NOVARTIS

Clinical Development

LCZ696/Sacubitril/Valsartan/Entresto®

CLCZ696DUS01 / NCT03988634

A multicenter, randomized, double-blind, double-dummy, parallel group, active controlled study to evaluate the effect of sacubitril/valsartan prior (LCZ696) versus valsartan on changes in NT-proBNP, safety, and tolerability in HFpEF patients with a WHF event (HFpEF decompensation) who have been stabilized and initiated at the time of or within 30 days post-decompensation (PARAGLIDE- HF)

Statistical Analysis Plan (SAP) Amendment 1

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18-June-2019	Prior to FPFV	Creation of first version	NA - First version	NA
21-Feb-2023	Prior to database lock	Protocol Amendment 4.0	Amendment 1	The vast majority of sections have been impacted.

Table of contents

List of abbreviations

ACEi	angiotensin converting enzyme inhibitor
ADP	adenosine diphosphate
AE	adverse event
AESI	adverse event of special interest
AF	atrial fibrillation
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ANP	atrial natriuretic peptide
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BNP	B-type natriuretic peptide
BUN	Blood urea nitrogen
CCB	Calcium channel blocker
CCU	cardiac care unit
CI	confidence interval
CKD	chronic kidney disease
CSR	clinical study report
CRT	Cardiac resynchronization therapy
CV	cardiovascular
DBL	database lock
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
DOAC	Direct-acting oral anticoagulant
ECG	Electrocardiogram
eCRF	electronic case report form
ED	emergency department
EF	ejection fraction
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FAS	full analysis set
[redacted]	[redacted]
hCG	human chorionic gonadatropin
HF	heart failure
HFimpEF	Heart failure with improved ejection fraction
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
hs-Troponin	high sensitivity troponin
ICD	implantable cardioverter defibrillator
ICU	intensive care unit
IV	intravenous

IRT	Interactive Response Technology
KM	Kaplan Meier
LS	least squares
LVEF	left ventricular ejection fraction
MedDRA	Medical dictionary for regulatory activities
mmHg	millimeters of mercury
MRA	Mineralocorticoid receptor antagonist
NA	not applicable
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PT	preferred term
RAN	Randomized Analysis Set
RBC	red blood cell
SAE	serious adverse event
SAF	Safety Set
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SGLT2i	Sodium-glucose Cotransporter-2 inhibitor
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TFL	Tables, Figures, Listings
US	United States
WBC	white blood cell(s)
WHF	Worsening heart failure
WHO	World Health Organization

1 Introduction

The statistical analysis plan (SAP) will outline in detail the analyses planned in the protocol. The analyses will be used to generate the clinical study report (CSR). The SAP is based on the Amendment Protocol Version No. 04 dated 08-Dec-2021 and the data collection tool (DCT) Version: EDC 2021.2.1, Date: 10 Dec 2021 .

The details on the study background can be found in the study protocol and in the Appendix Section 5.6.

1.1 Study design

This study will use a randomized, double-blind, double-dummy, active-controlled, parallel group design. The goal is to randomize approximately 450 subjects to sacubitril/valsartan or valsartan in a 1:1 ratio in approximately 130 centers in the United States (US) and Canada. There is no stratification planned.

Subjects currently or recently taking an angiotensin converting enzyme inhibitor (ACEi): To provide for a necessary 36-hour washout of prior ACEi treatment before receiving sacubitril/valsartan, eligible subjects will be randomized no earlier than 36 hours from their last ACEi dose. Hospital medication administration and medication reconciliation records should be reviewed to confirm that eligible subjects have not received ACEi for at least 36 hours prior to randomization and the first dose of study medication. Due to this washout period, Amendment 3 and earlier versions did not allow subjects to be enrolled prior to 36 hours.

In Protocol Amendment 04, one can be enrolled any time during the admission or worsening HF event as long as they have washed out from the prior/current ACEI (if applicable).

Randomized subjects will have been hemodynamically stabilized defined in this study as:

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

b) No increase (intensification) in intravenous (IV) diuretic dose within last 6 hours prior to randomization

c) No IV inotropic drugs for 24 hours prior to randomization

d) No IV vasodilators including nitrates within last 6 hours prior to randomization

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

Subjects will be randomized 1:1 to sacubitril/valsartan or valsartan. Initial dose at randomization will be determined based on the subject's previous dose of or lack of ACEi/angiotensin receptor blocker (ARB) immediately prior to current worsening heart failure (WHF) event (heart failure with preserved ejection fraction (HFpEF) decompensation, or at the time of post-decompensation randomization.

In this study, approximately 450 subjects across 130 sites will be recruited. The maximum planned duration of follow-up after randomization (for subjects enrolled under Amendment 01 or later) is approximately 20 months; the anticipated minimum follow-up would be for 8 weeks.

The first amended protocol (Amendment 01) extended duration of treatment from 12 weeks (Original Protocol) to a maximum of approximately 20 months, and increased the sample size to 800 subjects. The average duration of study for all participants was anticipated to be approximately 11 months based in modeling from December 2019.

With Protocol Version 01 (Amendment 01) and subsequent amendments, all participants will be in double-blind treatment throughout the study, and there is no open label treatment phase.

Protocol Version 00 (Original Protocol) includes participants who signed Informed Consent and were randomized prior to execution of Protocol Version 01 (Amendment 1). Some of these participants already have completed the full 8 week double-blind period and have either finished or already commenced the 4 weeks open-label period; these participants were not eligible for continuation into Amendment 1, although their data is eligible for inclusion with all participants.

Another subset is those participants who were randomized to Protocol Version 00 who are still active in the 8 week double-blind period, and have not entered the open-label period.

If these participants are interested and can provide their voluntary signature to the revised Informed Consent prior to completion of the double-blind period, these participants would be eligible to continue in Amendments 01, 02, 03 and 04 with no open-label period. Lastly, those participants randomized subsequently to Institutional Review Board approval of Amendments 01, 02, 03, and 04 and the appropriate Informed Consent for the amended protocols would enter directly into the protocol as defined in the respective amended protocols.

Throughout all protocol versions, the primary endpoint remains the time-averaged proportional change in N-terminal pro-brain natriuretic peptide (NT-proBNP) from Baseline to Weeks 4 and 8. The most recent protocol amendment (Amendment 04) changed the sample size to 450 subjects with 85% power, deemphasizing the statistical power for key secondary clinical endpoints, however clinical events will still be assessed as secondary endpoints.

Section 1.2 shows the most recent version of the study objectives and endpoints according to protocol Amendment 04.

The planned duration of treatment is up to approximately 20 months of double-blind treatment and the last subject randomized will be followed for a minimum of 8 weeks. Subjects may be discontinued from treatment earlier due to adverse event, disease progression and/or if treatment is discontinued at the discretion of the investigator or the subject.

At the randomization visit, all eligible subjects will be randomized via interactive response technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which 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 randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis

Global Clinical Supply using a validated system that automates the random assignment of medication numbers to bottles containing the study treatment.

There is no planned interim analysis for efficacy in the study. Interim safety assessments are planned to be performed and results will be provided to the Data Monitoring Committee (DMC) for their review and recommendation. The number and/or timing of these safety assessments will be mentioned in the DMC Charter. No adjustment of the level of significance will be made for these interim safety assessments.

1.2 Study objectives and endpoints

	Objectives	**Endpoints**
	Primary Objective	**Endpoint for primary objective**
1	To demonstrate the effect of sacubitril/valsartan vs. valsartan on time-averaged proportional change in NT-proBNP from Baseline to Weeks 4 and 8 in HFpEF patients with a WHF event (HFpEF decompensation) who have been stabilized for and initiated at the time of or within 30 days post-decompensation	The time-averaged proportional change in NT-proBNP from Baseline to Weeks 4 and 8.
	Secondary Objectives	**Endpoints for secondary objectives**
2	To determine the effect of sacubitril/valsartan vs. valsartan on the composite hierarchical outcome consisting of: a) time to CV death, b) total HF hospitalizations, c) total urgent HF visits, and d) time-averaged proportional change in NT-proBNP (from Baseline to Weeks 4 and 8) using win ratio methodology	The composite hierarchical outcome consisting of: a) time to CV death, b) number and times of HF hospitalizations during follow-up, c) number and times of urgent HF visits during follow-up, and d) time-averaged proportional change in NT-proBNP (from Baseline to Weeks 4 and 8)
3	To assess the effect of sacubitril/valsartan vs. valsartan on total composite events based on CV death, HF hospitalizations, and urgent HF visits	The cumulative number of recurrent composite events overtime, the total number of composite events of HF hospitalizations, urgent HF visits, and CV death.
4	To assess the effect of sacubitril/valsartan vs. valsartan on the incidences of a composite endpoint of worsening renal function (renal death, reaching ESRD, or decline in eGFR ≥ 50%)	The incidences of a composite endpoint of worsening renal function, defined as: • renal death • reaching end-stage renal disease (ESRD) • ≥ 50% decline in estimated glomerular filtration rate (eGFR) relative to Baseline

5	To assess the effect of sacubitril/valsartan vs. valsartan on change in NT-proBNP from Baseline to Week 8	Proportional change in NT-proBNP from Baseline to Week 8
6	To assess the effect of sacubitril/valsartan vs. valsartan on change from Baseline in hs-Troponin (high sensitivity) at Weeks 4 and 8	Proportional change from Baseline in hs-Troponin (high sensitivity) at Weeks 4 and 8
7	To assess the effect of sacubitril/valsartan vs. valsartan on tolerability and the incidence of adverse events of special interest during treatment	Dosing levels and discontinuations
		Incidence of symptomatic hypotension during treatment
		Incidence of hyperkalemia (potassium >5.5 mEq/L)
		Incidence of angioedema
		Incidence of worsening renal function, defined as an increase in serum creatinine of ≥0.5mg/dl and worsening of the eGFR by at least 25%

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2 Statistical methods

2.1 Data analysis general information

All statistical analyses outlined in this SAP will be performed by Novartis Medical & Clinical Solutions. SAS® version 9.3 (or higher) will be used for all analyses.

Data from all centers that participate in this Protocol Amendment 4.0 or previous versions of the Protocols will be combined. All data as collected to date at the time of database lock (DBL) will be included in the analysis.

Unless otherwise specified, for continuous data, the mean, standard deviation (SD), median, first and third quartile, interquartile range, and minimum and maximum values will be presented. Minimum and maximum will be displayed to the same number of decimal places as raw values; mean, median, quartiles, and interquartile range will be presented to 1 additional decimal place; and SD to 2 additional decimal places.

For categorical data, frequencies and percentages will be presented. All statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

Due to participants being recruited under the original protocol and participants being recruited under the amended protocols, there will be a mix of participants that are observed for different lengths of time. Therefore, exposure adjusted summaries will be presented for relevant outputs. There will be a mix of participants that are observed for different visits and lengths of time because of the recruitment under the Original Protocol Version 00 and under the amended protocols (01 to 04). However, all the analysis planned here will be a pooled analysis unless otherwise stated.

Additionally, summary statistics will be provided by treatment group and Baseline classification of in-hospital/out-of-hospital randomization group. Geometric means will be used to summarize the NT-proBNP [redacted].

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

2.1.1 General definitions

Study treatment/ study drug

- Participants recruited under the Protocol Version 00 (Original Protocol) received either sacubitril/valsartan or valsartan during the first 8 weeks of the study.

- Participants recruited under the amended protocols (01 to 04) will receive either sacubitril/valsartan or valsartan during the approximately 84 weeks of the study.
- Participants recruited under Protocol Version 00 (Original Protocol) and who have not completed the double-blind period are eligible to continue in Amendment 01 with no open-label period.

Study treatment or study drug will refer to either of these 2 drugs.

Baseline

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

For safety labs and biomarkers, Baseline is defined as the last non-missing assessment collected before the first dose of study treatment, including matching placebos. For subjects not treated, Baseline is defined as the last non-missing assessment prior to or on the date of randomization.

Visit 1 biomarkers will be processed by the local laboratory and can be either NT-proBNP or B-type natriuretic peptide (BNP) for the purposes of study screening. From Visit 2 (Randomization/Baseline) onwards, NT-proBNP values will be based on clinical laboratory samples processed and assessed by the central laboratory (Visits 2, 3, 5, and 7; Weeks 0, 1, 4, and 8); BNP will not be collected.

For other assessments, including those for which assessment time is collected (electrocardiograms (ECGs), heart failure (HF) signs and symptoms, and pregnancy tests), Baseline is defined as the last non-missing assessment prior to or on the start date of study treatment (randomization date for subjects not treated), including matching placebos.

Date of first administration of study treatment

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

Open-label phase: The date of first administration of study treatment in the open-label phase is defined as the first date a dose of sacubitril/valsartan is administered in the open-label phase and recorded on the Study Treatment – Open Label eCRF.

The double-blind phase and open-label phase is only applicable for subjects enrolled under original protocol version 00.

With Protocol Versions 01, 02, 03 and 04 (Amendment 1, Amendment 2, Amendment 3, Amendment 4), all subjects will be in double-blind treatment throughout the study, and there is no open-label treatment phase.

Date of last administration of study treatment

Double-blind phase: The date of last administration of study treatment in the double-blind phase is defined as the last date a dose of study treatment is administered in the double-blind phase and recorded on the Study Treatment – Double Blind eCRF, or earlier if prematurely discontinued and recorded on the Study Treatment – Double Blind eCRF.

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

The double-blind phase and open-label phase is only applicable for subjects enrolled under original protocol version 00.
With Protocol Versions 01, 02, 03, and 04 (Amendment 1, Amendment 2, Amendment 3, Amendment 4), all subjects will be in double-blind treatment throughout the study, and there is no open-label treatment phase.

Study day

The study day describes the day of the assessment relative to the first date of study treatment.

The study day will be calculated as the difference between the date of assessment and the date of the first date of study treatment plus 1. If the date of assessment is prior to the date of the first date of study treatment, the study day will be negative and will be calculated as the difference between the date of the assessment and the date of the first date of study treatment. The descriptor "Study Day 0" will not be used.

Study phase

Double-blind phase
Participants recruited under Protocol Version 00 (Original Protocol) will receive either sacubitril/valsartan or valsartan during the first 8 weeks of the study. Assessments performed at Weeks 1, 2, 4, 6, 8 (including, but not limited to, vital signs) are assigned to the double-blind phase for summarization purposes. Unscheduled assessments are not assigned to a study phase for purposes of by-visit summaries.

Participants recruited under the amended protocols (verisons 01, 02, 03) and those participants recruited under Protocol Version 00 (Original Protocol) who opted to continue in an amendment protocol will receive either sacubitril/valsartan or valsartan during the approximately 84 weeks of the study. The assessments performed at Weeks 1, 2, 4, 6, 8, 10, 12, 16, 24, 32, 40, 48, 56, 68 or 84 (including, but not limited to, vital signs).

Participants recruited under the amended Protocol Version 04, assessments performed at Weeks 1, 4, 8, 24, 40, 56, 68 or 84 (including, but not limited to, vital signs) are assigned to the double-blind phase for summarization purposes. Unscheduled assessments are not assigned to a study phase for purposes of by-visit summaries.

For summarization of adverse events (AEs), notable vital signs and laboratory abnormalities, worsening renal function, defined as an increase in serum creatinine of $\geq$ 0.5mg/dL and worsening of the eGFR by at least 25%, hyperkalemia (Potassium > 5.5 mEq/l), angioedema and symptomatic hypotension by study phase, an assessment during the double-blind phase is defined as any assessment obtained in the following time interval:

- For participants recruited under the Protocol Version 00 (Original Protocol) date of first administration of study treatment through the date of the Week 8 visit, inclusive. For participants without a Week 8 visit, a projected Week 8 visit date will be derived relative to their treatment start date.

- For participants recruited under the amended protocols (versions 01, 02, 03 and 04) and participants recruited under Protocol Version 00 (Original Protocol) who opted to continue in the amended protocols date of first administration of study treatment through the date of the Week 84 visit, inclusive.

*Open-label phase (*under the Protocol Version 00 (Original Protocol))

For participants recruited under the Protocol Version 00 (Original Protocol) who do not continue in amendment protocol assessments performed at Weeks 10 or 12 (including, but not limited to, vital signs) are assigned to the open label phase for summarization purposes, unless otherwise noted. Unscheduled assessments are not assigned to a study phase for purposes of by-visit summaries.

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

After the date of the Week 8 visit. For participants without a Week 8 visit, a projected Week 8 visit date will be derived relative to their treatment start date.

Participants enrolled under Protocol Version 00 (Original Protocol) who died, withdrew consent, or were lost to follow-up prior to or on their projected Week 8 visit date will be excluded from the open-label phase.

End of Study (EOS)

EOS is obtained directly from the source data. A subject can discontinue treatment (EOT) at any time but continue the study, then the EOS is the study completion date. A subject who completes the study and has an EOS visit. If a subject discontinues the study for any reason, the discontinuation date is the EOS for that subject.

Follow-up for time-to-event analyses

For patients enrolled in the original protocol and continue to an open-label period, events are considered up to the end of their double-blind period (up to Week 8). For patients enrolled in Protocol Amendments 1-4, the events are considered up to their end of double-blind phase (EOS).

In-Hospital / Out-of-Hospital Randomization Status

The status for patient's in-hospital/out-of-hospital randomization is collected as "In-Patient or Out-Patient" category and will be provided by the Interactive Response Technology (IRT).

Year, month and week

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

1 year = 365.25 days

1 month = 30.4375 days

1 week = 7 days

1 day = 24 hours

COVID-19 pandemic phases

The participants in this trial may be divided into 3 subsets based on the COVID-19 pandemic status:

- Before pandemic set: Participants who completed (or discontinued) the trial (or completed study treatment period) before the pandemic start date
- During pandemic set: Participants with at least one on-treatment assessment or treatment-emergent event during the pandemic date
- After pandemic set: Participants who were enrolled (based on informed consent date) in the study after the pandemic end date (if applicable)

Where 01-Mar-2020 is the defined start date for the COVID-19 pandemic in the US and Canada according to the COVID-19 Guidance Dates by region for sensitivity analyses V5.0 (novartis.net).

2.2 Analysis sets

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

Randomized Analysis Set (RAN)	The RAN will consist of all randomized subjects.
The Full Analysis Set (FAS)	The FAS will consist of all subjects to whom study treatment has been assigned by randomization and at least one dose of study treatment recieved. According to the intent-to-treat principle, participants will be included for analysis according to the treatment they have been assigned to during the randomization procedure.
The Safety Set (SAF)	The SAF includes all participants who received at least one dose of the study treatment. Participants will be included for analysis according to the study treatment they received, where treatment received is defined as the randomized treatment if the participant took at least one dose of that treatment or the first study treatment received if the randomized treatment was never received.

The subjects in this trial are divided in 2 groups, (1) those who are randomized under Protocol Version 00 (Original Protocol subjects) and (2) those who are randomized after site execution of the amended protocols (Amendment 01, 02, 03, and 04 subjects). The FAS includes subjects from both groups.

2.2.1 Subgroups of interest

The following subgroups will be analyzed for the primary endpoint and for selected secondary endpoints based on clinical decision:

1. Age group (< 65, ≥ 65 years) and (< 75, ≥ 75 years)
2. Left ventricular ejection fraction (LVEF) categories prior to randomization:
    - > 40 to < 45% vs. ≥ 45%;

- > 40 to < 50% ((HFmrEF (mildly reduced)), ≥ 50% ((HFpEF) preserved)
- ≥ 50 to ≤ 60% vs. >60*
- >40 to ≤60 vs. > 60*
- ≤ median vs. > median

3. Prior use of ACEi/ARB (at the time of hospitalization)
4. Four groups defined by the Baseline quartiles of NT-proBNP
5. Baseline eGFR (< 45, 45 to < 60, ≥ 60 ; <30 or ≥ 30 mL/min/1.73 m^2)
6. SBP at randomization (< 110, ≥ 110 mm Hg)
7. Race
8. Ethnicity
9. Atrial fibrillation (AF) vs. no AF at the time of consent
10. Body mass index (BMI) ≥ 30 vs. BMI < 30; BMI ≤50 vs. >50 kg/m^2
11. Sex
12. New onset HF (at the time of hospitalization) – 'de novo heart failure'
13. New York Heart Association (NYHA) class at randomization
14. Recovered EF / Improved EF (HFimpEF) (most recent left ventricular ejection fraction (LVEF) > 40% (within past 3 months), but history of prior documented LVEF < 40%)
15. Time from presentation to hospital (if applicable) to randomization time
16. Prior history of HF
17. Prior Hospitalization for Heart Failure
18. Duration of Heart Failure (< 12 months, 12-24 months, 24-60 months, and > 60 months)
19. In-hospital/out-of-hospital randomization status
20. Structural heart disease (yes/no)
21. Subjects without COVID-19 positive during the trial.
22. Enrollment Country: Canada vs United States

* LVEF of >60% is defined as normal; LVEF <= 60% is defined as "below normal"

See Sections 2.5 and 2.6 for further details on the primary and secondary objectives, respectively.

2.3 Subject disposition, demographics and other baseline characteristics

2.3.1 Subject disposition

The number and percentage of subjects successfully screened will be presented. In addition, the reasons for screen failures will be provided. For subjects who are screened more than once, the information from the last screen will be used in the summary. This analysis will be performed on All subjects.

Number of subjects who were randomized will be presented on screen passed subjects.
The following categories will be summarized on RAN:

- Number and percentage of subjects who were treated
- Number and percentage of subjects who prematurely discontinued study treatment during double-blind phase
- Number and percentage of subjects who prematurely discontinued study treatment during double-blind phase, excluding deaths
- Number and percentage of subjects who prematurely discontinued study treatment during open-label phase
- Number and percentage of subjects who prematurely discontinued study treatment during open-label phase, excluding deaths
- Reasons for premature discontinuation of study treatment (separately for double-blind phase and open-label phase)
    - Adverse Event
    - Death
    - Lost of Follow-Up
    - Study terminated by sponsor
    - Patient/Guardian decision
    - Protocol deviation
    - Physician decision
    - Pregnancy

Study duration in months [(date of last contact/death – date of first dose of study treatment + 1)/30.4375]
The following categories will be summarized by treatment group for the full study period (Baseline – Week 84 end)

- Subjects who received at least 1 dose of study treatment in the study period
- Subjects who did not receive at least 1 dose of study treatment in the study period and the reason

Furthermore, it will only be feasible to determine loss to follow-up at Week 84 end.

Subject disposition (total enrolled, total discontinued, total completed) by region (US and Canada) and pandemic phase will also be summarized for the RAN.

A summary of subjects who were randomized but did not met the inclusion criteria #3 , i.e. subjects enrolled outside of the respective protocol window will be provided. The summary will include subjects randomized with/without the protocol specified enrollment window (i.e., Original protocol 36H-10Days; Amendment 1-3 36H-30Days; Amendment 4 0H-30Days) by original protocol and amendments by treatment for RAN.

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

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

2.3.2 Subject Protocol deviations

The number and percentages of protocol deviations by category will be summarized. Additionally, a listing of protocol deviations during the study will also be presented. The FAS will be used.

In addition pandemic related protocol deviations will be summarized by category and relationship. All COVID-19 related protocol deviations will also be listed.

2.3.3 Qualifying Hospitalization/ED Visit/Out-of-Hospital Urgent HF

The number and percentages of the following information about subjects and their qualifying hospitalization visit will be summarized by treatment group. The RAN will be used.

- Qualifying Healthcare Encounters
    - Hospitalization
    - Emergency Department (ED) Visit
    - Out-of-Hospital Urgent HF Visit
- Subject in shock (No, Yes, Unknown)
- Subjects receiving following treatment from qualifying hospitalization to randomization
    - Vasopressor (No, Yes, Unknown)
    - Inotrope (No, Yes, Unknown)
    - Nitroprusside (No, Yes, Unknown)
    - Nesiritide (No, Yes, Unknown)
    - IV Nitroglycerin (No, Yes, Unknown)
- Subject cared for in the intensive care unit (ICU) (No, Yes, Unknown)

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

- Duration of qualifying hospitalization stay in days [(date:time of discharge – date:time of arrival)/(3600*24)]
- Discharge disposition (Home or with family/friends, Rehabilitation facility, Skilled nursing facility, Death, Unknown)
- Discharge weight (kg)
- NYHA class (I, II, III, IV)
- Subject experienced worsening HF since randomization (No, Yes, Unknown)
- Subject cared for in ICU (No, Yes, Unknown)
    - Number of nights in ICU since randomization
- Subject treated with any of the following medication classes since randomization (IV inotrope, IV vasopressor, Nitroprusside, IV Nitroglycerin,)

All information relating to the qualifying hospitalization will be listed.

With Amendment 4, not all subjects will have a qualifying hospitalization, with some qualifying based on a worsening HF event (e.g. ED visit or Urgent HF visit).

2.3.4 Demographics and other baseline characteristics

Demographics, baseline characteristics, and disease history are collected at the screening visit. Descriptive summaries and/or listings will be provided. The number and percentage (categorical variables) and descriptive statistics (continuous data) for the information below will be summarized by treatment group for both double-blind and open-label subjects.

The FAS will be used. Summary statistics will be provided for Original Protocol subjects, and subjects recruited under the amended protocols, and all subjects in FAS.

In addition, demographics and baseline characteristics may be summarized by pandemic phases if needed.

2.3.4.1 Demographics and baseline characteristics

Demographic variables include:

- Age (years), age group (derived; < 65 years, 65 to <75 years, and ≥ 75 years)
- Sex (Male, Female, Unknown, Undifferentiated)
- Race (White, Black, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Total subjects recruited under each country (Total recruited, Recruited in Canada, Recruited in the US)

Baseline characteristic variables include:

- Height (cm)
- Weight (kg)
- BMI (kg/m^2) [= *weight (kg)/height (m)^2 from screening visit 1*]
  - BMI categories (< 20, 20 to < 25, 25 to 30, ≥ 30 kg/m^2)
- Smoking history (Former, Current, Never)
- Heart rate (beats per minute)
- Bundle branch block (or Intraventricular conduction delay [IVCD]) present (No, Yes)
  - Bundle branch block type (Left bundle branch block, Right bundle branch block, Non-specific IVCD)
- NT-proBNP (pg/mL) values based on clinical laboratory samples processed and assessed by the central laboratory
  - NT-proBNP quartiles and IQR
  - Log-transform of NT-proBNP
- BNP (pg/mL) (screening visit 1 only), based on clinical laboratory samples processed and assessed by the local laboratory
  - BNP quartiles and IQR
  - Log-transform of BNP
- NT-proBNP (pg/mL) (screening visit 1 only), based on clinical laboratory samples processed and assessed by the local laboratory

- NT-proBNP quartiles and IQR
- Log-transform of NT-proBNP

2.3.4.2 Disease characteristics

Disease characteristic variables include:

- Category of prior cardiovascular (CV) medication:
  (Diuretic class (Loop diuretic, Thiazide diuretic)), Mineralocorticoid receptor antagonist (MRA), ACEi, ARB, Digoxin, Beta blocker, Calcium channel blocker (CCB), Long-acting nitrate, Anticoagulant class (Warfarin, Direct-acting oral anticoagulants (DOACs)), Aspirin, Statin, Non-statin lipid lowering therapy, Antiplatelet (excluding aspirin), Adenosine diphosphate (ADP) antagonist), SGLT2 inhibitors with relevant Anatomical Therapeutic Chemical (ATC) drug class codes.
- ACEi/ARB naïve (never exposed); Previously on ACEi/ARB but not currently taking (previously exposed); Currently taking (up until randomization).
- Primary HF etiology: Ischemic; Non-ischemic
  - Hypertensive (No, Yes)
  - Diabetic (No, Yes)
  - Alcoholic (No, Yes)
  - Viral cardiomyopathy (No, Yes)
  - Infectious cardiomyopathy (No, Yes)
  - Peripartum (No, Yes)
  - Drug induced (No, Yes)
  - Other (No, Yes)
- History of HF prior to qualifying HF event (No, Yes, Unknown)
- Number of hospitalizations with primary diagnosis of HF within past 12 months not including qualifying hospitalization
  - Number of hospitalizations categories (0, 1, 2, ≥ 3, Not Applicable)
- Total number of hospitalizations for any reason within past 12 months
- NYHA classification approximately 1 month prior to admission of the trial (I, II, III, IV, Unknown)
- Most recent left ventricular ejection fraction (LVEF) (%)
- Left ventricular ejection fraction (LVEF) categories prior to randomization:
  - > 40 to < 45% vs. ≥ 45%;
  - > 40 to < 50% ((HFmrEF (mildly reduced)), ≥ 50% ((HFpEF) preserved)
  - ≥ 50 to ≤ 60% vs. >60*
  - >40 to ≤60 vs. > 60*
  - ≤ median vs. > median)
- Left atrial enlargement defined by at least one of the following:
  - LA width ≥3.8 cm
  - LA length ≥5.0 cm

  - LA area ≥20 Square Centimeter
  - LA volume ≥ 55 mL 28
  - LA volume index ≥ 29 Milliliters per Square Meter
- Left ventricular hypertrophy (Septal thickness or posterior wall thickness ≥1.1 cm,
- Time from hospital presentation to randomization (days)
- Any prior EF < 40% (LVEF < 40%) (No, Yes, Unknown)
- Presence of structural heart disease (No, Yes, Unknown)

* LVEF of >60% is defined as normal; LVEF <= 60% is defined as "below normal"

2.3.4.3 Cardiovascular history

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

- Hypertension (No, Yes, Unknown)
- Transient ischemic attack (No, Yes, Unknown)
- Stroke (No, Yes, Unknown)
- Peripheral vascular disease (No, Yes, Unknown)
- Chronic renal insufficiency (CRI) [eGFR <60 ml/min/1.73m^2 prior to qualifying hospitalization or WHF event] (No, Yes, Unknown)
- Chronic kidney disease (CKD) stage (CKD Stage 3 [eGFR 30 to 59], CKD Stage 4 [eGFR 15 to 29], CKD Stage 5 [eGFR < 15 or dialysis] and Other
- CKD defined as either CRI=yes or CKD stages (3 or 4 or 5) =yes. (No, Yes, Unknown)
- eGFR categories prior to randomization
  - < 60 ml/min/1.73m^2
  - ≥ 60 ml/min/1.73m2
- Arrhythmia (No, Yes, Unknown)
  - Arrhythmia type (AF, Atrial flutter, Supraventricular tachycardia, Ventricular tachycardia)
- Pacemaker/Implantable cardioverter defibrillator (ICD) (No, Yes, Unknown)
  - Device type (Pacemaker [conventional], Cardiac resynchronization therapy – no ICD [CRT-P], Cardiac resynchronization therapy – with ICD [CRT-D], ICD only [single/dual], Other, Unknown)
- Moderate to severe valvular heart disease (No, Yes, Unknown)
  - Heart disease type (Mitral regurgitation, Aortic regurgitation, Aortic stenosis, Tricuspid regurgitation)
- Prior valvular heart surgery (No, Yes, Unknown)
  - Valvular surgery type (Mitral, Aortic, Tricuspid, Pulmonic)

2.3.4.4 Non-Cardiovascular Medical History

Non-cardiovascular medical history and ongoing conditions will be summarized and listed. The summaries will be presented by primary system organ class (SOC), preferred term (PT) and treatment group for both double-blind and open-label subjects. Incidence of SARS-CoV-2 (COVID-19) infection in the subjects' medical history will be included in the non-cardiovascular medical history summaries and listings. Non-cardiovascular medical history and ongoing conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology (latest version at the time of data cut-off will be used).

2.3.4.5 Surgeries and Medical Procedures

Surgeries and medical procedures will be listed, including the reason, start date and end date. Surgeries and medical procedures will be coded using MedDRA terminology (latest version at the time of DBL will be used).

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

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

2.4.1 Study treatment / compliance

The duration of study treatment is defined as:

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

The first date of study treatment is recorded on the First Dose of Study Treatment eCRF.

Summary statistics will be displayed for the duration of study treatment by treatment group and in-hospital/out-of-hospital randomization category using mean, SD, median, minimum, and maximum. Additionally, the number and percentage of participants will be summarized by treatment group and in-hospital/out-of-hospital randomization for duration category.

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

Total subject-days of exposure will also be summarized.

In addition, the number and percentages of each dose level dispensed by visit will be summarized by treatment group. The number and percentage of the maximum dose levels dispensed will also be presented by treatment group. Similarly, the up-titrated doses, down-titrated doses and unchanged doses will be summarized by visit and treatment group. The number and percentage of subjects who were dispensed Dose Level 3 by Week 6 will be summarized by treatment group.

All information on dose administration will be listed.

The duration of exposure by pandemic impact may also be summarized.

2.4.2 Prior, concomitant and post therapies

2.4.2.1 Prior and concomitant medications definition

Prior and concomitant medications will be coded according to the World Health Organization (WHO) Drug Reference List (latest version at the time of data cut-off will be used). Prior and concomitant medications are mutually exclusive, as defined below:

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

The number and percentage of subjects with concomitant medications that started after study treatment will be summarized by ATC class, PT and study phase (refer to Section 2.1.1 for study phase definitions). All medications will be listed. Concomitant medications and significant non-drug therapies, prior to and after the randomization, will be summarized by therapeutic class, PT, treatment group, and in-hospital/out-of-hospital randomization category. The SAF population will be used for the above analyses.

2.4.2.2 Medications of interest

The following medication classes of interest will be summarized by treatment group and in-hospital/out-of-hospital randomization status at Baseline:

- Previous use of medication, n(%)
- Any Diuretic agent

a) Diuretics prior to index (qualifying event)

b) Loop diuretics

- ACEi or ARB
- MRA
- BB
- SGLT2i

Medication names will be coded using the WHO Drug Reference List (latest version at the time of Database Lock will be used).

2.4.2.3 COVID-19 vaccination status

COVID-19 vaccination status will be summarized by treatment group and by study phase. The descriptive summary will present the number and percentage of subjects who are fully vaccinated, partially vaccinated (received 1 out of 2 doses of vaccine, where applicable). Booster doses will not be included as an indication of full vaccination status, however will be recorded and provided.

Total number of COVID-19 vaccine doses (No vaccine, 1, 2, 3, 4 and 5 (if applicable)) will also be reported along with a complete. Listing for COVID-19 vaccination status.

The SAF population will be used for the above analysis.

2.4.3 Unscheduled visit mapping

When visit mapping are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the Week 4 visit of a subject is delayed and occurs on Day 46 instead of on Day 29, say, it will be re-aligned to visit window Week 8. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below in Section 2.4.4.

An unscheduled visit will be mapped according to the following visit windows:

For subjects recruited under Original protocol (00) to Amendment 01-03:

Visit Name	Visit Number	Target Day (Study Days)	Visit Window (Study Days)
Week 1	Visit 3	7	2 to 10
Week 2	Visit 4	14	11 to 21
Week 4	Visit 5	28	22 to 35
Week 6	Visit 6	42	36 to 49
Week 8	Visit 7	56	50 to 63
Week 10	Visit 8	70	64 to 77
Week 12	Visit 9	84	78 to 98
Week 16	Visit 10	112	99 to 140
Week 24	Visit 11	168	141 to 196
Week 32	Visit 12	224	197 to 252
Week 40	Visit 13	280	253 to 308
Week 48	Visit 14	336	309 to 364
Week 56	Visit 15	392	365 to 434
Week 68	Visit 16	476	435 to 532
Week 84	Visit 17	588	>532;

Visit Schedule to be followed for subjects recruited under protocol Amendment 04:

Visit Name	Visit Number	Target Day (Study Days)	Visit Window (Study Days)
Week 1	Visit 3	7	2 to 17
Week 4	Visit 5	28	18 to 42
Week 8	Visit 7	56	43 to 112
Week 24	Visit 11	168	113 to 224
Week 40	Visit 13	280	225 to 336
Week 56	Visit 15	392	337 to 434
Week 68	Visit 16	476	435 to 532
Week 84	Visit 17	588	>532

2.4.4 Multiple assessments within visit windows

When there are *multiple assessments* in a particular visit window, the following rules are applied to select one value "representing" the subject in summary statistics in a visit window.

In cases where there are multiple assessments in the Screening period, the value closest to the baseline will be considered for the analysis.

For baseline assessment definition see Section 2.1.1. For post-baseline visit windows with multiple assessments, the following applies (unless otherwise specified):

1. for *quantitative variables*, the *closest* to the actual visit is chosen (if two assessments have the same distance, then the earlier one will be chosen);
2. for *qualitative variables*, the *worst* record is selected. It is noted that in the analyses performed, worst case is always well defined.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary endpoint is the comparison of the time-averaged proportional change from Baseline in NT-proBNP between sacubitril/valsartan and valsartan to Week 4 and 8.

Primary analysis timepoint will be the change from Baseline to averages of Week 4 and 8.

The analysis of the primary endpoint will be based on the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary analysis to address the primary objective will be based on the following estimand:

Estimand 1

Population: Defined through the appropriate inclusion/exclusion criteria to reflect the targeted study population currently hospitalized for or within 30 days of a WHF event (HFpEF decompensation). A WHF event (HFpEF decompensation) is defined as a hospitalization, emergency department (ED) visit or out-of-hospital urgent HF visit, all requiring IV diuretics.

Endpoint: Time-averaged proportional change between Baseline and weeks 4 and 8 in NT-proBNP

Treatment: The randomized treatment sacubitril/valsartan or valsartan

Intercurrent event: Using a treatment policy strategy to handle the intercurrent event of treatment discontinuation.

Summary measure: Difference between treatment in ratios of geometric means

The primary null hypothesis to be tested is the ratio of the geometric means of NT-proBNP (average of Weeks 4 and 8 divided by Baseline) for the sacubitril/valsartan and valsartan treatment groups are equal (H_{10}) versus the alternative hypothesis that the ratio of the geometric means of NT-proBNP are not equal (H_{1a}).
For NT-proBNP, the time-averaged proportional change from Baseline in a natural logarithmic scale will be analyzed using an ANCOVA model using data from Weeks 4 and 8 with treatment,

in-hospital/out-of-hospital randomization status, gender, and Baseline LVEF (≤ Median, > Median) as fixed effect factors, age and the logarithmic Baseline NT-proBNP as covariates.

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

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

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

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

exp(LS mean)

The FAS will be used for the primary endpoint analysis.

2.5.3 Handling of missing values/censoring/discontinuations

The analysis will be performed based on all available data in the FAS. Missing values caused due to unevaluable samples or early discontinuations will not be imputed.

Also, NT-proBNP from unscheduled visits will not be used for the analysis.

2.5.4 Sensitivity analyses 1

Robustness of the primary efficacy results will be explored by multiple imputation assuming MAR i.e., missing at random algorithm to impute missing values in the primary analysis, except the Baseline value. Baseline value will not be imputed.

To investigate the sensitivity of the analysis results based on the MAR assumption, we will perform an analysis using a pattern mixture model approach which assumes, besides the imputation with 0 for the NT-proBNP values after death. This sensitivity analysis would first create multiple (100) imputations of missing NT-proBNP values under a MAR assumption, resulting in multiple (100) complete data sets. The imputation model assumes a multivariate normal model for the 3 NT-proBNP measurements at baseline, Week 4 and Week 8. To the resulting 100 datasets, the original analysis model described above will be fitted, yielding 100 sets of parameter estimates and associated covariance matrices. These are then combined by using Rubin's rules to derive overall estimates, and confidence intervals that adequately reflect missing data uncertainty as well as associated p-values.

The sensitivity analysis to address the primary objective will be based on the same primary estimand.

2.5.5 Sensitivity analyses 2

A second sensitivity analysis will be performed based on the subjects recruited under Amendment 1 to Amendment 4 protocol versions. The analysis will be performed like the main analysis of the primary endpoint.

The sensitivity analysis to address the primary objective will be based on the same primary estimand.

The analysis will be performed based on all available data in the FAS. Missing values caused due to unevaluable samples or early discontinuations will not be imputed.

2.5.6 Sensitivity analyses 3

A third sensitivity analysis will be performed by excluding assessments after COVID-19 positive status at the subject level. The analysis will be performed similar to the main analysis of the primary endpoint.

The sensitivity analysis to address the primary objective will be based on the same primary estimand.

The analysis will be performed based on all available data in the FAS. Missing values caused due to unevaluable samples or early discontinuations will not be imputed.

2.5.7 Sensitivity analyses 4

A fourth sensitivity analysis will be performed on all the subjects randomized in the study with and without the prespecified enrollment windows specified in the respective protocol (00, 1-4). The analysis will be performed similar to the main analysis of the primary endpoint.

The sensitivity analysis to address the primary objective will be based on the same primary estimand.

The analysis will be performed on 2 sub populations:

1. Outside enrollment window : This will consist of all subjects randomized in the study who did not meet the inclusion criteria #3, for the respective pre-specified protocol enrollment window (protocol versions, 00, 1 – 4). No statistical analysis will be performed if the total number of subjects are less than 5 for this subgroup.
2. Within enrollment window : This will consist of the total FAS population excluding the subjects enrolled outside enrollment window.

The analysis will be performed based on all available data in the FAS. Missing values caused due to unevaluable samples or early discontinuations will not be imputed.

2.5.8 Supplemental analysis

In this supplementary analysis the variables to be analyzed are: Achieving a pre-specified percent change from Baseline in NT-proBNP (binary). Three binary outcome variables will be created for subjects achieving a 25%, 50% and 75% decline in NT-proBNP (0-no, 1-yes). The dataset used in the primary analysis will be used to define these categorical variables using the NT-proBNP. Logistic regression model will be fitted. The odds ratio, CI and p-value will be provided for each analysis. The dependent variable will be achieving a target decline in NT-proBNP and the predictor of response will be treatment group and in-hospital/out-of-hospital randomization status.

In addition, an analysis of the primary endpoint will be performed with subjects randomized to Amendment 4 (yes, no) as an additional factor to the model mentioned in Section 2.5.2.

The supplemental analysis will be based on the following estimand.

Estimand

Population: Defined through the appropriate inclusion/exclusion criteria to reflect the targeted study population currently hospitalized for or within 30 days of a WHF event (HFpEF decompensation). A WHF event (HFpEF decompensation) is defined as a hospitalization, ED visit or out-of-hospital urgent HF visit, all requiring IV diuretics.

Endpoint: Dichotomized (25%, 50% and 75% reduction) change from Baseline in NT-proBNP from Weeks 4 and 8

Treatment: The randomized treatment sacubitril/valsartan or valsartan

Intercurrent event: Using a treatment policy strategy to handle the intercurrent event of treatment discontinuation.

Summary measure: Difference between treatment in odds ratio

The values from Weeks 4 and 8 will be averaged and the change from Baseline in NT-proBNP will be calculated and the reductions categorized.

The analysis will be performed based on all available data in the FAS. Missing values caused due to unevaluable samples or early discontinuations will not be imputed.

2.5.9 Subgroup analyses

All subgroups as defined in Section 2.2.1 will be analyzed for the primary endpoint.

The subgroup analysis will be based on the same primary estimand.

- The analyses will be performed like the main analysis of the primary endpoint with the addition of an interaction term for the subgroup and treatment.

An interaction p-value will be generated from a likelihood ratio test comparing the interaction model to the model without the interaction.

- Forest plots will be produced including interaction p-values for treatment by subgroup interactions.

2.6 Analysis of secondary objectives

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

2.6.1 Secondary endpoints

Secondary endpoints include the following:

1. The composite hierarchical outcome consisting of a) time to CV death, b) number and times of HF hospitalizations during follow-up, c) number and times of urgent HF visits during follow-up, and d) time-averaged proportional change in NT-proBNP (from Baseline to Weeks 4 and 8)

2. The cumulative number of recurrent composite events overtime, ie, the total number of composite events of HF hospitalizations, urgent HF visits, and CV death.
3. Incidences of a composite endpoint of worsening renal function defined as:
   - renal death
   - reaching end-stage renal disease (ESRD)
   - ≥ 50% decline in estimated glomerular filtration rate (eGFR) relative to baseline
4. Proportional change in NT-proBNP from Baseline to Week 8
5. Proportional change in hs-Troponin (high sensitivity) from Baseline to Weeks 4 and 8
6. Dosing levels and discontinuations
7. Incidence of adverse events of special interest during treatment
   - Incidence of symptomatic hypotension
   - Incidence of hyperkalemia (potassium > 5.5 mEq/L)
   - Incidence of angioedema
   - Incidence of worsening renal function, defined as an increase in serum creatinine of ≥0.5mg/dl and worsening of the eGFR by at least 25% (based on central laboratory data).

All these secondary endpoints will be analyzed using FAS and nominal p-values will be reported. There will be no adjustment for multiplicity.

2.6.1.1 Adjudication of Events

Among the secondary variables above, some of them or their components need to be adjudicated to confirm the reported types and occurrences based on a unified criteria for analyses. The adjudication of these events is based on an adjudication process through an independent Endpoint Adjudication Committee (EAC). The role of the EAC is to ensure that all clinical outcomes are judged uniformly, using standard criteria and processes. Specific details regarding endpoint definitions can be found in the adjudication charter (ref CEC Charter, final version 16 July 2021).

All deaths, (re-)hospitalizations, and urgent HF visits will be adjudicated. The following events will be assessed by the EAC during the study:

- DEATH;
  - Cardiovascular Death
    - Fatal Myocardial Infarction (MI)
    - Heart Failure Death
    - Sudden Death
    - Presumed Sudden Death

- Presumed Cardiovascular Death
- Fatal Stroke
- Fatal Pulmonary Embolism
- Cardiovascular Procedure-Related Death
- Other Cardiovascular Death

  - Non-Cardiovascular Death
  - Undetermined Cause of Death

- HOSPITALIZATIONS:
  - Cardiovascular (CV) hospitalization
    - Hospitalization for Heart Failure
    - Possible Hospitalization for Heart Failure
    - Cardiovascular Hospitalization for a reason other than Heart Failure
    - Cardiovascular Hospitalization that cannot be further classified
  - Non-Cardiovascular (non-CV) Hospitalization
  - Undetermined Cause of Hospitalization
- URGENT HEART FAILURE VISITS

Urgent Heart Failure visits as defined in EAC charter :

Urgent, unscheduled office/practice or emergency department visit for heart failure management not requiring overnight hospitalization and associated with all of the following:

1. New or worsening signs and symptoms of heart failure, defined by the same criteria as for the heart failure hospitalization end point above and
2. Intravenous therapy directed at heart failure management

2.6.2 Statistical hypothesis, model, and method of analysis

2.6.2.1 Analysis of secondary endpoint 1

The composite hierarchical outcome consisting of below 4 variables

a) time to CV death (Adjudicated by EAC),

b) number and times of HF hospitalizations during follow-up (Adjudicated by EAC - only the confirmed events will be considered, i.e. HF hospitalizations meeting PARAGLIDE-HF criteria),

c) number and times of urgent HF visits during follow-up (Adjudicated by EAC), and

d) time-averaged proportional change in NT-proBNP (from baseline to Weeks 4 and 8)

This secondary efficacy endpoint of the composite hierarchical outcome will be analyzed estimating the unmatched win ratio by comparing every participant in the sacubitril/valsartan arm to every participant in the valsartan arm to determine a winner (unmatched pairing method). The estimated win ratio (the total number of wins in the sacubitril/valsartan arm divided by the total number of wins in the valsartan arm) will be calculated. The corresponding null and alternative hypotheses are:

H_{20}: Win ratio is equal to 1, verses

H_{2a}: Win ratio is not equal to 1.

A win ratio greater than 1 will be in favor of sacubitril/valsartan arm. The testing of hypothesis H_{20} and calculation of the corresponding two-sided 95% CIs will be performed.

A component will only be used as tie-breaker in the pairwise comparison between two subjects if the comparison of components with a higher priority resulted in a tie. For component a) the subject with the later time to CV death is the winner. For component, b) the subject with the smaller number of HF hospitalizations in time at risk that is common for both subjects (for definition see Section 2.6.2.1.1) is the winner. If the number of HF hospitalizations in the time at risk is common for both subjects it is tied, the subject with the later time of the last HF hospitalization is the winner. For component c) the same algorithm is applied as for component b). For component d), the subject with the larger decrease or smaller increase in the proportional change is considered a winner; if the ratio of the proportional changes from two subjects is between 0.75 and 1/0.75, then the pairwise comparison of the change in NT-proBNP is considered tied. This proportional change is equivalent to ± 0.2876 on the natural log scale ln(0.75) and ln(1/0.75).

The analysis will be performed using the unmatched pair win ratio approach. Contributions of each component of the composite endpoint to the total number of winners used in the estimation of the win ratio will be reported. More details on win ratio approach are in Section 5.4.2

2.6.2.1.1 Handling of missing values/censoring/discontinuations

For the calculation of the win-ratio an initial time “at risk” (follow-up) for each subject will be calculated as number of days from treatment start date to their attained:

- Date of last visit (End of Study visit)
- Date of death from any cause
- Date of withdrawal of informed consent
- Date of loss to follow up

CV death events

In the case of CV death in one or both subjects the following censoring rules will be applied:

- If a CV death occurs in both subjects then all time at risk will be considered and the subject with the latest time to CV death will be considered the winner
- If a CV death occurs in one subject and it occurs before the second subject time at risk is censored then the subject who does not experience the CV death will be considered the winner

- If a CV death occurs in one subject and it occurs after the second subject time at risk is censored then the pair will be considered a tie

Note: for this event deaths from non-CV causes will be censored.

HF hospitalization events and urgent HF visits

For these events only those that occur in the time at risk that is common for both subjects in the pair will be used for analysis to define win or tie. For example, if subject 1 of a pair has 145 days at risk and subject 2 has 126 days only events that occur days 1-126 are considered.

Time-averaged proportional change in NT-proBNP (from baseline to Weeks 4 and 8)

If the NT-proBNP value is missing for one or both subjects in the pair then the pairwise comparison of the change in NT-proBNP is considered tied.

2.6.2.1.2 Sensitivity Analysis*:*

Three sensitivity analyses are planned for secondary endpoint 1.

- The primary analysis of the win ratio will be repeated but will also include HF hospitalizations that are adjudicated as Possible HF Hospitalization (i.e. are insufficient data to meet PARAGLIDE-HF criteria) in addition to confirmed HF hospitalizations.
- The primary analysis of the win ratio will be repeated but data for CV death, HF hospitalizations and urgent HF visits will be based on investigator reporting and not adjudicated data.
- The primary analysis of the win ratio will be repeated but data that occurs after diagnosis as COVID-19 positive will be censored at the subject level.

2.6.2.2 Analysis of secondary endpoint 2

The cumulative number of recurrent composite events over time, i.e., the total number of composite events of

a) CV death (Adjudicated by EAC),

b) HF hospitalizations (Adjudicated by EAC - only the confirmed events will be considered, i.e. HF hospitalizations meeting PARAGLIDE-HF criteria),

c) Urgent HF visits (Adjudicated by EAC),

The FAS will be used in the main analysis of the secondary endpoint 2.

The cumulative number of composite events, ie, the total number of composite events of CV death, recurrent HF hospitalizations, and recurrent urgent HF visits for a subject over time will be calculated. The time to these recurrent events will be analyzed using the semi-parametric proportional rates model (abbreviated as LWYY model)(Lin 2000). The hypotheses of interest are:

H_{30}: Rate ratio of sacubitril/valsartan arm over valsartan arm equal to 1, versus

H_{3a}: Rate ratio of sacubitril/valsartan arm over valsartan arm not equal 1.

A rate ratio < 1 indicates an effect in favor of sacubitril/valsartan arm.

The hypothesis (H_{30}) will be tested, and 95% CIs will be provided. The rate ratio will be estimated from the above proportional rates model with treatment and in-hospital/out-of-hospital randomization as fixed factors through maximization of a partial likelihood score function. The CIs will be based on the robust estimate of the standard errors. The number and percentage of CV events by event type will be summarized.

Censoring Variables:

The CV death will not be considered a censoring variable, but a composite endpoint event and a conditional factor in this analysis. Time to non-CV death will be considered as a censoring variable. Any censoring due to non-CV death is assumed to be non-dependent in the analysis.

2.6.2.2.1 Sensitivity Analysis*:*

Four sensitivity analyses are planned for secondary endpoint 2.

- The primary analysis of the LWYY model will be repeated but will also include HF hospitalizations that are adjudicated as Possible HF Hospitalization (i.e. are insufficient data to meet PARAGLIDE-HF criteria) in addition to confirmed HF hospitalizations meeting PARAGLIDE-HF criteria
- The primary analysis of the LWYY model will be repeated but data for CV death, HF hospitalizations and urgent HF visits will be based on investigator reporting and not adjudicated data.
- The primary analysis of the Secondary endpoint 2 will be repeated with Kaplan-Meier estimates for time to the first composite event by the treatment group, in tables and graphs.
- The primary analysis of the LWYY model will be repeated but data that occurs after diagnosis with COVID-19 positive will be censored at the subject level.

2.6.2.3 Analysis of secondary endpoint 3

Incidences of a composite endpoint of worsening renal function are defined as:

- renal death (from AE data)
- reaching end-stage renal disease (ESRD) (Sustained eGFR <15mL/min/m2, chronic dialysis, or renal transplant)
- ≥ 50% decline in estimated glomerular filtration rate (eGFR) relative to baseline [using central laboratory measurements (scheduled or unscheduled visits)]

Among the variables above, none of their components will be adjudicated. The Investigator-reported AE and central laboratory data will be used to identified event of interest in this secondary endpoint 3.

ESRD is defined as one of the following:

- Initiation of dialysis (e.g., hemodialysis, peritoneal dialysis, or continuous eno-venous hemodialysis) after randomization (post-baseline). [from the procedure (PR) data]

- A drop in eGFR from baseline (randomization, i.e. Visit 2) to a value <15 mL/min/1.73m^2 on two consecutive central laboratory measurements [scheduled or unscheduled visits] separated by ≥ 30 days. This event will be identified programmatically by the programming team.

- Occurrence of kidney transplantation. [from the procedure (PR) data]

The main analysis of the total number of composite events will be performed using a negative binomial regression model with the count data as the dependent variable. Treatment group and in-hospital/out-of-hospital randomization as fixed-effect factors and log (follow-up duration) as the off-set. The model will be used to estimate event rates and their 95% CIs by treatment group.

2.6.2.3.1 Sensitivity Analysis:

Three sensitivity analyses are planned for secondary endpoint

- The time to the first composite event will be analyzed using Cox's proportional hazard model with factors treatment and in-hospital/out-of-hospital randomization. Hazard ratio for treatment and its 95% CIs will be reported.
- The Kaplan-Meier estimates for time to the first composite events will be provided by the treatment group, in tables and graphs.
- The primary analysis of secondary endpoint 3 will be repeated but data that occurs after diagnosis as COVID-19 positive will be censored at the subject level.

2.6.2.4 Analysis of secondary endpoint 4

The proportional change in NT-proBNP from Baseline to Week 8 will be analyzed using an ANCOVA model similar to the primary efficacy analysis.

- The primary analysis of secondary endpoint 4 will be repeated but data tha occurs after diagnosis as COVID-19 positive will be censored at the subject level.

2.6.2.5 Analysis of secondary endpoint 5

The proportional change in high-sensitivity Troponin (hs-Troponin) from Baseline to Week 4 will be analyzed using an ANCOVA model similar to that of the primary efficacy analysis. Log transformed hs-Troponin will be used for analysis. The analysis will be repeated for Week 8.

- The primary analysis of secondary endpoint 4 will be repeated but data that occurs after diagnosis as COVID-19 positive will be censored at the subject level.

2.6.2.6 Analysis of secondary endpoint 6

The dosing level will be summarized by treatment group and in-hospital/out-of hospital randomization status.

Incidence of discontinuations (all causes) will be summarized by treatment group and in-hospital/out-of-hospital randomization status.

- The primary analysis of secondary endpoint 6 will be repeated but data tha occurs after diagnosis as COVID-19 positive will be censored at the subject level.

2.6.2.7 Analysis of secondary endpoint 7

Incidence of below adverse events of special interest (AESI) during treatment will be considered.

- Incidence of symptomatic hypotension (Collected in AESI CRF)
- Incidence of hyperkalemia (potassium >5.5 mEq/L) (Collected in AESI CRF)
- Incidence of angioedema (Collected in AESI CRF)
- Incidence of worsening renal function, defined as an increase in serum creatinine of ≥0.5mg/dl and worsening of the eGFR by at least 25% [using Central Lab data from same scheduled or unscheduled visits]

Incidence of adverse events of special interest (AESIs) will be analyzed using a logistic regression model with treatment and in-hospital/out-of-hospital randomization as fixed factors. The model will be used to estimate the odds ratio for treatment and its 95% CIs.

- The number (and proportion) of subjects with AESI will be summarized by treatment.
- The primary analysis of secondary endpoint 7 will be repeated but data that occurs after diagnosis as COVID-19 positive will be censored at the subject level.

2.6.3 Handling of missing values/censoring/discontinuations

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

2.7 Safety analyses

For all safety analyses, the SAF will be used. All listings and tables will be presented by treatment group and in-hospital/out-of-hospital randomization category.

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 (eg, change from Baseline summaries). In addition, a separate listing for death including on-treatment and post treatment deaths will be provided. In particular, summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs (TEAEs)). The on-treatment period lasts from the date of first administration of study treatment to the last study visit.

2.7.1 Adverse events

2.7.1.1 Coding of adverse events

Adverse events will be coded using the latest version of MedDRA terminology at the time of DBL.

2.7.1.2 General rules for AE reporting

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

The number (and percentage) of subjects with TEAEs (events started after the first dose of study medication, or events present prior to start of double-masked treatment but increased in severity based on PT) will be summarized in the following ways:

- By treatment, primary SOC and PT.
- By treatment, primary SOC, PT and maximum severity.
- By treatment, pre-defined topic of interest, primary SOC and PT.

Separate summaries will be provided for study medication-related AEs, serious adverse events (SAEs), and other significant AEs leading to discontinuation.

A subject with multiple adverse events within a primary SOC is only counted once towards the total of the primary SOC.

2.7.1.3 Treatment-emergent adverse events

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

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

TEAEs will be summarized by presenting the number and percentage of subjects having at least 1 TEAE, having at least 1 TEAE in each primary SOC, and for each PT using MedDRA coding.

A subject with multiple occurrences of a TEAE will be counted only once in the AE category.

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

Any information collected will be listed as appropriate.

2.7.1.4 Adverse event summaries

The following summary tables will be provided:

- AEs, regardless of study treatment relationship, by primary SOC, PT and maximum severity
- Most frequent (≥5%) AEs, regardless of study treatment relationship, by PT
- AEs, related to study treatment reported by investigator , by primary SOC and PT
- SAEs, regardless of study treatment relationship, by primary SOC and PT
- SAEs, related to study treatment reported by investigator, by primary SOC and PT
- SAEs occurring with a frequency of ≥0.5%, regardless of study treatment relationship, by PT
- SAEs, regardless of study treatment relationship, by primary SOC, PT, and seriousness criteria
- AEs leading to discontinuation, regardless of study treatment relationship, by primary SOC and PT

- AEs requiring dose adjustment or study treatment interruption, regardless of study treatment relationship, by primary SOC and PT
- AEs requiring additional therapy, regardless of study treatment relationship, by primary SOC and PT
- Death resulting from AEs, regardless of the study treatment relationship, by primary SOC and PT

2.7.1.5 Adverse events of special interest / grouping of AEs

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

In addition, suspected or confirmed SARS-CoV-2 infections will be listed.

Additionally, a sensitivity analysis will be performed on the AESIs for subjects randomized to sacubitril/valsartan. The number and percentages of AESIs occurring prior to the active dose of sacubitril/valsartan will be presented along with the number and percentages of AEs of special interest occurring on or after the active dose of sacubitril/valsartan during the study. The following definitions will be used:

Angioedema:

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

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

Symptomatic hypotension:

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

AE after active study treatment = event ≤ Last dose date of medication

Elevated creatinine:

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

AE after active study treatment = event ≤ Last dose date:time of medication

Hyperkalemia:

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

AE after active study treatment = event ≤ Last dose date:time of medication

2.7.1.6 Exposure Adjusted Adverse Events

The following Exposure adjusted incidence rate of adverse events will be presented by study phase and treatment group:

- Exposure-adjusted incidence rate of adverse events by preferred term

- Exposure-adjusted incidence rate of study treatment related adverse events by primary system organ class and preferred term
- Exposure-adjusted incidence rate of adverse events leading to permanent study treatment discontinuation by primary system organ class and preferred term
- Exposure-adjusted incidence rate of serious adverse events by primary system organ class and preferred term
- Exposure-adjusted incidence rate of deaths by primary system organ class and preferred term

The exposure adjusted incidence rate (IR) will be derived by the number of subjects with an event divided by the corresponding sum of the exposure duration for all subjects, where duration of exposure in Subject Treatment Years (STY) is counted up to the first qualifying event (or end of time at risk for subjects without event).

Incidence rate will be set to the 100 STY and only on treatment events (TEAE) will be included.

2.7.2 Deaths (EAC Adjudicated)

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

- A KM curve will be presented for all-cause deaths.

2.7.3 Laboratory data

All laboratory data will be listed by treatment group, in-hospital/out-of-hospital randomization, subject, and visit/time and if normal ranges are available abnormalities will be flagged.

Shift tables using the low/normal/high/ classification will be used to compare Baseline to the worst post Baseline value. The number and percentage of subjects with laboratory values will be presented by low/normal/high (low and high) classifications to compare Baseline to worst post Baseline value.

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

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

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

2.7.3.1 Laboratory Assessments

Hematology
Hemoglobin, hematocrit, red blood cell (RBS) count, white blood cell (WBC) count with differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other (absolute value preferred , %s are acceptable), and platelet count will be measured at Visits 1, 2, 7, 11, 13, 15, and 17 (central lab). Hemoglobin A1c will be measured at Visit 2 and 17 (central lab).

Chemistry
Assessments required for eligibility that need to be measured at Visit 1 include creatinine, potassium, and total bilirubin. Blood urea nitrogen (BUN), glucose, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), alkaline phosphatase, sodium, potassium, chloride, calcium , total protein, albumin, uric acid, and lipid profile be measured at Visits 1 (local lab), 2, 3, 5, 7, 9, 11, 13, 15, 16 and 17 (central lab).

Urinalysis
Dipstick-test determination of specific gravity, pH, blood, total protein, bilirubin, ketones, and leukocytes will be measured at Visit 2 (central lab). If dipstick is positive, a qualitative microscopic determination, including WBCs high power field and RBCs high power field will be performed.

Pregnancy Test
All female subjects of childbearing potential will have a serum pregnancy test (hCG) performed at Visit 1 (local lab). In addition, these subjects will have a urine pregnancy test conducted in the local laboratory at Visits 2, 5, 7, 11, 13, 15, 16, and 17. If any of these tests are positive at Visits 1 and 2, the subject should not be enrolled in the trial. If a subject should become pregnant during the trial, the subject may remain in the trial for follow-up visits but must discontinue study drug.

2.7.4 Other safety data

2.7.4.1 Electrocardiogram and cardiac imaging data

A standard 12 lead ECG will be performed by Visit 1. ECG data will be collected at Visit 1 will also be listed along with the summary statistics.

2.7.4.2 Vital signs

All vital signs (SBP and diastolic blood pressure (DBP) (mmHg), pulse rate (sitting/beats per minute), weight (kg), height (cm), BMI (kg/m^2) and waist/hip circumference) will be descriptively summarized at each visit by treatment group. Change from Baseline will also be presented, excluding height and waist/hip circumference.

A separate summary table will be presented with the number and percentages of subjects having notable vital signs based on changes relative to Baseline values (see Section 2.1.1 for study phase definitions and Section 5.3.3 for the list of notable vital signs).

The number and percentages of subjects having symptomatic hypotension will also be summarized. The following variables associated with symptomatic hypotension will also be presented: symptoms occurring while standing, any treatment or medication change as a result of episode, lowest documented SBP, SBP position, lowest documented DBP and DBP position. A listing for symptomatic hypotension will also be presented.

2.7.4.3 Heart Failure Event

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

- Type of event (HF hospitalization [hospital stay ≥24 hours], HF ED visit, Urgent/unplanned HF office visit, Worsening HF during the index hospitalization [qualifying HF event], None of the aforementioned types occurred with, or apply to, this HF event)
- Symptoms of worsening HF (Dyspnea – [Dyspnea at rest, Dyspnea on exertion, Orthopnea, Paroxysmal nocturnal dyspnea, Tachypnea], Decreased exercise tolerance [reduced ability to perform activities that induce physical exertion due to dyspnea or fatigue], Fatigue [lack of energy, extreme tiredness, inability to complete usual activities], Worsening end-organ perfusion – [Confusion (thought to be from low cardiac output), Reduced urine output], Symptoms of volume overload – [Lower extremity swelling, Increased abdominal distension)], Other)
- Physical exam signs of worsening HF (Peripheral edema, Increased abdominal distension or ascites [in the absence of hepatic disease], Pulmonary rales/crackles, Elevated jugular venous pressure and/or hepatojugular reflux, New or worsening 3rd heart sound, Clinically significant weight gain thought to be related to fluid retention [>3 to 4 lbs. in 3 to 4 days], Other)
- Laboratory evidence of worsening HF (Increased NT-proBNP [> 2,000 pg/mL], Radiographic evidence of pulmonary congestion, Right heart catheterization with pulmonary capillary wedge pressure ≥18 mmHg, central venous pressure ≥12 mmHg, or a cardiac index of < 2.2 L/min/m^2, Other)
- Increased or additional therapy (No, Yes, Unknown)
  - Therapy type (Augmentation of oral diuretic therapy with additional diuretic; Initiation of intravenous diuretic; Uptitration of intravenous therapy, if already on therapy; Initiation of inotrope, or vasodilator therapy; Initiation of percutaneous mechanical circulatory support; Initiation of temporary surgical support [extracorporeal membrane oxygenation or temporary surgical ventricular assist device ie, centrimag]; Implantation of durable left ventricular assist device; Listed for heart transplantation)
- Evidence of cardiogenic shock (No, Yes, Unknown)
- Blood sample collected for BNP or NT-proBNP (No, Yes, Unknown)
  - BNP result (pg/mL)
  - NT-proBNP result (pg/mL)
- Contributors/precipitants of worsening HF (Medication nonadherence, Dietary indiscretion, Acute coronary syndrome, Other systemic illness – [Respiratory infection, Urinary tract infection, Other])

2.7.4.4 HF Signs and Symptoms

- NYHA Classification (Class I: no limitation of physical activity; Class II: slight limitation of physical activity; Class III: marked limitation of physical activity; Class IV: unable to carry out any physical activity without discomfort).
- Paroxysmal nocturnal dyspnea (Absent, Present)
- Dyspnea at rest (Absent, Present)
- Dyspnea on effort (Absent, Present; if Present: Mild, Moderate, Severe)
- Fatigue (Absent, Present)
- Orthopnea (Absent, Present; if Present: 1 pillow (10cm elevation); 2 pillows (20 cm elevation); >2 pillows (>20 cms elevation))
- Jugular venous distention (Absent, Present, Not Available; if Present: <6 cm; 6 to 10 cm; >10 cm)
- Edema (Absent, Present; if Present: Trace; 1+; 2+; 3+; Feet and Ankles (no/yes); Lower legs of thighs (no/yes); Sacrum (no/yes))
- Rales (Absent, Present; if Present: Rales <1/3; Rales 1/3 to 2/3; Rales > 2/3)
- Third heart sound (Absent, Present, Not Available)

2.7.4.5 Hospitalization

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

- Type of hospitalization (Elective, Planned, Unplanned)
- Reason for hospitalization (refer to eCRF for list of reasons)
- Subject discharged (No, Yes, Unknown)
  - Duration of hospitalization in days [date of discharge – date of admission + 1]
- Subject admitted to ICU or Coronary Care Unit (CCU) (No, Yes, Unknown)
  - Number of days in ICU or CCU
- Discharge disposition (Home or with family/friends, Rehabilitation facility, Skilled nursing facility, Death, Unknown)

All hospitalizations (Cardiovascular (CV) Hospitalization, Non-Cardiovascular (non-CV Hospitalization and Undetermined Cause of Hospitalization)) will be adjudicated by the Events Adjudication Committee at Brigham and Women's Hospital.

Information on time from index hospitalization to randomization will be summarized.

2.7.4.6 Angioedema

Data collected from the Questionnaire for Angioedema-Like Event at Screening, Randomization and Follow-up visits will be summarized. Separate summaries will be produced for all angioedema events. The number and percentage for categorical variables and summary statistics for continuous variables of the following will be presented by visit, treatment group and open-label sacubitril/valsartan:

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

  - Duration of angioedema in days [*end date – start date + 1*]
- Timing of event (After first dose, after multiple doses, dose not given) [not asked at screening]
  - Study medication discontinued due to event (No, Yes, Unknown)
  - Event occurred within 1 day of dosing (Within 1 day of dose but less than or equal to 1 hour, within 1 day of dose but greater than 1 hour, After 1 day of dosing, Unknown)
- History of prior angioedema or angioedema like event (No, Yes, Unknown)
  - If yes, medications taken at time of previous event:
    - ACE inhibitor (No, Yes, Unknown)
    - ARB (No, Yes, Unknown)
    - Renin inhibitor (No, Yes, Unknown)
    - Other medications (No, Yes, Unknown)
- Presence of hereditary angioedema (No, Yes, Unknown)
- Any family members with history of angioedema-like events (No, Yes, Unknown)
- Signs and symptoms for current event
  - Shortness of breath/dyspnea (No, Yes, Unknown)
  - Difficulty swallowing/dysphagia (No, Yes, Unknown)
  - Difficulty speaking/dysarthria (No, Yes, Unknown)
  - Pain on swallowing/odynophagia (No, Yes, Unknown)
  - Stridor (No, Yes, Unknown)
  - Abdominal pain (No, Yes, Unknown)
  - Other (No, Yes, Unknown)
- Edema present (No, Yes)
  - Periorbital edema (No, Yes, Unknown)
  - Head edema (No, Yes, Unknown)
  - Neck edema (No, Yes, Unknown)
  - Lip edema (No, Yes, Unknown)
  - Tongue edema (No, Yes, Unknown)
  - Throat edema (No, Yes, Unknown)
  - Submandibular edema (No, Yes, Unknown)
  - Genitalia edema (No, Yes, Unknown)
  - Extremities edema (No, Yes, Unknown)
  - Other (No, Yes, Unknown)
- Previous edematous episodes (No, Yes, Unknown)
  - Number of previous edematous episodes
- ACEi taken in the past (No, Yes, Unknown)
- ACEi taken during trial participation after Screening (No, Yes, Unknown) [not asked at Screening]

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

All assessment data will be listed as collected in the CRF.

2.8 Pharmacokinetic endpoints

Not applicable.

2.9 Pharmacodynamic and pharmacokinetic/pharmacodynamic analyses

Not applicable.

[redacted]

2.11 Biomarkers

NT-proBNP will be collected and descriptively summarized by visit, treatment group. NT-proBNP will be measured in all subjects using the central laboratory at Visits 2 (randomization), 3, 5, and 7 (Weeks 0, 1, 4, and 8 respectively). Values and the change from Baseline for each parameter will be summarized by visit and treatment group. Analyses will be based on the FAS.

NT-proBNP values will be based on clinical laboratory samples processed and assessed by the central laboratory.

[redacted]

[redacted]
P
D
[redacted]

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

Biomarker samples from subjects who withdrew consent will not be analyzed by the central laboratory.

[redacted]

[redacted]

[redacted]

2.13 Interim analysis

There is no planned interim analysis for efficacy in the study.

Interim Safety Assessment

An independent DMC will be responsible for performing interim safety assessment using independent statistician and programmer who will not be involved in the trial conduct. The DMC charter will contain the committee's responsibilities regarding the interim safety assessment. Details of this safety assessment will be included in the DMC-SAP.

Interim safety assessments are planned to be performed and results will be provided to DMC for their review and recommendation. There are 3 DMC planned and the timing of these safety

assessments are mentioned in the DMC Charter. No adjustment to the level of significance will be made for these interim safety assessments.

3 Sample size calculation

The target sample size for this study is approximately 450 total subjects (including original protocol and all Amendment subjects), randomized into the 2 treatment groups in a 1:1 ratio. The maximum planned duration of follow-up after randomization of these subjects is approximately 20 months and the planned duration of follow-up for the last subject in the group is 2 months.

The power of the study is determined based on these 450 subjects for the primary endpoint.

Sample size for the primary endpoint

This sample size of 450 subjects would have 85% power to detect a 23% reduction in the geometric mean of the proportional change from Baseline to an average of Weeks 4 and 8 in NT-proBNP for the sacubitril/valsartan treatment group. This 23% reduction in geometric mean is equivalent to -0.2614 in natural log scale (=ln(0.77)). The power is estimated assuming a two sided significance level of 0.05, a common SD of 0.85 for change in log transformed NT-proBNP and a 15% rate of missingness in NT-proBNP at baseline or at both Week 4 and Week 8.

nQuery Version 8.4.1.0 (2019) software package is used in calculating the power of the test.

4 Change to protocol specified analyses

[redacted]

5 Appendix A

5.1 Imputation rules

5.1.1 Study drug

Full dates for study treatment collected on the eCRF are required; therefore, no imputations will be made.

5.1.2 AE date imputation

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

- Missing day and month

- If the year is the same as the year of first study treatment, then the day and month of the start date of treatment will be assigned to the missing fields.
- If the year is prior to the year of first study treatment, then December 31 will be assigned to the missing fields.
- If the year is after the year of first study treatment, then January 1 will be assigned to the missing fields.

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

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

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

- Missing year
  - Date left missing.
- Missing month
  - Impute ‘December’.
- Missing day
  - Impute ‘last date of that month’.

5.1.3 Concomitant medication date imputation

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

- Missing day and month
  - If the year is the same as the year of first study treatment, then the day and month of the start date of treatment will be assigned to the missing fields.
  - If the year is prior to the year of first study treatment, then December 31 will be assigned to the missing fields.
  - If the year is after the year of first study treatment, then January 1 will be assigned to the missing fields.

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

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

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

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

5.1.3.1 Prior therapies date imputation

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

5.1.3.2 Post therapies date imputation

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

5.1.3.3 Other imputations

Not applicable

5.2 AEs coding/grading

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

5.3 Laboratory parameters derivations

5.3.1 Laboratory grading

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

5.3.2 Notable laboratory values

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

Hematology	
RBC count	>50% increase, >20% decrease
Hemoglobin	>50% increase, >20% decrease
Hematocrit	>50% increase, >20% decrease
WBC count	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease

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

5.3.3 Clinically notable changes in vital signs

Vital Sign (unit)	Clinically notable criteria
Weight (kg)	decrease > 7% from Baseline increase > 7% from Baseline
Sitting systolic blood pressure (mmHg)	<90 and decrease from baseline of >20 >180 and increase from baseline of >20

Sitting diastolic blood pressure (mmHg)	<50 and decrease from baseline of >15 >105 and increase from baseline of >15
Pulse (bpm)	<50 and decrease from baseline of > 15 >120 and increase from baseline of >15

5.4 Statistical models

5.4.1 Primary analysis

The null hypothesis for the primary analysis is the ratio of the geometric means of NT-proBNP for the sacubitril/valsartan and valsartan groups are equal. For NT-proBNP, the time-averaged proportional change from Baseline in a natural logarithmic scale will be analyzed using an analysis of covariance (ANCOVA) model with treatment, in-hospital/out-of-hospital randomization status, gender, and baseline LVEF (≤ Median, > Median) as fixed effect factors, age and the logarithmic Baseline NT-proBNP as covariates.

The general form for the ANCOVA model is:

$$y_{ij} = \mu + \tau_i + B(x_{ij} - \bar{x}_i) + \epsilon_{ij}$$

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

```
proc mixed data=<.....>;
        class treatment in-hospital/out-of-hospital gender baseLVEF;
        model chg = treatment in-hospital/out-of-hospital gender baseLVEF age base NT-proBNP;
        lsmeans treatment / OM pdiff cl;
run;
```

where,

treatment = treatment the subject is randomized to

in-hospital/out-of-hospital = whether the subject randomized in hospital or out of hospital

gender = gender of the subject

baseLVEF = Baseline LVEF (≤ Median, > Median)

chg = NT-proBNP, the time-averaged proportional change from Baseline in a natural logarithmic scale

age = age of the subject

baseNT-proBNP = the logarithmic Baseline NT-proBNP

5.4.2 Secondary analysis endpoint 1

The composite hierarchical outcome consisting of: a) time to CV death, b) number and times of HF hospitalizations during follow-up, c) number and times of urgent HF visits during follow-up, and d) time-averaged proportional change in NT-proBNP (from Baseline to Weeks 4 and 8)

This secondary efficacy endpoint 1analysis is described in Section 2.6.2.1.

This hierarchical composite endpoint consists of the following four ordered components:

a) Time to CV death,

b) Number and times of HF hospitalizations during follow-up,

c) Number and times of urgent HF visits during follow-up, and

d) Time-averaged proportional change in NT-proBNP (from Baseline to Weeks 4 and 8)

Table 5-1 Step wise determination of win ratio winners

Hierarchy/Outcome	Category	Criteria	Winner Definition	Result
1 Time to CV death	A	Both subjects experienced CV death	Subject with longest time to death	sacubitril/valsartan or valsartan winner
	B	One subject only experienced CV death and it occurred before the censoring time of the other subject in the pair	Subject who did not experience CV death	sacubitril/valsartan or valsartan winner
	C	One subject only experienced CV death and it occurred after the censoring time of the other subject in the pair	N/A	Tie
	D	Neither subject experience CV death	N/A	Tie
	E	For one or both subjects the cause of death is not known	N/A	Tie
2 Number and times of HF hospitalizations during common follow-up+*	F	Count of both subjects HF hospitalizations	Subject with fewest HF hospitalizations	sacubitril/valsartan or valsartan winner
	G	If equal number of HF hospitalizations	Subject with longer time to last HF hospitalization	sacubitril/valsartan or valsartan winner
	H	If counts equal and time to last HF hospitalization equal	N/A	Tie
	I	For one or both subjects the number of HF hospitalizations is not known	N/A	Tie
3 Number and times of urgent HF visits during common follow-up+**	J	Count of both subjects' urgent HF visits	Subject with fewest urgent HF visits	sacubitril/valsartan or valsartan winner
	K	If equal number of urgent HF visits	Subject with longer time to last urgent HF visit	sacubitril/valsartan or valsartan winner
	L	If counts equal and time to last urgent HF visit equal	N/A	Tie
	M	For one or both subjects the no of urgent HF visits is not known	N/A	Tie
	N	Subject has urgent HF visit after the end of another subject’s time at risk.	N/A	Tie

4 Time-averaged proportional change in NT-proBNP from Baseline to Weeks 4 and 8***	O	Compare subjects proportional change from Baseline	Difference of the proportional change from two subjects is between -0.2876 and 0.2876	Tie
	P	Compare subjects proportional change from Baseline	Difference of proportional change between subjects is < -0.2876 OR >0.2876: The subject with the larger decrease or smaller increase is the winner	sacubitril/valsartan or valsartan winner
	Q	A comparison is not possible as the NT-proBNP value is missing for one or both subjects in the pair	N/A	Tie

+ For these events only those that occur in the common follow-up time for both subjects in the pair will be used for analysis to define win or tie. For example, if subject 1 of a pair has 145 days at risk and subject 2 has 126 days only events that occur on days 1-126 are considered.

* Patients in categories C, D & E only are evaluated

** Patients in categories H & I only are evaluated

*** Patients in categories L, M & N only are evaluated

Table 5-2 Win Ratio Winner Categories

Category	Description	Winner
a	Time to CV death	sacubitril/valsartan
b		valsartan winner
c	Number and times of HF hospitalizations during common follow-up	sacubitril/valsartan
d		valsartan winner
e	Number and times of urgent HF visits during common follow-up	sacubitril/valsartan
f		valsartan winner
g	Time-averaged proportional change in NT-proBNP from Baseline to Weeks 4 and 8	sacubitril/valsartan
h		valsartan winner
i	None of the above	None of the above

Let N_v and N_{vs} be the number of subjects on sacubitril/valsartan and valsartan treatments. Then one makes all Nn× Ns paired comparisons. Each pair is classified into one of categories a through i in Table 5-2 and will be reported.

The trial's composite endpoint results are summarized by N_a, N_b, N_c, N_d, N_e, N_f, N_g, N_h and N_i the numbers of pairs in categories (a), (b), (c), (d), (e), (f), (g), (h) and (i) respectively.

Categories (a), (c), (e) and (g) "are winners" for sacubitril/valsartan while (b), (d), (f) and (h) are "losers."

$N_a + N_c + N_e + N_g = N_w$ and $N_b + N_d + N_f + N_h = N_L$ are the numbers of 'winners' and 'losers' for the sacubitril/valsartan and $R_w = N_w/N_L$ is the "win ratio."

We will apply a more efficient approach proposed in Bebu, I & Lachin, JM. (2015) [9] to calculate the p-value and 95% CI. The proposed method [9] constructs tests of significance and confidence intervals in the context of composite outcomes using the large sample distribution.

5.4.3 Secondary analysis endpoint 2

The cumulative number of composite events, ie, the total number of composite events of CV death, recurrent HF hospitalizations, and recurrent urgent HF visits for a subject over time will be calculated. The time to these recurrent events will be analyzed using the semi-parametric proportional rates model (abbreviated as LWYY model) (Lin 2000).

Specifically, let λ_i, (t,x_i) be the individual rate of composite events for subject i, given that the subject has not died from a CV reason at time t. It is dependent on the time from randomization (t) and treatment group (x_i). Let $x_i = 1$ if the subject is in the sacubitril/valsartan group and $x_i = 0$ if the subject is in the valsartan group.

Under the proportional rates model, the individual rate function for the composite endpoint of CV death and total HF hospitalizations is assumed to be, $\lambda_i(t,x_i) = Y_i(t)\lambda_0(t)exp(\beta_0 x_i)$, where $Y_i(t) = 1$ if subject i is at risk for CV death, recurrent HF hospitalizations, and recurrent urgent HF visits at time t and $\lambda_0(t) = 0$ if subject i is censored or died from a CV reason at time t

The primary hypothesis to be tested is, H_{30}: $\beta_0 = 0$ versus H_{3a}: $\beta_0 < 0$, where $\exp(\beta_0)$ is the relative risk or rate ratio of CV death, recurrent HF hospitalizations, and recurrent urgent HF visits in the sacubitril/valsartan group relative to the valsartan group given the subject has not died from a CV reason at time t, which is assumed to be constant over time .

The primary hypothesis could be equivalently written as:

H_{30}: Rate ratio (sacubitril/valsartan)/(valsartan) = 1

versus

H_{3a}: Rate ratio (sacubitril/valsartan)/(valsartan) < 1,

A rate ratio < 1 indicates an effect in favor of sacubitril/valsartan.

The rate ratio and its 95% CI will be estimated from the above proportional rates model through maximization of a partial likelihood score function. The resulting estimate of $\exp(\beta_0)$ is identical to the one described by Anderson and Gill (1982), but unlike Anderson-Gill, a robust variance

estimator (sandwich estimator) is used to account for the dependency of within subject events. The number and percentage of CV events by event type will be summarized.

The LWYY analysis can be carried out using the following SAS code:

```
proc phreg data=primary_data covs(aggregate);
       model (time_start, time_rec)*status_rec(0)=treat/ties=efron rl;
       id usubjid;
run;
```

where primary_data is the input dataset, time_start is the previous event stop time and time_rec is the current event stop time, the censoring variable status_rec (0 for censored and 1 for event) should take the value 1 if the last event is a CV death and 0 if it is censored for any non-CV death reasons for the given subject; usubjid is the subject ID.
As a supportive part of the analysis, the two components in the composite endpoint (recurrent HF hospitalizations, and recurrent urgent HF) will be analyzed separately to quantify the respective treatment effects and check the consistency between the composite and the components.
For details on the steps, consider the primary endpoint analysis from CLCZ696D2301 as reference.

5.5 Rule of exclusion criteria of analysis sets

There is no Per Protocol Set and defined protocol deviations will not lead to exclusion from FAS and RAS.

Table 5-3 Subject Classification

Analysis Set	Protocol deviations ID that cause subjects to be excluded	Non-protocol deviation criteria that cause subjects to be excluded
RAS	NA	Not randomized

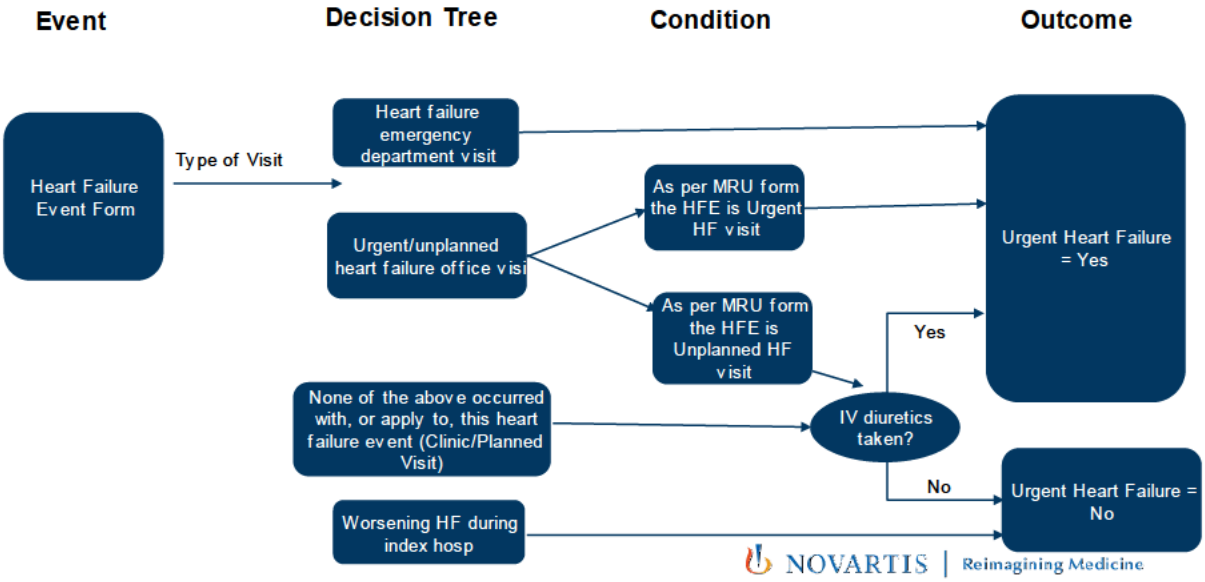
5.6 Study background

In the United States, sacubitril/valsartan is approved to "reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure", based on data from the PARAGON-HF trial. The indication goes on to say "benefits are most clearly evident in patients with a left ventricular ejection fraction (LVEF) below normal." The term "below normal" can vary between patients depending on age, gender, race/ethnicity, and other factors, with normal being defined as a LVEF of 62% (range 52-72) and 64% (range 54-74) for men and women, respectively.

PARAGLIDE-HF seeks to study potential heart failure biomarker changes (NTproBNP) and clinical benefits of sacubitril/valsartan vs. valsartan in HFimpEF, HFmrEF, and HFpEF patients following a worsening heart failure event. Analyses will include multiple subgroups, including those with an LVEF "below normal" vs. normal, defined as >60% here using a conservative estimate of normal.

5.7 Identification of Urgent Heart Failure Visit (Investigator Reported)

The following criteria is used after discussion with Data Management team to identify the Investigator reported Urgent Heart Failure events.



6 Reference

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Appendix B: Additional Analysis- not for CSR reporting

This section describes a pre-planned additional analysis for publications. The analysis will not be intended to be reported as part of the study CSR.

For the below defined analyses (Section 1, 2 and 3), all subgroups defined in Section 2.2.1 can be analyzed as categorical and / or continuous based on the clinical decision wherever applicable. For example, age group, LVEF categories can be considered as continuous for analyses if needed.

[redacted]

[redacted]

Section 2: PARAGLIDE-HF and PARAGON-HF

As a part of the additional analysis, all subjects enrolled in PARAGLIDE-HF will be combined with those all enrolled subjects from PARAGON-HF within 30 days from the date of last discharge from the hospital to the date of screening (approximately n = 622).

The following variables will be analyzed based on the pooled data. These variables will be analyzed using the respective model described in this document (Section 2.6 and Section 2.12), with the study as an additional independent variable. Otherwise, the statistical model for the composite/ component variables is specified below paragraphs.

1. The incidences of the cumulative number of recurrent composite events over-time, i.e., the total number of composite events of HF hospitalizations, urgent HF visits, and CV death.

    - Composite events:
        - HF hospitalizations
        - Urgent HF visits
        - CV death

Statistical analysis will be performed using the same proportional rates model (LWYY) as described in Sections 2.12.1 and 5.4.3.

- Component events:

The three components in the composite endpoint (total HF hospitalizations, urgent HF visits, and CV death) will be analyzed separately to quantify the respective treatment effects and check the consistency between the composite and the components.

- Total HF hospitalizations:
- Urgent HF visits:
- CV death:

Statistical analysis for the individual component events will be performed using the same proportional rates model (LWYY) as proposed for the analysis of the composite events. The estimated rate ratios and the corresponding two-sided 95% confidence intervals will be provided for the composite endpoint and its components.

2. The incidences of time-to first composite endpoint of worsening renal function, defined as:

    - Composite events:

- renal death
- reaching end-stage renal disease (ESRD)
- ⩾ 50% decline in estimated glomerular filtration rate (eGFR) relative to baseline

- It will be analyzed using Cox's proportional hazards model proposed in Section 2.12.2 with the study as an additional independent variable. The estimated hazards ratio and the corresponding two-sided 95% confidence interval will be provided.
- The Kaplan-Meier curves by treatment group will be presented.

- Component events:

The three components in the composite endpoint will be analyzed separately to quantify the respective treatment effects and check the consistency between the composite and the components.

- renal death:
- reaching end-stage renal disease (ESRD)
- ⩾ 50% decline in estimated glomerular filtration rate (eGFR) relative to baseline)

A similar statistical model used for composite event analysis will be used for the three individual components.

3. Incidence of worsening renal function, defined as an increase in serum creatinine of ≥0.5mg/dl and worsening of the eGFR by at least 25%.

The statistical model as described in Section 2.6.2.7 will be used for this analysis.

[redacted]

6. Time to first all-cause death.

It will be analyzed similar model as above.

Adjudicated (EAC) and Investigator-reported events

As mentioned in Section 2.6.1.1, some of the secondary variables or their components will be adjudicated by EAC. The posthoc analysis (Appendix B) will be analyzed and presented considering both the Adjudicated and Investigator-reported events where applicable:

- Events adjudicated (EAC) in PARAGLIDE-HF and PARAGON-HF studies
- Events adjudicated in PARAGON-HF but Investigator-reported events from PARAGLIDE-HF

- Investigator-reported events from both PARAGON-HF and PARAGLIDE-HF studies

Section 3: PARAGLIDE-HF and PIONEER-HF

In addition, an additional analysis, all subjects randomized in PARAGLIDE-HF will be combined with those all randomized patients from PIONEER-HF.