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Novartis Research and Development

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

Clinical Trial Protocol Number: CLCZ696B2319E2 / NCT06149104

Version Number: 00 (Original Protocol)

Compound: LCZ696/ Sacubitril Valsartan Sodium Hydrate

Brief Title: A safety study of sacubitril/valsartan in Japanese pediatric patients with heart failure due to systemic left ventricle systolic dysfunction who have completed CLCZ696B2319E1 study

Study Phase: Ⅲb

Sponsor Name: Novartis

Regulatory Agency Identifier Number(s): NA

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1 Protocol summary

1.1 Summary

Protocol Title:

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

Brief Title:

A safety study of sacubitril/valsartan in Japanese pediatric patients with heart failure due to systemic left ventricle systolic dysfunction who have completed CLCZ696B2319E1 study

Purpose

The purpose of this open-label study is to collect additional safety information of sacubitril/valsartan and to provide post-trial access to sacubitril/valsartan for the eligible Japanese patients who completed CLCZ696B2319E1 study until marketed product of pediatric formulation, film-coated granules in capsule, is available in Japan.

Study Indication /Medical Condition:

Heart Failure

Treatment type

Drug

Study type

Interventional

Objectives, Endpoints, and Estimands:

Table 1-1 Primary and secondary objectives, endpoints and estimands

Objectives	Endpoints
Primary	
To collect additional safety information of sacubitril/valsartan in Japanese patients after long-term treatment of sacubitril/valsartan in CLCZ696B2319E1 study	Adverse events (AEs)
Secondary	
Not applicable	Not applicable

Trial Design:

This trial (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 (see Section 5) 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 (see Section 5.2).

For all consenting patients eligibility for this study will be assessed at the first visit (Visit Day1) and the study medication will be initiated (see Section 8 for details). 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 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.

Brief Summary:

The purpose of this open-label study is to collect additional safety information of sacubitril/valsartan and to provide post-trial access to sacubitril/valsartan for the eligible Japanese patients who completed CLCZ696B2319E1 study until marketed product of pediatric formulation, film-coated granules in capsule, is available in Japan.

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.

Treatment Groups:

All participants will receive open-label sacubitril/valsartan.

Data Monitoring/Other Committee:

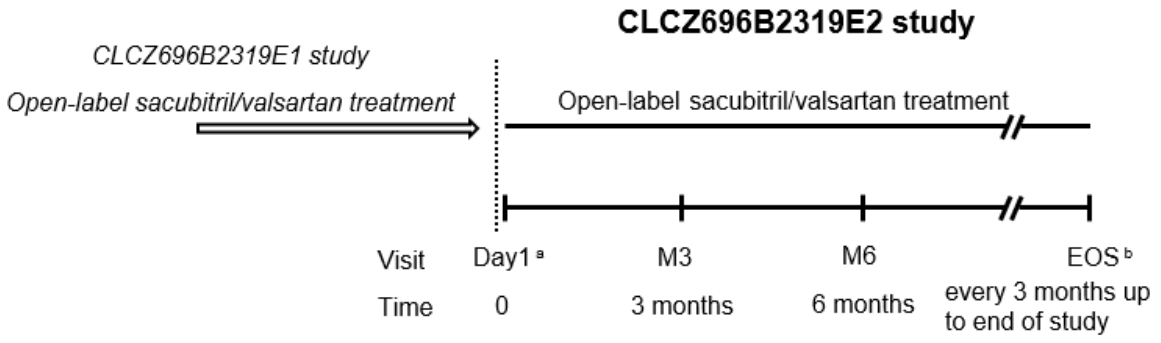
No

Key words

Pediatric, Japanese, LCZ696, sacubitril/valsartan, heart failure, open-label study, angiotensin receptor neprilysin inhibitor (ARNI)

1.2 Schema

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.

1.3 Schedule of activities (SoA)

The Assessment Schedule (Table 1-2) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. The "X" in the table denotes the assessments to be recorded in the clinical

database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Sacubitril/valsartan treatment will start at Visit Day1, which is the same day as the End of Study visit (Visit 599) of CLCZ696B2319E1 (PANORAMA-HF OLE) study. A telephone visit (Visit M3) and an on-site visit (Visit M6) will occur 3 months and 6 months after Visit Day1, respectively. The visits as same Visit M3 and Visit M6 will then be repeated every 3 months until the end of the study. When the pediatric formulation of sacubitril/valsartan becomes available in Japan, or this study is terminated by Novartis, any participants should return to the study site as soon as possible for End of Study (EOS) visit (Visit EOS) regardless of subsequent scheduled visit, and all of the assessments listed for Visit EOS will be performed.

Participants should take their scheduled dose of sacubitril/valsartan in the morning of their study visits. Participants are not required to fast overnight on the day prior to or the day of the study visit.

Participants should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. If one visit is postponed or brought forward, it should not result in the next visit being postponed or brought forward. The next visit, if at all possible, should adhere to the original schedule in relation to Visit Day1. Missed or rescheduled visits should not lead to automatic discontinuation. Specific circumstances surrounding missed or rescheduled visits must be discussed with the study monitor. Participants who prematurely discontinue the study treatment, or prematurely withdraws from the study for any reason should be scheduled for a final visit as soon as possible, at which time all of the assessments listed for the final visit (Visit EOS) will be performed.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the Investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 1-2 Assessment Schedule

Period	Treatment				
Visit name	Day1 #, 1	M3 †	M6 *	UNS	EOS 2
Day/ Month	Day 1	Mo 3	Mo 6	-	-
Obtain Informed Consent (parent (s)-legal guardian (s)/consent-assent (patient, as applicable) 3	X				
Inclusion/ Exclusion	X				
Demographics/ Medical histories	X				
Pediatric Heart Failure History	X				
Physical Examination	S		S	S	S
Vital Signs (BP and pulse)	X 5		X	X	X
Height 4	X 5		S	(S)	X
Weight	X 5		X	X	X
Laboratory assessments (locally) 6			X	(X)	X
Serum/Urine Pregnancy test (locally) 7			S (Urine)	S (Urine)	S (Serum)
AEs/SAEs	X	X	X	X	X
Concomitant medication/ Non-drug therapies	X	X	X	X	X
Dosage Administration Record	X	X	X	(X)	X
Study Medication Compliance	S		S	(S)	S
Dispense Study Medications	S	S	S	(S)	

UNS= Unscheduled visit, EOS= End of study visit

X: Assessment to be recorded in the clinical database or received electronically from a vendor

S: Assessment to be recorded in the source documentation only

(X) / (S) = parentheses indicate that this is an optional assessment

Visit Day1 is the same day as Visit 599 (EOS visit) of PANORAMA-HF OLE (CLCZ696B2319E1) study

† Visit M3 is a telephone visit.

* If the trial is extended, Visits M9, M12 to be performed at the same intervals and with same measurements as at Visits M3 and M6, respectively.

1. Patients who permanently discontinued the study drug treatment during PANORAMA-HF OLE study cannot be enrolled in this study (Section 5.2), however, patients who temporally discontinued the study drug for any reason at the End of Study visit (Visit 599) in PANORAMA-HF OLE study may be enrolled in this study. In this case, the assessments specified for Visit Day1 should be performed at the visit when the study treatment starts. They will have to discontinue the study unless the study treatment starts within 3 months from Visit Day1, and will be considered an early study termination (Section 5.3).
2. End of Study (EOS) visit will be completed when marketed product of sacubitril/valsartan pediatric formulation becomes commercially available in Japan, the study treatment is permanently discontinued based on the Investigator's judgement, or participant prematurely withdraws from the study, whichever occurs first.
3. Signed informed consent as well as assent at an appropriate age must be obtained prior to participation in the study. Patient Assent document is captured as a source document and is not stored in the clinical database.
4. If the trial is extended 1 year or over, height at Visit M12 should be recorded in the electronic Case Report Form (eCRF)
5. The data measured at the End of Study visit (Visit 599) in PANORAMA-HF OLE study will be utilized as the data at Visit Day1 for this study.

6. Serum sodium, potassium, creatinine, and estimated Glomerular Filtration Rate (eGFR, modified Schwartz formula) will be measured locally, and recored in the eCRF. Additional laboratory evaluation including hematology and urinalysis may be performed optionally by Investigator's clinical judgement at any visits. There is no local assessment at Visit Day1, but the results of central laboratory at the End of Study visit (Visit 599) in PANORAMA-HF OLE study should be reviewed by the Investigator soon after the results are obtained.
7. For child-bearing potential females (CHBP) only. Urine pregnancy test is analyzed locally and done at Visit M6 and unscheduled visits on all female participants ≥11 years of age and all female participants who are <11 years of age if they are menstruating. There is no assessment at Visit Day1, but the result of central laboratory (serum test) at the End of Study visit (Visit 599) in PANORAMA-HF OLE study should be reviewed by the Investigator soon after the result is obtained. Additionally, for all CHBP, a urine pregnancy test will be performed at monthly intervals during the study. The monthly urine pregnancy test can be performed either via: 1) monthly study site visits for urine pregnancy tests, or 2) providing the participant with urinary pregnancy tests for home monthly tests. See Section 8.4.5 for additional details. A serum pregnancy test is performed and analyzed locally at Visit EOS.

2 Introduction

2.1 Study rationale

The purpose of this open-label study is to collect additional safety information of sacubitril/valsartan and to provide post-trial access to sacubitril/valsartan for the eligible Japanese patients who completed CLCZ696B2319E1 study until marketed product of pediatric formulation, film-coated granules in capsule, is available in Japan.

2.2 Background

Pediatric heart failure (HF) is characterized by significant morbidity and mortality, frequent hospitalization and medical care, and poor quality of life. It is estimated that between 12,000 to 35,000 children below age 19 are diagnosed with HF in the United States (US) each year (Hsu, Pearson 2009). Congenital heart disease and cardiomyopathy are the two most common causes of pediatric HF (Sharma et al 2003, Andrews et al 2008). HF can develop or exacerbate in childhood, during adolescence and later in adulthood as made evident by the growing number of adults with congenital heart disease.

The clinical course and outcome for pediatric HF depends on the etiology. For congenital heart disease, corrective surgery will have a major impact on the clinical course. Following congenital heart surgery, HF can still develop for a number of reasons including myocardial systolic dysfunction.

Many pediatric patients with severe HF are usually listed for heart transplant if available; however, cardiac transplantation is usually a last resort given the limited availability of donor organs, complicated clinical course management and associated morbidity and mortality. In the US, one in four infants listed for heart transplant dies before a donor heart is available (Mah et al 2009).

In contrast to HF in adults, there is very limited research in pediatric HF. Consequently, the treatment of HF in children is based on information and results provided by adult studies (Kantor, Mertens 2010). The Diovan Pediatric Heart Failure Survey study confirmed that two factors; ‘efficacy shown in adult heart failure trials’ and ‘Consensus Statements and Guidelines’ were the most important factors considered when making treatment decisions for pediatric patients with HF (CVAL489K2304 HF Survey 2011). According to this survey of pediatric cardiologists, current clinical management of pediatric HF includes angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), β-blockers, diuretics, aldosterone-blocking agents, digoxin and anticoagulants. At present, no trial has demonstrated an outcome benefit of any pharmacotherapy in children with HF.

Entresto (sacubitril/valsartan), also known as LCZ696, is a first-in-class, angiotensin receptor neprilysin inhibitor (ARNI) treatment for chronic HF. Neprilysin (NEP) inhibition with chronic oral administration of sacubitril/valsartan can promote the endogenous capacity of the body to compensate for HF exacerbations by potentiating the activity of natriuretic peptides secreted by the heart in response to cardiac stress and increased intravascular volume. Sacubitril/valsartan, unlike any other therapy for HF, provides concomitant inhibition of NEP and the angiotensin II type 1 (AT1) receptor. The resulting increase in natriuretic peptide activity due to NEP

inhibition and AT1 receptor blockade through renin-angiotensin-aldosterone system (RAAS) inhibition have complementary effects on the cardiovascular (CV) system that benefit HF patients.

In PARADIGM-HF study (CLCZ696B2314; N = 8442), the pivotal Phase 3 study in adult patients with HF with reduced ejection fraction (HFrEF), sacubitril/valsartan was superior to enalapril (the standard of care) in delaying time to first occurrence of composite endpoint of CV death or HF hospitalization, with a 20% relative risk reduction (RRR) (p = 0.0000002). In addition, sacubitril/valsartan was superior to enalapril in delaying time to CV death with a 20% RRR (p=0.00004) and in delaying time to first HF hospitalization with a 21% RRR (p=0.00004). PARADIGM-HF also showed that sacubitril/valsartan is generally safe and well tolerated in adult patients with HF (McMurray et al 2014).

PARALLEL-HF study (CLCZ696B1301) in Japanese adult patients with HFrEF showed no difference in efficacy for mortality and morbidity between sacubitril/valsartan group and enalapril group, but favorable results were obtained with sacubitril/valsartan in other clinical indices (Tsutsui et al 2021).

Sacubitril/valsartan has been approved for adult use worldwide mainly based on the results of PARADIGM-HF study, and the results of both of PARADIGM-HF and PARALLEL-HF studies for Japan.

PANORAMA-HF study (CLCZ696B2319) was a large, multicenter, double-blind, active controlled pediatric HF trial and includes patients with systemic left ventricular systolic dysfunction <18 years of age (Shaddy et al 2017). PANORAMA-HF was designed to demonstrate whether sacubitril/valsartan provides greater clinical treatment benefit than enalapril as well as to assess its safety profile compared to enalapril over a 52-week treatment duration. PANORAMA-HF study has been completed, and demonstrated a favorable benefit-risk balance of sacubitril/valsartan in the treatment of HF in pediatric patients, and sacubitril/valsartan has been approved for pediatric HF (1 year and above) due to systemic left ventricle systolic dysfunction in the US and European Union. Regulatory approval was also received in countries referencing the US label.

The collection of long-term safety and tolerability data in a pediatric population is equally important, as patients may be dependent on HF medication for a long period of time. PANORAMA-HF Open-Label Extension (OLE) study (CLCZ696B2319E1) is ongoing to provide the opportunity to receive open-label sacubitril/valsartan for patients who successfully complete the 52 weeks double-blind treatment period of PANORAMA-HF study. Since PANORAMA-HF OLE study is going to end approximately December 2023 as planned, this study (CLCZ696B2319E2) was planned to provide an additional sacubitril/valsartan treatment opportunity to Japanese patients enrolled in PANORAMA-HF OLE study until marketed product of sacubitril/valsartan formulation for pediatrics is available in Japan.

2.3 Benefit/Risk assessment

This is an extension study for Japanese participants who have successfully completed PANORAMA-HF OLE study, with a goal to collect the safety information of sacubitril/valsartan in pediatric heart failure patients, and to provide post-trial access to sacubitril/valsartan until marketed product of pediatric formulation is available in Japan.

Based on the results of PANORAMA-HF study, the benefit of sacubitril/valsartan treatment for pediatric HF due to systemic left ventricle systolic dysfunction has been proven, and sacubitril/valsartan has been approved in the US and European countries. Especially, extended treatment of sacubitril/valsartan from PANORAMA-HF OLE study is expected to be beneficial and safe since the eligible patients in this study have successfully completed long-term treatment of sacubitril/valsartan in PANORAMA-HF OLE study.

Appropriate eligibility criteria (Section 5), as well as specific dose modification (Section 6.4) and stopping rules (Section 7.1), are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Appendix 6, Appendix 8, and Appendix 9 (guidelines for the management of renal dysfunction, blood pressure, and hyperkalemia, respectively).

Female participants of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any concern that the participant will not reliably comply, they should not be entered or continue in the study.

3 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 3-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To collect additional safety information of sacubitril/valsartan in Japanese patients after long-term treatment of sacubitril/valsartan in CLCZ696B2319E1 study	• Adverse events (AEs)
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
Not applicable	Not applicable
Exploratory Objective(s)	**Endpoint(s) for exploratory objective(s)**
Not applicable	Not applicable

3.1 Primary estimands

Not applicable

3.2 Secondary estimands

Not applicable

4 Study design

4.1 Overall design

This trial (CLCZ696B2319E2) is a multicenter, open-label extension study for Japanese patients who have successfully completed the PANORAMA-HF OLE study (Refer to Section 1.2 Schema for study design figure). 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 PANORAMA-HF participants.

Only Japanese patients who successfully completed PANORAMA-HF OLE study and fulfill protocol requirements (see Section 5) 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 (see Section 5.2).

For all consenting patients eligibility for this study will be assessed at the first visit (Visit Day1) and the study medication will be initiated (see Section 8 for details). The first visit (Visit Day1) is the same day as the End of Study visit (Visit 599) of PANORAMA-HF OLE study. Participants who turned 18 years old during PANORAMA-HF OLE study, and who qualify, are eligible to participate in this study.

The starting dose of study drug will be determined by the Investigator considering the participant's condition The dose level 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.

All participants have a target dose (dose level 4) of 3.1 mg/kg bid. If a participant is unable to tolerate up-titration to a higher sacubitril/valsartan dose level or at the discretion of the Investigator, participants may be maintained on lower dose levels of sacubitril/valsartan (dose level 1-3, see Table 4-1). Please see Section 6.4.1 for dose adjustments. In case of a consecutive 3-month interruption of study treatment, participant should be discontinued from the study and should complete the End of Study visit（Visit EOS).

Table 4-1 Study drug dose levels for sacubitril/valsartan

Dose levels for pediatric formulation	
Dose level 1	0.8 mg/kg bid.
Dose level 2	1.6 mg/kg bid.
Dose level 3	2.3 mg/kg bid.
Dose level 4	3.1 mg/kg bid.
Dose levels for adult formulation	
Dose level 1	50 mg bid.
Dose level 2	100 mg bid.
Dose level 3	150 mg bid.
Dose level 4	200 mg bid.

4.2 Scientific rationale for study design

The purpose of this open-label study is to collect additional safety information of sacubitril/valsartan and to provide post-trial access to sacubitril/valsartan for the eligible Japanese patients who completed CLCZ696B2319E1 study until marketed product of pediatric formulation, film-coated granules in capsule, is available in Japan. Open-label design is adopted to fulfill this purpose.

4.3 Justification for dose

This study is extended from PANORAMA-HF OLE study, with a similar study design as PANORAMA-HF OLE study. The starting dose of study drug will be determined by the Investigator considering the participant's condition The dose level 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. Maintaining the dose level at the end of study visit in PANORAMA-HF OLE study is considered appropriate, to ensure a smooth transition to this study medication taking safety and tolerability aspects into account. However, since it may not be appropriate to maintain the dose due to changes in the participant's condition, etc., the dose level could be changed at the discretion of the Investigator.

4.4 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable

4.5 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster), mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by local or regional health authorities and ethics committees as appropriate.

4.6 Purpose and timing of interim analyses/design adaptations

Not applicable

4.7 End of study definition

Study completion is defined as when the last participant finishes their End of study visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

5 Study population

The study population consists of Japanese pediatric HF patients, in-patients or outpatients. Only patients who successfully completed PANORAMA-HF OLE study and fulfill protocol

requirements (see Section 5.1 and Section 5.2) are eligible to participate in this study. Patients in PANORAMA-HF OLE study for whom study medication had been temporarily interrupted during the study (including at the study completion), may be considered for this study if they meet all entry criteria. A maximum of 8 Japanese patients will be enrolled into the study.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following 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.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

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.
6. Patient breastfed by a mother taking ACEI.
7. Pregnant or nursing (lactating) female patients.
8. Female patients of child-bearing potential, defined as all females physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and for 7 days after stopping medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female bilateral tubal ligation, female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or total hysterectomy at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the female has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant

- Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example, hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception, females should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Females are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age-appropriate history of vasomotor symptoms). Females are considered not of child-bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to enrollment on study. In the case of oophorectomy alone, only when the reproductive status of the female has been confirmed by follow-up hormone level assessment is she considered to be not of child-bearing potential.

If local regulations are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

5.3 Screen failures

Participants or parents/guardians who sign an informed consent form for themselves or for their child, respectively, and who (i.e. the participant) are subsequently found to be ineligible for this study, will be considered a screen failure. The reason for screen failure should be entered on the applicable electronic Case Report Form (eCRF). The baseline characteristics at Visit Day1, demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event (SAE) during the screening phase (see SAE section for reporting details).

Participants or parents/guardians who sign an informed consent for themselves or for their child, respectively, and who are considered eligible but fail to be started on treatment on Visit Day1 for any reason may be enrolled in this study. However, they will have to discontinue the study unless the study treatment starts within 3 months from Visit Day1 and will be considered an early study termination. The reason for early study termination should be captured on the appropriate disposition eCRF at Visit EOS.

5.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.). The Participant No. consists of the Site Number (Site No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant will be assigned the same Participant Number as he/she had in the PANORAMA-HF OLE study.

6 Study treatment(s) and concomitant therapy

6.1 Study treatment(s)

The sacubitril/valsartan study medication is available in 3 formulations: tablets, granules or liquid formulation (Table 6-1). For liquid formulation, please refer to the Pharmacy Manual.

Table 6-1 Open-label sacubitril/valsartan formulation

Formulation	Strength	Comments
capsule containing 4 granules (3.125 mg/granule)	12.5 mg	capsules in bottles
capsule containing 10 granules (3.125 mg/granule)	31.25 mg	capsules in bottles
tablets	50 mg	tablets in bottles
tablets	100 mg	tablets in bottles
tablets	200 mg	tablets in bottles
liquid suspension		Prepared from tablets 100 mg (please refer to Pharmacy Manual)

All pediatric formulations of study medication (sacubitril/valsartan granules or liquid) will be made available to all participants. The tablet formulations of sacubitril/valsartan will be available for participants based on the participant's dosing and ability to swallow adult tablets (refer to Pharmacy Manual).

An overview of available sacubitril/valsartan formulations is illustrated in Table 6-1. Capsules of sacubitril/valsartan containing 4 granules or 10 granules per capsule will be provided for oral use. The granules can be swallowed by the participant, after the removal of the outer capsule. Participants who cannot use tablets or granules can use the liquid formulation. Sacubitril/valsartan liquid formulation will be compounded by the site / pharmacy (please refer to Pharmacy Manual).

Sufficient medication will be provided for treatment according to the study protocol. Medication labels will be in the local language and comply with the legal requirements of the country. The labels will include storage conditions for the drug, and will not include information about the participant.

Participants taking the liquid formulation of sacubitril/valsartan will need to have a resupply every 4 weeks. Given the burden of traveling to the site for study visits for participants and families, the parent/caregiver can come to the site without the participant for dispensation of study drug between scheduled study visits (see Table 1-2). Delivery of study drug to the participant can also be used, where possible and where allowed by local regulations.

6.1.1 Additional study treatments

No other treatment beyond investigational drug is included in this trial.

6.1.2 Treatment arms/group

There is 1 treatment arm in this open-label study. All participants will receive open-label sacubitril/valsartan.

6.1.3 Treatment duration

The study will continue until marketed product of pediatric formulation is available in Japan.

6.2 Preparation, handling, storage, and accountability

Each study site will be supplied with study treatment in packaging as described under Table 6-1.

Medication will be provided as tablets, granules or liquids. Tablets and granules will be provided by Novartis to the study site. Liquid preparation will be provided by the site For liquid preparation, please refer to Pharmacy Manual.

As per the treatment assigned to the participant, Investigator staff will select the study treatment to dispense to the participant.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by local or regional health authorities and ethics committees, as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 3-months supply. In this case, regular phone calls or virtual contacts (every 4 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

6.2.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant.

The Investigator or designated site staff must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability

will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial. The Investigator must provide accountability also for locally sourced materials used for administration (e.g. i.v. bags).

The site may destroy and document destruction of unused study treatment, drug labels and packaging, as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

6.2.2 Handling of other treatment

The Investigator should instruct the participant/parent/guardian to notify the study site about any new medications he/she/their child takes after the participant was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded.

The participant should be receiving optimal standard of medical care or surgical treatment for their HF and comorbidities.

6.2.3 Instruction for prescribing and taking study treatment

Novartis will supply the Investigators with all study medications required for the course of the study. Participants will be provided with bottles containing study drug corresponding to their assigned dose level, sufficient to last until the next scheduled visit (Table 1-2). Study drug will be supplied to participants as:

Sacubitril/valsartan tablets: 50 mg, 100 mg or 200 mg

Sacubitril/valsartan granules: 12.5 mg or 31.25 mg (3.125 mg/granule, either 4 or 10 granules packaged in capsule) supplied in a bottle

Sacubitril/valsartan liquid formulation (compounded by site / pharmacy) (refer to Pharmacy Manual)

Details regarding preparation of liquid formulation for sacubitril/valsartan are provided in the Pharmacy Manual.

Participants will be instructed to take their morning study drug doses between 6:00 and 09:00 (6 – 9 AM) and their evening study drug dose between 18:00 and 21:00 (6 – 9 PM). The study drugs (tablets) should be taken with a glass of water with or without food. For granules and liquid administration, see Pharmacy Manual.

All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded on the Dosage Administration Record (DAR) eCRF.

See Section 6.3 for Study treatment compliance.

6.3 Study treatment compliance

The Investigator must promote compliance by instructing the participant/parent/guardian to take/administer the study treatment exactly as prescribed and by stating that compliance is

necessary for the participant's safety and the validity of the study. The participant/parent/guardian must also be instructed to contact the Investigator if he/she is unable for any reason to take the study treatment as prescribed.

6.3.1 Recommended treatment of adverse events

Recommendations for handling Renal events, hypotension and hyperkalemia are described in Appendix 6, Appendix 8, and Appendix 9, respectively.

Medication used to treat adverse events (AEs) must be recorded on the appropriate eCRF.

6.4 Dose modification

6.4.1 Dose modifications

The maximum tolerated or target dose (dose level 4) will be maintained for the duration of the study. Both scheduled and unscheduled visits can be utilized for up-titration and/or down-titration throughout the study based on Investigator judgment.

For participants who are unable to tolerate the study drug, dose level adjustments and temporary interruptions of less than 3 months of study treatment are permitted. The following guidelines should be followed:

- The Investigator should adjust/interrupt/discontinue doses of concomitant medications if it is believed that they are the most likely cause of an adverse event.
- If adjustment/elimination of concomitant medications is not possible or does not alleviate the adverse event of concern, the Investigator may down-titrate to the next lower study drug dose level (Table 4-1) to temporary or permanent discontinuation of study drug.
- The participant may reinitiate the higher dose when the Investigator feels it is appropriate to do so per the directions provided below in this section.
- If the study drug is permanently discontinued, the participant should be discontinued from the study (Visit EOS).

Participants may be seen at any time for unscheduled visits during the study for re-evaluation of safety criteria parameters. Study drug dose level adjustments should mainly be based on overall safety and tolerability with focus on a) hyperkalemia, b) symptomatic hypotension and c) renal dysfunction. Laboratory assessments of serum sodium, potassium, creatinine, and eGFR (calculated based on the modified Schwartz formula (Schwartz, Work 2009) will be utilized. Refer to Appendix 6, Appendix 8, and Appendix 9 for treatment guidelines for renal dysfunction, management of hypotension and hyperkalemia, respectively.

Adjustment of study-drug dose level

During the study, down titration of the study drug at any time is allowed based on the safety and tolerability criteria defined in Table 6-2 and per the Investigator's clinical judgement.

The Investigator may down-titrate the study drug to the next lower dose level or may down-titrate 2 or 3 dose levels (e.g. from dose level 4 to dose level 1), based on their clinical judgement. If the tolerability issues are not alleviated despite down titration by multiple dose levels, the Investigator may temporarily discontinue study drug. Once the participant's condition is stable,

the participant can be up-titrated to the next higher dose level using unscheduled visits in an attempt to bring back the participant gradually to the target study drug dose level. The Investigator may select the next dose level for down- or up-titration according to his or her judgment (Table 4-1). For up-titration of the study drug, participants have to meet all criteria in Table 6-2 before administering the higher dose level.

Table 6-2 Safety monitoring criteria for adjustment of study-drug dose level

Parameter	Description
Potassium level	Serum K ≤ 5.4 mmol/L (mEq/L) or plasma K ≤ 5.0 mmol/L (mEq/L)
Kidney function	eGFR (calculated using the modified Schwartz formula) ≥ 30% mean GFR for age (Appendix 5, Table 10-4)
Kidney function	eGFR reduction < 35% compared to Visit Day1.
Blood pressure	Systolic blood pressure (SBP) > than the calculated 5th percentile SBP for age as described in Appendix 7
AEs or conditions	No conditions that preclude continuation according to Investigator's judgment, including hypotension.

All changes should be recorded on the DAR eCRF.

Study drug restart after temporary treatment interruption

Participants who have temporarily discontinued study drug should be restarted as soon as possible as deemed appropriate by the Investigator. The Investigator should restart the participant on the study drug at the most appropriate dose level (Table 4-1) as per the Investigator's clinical judgment. If the participant does not tolerate the newly restarted study-drug dose level, they may be down-titrated again (if appropriate) or the study medication may be temporarily discontinued again.

Participants restarted on the study drug will retain their original study identification numbers.

Investigators may discontinue a participant's study drug due to serious or intolerable AEs suspected to be causally related to study drug. If study drug is discontinued for any reason, this must be recorded on the DAR eCRFs. In addition, participants who permanently discontinued study drug should be scheduled for the discontinuation study Visit EOS. Note that after a consecutive 3-month interruption of study treatment, participant should be discontinued from the study and should be seen at the site for Visit EOS).

If during study treatment interruption a participant requires treatment with an ACEI a ≥36 hours washout should be observed before the ACEI is initiated. The ACEI must be discontinued ≥36 hours prior to restarting study drug. Participants who have temporarily discontinued study drug and are presently taking an ARB or a renin inhibitor must discontinue their current ARB or renin inhibitor on the day study drug is restarted.

If the participant becomes pregnant during the course of the study, the participant has to discontinue study drug immediately and should be seen at the site for Visit EOS and evaluated for transition to alternative treatment per the Investigator's clinical judgement.

Refer to (Section 8.4.5) for further details on pregnancies and reporting guidelines.

6.4.2 Follow-up for toxicities

Refer to Appendix 5 and Appendix 6 (Section 10.5 and Section 10.6) for the follow-up of renal events.

6.5 Continued access to study treatment after the end of the study

Not applicable

6.6 Treatment of overdose

In the event of an overdose, the Investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with Novartis medical monitor, whether study treatment should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.6.1 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE. Study treatment errors and uses outside of what is foreseen in the protocol, misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness. For more information on AE and SAE definition and reporting requirements, please see the respective sections.

6.7 Concomitant and other therapy

Participants may be on a HF regimen throughout the study duration on the Investigator's discretion, except for the use of ACEI, ARBs and renin inhibitors, which are strictly prohibited. Prohibited and important concomitant medications during the conduct of the clinical trial are listed below.

6.7.1 Concomitant therapy

The Investigator must instruct the participant to notify the study site about any new medications he/she takes after the participant was enrolled into the study.

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate eCRFs.

Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication. If in doubt, the Investigator should contact the Novartis medical monitor before enrolling a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.7.1.1 Permitted concomitant therapy requiring caution and/or action

The active metabolites of sacubitril (sacubitrilat) and valsartan are OATP1B1, OATP1B3 and OAT3 substrates; valsartan is also a Multidrug resistance protein 2 (MRP2) substrate. Therefore, co-administration of sacubitril/valsartan with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampin, cyclosporine) or MPR2 (e.g. ritonavir) may increase the systemic exposure to sacubitrilat or valsartan, respectively. The Investigator should exercise appropriate care when initiating or ending concomitant treatment with such drugs.

The co-administration of sacubitril/valsartan has increased maximum plasma concentration of atorvastatin. These effects may potentially be due to the OATP1B1 and OATP1B3 inhibitory effects of sacubitril. Therefore, caution is recommended when co-administering sacubitril/valsartan with atorvastatin and other statins that are substrates of OATP1B1 and OATP1B3.

Antihypertensive medication should be co-administered with caution due to blood pressure lowering characteristics of the study medication sacubitril/valsartan.

Concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium, if co-medication is considered necessary, monitoring of serum potassium is advised.

In volume depleted patients (including those on diuretic therapy), or patients with compromised renal function, concomitant use of sacubitril/valsartan and Non-steroidal anti-inflammatory drugs (NSAIDs) may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying treatment in participants on sacubitril/valsartan who are taking NSAIDs concomitantly.

The potential for a drug interaction between sacubitril/valsartan and lithium has not been investigated. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACEI or ARBs. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use with sacubitril/valsartan.

Guidelines for the management of renal dysfunction, hypotension, and hyperkalemia are provided in Appendix 6, Appendix 8, and Appendix 9, respectively.

6.7.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed while taking study drug due to safety reasons. If the medication included in Table 6-3 is administered, study drug must be discontinued and the actions specified below must be taken.

Table 6-3 Prohibited medication

Medication	Prohibition period	Action taken
any ACEI	36 hours washout period	Discontinue study drug. ACEI must be stopped for 36 hours prior to re-initiation of study drug.
Any ARB		Discontinue study drug. ARB must be stopped for prior to re-initiation of study drug.
Renin inhibitor (aliskiren)		Discontinue study drug. Renin inhibitor must be stopped prior to re-initiation of study drug.

ACEIs, ARBs, and renin inhibitors

The concomitant use of open-label ACEI, ARB, or renin inhibitor is strictly prohibited while the participant is receiving study drug. If the Investigator believes the addition of an ACEI, ARB or renin inhibitor is required, the study drug must be temporarily discontinued. Study drug must be stopped 36 hours prior to starting open-label ACEI. Study drug must be stopped prior to starting open-label ARB or renin inhibitor. Similarly, if study drug is to be restarted, the open-label ACEI must be stopped ≥ 36 hours prior to resuming study drug. Open-label ARB or renin inhibitor must be stopped prior to resuming study drug.

6.7.3 Rescue medicine

If in the opinion of the Investigator, the participant does not tolerate the assigned study medication, the Investigator should consider whether non-disease-modifying medication [e.g. calcium channel blockers (CCBs), diuretics, α-blockers] could be adjusted to rectify the situation.

Guidance on handling renal dysfunction, hypotension, and hyperkalemia are provided to Investigators in Appendix 6, Appendix 8, and Appendix 9, respectively.

The Investigator may prescribe any medications and/or supportive care during the study based on clinical needs (excluding use of the prohibited medications described above). Use of rescue medication and/or supportive care must be recorded on the Concomitant medications eCRF.

7 Discontinuation of study treatment and participant discontinuation/withdrawal

7.1 Discontinuation of study treatment

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the participant or the Investigator. In this study, if the study treatment is permanently discontinued, the participant

should be discontinued from the study and the end of study visit (Visit EOS) should be conducted (Section 6.4.1).

The Investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the participant
- Any laboratory abnormalities that in the judgment of the Investigator prevents the participant from continuing participation in the study
- A consecutive 3-month interruption of study treatment

If discontinuation of study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information.

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section).

7.2 Participant discontinuation from the study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in Section 1.3 Schedule of Activities.

7.3 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore

very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data privacy rights should be made as detailed in Section 1.3 Schedule of Activities.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

7.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

7.5 Early study termination by the Sponsor

The study can be terminated by Novartis at any time. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons.

Reasons for early termination (but not limited to)

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study treatment development in this indication

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment. The Investigator must provide follow-up medical care for all patients who are prematurely withdrawn from study drug or refer them for appropriate ongoing care. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the

participant's interests. The Investigator or Novartis depending on local regulation will be responsible for informing Institutional Review Boards (IRBs) / Independent Ethics Committees (IECs) of the early termination of the trial.

8 Study Assessments and Procedures

After identifying a potential participant, an ICF and assent (if applicable) must be signed by the parent(s)/legal guardian(s) and by the participant (as applicable) before performing any study-related procedures that are not considered standard of care for pediatric HF participants at that site. Procedures that are part of a site's standard of care for a pediatric participant or that were done as part of the End of Study visit (Visit 599) of PANORAMA-HF OLE study may pre-date the signed ICF for this study. The AE and SAE reporting period will begin at the time the ICF is signed.

The Assessment Schedule (Table 1-2) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Sacubitril/valsartan treatment will start at Visit Day1, which is the same day as the End of Study visit (Visit 599) of PANORAMA-HF OLE study. The data of some assessments (such as vital sign, height, and weight) at the End of Study visit (Visit 599) in PANORAMA-HF OLE study will be utilized as the data at Visit Day1 for this study.

A telephone visit (Visit M3) and an on-site visit (Visit M6) will occur 3 months and 6 months after Visit Day1, respectively. The visits as same Visit M3 and Visit M6 will then be repeated every 3 months until the end of the study. When the pediatric formulation of sacubitril/valsartan becomes available in Japan, or this study is terminated by Novartis, any participants should return to the study site as soon as possible for End of Study (EOS) visit (Visit EOS) regardless of subsequent scheduled visit, and all of the assessments listed for Visit EOS will be performed.

Participants should take their scheduled dose of sacubitril/valsartan in the morning of their study visits. Participants are not required to fast overnight on the day prior to or the day of the study visit.

Participants, who discontinue sacubitril/valsartan for 3 consecutive months, will be discontinued from the study and are to attend Visit EOS.

Participants should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. If one visit is postponed or brought forward, it should not result in the next visit being postponed or brought forward. The next visit, if at all possible, should adhere to the original schedule in relation to Visit Day1. Missed or rescheduled visits should not lead to automatic discontinuation. Specific circumstances surrounding missed or rescheduled visits must be discussed with the study monitor. Participants who prematurely discontinue the study treatment, or prematurely withdraws from the study for any reason should be scheduled for a final visit as soon as possible, at which time all of the assessments listed for the final visit (Visit EOS) will be performed. At this final visit, all dispensed investigational

product should be reconciled, and the adverse event and concomitant medications recorded on the eCRF.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the Investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

8.1 Screening

Participants or parents/guardians who sign an informed consent form for themselves or for their child, respectively, will be screened. The inclusion/exclusion criteria at Visit Day1 will be checked.

8.2 Participant demographics/other baseline characteristics

Participant demographic and baseline characteristic data at Visit Day1 will be collected including: year of birth (where allowed) age in years (age in months for participants < 2 years, where allowed), sex, race and ethnicity, as well as the Identification Number (ID No.). Additionally, pediatric heart failure history, vital signs, weight and height will be collected. Relevant medical history/current medical condition data includes data until the start of study drug. HF medications will be recorded on the Concomitant Medications eCRF.

8.3 Efficacy assessments

Efficacy will not be measured in this study.

8.4 Safety assessments

The Sponsor may request additional information on specific adverse events or laboratory events of interest and may make requests to perform additional diagnostic tests to further assess the safety profile of sacubitril/valsartan. Such information may include diagnostic procedure reports, discharge summaries, autopsy reports, and other relevant information that may help in assessing the reported adverse event. All additional information will be de-identified prior to collection by Novartis or its agents.

In addition to AE/SAEs, the following safety-related evaluations will be done:

- Physical examinations (data recorded only in source)
- Vital signs
- Height, weight
- Laboratory evaluations

- Pregnancy test

Safety assessments are specified below with Section 1.3 Schedule of Activities detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 8.6.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 3 months or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

8.4.1 Physical examinations

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.

8.4.2 Vital signs

Vital signs include blood pressure (BP) and pulse measurements and are assessed when a physical examination is performed. After the participant has been sitting for approximately 5 minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using an automated validated device, e.g. OMRON, or a standard sphygmomanometer with an appropriately sized cuff on the non-dominant arm. Supine BP instead of sitting BP will be measured in participants who are infants or who cannot sit comfortably. Clinically notable vital signs are defined in Appendix 3.

8.4.3 Height and weight

Height in centimeters (cm). It is recommended to measure standing height using a stadiometer without shoes.

Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at every site visit. Body weight during hospitalization is to be recorded only if available as per standard of care.

8.4.4 Clinical safety laboratory tests

Laboratory assessments will be analyzed locally during the study. It is the responsibility of the Investigator to review all laboratory results and make an assessment of whether an abnormal or notable value is clinically significant, whether additional evaluations should be performed as

judged appropriate, and whether the patient may continue in the trial. Sample collection should be conducted according to the standards and requirements of the local laboratory.

Serum sodium, potassium, creatinine, and eGFR (modified Schwartz formula) will be evaluated locally at visits defined in Table 1-2, and recorded in the eCRF. Additional laboratory evaluation including hematology and urinalysis may be performed optionally by Investigator's clinical judgement at any visits. There is no local assessment at Visit Day1, but the results of central laboratory at the End of Study visit (Visit 599) in PANORAMA-HF OLE study should be reviewed by the Investigator soon after the results are obtained.

Clinically notable laboratory findings are defined in Appendix 3 Table10-1. These findings must be commented on by the Investigator in the source documents and additional laboratory evaluations may be required, as judged appropriate by the Investigator.

If the laboratory abnormality induces clinical signs or symptoms, or requires therapeutic intervention, and satisfies the criteria defined in Section 8.6 Safety reporting, then the diagnosis or medical condition must be entered on the AEs page of the participant's eCRF and any treatment necessary should be documented. If the laboratory abnormality is the primary reason for an unforeseen hospitalization or otherwise fulfills the seriousness category of an AE, then the procedure for rapid notification of SAEs must be followed.

Likewise, if the laboratory abnormality leads to discontinuation of the study drug, the participant must be followed until the abnormality resolves or until it is judged to be permanent. This investigation may include continued monitoring by repeat laboratory testing or by performing additional laboratory tests as deemed necessary by the Investigator or the Sponsor's medical monitor.

For child bearing potential females only, serum pregnancy testing will be performed at the End of Study visit (Visit EOS). Please see details in Section 8.4.5.

A table, which provides the maximum, allowable blood-draw volumes by weight, can be found in Appendix 10.

Plasma potassium may be used instead of serum potassium in this study. Serum potassium thresholds in the study protocol, including those values cited in Appendix 3 and Appendix 9 can be converted to plasma potassium thresholds for the study by subtracting 0.4 mmol/L from the serum potassium threshold.

As per Section 4.5, during a public health emergency as declared by local or regional authorities' i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site for protocol-specified safety lab assessments, an alternative lab (local) collection site may be used.

8.4.5 Pregnancy testing

All child-bearing potential female participants who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

Childbearing potential females (CHBP) are defined as all female participants ≥ 11 years of age and all female participants who are <11 years of age if they are menstruating. Pre-menarchal girls <11 years of age should notify the study site if they start menstruating after the study has started so pregnancy testing can be initiated. Urine pregnancy test is analyzed locally and done at all in-person scheduled/unscheduled visits (except for End of Study visit: Visit EOS) on all CHBP female participants. There is no assessment at Day1, but the result of central laboratory (serum test) at the End of Study visit (Visit 599) in PANORAMA-HF OLE study should be reviewed by the Investigator soon after the result is obtained. A positive urine pregnancy test should be confirmed with a serum pregnancy test. Participants with a positive serum pregnancy at any time in the study must be discontinued immediately from the study and should be seen at the site for Visit EOS. Serum pregnancy testing will be performed at Visit EOS.

For child-bearing potential females, a urine pregnancy test will also be performed at monthly intervals between study visits, during the study. The between-study-visit monthly urine pregnancy test can be performed either via: 1) monthly study site visits for urine pregnancy tests, or 2) providing the participant with urinary pregnancy tests for home monthly tests.

If monthly home urine pregnancy tests are utilized, child-bearing potential female participants will be given a urine pregnancy test kit for each month between study visits and will be instructed to perform a urine pregnancy test at home, once per month (approximately every 30 days). Participants will be given a Pregnancy Test Diary in which they are to record the date and the results of their pregnancy tests that are done at home, each time they run the test. Study Site personnel will contact the participant on a monthly basis to check that the participant has completed the urine pregnancy test and has recorded the result in the Pregnancy Test Diary. The Study Site personnel may also ask for the result of the pregnancy test. The contact by the Study Site personnel and the result of the pregnancy test will be documented in the source documentation for the participant. The Pregnancy Test Diary will be part of the source documentation for the participant. If the pregnancy test is positive, the participant/parents/guardian must contact the Investigator immediately. The aforementioned pregnancy testing (i.e. done at home or at the study site) will be maintained during treatment and until the end of relevant systemic exposure.

All menarchal girls and their parents/caregivers should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study. It is important to be sensitive in introducing this issue, as understanding and comprehension of puberty, sexual activity, pregnancy and contraception is influenced by age; as well as, factors such as precocity, socio-educational economic and familial background. These discussions are therefore best performed by Investigators familiar with the pediatric participant and her family and should be guided by requirements of the local regulatory authorities. These discussions should take into account the socio-economic, cultural factors and religious beliefs of the adolescent participant and her family. The Investigator should also discuss the management of the pregnancy test results with the participant and her parents/caregivers. The privacy of the participant should be considered in accordance with the local law and ethics.

Any participant with a positive pregnancy test must discontinue study drug immediately, should be discontinued from the study, and should be seen at the site for Visit EOS .

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the female is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, Follicle Stimulating Hormone (FSH) testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

8.4.6 Other safety evaluations

Not applicable

8.4.7 Appropriateness of safety measurements

The safety and clinical laboratory assessments performed in this study are similar to those used in PANORAMA-HF OLE study. These assessments are appropriate for an investigational drug with the mechanism(s) of action of sacubitril/valsartan (angiotensin receptor neprilysin inhibitor), the safety profile described in LCZ696 Investigator's Brochure (IB), and the indication/participant population under study.

8.5 Additional assessments

No additional tests will be performed on participants entered into this study.

8.6 Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

The definitions of AEs and SAEs can be found in Section 8.6.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant’s legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 8.6.3.

8.6.1 Adverse events

An AE is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The Investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial-related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 8.6.2):

1. The severity grade
- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities
2. Its relationship to the study treatment and other investigational treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 8.6.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/permanently discontinued

6. Its outcome

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (e.g. continuing at the end of the study), and assessment must be

made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the IB.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 10.3.

8.6.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect, fetal death or a congenital abnormality or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately

life-threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

All reports of intentional misuse and abuse of the product are also considered serious adverse events irrespective of whether a clinical event has occurred.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

8.6.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the eSAE (electronic Serious Adverse Event) with paper backup Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

Investigators will report events that are commonly seen in the study population, but they will not be reported as Suspected Unexpected Serious Adverse Reactions (SUSARs) to regulatory agencies, ethics committees, or Investigators during the study (Table 8-1).

Table 8-1 Events commonly seen in study population

Cardiovascular events	Non-cardiovascular events	
Worsening HF	Bronchitis	Influenza
Edema	Vomiting	Nasopharyngitis
Hypotension	Cough	Nausea
Renal impairment	Diarrhea	Pneumonia
	Failure to thrive	Upper respiratory infection
	Fatigue	Weight change

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information (Note: If more stringent, local regulations

regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, the Novartis Chief Medical Office and Patient Safety and Pharmacovigilance (PS & PV) Department associate may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study treatment that this SAE has been reported.

SUSARs with the exception of those terms listed in Table 8-1 will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30-day period following end of study should only be reported to Novartis Safety using the paper SAE form provided to the site if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

8.6.4 Pregnancy

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. After informed consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery. Post-natal follow up should occur at 1, 3 and 12 months after delivery.

Pregnancy should be recorded and reported by the Investigator to the Novartis PS&PV. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment with any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

8.7 Pharmacokinetics

PK parameters are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Immunogenicity assessments

Immunogenicity is not evaluated in this study.

8.10 Health economics OR Medical resource utilization and health economics

Health economics OR Medical resource utilization and health economics parameters are not evaluated in this study.

9 Statistical considerations

9.1 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 the extension open-label study.

9.2 Statistical analyses

9.2.1 General considerations

- 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.
- 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 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.
- 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.

9.2.2 Participant 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.

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.

9.2.3 Treatments

Duration of exposure to the study treatment will be summarized for continuous variable.

Dose levels will be summarized for continuous variable by visit.

Concomitant medications and significant non-drug therapies prior to and after Visit Day1 will be summarized by anatomical therapeutic classification (ATC), preferred term.

The SAF will be used for the above analyses.

9.3 Primary endpoint(s)/estimand(s) analysis

The primary objective is to collect additional safety information of sacubitril/valsartan in eligible heart failure patients from PANORAMA-HF OLE study receiving open-label investigational drug.

The primary safety information to analyze will be based on adverse events, which will be analyzed using frequencies and percentages.

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.

9.3.1 Definition of primary endpoint(s)

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

9.3.2 Statistical model, hypothesis, and method of analysis

Not applicable. There are no statistical hypotheses to be tested in this study and no model analyses will be performed.

9.3.3 Handling of intercurrent events of primary estimand (if applicable)

Not applicable

9.3.4 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 according to the imputation rules specified in the Statistical Analysis Plan (SAP).

9.3.5 Multiplicity adjustment (if applicable)

Not applicable. No statistical tests will be performed in this study.

9.3.6 Sensitivity analyses

Not applicable

9.3.7 Supplementary analysis

Not applicable

9.4 Secondary endpoint(s)/estimand(s) analysis

Not applicable. There are no secondary endpoints.

9.5 Exploratory endpoint(s)/estimand(s) analysis

Not applicable. There are no exploratory endpoints.

9.6 (Other) Safety analyses

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.

- Any serious adverse event (treatment emergent or not)
- Treatment emergent adverse event (TEAE*)
- Treatment emergent serious adverse event
- Treatment emergent adverse event of special interest, i.e. events of important identified risks and important potential risks defined in the Risk Management Plan (RMP)

*TEAEs is any adverse events (new or worsened) occurring on or after Visit Day 1.

Descriptive statistics of vital signs (raw values) and the number of patients and percentages with clinically notable vital signs during the treatment period will be provided by visit (Day1, M3, M6, EOS). Criteria of clinically notable vital signs are given in the Appendix 3 Table 10-2.

Descriptive statistics (raw values) will be provided for weight, height, BMI, age adjusted percentile for weight and height, and z-score for height by visit.

BMI will be calculated as weight (kg) / height^2 (m^2) using the collected height and weight at each visit.

9.7 Other analyses

Not applicable

9.8 Interim analysis

Not applicable

9.9 Sample size determination

9.9.1 Primary endpoint(s)

All patients who have completed PANORAMA-HF OLE study and who meet all Inclusion and Exclusion criteria (Section 5.1 and Section 5.2), 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.

9.9.2 Secondary endpoint(s)

Not applicable

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

Signing a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required

Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC or European Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

10.1.2 Informed consent process

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Information about common side effects already known about the investigational treatment can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant upon obtaining consent and also during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents and assents are included in this study:

- Main study consent and assent, which also included:
  - A subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples collected during this study
  - Optional consent for activities that may be done outside of the study site
- As applicable, Pregnancy Outcomes Reporting Consent for female participants

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local health authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

10.1.3 Data protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

10.1.4 Committees structure

Not applicable

10.1.5 Data quality assurance

Monitoring details describing strategy, including definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

10.1.5.1 Data collection

Data not requiring a separate written record will be defined in the protocol and Section 1.3 Schedule of Activities and can be recorded directly on the eCRFs. All other data captured for

this study will have an external originating source (either written or electronic) with the CRF not being considered as source

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Designated Investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the Electronic data capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the Investigator staff.

The Investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the Investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

10.1.5.2 Database management and quality control

Novartis personnel will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

10.1.6 Source documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant). Definition of what constitutes source data and its origin can be found in monitoring guidelines.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/ Clinical research associate (CRA) organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

10.1.7 Publication policy

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last participant last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required health authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial Investigator meetings.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

10.1.8 Protocol adherence and protocol amendments

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the Investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

10.1.8.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

10.2 Appendix 2: Abbreviations and definitions

10.2.1 List of abbreviations

ACEI	Angiotensin Converting Enzyme (inhibitor)
AE	Adverse Event
AHA	American Heart Association
AKI	Acute Kidney Injury
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor Neprilysin Inhibitor
AT1	Angiotensin II Type 1
ATC	Anatomical Therapeutic Classification
bid	bis in die/twice a day
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CCB	Calcium Channel Blocker
CHBP	Child Bearing Potential Females
CIOMS	Council for International Organizations of Medical Sciences
COX	Cyclo-oxygenase
Cr	Creatinine
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical Study Report
CV	Cardiovascular
DAR	Dosage Administration Record
DBP	Diastolic Blood Pressure
eCRF	electronic Case Report/Record Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ENR	Enrolled Set
EOS	End of Study
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HF	Heart Failure
HFrEF	HF with Reduced Ejection Fraction
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine System

KDIGO	Kidney Disease: Improving Global Outcomes
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
MRP2	Multidrug resistance protein 2
NEP	Neprilysin
NSAID	Non-steroidal Anti-Inflammatory Drug
PALS	Pediatric Advanced Life Support
PCR	Protein-Creatinine Ratio
PK	Pharmacokinetic(s)
PS	Patient Safety
PV	Pharmacovigilance
OLE	Open Label Extension
RAAS	Renin-Angiotensin-Aldosterone System
RMP	Risk Management Plan
RRR	Relative Risk Reduction
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SoA	Schedule of Activities
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment- Emergent Adverse Event
ULN	Upper Limit of Normal
UNS	Unscheduled
WHO	World Health Organization

10.2.2 Definitions

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study intervention administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.

Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.

Withdrawal of consent	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

10.3 Appendix 3: Clinical laboratory tests

10.3.1 Clinically notable laboratory values and vital signs

Table 10-1 Clinically notable laboratory values

Parameter	Conventional Units	SI Alert Value	SI Units
Hematology			
Red Blood Cell Count	x10E6/uL	>50% increase and > Upper limit of normal (ULN); >30% decrease and < Lower limit of normal (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

Increase and decrease are defined as compared to the baseline value of PANORAMA-HF OLE study (i.e. Visit 500).

Table 10-2 Criteria for clinically notable vital signs

Age	HR [min^{-1}]	SBP [mmHg]	DBP [mmHg]	RR [min^{-1}]
1-3 years	<60, >120	<76, >115	<45, >75	<14, >35
3-6 years	<55, >120	<82, >120	<50, >80	<12, >30

Age	HR [min^{-1}]	SBP [mmHg]	DBP [mmHg]	RR [min^{-1}]
6-12 years	<50, >105	<90, >130	<50, >80	<10, >27
>12 years	<45, >95	<90, >145	<55, >90	<8, >23

10.4 Appendix 4: Participant Engagement

The following participant engagement initiative is included in this study and will be provided, as available for distribution to study participants at the time points indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Plain language trial summary - after clinical study report (CSR) publication

10.5 Appendix 5: Renal safety monitoring

10.5.1 Specific Renal Alert Criteria and Actions and Event Follow-up

Table 10-3 Specific renal alert criteria and actions

Renal Event	Actions
eGFR decrease 25 – 49%	• Consider causes and possible interventions • Repeat laboratory values within 48 hrs of receipt of abnormal test results. Assess patient for signs and symptoms of illness, acute kidney injury (AKI), etc.
eGFR decrease ≥ 50% * OR if <18 years old, eGFR < 35 mL/min/1.73 m^2	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Repeat laboratory values within 48 hrs of receipt of abnormal test results. Assess patient for signs and symptoms of illness, AKI, etc. • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider referral to nephrologist for diagnosis and management • Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine ratio (PCR) ≥ 1g/g creatinine (Cr)	• Confirm presence of true proteinuria by quantification: protein:creatinine on first morning void • Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider referral to a nephrologist
New onset hematuria ≥ 3+ on urine dipstick	• Obtain urine microscopy to distinguish hemoglobinuria or myoglobinuria from hematuria • Assess serum Cr • Exclude infection, trauma, calculi, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

* Corresponds to KDIGO criteria for Acute Kidney Injury

eGFR is calculated using a modified Schwartz formula for participants <18 years:

eGFR (ml/min/1.73m^2) = 0.413 x height (cm) / serum creatinine (mg/dl). The most recently available height should be used for calculation.

eGFR decrease are defined as compared to the baseline value of PANORAMA-HF OLE study (i.e. Visit 500).

Urine samples for testing for renal monitoring, and particularly those for the PCR ratio determination, must be collected at the first morning void.

Table 10-4 GFR by age for up-titration

Age range*	≥ 30% mean GFR for age (mL/min/1.73m^2)**	< 30% mean GFR for age (mL/min/1.73m^2)
12 months to < 19 months (1 year, 7 months)	≥ 31	< 31
19 months to < 18 years	≥ 38	< 38
≥ 18 years	≥ 30	< 30

* Age rounded to nearest whole number
** up-titration criteria

Source: (Peters, Gordon 1999)

10.6 Appendix 6: Guidelines for the management of renal dysfunction

General principles:

Glomerular filtration rate in HF patients depends on intrinsic renal function and on a balance between afferent and efferent glomerular arterial tonicity. This tonicity is partly regulated by a stimulation of angiotensin II and could be affected by either study medication. Moreover, renal dysfunction may develop or may deteriorate in some patients after study drug administration. These recommendations have been developed to guide the investigators in managing patients with renal dysfunction after enrollment and the first dose of sacubitril/valsartan.

Two types of response to serum creatinine increase are described:

Surveillance situation

If, at any time after enrollment and the first open-label dose of sacubitril/valsartan, eGFR%* decreases by ≥ 50% from baseline in PANORAMA-HF OLE study (i.e. Visit 500), the investigator will check for potentially reversible causes of renal dysfunction such as:

- non-steroidal anti-inflammatory drug intake, antibiotics, or other treatments known to cause creatininemia
- volume decrease, including that resulting from excessive dosing of diuretics
- urinary infection
- urinary tract obstruction
- study medication

Action situation

If a patient eGFR* decreases by ≥ 50% from baseline of PANORAMA-HF OLE study (i.e. Visit 500) (or if serum creatinine concentration rises above 3 mg/dL (265 μmol/L), the investigator will check for potentially reversible causes of renal dysfunction (see above). If the investigator judges that study medication has to be stopped, he/she will have to contact the Novartis medical monitor or his/her designee. Thereafter, serum creatinine assessments will have to be repeated at least each week until levels return to acceptable values. If study medication was stopped, every effort will be done to restart it again, according to clinical conditions.

*eGFR is calculated using a modified Schwartz formula for participants <18 years.

For participants ≥18 years, an adult formula for eGFR will be utilized (Reference: Novartis Nephrology Guidance document)

10.7 Appendix 7: American heart association (AHA) pediatric advanced life support (PALS) guidelines

Table 10-5 5th percentile systolic blood pressure (SBP) table

Age	SBP percentile	SBP (mmHg)
1 month to < 1 year	5th	70
1 year	5th	72
2 years	5th	74
3 years	5th	76
4 years	5th	78
5 years	5th	80
6 years	5th	82
7 years	5th	84
8 years	5th	86
9 years	5th	88
10 years	5th	90
11 years	5th	90
12 years	5th	90
13 years	5th	90
14 years	5th	90
15 years	5th	90
16 years	5th	90
17 years	5th	90

* AHA PALS guidelines 2010 (Kleinman et al 2010) are widely used criteria for hypotension in acute HF patients. The formula (for 1 year and older: 70 mmHg + 2 x Age, up to age 10) is understood to provide the 5th SBP percentile up to 10 years. For children 1 month to < 1 year and ≥ 10 years, the AHA PALS guidelines 2010 5th percentile is set at 70 mmHg and 90 mmHg respectively. NOTE:

This formula approximates the population-based 5th percentile BP data; however, the margin of error increases with increasing age, with the PALS formula value generally providing a lower value.

10.8 Appendix 8: Guidelines for the management of hypotension

1. Investigator should monitor blood pressure closely.
2. If symptomatic hypotension occurs:
   - Correct any treatable cause, e.g. hypovolemia
   - If hypotension persists, any antihypertensive drug and non-disease-modifying drugs, such as diuretics, calcium channel blockers (CCBs), nitrates, and α-blockers, should be down-titrated or stopped first before down-titration of the study drug is considered
   - If hypotension persists, the study drug should be down-titrated or even temporarily withdrawn.

10.9 Appendix 9: Treatment guidelines for elevated potassium and hyperkalemia (serum potassium ≥ 5.3 mmol/L)

General principles

Elevation of potassium levels on a non-hemolyzed specimen above the predefined values should be repeated and confirmed before any action, if appropriate based on investigator's medical judgment.

For assessment of potassium, no blood sample should be drawn by finger or heel stick. Also note that pH can affect potassium values, and that abnormal potassium values should include assessment of pH. Each 0.1 increase in pH represents a 0.6 mEq/L change in the opposite direction of the pH change.

Patients with elevated potassium value will be managed according to the corrective actions outlined below. Hyperkalemia should be followed until resolution.

Corrective action for management of elevated potassium and hyperkalemia

Serum potassium > 5.2 and ≤5.4 mmol/L

Confirm potassium concentration in a non-hemolyzed sample.

Reinforce low potassium diet and restriction of food/drinks with high potassium content (e.g. orange juice, melon, bananas, low-salt substitutes etc.).

Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia. Consider reduction in dose or discontinuation of these agents:

- Aldosterone antagonists (if they are believed to be the most likely cause of hyperkalemia)
- Potassium-sparing diuretics (e.g. amiloride and triamterene) including in combination products with thiazide or loop diuretics
- Potassium supplements, e.g. potassium chloride
- Salt substitutes
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Cyclo-oxygenase-2 (COX-2) inhibitors
- Trimethoprim and trimethoprim-containing combination products, such as Bactrim® and Septra® (trimethoprim/sulfamethoxazole fixed combination)
- Herbal Supplements: For example, Noni juice, alfalfa (*Medicago sativa*), dandelion (*Taraxacum officinale*), horsetail (*Equisetum arvense*), nettle (*Urtica dioica*), milkweed, lily of the valley, Siberian ginseng, hawthorn berries.

Repeat serum potassium measurement within 3 to 5 days. If serum potassium remains > 5.2 and ≤ 5.4 mmol/L, regularly monitor serum potassium levels to ensure stability suggested once monthly.

Consider down-titration of study medication, according to investigator's medical judgment.

Serum potassium > 5.4 and < 6.0 mmol/L

Confirm potassium concentration in a non-hemolyzed sample.

Consider down-titration or temporarily discontinue study drug according to investigator medical judgment.

Apply all measures outlined for serum potassium > 5.2 and ≤ 5.4 mmol/L.

Repeat serum potassium measurement after 2-3 days.

- If serum potassium < 5.4 mmol/L, consider resumption of study drug at lower dose with repeat potassium within 5 days.

Serum potassium ≥ 6.0 mmol/L

Confirm potassium concentration in a non-hemolyzed sample.

Urgently evaluate patient and treat hyperkalemia as clinically indicated.

Apply all measures outlined for serum potassium > 5.4 and < 6.0 mmol/L.

Study drug should be immediately interrupted or discontinued if the serum potassium is greater than or equal to 6.0 mmol/L.

No resumption of study drug without individualized case discussion with and permission from Novartis medical monitor or his/her designee.

10.10 Appendix 10: Reference table – blood volume by weight

Table 10-6 Reference table – blood collection volumes by body weight (kg)

2.5% and 5% Blood volume table by weight (up to 35 kg)[1]

Body Weight (Kg)	Total blood volume of the patient (mL)	Maximum allowable volume (mL) in one blood draw (= 2.5% of total blood volume of the patient)	Total maximum volume (mL) drawn in a 28-day period (= 5% of total blood volume of the patient)
2.5	200	5	10
3	240	6	12
3.5	280	7	14
4	320	8	16
4.5	360	9	18
5	400	10	20
5.5	440	11	22
6	480	12	24
6.5	520	13	26
7	560	14	28
7.5	600	15	30
8	640	16	32
8.5	680	17	34
9	720	18	36
9.5	760	19	38
10	800	20	40
10.5	840	21	42
11	880	22	44
11.5	920	23	46
12	960	24	48
12.5	1000	25	50
13	1040	26	52
13.5	1080	27	54
14	1120	28	56
14.5	1160	29	58
15	1200	30	60
15.5	1240	31	62
16	1280	32	64
16.5	1320	33	66
17	1360	34	68
17.5	1400	35	70
18	1440	36	72
18.5	1480	37	74
19	1520	38	76
19.5	1560	39	78

2.5% and 5% Blood volume table by weight (up to 35 kg)[1]

Body Weight (Kg)	Total blood volume of the patient (mL)	Maximum allowable volume (mL) in one blood draw (= 2.5% of total blood volume of the patient)	Total maximum volume (mL) drawn in a 28-day period (= 5% of total blood volume of the patient)
20	1600	40	80
20.5	1640	41	82
21	1680	42	84
21.5	1720	43	86
22	1760	44	88
22.5	1800	45	90
23	1840	46	92
23.5	1880	47	94
24	1920	48	96
24.5	1960	49	98
25	2000	50	100
25.5	2040	51	102
26	2080	52	104
26.5	2120	53	106
27	2160	54	108
27.5	2200	55	110
28	2240	56	112
28.5	2280	57	114
29	2320	58	116
29.5	2360	59	118
30	2400	60	120
30.5	2440	61	122
31	2480	62	124
31.5	2520	63	126
32	2560	64	128
32.5	2600	65	130
33	2640	66	132
33.5	2680	67	134
34	2720	68	136
34.5	2760	69	138
35	2800	70	140

Blood volume drawn for the purpose of this study is limited to a maximum of 2.5% of the circulating blood volume per sampling session and to a maximum of 5% over a 4-week period (Howie 2011). Investigators may further limit the volume of blood withdrawn based on local institutional guidelines and if the clinical condition of the patient may be adversely affected by removal of the blood volumes stated above.

[1] For body weights >35 kg, use the following formulas to calculate 2.5% and 5% of total blood volume:

2.5% of total blood volume = body weight (in kg to the closest 0.5 kg) X 2

5% of total blood volume = body weight (in kg to the closest 0.5 kg) X 4

11 References

References are available upon request

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