NOVARTIS

Clinical Development

LCZ696/ Sacubitril Valsartan Sodium Hydrate /Entresto®

CLCZ696B2319E2 / NCT06149104

A multicenter, open-label study to collect the safety information of sacubitril/valsartan in Japanese pediatric patients with heart failure due to systemic left ventricle systolic dysfunction who have completed CLCZ696B2319E1 study

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
27-Nov-2023	Prior to DB lock	Creation of final version	N/A - First version	NA
30-August 2024	Prior to DB lock	To Add software used for analysis	Unless otherwise specified, the data will be analyzed according to the study protocol using SAS® 9.4 or higher and current version R® at time of analysis, by Novartis personnel.	2.1 Data analysis general information
30-August - 2024	Prior to DB lock	To clear the definition of each scheduled visit	Each scheduled visit is defined using the study day as follows: · Visit 3M = day 91 · Visit 6M = day 183	2.1.1 General definitions
30-August - 2024	Prior to DB lock	To correct a typo	The z-score formula is corrected.	2.3.2 Demographics and other baseline characteristics
30-August - 2024	Prior to DB lock	To clear the definition of the visit date	The dose level for each visit is defined as the dose level of dosing interval with its start date prior to or equal to the scheduled visit date and its end date later than or equal to the scheduled visit date. For EOS visit, actual visit date is used to identify the dose level.	2.4.1 Study treatment/ compliance
30-August - 2024	Prior to DB lock	To correct the summarization category	summarized by medication category and preferred term	2.4.2 Prior, concomitant and post therapies
30-August - 2024	Prior to DB lock	To remove RMP text from description of	The following treatment emergent adverse event of special interest will be summarized.	2.7.1.1 Adverse events of special interest

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		adverse event of special interest		/ grouping of AEs
30-August-2024	Prior to DB lock	Updated eCRS to remove some risk definitions from the eCRS and change some risk names.	- Anaphylaxis, Hypersensitivity, and Malignancy were removed from event list. - Changed 'Change in bone growth and density' to 'Long term effects on growth bone growth and mineralisation in the pediatric population' - Removed "(Narrow SMQ)" following risk name	2.7.1.1 Adverse events of special interest / grouping of AEs
30-August-2024	Prior to DB lock	To add rules for handling overlap between EOS and Visit M6	If the timing of EOS and Visit M6 overlaps and two visits are made simultaneously, the data will be used for both EOS and Visit M6. The window of Visit M6 is defined as ±1 month of the scheduled visit date (day183±30).	2.7.4.2 Vital signs
30-August-2024	Prior to DB lock	To add rules for handling overlap weight data between EOS and Visit M6	For weight, if the timing of EOS and Visit M6 overlaps and two visits are made simultaneously, the data will be used for both EOS and Visit M6. The window of Visit M6 is defined as ±1 month of the scheduled visit date (day183±30).	2.7.4.3 Hight and Wight

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List of abbreviations

ACEI	Angiotensin Converting Enzyme Inhibitor
AE	Adverse Event
AGB	ADaM Governance Board
ARB	Angiotensin Receptor Blocker
CRF	Case Report Form
CSR	Clinical Study Report
eCRS	electronic Case Retrieval Strategy
EOS	End of Study
ENR	Enrolled Set
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRAs	Mineralcorticoid Receptor Antagonists
PDs	Protocol deviations
PK	Pharmacokinetics
SAF	Safety Set
SAP	Statistical Analysis Plan
SGLT2i	Sodium-GLucose co-Transporter2 inhibitor
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) describes details of the analyses as outlined in section 9 of the study protocol. Results will be summarized in the clinical study report (CSR).

1.1 Study design

This study (CLCZ696B2319E2) is a multicenter, open-label extension study for Japanese patients who have successfully completed the CLCZ696B2319E1 (PANORAMA-HF OLE) study (Figure 1-1). PANORAMA-HF OLE study is an on-going Phase 3b study in pediatric patients with systemic left ventricular systolic dysfunction to evaluate long- term safety and tolerability of sacubitril/valsartan in eligible CLCZ696B2319 (PANORAMA-HF) participants.

Only Japanese patients who successfully completed PANORAMA-HF OLE study and fulfill protocol requirements are eligible to participate in this study, and will be offered the option to initiate treatment with sacubitril/valsartan by enrolling into this study at the discretion of the Investigator. Participants who permanently discontinued study drug treatment during PANORAMA-HF OLE study are not eligible for this study.

For all consenting patient's eligibility for this study will be assessed at the first visit (Visit Day1) and the study medication will be initiated. The first visit (Visit Day1) is the same day as the End of Study visit (Visit 599) of PANORAMA-HF OLE study.

The starting dose of study drug will be determined by the Investigator considering the participant's condition. The dose level of open-label sacubitril/valsartan at the end of study visit of PANORAMA-HF OLE study may remain the same, or the dose level may be changed at the discretion of the Investigator.

Study Duration:

Actual duration depends on the timing of sacubitril/valsartan formulation for pediatrics available on the market in Japan.

Treatment Duration:

Until marketed product of pediatric formulation is available in Japan

Visit Frequency:

Every 3 months (including telephone visits)

Treatment of interest

The investigational treatment sacubitril/valsartan

Number of Participants:

A maximum of 8 Japanese patients will be enrolled into the study.

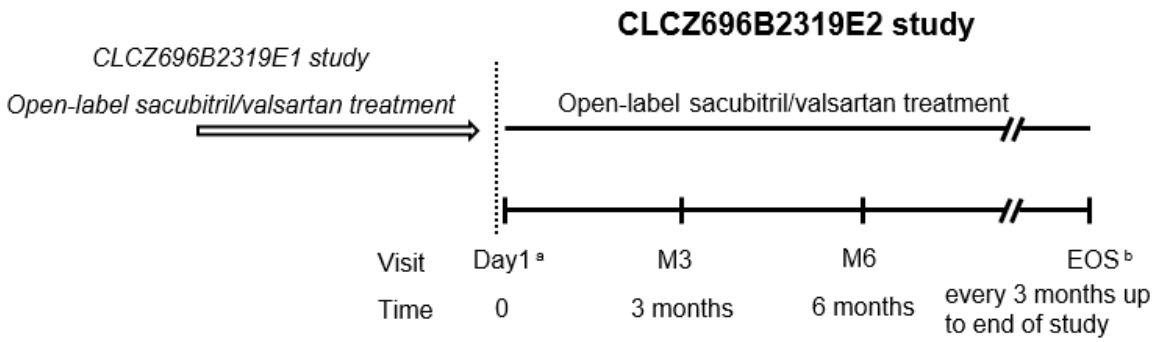
Key Inclusion criteria

1. Signed informed consent as well as assent at an appropriate age must be obtained prior to participation in the study.
2. Male or female, inpatient or outpatient, and < 18 years of age (at the time of signing informed consent).
3. Patients who have completed PANORAMA-HF OLE study and are able to be safely enrolled into this study as judged by the Investigator.

Key Exclusion criteria

1. Patients who permanently discontinued the study drug treatment during PANORAMA-HF OLE study.
2. Renal vascular hypertension (including renal artery stenosis).
3. Patients with a history of angioedema.
4. Patients who have parents or legal guardians who do not give consent or allow the child to give assent, or inability of the patient or the parents/legal guardians to follow instructions or comply with follow-up procedures.
5. Any medical condition(s) that may put the patient at risk in the Investigator's opinion, or that the Investigator deems unsuitable for the study.

Figure 1-1 Study design



EOS = End of study visit

a. Visit Day1 is the same day as the End of Study visit (Visit 599) of CLCZ696B2319E1 study.
b. This study will end when marketed product of pediatric formulation is available in Japan.

1.2 Study objectives, endpoints and estimands

The primary objective is to collect additional safety information of sacubitril/valsartan in the eligible Japanese patients who completed CLCZ696B2319E1 study.

There are no secondary or exploratory objectives for this study.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)** • Adverse events (AEs)

Objective(s)	Endpoint(s)
• To collect additional safety information of sacubitril/valsartan in Japanese patients after long-term treatment of sacubitril/valsartan in CLCZ696B2319E1 study	

1.2.1 Primary estimand(s)

Not applicable

1.2.2 Secondary estimand(s)

Not applicable

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 current version R® at time of analysis, by Novartis personnel.

In general, continuous variables will be summarized using number of observations, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized using frequencies and percentages.

Study completion is defined as having reached the end of study visit (Figure 1-1).

Data from all study centers will be combined.

2.1.1 General definitions

- The study treatment is sacubitril/valsartan.
- The date of first administration of study treatment during this study is the day of the first non-zero dose of sacubitril/valsartan after patient is enrolled in CLCZ696B2319E2 study.
- The date of last administration of study treatment is the day of the last non-zero dose of sacubitril/valsartan.
- The study period starts with the date of the signature on informed consent (Visit Day 1, the same day as Visit 599 (EOS visit) of PANORAMA-HF OLE study) and ends with the date of end-of-study or premature study discontinuation visit (Visit EOS).
- The treatment period starts with the date of first administration of study treatment in CLCZ696B2319E2 study and ends with the date of treatment disposition. In the case that no EOS visit is undertaken (e.g., because the participant died or withdrew from the study without such a visit), the treatment period ends with the death/withdrawal date, or the last dose taken.
- Baseline is defined as the variable on the date of Visit Day 1 regardless of whether the study treatment is administered on Visit Day 1.
- Study day is defined as actual date – date of Visit Day1 + 1

- Treatment day is defined as actual date – the date of first administration of study treatment + 1
- Each scheduled visit date is defined using the study day as follows:
  - Visit M3 = day 91
  - Visit M6 = day 183

2.2 Analysis sets

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

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

The number of patients and percentage for all patients who enrolled in this study will be provided for each analysis set.

2.2.1 Subgroup of interest

No subgroup analysis will be provided in this study considering the small number of patients.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number and percentage of patients who don't meet a screen failure will be provided. For screen failures, the inclusion/ exclusion criteria they did not meet will be summarized using the numbers and percentages of patients.

These summaries will be performed for the ENR.

The number and percentage of patients who complete the study, who discontinue from the study and the primary reasons for discontinuation will be summarized. In addition, the number and percentage of patients with protocol deviations (PDs) will be provided.

These summaries will be performed based on the SAF.

2.3.2 Demographics and other baseline characteristics

Demographic and other characteristics at Visit Day1, including age, age group (6 years and older, < 6 years), sex, weight, height, body mass index (BMI), vital signs, and age adjusted percentile for weight and height, and z-score for height will be summarized descriptively.
BMI will be calculated as weight (kg) / height^2 (m^2) using the collected height and weight at Visit Day1.

For the calculation of z-score and age adjusted percentile, the child growth database presented by World Health Organization (WHO) (WHO global database) will be used. Z-score will be calculated using the Box-Cox power, median and coefficient of variation in the database

following the procedure recommended in database instructions (WHO computation instructions).

The individual z-score (z_{ind}) for a measurement at age t is defined as:

$$z_{ind} = \frac{\left[\frac{x}{M(t)}\right]^{L(t)} - 1}{S(t)L(t)}$$

where, the Box-Cox power, median and coefficient of variation corresponding to age *t* are denoted by $L(t)$, $M(t)$ and $S(t)$, respectively.
Final z-score is calculated as:

- $|z_{ind}| \leq 3$ $\quad z\text{-}score = z_{ind}$
- $z_{ind} > 3$ $\quad z\text{-}score = 3 + \frac{x - M(t)[1+3L(t)S(t)]^{\frac{1}{L(t)}}}{M(t)[1+3L(t)S(t)]^{\frac{1}{L(t)}} - M(t)[1+2L(t)S(t)]^{\frac{1}{L(t)}}}$
- $z_{ind} < -3$ $\quad z\text{-}score = -3 + \frac{x - M(t)[1+(-3)L(t)S(t)]^{\frac{1}{L(t)}}}{M(t)[1+(-2)L(t)S(t)]^{\frac{1}{L(t)}} - M(t)[1+(-3)L(t)S(t)]^{\frac{1}{L(t)}}}$

Age adjusted percentile will be calculated from z-score as the probability that an observation from the standard normal distribution is less than or equal to z-score.

Relevant medical histories at Visit Day1 will be summarized, by system organ class and preferred term.

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

The study treatment administration is recorded on the Case Report Form (CRF) page: "Dosage Administration Record" using start date, end date, dispensing name of the study treatment and the type of change. Each pair of start date and end date will be considered as a dosing interval, if type of change is recorded as 'Dose interrupted' then this dosing interval will be considered as temporary interruptions.

Duration of exposure to the study treatment will be defined as both the treatment period including temporary interruptions and the treatment period excluding temporary interruptions and summarized for continuous variable.

Dose levels will be summarized for continuous variable by visit, regardless of the pediatric or adult dose level. In addition, the number and percentage of patients for each dose level (Dose level 1 to 4, and No treatment) will be provided by visit.

The dose level for each visit is defined as the dose level of dosing interval with its start date prior to or equal to the scheduled visit date and its end date later than or equal to the scheduled visit date. For EOS visit, actual visit date is used to identify the dose level.

In addition, the following information will be listed.

- Subject ID
- Date of Visit Day1
- Start date (Study day)

  Displays the start date entered on CRF or imputed and corresponding Study day (number of days from Visit Day1).
- End date (Study day)

  Displays the end date entered on CRF or imputed and corresponding Study day (number of days from Visit Day1).
- Dose Form (Granule/ Liquid/ Tablet)
- Dispensing Name (Dose Level)
- Dose administered
- Unit
- Type of Change (Dose changed/ Dose interrupted/ Dose permanently discontinued)
- Reason for Change（Adverse event/ Disease improvement under study/ Dosing error/ Dispensing error/ Technical problems/ Subject decision/ Guardian decision/ Physician decision/ As per protocol）

The SAF will be used for the above analyses.

2.4.2 Prior, concomitant and post therapies

Prior medications and significant non-drug therapies are defined as any medication or significant non-drug therapy within 30 days prior to Visit Day1 with its start date prior to the date of Visit Day1. Concomitant medications and significant non-drug therapies are defined as any medication or significant non-drug therapy with its end date later than or equal to the date of the Visit Day1 and start date prior to or equal to the end date of the treatment period.

Prior and concomitant medications and significant non-drug therapies will be summarized by anatomical therapeutic classification (ATC), preferred term.

Concomitant heart failure medications (Angiotensin converting enzyme inhibitor (ACEI), Angiotensin receptor blocker (ARB), Beta-blockers, mineralcorticoid receptor antagonists (MRAs), diuretics (excluding MRAs), Cardiac glycocytes (Digoxin/digitalis glycoside), and sodium-glucose co-transporter2 inhibitors (SGLT2i)) will be summarized by medication category and preferred term.

In addition, the prior or concomitant medications and other non-drug therapies will be listed as follows:

- Medications
  - Subject ID
  - Date of Study Treatment start
  - Start date (Treatment day)

    Displays the start date entered on CRF or imputed and corresponding Treatment day (the number of days from the date of treatment start).
  - End date (Treatment day)

    Displays the end date entered on CRF or imputed and corresponding Treatment day (the number of days from the date of treatment start).
  - On going

    If the check box of 'On going' on CRF (the medication is ongoing at the end of the study), provide 'Yes'.
  - Primary indication
  - ATC
  - Preferred term
  - Reported medication name
  - Dose
  - Dose unit
  - Frequency
  - Route

- Non-drug therapies
  - Subject ID
  - Date of Study Treatment start
  - Start date (Treatment day)

    Displays the start date entered on CRF or imputed and corresponding Treatment day (the number of days from the date of treatment start).
  - End date (Treatment day)

    Displays the end date entered on CRF or imputed and corresponding Treatment day (the number of days from the date of treatment start).
  - Primary Indication

- Procedure name

The SAF will be used for the above analyses.

2.5 Analysis supporting primary objective(s)

2.5.1 Primary endpoint(s)

Any adverse events (treatment emergent or not) are considered primary endpoints.

2.5.2 Statistical hypothesis, model, and method of analysis

There are no statistical hypotheses to be tested in this study and no model analyses will be performed.

Adverse events will be summarized by primary system organ class and preferred term, using numbers and percentages of patients with at least one adverse event in the corresponding class.

The SAF will be used for analyses for primary endpoints.

2.5.3 Handling of intercurrent events

Not applicable.

2.5.4 Handling of missing values not related to intercurrent event

The missing value for laboratory assessments, vital signs, height, weight, and other assessments will be not imputed.

The missing or partially missing start/end date for AEs, prior/concomitant therapies, and study drug will be imputed using the Novartis ADaM Governance Board (AGB) global standard approach. Details are provided in Section 5.1.

2.5.5 Sensitivity analyses

Not applicable

2.5.6 Supplementary analyses

Not applicable

2.6 Analysis supporting secondary objectives

Not applicable. There are no secondary endpoints.

2.7 Safety analyses

2.7.1 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.

The following adverse events will be summarized by primary system organ class, and preferred term as appropriate using numbers and percentages of patients with at least one adverse event in the corresponding class. Similarly, Summarization by maximum severity will be conducted.

- Any serious adverse event (treatment emergent or not)
- Treatment emergent adverse event (TEAE)
- Treatment emergent serious adverse event

TEAEs are defined as any recorded AE with its start date (recorded or imputed) on or after Visit Day 1 (the date of first administration of study treatment if treatment did not start at Visit Day1) and end date as the end date of the treatment period or the date of last dose taken as reported in the DAR page. Any AE happening after treatment discontinuation 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.

All outputs will be created for AEs regardless of study-drug relationship, and for study-drug related AEs. Study drug related AEs are defined as any recorded AE with "Relationship to study treatment" answered as "Related". Serious adverse events (SAEs) are defined as any recorded AE with "Was the adverse evevnt serious?" answered as "Yes".

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.

In addition, the following information will be listed for all AEs.

- Subject ID
- Date of Study Treatment start
- Start date (Treatment day)

  Displays the start date entered on CRF or imputed and corresponding Treatment day (the number of days from the date of treatment start).
- End date (Treatment day)

  Displays the end date entered on CRF or imputed and corresponding Treatment day (the number of days from the date of treatment start).
- Duration

  End date – Start Date + 1 will be calculated. For on-going AE, leave blank.
- Reported Name of AE
- SOC
- PT

- Relationship to study treatment (Related/ Not related)
- SAEs (Yes/No)
- Severity (Mild/ Moderate/ Severe)
- Action Taken with Study Treatment (Dose increased/ Dose not changed/ Dose reduced/ Drug interrupted/ Drug withdrawn/ Not applicable/ Unknown)
- Concomitant or additional treatment (Yes/ No)
- Outcome
- TEAE (Yes/No)

The SAF will be used for the above analyses.

2.7.1.1 Adverse events of special interest / grouping of AEs

The following treatment emergent adverse event of special interest will be summarized.

- Angioedema
- Long term effects on growth bone growth and mineralisation in the pediatric population
- Cognitive impairment
- Embryo-fetal toxicity or lethality
- Hepatotoxicity
- Hyperkalaemia
- Hypotension
- Neonatal or infantile toxicity through exposure from breast milk
- Renal impairment
- Statin drug-drug interaction

The definitions of these events will be defined in the electronic Case Retrieval Strategy (eCRS, ID: 6511 LCZ696 Hf (adult and pediatric)).

For each risk, the following analyses will be conducted.

- Numbers and percentages of patients with any TEAE within the risk category (or SOC/PT within risk category) by risk category, SOC, PT and maximum severity.
- Listing of Subject ID per risk.

In addition, the MedDRA coding definitions for each risk on the eCRS used to analysis will be listed regardless of the presence or absence of applicable patients.

The SAF will be used for the above analyses.

2.7.2 Deaths

Death 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.

The SAF will be used for the above analyses.

2.7.3 Laboratory data

A listing of laboratory data collected in eCRF (i.e. Serum sodium, potassium, creatinine, and estimated Glomerular Filtration Rate (eGFR)) will be provided for the following information by each test item.

- Subject ID
- Date of Study Treatment start
- Collection date (Treatment day)

  Displays the collection date entered on CRF or imputed and corresponding Treatment day (the number of days from the date of treatment start) .
- Test name
- Test value

  Displays the value converted to SI units.
- SI Unit
- Normal range

  Displays the normal range converted to SI units.
- Abnormality (H/L)

  Displays ‘H’ if the test value is above the upper limit of the normal range, ‘L’ if the test value is below the lower limit, otherwise leave blank.

The SAF will be used for the above analyses.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

Not applicable

2.7.4.2 Vital signs

Descriptive statistics of vital signs (pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP)) for test values and the number of patients and percentages with clinically notable vital signs during the treatment period will be provided by visit (Day1, M6, EOS). These by-visit summaries will only include scheduled assessments. If the timing of EOS and Visit M6

overlaps and two visits are made simultaneously, the data will be used for both EOS and Visit M6. The window of Visit M6 is defined as ±1 month of the scheduled visit date (day183±30).

Criteria of clinically notable vital signs are shown in the Table 2-1.

Table 2-1 Criteria for clinically notable vital signs

Age	PR [min-1]	SBP [mmHg]	DBP [mmHg]
1- <3 years	<60, >120	<76, >115	<45, >75
3- <6 years	<55, >120	<82, >120	<50, >80
6- <12 years	<50, >105	<90, >130	<50, >80
≥12 years	<45, >95	<90, >145	<55, >90

In addition, all vital signs data collected in eCRF (including unscheduled assessments) will be listed for the following information.

- Subject ID
- Date of Study Treatment start
- Collection date (Treatment day, Visit name)

  Displays the collection date entered on CRF or imputed, corresponding Treatment day (the number of days from the date of treatment start) and Visit name.
- Test name
- Test value
- Unit
- Clinically notable vital signs

  Displays 'Yes' if the criteria of clinically notable vital signs is met.

The SAF will be used for the above analyses.

2.7.4.3 Height and Weight

Descriptive statistics will be provided for test values of weight, height, BMI, age adjusted percentile for weight and height, and z-score for height by visit. For weight, if the timing of EOS and Visit M6 overlaps and two visits are made simultaneously, the data will be used for both EOS and Visit M6. The window of Visit M6 is defined as ±1 month of the scheduled visit date (day183±30).

A listing for these items (i.e. weight, height, BMI, age adjusted percentile for weight and height, and z-score for height) will be provided for all visits including unscheduled assessments.

- Subject ID
- Date of Study Treatment start
- Assessment date (Treatment day, Visit name (Weight only))

Displays the assessment date entered on CRF or imputed, corresponding Treatment day (the number of days from the date of treatment start) and Visit name (Weight only)

- Test name
- Value
- Unit
- Adjusted percentile (Weight, height)
- Z-score (Height only)

BMI will be calculated as weight (kg) / height^2 (m^2) using the collected height and weight at each visit.
Refer to Section 2.3.2 for Z-score and age adjusted percentile.

The SAF will be used for the above analyses.

2.8 Pharmacokinetic endpoints

Not applicable

2.9 PD and PK/PD analyses

Not applicable

2.10 Patient-reported outcomes

Not applicable

2.11 Biomarkers

Not applicable.

2.12 Other Exploratory analyses

Not applicable. There are no exploratory endpoints.

2.13 Interim analysis

Not applicable

3 Sample size calculation

All patients who have completed PANORAMA-HF OLE study and who meet all Inclusion and Exclusion criteria (Section 1.1), are eligible for this extension study.

There is no specific sample size required for the study. A maximum of 8 Japanese patients will be enrolled into the 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.

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 treatment start date is missing, then the planned start date (the date of Visit Day1) will be used. If only the start day is missing (but the month is known), then the start day will be the 1st day of that month, unless the planned date of the Visit Day1 is in the same month, then it will be the planned date of the Visit Day1.

5.1.2 AE date imputation

5.1.2.1 Adverse Event End Date Imputation

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

5.1.2.2 Adverse Event Start Date Imputation

The following table explains the notation used in the logic matrix. Please note that missing start dates will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.c) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min(informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date

Impute AE start date;

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
4. If the AE start date year value is equal to the treatment start date year value:
    a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
    b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
    c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.3 Concomitant medication date imputation

- Concomitant medication end date imputation

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of treatment end date and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of treatment end date and the end of the year (31DECYYYY).
3. If CM day/month/year is missing then use the treatment end date + 1 day as the imputed CM end date.

4. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

➢ Concomitant medication start date imputation

The following table explains the notation used in the logic matrix. Please note that missing start dates will not be imputed.

	Day	Month	Year
Partial CMD Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) Uncertain	(1) Uncertain	(1) Uncertain	(1) Uncertain
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.a) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

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

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

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.1.3.1 Prior therapies date imputation

See Section 5.1.3.

5.1.3.2 Post therapies date imputation

See Section 5.1.3.

5.1.3.3 Other imputations

None

5.2 AEs coding/grading

Not applicable

5.3 Laboratory parameters derivations

Not applicable

5.4 Statistical models

Not applicable

5.4.1 Analysis supporting primary objective(s)

Not applicable

5.4.2 Analysis supporting secondary objective(s)

Not applicable

5.5 Rule of exclusion criteria of analysis sets

PDs excluded from the ENR or SAF are shown in Table 5-1. Patients with only PDs that are not included in the list will not be excluded from any analysis sets.

Table 5-1 Protocol deviation criteria leading to exclusion from the analysis sets

PD ID	Description	ENR	SAF
INCL01A	No informed consent.	X	X
INCL01C	ICF was not signed by subject/ parent/legal guardian; however, other family member signed on behalf the subject.	X	X

PD ID	Description	ENR	SAF
INCL02	Patients aged >= 18 was enrolled in the study.		X
EXCL04A	Patient who has parents or legal guardians who do not give consent or allow the child to give assent.	X	X

6 Reference

1. WHO Global Database on Child Growth and Malnutrition (Internet) Available from: [https://iris.who.int/bitstream/handle/10665/63750/WHO_NUT_97.4.pdf] (Accessed 11 September 2023).
2. COMPUTATION OF CENTILES AND Z-SCORES FOR HEIGHT-FOR-AGE, WEIGHT-FOR-AGE AND BMI-FOR-AGE (Internet) Available from: [https://cdn.who.int/media/docs/default-source/child-growth/growth-reference-5-19-years/computation.pdf] (Accessed 16 Oct 2023).