NOVARTIS

Clinical Development

Sacubitril/Valsartan

CLCZ696B2319E1 / NCT03785405

A multicenter study to evaluate long-term safety and tolerability of open label sacubitril/valsartan in pediatric patients with heart failure due to systemic left ventricle systolic dysfunction who have completed study CLCZ696B2319

Statistical Analysis Plan (SAP), Amendment 2

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17-April-2023	Prior to LPLV	Adding analysis of height for patients in the age range of 2-9 years throughout the OLE study		Section 2.8.4.3
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14-Dec-2023	Prior to LPLV	Changing the rule for counting treatment emergent adverse event		Section 2.8.1
22-Dec-2023	Prior to LPLV	Adding Table 2-2 to further clarify tablet use for patients		Section 2.4.1
30-Jan-2024	Prior to DBL	Adding clarification for the analysis of clinically notable laboratory abnormality		Section 2.8.3

Table of contents

List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dose administration record
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PDS	Programming datasets specifications
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que die / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This document describes details of the analyses as outlined in section 12 of the study protocol. Results will be summarized in the clinical study report (CSR). However, since this is an open-label study with regular review of safety outcomes, selected outputs may also be generated during the course of the study.

1.1 Study design

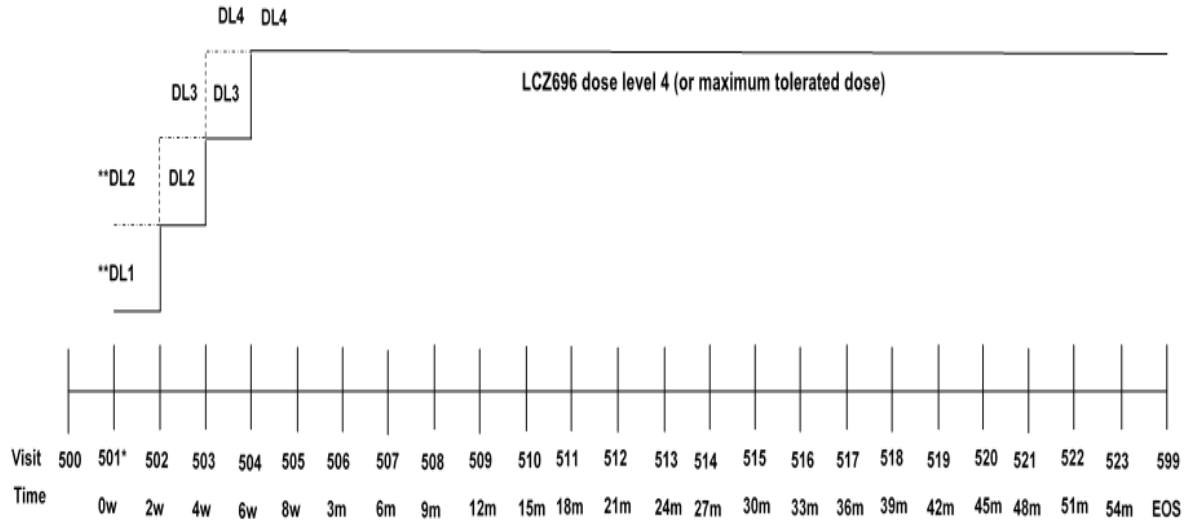
This trial is a multicenter, open-label long-term extension (OLE) study for subjects who have successfully completed Part 2 of the PANORAMA-HF trial. Subjects will be enrolled into two different age groups (Age Group 1: 6 years and older; Age Group 2: 1 to < 6 years) in the OLE study. Age Groups 1 and 2 in the OLE have a target dose (dose level 4) of 3.1 mg/kg bid. Subjects will be up titrated to the target dose of sacubitril/valsartan, dose level 4, according to their tolerability, in 2-weeks intervals. An outline of the study design is presented in Figure 1-1.

No specific sample size is required for the study. However, all patients who have completed the double-blind phase of the study PANORAMA-HF, and fulfill all inclusion/exclusion criteria, are eligible for the study.

The primary analysis will be conducted when all patients who are still ongoing (i.e., did not prematurely discontinue) have had their end of study visit (EoS).

No interim analysis is planned. However, the safety will be monitored through regular review of adverse events and related data.

Figure 1-1 Study design



w=weeks; m=months; DL=LCZ696 dose level
* ≥36 hour of ACEI or double-blind study medication-free washout before starting OLE study medication at Visit 501
** The starting dose at V501 can vary according to prior dose of AECI/ARBs or PANORAMA-HF study drug

1.2 Study objectives and endpoints

This study has only primary objective as described in Table 1-1.

Table 1-1 Objectives and related endpoints

Primary Objective	Endpoint(s) for primary objective
• To further evaluate long-term safety and tolerability of sacubitril/valsartan in eligible PANORAMA-HF subjects receiving open-label sacubitril/valsartan	• AEs, SAEs, laboratory values, vital signs, and duration of drug exposure

2 Statistical methods

2.1 Data analysis general information

Unless otherwise specified, the data will be analyzed according to the study protocol using SAS 9.4 or higher and R 3.4.3 or higher, by Novartis personnel.

In general, continuous variables will be summarized using number of observations, mean, standard deviation, median, quartiles, minimum and maximum. Categorical variables will be summarized using frequencies and percentages. Unless otherwise specified, the by age group summaries will include: summary for the two age groups (6 years and older, 1 year to < 6 years) and summary for the entire analysis set.

Study completion is defined as having reached the end of study visit (December 2023 from Protocol Amendment V.01 and later versions or December 2022 for Protocol V.00) while on treatment, or having completed 12 months of study while being on treatment and being transitioned to commercial Entresto.

Data from all study centers will be combined.

2.1.1 General definitions

Study treatment is sacubitril/valsartan.

The date of first administration of study treatment is the day of the first dose of sacubitril/valsartan.

The date of last administration of study treatment is the day of the last non-zero dose of sacubitril/valsartan.

Study day is defined as actual date – date of first administration of study treatment + 1.

Baseline is defined as last non-missing value before starting treatment, where for the same parameter, central laboratory result takes precedence over local laboratory result; in general values are obtained at the baseline visit (501), with the exception of urinalysis and complete laboratory, which are obtained at the screening visit (500). In case these two visits happened on the same day, results from the central laboratory will be considered as baseline values. Note that per protocol, in the case that visit 500 and, if applicable visit 501, is scheduled within 14

days of the PANORAMA-HF End of Study visit (Visit 416), the assessment results from PANORAMA-HF End of Study visit can be used as screening/baseline.

The **study period** starts with the date of screening visit (500) and ends with the date of end-of-study (EOS) or premature study discontinuation (PSD) visit (599).

Treatment period starts with the date when the first dose of study treatment is given (visit 501, unless no dose is given at that visit) and ends with the date of treatment disposition. In the case that no EOS visit was undertaken (e.g., because the patient died or withdrew from the study without such a visit), the treatment period ends with the death/withdrawal date or the last dose taken as reported in the DAR page. Subjects who permanently discontinued study drug should be scheduled for the discontinuation study Visit 599. Note that after a consecutive 3-month interruption of study treatment, subject should be discontinued from the study and should be seen at the site for Visit 599.

2.2 Analysis sets

The following analysis sets will be used:

- Screened set (SCR): All patients who signed the informed consent for the extension open-label study.
- Safety Set (SAF): All SCR patients who received at least one dose of open-label study treatment during the extension open-label study.

2.2.1 Subgroup of interest

The patients satisfying the criterion of being within the age range of 2-9 years at each 12-month visit (e.g., patients aged 8 years at baseline will only be included in the analysis of height at their first 12-month visit) starting from baseline until EOS will be investigated, other than the age groups specified in Section 2.1.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number and percentage of patients who completed the screening phase will be provided by age group. In addition, the primary reason for not completing the screening phase will be summarized by age group using the numbers and percentages of patients not qualifying for such reasons and criteria leading to exclusion from the analysis will be provided by age group. For patients who are screen failures and re-screened, the rescreening visit will be used. These summaries will be performed for the SCR.

The number and percentage of patients who complete the treatment, who discontinue from the treatment and the primary reasons for discontinuation will be summarized by age group. In addition, the number and percentage of patients with protocol deviations will be provided by age group. These summaries will be performed based on the SAF.

2.3.2 Demographics and baseline characteristics

Summary statistics will be provided by age group and for overall for demographics and baseline characteristics, including age, age group (only for overall), sex, race, ethnicity, weight, height, head circumference (for subjects ≤ 3 years old), BMI, vital signs, age adjusted percentile for weight, height and body mass index (BMI = weight (kg) / height^2 (m^2)), z-score for height .

Continuous variables will be summarized using n, mean, standard deviation, median, minimum, the first quartile (Q1), the third quartile (Q3), and maximum. Categorical variables will be summarized using frequencies and percentages. The SAF will be used for the above analyses.

2.3.3 Medical history

Any condition entered on the relevant medical history/current medical conditions CRF will be coded using the MedDRA dictionary. Medical history includes heart failure history and other medical history in this study, which are collected at screening (Visit 500). The number and percentage of patients with each medical condition will be provided by age group and for overall, by system organ class (SOC), high level group term (HLGT) and preferred term (PT).

The SAF will be used for the above analyses.

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

2.4.1 Study treatment / compliance

All analyses in this section will use the SAF.

The study drug administration is recorded on the CRF page: “Dosage Administration Record” using start date-time, end date-time and dispensing level of the study drug. Each pair of start date and end date will be considered as a dosing interval.

For each patient, the dosing intervals will be sorted according to the start date and the end date of the dose. For subject with gaps and/or overlaps among dosing interval (e.g., when the patient takes the previous dispensing level in the morning and starts a different dispensing level in the evening, the end date of a dosing interval is the same as the start date of the next dosing interval), a conventional data imputation algorithm will be applied to the start date and end date. The detailed algorithm will be provided in the study programming datasets specifications (PDS).

For patients who permanently discontinue study treatment, there should be a dosing interval with its start date equal to the date of the permanent discontinuation of the study drug, its end date equal to the study discontinuation date, and its dispensing level equal to “No treatment”.

Patients who complete the treatment are defined as receiving study treatment as reported in the DAR page until the day of EoS or the date marked as “treatment complete” in the disposition page.

The specific doses based on the dispensing dose levels are defined in Table 2-1 for both the pediatric and adult formulation. If the dispensing level is no treatment, the dose level is defined as 0.

For a dosing interval with a pediatric dose level, the daily dose (mg/day) during the interval is defined as the product of the weight based daily dose (mg /kg/day) during the interval and the weight during the interval, where the weight based daily dose (mg /kg/day) during the interval is defined in Table 2-1 and Table 2-2 and the weight during the interval is defined as the weight from the last non-missing assessment (scheduled or unscheduled) prior to or equal to the start dose time of the study drug of the interval.

Table 2-1 Study drug dose levels and doses for sacubitril/valsartan

Age groups 1 and 2 *		
Dispensing dose levels for pediatric formulation		**Weight based daily dose**
Dose level 1	0.8 mg/kg bid.	1.6 mg/kg/day
Dose level 2	1.6 mg/kg bid.	3.2 mg/kg/day
Dose level 3	2.3 mg/kg bid.	4.6 mg/kg/day
Dose level 4	3.1 mg/kg bid.	6.2 mg/kg/day
Dispensing dose levels for adult formulation		**Weight based daily dose**
Dose level 1	50 mg bid.	1.6 mg/kg/day
Dose level 2	100 mg bid.	3.2 mg/kg/day
Dose level 3	150 mg bid.	4.6 mg/kg/day
Dose level 4	200 mg bid.	6.2 mg/kg/day

*Note: sacubitril/valsartan target dose (dose level 4) for age groups 1 and 2 is 3.1 mg/kg bid.

Table 2-2 Tablet use for sacubitril/valsartan (43 to < 57 kg patients)

Study drug	Pediatric dose level	Patient weight (kg)	Pediatric dose	Tablet dose
LCZ696	Dose level 4	43 to < 57 kg	>= 133 to < 177 mg	150 mg
	Dose level 3	43 – 54 kg	>= 98 to <125 mg	100 mg
	Dose level 3	>54 to <57 kg	>= 125 to < 131 mg	150 mg

Dispensing level (dose level) and daily dose at each visit

For a given visit, the visit associated dosing interval is defined as the dosing interval with its start date prior to or equal to the date of visit AND its end date later than or equal to the date of visit; the dose level and weight based daily dose (mg/ kg/day) at the visit are defined as the dose level and weight based daily dose (mg/kg/day) for the visit associated dosing interval. In the case that, the visit date is equal to the end date of an earlier dosing interval as well as the start date of a later dosing interval, the later dosing interval will be taken as the visit associated dosing interval.

The dose level will be summarized by visit, for overall and for each age group, using the number and percentage of patients on each level; and further be summarized using number of observations, mean, standard deviation, median, minimum, Q1, Q3, and maximum; the weight based daily dose (mg /kg/day) will be summarized by visit, for overall and for each age group, using number of observations, mean, standard deviation, median, minimum, Q1, Q3, and maximum.

The summary will include all scheduled visits in the study or until treatment discontinuation date.

Duration of treatment exposure

Duration of exposure to treatment regardless of temporary interruptions is defined as: date of last dose of study treatment – date of first dose of study treatment + 1.

Conversion for treatment exposure durations is as follows:

- 1 week = 7 days
- 1 month = 30.4375 days
- 1 year = 365.25 days

Total (sum of patient-years) and per-patient duration of exposure to the study treatment will be summarized for each age group and for overall in years, using mean, standard deviation, median, Q1, minimum, Q3 and maximum.

The duration (day) of treatment exposure excluding study drug interruptions is defined as the sum of the duration (day) on dose level 1 to 4 during the study without counting any days that patients are not taking the treatment.

The analyses specified in the Section “Dispensing level (dose level) and daily dose at each visit” will be used here. In addition, the duration of study drug exposure with and without study drug interruptions, respectively, will be categorized into:

- < 6 months
- 6 months to < 1 year
- 1 to < 2 years
- 2 to < 3 years
- 3 to < 4 years
- >=4 years.

The number and percentage of patients within each category by age group and overall will be tabulated.

Duration on each dose level

For a given dose level, the duration (day) on this dose level is defined as the number of days on this dose level during the period from the date of the first dose of the study drug to the date of the last dose of the study drug. In the case that the end date of an earlier dosing interval is the same as the start date of a later dosing interval, the day will be counted as 0.5 day on both the earlier dose level and the later dose level. In the case that the date of permanent discontinuation of the study drug is the same as the date of the last dose of the study drug, the day will be counted as 0.5 day on the dose level of the last dose but not counted on dose level 0.

The median and interquartile range will be presented for duration on each dose level. The number of patients who have ever been on a specific dose level will be reported.

Time to permanent discontinuation of the study drug

The time (day) to permanent discontinuation of the study drug during the study (excluding death) will be summarized for each age group and overall by duration categories (refer to the Section "Duration of study drug exposure" for specific categories) using the Kaplan-Meier curves, considering time-to-death, completion of the study and switch to commercial entresto as independent censoring.

Mean weight based daily dose and mean dose level

For each patient, the mean weight based daily dose (mg/kg/day) during the study is defined as the weighted mean of the weight based daily dose (mg/kg/day) among dose level 0 to 4 using the duration (day) on each dose level as the weight, i.e.

$$\frac{\sum_{k=0}^{4} \text{Weight Based Daily Dose (mg/kg/day) for Dose Level } k \times \text{Duration (day) on Dose Level } k}{\sum_{k=0}^{4} \text{Duration (day) on Dose Level } k}$$

the mean dose level is defined as the weighted mean of the dose level among dose level 0 to 4 using the duration (day) on each dose level as the weight, i.e.,

$$\frac{\sum_{k=0}^{4} k \times \text{Duration (day) on Dose Level } k}{\sum_{k=0}^{4} \text{Duration (day) on Dose Level } k}.$$

The mean weight based daily dose (mg /kg/day) and the mean dose level during the study will be summarized for each age group and overall, using number of observations, mean, standard deviation, median, minimum, Q1, Q3, and maximum.

Dose down titration

A down-titration dosing interval is defined as a dosing interval whose dose level is changed to a lower dose level from its previous dosing interval.

The dose down titration during the study will be summarized by each age group and overall, using the numbers and percentages of patients with at least one down-titration dosing interval during the study.

Dose interruption

A dose-interruption dosing interval is defined as a dosing interval with "NO TREATMENT".

The numbers and percentages of patients with at least one dose-interruption greater than 24-hour dosing interval during the study will be provided by age group and the overall.

The numbers and percentages of patients having at least one dose-interruption dosing interval with duration (day) of dose-interruption larger than 14 days will be provided by each age group and overall.

2.4.2 Prior, concomitant and post therapies

Missing or partially missing start/end dates for prior/concomitant therapies will be imputed using the Novartis ADaM Governance Board (AGB) global standard approach.

Prior and concomitant medications/non-drug therapies will be identified based on recorded or imputed start and end dates. Details will be provided in the study programming datasets specifications (PDS).

Prior medications are defined as any recorded medication with its start date (recorded or imputed) prior to the date of the first dose of the study drug. Concomitant medications are defined as any recorded medication with its end date (recorded or imputed) later than or equal to the date of the first dose of the study drug and start date (recorded or imputed) prior to or equal to the end date of the treatment period.

Prior non-drug therapies are defined as any procedure/significant non-drug therapy with its start date (recorded or imputed) prior to the date of the first dose of the study drug.

Concomitant non-drug therapies are defined as any recorded procedure/significant non-drug therapy with its end date (recorded or imputed) later than or equal to the date of the first dose of the study drug and start date (recorded or imputed) prior to or equal to the end date of the treatment period. Whereas patients who undergo heart transplant will also be listed for the treatment period and the study period together.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized by anatomical therapeutic classification (ATC 3) and preferred term, for overall and for each age group.

Concomitant heart failure medications (including ACE-inhibitors, ARBs, renin inhibitors, beta-blockers, calcium antagonists, diuretics, aldosterone antagonists, cardiac glycocytes, aspirin, oral anticoagulants, antiarrhythmics agents, nitrates) will be summarized by ATC and preferred term, for overall and for each age group.

The SAF will be used for the above analyses.

2.5 Analysis of the primary objective

The primary objective is to evaluate safety and tolerability of LCZ696 in eligible heart failure patients from PANORAMA-HF receiving open-label investigational drug.

2.5.1 Primary endpoint

Adverse events, laboratory assessments, vital signs, and duration of drug exposure are considered primary endpoints.

2.5.2 Statistical hypothesis, model, and method of analysis

Refer to Section 2.8.1, Section 2.8.2, Section 2.8.3 and Section 2.8.4.

2.5.3 Handling of missing values/censoring/discontinuations

Refer to Section 2.8.1, Section 2.8.2, Section 2.8.3 and Section 2.8.4.

2.5.4 Supportive analyses

Not applicable, there are no supportive analyses.

2.6 Analysis of the key secondary objective

Not applicable, there is no key secondary objective.

2.7 Analysis of secondary efficacy objective(s)

Not applicable, there are no secondary objectives.

2.8 Safety analyses

The SAF will be used for all safety analyses, unless specified otherwise.

2.8.1 Adverse events (AEs)

All AEs will be identified using Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA version used for reporting the study will be described in a footnote.

An AE with its severity increased should be considered and recorded as a new AE.

Treatment emergent adverse events (TEAEs) are defined as any recorded AE with its start date-time (recorded or imputed) on or after the start date-time of the treatment period and end date as the end date of the treatment period or the date of last dose taken as reported in the DAR page + 30 days. Any AE happening after treatment discontinuation +30 days but still within the study period (e.g., where patient did not discontinue the study on the same date of treatment discontinuation) would not be considered as a TEAE and will be reported in the listing of AE.

The following adverse events will be summarized by primary system organ class, preferred term, and maximum severity as appropriate, for each age group and for overall, using numbers and percentages of patients with at least one adverse event in the corresponding class (see list below). Outputs will be produced for AEs regardless of study-drug relationship, and for study-drug related AEs. Study drug related AEs are defined as any recorded AE with “Reasonable possibility that AE is related to study treatment” answered as “YES”. Serious adverse events (SAEs) are defined as any recorded AE with “Does AE meet the definition of an SAE” answered as “Yes”.

Adverse events summaries

- Any adverse event (treatment emergent or not)
- Any serious adverse event (treatment emergent or not)
- Treatment emergent adverse event (TEAE)
- Treatment emergent serious adverse event
- Treatment emergent adverse event (TEAE) occurred in >5% of patients
- Treatment emergent serious adverse event (TESAE) occurred in >5% of patients

- Treatment emergent adverse event of special interest, e.g. angioedema (both, adjudicated and non-adjudicated), change in bone growth and density, cognitive impairment (narrow SMQ), embryo-fetal toxicity or lethality, hepatotoxicity, hyperkalemia, hypersensitivity, hypotension, malignancy. neonatal or infantile toxicity through exposure from breast milk, renal impairment (narrow SMQ), and/or statin drug interaction as defined in the Case Retrieval Sheet for LCZ696 (see Section 2.8.1.1)
- TEAE and TESAE leading to dose adjustment, temporary dose interruption, or permanent discontinuation (including death) of study treatment
- TEAE and TESAE leading to permanent discontinuation (including death) of study treatment
- TEAE and TESAE leading to death

The following rules are applicable to the summaries:

- If a patient reported more than one AE with the same PT, the patient will be counted only once with the greatest severity at the PT level
- If a patient reported more than one AE within the same SOC, the patient will be counted only once with the greatest severity at the SOC level, where applicable.

2.8.1.1 Adverse events of special interest / grouping of AEs

Most common TEAEs are defined as any recorded TEAE corresponding to a PT with at least 5% of patients having at least one TEAE of this PT. Most common TEAEs will be derived overall and by age group and will be summarized by age group and for overall, by SOC and PT, in descending frequency according to incidence, starting from the most common event.

Table 2-1 shows the identified and potential risks for LCZ696 and the specifically specified analyses for each risk. In addition, the following standard analyses will be applied to all risks.

- Numbers and percentages of patients with any TEAE within the risk category (or SOC/PT within risk category) by age group and risk category, SOC, PT and maximum severity.
- Exposure adjusted incidence rates per 100 patient-years for TEAEs within the risk category by age group and risk category.
- Listing of patient numbers per risk.

Table 2-3 Identified and potential risks

Risk	Analysis
Hyperkalemia	1. Standard analyses; 2. Numbers and percentages of patients with treatment emergent hyperkalemia among patients with/without hyperkalemia at baseline by age group and overall 3. Numbers and percentages of patients with any post-baseline serum potassium ≥5.5 mEq/L, >6.0 mEq/L and >6.5 mEq/L by age group and overall
Hypotension	1. Standard analyses;

Risk	Analysis
	2. Blood pressures and change from baseline in blood pressures will be summarized by visit, time point, age group and overall using number of observations, mean, standard deviation, median, minimum, Q1, Q3, and maximum; 3. Numbers and percentages of patients with the following events during the treatment period will be provided by age group and overall: • Post-baseline systolic blood pressure (SBP) < 5th percentile per age (Table 16-7 in the protocol); • At least 20 mmHg drop in SBP (post-baseline assessments comparing to baseline); • Simultaneous treatment emergent symptomatic hypotension and postbaseline SBP < 5th percentile per age (Table 16-7 in the protocol); • Simultaneous treatment emergent symptomatic hypotension and at least 20 mmHg drop in SBP (post-baseline assessments comparing to baseline); • Simultaneous post-baseline SBP < 5th percentile per age (Table 16-7 in the protocol) and at least 20 mmHg drop in SBP (post-baseline assessments comparing to baseline).
Angioedema (positively adjudicated events)	Standard analyses;
Renal impairment	1. Standard analyses; 2. For serum creatinine and eGFR, the test values and changes from baseline will be summarized by visit, age group and overall using number of observations, mean, standard deviation, median, minimum, Q1, Q3, and maximum; the summaries will be provided for local and central lab separately; 3. Numbers and percentages of patients with the following events will be provided by age group and overall (the summaries will be provided for local and central lab together and if both central lab and local lab data are available, central lab result will take precedence over local lab result): • eGFR decline by >25%, >40%, >50%, and/or >30 mL/min/1.73 m2 (postbaseline assessments comparing to baseline) and <LLN; • eGFR < 45 mL/min/1.73 m2 and/or eGFR < 30 mL/min/1.73 m2 • Serum creatinine increase by >50% (post-baseline assessments comparing to baseline) and >ULN; • Serum creatinine increase by >0.5 mg/dL and >ULN (post-baseline assessments comparing to baseline), • serum creatinine post-baseline >2.0 mg/dL, >2.5 mg/dL, >3.0 mg/dL ; • Standard analyses within the subgroups additionally if possible: patients with baseline eGFR ≤170 mL/min/1.73 m^2 and >170 mL/min/1.73 m^2.

For safety topics of special interest defined in the CRS, the standard analyses will be performed.

2.8.2 Deaths

For overall and for each age group, death (including both cardiovascular and non-CV deaths) during the treatment period and the primary cause of death will be summarized using frequencies and percentages.

A listing of all deaths and heart transplant will also be provided for the SAF.

2.8.3 Laboratory data

Complete and abbreviated laboratory evaluations are described in Table 2-2. Complete laboratory evaluations (hematology, blood chemistry, and urine) are performed at screening (Visit 500), and subsequently every 12 months from Visit 501 until End of Study (Visit 599); these analyses are performed at central laboratory.

Abbreviated safety laboratory evaluation consists of serum sodium, potassium, creatinine, and eGFR. Abbreviated laboratory evaluations are performed every 12 months starting from visit at 6 months (Visit 507). In addition, abbreviated laboratory assessments are performed at up-titration visits (visits 501, 502, 503, 504 and 505, as applicable), and unscheduled visits with planned dose level changes; these analyses can be performed at central or local laboratories. Laboratory data will be reported for the treatment period. Note that a window of 5-day will be used to include laboratory data performed within 5 days after the discontinuation of treatment.

Table 2-4 Laboratory Assessments

Hematology	Biochemistry	Urine measurements**
Hematocrit	Alanine aminotransferase (ALT)	Specific gravity
Hemoglobin	Albumin (Alb)	pH
Platelet count	Alkaline phosphatase (ALP)	Glucose
Red blood cell count (RBC)	Asparate aminotransferase (AST)	Protein (Total)
White blood cell count (WB)	Blood urea nitrogen (BUN)	Ketones
WBC differential	Calcium	Bilirubin
	Magnesium	Urobilinogen
	Phosphate	Hemoglobin (blood)
Red blood cell distribution width (RDW)	Chloride	Leukocyte esterase
Mean corpuscular volume (MCV)	Creatinine*	Nitrite
Mean corpuscular hemoglobin concentration (MCHC)	Glucose	WBC
	Potassium	RBC sediments
	Sodium	Hyaline casts
	Bicarbonate	Granular casts
	Total bilirubin (TBL)	Waxy casts
	Fractionated bilirubin (if total bilirubin > 2x ULN)	WBC casts
	Total protein	RBC casts
	Uric acid	
	eGFR*	

*Abbreviated laboratory evaluations must include these parameters

**Urinalysis with dipstick includes specific gravity, pH, glucose, total protein, bilirubin, ketones, urobilinogen, nitrite, leukocytes esterase and hemoglobin (blood). Other urine measurements listed are not required. If a urine dipstick is positive, other urine measurements such as a qualitative microscopic determination of WBC, RBC sediments (and casts) should also be measured.

Both complete laboratory evaluations and abbreviated laboratory evaluations will be included in the summaries for laboratory data. In general, local lab and central lab data will be analyzed separately. However, for shift tables, where only abnormal/normal values are used, they may be summarized together. Here, "summarized together" means the following:

1) For each patient, the shift will be calculated either within local lab, or within central lab.
2) In the shift table, these shifts will be presented together. If shifts within both, local lab and central lab are available, at the same visit, only shifts within the central lab will be shown.

Test values and change from baseline based on the local laboratory assessments and the central laboratory assessments will be summarized by laboratory parameter, age group (and overall) and visit, using number of observations, mean, standard deviation, median, minimum, Q1, Q3, and maximum.

The shift from baseline will be summarized by laboratory parameter, age group and visit, using the numbers and percentages of patients in each category (low/normal/high).

For missing lab data at a given visit (except for lab performed after IMP discontinuation), the missing data will be taken from an unscheduled visit between two scheduled visits if they are available. Otherwise will leave them as missing. The data from the unscheduled visit for the missing data imputation will use the central lab data for tables reporting central lab analyses, and local lab data for table reporting local lab analyses.

Clinically notable laboratory abnormality

Table 2-3 provides criteria for clinically notable laboratory abnormalities.

The clinically notable laboratory abnormalities during the treatment period based on the local laboratory assessments and the central laboratory assessments will be summarized together (the definition of "summarized together" is the same as that for the shift tables described above) by criteria and age group, using the numbers and percentages of patients satisfying such criteria.

Table 2-5 Clinical notable criteria for laboratory values

Parameter	Conventional Units	SI Alert Value	SI Units
Hematology			
Red Blood Cell Count	x10E6/uL	>50% increase and >ULN; >30% decrease and <LLN.	x10E12/L
Hemoglobin	g/dL	>50% increase and >ULN; (>30% decrease and <LLN) or any value <70.	g/L
Hematocrit	%	>50% increase and >ULN; >30% decrease and <LLN.	L/L
White Blood Cell Count	x10E3/uL	>50% increase and >ULN; >50% decrease and <LLN.	x10E9/L
Platelet Count	x10E3/uL	>75% increase and >ULN; >50% decrease and <LLN.	x10E9/L
Chemistry			

BUN	mg/dL	>50% increase and >ULN	mmol/L
Creatinine	mg/dL	>50% increase and >ULN	umol/L
Albumin	g/dL	<20	g/L
Glucose	mg/dL	>50% increase and >ULN; (>50% decrease and <LLN) or any value <3.3.	mmol/L
Total Bilirubin	mg/dL	>100% increase and >ULN	umol/L
AST (SGOT)	U/L	>150% increase and >ULN	U/L
ALT (SGPT)	U/L	>150% increase and >ULN	U/L
Sodium	mEq/L	(>5% increase and >ULN) or any value >150; (>5% decrease and <LLN) or any value <125	mmol/L
Potassium	mEq/L	(>20% increase and >ULN) or any value >6; (>20% decrease and <LLN) or any value <3.	mmol/L
Chloride	mEq/L	>10% increase and >ULN; >10% decrease and <LLN	mmol/L
Calcium	mg/dL	>10% increase and >ULN; >10% decrease and <LLN.	mmol/L
Uric Acid	mg/dL	>50% increase and >ULN	mmol/L

Liver events

Table 2-4 provides criteria for liver laboratory triggers and liver events.

The liver laboratory triggers and liver events during the treatment period based on the local laboratory assessments and the central laboratory assessments will be summarized together by criteria and age group, using the numbers and percentages of patients satisfying such criteria.

Table 2-6 Liver event and laboratory trigger definitions

	Definition / threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

Definition / threshold
*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal

Renal events

Renal events are defined using the following two categories of criteria.

1. Serum event:
    a. Serum estimated GFR* decrease ≥ 25% compared to baseline AND eGFR < 90 mL/min/1.73m^2
    b. Serum estimated GFR* decrease ≥ 50% compared to baseline

Note that *eGFR is calculated using a modified Schwartz formula for patients <18 years: eGFR (ml/min/1.73m^2) = 0.413 x height (cm) / serum creatinine (mg/dl).

2. Urine event:
    a. New onset (≥1+) proteinuria
    b. New onset (≥1+) hematuria
    c. New onset (≥1+) glucosuria

The renal events during the treatment period based on the local laboratory assessments and the central laboratory assessments will be summarized together by criteria and age group (and overall), using the numbers and percentages of patients satisfying such criteria.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Not applicable, there are no ECG/cardiac imaging data.

2.8.4.2 Vital signs

The test values and the changes from baseline in vital signs (sitting/supine pulse rate, sitting/supine systolic blood pressure, sitting/supine diastolic blood pressure) will be summarized by vital sign parameter, age group and visit, using number of observations, mean, standard deviation, median, minimum, Q1, Q3, and maximum. By-visit summaries will only include scheduled assessments.

The number (percentage) of patients with clinically notable vital signs (Table 2-5) during the treatment period will be summarized by visit, separately by criteria and age group.

Table 2-7 Criteria for clinically notable vital signs

Age (years)	HR [min^{-1}]	SBP [mmHg]	DBP [mmHg]
1- <3	<60, >120	<76, >115	<45, >75
3- <6	<55, >120	<82, >120	<50, >80
6- <12	<50, >105	<90, >130	<50, >80

Age (years)	HR [min^{-1}]	SBP [mmHg]	DBP [mmHg]
≥ 12	<45, >95	<90, >145	<55, >90

2.8.4.3 Changes in height, weight and head circumference

Summary statistics and change from baseline will be provided for weight, height, and head circumference (patients ≤ 3 years) by visit and age group (and overall). Subgroup analysis of height (i.e., height, z-score for height and age-adjusted percentile for height) will be performed for patients satisfying the criterion of being within the age range of 2-9 years at each 12-month visit throughout the OLE study and for overall group. Summary statistics by yearly visit will be provided.

In addition, age-adjusted percentile will be calculated for height, weight and BMI; Z-score will be calculated for height, as done by the WHO to assess child growth. For more details, see World Health Organization (WHO) 1997.

The same summaries as for the raw values will be produced for these Z-scores. In addition, shift tables will be produced using the following rules for severe low/moderate low/normal classification (Dibley et al, Mei Z and Grummer-Strawn LM, World Food Programme):

- Z-score < -3: severe low
- -3 ≤ Z-score < -2: moderate low
- Z-score ≥ -2 : normal

2.9 Pharmacokinetic endpoints

Not applicable. There are no PK analyses.

2.10 PD and PK/PD analyses

Not applicable. There are no PD and PK/PD analyses.

2.11 Patient-reported outcomes

Not applicable, there are no patient-reported outcomes.

2.12 Biomarkers

Not applicable, there are no biomarkers.

2.13 Other Exploratory analyses

Not applicable. There are no other exploratory analyses.

2.14 Interim analysis

No interim analysis is planned. However, the safety will be monitored through regular review of adverse events and related data.

3 Sample size calculation

There is no specific sample size required for the study. All patients who have completed the double-blind phase of the study PANORAMA-HF, as defined in the protocol Inclusion Criteria, and who meet all other Inclusion and Exclusion criteria, are eligible for the extension study.

4 Change to protocol specified analyses

None.

5 Appendix

5.1 Imputation rules

The missing or partially missing start/end date for AEs and prior/concomitant therapies will be imputed using the Novartis AGB global standard approach. Details will be provided in the study PDS.

If the visit date is missing, the scheduled date (per protocol) of the visit will be used.

5.1.1 Study drug

If the study drug start date is missing, then the planned start date will be used. If only the study start day is missing (but the month is known), then the study start day will be the 1st day of that month, unless the planned date of the first dose is in the same month, then it will be the planned date of the first dose.

5.1.2 AE date imputation

See Section 5.1.

5.1.3 Concomitant medication date imputation

See Section 5.1.

5.1.3.1 Prior therapies date imputation

See Section 5.1.

5.2 Rule of exclusion criteria of analysis sets

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

Deviation ID	Description of Deviation	Exclusion from analyses
INCL01	No informed consent.	Excluded from all analyses.

Table 5-2 Subject classification

Analysis set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
SCR	INCL01	Not applicable.
SAF	INCL01A and INCL01B	Not obtaining any study medication.

6 Reference

WHO Global Database on Child Growth and Malnutrition (Internet) Available from: [https://apps.who.int/iris/bitstream/handle/10665/63750/WHO_NUT_97.4.pdf] (Accessed 02 May 2019).

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World Food Programme, 2005. A manual: measuring and interpreting malnutrition and mortality. Rome, World Food Programme.

Mei Z and Grummer-Strawn LM, 2007. Standard deviation of anthropometric Z-scores as a data quality assessment tool using the 2006 WHO growth standards: a cross country analysis. Bulletin of the World Health Organization, 85, pp. 441-448.