysis to exclude possible bias related to scar tissue in subjects with ischemic myopathy. Analyses for this parameter will be done using the same approach as is applied for the primary endpoint.

2.4.6 Supplementary analyses

A Per-protocol analysis is planned for the primary endpoint.

Under the assumption that the primary analysis, based on FAS which is aimed to be conducted according to the intention-to-treat (ITT) principle, would correspond approximately to a treatment policy estimand analysis, then an analysis based on the PPS, which may not be conservative and potentially biased, would be an analysis which is not reflecting the same estimand as the primary analysis and is therefore considered a supplemental analysis.

This analysis will be conducted using the same methods as applied for the analysis of the primary endpoint, although any result based on this will be considered highly exploratory. No imputations using multiple imputation will be done for the PPS analysis.

The primary endpoint will in addition to overall be summarized by strata and an exploratory ANCOVA will be done where the treatment by strata interaction will be evaluated. Based on this model, the within stratum treatment difference will be estimated.

2.5 Analysis supporting secondary objectives

2.5.1 Secondary endpoint(s)

The changes in the following cardiac and systemic hemodynamics parameters will be evaluated as exploratory secondary efficacy endpoints:

- Ejection fraction (EF)
- N-terminal prohormone brain natriuretic peptide (NT-proBNP)
- Systemic BP, evaluated in relation to PET and Echocardiography
- Systemic vascular resistance (SVR)
- Coronary Vascular Resistance
- Cardiac Oxygen Consumption (k_{mono})

Systemic vascular resistance (SVR) will be derived as SBP/(SV x HR) and Coronary Vascular Resistance will be derived as SBP/myocardial perfusion (measured from acetate scan using K1).

2.5.2 Statistical hypothesis, model, and method of analysis

The change from baseline in these parameters after 6 weeks on stable sacubitril/valsartan or valsartan therapy will be analyzed by an ANCOVA including treatment and stratification as

independent factors and covariate adjustment for baseline cardiac efficiency. From this model, the within treatment group changes will be estimated by least square means and the corresponding treatment difference (sacubitril/valsartan-valsartan) will be calculated with a 95% confidence interval and p-value.

Descriptive statistics will be provided for these secondary endpoints by treatment arm including levels at each visit and change from baseline.

2.5.3 Handling of intercurrent events

The secondary endpoints are considered exploratory. In general, all available data in applicable analysis set will be used for the analyses of secondary endpoints, irrespective of if any intercurrent events have occurred.

2.5.4 Handling of missing values not related to intercurrent event

No imputations will be done for any missing data related to secondary endpoints as these are considered exploratory.

2.5.5 Sensitivity analyses

No sensitivity analysis will be conducted for secondary endpoints.

2.5.6 Supplementary analyses

In addition to the secondary endpoints stated above, a number of additional parameters related to the PET and Echocardiography will be collected (see DTS). All of these parameters will be summarized using descriptive statistics including levels by visit and the corresponding changes from baseline.

2.6 Safety analyses

Analyses of all safety endpoints will be based on the Safety set.

2.6.1 Adverse events (AEs)

Adverse Events (AEs) will be coded using MedDRA and will be reported by system organ class (SOC) and preferred terms (PT). AEs will be considered treatment emergent if occurring on or after the date of randomization. All AE tables will be reported for treatment emergent events. Non treatment emergent, during run-in, will be listed separately.

A summary table will be presented with number (No.) of subjects with Treatment Emergent Adverse Events (TEAEs), No. of subjects with serious TEAEs, No. of subjects with severe TEAEs, No. of subjects with related TEAEs, No. of subjects with at least one TEAE leading to discontinuation, and also the No. of TEAEs, severe TEAEs, serious TEAEs.

The total No. of subjects with at least one TEAE and the No. of TEAEs will be summarized in a table by SOC. PT. A similar table will be created for serious adverse events (SAEs). All

TEAEs will also be tabulated by severity (mild, moderate and severe) and causality to the treatment (related, not related).

In listings of AEs the relative day counted from first administration of IMP (Day 1) will be presented together with the relative day from the latest administration of IMP (the actual dates will also be included).

2.6.1.1 Adverse events of special interest / grouping of AEs

There are no AEs of special interest defined in this study.

2.6.2 Deaths

Deaths are expected to be rare in this study. In case any deaths are occurring, then these will be listed separately including detailed information of AE leading to death.

2.6.3 Laboratory data

The following laboratory tests are performed at all site visits during the study:

Chemistry:

- Potassium
- Creatinine

Haematology:

- Haemoglobin

These laboratory variables and their changes from baseline will be evaluated and summarized using descriptive statistics by visit and treatment arm. There will be two separate baseline values defined for the safety laboratory assessments: the first safety laboratory baseline values will be the ones taken on screening visit 1. The subsequent laboratory results obtained during the screening/run-in period will be compared to these. The second safety laboratory baseline values will be the ones taken at the baseline visit. The subsequent laboratory results obtained during the double-blind treatment period will be compared to these. Laboratory values will also be categorized into low, normal and high according to their reference ranges, and shift tables will be constructed. The reference ranges of all laboratory determinations will be included in the ISF before study start and updated whenever necessary.

Clinically significant laboratory abnormalities and any additional laboratory tests taken for subject safety will be listed and reported in the study report.

Urine pregnancy test will be performed for all female subjects with childbearing potential prior to the PET-scans.

2.6.4 Other safety data

2.6.4.1 Vital signs

The actual values of systolic and diastolic blood presure (BP) and heart rate (HR) and their changes from baseline will be evaluated with descriptive statistics by treatment arm. There will be two separate baseline values defined for the BP and HR measurements: the first BP and HR baseline value will be the one taken on the first screening visit. The subsequent BP and HR measurements during the screening/run-in period will be compared to this. The second baseline value will be the one taken before randomization at the baseline visit. The subsequent BP and HR measurements during the double-blind treatment period will be compared to this.

2.7 Pharmacokinetic endpoints

NA

2.8 PD and PK/PD analyses

NA

2.9 Subject-reported outcomes

NA

2.10 Biomarkers

Biomarkers will be measured to understand the potential mechanisms of how sacubitril/valsartan changes myocardial efficiency. Blood samples will be obtained for measurement of NT-proBNP hs-troponin and creatinine to assess effects of interventions on hemodynamics before randomization and repeatedly on visit 3, after 6 weeks of stable sacubitril/valsartan or valsartan treatment.

These biomarkers will be summarized using descriptive statistics including levels at baseline and Visit 3, and change from baseline at Visit 3. Creatinine is collected as a safety laboratory parameter at all visits as described in Section 2.6.3, and will thus be summarized as part of safety laboratory. In addition NT-proBNP will be analysed by an ANCOVA according to description under secondary endpoints (Section 2.5.1).A shift table corresponding to those for safety lab will be provided.

2.11 Other Exploratory analyses

NA

2.12 Interim analysis

There are no interim analyses during the study.

3 Sample size calculation

In previous studies using the same techniques (i.e. ^{11}C-acetate PET scan and echocardiography), beta-blockers in drug-naïve subjects increased cardiac efficiency by 45% (Beanlands 2000). In later studies using e.g. new biventricular pacing techniques in previously medicated subjects, the cardiac efficiency was improved by 20% (Sundell 2004). Therefore, we assume that the clinically significant change in cardiac efficiency in medicated subjects would be about 20%. In our previous studies in subjects with heart failure (Nesterov 2015, Tuunanen 2008), the same subjects were studied twice in the interval of 3 months, the coefficient of variation (CV%) of Kmono in placebo group was 18.4% and in efficiency 19.7%. Based on sample size calculations, in order to detect a 15% change in cardiac efficiency, 27 subjects would need to be included in each treatment arm (assuming $\alpha = 0.05$ and $\beta = 0.2$). Due to potential drop outs during the study, the target is to enroll 30 + 30 subjects in the treatment arms.

4 Change to protocol specified analyses

An additional parameter, viable myocardium energetic efficiency, is added as a sensitivity analysis for the primary endpoint as described in section 2.4.5.

In the protocol it was stated that all summary statistics will be done by dose level. Split of summary statistics by dose level, ie stratification factor, will be limited to the subject disposition, primary endpoint and overview of TEAEs.

5 Appendix

5.1 Imputation rules

If the visit 3 assessment for the primary endpoint is missing for a subject then this will be imputed using a monotone regression approach including treatment and stratification as class variables. One hundred imputations will be done. Each replication of the data, including the imputed missing values, will then be analyzed using the ANCOVA used in the primary analysis, and estimates will be pooled using proc MIANALYZE SAS®.

5.1.1 Study drug

Actual dates and time points of study drug adminstrations are not captured in the eCRF. The last drug date is recorded on the study termination page, the first drug date is assumedto be on the day of randomization.

5.1.2 AE date imputation

AEs with incomplete dates will be regarded as TEAEs if year and month are available and are the same as the date of first dose of randomized treatment or if only year is available and is the same year as the date of first dose of randomized treatment.

5.1.3 Concomitant medication date imputation

For medication and therapies with partial dates:

- If start date is completely missing, it will be assumed that the medication started before date of first administration of randomized treatment.
- If end date is completely missing and ongoing is not ticked, it will be assumed that the medication ended before date of first administration of randomized treatmenttreatment.
- For medications/therapies where only partial dates are available, either only year or year and month, then this information will be used in analogy with how complete dates are used for classification.

Relative day will not be calculated for medications with incomplete dates.

5.1.3.1 Other imputations

NA

5.2 AEs coding/grading

All AEs and medical history verbatim terms were encoded as SOC and PT using MedDRA, latest version available when approving the data management plan (DMP). Severity is graded as mild, moderate and severe. Relation to treatment is captured as related and not related.

5.3 Laboratory parameters derivations

NA

5.4 Statistical models

NA

5.4.1 Analysis supporting primary objective(s)

See Section 2.4

5.4.2 Analysis supporting secondary objective(s)

See Section 2.5

5.5 Rule of exclusion criteria of analysis sets

The final criteria for PPS, regarding which protocol deviations and other criteria that warrant exclusions will be determined when all data on protocol deviations are available and before breaking the blind. Final classification of subjects according to study populations will be documented and included in a “pre-analysis review” document, which will be signed before unblinding.

5.6 Tables, Listings and Figures Overview

Tables to be Produced for the Clinical Study Report (Section 14 according to ICH E3)

(Table numbers refer to section numbers in ICH E3.)

14.1 Demography and Background Characteristics

Table	SAF	FAS	PPS
Subject disposition	X		
Subject disposition by strata	X		
Subject discontinuation	X		
Subject discontinuation by strata	X		
Demography	X		
Demography by strata	X		
Number of subjects by visit	X		
Medical history	X		

14.2 EFFICACY DATA

14.2.1 Primary Endpoint

Table	SAF	FAS	PPS
Summary of Myocardial energetic efficiency by visit and change from baseline		X	X
Analysis of change from baseline in Myocardial energetic efficiency (ANCOVA)		X	X
Boxplots of change from baseline in Myocardial energetic efficiency		X	X
Summary of Myocardial energetic efficiency by visit and change from baseline by strata		X	X
Analysis of change from baseline in Myocardial energetic efficiency (ANCOVA) including treatment by strata interaction		X	X
Summary of Viable myocardium energetic efficiency by visit and change from baseline		X	X
Analysis of change from baseline in Viable myocardium energetic efficiency (ANCOVA)		X	X
Boxplots of change from baseline in Viable Myocardial energetic efficiency		X	X

14.2.2 Secondary Endpoints

Table	SAF	FAS	PPS
Summary of Ejection fraction (Echocardiography) by visit and change from baseline		X	
Analysis of change from baseline in Ejection fraction (Echocardiography) (ANCOVA)		X	
Summary of N-terminal prohormone brain natriuretic peptide (NT-proBNP) by visit and change from baseline		X	
Analysis of change from baseline in N-terminal prohormone brain natriuretic peptide (NT-proBNP) (ANCOVA)		X	
Summary Systemic BP during PET by visit and change from baseline		X	

Analysis of change from baseline in Systemic BP (ANCOVA) collected in relation to Echocardiograph and PET		X	
Summary of Systemic vascular resistance (SVR) by visit and change from baseline		X	
Analysis of change from baseline in Systemic vascular resistance (SVR) (ANCOVA)		X	
Summary of Coronary Vascular Resistance by visit and change from baseline		X	
Analysis of change from baseline in Coronary Vascular Resistance (ANCOVA)		X	
Summary of Cardiac Oxygen Consumption (k_{mono}) by visit and change from baseline		X	
Analysis of change from baseline in Cardiac Oxygen Consumption (k_{mono}) (ANCOVA)		X	
Summary of Resting perfusion (PET) by visit and change from baseline		X	
Summary of Viable myocardiumResting perfusion (PET) by visit and change from baseline		X	
Summary of Viable myocardium clearance rate (PET) by visit and change from baseline		X	
Summary of Left ventricle mass (Echocardiography) by visit and change from baseline		X	
Summary of Stroke volume (Echocardiography) by visit and change from baseline		X	
Summary of Cardiac output (Echocardiography) by visit and change from baseline		X	
Summary of Left ventricular mechanical work (SBP x SV x HR)/ LV mass (Echocardiography) by visit and change from baseline		X	
Summary of Global Longitudinal Strain (Echocardiography) by visit and change from baseline		X	
Summary of left ventricular systolic volume (Echocardiography) by visit and change from baseline		X	
Summary of left ventricular diastolic volume (Echocardiography) by visit and change from baseline		X	

14.3 SAFETY DATA

14.3.1 Display of Adverse Events

Item	SAF	FAS	PPS
Summary of Treatment-Emergent Adverse Events	X		
Summary of Treatment-Emergent Adverse Events by strata	X		
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	X		
Treatment-Emergent Adverse Events by Severity and System Organ Class and Preferred Term	X		
Treatment-Emergent Adverse Events by Relation and System Organ Class and Preferred Term	X		

14.3.2 Listings of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Item	SAF	FAS	PPS
Listing of Serious Adverse Events	X		
Adverse Events Leading to Death	X		
Adverse Events Leading to Withdrawal	X		

14.3.3 Reserved for narratives

14.3.4 Laboratory Assessments

Item	SAF	FAS	PPS
Abnormal Laboratory Value Listing	X		
Summary of Safety Laboratory Assessments	X		
Safety Laboratory Assessments Shift Table	X		
Summary of Laboratory Biomarker Assessments		X	
Biomarker Laboratory Assessments Shift Table		X	

14.3.5 Extent of Exposure

Item	SAF	FAS	PPS

Exposure to Study Drug	X		
Summary of subjects by dose group and visit	X		
Compliance	X		

14.3.6 Vital Signs

Item	SAF	FAS	PPS
Summary of Vital Signs	X		
Vital Signs Shift Table	X		

14.3.9 Concomitant Medication and Therapy

Item	SAF	FAS	PPS
Concomitant Medication and Therapy	X		

Listings of Individual Subject Data and Other Information to be Produced for the Clinical Study Report

(Listing numbers refer to the relevant appendix number in ICH E3. CRF check questions/ reminders will not be listed.)

16.1.7 Randomisation Scheme

Listing	SAF	FAS	PPS
Randomisation scheme	X		

16.2.1 Discontinued Subjects, Reason for Discontinuation

Listing	SAF	FAS	PPS
Study discontinuation and reasons for withdrawal	X		
Visit Dates and Other Important Dates	X		

16.2.3 Subjects Excluded from the Efficacy Analysis (Evaluability, Reason for Evaluability Classification)

Listing	SAF	FAS	PPS
Subject disposition and analysis data sets and reasons for exclusion	X		

16.2.4 Demographics and Other Background Characteristics

Listing	SAF	FAS	PPS
Demographics data	X		
Medical history	X		

16.2.5 Compliance and/or Drug Concentration Data

Listing	SAF	FAS	PPS
Compliance	X		
Drug accountability	X		
Titration data	X		

16.2.6 Individual Efficacy Response Data

Listing	SAF	FAS	PPS
Primary efficacy parameter		X	
Secondary efficacy parameters for PET-scan, Echocardiography		X	

16.2.7 Adverse Events by Treatment, Subject, Relative Day or Week.

Listing	SAF	FAS	PPS
Adverse events by subject, relative day	X		
Adverse events by SOC, PT and subject	X		
Serious adverse events by subject, relative day	X		

16.2.8 Laboratory parameters

Listing	SAF	FAS	PPS
Safety Laboratory Assessments	X		
Laboratory Biomarker Assessments	X		
Pregnancy test	X		
Listing of reference ranges.			

16.2.9 Vital Signs

Listing	SAF	FAS	PPS
Vital Signs	X		

16.2.10 Physical Examination

Listing	SAF	FAS	PPS
Physical Examination	X		

16.2.11 Concomitant Medication and Therapy

Listing	SAF	FAS	PPS
Concomitant medication and therapy	X		

6 Reference

ICH E9(R1) Harmonized Guideline: addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Final version on 20 November 2019.

[redacted]

ADDENDUM OF STATISTICAL ANALYSIS PLAN

Study Title:	Controlled trial on the short-term effects of sacubitril/valsartan therapy on cardiac oxygen consumption and efficiency of cardiac work in patients with NYHA II-III heart failure and reduced systolic function using ^{11}C-acetate positron emission tomography and echocardiography
Investigational product:	Sacubitril/Valsartan
Sponsor:	Novartis Finland Oy
Sponsor Study Code:	CLCZ696BFI03
[redacted] Project Code:	NOV1154

Date of approved SAP: 25/04/2022

Addendum no: 01 **Date written:** 04/07/2022 **Author:** [redacted]

Review and Approval of SAP addendum:

Sponsor:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 05-Jul-2022 | 08:17 GMT
FFBB2CD38CC84AF8AF1CFB8BB0110D32

05-Jul-2022 | 08:17 GMT

Date Signature

Principal Investigator:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: Hyväksyn tämän asiakirjan
Signing Time: 05-Jul-2022 | 01:18 PDT
9C7FEDBF05834A3EA7881C9A201DE9BF

05-heinä-2022 | 01:19 PDT

Date Signature

Reviewing Statistician:

DocuSigned by:
[redacted]
Nombre del firmante [redacted]
Motivo de la firma: He revisado este documento
Hora de firma: 05-Jul-2022 | 10:09 CEST
7037A92682314474A3250E859891479A

05-jul.-2022 | 10:09 CEST

Date | Signature

Author/Project Statistician:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I am the author of this document
Signing Time: 05-Jul-2022 | 08:52 CEST
22FD0ACA2F8D4BB7A7540218E04A6F26

05-Jul-2022 | 08:52 CEST

Date | Signature

1.1 Amendment(s) of the SAP

As SAP states: analyses for Viable myocardium energetic efficiency will be done using the same approach as is applied for the primary endpoint. For this reason, a summary statistic by strata and an ANCOVA model is added, where the treatment by strata interaction will be evaluated. Based on this model, the within stratum treatment difference will be estimated.

Regarding secondary endpoints. The SAP did not include ANCOVA models for the following parameters:

- Resting perfusion (PET)
- Viable myocardium resting perfusion (PET)
- Viable myocardium clearance rate (PET)
- Left ventricle mass (Echocardiography)
- Stroke volume (Echocardiography)
- Cardiac output (Echocardiography)
- Left ventricular mechanical work (SBP echocardiography x SV x HR)/ LV mass (Echocardiography)
- Global Longitudinal Strain (Echocardiography)
- Left ventricular systolic volume (Echocardiography)
- Left ventricular diastolic volume (Echocardiography)

Additional ANCOVA models will be added according to description under secondary endpoints: The change from baseline in these parameters after 6 weeks on stable sacubitril/valsartan or valsartan therapy will be analyzed by an ANCOVA including treatment and stratification as independent factors and covariate adjustment for baseline. From this model, the within treatment group changes will be estimated by least square means and the corresponding treatment difference (sacubitril/valsartan-valsartan) will be calculated with a 95% confidence interval and p-value.

1.2 Result

The following tables highlighted in bold will be added

14.2 EFFICACY DATA

14.2.1 Primary Endpoint

Table	SAF	FAS	PPS
Summary of Myocardial energetic efficiency by visit and change from baseline		X	X
Analysis of change from baseline in Myocardial energetic efficiency (ANCOVA)		X	X
Boxplots of change from baseline in Myocardial energetic efficiency		X	X
Summary of Myocardial energetic efficiency by visit and change from baseline by strata		X	X
Analysis of change from baseline in Myocardial energetic efficiency (ANCOVA) including treatment by strata interaction		X	X
Summary of Viable myocardium energetic efficiency by visit and change from baseline		X	X
Analysis of change from baseline in Viable myocardium energetic efficiency (ANCOVA)		X	X
Boxplots of change from baseline in Viable Myocardial energetic efficiency		X	X
Summary of Viable Myocardial energetic efficiency by visit and change from baseline by strata		X	X
Analysis of treatment by stratification interaction on change from baseline in Viable Myocardial energetic efficiency (ANCOVA)		X	X

14.2.2 Secondary Endpoints

Table	SAF	FAS	PPS
Summary of Ejection fraction (Echocardiography) by visit and change from baseline		X	
Analysis of change from baseline in Ejection fraction (Echocardiography) (ANCOVA)		X	
Summary of N-terminal prohormone brain natriuretic peptide (NT-proBNP) by visit and change from baseline		X	

Analysis of change from baseline in N-terminal prohormone brain natriuretic peptide (NT-proBNP) (ANCOVA)		X	
Summary Systemic BP during PET by visit and change from baseline		X	
Analysis of change from baseline in Systemic BP (ANCOVA) collected in relation to Echocardiograph and PET		X	
Summary of Systemic vascular resistance (SVR) by visit and change from baseline		X	
Analysis of change from baseline in Systemic vascular resistance (SVR) (ANCOVA)		X	
Summary of Coronary Vascular Resistance by visit and change from baseline		X	
Analysis of change from baseline in Coronary Vascular Resistance (ANCOVA)		X	
Summary of Cardiac Oxygen Consumption (k_{mono}) by visit and change from baseline		X	
Analysis of change from baseline in Cardiac Oxygen Consumption (k_{mono}) (ANCOVA)		X	
Summary of Resting perfusion (PET) by visit and change from baseline		X	
Analysis of change from baseline in Resting perfusion (PET) (ANCOVA)		X	
Summary of Viable myocardium Resting perfusion (PET) by visit and change from baseline		X	
Analysis of change from baseline in Viable myocardium Resting perfusion (PET) (ANCOVA)		X	
Summary of Viable myocardium clearance rate (PET) by visit and change from baseline		X	
Analysis of change from baseline in Viable myocardium clearance rate (PET) (ANCOVA)		X	
Summary of Left ventricle mass (Echocardiography) by visit and change from baseline		X	
Analysis of change from baseline in Left ventricle mass (Echocardiography) (ANCOVA)		X	
Summary of Stroke volume (Echocardiography) by visit and change from baseline		X	
Analysis of change from baseline in Stroke volume (Echocardiography) (ANCOVA)		X	

Summary of Cardiac output (Echocardiography) by visit and change from baseline		X	
Analysis of change from baseline in Cardiac output (Echocardiography) (ANCOVA)		X	
Summary of Left ventricular mechanical work (SBP x SV x HR)/ LV mass (Echocardiography) by visit and change from baseline		X	
Analysis of change from baseline in Left ventricular mechanical work (SBP x SV x HR)/ LV mass (Echocardiography) (ANCOVA)		X	
Summary of Global Longitudinal Strain (Echocardiography) by visit and change from baseline		X	
Analysis of change from baseline in Global Longitudinal Strain (Echocardiography) (ANCOVA)		X	
Summary of left ventricular systolic volume (Echocardiography) by visit and change from baseline		X	
Analysis of change from baseline in left ventricular systolic volume (Echocardiography) (ANCOVA)		X	
Summary of left ventricular diastolic volume (Echocardiography) by visit and change from baseline		X	
Analysis of change from baseline in left ventricular diastolic volume (Echocardiography) (ANCOVA)		X	