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Sacubitril/Valsartan

Clinical Trial Protocol CLCZ696B2319E1 / NCT03785405

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

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List of abbreviations

ACEI	Angiotensin Converting Enzyme (inhibitor)
AE	Adverse Event
Alb	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor Neprilysin Inhibitor
AST	Aspartate Aminotransferase
AT1	Angiotensin Type 1
bid	bis in die/twice a day
BUN	Blood Urea Nitrogen
CCB	Calcium Channel Blocker
CHBP	Child Bearing Potential Females
CHF	Chronic Heart Failure
CMO	Chief Medical Office
CMV	Cytomegalovirus
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTT	Clinical Trial Team
CV	Cardiovascular
DAR	Dosage Administration Record
DBP	Diastolic Blood Pressure
EBV	Epstein-Barr virus
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EoS	End of Study
eSource	Electronic Source
EU	European Union
FDA	Food and Drug Administration
FPFV	First Patient First Visit
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HF	Heart Failure
HFrEF	HF with Reduced Ejection Fraction
HSV	Herpes Simplex Virus
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
INR	International Normalized Ratio

IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
LFT	Liver function test
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MRP2	Multidrug resistance protein 2
NEP	Neprilysin
NSAID	Non-steroidal Anti-Inflammatory Drug
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PS	Patient Safety
PSD	Premature Subject Discontinuation
PT	Prothrombin Time
OLE	Open Label Extension
QMS	Quality Management System
RBC	Red Blood Cell(S)
RoW	Rest of World
RRR	Relative Risk Reduction
R Value	ALT/ALP ×ULN
SAE	Serious Adverse Event
SAF	Safety Set
SBP	Systolic Blood Pressure
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOPs	Standard Operating Procedures
STD	Study Treatment Discontinuation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin
TEAE	Treatment- Emergent Adverse Event
ULN	Upper Limit of Normal
USM	Urgent safety measure
UTI	Urinary Tract Infection
WBC	White Blood Cell(S)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

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
Biological Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Cohort	A specific group of subjects fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the subject 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 paper source forms 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 subject or at a later point in time as defined by the protocol
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained
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 subjects with established disease and in those with newly-diagnosed disease
Patient	An individual with the condition of interest for the study
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	Subject information collected by the investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized subject
Screen Failure	A subject 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 an electronic source (eSource).
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first subject

Study treatment	Any single drug or combination of drugs or intervention administered to the subject as part of the required study procedures
Study treatment discontinuation	When the subject permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 2

Amendment rationale

This is the second amendment to the protocol.

On 26-Oct-2021, an urgent safety measure (USM) was implemented by Novartis in the PANORAMA-HF study (CLCZ696B2319).

As a result, not all the patients were on study drug treatment at PANORAMA-HF Part 2 End of Study visit (Visit 416). The purpose of the second protocol amendment is to amend the inclusion and exclusion criteria to allow patients impacted by the USM to enroll into this open-label extension (OLE) study.

Changes to the protocol

The following changes have been implemented in the protocol and protocol summary:

1. Section 5.1 Inclusion criteria#2: Patient was on study medication at the PANORAMA-HF Part 2 End of Study visit (Visit 416) or discontinued study drug treatment early due to the implementation of the USM and does not have any significant safety issue as determined by the investigator. Based on the investigator judgement, the patient is able to safely enroll in the OLE study.
2. Section 5.2 Exclusion criteria#1: Patient who only participated in Part 1 of the PANORAMA-HF study or was a screen failure in PANORAMA-HF or permanently discontinued study drug in Part 2 of the PANORAMA-HF study for reasons other than the implementation of the USM.
3. Section 3, Section 5 and Table 8-1 were updated accordingly.
4. Section 8.1 clarified that the use complete lab results from Visit 416 of PANORAMA-HF for Visit 500 screening assessment would not be applicable to patients who discontinued study drug treatment early due to the implementation of the USM.
5. Section 10.1.3 updated SAE reporting language per recent Health Authority Requirement in Germany.
6. Updates have been made to the List of abbreviations.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font~~ for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities, if applicable.

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Amendment 1

Amendment rationale

This is the first amendment to the protocol. The primary purpose of the current protocol amendment is to extend the duration of the study. The current duration of the original protocol is expected to end as early as May-2022 and no later than Dec-2022. In this amendment the duration of the study is extended to ensure that study patients continue to receive age-appropriate study drug treatment (especially those requiring the pediatric formulations not currently available outside investigational use) and safety follow-up until the expected time when pediatric use of sacubitril/valsartan receives local marketing authorization and becomes commercially available to patients.

First patient first visit of this open-label extension (OLE) study occurred on 02-May-2019. As of 31-Jul-2021, 178 patients have been screened and 173 patients have been enrolled into this study.

Major changes to the protocol

The following changes have been implemented throughout the protocol:

- The duration of the study is extended to 2 years from last patient last visit (LPLV) of part 2 of the PANORAMA-HF core study (i.e., until approximately Dec-2023), receipt of local marketing authorization and commercial availability, or reaching the maximum limit allowed by local regulations, whichever occurs first (Section 4.2, Section 6.1.4, Table 8-1, and other places of the protocol).
- In countries where the sacubitril/valsartan is already authorized for pediatric use (e.g., the United States), patients may participate in the study for up to 1 year before being transitioned to commercially available product. If the formulation the patient is taking is not yet commercially available at the end of 1 year, the patient may continue in the study until the formulation becomes commercially available or until the maximum limit allowed by local regulations or until Dec-2023, whichever occurs first (Section 4.2, Section 6.1.4, and other places of the protocol)
- Clarification was added that the study may also be terminated prematurely if the results of the core study does not support local registration (Section 9.1.4).

Other changes to the protocol are:

- The purpose of this study was updated by adding “to provide post-trial access to sacubitril/valsartan to eligible CLCZ696B2319 (PANORAMA-HF) patients” (Section 1.2).
- The phase of the study has been corrected from “2b” to “3” in protocol summary and Section 3.
- A 30-day window from the PANORAMA-HF core study Visit 416 [End of study (EOS)]to the initiation of study treatment of this OLE study (Visit 501) was defined to ensure minimal change in health status of these patients roll-over to the OLE study (Section 3 and Section 8.1).

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- Study design Figure 3-1 was updated to clarify that there is no additional up-titration step after Dose level 4. Additional visit schedules were added to reflect change of the duration of the study.
- Maximum study duration for patients in Germany was updated to 4 (Section 4.2).
- Section 4.6 was added to include the disruption proofing aspects with respect to study procedures in case of a public health emergency per new Novartis guidelines. Section 7 and Section 8 included this change accordingly.
- Clarification that the complete laboratory assessment at screening (Visit 500) should be conducted to assess eligibility. To reduce the burden to the patients, when Visit 500 is conducted within 14 days from the core study Visit 416 and when Visit 416 laboratory results are available at the time of Visit 500, Visit 416 laboratory assessments can be used to evaluate the OLE screening criteria instead of obtaining additional screening laboratory assessments at Visit 500 (Section 8.1 and Table 8-1).
- Clarification that Visit 501 is the visit for first drug administration. Abbreviated local lab may be performed at Visit 501 per the investigator's clinical judgement (e.g., if it is believed that the patient's health status may have changed since the screening visit laboratory tests were performed) (Section 8.1 and Table 8-1).
- Clarification that the baseline laboratory assessments is the complete lab performed at screening (Visit 500), not the abbreviated lab performed at Visit 501 (Table 8-1 and other places of the protocol).
- Considering the rapid growth in pediatric patients, additional height measurements at 6-month intervals will be recorded in the source documents (Table 8-1). Statement was added for standing height measurement using a stadiometer in stocking feet (Table 8-2).
- Clarification that if the study drug treatment is permanently discontinued, the patient should be discontinued from the entire study (Section 6.5.1 and Section 9.1.1).
- In Section 10.2.2 the guidance statements for renal safety monitoring were removed since the renal safety monitoring guidance detailed in Appendix 3 are considered sufficient for the purposes of this study.
- Clarification was added in Appendix 3 that the most recently available height should be used for eGFR calculation. The modified Schwartz formula was added for calculation of estimated glomerular filtration rate (eGFR) for patients < 18 years of age.
- Table 16-2 criteria for clinically notable vital signs for age groups less than 1 year, which is not applicable to this study, was removed.
- Miscellaneous changes were made to clarify some study procedures and details, to remove redundant text, and to correct typographical errors, and inconsistencies in the protocol.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font~~ for deletions and red underlined for insertions.

IRBs/IECs

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A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities, if applicable.

The changes herein are also reflected in the Informed Consent.

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Protocol summary

Protocol	CLCZ696B2319E1
Full Title	A multicenter study to evaluate long-term safety and tolerability of open-label sacubitril/valsartan in pediatric patients with heart failure due to systemic left ventricle systolic dysfunction who have completed study CLCZ696B2319
Brief Title	CLCZ696B2319E1 open-label extension (OLE) study to evaluate long-term safety and tolerability of sacubitril/valsartan in pediatric patients with heart failure
Sponsor and Clinical Phase	Novartis; Phase 3b
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate long-term safety and tolerability data and to provide post-trial access to sacubitril/valsartan to eligible CLCZ696B2319 (PANORAMA-HF) patients receiving open-label sacubitril/valsartan. The rationale of providing post-trial access is to provide uninterrupted access to the study medication to patients until the medication can be obtained commercially.
Primary Objective(s)	The primary objective is to evaluate safety and tolerability of sacubitril/valsartan in eligible PANORAMA-HF subjects receiving open-label sacubitril/valsartan.
Secondary Objectives	There are no secondary objectives for this study
Study design	This trial is a multicenter, open-label long-term study for subjects who have successfully completed Part 2 of the PANORAMA-HF trial. Subjects who successfully completed the 52-week randomized double-blind, treatment period of PANORAMA-HF (i.e. on dose level 1 or higher at the PANORAMA-HF End of Study visit) and are eligible for the Open-Label Extension (OLE) or who discontinued study drug treatment early in Part 2 due to the implementation of USM of PANORAMA-HF, according to the protocol and in the opinion of the investigator, will be offered the option to initiate treatment with sacubitril/valsartan by enrolling into this study (CLCZ696B2319E1). For all consenting subjects eligibility for the OLE will be assessed at the Screening visit (Visit 500). During the study, visits to assess safety will be conducted at Visit 501 and at 3-month intervals until the conclusion of the study (except for Visits 502, 503, 504 and 505 for the up-titration steps, which are at 2-week intervals).
Population	Study population consists of pediatric Heart Failure (HF) patients ≥ 13 months, in-patients or outpatients. Subjects will be divided into two age groups (Age Group 1: 6 years and older; Age Group 2: 1 to < 6 years old). All patients who safely tolerated study drug in PANORAMA-HF, as defined by the Inclusion/Exclusion criteria for the OLE, can be considered for eligibility in this open-label study.
Key Inclusion criteria	• Signed informed consent as well as assent at an appropriate age based on country regulations must be obtained prior to participation in the study.

[redacted]

	• Patient was on study medication at the PANORAMA-HF Part 2 End of Study visit (Visit 416) or discontinued study drug treatment early due to the implementation of the urgent safety measure (USM) and does not have any significant safety issue as determined by the investigator. Based on the investigator judgement, the patient is able to safely enroll in the OLE study.
Key Exclusion criteria	• Patient who only participated in Part 1 of the PANORAMA-HF study or was a screen failure in PANORAMA-HF or permanently discontinued study drug in Part 2 of the PANORMA-HF study for reasons other than the implementation of the USM. • Use of investigational drugs within 5 half-lives of enrollment or within 30 days whichever is longer; or longer if required by local regulations – with the exception of PANORAMA –HF study drug. For PANORAMA-HF study drug (sacubitril/valsartan/placebo; enalapril/placebo), a minimum of 36-hour washout period is required before the initiation of study medication visit (Visit 501). • History of hypersensitivity or allergy to any of the study treatments or its excipients or to drugs of similar chemical classes, Angiotensin Converting Enzyme (inhibitor) (ACEIs), Angiotensin Receptor Blockers (ARBs), or Neprilysin (NEP) inhibitors as well as known or suspected contraindications to sacubitril/valsartan. • Renal vascular hypertension (including renal artery stenosis). • Patients with significant renal estimated glomerular filtration rate (eGFR calculated using the modified Schwartz formula < 30% mean GFR for age, Appendix 3, Table 16-6); hepatic (serum aspartate aminotransferase or alanine aminotransferase > 3 times upper limit of normal); gastrointestinal or biliary disorders (that could impair absorption, metabolism, or excretion of orally administered medications). • Patients with a history of angioedema. • 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. • 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.
Study treatment	Sacubitril/valsartan
Efficacy assessments	There will be no efficacy assessments in this study.
Key safety assessments	Adverse Events (AEs), Serious Adverse Events (SAEs), laboratory values, vital signs, and duration of exposure
Data analysis	The primary safety assessment will be based on adverse events, which will be analyzed using frequencies and percentages. Summary statistics will be provided for each age group and overall for demographics and baseline characteristics, including age, age group (only for overall), sex, race, ethnicity, weight, height, vital signs. Continuous variables will be summarized using n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequencies and percentages. Relevant medical histories will be summarized, by system organ class and

[redacted]

	preferred term, for overall and for each age group. The Safety Set (SAF) will be used for the above analyses.
Key words	Pediatric, LCZ696, sacubitril/valsartan, heart failure, open-label study, angiotensin receptor neprilysin inhibitor (ARNI)

[redacted]

1 Introduction

1.1 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 and 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 and Mertens 2010). The Diovan Pediatric Heart Failure Survey study confirmed that two factors; 'efficacy shown in an adult trial' 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 treatment for chronic HF (CHF) and reduced ejection fraction. 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 type 1 (AT_1) receptor. The resulting increase in natriuretic peptide activity due to NEP inhibition and AT_1 receptor blockade through renin-angiotensin-aldosterone system (RAAS) inhibition have complementary effects on the cardiovascular (CV) system that benefit HF patients.

In PARADIGM-HF (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,

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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).

Study CLCZ696B2319 (PANORAMA-HF) is a large, multicenter, double-blind, active controlled pediatric HF trial and includes patients with systemic left ventricular systolic dysfunction <18 years of age. PANORAMA-HF is 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.

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. For this purpose, upon successful completion of the 52-week double-blind treatment period in PANORAMA-HF, patients will be offered the opportunity to enroll in this open-label, long-term extension study and receive open-label sacubitril/valsartan treatment. For subjects who may have successfully completed the double-blind study before the PANORAMA-HF Open Label Extension (OLE) CLCZ696B2319E1 study starts at their study center, participation in the OLE will be offered to them once the study is available.

1.2 Purpose

The purpose of this study is to evaluate long-term safety and tolerability and to provide post-trial access to sacubitril/valsartan to eligible CLCZ696B2319 (PANORAMA-HF) patients.

2 Objectives and endpoints

The primary objective is to further evaluate long- term safety and tolerability of sacubitril/valsartan in eligible PANORAMA-HF subjects receiving open-label sacubitril/valsartan.

There are no secondary or exploratory objectives for this study.

Table 2-1 Objectives and related endpoints

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

[redacted]

3 Study design

This trial is a multicenter, open-label long-term extension study for subjects who have successfully completed Part 2 of the PANORAMA-HF trial. PANORAMA-HF is a Phase 3b study in pediatric subjects with systemic left ventricular systolic dysfunction.

Only subjects who successfully completed the 52-week randomized double-blind treatment period of PANORAMA-HF (Part 2, efficacy, safety) on study medication (i.e. on dose level 1 or higher at the PANORAMA-HF End of Study visit) or who discontinued study drug treatment early in Part 2 due to the implementation of USM of PANORAMA-HF and fulfill protocol requirements (see Section 5) are eligible to participate in the OLE, and will be offered the option to initiate treatment with sacubitril/valsartan by enrolling into this study (CLCZ696B2319E1) at the discretion of the investigator. Subjects who only participated in Part 1 of PANORAMA-HF, who were screen failures in PANORAMA-HF or who permanently discontinued study drug treatment during Part 2 of PANORAMA-HF for reasons other than the implementation of the USM are not eligible for this study (see Section 5 for details).

For all consenting subjects eligibility for the OLE will be assessed at the screening visit (Visit 500) and the study medication will be initiated no later than 30 days after completion of Part 2 of PANORAMA-HF Visit 416 (see Section 8.1 for details).

Required 36-hour washout:

- A 36-hour washout after the last dose of study medication taken in the PANORAMA-HF study (Visit 416) is required for all subjects before starting OLE study medication.
- A 36-hour washout before starting OLE study medication is also required for all subjects that have transitioned to an ACEI after completion of PANORAMA-HF.

An ARB or a renin inhibitor must be discontinued the morning of Visit 501 for subjects taking either of these drugs.

Subjects will be enrolled into two different age groups (Age Group 1: 6 years and older; Age Group 2: 1 to <6 years) in the OLE study. Subjects who turned 18 years old during the PANORAMA-HF double-blind study, and who qualify, are eligible to participate in the OLE study.

Age Groups 1 and 2 in the OLE have a target dose (dose level 4) of 3.1 mg/kg bid.

Subjects will be up titrated to the target dose of sacubitril/valsartan, dose level 4 (see Table 3-2) according to their tolerability. Subjects have to meet all criteria in Table 3-1 during the up-titration phase for safety monitoring before administering the next higher dose level.

Visits 502, 503, 504 and 505, as applicable, are intended to be used for study drug up-titration and abbreviated safety follow-up at an interval of approximately 2 weeks between the visits. During that time, subjects should be up titrated to the maximum tolerated oral dose of sacubitril/valsartan with a goal of reaching the target dose of 3.1 mg/kg. (Refer to Table 3-2 for study-drug dose levels 1 to 4.)

[redacted]

Table 3-1 Safety monitoring criteria for initiation/up-titration of study drug

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 3, Table 16-6)
Kidney function	eGFR reduction < 35% compared to screening Visit 500.
Blood pressure	SBP > than the calculated 5th percentile SBP for age as described in Appendix 6
AEs or conditions	No conditions that preclude continuation according to investigator's judgment, including hypotension.

Table 3-2 Study drug dose levels for sacubitril/valsartan

	age groups 1 and 2 *
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.

*Note: sacubitril/valsartan target dose (dose level 4) for age groups 1 and 2 is 3.1 mg/kg bid. (see Section 4.2 for additional details).

If a subject is unable to tolerate up-titration to a higher sacubitril/valsartan dose level or at the discretion of the investigator, subjects may be maintained on lower dose levels of sacubitril/valsartan (dose level 1-3, see Table 3-2). In case of a consecutive 3-month interruption of study treatment, subject should be discontinued from the study and should complete Visit 599.

An outline of the study design is presented in Figure 3-1. Depending on when and where the patient is enrolled, the duration of the study varies from 1 to approximately 4.5 years.

The OLE study drug starting dose will depend either upon the dose of ACEI/ARB that the subject was transitioned to after completion of the PANORAMA-HF or the dose the subject was on at the End of Study visit for the core study PANORAMA-HF prior to screening (Visit 500; refer to Table 3-2).

At Visit 501, subjects who meet eligibility criteria will start the study drug at dose level 1 or 2 (Table 3-2). Subjects who were on dose level 1 at the PANORAMA-HF End of Study (PANORAMA-HF visit 416) or who are on a low dose of ACEI/ARB (dose levels 1; Table 3-3) or not on an ACEI/ARB prior to screening (Visit 500) should start at dose level 1 at Visit 501.

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Subjects who were on dose level 2, 3 or 4 at PANORAMA-HF visit 416 or who are on a higher dose of ACEI/ARB (dose levels 2, 3 or 4; Table 3-3) prior to screening (Visit 500) should start at dose level 2 at Visit 501 (Table 3-2) or at dose level 1 at investigator's discretion.

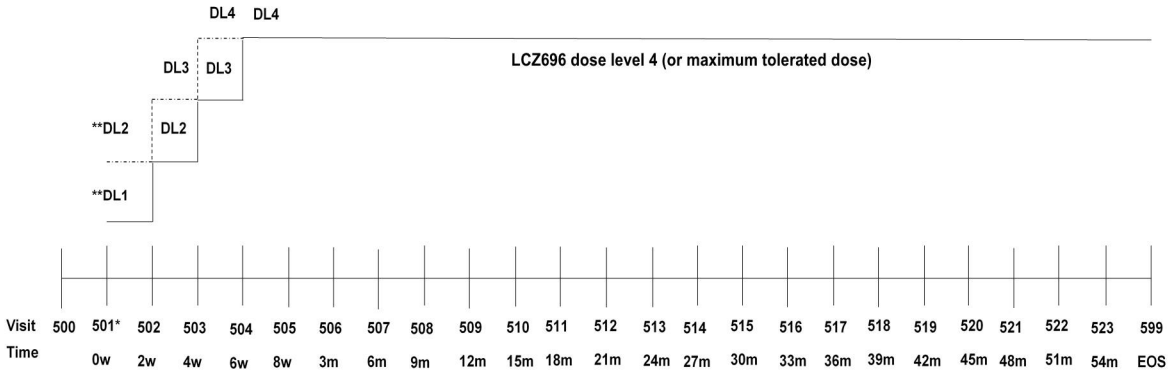
During the study, visits to assess safety will be conducted at Visit 501 and at 3-months intervals until the conclusion of the study (except for titration visits, which are at 2-week intervals). Unscheduled visits are allowed for subject's safety and for dose adjustment purposes

Table 3-3 Total daily dose levels of commonly prescribed ACEI/ARBs for the purpose of comparing to dose levels of study drug

Dose levels for pediatric formulation	**Enalapril/Lisinopril total daily dose**	**Captopril total daily dose**	
Dose level 1	0.1 mg/kg	0.3 mg/kg	
Dose level 2	0.2 mg/kg	0.6 mg/kg	
Dose level 3	0.3 mg/kg	1.2 mg/kg	
Dose level 4	0.4 mg/kg	1.5 mg/kg	
Dose levels for adult formulation	**Enalapril/Lisinopril total daily dose**	**Captopril total daily dose**	**Cilazapril total daily dose**
Dose level 1	5 mg	18.75 mg	0.5 mg
Dose level 2	10 mg	37.5 mg	1.0 mg
Dose level 3	15 mg	75 mg	2.5 mg
Dose level 4	20 mg	150 mg	5.0 mg
Dose levels for pediatric formulation	**Valsartan total daily dose**	**Losartan total daily dose**	**Candesartan total daily dose**
Dose level 1	0.7 mg/kg	0.4 mg/kg	0.2 mg/kg
Dose level 2	1.4 mg/kg	0.7 mg/kg	0.25 mg/kg
Dose level 3	2.0 mg/kg	1.0 mg/kg	0.32 mg/kg
Dose level 4	2.7 mg/kg	1.4 mg/kg	0.64 mg/kg
Dose levels for adult formulation	**Valsartan total daily dose**	**Losartan total daily dose**	**Candesartan total daily dose**
Dose level 1	40 mg	25 mg	4 mg
Dose level 2	80 mg	50 mg	8 mg
Dose level 3	160 mg	75 mg	16 mg
Dose level 4	320 mg	100 mg	32 mg

[redacted]

Figure 3-1 Study Design



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

4 Rationale

4.1 Rationale for study design

The purpose of this open-label extension study of PANORAMA-HF is to further evaluate the long-term safety and tolerability and to provide post-trial access of sacubitril/valsartan to eligible patients that successfully completed the PANORAMA-HF study (see Inclusion/Exclusion criteria Section 5.1).

4.2 Rationale for dose/regimen and duration of treatment

The starting dose will be dose level 1 or 2, based on the dose level the subject was on at the final visit of PANORAMA-HF or the dose levels of ACEI/ARBs to which the subject was transitioned after completion of the double-blind core study, PANORAMA-HF. The respective starting dose levels were chosen to ensure a smooth transition to the open-label study medication taking safety and tolerability aspects into account. Subjects will be up-titrated to next dose level at approximately 2-week intervals, per investigator judgement, until the target dose of 3.1 mg/kg or the maximum tolerated dose is reached.

The duration of the study will continue up to 2 years from LPLV of part 2 of the core study (i.e., until approximately Dec-2023), receipt of local marketing authorization and commercial availability, or reaching maximum limit allowed by local regulations, whichever occurs first.

In countries where the sacubitril/valsartan is already authorized for pediatric use during the core study, patients may participate in the study for up to 1 year before being transitioned to commercially available product. If the formulation the patient is taking is not yet commercially available at the end of 1 year, the patient may continue in the study until the formulation becomes commercially available or any of the above conditions are met (also see details in Section 6.1.4).

This timeframe will allow for meaningful capture of long-term safety data and will ensure sufficient access to study drug, which patients have relied on for their treatment, for an extended period until they can obtain it using normal local commercial process. In addition the results of

[redacted]

the PANORAMA-HF core study results will be available during this time frame and will determine whether patients in PANORAMA-HF derived benefit from treatment with LCZ696.

[* The following text applies to subjects enrolled in the OLE in Germany: Each eligible subject enrolled in Germany has a maximum study duration of 4 years. The treatment duration may be re-evaluated at a later time point as needed.]

4.3 Rationale for choice of control drugs

Not applicable.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.5 Risks and benefits

This is an extension study for subjects who have successfully completed the double-blind PANORAMA-HF trial, with a goal to further evaluate long-term safety and tolerability of sacubitril/valsartan in pediatric heart failure subjects.

Details regarding preclinical data from sacubitril/valsartan juvenile animal studies are described in the Sacubitril/Valsartan Investigator's Brochure (IB), which is provided to every participating study site.

Sacubitril/valsartan has proven to have a significant mortality and morbidity benefit compared to the standard of care enalapril for the treatment of adult HF with reduced systolic function (HFrEF) in the PARADIGM-HF study (CLCZ696B2314). Continuous treatment with sacubitril/valsartan over a median follow-up time of 27 months led to a 20% RRR in the primary endpoint of CV death or first HF hospitalization over optimized enalapril treatment. Clinical trial data in adults demonstrate that sacubitril/valsartan has an overall safety profile generally comparable to other RAS inhibiting agents. Hypotension, hyperkalemia, renal impairment, and angioedema have been identified as possible safety risks in sacubitril/valsartan studies. While the incidence rate of hypotension in Study CLCZ696B2314 was higher for sacubitril/valsartan compared with enalapril, hypotension assessed as severe or serious was not higher in the sacubitril/valsartan group compared to the enalapril group. In addition, no major difference was observed for hypotension leading to study drug discontinuation. In contrast, the incidence of hyperkalemia, renal impairment and cough was numerically lower in the sacubitril/valsartan group compared to the enalapril group.

Data are not yet available from the double-blind study PANORAMA-HF. An external independent Data Monitoring Committee (DMC) monitors the safety of the PANORAMA-HF study participants in an unblinded manner. DMC findings (safety and/or efficacy) and recommendations may impact the conduct of PANORAMA-HF as well as this open-label-extension study.

Although the DMC regularly monitors ongoing data in the core study PANORAMA-HF, one risk for patients enrolling in the open-label study is that, they are doing so without knowing the results of the double-blind core study PANORAMA-HF. It should also be noted that the long-term exposure to sacubitril/valsartan on cognitive function is not known.

[redacted]

Risks to subjects in this trial (e.g. renal dysfunction, blood pressure, and hyperkalemia) can be minimized by rigorous compliance with the inclusion and exclusion criteria and study procedures, as well as clinical safety monitoring (vital signs, physical exam, hematology, blood chemistry and urinalysis tests). Recommended guidelines for prophylactic or supportive management of study drug-induced adverse events are provided in Appendix 4, Appendix 6, and Appendix 7 (guidelines for the management of renal dysfunction, blood pressure, and hyperkalemia, respectively).

Women of childbearing 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 subject will not reliably comply, they should not be entered or continue in the study.

4.6 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 patients safety and trial integrity 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.

5 Population

The study population consists of pediatric HF patients ≥ 13 months, in-patients or outpatients. Subjects will be divided into two age groups, Age Group 1, ≥ 6 years old and Age Group 2, 13 months to <6 years old). All patients who safely tolerated study drug in PANORAMA-HF, who were receiving study drug at Visit 416 of the double-blind study or discontinued from study drug treatment early due to implementation of the USM and who successfully completed the double-blind study, and fulfilled the Inclusion/Exclusion criteria for the OLE (Section 5.1 and Section 5.2), can be considered for this open-label study. Patients in the double-blind study for whom study medication had been temporarily interrupted during the study, may be considered for the OLE if they were receiving study medication at Visit 416 and they meet all entry criteria.

5.1 Inclusion criteria

Subjects 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 based on country regulations must be obtained prior to participation in the study.
2. Patient was on study medication at the PANORAMA-HF Part 2 End of Study visit (Visit 416) or discontinued from the study drug treatment early due to the implementation of the USM and does not have any significant safety issue as determined by the investigator. Based on the investigator judgement, the patient is able to safely enroll in the OLE study.

[redacted]

5.2 Exclusion criteria

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

1. Patient who only participated in Part 1 of the PANORAMA-HF study or was a screen failure in PANORAMA-HF or permanently discontinued study drug in Part 2 of the PANORAMA-HF study for reasons other than the implementation of the USM.
2. Use of investigational drugs within 5 half-lives of enrollment or within 30 days whichever is longer; or longer if required by local regulations – with the exception of PANORAMA-HF study drug. For PANORAMA-HF study drug (sacubitril/valsartan/placebo; enalapril/placebo), a minimum of 36-hour washout period is required before the initiation of study treatment (Visit 501).
3. History of hypersensitivity or allergy to any of the study treatments or its excipients or to drugs of similar chemical classes, ACEIs, ARBs, or NEP inhibitors as well as known or suspected contraindications to sacubitril/valsartan.
4. Renal vascular hypertension (including renal artery stenosis).
5. Patients with significant renal (eGFR calculated using the modified Schwartz formula < 30% mean GFR for age, Appendix 3, Table 16-6); hepatic (serum aspartate aminotransferase or alanine aminotransferase > 3 times upper limit of normal); gastrointestinal or biliary disorders (that could impair absorption, metabolism, or excretion of orally administered medications).
6. Patients with a history of angioedema.
7. 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.
8. Pregnant or nursing (lactating) women.
9. 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.
10. Patient breastfed by a mother taking ACEI.
11. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and for 5 days of sacubitril/valsartan after stopping medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - 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

[redacted]

(failure rate <1%), for example, hormone vaginal ring or transdermal hormone contraception.

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

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

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

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Table 6-1 Open-label sacubitril/valsartan formulations

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		please refer to OLE Pharmacy Manual

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

All pediatric formulations of study medication (sacubitril/valsartan granules or liquid) will be made available to all age groups. The adult tablet formulations of sacubitril/valsartan will be available for subjects based on the subject's dosing and ability to swallow adult tablets (refer to OLE Pharmacy Manual). The dispensing of medication to the subjects will be controlled by an Interactive Response Technology (IRT) system based on the dose level, subject's body weight and ability to swallow tablets/granules.

An overview of available sacubitril/valsartan formulations is illustrated in Table 6-1. Capsules of LCZ696 containing 4 granules or 10 granules per capsule will be provided for oral use. The granules can be swallowed by the subject, after the removal of the outer capsule. Subjects who

[redacted]

cannot use tablets or granules can use the liquid formulation. Sacubitril/valsartan liquid formulation will be compounded by the site / pharmacy (please refer to OLE 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 the medication number, and will not include information about the subject.

Subjects 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 subjects and families, the parent/caregiver can come to the site without the subject for dispensation of study drug between scheduled study visits (see Table 8-1). Delivery of study drug to the subject can also be used, where possible and where allowed by local regulations.

6.1.2 Additional study treatments

No other study treatments beyond the investigational treatment (sacubitril/valsartan) are planned for this trial.

6.1.3 Treatment arms/group

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

6.1.4 Treatment duration

The study will continue up to 2 years from LPLV of part 2 of the core study (i.e., until approximately Dec-2023), receipt of local marketing authorization and commercial availability, or reaching maximum limit allowed by local regulations, whichever occurs first.

In countries where the sacubitril/valsartan is already authorized for pediatric use during the core study, patients may participate in the study for up to 1 year before being transitioned to commercially available product. If the formulation the patient is taking is not yet commercially available at the end of 1 year, the patient may continue in the study until the formulation becomes commercially available or until the maximum limit allowed by local regulations or until Dec-2023, whichever occurs first.

6.2 Other treatment(s)

Subjects 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.

6.2.1 Concomitant therapy

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

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

[redacted]

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

6.2.1.1 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.

Medications known to raise potassium levels (e.g. potassium-sparing diuretics, potassium supplements) should be used with caution. In case of hyperkalemia adequate measures should be considered, e.g. reduce dietary potassium and/or adjust the dose of concomitant medication(s). Monitoring of serum potassium is recommended especially in subjects with risk factors.

In subjects 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 subjects on sacubitril/valsartan who are taking NSAIDs concomitantly.

Guidelines for the management of hyperkalemia, hypotension and renal dysfunction are provided in Appendix 7, Appendix 6, and Appendix 4, respectively.

[redacted]

6.2.2 Prohibited medication

Use of the treatments included in the below table are not allowed while taking study drug due to safety reasons. If the medication included in Table 6-2 must be administered, study drug must be discontinued and the actions specified below must be taken.

Table 6-2 Prohibited medications

Medication	Prohibition period	Action taken
any ACEI	36 hour 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 subject 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.

6.2.3 Rescue medication

If in the opinion of the investigator, the subject 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 4, Appendix 6, and Appendix 7, 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.

6.3 Subject numbering and treatment assignment

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing

[redacted]

the informed consent form, the subject will be assigned the same Subject Number as he/she had in the PANORAMA-HF core study.

Upon signing the informed consent form, the investigator or his/her staff will contact the IRT and provide the requested identifying information to register the subject into the IRT system.

If the subject fails to be treated for any reason, the IRT must be notified as soon as possible that the subject was not treated. The reason for not being treated will be entered on the Screening Disposition eCRF.

6.3.2 Treatment assignment

This is an open-label study and subjects will not be randomized to treatment in this trial. All eligible subjects previously treated with sacubitril/valsartan or enalapril in PANORAMA-HF will be treated with open-label sacubitril/valsartan at maximally tolerated doses up to the target dose that has been determined for each age group. The target dose of sacubitril/valsartan will be 3.1 mg/kg bid for Age Group 1. The target dose for Age Group 2 is 3.1 mg/kg bid (see Section 4.2 for additional details).

An Interactive Response Technology (IRT) system will be used to enroll subjects into the study and dispense study drug. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all of the inclusion/exclusion criteria. The IRT system will prompt the investigator to enter the subject's Subject Number into the system and will then assign a uniquely numbered medication kit for the first investigational treatment to be dispensed to the subject (at the time of completing Visit 501).

The IRT will be used to assign additional uniquely numbered medication kits at subsequent visits throughout the duration of the trial (except End of Study visit).

6.4 Treatment blinding

Not applicable. Treatment will be open to subjects, investigator staff, persons performing the assessments, and the Clinical Trial Team (CTT).

6.5 Dose escalation and dose modification

6.5.1 Dose modifications

The study drug is up titrated every 2 weeks as tolerated to target dose (dose level 4) as outlined in Table 3-2 and based on the safety monitoring criteria (Table 3-1). Following up titration, the maximum tolerated or target dose will then 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 subjects who are unable to tolerate the protocol-specified dosing scheme, 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.

[redacted]

- 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 3-2) to temporary or permanent discontinuation of study drug.
- The subject 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 subject should be discontinued from the study (Visit 599).

Subjects 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 and Work 2009) will be utilized. Refer to Appendix 4, Appendix 6, and Appendix 7 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 3-1 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 subject's condition is stable, the subject can be up titrated to the next higher dose level using unscheduled visits in an attempt to bring back the subject 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 3-2).

All changes should be recorded on the Drug Administration Record (DAR) eCRF. In addition, IRT should be contacted to register any changes in the subject's study-drug dose level, in cases of temporary and permanent discontinuation of the study drug, and to obtain the medication numbers of the study drug supplies required for the new study-drug dose level.

Study drug restart after temporary treatment interruption

Subjects who have temporarily discontinued study drug should be restarted as soon as possible as deemed appropriate by the investigator. The investigator should restart the subject on the study drug at the most appropriate dose level (Table 3-2) as per the investigator's clinical judgment. If the subject 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.

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

Investigators may discontinue a subject'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, subjects who permanently discontinued study drug should be scheduled for the discontinuation study Visit 599.

[redacted]

If during study treatment interruption a subject 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. Subjects 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.

Note that after a consecutive 3-month interruption of study treatment, subject should be discontinued from the study and should be seen at the site for Visit 599).

If the subject becomes pregnant during the course of the study, the subject has to discontinue study drug immediately and should be seen at the site for Visit 599 and evaluated for transition to alternative treatment per the Investigator's clinical judgement.

Refer to (Section 8.4.2) for further details on pregnancies and reporting guidelines.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the subject/parent/guardian to take/administer the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject/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.

6.6.2 Emergency breaking of assigned treatment code

This is an open-label study therefore emergency breaking of treatment assignment is not applicable.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

Medication will be provided as tablets, granules (mini-tablets) or liquids. Tablets and granules (mini-tablets) will be provided by Novartis to the study site. Liquid preparation will be provided either by the site or by the pharmacy according to local regulations. For liquid preparation, please refer to OLE Pharmacy Manual.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label). Before dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

[redacted]

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study drug 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 designees have access. Upon receipt, all study drugs 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 CO 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 drug but no information about the subject except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study drug and packaging at the end of the study or at the time of discontinuation of study drug.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study drug, 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.

Where applicable and as per local regulations, the study medication can be shipped from the study site or pharmacy to subject's home. Pharmacy to home operating procedures will be provided to the site/pharmacy by the sponsor.

6.7.1.2 Handling of additional treatment

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

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

6.7.2 Instruction for prescribing and taking study treatment

Novartis will supply the investigators with all study medications required for the course of the study. Subjects will be provided with bottles containing study drug corresponding to their assigned dose level, sufficient to last until the next scheduled visit (Table 8-1). Study drug will be supplied to subjects as:

- sacubitril/valsartan tablets: 50 mg, 100 mg or 200 mg
- sacubitril/valsartan granules: 3.125 mg/granule (packaged in capsule containing either 4 or 10 granules) supplied in a bottle

[redacted]

- sacubitril/valsartan liquid formulation (compounded by site / pharmacy) (refer to OLE Pharmacy Manual)

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

Subjects 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 OLE Pharmacy Manual.

All dosages prescribed and dispensed to the subject and all dose changes during the study must be recorded on the Dosage Administration Record (DAR) eCRF. All kits of study treatment assigned by the IRT will be recorded in the IRT system.

The investigator must promote compliance by instructing the subject/parent/guardian to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject/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.

7 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing written (witnessed, where required by law or regulation), Institutional Review Board /Independent Ethics Committee (IRB/IEC)-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her level of understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. the procedures described in the protocol). The process of obtaining informed consent and adolescent/child assent where applicable must be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form and age appropriate assent forms that comply with the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women 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 requirement for the duration of the study as outlined in the exclusion criteria. If there is any concern that the patient will not reliably comply, they must not be entered in the study.

[redacted]

As per Section 4.6, 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, if re-consenting the patient on amended informed consent form, the 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 patients and person obtaining informed consent, etc.).

Informed consent at study entry will need to be conducted face-to-face with patients/ caregivers following the standard guidelines.

8 Visit schedule and assessments

After identifying a potential subject, an informed consent form (ICF) and assent (if applicable) must be signed by the parent(s)/legal guardian(s) and by the subject (as applicable) before performing any study-related procedures that are not considered standard of care for pediatric HF subjects at that site. Procedures that are part of a site‘s standard of care for a pediatric subject or that were done as part of core study PANORAMA-HF End of Study visit 416 may pre-date the signed ICF for the OLE. The AE and SAE reporting period will begin at the time the ICF is signed (e.g. screening visit– Visit 500).

Following the start of sacubitril/valsartan treatment (at Visit 501), initial visits for up titration (i.e. Visits 502, 503, 504 and 505) will be scheduled approximately 2 weeks apart. The number of up-titration visits that a subject requires may vary depending upon the starting dose at visit 501 and the maximally tolerated/target dose. After the subject’s target dose is reached, one more visit can be scheduled approximately 2 weeks later for a safety evaluation.

Three (3) months after Visit 501, a telephone visit will occur (Visit 506). The subsequent site visits will occur at intervals of 6 months beginning at Visit 507, which is scheduled 6 months after starting study treatment. There will be telephone visits every 3 months in between the in-person visits.

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

Subjects, who discontinue sacubitril/valsartan for 3 consecutive months, will be discontinued from the study and are to attend Visit 599.

The Assessment Schedule table (Table 8-1) lists all of the assessments when they are performed (indicated with an “x”). All data obtained from these assessments must be supported in the subject’s source documentation.

The table indicates which data remain in the source documents only (S). Assessments that generate data for database entry are recorded on eCRFs.

Subjects 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 501. Missed or rescheduled

[redacted]

visits should not lead to automatic discontinuation. Specific circumstances surrounding missed or rescheduled visits must be discussed with the study monitor. Subjects who prematurely discontinue 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 599) 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 4.6, 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. In case of missed visits/ assessments due to any such events/ disruptions, the site must refer to the "Panorama-HF OLE Patient visit guide during Public Health Emergencies" document and discuss with the site monitor for guidance on the steps that need to be followed for collection of missed data.

Table 8-1 Assessment Schedule

Visit	**500**	**501** **	**502** *	**503** *	**504** *	**505** *	**506**†	**507**	**508** †	**509**	**510** †	**511**	**512** †	**513**	**514** †	**515**	**516** †	**517**	**518 520 522** †	**519 521 523**	**UNS**	**599**
Week/Month	Screening	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Mo 3	Mo 6	Mo 9	Mo 12	Mo 15	Mo 18	Mo 21	Mo 24	Mo 27	Mo 30	Mo 33	Mo 36	Mo 39 Mo 45 Mo 51	Mo 42 Mo 48 Mo 54		EOS[6]
Obtain Informed Consent (parent (s)-legal guardian (s)/consent-assent (patient, as applicable)[1]	x S																					
Demography	x																					
Inclusion/Exclusion Criteria	x	x[4]																				
Medical History	x																					
Pediatric Heart Failure History	S																					
Concomitant Medications[5]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs (BP and pulse)	x	x	x	x	x	x		x		x		x		x		x		x		x	x	x
Height	x	x						S		x		S		x		S		x		S		x
Weight	x	x	x	x	x	x		x		x		x		x		x		x		x	x	x

[redacted]

Visit	**500**	**501** **	**502** *	**503** *	**504** *	**505** *	**506**†	**507**	**508** †	**509**	**510** †	**511**	**512** †	**513**	**514** †	**515**	**516** †	**517**	**518 520 522** †	**519 521 523**	**UNS**	**599**
Week/Month	Screening	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Mo 3	Mo 6	Mo 9	Mo 12	Mo 15	Mo 18	Mo 21	Mo 24	Mo 27	Mo 30	Mo 33	Mo 36	Mo 39 Mo 45 Mo 51	Mo 42 Mo 48 Mo 54		EOS[6]
Head Circumference (≤ 3 years old)		x								x				x				x		x		x
Physical Examination (complete)	S	S								S				S				S		S		S
Physical Exam (abbreviated)			S	S	S	S		S				S				S					S	S
Urinalysis	x[4]									x				x				x		x	(x)	x
Serum/Urine Pregnancy Test[2]	x[4]	x	x	x	x	x		x		x		x		x		x		x		x	x	x
Complete Laboratories	x[4]									x				x				x		x[6]	(x)	x
Abbreviated Laboratories[3]		x[4]	x	x	x	x		x				x				x				x[6]	(x)	
AEs/SAEs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dosage Administration Record		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)	x
Study Medication Compliance			S	S	S	S		S		S		S		S		S		S		S	(S)	S

[redacted]

Visit	**500**	**501** **	**502** *	**503** *	**504** *	**505** *	**506**†	**507**	**508** †	**509**	**510** †	**511**	**512** †	**513**	**514** †	**515**	**516** †	**517**	**518 520 522** †	**519 521 523**	**UNS**	**599**
Week/Month	Screening	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Mo 3	Mo 6	Mo 9	Mo 12	Mo 15	Mo 18	Mo 21	Mo 24	Mo 27	Mo 30	Mo 33	Mo 36	Mo 39 Mo 45 Mo 51	Mo 42 Mo 48 Mo 54		EOS[6]
Contact IRT	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dispense Study Medications		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)	
End of Study Treatment Discontinuation																						x

UNS = Unscheduled visit

S = assessment to be recorded on source documentation only

X = assessment to be recorded in the clinical database or received electronically from a vendor

PSD = Premature subject discontinuation

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

† Visit numbers 506, 508, 510, 512, 514, 516, 518, 520, 522 are telephone visits.

[1] Patient Assent document is captured as a source document and is not stored in the clinical database.

[2] For child bearing potential females (CHBP) only. Urine pregnancy test is analyzed locally and done at all in-person scheduled/unscheduled visits on all female subjects ≥11 years of age and all female subjects who are <11 years of age if they are menstruating. A serum pregnancy test is performed and analyzed at Visit 500 (if >14 days after PANORAMA-HF EOS visit) and at Visit 599 respectively. 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 subject with urinary pregnancy tests for home monthly tests. See Section 8.4.2 for additional details.

[3] Abbreviated laboratories consist of serum sodium, potassium, creatinine, eGFR (modified Schwartz formula).

[redacted]

Visit	**500**	**501** **	**502** *	**503** *	**504** *	**505** *	**506**†	**507**	**508** †	**509**	**510** †	**511**	**512** †	**513**	**514** †	**515**	**516** †	**517**	**518 520 522** †	**519 521 523**	**UNS**	**599**
Week/Month	Screening	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Mo 3	Mo 6	Mo 9	Mo 12	Mo 15	Mo 18	Mo 21	Mo 24	Mo 27	Mo 30	Mo 33	Mo 36	Mo 39 Mo 45 Mo 51	Mo 42 Mo 48 Mo 54		EOS[6]

[4] If Visit 500 is scheduled within 14 days of the PANORAMA-HF End of Study visit (Visit 416) and lab results from Visit 416 are available at Visit 500, the assessment results from PANORAMA-HF End of Study visit can be used for Visit 500 instead, except these discontinued study drug treatment early due to the implementation of the USM. Visit 501 is the visit for first drug administration. The inclusion/exclusion criteria and the abbreviated local lab at Visit 501 may be performed per the investigator's clinical judgement (e.g., if it is believed that the patient's health status may have changed since the screening visit) (See Section 8.1 for details). Note: In addition to the scheduled complete and abbreviated laboratories per the Assessment Schedule, laboratory evaluations may also be performed at any scheduled or unscheduled visit based on the investigator's clinical judgement.

[5] Includes Prior and Concomitant Heart Failure Medications

[6] Complete labs at V521 and abbreviated labs at V519 and V523. If the EOS coincides with a scheduled visit, the assessments of EOS visit will take precedence.

* Visits 502 (Week 2), 503 (week 4), 504 (week 6) and 505 (week 8) are for up-titration purposes and safety evaluation. Number of visits can vary dependent on starting dose (DL1 or DL2) and maximal tolerated/target dose. After subject's target dose is achieved, one more visit can be scheduled approximately within the next 2 weeks for safety evaluation, subsequent visits are optional up to visit 506 (3 months).

** Visit 501 must occur within 30 days following completion of PANORAMA-HF core study Visit 416 (See Section 8.1 for details).

[redacted]

8.1 Screening

Please refer to Table 8-1, Assessment Table, for the information to be collected during the Screening visit. All consenting subjects will be assessed for eligibility at the screening (Visit 500).

- Complete laboratory tests at Visit 500 as indicated in Table 8-11 & Table 8-3 should be conducted to assess eligibility.
- The Investigator can use complete lab results from Visit 416 of PANORAMA-HF, except those who discontinued study drug treatment early due to the implementation of the USM, for Visit 500 to evaluate the OLE screening criteria when: 1) Visit 500 is conducted within 14 days from Visit 416, and 2) when Visit 416 results are available at the time of Visit 500.
- In the case where a safety laboratory value at screening is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to Visit 501 (please see details for re-screening in Section 8.1.1). If the repeat value remains outside of the specified ranges, the subject must be excluded from the study.

Visit 501 is the visit for first drug administration. The inclusion/exclusion criteria and the abbreviated local lab at Visit 501 may be performed per the investigator's clinical judgement (e.g., if it is believed that the patient's health status may have changed since the screening visit laboratory assessment was performed).

Visits 500 and 501 and all their procedures, including all required screening procedures and safety labs, must be completed such that the study medication is initiated no later than 30 days after Visit 416 of the core study.

Before starting OLE study medication at Visit 501, a 36-hour double-blind study medication/ACEI-free washout is required after the last dose of study medication taken in the PANORAMA-HF study (Visit 416) and for those that have transitioned to an ACEI after completion of PANORAMA-HF, the core study.

8.1.1 Information to be collected on screening failures

Subjects or parents/guardians who sign an informed consent form for themselves or for their child, respectively, and who (i.e. the subject) 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 Case Report Form. The baseline characteristics, demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see SAE section for reporting details).

Subjects 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 for any reason will have to discontinue the study and will be considered an early study termination. The reason for early study termination should be captured on the appropriate disposition Case Report Form at Visit 599.

[redacted]

Re-screening:

The investigator may consider re-screening a screen failure subject if he/she believes that the subject's condition has changed and they may potentially be eligible. Re-screening should be arranged as soon as possible to ensure initiation of study treatment (Visit 501) within 30 days after Visit 416 of the PANORAMA-HF core study. The subject (if applicable) /parent(s)/legal guardian(s) for the subject must provide new written informed consent before when the subject is re-screened. Subjects required to provide assent must also provide new assent before being re-screened.

8.2 Subject demographics/other baseline characteristics

Country specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with eCRF.

Subject demographic and baseline characteristic data will be collected including: year of birth (where allowed) age in years (age in months for subjects < 2 years, where allowed), sex, race and ethnicity, as well as the Identification Number (ID No.) the subject was formerly assigned in the PANORAMA-HF study (CLCZ696B2319). Additionally, vital signs, weight and height will be collected. Relevant medical history/current medical condition data includes data until the start of study drug. (Information regarding pediatric heart failure history will be recorded only in source documentation.) HF medications will be recorded on the Concomitant Medications eCRF.

8.3 Efficacy

Efficacy will not be measured in this study.

8.4 Safety/Tolerability

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, and head circumference (head circumference is only collected in subjects who are ≤ 3 years of age at enrollment)
- Laboratory evaluations
- Pregnancy
- Angioedema

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

[redacted]

For details on AE collection and reporting, refer to AE section (Section 10.1).

Table 8-2 Physical Assessments

Assessment	Specification
Physical examination	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. An abbreviated physical exam will include the examination of general appearance and vital signs (systolic and diastolic blood pressure [SBP and DBP] and pulse)as well as other examinations based on the investigator's discretion. . 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 as medical history on the appropriate eCRF. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event on the corresponding eCRF.
Vital sign	Vital signs include BP and pulse measurements and are assessed when a complete or abbreviated physical examination is performed. After the subject 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 subjects who are infants or who cannot sit comfortably. Clinically notable vital signs are defined in Appendix 1.
Height, weight and head circumference	Height/ length 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. For subjects ≤ 3 years, head circumference in centimeters (cm) is measured.

8.4.1 Laboratory evaluations

Complete laboratory evaluations (hematology, blood chemistry, and urine) as outlined in Table 8-3 are performed at screening (Visit 500), and subsequently every 12 months from Visit 501 (Week 0) until End of Study (Visit 599). Complete laboratory evaluations will be performed at central laboratory facilities.

Abbreviated safety laboratory evaluation consists of serum sodium, potassium, creatinine, and eGFR (Table 8-3). Abbreviated laboratory evaluations are to be performed every 12 months starting from month 6 (Visit 507) at the central laboratory when possible, as indicated in Table 8-1.

In addition, abbreviated laboratory assessments should be performed at up-titration visits (Visits 502, 503, 504 and 505, as applicable), and unscheduled visits with planned dose level changes and should be performed locally. Local laboratory results will allow investigators to proceed

[redacted]

with study visit procedures without the need to wait for central laboratory results. The local laboratory results must be recorded in the appropriate eCRF. Given limitations of blood volume, the local laboratory assessments will be a priority for urgent medical decision-making (including for study-drug dose titration).

Details on the collections, shipment of samples and reporting of results by the central laboratory will be provided to the investigators in the Laboratory Manual. If the central laboratory is unavailable and/or when dose level changes are intended (either for abbreviated or complete labs), the local laboratory should be used.

Local and central laboratory results need not agree in reported results and reference ranges. The Investigator should use his/her clinical judgement on how to best manage the safety of the patient when making decisions.

Clinically notable laboratory findings are defined in Appendix 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 10 Safety reporting, then the diagnosis or medical condition must be entered on the AEs page of the subject'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 subject 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 screening (visit 500), and End of Study visit (Visit 599). Please see details in Section 8.4.2.

A table, which provides the maximum, allowable blood-draw volumes by weight, can be found in Appendix 8.

There are countries where plasma potassium is used instead of serum potassium for routine clinical care. Plasma potassium can be used instead of serum potassium in this study. Serum potassium thresholds in the study protocol, including those values cited in Appendix 1 and Appendix 7 can be converted to plasma potassium thresholds for the study by subtracting 0.4 mmol/L from the serum potassium threshold.

Table 8-3 Laboratory Assessments

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

*Abbreviated laboratory evaluations must include these parameters. eGFR should be calculated based on most recently available height.

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

8.4.2 Pregnancy and assessments of fertility

Pregnancy

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

Serum pregnancy testing will be performed at screening (Visit 500), and End of Study visit (Visit 599). Childbearing potential females (CHBP) are defined as all female subjects ≥ 11 years of age and all female subjects 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 on all CHBP female subjects. If screening visit (Visit 500) is scheduled within 14 days after PANORAMA-HF End of Study visit for the

[redacted]

subject, no serum pregnancy test will be performed, only urine pregnancy test will be needed (see Table 8-1 for additional details regarding pregnancy testing). A positive urine pregnancy test should be confirmed with a serum pregnancy test. Subjects 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 599.

For child-bearing potential females, a urine pregnancy test will also be performed at monthly intervals between study visits, during the study. Based on local regulatory requirements and/or cultural differences across participating countries, 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 subject with urinary pregnancy tests for home monthly tests.

If monthly home urine pregnancy tests are utilized, child-bearing potential female subjects 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). Subjects 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. Where possible, Study Site personnel will contact the subject on a monthly basis to check that the subject 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 subject. The Pregnancy Test Diary will be part of the source documentation for the subject. If the pregnancy test is positive, the subject/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 subject 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 subject and her parents/caregivers. The privacy of the subject should be considered in accordance with the local law and ethics.

Any subject 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 599 .

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman 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.

[redacted]

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

8.4.3 Other safety evaluations

Angioedema is a type of abrupt swelling that occurs under the skin and/or mucous membranes and is often localized to the head, neck, throat, and/or tongue, but may occur elsewhere, including the genitalia and intestines. Severe cases may be associated with airway compromise.

It is important that the investigator pays special attention to any swelling or edema that may resemble angioedema or angioedema-like events that may be reported by subjects. If such an event occurs, the investigator will complete angioedema case report forms to summarize the event, its treatment, and its ultimate outcome. This report along with the requisite medical documentation must be submitted to Novartis as soon as possible. Follow-up reports must be communicated to Novartis as soon as new information regarding the event becomes available. All hospital records related to the event must be communicated to Novartis.

The investigator may also be contacted by Novartis and be instructed to complete specific forms regarding AEs that may resemble an angioedema-like event. The investigator or his/her delegated staff must complete the required forms and provide the required medical records for all such events, regardless of whether the investigator views the event in question as angioedema or not.

All angioedema reports will be forwarded by Novartis to an external independent Angioedema Adjudication Committee for assessment. Information regarding this committee is outlined in Section 10.2.3. Details on the procedures for reporting angioedema events will be provided to investigators in a manual.

The study duration will provide at least 1 year of growth and safety data in growing children, and this will be additional to the 1 year of data provided by the PANORAMA-HF study.

8.4.4 Appropriateness of safety measurements

The safety and clinical laboratory assessments performed in this study are similar to those used in the core study PANORAMA-HF (CLCZ696B2319). 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 the sacubitril/valsartan Investigator Brochure, and the indication/subject population under study.

8.5 Additional assessments

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

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator. In this study, if the study treatment is permanently discontinued, the subject should be discontinued from the study and EOS visit (Visit 599) should be conducted (Section 6.5.1).

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

Study treatment must be discontinued under the following circumstances:

- Subject/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 subject
- Any laboratory abnormalities that in the judgment of the investigator prevents the subject 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 subject's premature discontinuation of study treatment and record this information.

Subjects 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,).

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

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 subject are not allowed unless safety findings require communicating or follow-up.

[redacted]

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

For the United States (US) and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For European Union (EU) and Rest of World (RoW): All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. 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. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. 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 subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development
- The results of the PANORAMA-HF core study do not support local registration

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.

[redacted]

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion 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.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject 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 subject 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 subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject 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 10.1.2):

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. For example, if the event is due to progression of the study indication, the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. whether it constitutes an SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met

[redacted]

5. action taken regarding with study treatment

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

- Study drug dose not changed
- Study drug dose Reduced/increased
- Study drug interrupted/withdrawn

6. its outcome

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

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 permanent (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, any potential 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 Investigator's Brochure (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 subjects with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

10.1.2 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 subject 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).

[redacted]

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  a. routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  b. 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
  c. social reasons and respite care in the absence of any deterioration in the subject's general condition
  d. 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 subject 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 subject 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 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.

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

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

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject 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.

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

[redacted]

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 (ECs), or investigators during the study (Table 10-1).

Table 10-1 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 (new occurrence) and is thought to be related to the study treatment, a CMO & PS 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 will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01, Food Drug Administration (FDA) Guidance 2012 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30-day period following end of study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

Should a pregnancy be discovered during the course of study, the following procedure must be followed. In case of pregnancy discovered during the screening period, the patient will be withdrawn from the study immediately.

To ensure patient 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.

[redacted]

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to study treatment any pregnancy outcome.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

10.1.5 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, subject or consumer [European Medicines Agency (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. Please refer to the Guidance for capturing the study treatment errors including misuse/abuse in Table 10-2.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. 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.

Table 10-2 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter

[redacted]

- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

Please refer to Table 16-3 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-3 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-4. Repeat liver chemistry tests (i.e. ALT, AST, Albumin, TBL, PT/INR, ALP and GGT) to confirm elevation.

- These liver chemistry repeats should be performed using the local laboratory used by the site. Repeated laboratory test results must be reported as appropriate.If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should be performed and evaluations may include additional investigations:
    - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

Follow up on potential drug-induced liver injury (DILI) cases

Subjects with transaminase increase combined with TBL increase may be indicative of potential DILI and should be considered as clinically important events.

The threshold for potential DILI may depend on the subject's baseline AST/ALT and TBL value; subjects meeting any of the following criteria will require further follow-up as outlined below:

- For subjects with normal ALT and AST and TBL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For subjects with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in subjects without bone metastasis, or elevation of ALP liver fraction in subjects with bone metastasis.

[redacted]

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury.

In the absence of cholestasis, these subjects should be immediately discontinued from study treatment, and repeat Liver Function Tests (LFT) testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment, and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

- Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR, and alkaline phosphatase.
- A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, and history of any pre-existing liver conditions or risk factors, should be collected.
- Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
-
- Additional testing for other hepatotropic viral infection [Epstein-Barr virus (EBV), cytomegalovirus (CMV), or herpes simplex virus (HSV)], autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of a serious adverse event (SAE) and should reported as SAE using the term "potential drug-induced liver injury." All events should be followed up with the outcome clearly documented.

10.2.2 Renal safety monitoring

Every renal laboratory trigger or renal event as defined in Table 16-5 should be followed up by the investigator or designated personnel at the trial site as summarized in Appendix 3.

10.2.3 Angioedema Adjudication committee

If an angioedema or angioedema-like event occurs, the investigator will complete an Adjudication Questionnaire for an Angioedema-like Event form (provided by Novartis). Details on the process of reporting angioedema and angioedema-like events are outlined in a manual provided to investigators.

Submission of an angioedema report is not a substitution for the submission of an SAE report. If an angioedema-like event satisfies the definition of an SAE, the investigator must submit an SAE report in addition to the Adjudication Questionnaire for an Angioedema-like Event.

The membership and responsibilities of the Angioedema Adjudication Committee are defined in a separate document that will be provided to the sites.

[redacted]

11 Data collection and database management

11.1 Data collection

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 Electronic Case Report Forms (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 subject data for archiving at the investigational site.

11.2 Database management and quality control

Novartis personnel [or designated Clinical Research Organization (CRO)] 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 members 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.

Data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Once 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.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/delegated CRO representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data.

[redacted]

The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. 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/delegated CRO/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/sponsor clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

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

12.1 Analysis sets

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

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

12.2 Subject demographics and other baseline characteristics

In the following, the term "age group" refers to the two age groups. Summary statistics will be provided by age group (6 years and older, 1 year to < 6 years) and for overall for demographics and baseline characteristics, including age, age group (only for overall), sex, race, ethnicity, weight, height and vital signs.

Continuous variables will be summarized using n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequencies and percentages.

Relevant medical histories will be summarized, by system organ class and preferred term, for overall and for each age group.

The SAF will be used for the above analyses.

12.3 Treatments

Duration of exposure to the study treatment will be summarized for each age group and for overall, using mean, standard deviation, median, minimum, and maximum. Additionally, the number and percentage of patients in meaningful duration categories will be summarized for each age group and for overall.

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

The SAF will be used for the above analyses.

12.4 Analysis of the primary endpoint(s)

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

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

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

- Any adverse event (treatment emergent or not)
- Any serious adverse event (treatment emergent or not)
- Treatment emergent adverse event (TEAE)
- Treatment emergent serious adverse event
- Treatment emergent adverse event of special interest, i.e. hyperkalemia, hypotension, angioedema, renal impairment
- TEAE leading to dose adjustment, temporary dose interruption, or permanent discontinuation (including death) of study treatment
- TEAE leading to permanent discontinuation (including death) of study treatment

For overall and for each age group, death during the treatment period and the primary cause of death will be summarized using frequencies and percentages.

For overall and for each age group, the vital signs and the laboratory evaluations will be summarized by visit.

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

[redacted]

12.4.1 Definition of primary endpoint(s)

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

12.5 Analysis of secondary endpoints

Not applicable. There are no secondary endpoints.

12.6 Analysis of exploratory endpoints

Not applicable. There are no exploratory endpoints.

12.7 Interim analyses

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

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

All patients who have completed the double-blind phase of the study PANORAMA-HF, as defined in the Inclusion Criteria (Section 5.1), and who meet all other Inclusion and Exclusion criteria (Section 5.1 and Section 5.2), are eligible for the extension study.

There is no specific sample size required for the study.

12.8.2 Secondary endpoint(s)

Not applicable.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign 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/sponsor monitors, auditors, Novartis/sponsor Quality Assurance representatives,

[redacted]

designated agents of Novartis/sponsor, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis/sponsor immediately that this request has been made.

13.3 Publication of study protocol and results

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 patient 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.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk-based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal Standard Operating Procedures (SOPs), and are performed according to written Novartis processes.

14 Protocol adherence

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 subjects 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.

14.1 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 subject 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 subject 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.

15 References

References are available upon request

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[redacted]

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Table 16-1 Clinically notable laboratory values

Parameter	Conventional Alert Value	Conventional Units	SI Alert Value	SI Units
Hematology				
Red Blood Cell Count	>50% increase, >30% decrease	x10E6/uL	>50% increase, >30% decrease	x10E12/L
Hemoglobin	>50% increase, >30% decrease, or any value <7	g/dL	>50% increase, >30% decrease, or any value <70	g/L
Hematocrit	>50% increase, >30% decrease	%	>50% increase, >30% decrease	L/L
White Blood Cell Count	>50% increase, >50% decrease	x10E3/uL	>50% increase, >50% decrease	x10E9/L
Platelet Count	>75% increase, >50% decrease	x10E3/uL	>75% increase, >50% decrease	x10E9/L
Chemistry				
BUN	>50% increase	mg/dL	>50% increase	mmol/L
Creatinine	>50% increase	mg/dL	>50% increase	umol/L
Albumin	<2	g/dL	<20	g/L
Glucose	>50% increase, >50% decrease, or any value <60	mg/dL	>50% increase, >50% decrease, or any value <3.3	mmol/L
Total Bilirubin	>100% increase	mg/dL	>100% increase	umol/L
AST (SGOT)	>150% increase	U/L	>150% increase	U/L
ALT (SGPT)	>150% increase	U/L	>150% increase	U/L
Sodium	>5% increase, or any value >150	mEq/L	>5% increase, or any value >150	mmol/L
Potassium	>20% increase, >20% decrease, or any value >5.3	mEq/L	>20% increase, >20% decrease, or any value >5.3	mmol/L
Chloride	>10% increase, >10% decrease	mEq/L	>10% increase, >10% decrease	mmol/L
Calcium	>10% increase, >10% decrease	mg/dL	>10% increase, >10% decrease	mmol/L
Uric Acid	>50% increase	mg/dL	>50% increase	mmol/L

[redacted]

Table 16-2 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
6-12 years	<50, >105	<90, >130	<50, >80	<10, >27
>12 years	<45, >95	<90, >145	<55, >90	<8, >23

[redacted]

16.2 Appendix 2: Liver event and laboratory trigger definitions and follow-up requirements

Table 16-3 Liver event and laboratory trigger definitions

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

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

Table 16-4 Follow-up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver eCRF	ALT, AST, TBL, Albumin (Alb), PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

[redacted]

Criteria	Actions required	Follow-up monitoring
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver eCRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality	Investigator discretion

[redacted]

Criteria	Actions required	Follow-up monitoring
	• Complete liver eCRF	

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

[redacted]

16.3 Appendix 3: Specific renal alert criteria and actions

Table 16-5 Specific renal alert criteria and actions

Serum event	
Estimated GFR* decrease ≥ 25% compared to baseline AND eGFR < 90 mL/min/1.73m^2	Confirm ≥ 25% decrease AND eGFR* < 90 mL/min/1.73m^2 after 24-48 hours (h). If it persists, follow up with repeat, if possible, within 2-5 days. Then do some frequent monitoring (preferably weekly) until event resolves or stabilizes. If event does not resolve or stabilize, consider consulting nephrologist and/or drug interruption.
Acute Kidney Injury: Serum estimated GFR* decrease ≥50% compared to baseline in the PANORAMA-HF core study (i.e. Visit 301 for Part 2)	Follow up within 24-48h if possible. If value persists, consider consulting nephrologist and/or drug interruption.
Urine event	Confirm by urinary protein creatinine ratio. If it persists, consider consulting nephrologist and/or drug interruption.
New dipstick proteinuria ≥ 1+	Confirm value after 24-48 h, if possible. If dipstick value confirmed: a) perform urinary protein/creatinine ratio (PCR) within 2-5 days, if possible. If PCR > 0.2 then: b) perform urine microscopy and evaluate. If PCR > 0.2 and /or urine microscopy has findings (e.g. crystals, casts, dysmorphic RBC, leukocytes), consider consulting nephrologist or drug interruption or discontinuation
New dipstick glucosuria ≥ 1+ not due to diabetes	Confirm value after 24-48 h, if possible. If it persists: a) perform, blood glucose (fasting) b) perform urinary protein/creatinine ratio. If PCR ratio > 0.2 and blood glucose abnormal consider consulting nephrologist and /or drug interruption or discontinuation
New dipstick hematuria ≥ 1+ not due to trauma	Confirm value after 24-48 h, if possible. If it persists: a) perform urinary protein creatinine ratio (PCR) within 2-5 days on a first morning urine collection b) perform urine microscopy and evaluate. If PCR > 0.2 and /or urine microscopy has findings (e.g. crystals, casts , dysmorphic RBC, leukocytes) consider consulting nephrologist or drug interruption or discontinuation

* eGFR is calculated using a modified Schwartz formula for subjects <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.

[redacted]

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

Document contributing factors in the eCRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed.

Monitor patient regularly (frequency at investigator's discretion) until either:

Event resolution: estimated GFR within 20% of baseline and > 90 mL/min/1.73m^2 or PCR < 0.2;

Event stabilization: estimated GFR within 20% of baseline OR > 90 mL/min/1.73m^2 or PCR < 0.3.

Table 16-6 GFR by age for initiation/up-titration and exclusion criteria

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
** Initiation/up-titration criteria
*** Exclusion criteria

Source: (Peters and Gordon 1999)

[redacted]

16.4 Appendix 4: 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 OLE enrollment and the first OL dose of LCZ696.

Two types of response to serum creatinine increase are described:

Surveillance situation

If, at any time after OLE enrollment and the first open-label dose of LCZ696, eGFR%* decreases by ≥ 50% from baseline in the PANORAMA-HF core study (i.e. Visit 301 for Part 2), 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 the core study (i.e. Visit 301 for Part 2) (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 subjects <18 years.

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

[redacted]

16.5 Appendix 5: American heart association (AHA) pediatric advanced life support (PALS) guidelines

Table 16-7 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:

[redacted]

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.

[redacted]

16.6 Appendix 6: Guidelines for the management of blood pressure

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.

16.7 Appendix 7: 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.

[redacted]

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.

16.8 Appendix 8: Reference table – blood volume by weight

Table 16-8 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

[redacted]

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. Details about blood volume requirement for safety samples are provide in the laboratory manual.

[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

[redacted]

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)

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

[redacted]