NOVARTIS

Clinical Development

PARACHUTE: Prevention And Reduction of Adverse outcomes in Chagasic Heart failUre Trial Evaluation.

Clinical Study Protocol CLCZ696B3302

A multicenter, prospective, randomized, open-label, blinded-endpoint, Phase 4 study to evaluate the efficacy and safety of sacubitril/valsartan compared with enalapril on morbidity, mortality, and NT-proBNP change in patients with chronic Chagas' cardiomyopathy

Statistical Analysis Plan (SAP)

Document type:	SAP Documentation
Document status:	Version 2.1
Release date:	29-Apr-2025
Number of pages:	42

Document History – Changes compared to previous final version of SAP

Version	Date	Changes
1.0	05/11/2020	First Version
2.0	09/04/2025	• Section 2.6.1 and 2.6.2.4 - Recurrent events included as secondary endpoint. • Section 2.6.1 and 2.6.2.3 - Definition of days alive and out of hospital modified to within one year from randomization. • Section 2.8 - NT-ProBNP evaluation at month 8 included as an exploratory endpoint. • Section 2.5.2.1 - Definition of cardiovascular death included. • Section 2.5.3 - Supplementary analysis for the primary outcome added to account for missing NT-ProBNP values and recurrent events. • Section 2.5.3 - Supplementary analysis for the primary outcome added to account for total death. • Section 2.8 - Exploratory analysis of the time-dependent interaction of SGLT2 inhibitors with treatment included. • Section 2.9 - Subgroup analysis comparing randomizations of COVID-19 during the pandemic period (and after) • Sections 2.5.1.1 and 2.5.1.2 - Estimands definitions
2.1	29/04/2025	• Section 2.2 - Per protocol set definition updated. • Section 2.1.3 - Added imputation logic for partial missing dates • Section 2.4.1 - Calculation of drug adherence • Section 2.5.2 – Clarification of time to event censoring. • Section 2.9 - Subgroup analyses variables updated

Table of contents

List of abbreviations

ACEIs	angiotensin-converting enzyme inhibitors
AE	adverse event
ARO	Academic Research Organization
BID	twice a day
CCC	chronic Chagas' cardiomyopathy
CEC	Clinical Endpoint (Adjudication) Committee
CRT-D	cardiac resynchronization therapy
CV	cardiovascular
DC	Data monitoring committee
DSMB	Data and Safety Monitoring Board
eCRF	electronic Case report form
EDC	electronic data capture
EOS	End-of-Study
ER	Emergency room
FAS	Full Analysis Set
HF	heart failure
HFH	heart failure hospitalization
HFrEF	heart failure with reduced ejection fraction
ICD	intracardiac device
IRT	Interative Response Technology
IWRS	Interactive Web Response System
LatAm	Latin America
LWYY	Lin, Wei, Yang, and Ying
NT-proBNP	n-terminal prohormone of brain natriuretic peptide
PPS	Per-Protocol Set
RAN	Randomized Analysis Set
SAE	serious adverse event
SAF	Safety Set
SAP	Statistical Analysis Plan
SC	Screening Visit
SD	Standard deviation

1 Introduction

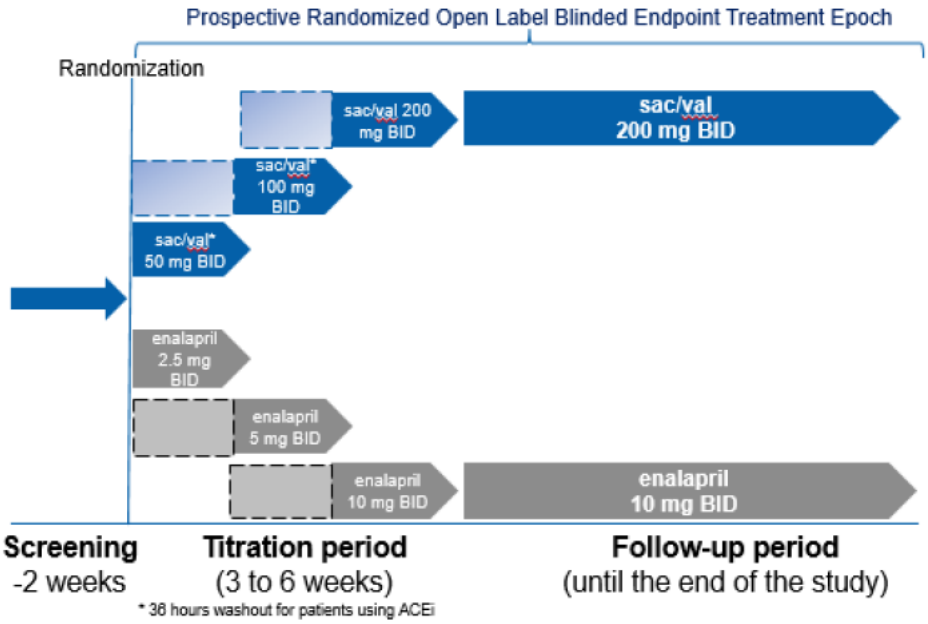
This Statistical Analysis Plan (SAP) is based on the protocol for the trial CLCZ696B3302 “A multicenter, prospective, randomized, open-label, blinded-endpoint, Phase 4 study to evaluate the efficacy and safety of sacubitril/valsartan compared with enalapril on morbidity, mortality, and NT-proBNP change in patients with chronic Chagas’ cardiomyopathy”, version 03 (Protocol - 10 November 2021) and describes the statistical methods to be performed in the clinical study report and for the main trial publication.

1.1 Study design

This is a Phase 4, multinational, multicenter, parallel-group, prospective, randomized, open-label, blinded-endpoint adjudication (PROBE), active-controlled study has been designed to evaluate the effect of sacubitril/valsartan over enalapril in CCC population. The study is aiming to validate the hypothesis that Sacubitril/Valsartan is superior as compared to Enalapril in improving a composite of Time to CV events (CV death or first HF hospitalization) or in causing a greater reduction or lesser increase in NT-proBNP levels at Week 12 in participants with HFrEF caused by CCC. The study will consist of a Screening Epoch, and a Randomized Treatment Epoch consisting of a Titration Period, and a Follow-up Periods shown in Figure 1.

The target projected sample size is 900 participants (450 in each arm). It is estimated that approximately 1800 participants will be screened at up to approximately 100 study sites due to an anticipated 50% screen failure rate, based on previous HF study experiences.

Figure 1. Study design



Upon signing the informed consent form, each subject is uniquely identified by the academic research organization (ARO) to the study site by interactive web response system (IWRS). Once assigned to a subject, the identification will not be reused. If the subject fails to be randomized for any reason, the IWRS must be notified within 2 days that the subject was not randomized. The reason for not being randomized will be entered on Screening phase disposition electronic Case Report Form (eCRF).

After confirming that the subject fulfills all the inclusion/exclusion criteria, the Investigator or his/her delegate will log in to IWRS to randomize the subject to one of the treatment arms. The subject identification will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the subject.

The primary endpoint is the hierarchically ordered composite endpoint consisting of time to CV death, time to first heart failure hospitalization (HFH) within 36 months follow-up and the relative change from baseline to Week 12 in NT-ProBNP.

1.2 Study objectives and endpoints

The study has been designed to test the hypothesis that sacubitril/valsartan is superior to enalapril in reducing a composite of CV events (CV death or first HF hospitalization) or in causing a greater reduction or lesser increase in NT-proBNP levels at week 12 in heart failure with reduced ejection fraction (HFrEF) participants with CCC.

The primary, secondary and exploratory objectives and the respective endpoints are described on Table 1.

Table 1. Study Objectives and Endpoints from the Protocol.

Objectives	Endpoints
Primary	
To assess whether sacubitril/valsartan is superior to enalapril in improving a composite hierarchical outcome of: a) time to CV death, b) time to first HF hospitalization, c) relative change in NT-proBNP levels between Baseline and Week 12 in participants with HFrEF caused by CCC.	The primary endpoint is the hierarchically ordered composite consisting of time to CV death, time to first HF hospitalization, and the relative change from Baseline to Week 12 in NT-proBNP levels.
Secondary	
1. To test whether sacubitril/valsartan is superior to enalapril in delaying the time from randomization to first occurrence of hospitalization due to HF or CV death.	1. A composite outcome consisting of time from randomization to the occurrence of the first HF hospitalization or CV death.
2. To test whether sacubitril/valsartan is superior to enalapril in delaying the time to death from any cause (all-cause mortality).	2. Time from randomization to all-cause mortality.
3. To test whether sacubitril/valsartan is superior to enalapril in delaying the time to the first occurrence of resuscitated sudden cardiac arrest or sudden cardiac death.	3. Time from randomization to sudden death or resuscitated sudden cardiac arrest.
4. To test whether sacubitril/valsartan is superior to enalapril in reducing the number of visits to ER for HF (where intravenous therapy is required).	4. Number of visits to an ER due to HF (where intravenous therapy is required).
5. To test whether sacubitril/valsartan is superior to enalapril in increasing the number of days alive out of the hospital.	5. Number of days alive out of the hospital.

6. To compare sacubitril/valsartan with enalapril as to their safety and tolerability in participants with CCC.	6. Safety and tolerability parameters: a. physical examination b. vital signs c. laboratory evaluations d. electrocardiogram e. pregnancy assessment f. adverse events g. serious adverse events h. adverse events of special interest (angioedema, arrhythmia, symptomatic hypotension, hyperkalemia, and renal dysfunction)
Exploratory	
1. To test whether sacubitril/valsartan is superior to enalapril in reducing ventricular fibrillation or sustained ventricular tachycardia needing specific pharmacological, electrical or other treatment.	1. Number of ventricular fibrillation or sustained ventricular tachycardia needing specific pharmacological, electrical, or other treatment.
2. In the subset of participants with an implantable cardioverter defibrillator (ICD) or CRT-D at randomization: to test whether sacubitril/valsartan is superior to enalapril in reducing anti-tachycardia pacing or shock therapies.	2. Number of anti-tachycardia pacing or shock therapies.

2 Statistical methods

2.1 Data analysis general information

Statistical analyses will be performed by BCRI statistician using R software (version 4.4.1). The blinding of the randomized treatments will be maintained for the clinical trial team until the database has been locked and released for statistical analysis. An independent statistician will be performing the interim analysis of unblinded data for the DSMB meetings.

Summary statistics will be provided by treatment arm for the variables considered in the study. Continuous variables will be summarized using n, mean or median, minimum, maximum, standard deviation or interquartile range. Categorical variables will be summarized using absolute and relative frequency.

Analysis will be performed after data lock when at least 302 participants with events have occurred (CV death or first hospitalization for HF) and when all patients have a minimum follow up of 12 weeks or if a recommendation is made by the Data Monitoring Committee (DMC) to prematurely stop the study.

Data from all sites will be analyzed together with treatment as fixed-effect factor and stratified by country.

2.1.1 General definitions

Study treatment

Study treatment is defined as sacubitril/valsartan or the active control enalapril.

Date of first administration of study treatment

The date of first administration of study drug is defined as the first date when a nonzero dose of the study drug is administered and recorded on the dose administration eCRF.

Date of last administration of study treatment

The date of last administration of study drug is defined as the last date when a nonzero dose of study drug is administered and recorded on the eCRF.

Study day

The study day for efficacy analysis is calculated as the (date of the event) – (reference start date) + 1 if the event is on or after the reference start date or as the (date of the event − reference start) date if event precedes the reference start date. For efficacy and safety analysis the reference start date is the randomization date.

Screening Visit (V1)

The Screening Visit (SC) will be performed up to 2 weeks before the Randomization Visit (Visit 101) to allow adequate time for the completion of all qualifying screening procedures. Using Study Day definition, screening visit ranges from Day -14 to Day -1. A complete physical examination is required at Visit 1.

Randomization Visit (Visit 101)

At the Randomization Visit all participants who fulfill the inclusion criteria and do not meet any exclusion criteria will be randomized to sacubitril/valsartan or enalapril. At the Randomization Visit, we expect most of the patients will receive the first dose of the study treatment. Participants taking ACEIs who are randomized to sacubitril/valsartan will do a 36-hour ACEI washout before they start taking the study drug. In this case, the reference start date for efficacy and safety analyses will be the randomization date.

Titration Period

Upon randomization, participants will enter the Titration Period and take the study drugs for 3 weeks. The initial dosage (Dose Level 1 [enalapril 2.5 mg BID or sacubitril/valsartan 50 mg BID] or Dose Level 2 [enalapril 5 mg BID or sacubitril/valsartan 100 mg BID]) will depend on the treatment the participants have been receiving before Randomization (ACEI/ARBs and participants treated with low dosages, less than 50% of the target dosage, and at least 50% standard doses of ACEIs/ARBs).

Visit 102

After 3 weeks, at Visit 102, initial dosages will be up-titrated for an additional 3 weeks to Dose Level 2 or to the target Dose Level 3 (enalapril 10 mg BID or sacubitril/valsartan 200 mg BID) if they tolerate it.

Visit 103

Patients receiving Dose Level 2 will receive Dose Level 3 for 3 weeks at Visit 103 if they tolerate it.

End of Study (EOS) (Visit 199)

The study will be completed when reaching 302 patients with CV events or if a recommendation is made by the DMC to prematurely stop the study. At the end of the study, all participants will return for the final end of study (EOS) visit (Visit 199)

Study completion

Study completion is defined as when the last subject finishes their End-of-study Visit, and any repeat assessments associated with this visit have been documented and followed up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision (e.g., each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them).

Baseline

Baseline value is the last non-missing assessment before the first administration of study drug, unless specified otherwise.

Last Contact

Last contact is set as the data of the latest performed visit, in several cases the End-of-study Visit. The last contact date will be used for censoring patients in the analysis of time to events endpoints.

2.1.2 Randomization

Patients were randomized stratified by Country and according to ACEI/ARBs use (not treated, treated with low dosages, less than 50% of the target dosage, and at least 50% standard doses of ACEIs/ARBs).

2.1.3 Partial information for dates

The heart failure diagnosis date, or the time from Chagas disease diagnosis date, will be considered as the first day of the reported month if only the month and year are provided. If only the year is reported, January 1st will be assumed. The same imputation logic will be applied to the start and end dates of adverse events or any other date when only partial information is available (month/year or just year).

2.2 Analysis sets

Randomized Analysis Set (RAN)

RAN consists of all randomized participants.

Full Analysis Set (FAS)

FAS comprises all participants to whom study treatment has been assigned at randomization. According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure. Randomization was stratified by country.

However, patients who did not qualify for randomization but were inadvertently randomized into the study and did not receive study medication will be excluded from FAS. Further exclusions from the FAS may only be justified in exceptional circumstances (e.g., serious GCP violations). These potential incidences imply the possibility that the FAS may be smaller than the RAN.

Safety Set (SAF)

SAF includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment they actually received, where treatment received is defined as the randomized/assigned treatment if the subject took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

Per-Protocol Set (PPS)

PPS is a subset of participants of the FAS and will include participants with no major protocol violations and who took at least one dose of the study treatment. Patients with any of the following protocol violations will be excluded from the PPS, but not limited:

- Not fulfilling all the inclusion criteria as described on CLCZ696B3302 Protocol last version;
- Fulfilling any of the exclusion criteria as described on CLCZ696B3302 Protocol last version;

PD definition will be done according to BCRI Work Instruction IT RE 012.

2.3 Patient disposition, demographics and other baseline disease characteristics

Summary statistics will be provided by treatment arm for demographics and baseline characteristics, including age, age group, sex, race, ethnicity, weight, height, body mass index, category of prior HF medication, chagas disease history, prior HF hospitalization, New York Heart Association class, ejection fraction, NT-proBNP, and vital signs (blood pressure and pulse rate). Body mass index will be calculated as weight (Kg)/height^2 (m^2) from the collected height and weight at the Screening Visit. Continuous variables will be summarized using n, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency and percentage. Additionally, summary statistics will be provided by treatment and age group.

The FAS will be the subject population for the above analyses.

2.3.1 Patient disposition

Patient disposition for all randomized patients will be summarized based on FAS. There will be one combined by-treatment summary showing:

- Count and percent of patients who discontinued study treatment;
- Reasons for study treatment discontinuation;
- Count and percent of patients who voluntarily withdraw consent to participate in the study for any reason at any time;
- Reasons for voluntarily withdrawal;
- Count and percent of loss to follow up;

The screen failure reasons will be recorded on the appropriated eCRF and presented in a separate summary.

2.4 Treatments

2.4.1 Study treatment

The overall duration of exposure will be summarized by the treatment arm. The number of patients who do not tolerate the target dosage and will be titrated down to the lower dose level will be summarized and listed by the treatment arm. The FAS and SAF will be used for this analysis.

The overall duration of exposure to study treatment (sacubitril/valsartan or the active control enalapril) will be calculated in days as: (Date of last administration of study treatment) – (Date of first administration of study treatment) + 1 in each visit interval, and then summed whitin each level os study medication. The calculation logic shaw be follow as below for each entry (rows) of intervals whitin visits:

- For the rows, if the Enalapril_ongoing/Sacubitril_ongoing is 1 (Ongoing) and the next visit Start date is available then we impute End date with available Next visit Enalapril/Sacubitril startDate.
- For rows where end date is missing and the next visit is missed and if its ongoing dose we impute with Start date of same record.
- For the row in the Dosage administration data if the end date is missing and if the dose is not ongoing, we will impute it with corresponding Sacubitril/Enapril Start date.
- For the last row in the Dosage administration data, if the end date is missing and dose is Ongoing then to impute below date only if its after the dosing Start date :
    - Death date (if available),
    - Last known Patient Alive date
    - Max Visit date Information available
    - if any of the above date is not available then to impute the end date with start date of same record.

- If after all these steps, same inconsistence still generates negative dates (end dates before start dates), then this interval should be considered as zero days.

As the follow up time may vary between participants, the treatment adherence will be presented as percentage from total follow up time as well.

2.4.2 Prior, concomitant and post therapies

Prior and concomitant medications will be coded according to the latest version of WHO Drug Reference List dictionary which employs the ATC. The number and percentage of patients taking prior and concomitant medications will be summarized for each treatment by ATC class and preferred term (PT) The number and the percentage of participants on different HFrEF background medications will be tabulated by treatment at baseline, during the double-blind stage. The FAS and SAF will be used for these analyses.

2.5 Analysis of the primary objective

2.5.1 Primary Endpoint

The primary endpoint is the hierarchically ordered composite endpoint consisting of time to CV death (worst category; earlier time to CV death is unfavorable), time to first Hospitalization due to Heart Failure (second worst category; earlier time to Hospitalization due to HF is unfavorable) and the relative change from baseline to Week 12 in NT-ProBNP (best category; more reduction or less increase are favorable) (Table 1). CV events will be confirmed by an independent Clinical Endpoint Adjudication Committee (CEC).

The effect is measured through the unmatched win ratio. The win ratio is based on pair-wise comparisons between participants receiving sacubitril/valsartan and participants receiving enalapril. A winner in the pair-wise comparison has a delayed time to the occurrence of CV death; if time to the occurrence of CV death is censored, a winner has a delayed time to the occurrence of first HF hospitalization event; if the times to both cardiovascular events are censored, winner has a smaller change (more

reduction or less increase) in NT-proBNP between baseline and Week 12. The FAS will be used for the primary analysis.

2.5.1.1 Primary Estimand

An estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level, what the outcomes would be in the same patients under each of the treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest. It also specifies how intercurrent events are addressed and provides a population-level summary for the variable.

Clinical question of Interest: To assess whether sacubitril/valsartan is superior to enalapril in participants with HFrEF caused by chronic Chagas' cardiomyopathy in improving a composite hierarchical outcome.

The primary estimand is described by the following attributes:

1. **Target Population**: Adult chronic Chagas' cardiomyopathy patients with NYHA Class II-IV HFrEF (LVEF ≤ 40%) with or without covid-19 events.
2. **Variable**: Composite endpoint in hierarchically order
    1. Time to CV death,
    2. Time to first Heart Failure Hospitalization, and
    3. Relative change from baseline to Week 12 in NT-ProBNP.

3.**Treatment condition**: Sacubitril/Valsartan or Enalapril, regardless of the treatment switching or discontinuation and concomitant use of SGLT2 inhibitors

4. **Intercurrent event (handling strategy)**:
    - Non-CV death (while alive)
5. **Summary measure**: Win ratio. Win ratio is the probability that a subject on Sacubitril/Valsartan has a better outcome than a subject on Enalapril divided by the probability that a subject on Enalapril has a better outcome than a subject on Sacubitril/Valsartan.

2.5.1.2 Supplementary Estimand for primary endpoint

This supplementary analysis will be conducted similar to primary endpoint above but on the hierarchically ordered composite endpoint consisting of time to all-cause death, time to first Hospitalization due to Heart Failure (second worst category; earlier time to Hospitalization due to HF is unfavorable) and the relative change from baseline to Week 12 in NT-ProBNP (best category; more reduction or less increase are favorable). When there is treatment crossover, only the data on the randomized treatment for that patient will be considered.

Clinical question of Interest: To assess whether sacubitril/valsartan is superior to enalapril in participants with HFrEF caused by chronic Chagas' cardiomyopathy in improving a composite hierarchical outcome.

1. **Target Population**: Adult chronic Chagas' cardiomyopathy patients with NYHA Class II-IV HFrEF (LVEF ≤ 40%) with or without covid-19 events.
2. **Variable**: Composite endpoint in hierarchically order
    1. Time to all-cause death,
    2. Time to first Heart Failure Hospitalization, and
    3. Relative change from baseline to Week 12 in NT-ProBNP.
3. **Treatment condition:** Sacubitril/Valsartan or Enalapril, regardless of the treatment discontinuation and concomitant use of SGLT2 inhibitors
4. **Intercurrent event (handling strategy):**
    - Treatment crossover (While on treatment)
5. **Summary measure:** Win-ratio

2.5.2 Statistical hypothesis, model, and method of analysis

The following primary analysis will be tested as (Wang and Pocock, 2016):
H0: $\Psi \leq 1$ (win ratio ≤ 1) - The true number of 'winners' for sacubitril/valsartan is less than or equal to the true number of winners for enalapril.

H1: Ψ>1 (win ratio > 1) - The true number of 'winners' for sacubitril/valsartan is larger than the true number of winners for enalapril.

The primary efficacy endpoint will be analyzed using the win ratio approach (Pocock et al 2012), with treatment as fixed-effect factor and stratified by country (Dong et al. 2017). Every patient in the sacubitril/valsartan arm will be compared to every patient in the enalapril arm within each stratum (country). All pairs will be compared first by time to CV death; if there is no winner, they will be compared for time to first HF hospitalization; if again there is no winner, they will be compared according to reduction in NT-proBNP levels between randomization and Week 12. If the comparison between changes in NT-proBNP levels does not result in a winner, the respective pairwise comparison is tied. When comparing the time to an event between two participants and at least one of the times is censored, the comparison is only performed up to the censoring time. The comparison of NT-proBNP is performed based on the relative change between randomization and Week 12 and takes into account that relative changes within ±25% are considered medically irrelevant; in detail, let x_{LCZ696} and x_{Enal} be the relative changes of participants in the sacubitril/valsartan and the enalapril arm, respectively. Then, a comparison of NT-proBNP is in favor of the subject in the sacubitril/valsartan arm if x_{LCZ696} <0.75 x_{Enal}. On the other hand, the comparison is in favor of the subject in the enalapril arm if x_{Enal} <0.75 x_{LCZ696}.

The win ratio is estimated by the ratio of the number of winners in the sacubitril/valsartan group and the number of winners in the enalapril group with weights defined as the reciprocal of the stratum (country) sample size.

$$\psi = \frac{\sum_m^M w^{(m)} n_{LCZ696}^{(m)}}{\sum_m^M w^{(m)} n_{Enal}^{(m)}}$$

Where $n_{LCZ696}^{(m)}$ and $n_{Enal}^{(m)}$ are the total number of wins in the m^{th} stratum for the sacubitril/valsartan and Enalapril groups, respectively; $w^{(m)} = {}^{1}/_{N^{(m)}}$ and $N^{(m)}$ is the total sample size in the m^{th} stratum.

The estimated win ratio and the corresponding two-sided 95% confidence interval will be provided. The overall type I error rate will be controlled at 2.5% (one-

sided). The contribution to the number of winners of each component of the composite endpoint will be reported. NT-proBNP at each visit and change from baseline will be summarized.

The summary will be presented by the treatment group for both the FAS and the PPS. The win ratio and its 95% confidence interval will be calculated using raw R code or the WINS package (version 1.4.3). The Appendix 4.1 presents the bootstrap algorithm description.

2.5.2.1 Time to CV death

The time from randomization to CV death will be considered as censored at the final analysis for participants who have not experienced a CV death. The censoring date for those participants without CV death prior to the analysis time point will be the following:

- date of death from non-CV causes, if the patient died.
- date of withdrawal of informed consent, if the patient withdrew the consent;
- date of last visit otherwise;

It will be considered as CV death for all the cases classified by the CEC as:

- Fatal Myocardial Infarction (MI);
- Heart Failure;
- Sudden Death;
- Fatal Stroke;
- Fatal Pulmonary Embolism;
- Cardiovascular Procedure-Related Death;
- Resuscitated Sudden Cardiac Arrest;
- All Undetermined causes of death (Presumed Cardiovascular Death, Presumed Sudden Death, Unknown death)

The definitions used to classify these events are described in detail in the CEC Charter, Version 1.0 – November 3rd, 2020. The classification frequencies for each cause will be presented descriptively.

2.5.2.2 Time to first HF hospitalization

The time from randomization to first HF hospitalization will be considered as censored at the final analysis for participants who have not experienced a HF hospitalization. The censoring date for those participants without a HF hospitalization prior to the analysis time point will be the following:

- date of death, if the patient died.
- date of withdrawal of informed consent, if the patient withdrew the consent;
- date of last visit otherwise

2.5.2.3 NT-proBNP measurement

Cardiovascular death and HF hospitalization are at a higher hierarchy level than NT-proBNP in the composite primary endpoint for win ratio analysis. Therefore, missing values due to CV death or after hospitalization due to HF do not affect the analysis. Missing NT-proBNP measurement at Week 12 due to other reasons (e.g., non-CV death) are expected to be infrequent; they may result in more ties with minimal impact on the power. Therefore, no imputation will be made for missing NT-proBNP measurement at Week 12 for primary analysis, any match against a participant without NT-proBNP measurement will be considered a tie.

Baseline NT-ProBNP values may be unavailable for some samples. In such cases, if participants provided a local NT-ProBNP sample during screening phase, those values will be imputed for primary evaluation. Exams results disposed as > or < then any value, will be considered as exactly the limit value.

2.5.3 Supportive analyses

In addition to the primary analysis, the primary efficacy endpoint will be supportively analyzed for the PPS using the same primary analysis model.

Additionally, a supplementary analysis will be performed using the same statistics described for the primary efficacy endpoint, using total hospitalizations for HF instead of time to first HF hospitalization, if participants tied in number of hospitalizations, the winner will be the one that had the first event later. All other cases where the NT-proBNP values are missing for baseline or W12 will be treated as a tie in NT-proBNP for every match also tied for both the previous hierarchical endpoints.

Additional analyses will be performed on each individual component of the primary endpoint that occurs during the Randomized Treatment Epoch of the study to quantify the strength of the effect of each component.

For CV death and first HF hospitalization:

- Cox's proportional hazard model will be used to analyze time to CV death, and time to first HF hospitalization, respectively, with treatment as fixed-effect factor and stratified by country performed for both the FAS and the PPS; Hazard Ratios with 95% confidence intervals will be presented,
- The survival function for each treatment arm will be estimated by the Kaplan-Meier method presenting curves for each treatment arm for both the FAS and PPS.

For NT-proBNP:

- ANCOVA model will be used to analyze relative changes of NT-proBNP from baseline to Week 12 with treatment and country as fixed-effect factors and baseline NT-proBNP as covariate. Results will be presented as mean differences in relative change with 95% confidence intervals.
- A supplementary analysis will be performed for the absolute value of NT-proBNP using the same model and covariates. If the assumptions of normality and homoscedasticity are rejected based on graphical verification, a generalized linear model with a different distribution, such as Gamma, Log-

Normal, or Inverse-Gaussian, will be tested. The model with the best likelihood function will be chosen, and results will be presented as a mean ratio with 95% confidence intervals.

2.6 Analysis of secondary efficacy objectives

2.6.1 Secondary endpoints

The secondary efficacy endpoints besides the primary decomposition as described above are:

1. Time from randomization to the occurrence of the first HF hospitalization or CV death;
2. Time from randomization to all-cause mortality.
3. Time from randomization to sudden death or resuscitated sudden cardiac arrest.
4. Number of visits to an ER due to HF that needs intravenous drugs.
5. Number of days alive out of the hospital within 1 year from randomization.
6. Recurrent events: number of HF hospitalizations and CV deaths.

2.6.2 Statistical hypothesis, model, and method of analysis

2.6.2.1 Analysis of time to events endpoints

The time from randomization to

- the first composite event of CV death or HF hospitalization,
- all-cause mortality, and
- to sudden death or resuscitated sudden cardiac arrest

will be analyzed using Cox's proportional hazards model with treatment as fixed-effect factor and stratified by country. The estimated hazards ratio and the corresponding 2-sided confidence interval will be provided for the FAS.

The Kaplan-Meier curves by treatment arm will be presented for the FAS. Additionally, the frequency and percentage of patients with a composite CV event will be provided by treatment arm.

Proportional hazard assumptions will be tested by weighted residuals diagnostics and by visual inspection. Alternative parametric survival models (Exponential, or Weibull, or Log-logistic, or log-normal survival models) will be used if

the risk proportional assumption did not meet. The model with the best likelihood function will be chosen in that case.

2.6.2.2 Analysis of number of visits to an ER due to HF that needs intravenous drugs

The rate of visits to an ER due to HF that needs intravenous drugs will be analyzed using a generalized linear model assuming a negative binomial distribution. The time at risk for a subject is the length of follow-up. The analysis model will include terms for treatment and country as fixed-effect factors and log (follow-up duration) as the offset. An estimate of the ratio of event rates between the treatment arms, together with the 95% confidence interval, will be presented for the FAS.

The number of visits to an ER due to HF that needs intravenous drugs during the treatment period will be summarized by treatment arms.

2.6.2.3 Analysis of number of days alive out of the hospital

The duration in days of hospital-free survival within 1 year from randomization will be summarized by treatment group, and descriptive statistics (N, mean, standard deviation, median, and quartiles) will be provided. The mean difference between treatment groups will be compared using linear regression model with treatment as fixed factor adjusted for country. The estimated within treatment means, between-treatment difference and 95% confidence interval will be provided for FAS.

2.6.2.4 Analysis of recurrent events (CV death and HF Hospitalizations)

Recurrent events will be examined by using 2 methods. Initially, the semiparametric proportional-rates model described by Lin et al. (2000) – Lin, Wei, Yang, and Ying (LWYY). This is an extension of the proportional-hazards model and is based on the gap-time approach that considers the times since the previous event, that is, the interevent time. The LWYY model uses robust standard errors to account for the interdependence of events within an individual. Results will be presented in Rate Ratios with 95% confidence intervals and the recurrent events within each group will

be presented with incidence per 100-patient year. The second statistical method will be the joint frailty model, in that case a treatment rate ratio will be presented by each outcome separately (CV deaths and HF Hospitalizations).

2.6.2.5 Handling of missing values/censoring/discontinuations

Patients will be censored for the secondary endpoints according to the same method described in section 2.5.2.1 and 2.5.2.2.

2.6.3 Safety analyses

The safety and tolerability assessments are:

a. Physical examination;

b. Vital signs (sitting systolic and diastolic blood pressure, and pulse);

c. Pregnancy assessment;

d. Electrocardiogram;

e. Adverse events;

f. Serious adverse events;

g. Adverse events of special interest:

- Arrhythmia
- Angioedema
- Symptomatic hypotension
- Hyperkalemia
- Renal dysfunction

For all safety analyses, the SAF will be used. All listings and tables will be presented by treatment arm.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g., change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In

particular, summary tables for the Adverse Events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

2.6.3.1 Vital signs

All vital signs (Pulse [beats/min], BMI [kg/m²], Supine systolic blood pressure [mmHg] and Supine diastolic blood pressure [mmHg])) data will be listed by treatment arm, subject, and visit/time and if ranges are available, abnormalities (Pulse below 50 bpm and above 120 bmp; Systolic Blood Pressure below 90 mmHg and above 180 mmHg; Diastolic Blood Pressure below 50 mmHg or above 105 mmHg) will be flagged. Summary statistics will be provided by treatment and visit/time and as change from baseline.

2.6.3.2 Twelve-lead ECG

All ECG data (Rhythm, P-wave duration, Heart rate, QRS Complex Duration, QT Interval, will be listed by treatment arm, subject and visit (Baseline and EOS), abnormalities (Pathological Q Waves, Left anterior fascicular block, Posterior fascicular block, Complete Left Bundle Branch Block, Right Bundle Branch Block, Left Ventricular Hypertrophy, Low QRS voltage) will be flagged. Summary statistics will be provided by treatment at V1 and EOS.

2.6.3.3 Adverse events

All information obtained on AEs will be displayed by treatment arm and listed by subject.

The treatment emergent adverse events (events started on or after the first dose of study medication or events present prior to the first dose of study medication but increased in severity based on preferred term on or after the first dose of study

medication until 30 days after study's treatment last dose) will be summarized by primary System Organ Class (SOC) and Preferred Term (PT).

Separate summaries will be provided for study medication-related AEs, death, SAEs, other significant AEs leading to discontinuation.

2.6.3.4 Adverse events of special interest

The number (and proportion) of participants with AEs of special interest, AESI (i.e., angioedema, arrhythmia, symptomatic hypotension, hyperkalemia, and renal dysfunction), will be summarized by treatment.

In order to identify any potential AESI a search query was applied on each category of pre-defined AEs. The search strategy is outlined in Table 4. The search query uses much broader list of terms, as well as additional clinically relevant terms that may represent AESI like events. All identified AEs were followed up with the site for further assessment and to confirm if they fulfil the criteria of AESI. Each AESIs had their own CRF form to be completed by the Investigator with detailed information.

Table 4. Adverse Events of Special Interest search strategy.

AESI	Search methodology
Angioedema	SMQ (narrow) Angioedema, and additional PTs Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock, Auricular swelling, Bronchial oedema, Endotracheal intubation, Gastrointestinal oedema, Genital swelling, Laryngeal dyspnea, Laryngeal obstruction, Laryngospasm, Ocular hyperemia, Oedema peripheral (only LLTs Edema extremity upper, Edema upper extremities, Edema upper limb, Oedema extremity upper, Oedema upper extremities, Oedema upper limb, Upper limb edema, Upper limb oedema), Oedema genital, Orbital oedema, Oropharyngeal spasm, Penile oedema, Penile swelling, Reversible airways obstruction, Scrotal oedema, Scrotal swelling, Skin oedema, Stridor, Throat tightness, Tracheal obstruction, Upper airway obstruction, Vaginal oedema, Visceral oedema, Vulval oedema, Vulvovaginal swelling.
Arrhythmia[1]	
Hyperkalemia	'Blood potassium abnormal', 'Blood potassium increased' and 'Hyperkalemia'
Symptomatic hypotension	Altered state of consciousness', 'Blood pressure abnormal', 'Blood pressure ambulatory abnormal', 'Blood pressure ambulatory decreased', 'Blood pressure decreased', 'Blood pressure diastolic abnormal', 'Blood pressure diastolic decreased', 'Blood pressure fluctuation', 'Blood pressure immeasurable', 'Blood pressure inadequately controlled', 'Blood pressure orthostatic abnormal', 'Blood pressure orthostatic decreased', 'Blood pressure systolic abnormal', 'Blood pressure systolic decreased', Blood pressure systolic inspiratory decreased', 'CT hypotension complex', 'Consciousness fluctuating', 'Depressed level of consciousness', 'Dialysis hypotension', 'Diastolic hypotension', 'Dizziness', 'Dizziness exertional', 'Dizziness postural', 'Hypotension', 'Hypotensive crisis', 'Labile blood pressure', 'Loss of consciousness', 'Mean arterial pressure decreased', 'Neonatal hypotension', 'Orthostatic hypotension', 'Post procedural hypotension', 'Presyncope', 'Procedural hypotension', 'Schellong test', 'Syncope', and 'Tilt table test positive'

AESI	Search methodology
Renal dysfunction	SMQ (narrow) Acute renal failure

(1) *In the event that a clinically significant ECG abnormality is identified at the study site (e.g., severe arrhythmia, conduction abnormality, or QTcF > 500 ms), a copy of the assessment is to be sent to the local laboratory for expedited review if applicable, and the ECG is repeated to confirm the diagnosis. If the participant is hemodynamically compromised, the Investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion). Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical conditions or AEs as appropriate.*

The incidences of AESI will be compared between arms using Fisher's Exact Test as an exploratory evaluation, since the trial was not designed or powered for those comparisons.

2.6.4 Laboratory data

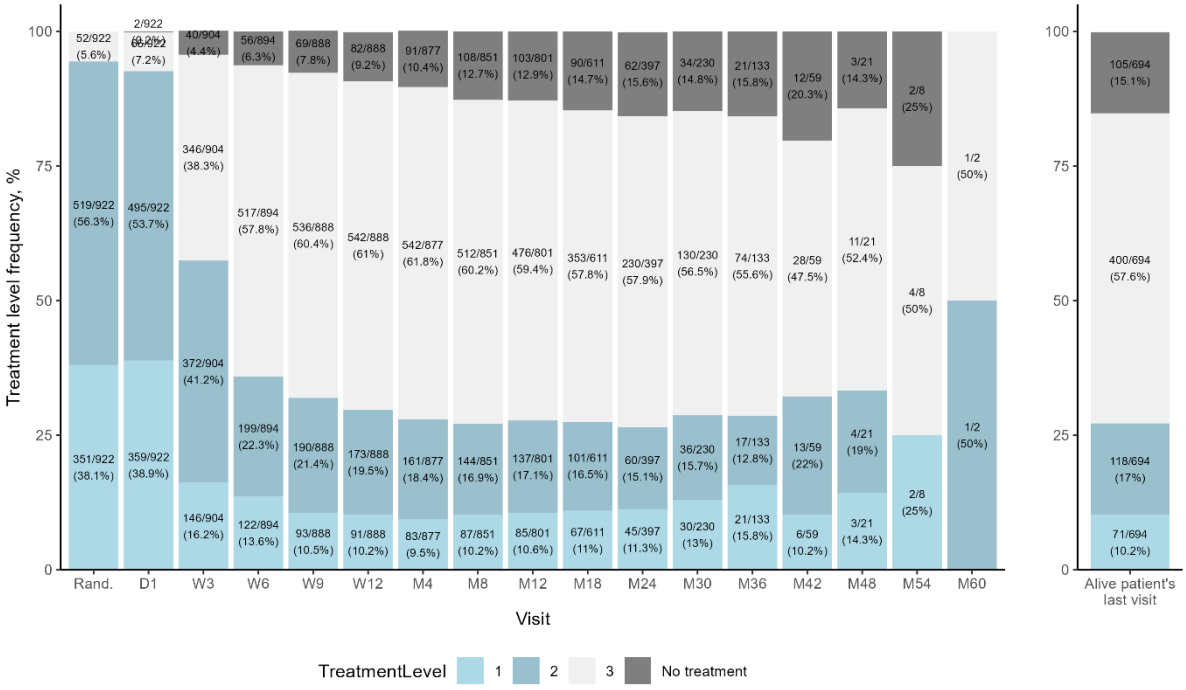
Laboratory evaluation of NT-proBNP will be used for primary efficacy analysis as mentioned before. The remaining laboratory evaluations will not be entered in the eCRF, values will only be used locally to trigger adverse events as described in the protocol.

2.7 Protocol adherence

Medication adherence will be presented as the percentage of time on medication during the study follow-up, excluding any temporary or permanent interruptions due to adverse events or patient choice. The percentage of medication use will be described by mean and standard deviation. Additionally, the number of patients who required temporary or permanent discontinuation of the medication due to adverse events, medical decision, personal choice, or other reasons will be reported.

Moreover, this time will be broken down into mean exposure times to dosages 1, 2, and 3 for each group, similarly, to presented on Figure 2 below.

Figure 2. Titration of the treatment drug at each visit.



2.8 Exploratory analyses

The exploratory endpoints are:

1. Number of ventricular fibrillation or sustained ventricular tachycardia needing specific pharmacological, electrical or other treatment.

2. Number of anti-tachycardia pacing or shock therapies (In the subset of patients with an ICD or CRT-D at randomization)

3. Change of NT-proBNP at month 8.

Exploratory analyses will be performed on the FAS. There will be no formal inferential analyses. Descriptive summary statistics over time for baseline, actual value, and change from baseline will be presented for each treatment arm.

The number of sustained ventricular tachycardia events needing specific treatment or ICD implantation will be analyzed using a negative binomial model (McCullagh and Nelder 1989) with the count data as the dependent variable and treatment group and country as fixed-effect factors and log (follow-up duration) as the

off-set. The model estimated event rates (intensities/risk rate) and their 95% confidence intervals will be provided by treatment group. The treatment comparison will be performed through the estimated ratio of risk rates. The estimated risk ratio and its 95% confidence interval will also be provided. Note that, in case when the follow-up durations depend on the treatments (informative censorings), the estimated rate reduction should be interpreted with caution. However, when sacubitril/valsartan has a reduction in mortality, the rate ratio estimated from the negative binomial model will become conservative.

Change from baseline of NT-proBNP at month 8 will be analyzed similarly as the evaluation at week 12, using ANCOVA models.

The impact of the concomitant use of SGLT2Inhibitors in CV death and hospitalizations due to HF will be evaluated with proportional hazard Cox models using the interaction of the use of SGTL2 Inhibitors as time dependent covariate with the treatment arm in FAS and PPS subsets. Results will be presented in hazard ratios with 95% confidence intervals.

Troponin will also be summarized at baseline, month 8 and for change from baseline at month 8 as well as absolute change from baseline at month 8 by treatment group.

2.9 Subgroup analysis

Subgroup analysis will consider the following variables according to PARADIGM study: age (<65, ≥65 yr), sex, race, NYHA class (I or II, III or IV), estimated GFR (<60 ml/min/1.73m², ≥60 ml/min/1.73m²), diabetes, systolic blood pressure (by median), ejection fraction (by median and ≤35%, >35%), atrial fibrillation, hypertension, prior use of ACE inhibitor or ARB, prior use of mineralocorticoid receptor antagonist, prior use of beta-blockers, prior use of SGLT2i, prior hospitalization for heart failure, time since diagnosis of heart failure (≤1 yr, >1 to 5 yr, >5 yr), and comparting participants randomized before December 31st, 2021 (during the Covid-19 pandemic) and after.

The subgroup analyses for the primary endpoint (win ratio) will be conducted, with results presented within each subgroup in forest plots or table.

Each win ratio variable (CV death, Time to first HF hospitalization, and NT-proBNP measurement at Week 12) will be presented as additional information if any subgroup performed differently for the primary endpoint. In that case, subgroup effects will be tested including interaction parameters in the models used to report the marginal treatment effect previously described in section 2.6.2.

2.10 Interim analysis

There are no Interim Analyses planned for this study. However, Interim safety assessments are planned to be performed according to Data and Safety Monitoring Board (DSMB) charter by an independent statistician not involved in the study conduct. The DSMB will typically meet twice a year, or as deemed necessary. It is expected approximately 6 DSMB meetings in 36 months' study duration. No alpha adjustment will be made once there are no prespecified interruption rule for superiority nor safety.

To reduce bias, all study team members involved in data analysis will remain masked to the treatment codes and the results of the interim analysis until all monitoring decisions are made and the database is locked for final analysis.

2.11 Sample size calculation

An analysis of the 55 patients with Chagas' disease in the enalapril group in PARADIGM (Ramires et al 2018) showed an event rate of 20 events per 100 subject-years for CV death plus hospitalization due to HF. Similar event rates, for CV death plus hospitalization due to HF in CCC patients, has also been seen in the BENEFIT and SHIFT studies. Therefore, we assumed a rate of approximately 20 events per 100 subject-years for the CV event (composite of CV death and first HF hospitalization) for the enalapril group. Approximately 66% of the first CV events are HF hospitalizations. For the sample size calculation, we assumed a rate of 16 events per 100 subject-years for the sacubitril/valsartan group, which corresponds to an effect of 20%.

The sample size was determined based on a simulation study under the assumptions of:

- a one-sided type I error rate of 2.5%,

- a target power of 85%,

- a uniform accrual of 18 months,

- a study duration of 36 months, i.e. the individual follow-up times varied between 18 and 36 months,

- an annualized event rate of 0.16 for the composite of CV death or first HF hospitalization in the sacubitril/valsartan group, and an annualized event rate of 0.20 for the composite of CV death or first HF hospitalization in the enalapril group,

- a relative change of NT-proBNP between week 12 and baseline that is 25% lower in the sacubitril/valsartan group compared to the enalapril group

During the simulation study, a simulated trial was considered to show superiority of sacubitril/valsartan over enalapril when the win ratio was significantly larger than one based on the one-sided significance level of 2.5%, and the estimated hazard ratio of sacubitril/valsartan versus enalapril for time to first HF hospitalization was less than one, and the estimated hazard ratio of sacubitril/valsartan versus enalapril for CV death was less than one.

Based on these assumptions and criteria for superiority, a study with 900 patients results in the target power of 85%. Moreover, 302 participants with events for the composite of CV death or first HF hospitalization can be expected in the study.

As the primary hierarchical composite endpoint is evaluable as long as subject experience either a HF hospitalization, CV death, or have a NT-proBNP value measured at Week 12, the sample size calculation did not assume any loss of follow-up.

A blinded sample size re-estimation may occur if the event rate is lower than expected or the number of patients lost to follow up is higher than expected during the

study. A review will be done when 50% of patients have been enrolled. Otherwise, the study will continue until 302 participants have experienced a CV event and all patients have a minimum follow-up of 12 weeks.

2.12 Justification for strategy used in Estimand framework

2.12.1 Primary Estimand

Table 5. Justification for strategy used in Estimand framework

Intercurrent Event	Strategy	Clinical Justification
Treatment discontinuation	Treatment policy	Treatment discontinuation is included in the treatment conditions of interest.
Non-CV death	While Alive	Only data before non-CV death is considered. Death naturally ends the observation period, only the observed part before the non-CV death should be taken into consideration.
Concomitant use of SGLT2 Inhibitor	Treatment policy	Concomitant use of SGLT2 inhibitor is included in the treatment conditions of interest. Use of this concomitant medication will be observed in both arms and is a usual clinical practice.
Covid-19	Treatment policy	Covid-19 is included in the target population of interest.
Treatment crossover (Switch after observing endpoint)	Treatment policy	Treatment crossover is included in the treatment condition of interest (since the switch doesn't has the confounding effect on the observed endpoint)
Treatment crossover (Switch	Treatment policy	Treatment crossover is included in the treatment condition of interest

before observing endpoint)		

2.12.2 Supplementary Estimand for primary endpoint

Table 6. Justification for strategy used in Estimand framework

Intercurrent event	**Strategy**	**Clinical Justification**
Treatment discontinuation	Treatment policy	Treatment discontinuation is included in the treatment conditions of interest.
Non-CV death	Composite strategy	No differentiation between CV and Non-CV death, consider any death as the endpoint. Non-CV death is included in the Estimand endpoint.
Concomitant use of SGLT2 Inhibitor	Treatment policy	Concomitant use of SGLT2 inhibitor is included in the treatment conditions of interest. Use of this concomitant medication will be observed in both arms and is a usual clinical practice.
Covid-19	Treatment policy	Covid-19 is included in the target population of interest.
Treatment crossover	While on treatment	The data is censored at the time of the switch and no imputation is performed for NTProBNP

2.13 Additional Assessments

Protocol version 2.0 added additional assessments to be reported as sub studies. Analyses of the sub studies will not be presented in the CSR.

2.13.1 Holter monitoring

2.13.1.1 Objectives

1. To estimate the prevalence of arrhythmias (i.e., premature ventricular contractions [PVC], non-sustained ventricular tachycardia [NSVT], ventricular tachycardia [VT]) in participants with CCC.

1.1 Endpoint to address the objective

1. Composite of reduction in PVC burden, sustained VT, and non-sustained VT episodes at Randomization and Month 8 (arrhythmia burden).

2. To evaluate the effect of sacubitril/valsartan versus enalapril on the arrhythmia burden from Randomization to Month 8

2.1 Endpoints to address the objective

1. Correlation of arrhythmia burden with biomarkers.
2. Correlation of arrhythmia burden with CV mortality
3. Incidence of associated safety events (AEs/SAEs)
4. Incidence of atrial arrhythmias

2.13.1.2 Substudy Sample size

The sample size was estimated based on data available in Table 2 of Diego et al (2018), which include the following parameters:

• PVC burden (PVC/hour)

• Sustained VT

• Non-sustained VT (NSVT)

It was estimated that approximately 400 participants were needed to have adequate 80% power for each parameter separately, acknowledging the limitation that in the reference source used for the calculations, the data were from the same group of 120 participants treated with angiotensin inhibition alone for 9 months followed by angiotensin-neprilysin inhibition for another 9 months.

However, it was only possible to enroll 21 patients to perform to Holter evaluation.

2.13.1.3 Statistical hypothesis, model, and method of analysis

Summary statistics by treatment arm will be estimated for PVC burden, sustained VT, and nonsustained VT.

Due to low enrollment in the sub-study, the primary endpoint, initially specified for analysis using generalized mixed linear models with study site as a random effect in the intercepts to account for hierarchical site effects, will now be compared using non-parametric Mann-Whitney tests.

The correlation between arrhythmia burden and biomarkers, mortality, related safety events, and atrial arrhythmia incidence (exploratory analysis) will be presented descriptively. If feasible, Cox proportional hazards models will be adjusted based on baseline Holter measures and treatment group interactions.

2.13.2 Magnetic resonance imaging

2.13.2.1 Objectives

To examine the changes in cardiac structure, function, and fibrosis after 8 months of treatment with sacubitril/valsartan or enalapril.

2.13.2.2 Endpoints

All baseline and 8-month MRI measurements are described in the Manual of Cardiovascular Magnetic Resonance Imaging Substudy, categorized into assessments of left ventricular (LV), right ventricular (RV), left atrium (LA), right atrium (RA), myocardial edema of LV, myocardial delayed enhancement – myocardial fibrosis, T1 mapping, T2 mapping, and clinical and laboratory data peri-MR.

2.13.2.3 Statistical hypothesis, model, and method of analysis

Summary statistics by treatment arm will be presented for each MRI measurement. Evaluations of all MRI measurement at 8-month will be performed adjusted for baseline values. The reduction of fibrosis and the improvement of cardiac structure after 8 months of treatment will be analyzed using generalized mixed linear models considering the hierarchical effect of study site and participant. Results will be graphically displayed in boxplots. Missing values will not be imputed; analyses will be performed on FAS populations, including only participants with available MRI data.

3 Change to protocol specified analyses

SAP second version includes the recurrent event as a key secondary endpoint, changed the number of days alive out of the hospital time definition changed to within 1 year from randomization, and the NT-ProBNP evaluation at month 8 was included as exploratory endpoint.

4 Appendix

4.1 PARACHUTE-HF Win Ratio bootstrap algorithm

1. The **win_ratio()** function determines the winner in each match between Enalapril and Sacubitril/Valsartan patients based on a hierarchical evaluation. The win_ratio function will be used in the pairs of patients from both groups within each stratum.

- If the Sacubitril patient dies, and their follow-up time is shorter (regardless of whether the other patient dies), Enalapril wins. Conversely, if the Enalapril patient dies and their follow-up time is shorter, Sacubitril wins. Otherwise, it is a tie.
- If the participants tied using previous comparison then a comparison tin time to first HF hospitalization is performed: if the Sacubitril patient is hospitalized for heart failure (HF) and the time to first hospitalization is shorter than that of the Enalapril patient (or shorter than their total follow-up time if they were hospitalized for HF), Enalapril wins. The same logic applies in reverse for Sacubitril. Otherwise, it is a tie.
- If the participants tied using previous comparison then a comparison in NT-ProBNP changes within 12 weeks is performed: The **NT_ProBNP_relative_change** endpoint is defined as the ratio: **NT-ProBNP at Week 12 / NT-ProBNP at Baseline**. The match outcome is determined as follows:
    - If **NT_ProBNP_change_Sacubitril < 0.75 × NT_ProBNP_change_Enalapril**, Sacubitril wins.
    - If **NT_ProBNP_change_Enalapril < 0.75 × NT_ProBNP_change_Sacubitril**, Enalapril wins.
    - Otherwise, it is a tie.

2. **Matrix W** contains the weight assigned to each country, calculated as $\mathbf{1/N_i}$, where $\mathbf{N_i}$ represents the number of patients per stratum **i**, with **i** belonging to {Argentina, Brazil, Colombia, Mexico}.
3. **resultados_wr(BR)** is a data frame containing match results for Sacubitril vs. Enalapril patients in **Brazil**, computed using the **win_ratio()** function. Similar datasets (**resultados_wr(AR), resultados_wr(CO), resultados_wr(MX)**) are created for the remaining strata.
4. **resultados_wr** compiles all match results into a single data frame.

5. Calculates the total number of wins for each group and the number of ties per stratum and overall. In each stratum, the observed **Win Ratio (WR)** is calculated as the number of Sacubitril wins divided by the number of Enalapril wins.
6. The **Dong's Win Ratio** is then computed using the weights from **W** and the number of wins in each stratum:

$$\psi = \frac{\sum_{i=1}^{4} w^{(i)} n_{Sacubitril}^{(i)}}{\sum_{i=1}^{4} w^{(i)} n_{Enalapril}^{(i)}}$$

To compute the bootstrap:

1. **Resampling:** Perform resampling of the patients with replacement, maintaining the original number of patients per group in each stratum **M** times. (M ≥ 10,000)

2. **Match Evaluation:** For each resampled stratum, compute match outcomes using **resultados_wr**.

3. **Win Ratio Computation:** Calculate the Win Ratio **M** times for each country.

4. **Dong's Win Ratio Estimation:** Compute the Dong's Win Ratio for all **M** samples using matrix **W** (since stratum sizes remain unchanged), storing results in an auxiliary variable **Strata_results**.

5. **Confidence Interval Calculation:** Compute and return the **95% confidence interval (CI)** for each stratum and the overall Dong's Win Ratio using the **2.5th and 97.5th percentiles** of the M resamples.

5 Reference

Bocchi, E. A., Rassi, S., & Guimarães, G. V. (2018). Safety profile and efficacy of ivabradine in heart failure due to Chagas heart disease: a post hoc analysis of the SHIFT trial. ESC Heart Failure, 5(3), 249–256. https://doi.org/10.1002/ehf2.12240

D. Y. Lin, L. J. Wei, I. Yang, & Z. Ying. (2000). Semiparametric Regression for the Mean and Rate Functions of Recurrent Events. Journal of the Royal Statistical Society. Series B (Statistical Methodology), 62(4), 711–730. http://www.jstor.org/stable/2680616

de Diego, C., González-Torres, L., Núñez, J. M., Centurión Inda, R., Martin-Langerwerf, D. A., Sangio, A. D., Chochowski, P., Casasnovas, P., Blazquéz, J. C., & Almendral, J. (2018). Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices. Heart Rhythm, 15(3), 395–402. https://doi.org/10.1016/j.hrthm.2017.11.012

Dong, G., Qiu, J., Wang, D., & Vandemeulebroecke, M. (2018). The stratified win ratio. Journal of Biopharmaceutical Statistics, 28(4), 778–796. https://doi.org/10.1080/10543406.2017.1397007

Grambsch P, Therneau T (1994), Proportional hazards tests and diagnostics based on weighted residuals. Biometrika, 81: 515-26.

Morillo, C. A., Marin-Neto, J. A., Avezum, A., Sosa-Estani, S., Rassi, A., Rosas, F., Villena, E., Quiroz, R., Bonilla, R., Britto, C., Guhl, F., Velazquez, E., Bonilla, L., Meeks, B., Rao-Melacini, P., Pogue, J., Mattos, A., Lazdins, J., Rassi, A., … Yusuf, S. (2015). Randomized Trial of Benznidazole for Chronic Chagas' Cardiomyopathy. New England Journal of Medicine, 373(14), 1295–1306. https://doi.org/10.1056/NEJMoa1507574

Pocock, S. J., Ariti, C. A., Collier, T. J., & Wang, D. (2012). The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. European Heart Journal, 33(2), 176–182. https://doi.org/10.1093/eurheartj/ehr352

Ramires, F. J. A., Martinez, F., Gómez, E. A., Demacq, C., Gimpelewicz, C. R., Rouleau, J. L., Solomon, S. D., Swedberg, K., Zile, M. R., Packer, M., & McMurray, J. J. V. (2018). Post hoc analyses of SHIFT and PARADIGM-HF highlight the importance of chronic Chagas' cardiomyopathy Comment on: "Safety profile and efficacy of ivabradine in heart failure due to

Chagas heart disease: a post hoc analysis of the SHIFT trial" by Bocchi et al. ESC Heart Failure, 5(6), 1069–1071. https://doi.org/10.1002/ehf2.12355

Rogers, J. K., Yaroshinsky, A., Pocock, S. J., Stokar, D., & Pogoda, J. (2016). Analysis of recurrent events with an associated informative dropout time: Application of the joint frailty model. Statistics in Medicine, 35(13), 2195–2205. https://doi.org/10.1002/sim.6853

Wang, D., & Pocock, S. (2016). A win ratio approach to comparing continuous non‐normal outcomes in clinical trials. Pharmaceutical Statistics, 15(3), 238–245. https://doi.org/10.1002/pst.1743