NOVARTIS

Global Clinical Development - General Medicine

LCZ696/Entresto®

Clinical Trial Protocol CLCZ696B2319 / NCT02678312

Multicenter, open-label, study to evaluate safety, tolerability, pharmacokinetics and, pharmacodynamics of LCZ696 followed by a 52-week randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared with enalapril in pediatric patients from 1 month to < 18 years of age with heart failure due to systemic left ventricle systolic dysfunction

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[redacted]

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List of abbreviations

γGT	Gamma-glutamyl transferase
ACEI	Angiotensin converting enzyme inhibitor
AE	Adverse Events
AHA	American heart association
Alb	Albumin
ALT	Alanine aminotransferase
ARB	Angiotensin receptor blockers
AST	Aspartate aminotransferase
AT1	Angiotensin type 1
AUC	Area under the curve
bid	Twice a day
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	Blood pressure
BUN	Blood urea nitrogen
CCB	Calcium channel blocker
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
cGMP	Cyclic guanosine monophosphate
CHBP	Child-bearing potential (female)
CHF	Chronic heart failure
CI	Confidence interval
CL or CL/F	Clearance
ClinRO	Clinician reported outcome
C_{max}	Maximum drug concentration
COA	Clinical outcome assessments
CPO	Country pharma organization
CRF	Case report form
CV	Cardiovascular
CV%	Coefficient of variation%
DAR	Dose administration record
DMC	Data monitoring committee
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECMO	Extracorporeal membrane oxygenation
EDC	Electronic data capture
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ENA	Enalapril

[redacted]

EU	European Union
FAS	Full analysis set
FS	Fractional shortening
FDA	Food and Drug Administration
GMR	Geometric mean ratio
HF	Heart failure
HFH	Heart failure hospitalization
HFrEF	Heart failure reduced ejection fraction
IB	Investigator brochure
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IEC	Independent ethics committee
IMP	Investigational medicinal product
IN	Investigator notification
INR	International normalised ratio
IRB	Institutional review board
IRT	Interactive response technology
ISHLT	International society for heart and lung transplantation
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
LBQ657	Active metabolite of AHU377(sacubitril)
LFT	Liver function test
LOCF	Last observation carried forward
LLOQ	Lowest limit of quantification
LVEF	Left ventricular ejection fraction
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
MUGA	Multi gated acquisition scan
NEP	Neprilysin
NP	Natriuretic peptide
NTproBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PBPK	Physiologically based pharmacokinetic
PCR	Protein-creatinine ratio
PD	Pharmacodynamics
PDCO	Paediatric Committee
PedsQL	Pediatric Quality of Life Inventory
[redacted]	[redacted]
PGIS	Patient Global Impression of Severity
PIP	Paediatric investigation plan

[redacted]

PK	Pharmacokinetics
PP	Per protocol
PRO	Patient reported outcome
PSD	Premature subject/patient discontinuation
PT	Preferred term
PVR	Peripheral vascular resistance
RAAS	Renin angiotensin aldosterone system
RAS	Renin-angiotensin system
RDW	Red blood cell distribution width
SAE	Serious adverse events
SAF	Safety population
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Time required for drug concentration to decrease by half
TBL	Total bilirubin
ULN	Upper limits of normal
UNOS	United Network for Organ Sharing
ULOQ	Upper limit of quantification
UNS	Unscheduled
UNS TD	Unscheduled study treatment discontinuation
US	United States
USM	Urgent Safety Measure
VAD	Ventricular assist device
WHF	Worsening heart failure
WHO	World Health Organization

[redacted]

Glossary of terms

Cohort	A specific group of patients/subjects fulfilling certain criteria
Control drug	Drugs(s) 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 patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
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.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug(s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of study consent: 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.

[redacted]

Amendment 7

Amendment rationale

An urgent safety measure (USM) has been implemented, effective 26 October 2021, in consideration of a quality event affecting the active comparator (Enalapril) used in this study in order to maintain the safety of the patients and the integrity of this ongoing study.

Recruitment closed in January 2021 and 339 of 375 randomized patients who received study drug, have completed or were discontinued from the study at the time the USM was issued. The study is expected to be completed by early January 2022. Thirty-six (36) patients were ongoing as of 26 October 2021, of whom 5 had discontinued study medication. Thirty-one (31) patients were taking study medication at the start of the USM. As of 31 October 2021, all patients had to discontinue study drug treatment and be changed to local standard of care, respecting required washout periods. The changes included in this amendment in the context of the USM are intended to maintain the scientific integrity of the study.

This amendment is to reflect the action taken under the USM and revise the primary analysis to account for the USM.

Changes to the protocol

The following changes have been made:

Section 27 Appendix 15 Urgent safety measure (USM): Details regarding the USM, instructions for patients impacted by the USM and USM implications regarding data collection and study results, are included in this Appendix.

Section 6, Table 6-2 Part 2 Assessment Schedule: Changes made to assessments done at visits UNS/TD (Unscheduled/Treatment discontinuation), UNS and 416/499 for patients impacted by the USM, are included. Two additional footnotes, 18 and 19, have been added to clarify what assessments need to be done at these visits for these patients.

References to Section 27 Appendix 15 Urgent safety measure (USM) and/or Section 6, Table 6-2 Part 2 Assessment Schedule have been made in multiple sections of the protocol, including the following:

- Section 3.1 Study design
- Section 3.3 Rationale for Global Rank primary endpoint
- Section 6.4.1 Efficacy Assessment
- Section 6.6.1.2 Patient reported outcomes (PRO)
- Section 6.6.2 Pharmacokinetics, Part 2 (Efficacy)

Section 7.2.2 SAE reporting: Revised text regarding SAE reporting as required by BfArM HA for all protocols and amendments submitted for sites in Germany

Section 9.4.2 Statistical model, hypothesis, and method of analysis: Added text related to USM

Section 9.4.3 Handling of missing values/censoring/discontinuations Part 2 (Efficacy): Added text related to USM

Section 9.4.4 Sensitivity analyses: Added text related to USM

Section 9.5.1 Efficacy variables Part 2 (Efficacy): Added text related to USM

Section 9.5.3 Biomarkers: Added text related to USM

[redacted]

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.

IRB/EC

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

This amendment is required for patient safety (i.e., necessary to eliminate immediate hazards to the trial subjects ICH GCP 3.3.8). Therefore, it will be implemented prior to IRB/IEC approval, but will be sent for approval as well.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Summary of previous amendments

Amendment 6 (08-Oct-2020)

Amendment 5 (18-Sep-2020

Amendment 4 (04-Feb-2019)

Amendment 3 (01-Oct-2018)

Amendment 2-JP (05-Sep-2017)

Amendment 2 (10-Jul-2017)

Amendment 1 (08-Aug-2016)

Original protocol (19-Nov-2015)

[redacted]

Amendment 6

Amendment rationale

The reason for this amendment is

1) to correct a typographical error in the dosing regimen for enalapril for Age Group 3.
2) to align study medication starting dose selection for Age Group 3 with Age Groups 1 and 2, based on prior ACEI/ARB use.
3) to align contraception language with the current LCZ696 Investigator's Brochure
4) to qualify the follow up duration for the babies of study participants who become pregnant during study participation

This study is ongoing. Age Groups 1, 2 and 3 in Part 1 have been completed. In Part 2, recruitment is ongoing for Age Groups 1 and 2, and approximately 335 patients have been enrolled in the study, thus far. These changes are not expected to influence the patient population or the study results.

Changes to the protocol

The following changes have been made:

- In the "Changes to the protocol" Section of Amendmdnt 5, a further description of the changes that were made to the protocol with Amendment 5, is provided.
- Section 3.1 Study Design, Part 2 (Efficacy) - Randomized treatment epoch (Visit 401 to Visit 416/499) Table 3-4 Total daily dose levels of commonly prescribed ACEI/ARBs to guide selection of the study medication starting dose: Clarified "low" and "higher" ACEI/ARB doses in the text. Removed dose levels 1x through 4x of commonly prescribed ACEI/ARBs from Table 3-4.
- Section 3.1 Study Design, Table 3-6 Part 2 (Efficacy) Study drug dose levels for double-blind enalapril and LCZ696 for age group 3: The enalapril dose for Dose Level 2x has been corrected to 0.075 mg/kg bid.
- Section 4.2 Exclusion Criteria, Exclusion Criterion 19: Expanded contraception requirements per the current LCZ696 Investigator's Brochure (i.e. contraception to continue for 7 days after discontinuation of study drug).
- Section 7.7 Pregnancy Reporting: Added revised follow up requirement (i.e. 12 months) after birth of the baby for participants who become pregnant during the study.
- Section 10.2 Informed consent procedures: Expanded contraception requirements per the current LCZ696 Investigator's Brochure (i.e. contraception to continue for 7 days after discontinuation of study drug)

Updates have been made to the List of abbreviations. Typographical and grammatical errors have also been corrected in various sections.

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.

[redacted]

IRB/EC

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Summary of previous amendments

Amendment 5 (18-Sep-2020

Amendment 4 (04-Feb-2019)

Amendment 3 (01-Oct-2018)

Amendment 2-JP (05-Sep-2017)

Amendment 2 (10-Jul-2017)

Amendment 1 (08-Aug-2016)

Original protocol (19-Nov-2015)

[redacted]

Amendment 5

Amendment rationale

The main reasons for this amendment are as follows:

- Based on review of Part 1 Age Group 3 PK/PD/Safety data, this amendment defines the target dose and dose regimen for Part 2 Age Group 3 to enable enrollment into Part 2 for Age Group 3. The planned target dose of LCZ696 2.3 mg/kg bid for Part 2 Age Group 3 together with the implementation of additional hypotension safety monitoring for Part 2 Age Group 3 during the initial up-titration phase is supported by the DMC and has been added to the protocol with this amendment. The DMC also supports the protocol changes with this amendment that enables Age Group 3 patients who turn 1 year old during Part 2 of the study and who are safely tolerating the LCZ696/placebo 2.3 mg/kg bid dose, to be able to up-titrate to LCZ696/placebo 3.1 mg/kg bid dose (the target dose for Age Group 2), if it is in the patient's best interest as assessed by the Investigator.
- Based upon agreement with the EMA/PDCO (PIP M04) to align the age groups with the ICH E11 guidelines on pediatric subsets, modified age groups that will be included in the analysis.
- The enrollment target of 25% ACEI/ARB naïve patients has been removed, as it is considered not attainable given that patients in this study population are often initially treated with some form of RAS inhibition when first diagnosed. Ninety percent (90%) of the patients have been randomized thus far and only a small percentage (approximately 5%) of these patients are ACEI/ARB naïve.
- The requirement to include 20% randomized patients per age group in the analysis of Part 2 has been removed. Given the challenges of recruiting patients 1 month to <1 year old (Age Group 3), it is considered not feasible to enroll 72 patients (20% of 360 patients) in this age group. The requirement for 80 patients with an event in Category 1 or 2 has also been removed. The study is sufficiently powered based on the Global Rank Endpoint and the number of patients expected to have a Category 1 or 2 event.
- [redacted]
- Patients in Age Group 2 will be required to be Ross class II or higher at randomization. This is based on the lower event rate observed in Age Group 2 patients vs. Age Group 1 patients.
- Measurement of height has been clarified with a statement recommending use of a stadiometer for standing height measurements.
- Text has been added to the protocol in order to be able to address health authority requests for data if required for an ongoing marketing authorization application regulatory review.

[redacted]

- Based upon Health Authority agreement, the rationale for collecting race and ethnicity data has been added to the protocol.

This study is ongoing. Age Groups 1, 2 and 3 in Part 1 have been completed. In Part 2, recruitment is ongoing for Age Groups 1 and 2, and approximately 325 patients have been enrolled in the study, thus far.

Changes to the protocol

The following changes have been made:

- Protocol Summary: Treatment Section: Added target dose level (Dose Level 4x) for Age Group 3. Added statement enabling Age Group 3 patients that turn 1 year old during the study, to be up-titrated to Group 3 Dose Level 5x (LCZ696 3.1 mg/kg bid/ enalapril 0.2 mg/kg bid). Data Analysis Section: Clarified age groups for Part 1 analysis. Added modified age groups for Part 2 analysis.

[redacted]

- Section 3.1 Study design: Removed enrollment target of 25% ACEI/ARB naïve patients. Removed requirement for 20% of the total n of 360 (72 patients) to be randomized and included for analysis in each age group. Removed required number of patients (80) with an event in Category 1 or 2 (in two places in this section). Clarified Part 1 age groups. Clarified target dose for Age Groups 1 and 2 (Dose Level 4) and added target dose level (Dose Level 4x) for Age Group 3. Modified Tables 3-4, 3-5 and 3-6. Added safety monitoring requirements for Part 2 Age Group 3 patients. Added details enabling Age Group 3 patients that turn 1 year old during the study, to be up-titrated to Group 3 Dose Level 5x (LCZ696 3.1 mg/kg bid/ enalapril 0.2 mg/kg bid). Also added a statement indicating that a scheduled or unscheduled visit may be used for these up-titrations and added detailed criteria for up-titration. Note: References to dose levels 1 through 4 throughout the protocol have been changed to dose levels 1x to 4x for Age Group 3 patients.
- Section 3.1 Part 2 (Efficacy) Table 3-4: Total daily dose levels of commonly prescribed ACEI/ARBs for purpose of comparing to dose levels of study drug: Added Part 2 Age Group 3 dose levels 1x through 4x comparative ACEI/ARB doses.
- Section 3.8 Risks and Benefits: Added text describing data from Part 1 Age Group 3 and additional safety monitoring requirements for Age Group 3 patients in Part 2.
- Section 4 Population: Clarified age groups and NYHA/Ross class group for Part 2 stratification. Removed requirement for 20% of the total n of 360 (72 patients) to be randomized and included for analysis in each age group.
- Section 4.1 Inclusion criteria: Removed the enrollment target of 25% ACEI/ARB naïve patients. Removed the option for Age Group 2 patients (with a prior history of Ross class II or higher) to be Ross class I at randomization. Age Group 2 patients must be Ross class II or higher at randomization.

[redacted]

- Section 5.1.1 Study treatment – Investigational and control drugs, Table 5-2: Added blister as packaging option for enalapril tablets (2.5 mg).
- Section 5.3 Treatment assignment and randomization: Clarified age groups and NYHA/Ross class group for Part 2 stratification.
- Section 5.5.4 Instructions for prescribing and taking study treatment, Part 2: Clarified Part 2 study drug supplies.
- Section 5.5.5 Permitted dose adjustments and interruptions of study treatment: Clarified target dose for Age Groups 1 and 2 (Dose Level 4) and added target dose for Age Group 3 (Dose Level 4x). Added safety monitoring requirements for Age Group 3 patients in Part 2.
- Section 6, Table 6-2 Part 2 Assessment Schedule: Footnote 6, clarified requirements regarding use of a Central Laboratory for laboratory analyses. Footnote 7, added text clarifying abbreviated labs for visits 402 and 404; added text with regard to abbreviated labs for Part 2 Group 3 patients who turn 1 year old during the study, who are up-titrated; Footnote 17, added text with regard to additional vital signs monitoring for Part 2 Group 3 patients at the initial dose for each dose level up-titration.
- Section 6.2 Patient demographics /other baseline characteristics: Added note regarding rationale for collecting race and ethnicity data.
- [redacted]
- Section 6.5.2 Vital Signs: Added instructions regarding additional vital sign measurement requirements for Part 2 Group 3 patients
- Section 6.5.3 Height/length head circumference and weight: Clarification added regarding measurement of height.
- Section 6.5.4 Laboratory Evaluations: added text clarifying abbreviated labs for visits 402 and 404
- Section 6.5.4.3 Estimated GFR: Corrected text stating that change in estimated GFR will be calculated from screening for local labs and from randomization for central labs.
- Section 6.5.9 Appropriateness of safety measurements: Correction: ICH E12 should have been ICH E11 (correct in the Reference section).
- Section 8.3 Data Monitoring Committee: Noted that data may be provided to Health Authorities, if required for an ongoing marketing authorization application regulatory review and Novartis will inform the DMC should this occur.
- Section 9.2 Patient demographics and other baseline characteristics: Added modified age groups for analysis.
- Section 9.3 Treatments Part 1 (PK/PD) and Treatments Part 2 (Efficacy): Minor clarifications to analysis text.
- Section 9.4.1 Analysis of the primary variable(s), Variables, Part 1 (PK/PD): Clarified PK/PD model analysis description text.

[redacted]

- Section 9.4.2 Statistical model, hypothesis and method of analysis: Added modified age groups and NYHA/Ross class groups and noted that the number and percentage of patients in each category will be provided by treatment group for each age group, each modified age group, and for overall.
- Section 9.5 Analysis of secondary variables: Added modified age groups for analysis to multiple subsections in this section and clarified the efficacy analysis text.
- [redacted]
- Section 12: References have been updated.
- Section 13 Appendix 1 Table 13-2 Criteria for clinically notable vital signs: Clarified criteria for clinically notable vital signs with the addition of missing < and ≥ signs.
- Section 25 Appendix 13 Safety Monitoring for Part 2 Age Group 3 patients: New Appendix added (Appendix 13)
- Section 26 Appendix 14 Up-titration dosing instructions for patients in Age Group 3 (1 month to <1 year at randomization) who turn 1 year old during Part 2: New Appendix added (Appendix 14).
- Updates have been made to the List of abbreviations. Typographical errors have also been corrected in various sections.

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.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Summary of previous amendments

Amendment 4 (04-Feb-2019)

Amendment 3 (01-Oct-2018)

Amendment 2-JP (05-Sep-2017)

Amendment 2 (10-Jul-2017)

Amendment 1 (08-Aug-2016)

Original protocol (19-Nov-2015)

[redacted]

Amendment 4

Amendment rationale

[redacted]

In addition, clarification is provided in this amendment regarding location alternatives if local requirements do not allow home urine pregnancy testing

This study is ongoing. In Part 1 of the study, Age Groups 1 and 2 have been completed and Age Group 3 is ongoing. In Part 2 of the study, approximately 144 patients have been randomized, thus far.

These changes will not influence the study population or results of the study and will not impact patient safety.

Changes to the protocol

The following changes have been made:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Section 6 Visit schedule and assessments: removed the words “at home” as it relates to urine pregnancy testing given the clarification added to Table 6-2 Part 2
- Table 6-2 Part 2 Assessment Schedule: Clarified footnote 5 providing location alternatives if local requirements do not allow home urine pregnancy testing

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.

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

[redacted]

The changes herein related to the clarification regarding location alternatives for urine pregnancy testing, affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Summary of previous amendments

Amendment 3 (01 October 2018)

Amendment 2-JP (05 September 2017)

Amendment 2 (10 July 2017)

Amendment 1 (08 August 2016)

Original protocol (19 November 2015)

[redacted]

Amendment 3

Purpose of the amendment

The main purposes of this amendment are to:

- expand the examination of the exposure-response relationship for Group 3 (i.e. 1 month to < 1 year) in the Part 1 pharmacokinetic (PK)/pharmacodynamic (PD) assessment. (This will be done by evaluating two dose levels of LCZ696, specifically LCZ696 0.4 mg/kg and LCZ696 1.6 mg/kg in Part 1 Group 3.)
- add the target dose level for Group 3 in Part 2
- add sparse PK assessment at steady state in a subset of patients in Part 2 Age Group 2 to further confirm the target dose for this age group
- modify the left ventricular ejection fraction (LVEF) and the fractional shortening (FS) inclusion threshold to expand the eligibility range for patients
- [redacted]

This study is ongoing. Age Group 1 and Group 2 in Part 1 have been completed. In Part 2 approximately 86 patients have been enrolled in the study, thus far.

These changes are not expected to influence the results of the study or to impact patient safety.

Changes to the protocol

The following changes have been made:

- For Part 1 Group 3 patients, removed the single dose level of LCZ696 0.8 mg/kg and replaced it with two dose levels: LCZ696 0.4 mg/kg and LCZ696 1.6 mg/kg. Inclusion criterion 7 has been modified accordingly. Total of approximately 4 observations per dose (approximately 8 in total) and a minimum of 4 patients is planned for Group 3 in Part 1.
- Added the target dose level for Group 3 in Part 2 (Table 3-6).
- Updated “Exclusion 4” and “Exclusion 7” to clarify the applicability only to Part 2.
- Modified “Inclusion 5" regarding left ventricular ejection fraction and the fractional shortening as described in Section 4.1.
- Added “Exclusion 26” to exclude a patient that is breast fed by a mother that is using an ACEI.
- Updated “Exclusion 19” to clarify the methods of contraception.
- Additional pregnancy testing (monthly) that must be done for women of child-bearing potential for studies that include study medication where highly effective contraception is required, has been added.
- Changed the Abbreviated laboratory evaluations at weeks 2 and 6 from required to optional (see Table 6-2).

[redacted]

- Added to Part 2 of the study, a steady-state Sparse PK blood collection visit, applicable to a subset of patients in Group 2 (approximately 24 patients of whom approximately 12 patients are expected to be randomized to LCZ696) who agree to participate. [redacted]
- [redacted]
- [redacted]
- Applies to sites in Japan only: Added an extra clinic visit to Part 2 of the protocol at week 1 (Visit 401JPN) in Table 6-2.
- Clarified and updated language around ACEI/ARB dosing prior to the dosing with LCZ696 for Part 1.
- Clarified and updated language around the weight measurement and visit schedule in Part 1.
- Added clarification to Section 3.1 regarding additional patients in Part 1 Group 3 to be evaluated if needed for dose determination for Part 2.
- Added instructions regarding "plasma potassium" in Section 6.5.4.
- Removed Endpoint collection from the Assessment Table for Part 1 (Table 6-1). Endpoints from Part 1 (open-label, single dose PK/PD) are not part of the efficacy analysis and will not be adjudicated.
- Added instructions regarding countries where blood samples cannot be shipped out of the country due to local regulations (Table 6-2).
- Made changes to "Glossary of Terms" and Section 5.6.3 to align with the new "Withdrawal of Consent" language. Corrected typographical errors in various sections.

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

A copy of this protocol amendment will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) for all sites and Health Authorities.

The changes described in this protocol amendment require IRB/IEC approval prior to implementation. In addition, as the changes herein affect the Informed Consent, sites are required to submit for approval an Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

Amendment 2

Purpose of the amendment

The main purpose of this amendment is to remove technical details pertaining to the preparation of liquid formulation of the study drugs, LCZ696 and enalapril.

These changes will not influence the study population or results of the study and will not impact patient safety.

Changes to the protocol

- Deleted information related to liquid formulation of LCZ696 and enalapril in Part 1 and Part 2.
- Clarified that instructions for the preparation of the liquid study drugs are provided in the Pharmacy Manual which is provided to the site/pharmacy as a separate document.
- Other clarification: Clarified the early study termination procedure (Section 5.6.5) according to the "Detailed Guidance from the European Commission, CT-1, 4.2.2-163".

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.

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

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

In addition, details regarding compounding the liquid formulation will be removed from the Informed Consent. Sites should update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 1

Purpose of the amendment

All of the amendment changes are made prior to enrolling patients into the study.

The main purpose of this amendment is to examine the exposure-response relationship for Groups 1 (6 to < 18 years) and 2 (1 to < 6 years) by the addition of a second (and lower) dose of LCZ696 (0.8 mg/kg) to the LCZ696 (3.1 mg/kg) Part 1 pharmacokinetic (PK)/pharmacodynamic (PD) assessment.

In addition, to ensure an adequate number of clinical endpoints are included in the Global Rank primary endpoint in Part 2, the study will stop when at least 80 patients have an event in Category 1 or 2.

For the Global Rank primary endpoint determination, the Pediatric Quality of Life inventory (PedsQL) Physical Functioning domain will be used only for Group 1 (ages 6 to < 18 years),

[redacted]

since Group 1 is the only age group where all the patients will be doing a patient self-report PedsQL.

This amendment also adds a number of other clarification changes to the PK, PD biomarkers, and blood collection information; updated information about study drugs LCZ696 and enalapril; updates to endpoint and adjudication information. There are other changes included to add clarity, enhance readability, correct typographical errors and provide further details.

Changes to the protocol

The following changes have been made:

- Added second dose to Part 1 study design and other relevant sections. Assessment schedule, Safety, PK, and PD data review have been revised accordingly.
- Total of six patients per dose for each age group is planned. Two doses are being assessed in Groups 1 and 2, and one dose is being assessed in Group 3.
- Added plasma B-type natriuretic peptide (BNP) to Part 1. Relevant changes have been made to biomarker data and blood collection details.
- Detailed information about PK blood sample handling was moved to the laboratory manual.
- Added urine cGMP (cyclic guanosine monophosphate) collection at baseline pre-dose for PD assessment in Part 1.
- Updated and corrected blood volumes for PK and PD sampling in Part 1.
- Added information about at least 80 patients with events in Category 1 or 2.
- Added safety and tolerability Secondary objective in Part 1.
- For the PedsQL scale, the chronic version (one month recall period) was replaced with the acute version (7 days recall period). The reason for this change is that the patient reported assessment of 7 days is considered more appropriate compared to 1 month for pediatric heart failure patients. Added text indicating that the PedsQL Physical Functioning module will be used for the primary Global Rank endpoint only for Group 1 (6 to <18 years old) (Section 3.3 and Section 6.4.1).
- Updated Patient Global Impression of Severity (PGIS) age range to consistently state 5 to < 7 years and 7 to < 18 years old, and changed 'Very Mild' to 'None' for the PGIS scale.
- [redacted]
- Secondary objective was clarified for "delaying" for time to first occurrence of event.
- Inclusion and exclusion criteria updated to provide further information and clarity.
- Added that a confirmatory serum pregnancy test should be performed when urine pregnancy test is positive, and added serum pregnancy test at Visit 416/499.
- Deleted biomarkers from the list of the safety parameters in Section 6.5 as biomarkers are not a safety parameter in this study.
- Reference table for blood volume by weight was updated (Appendix 6, Table 18-1).
- Clinical events and adjudication information updated in Sections 6.4.1 and Section 9.7.

[redacted]

- Added systolic BP 5th percentile information for patients with age of 1 month to < 1 year (Appendix 4, Table 16-1) and ≥ 30% mean GFR (glomerular filtration rate) by age table (Appendix 10, Table 22-1).
- [redacted]
- Updated renal safety monitoring Section 7.5.
- Added reference for FDA guidance in Section 7.3.1 for safety reporting.
- Clarified and updated language around management of study drug.
- Typographical errors were corrected in various sections.

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.

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

Protocol summary

Protocol number	CLCZ696B2319
Title	Multicenter, open-label, study to evaluate safety, tolerability, pharmacokinetics and, pharmacodynamics of LCZ696 followed by a 52-week randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared with enalapril in pediatric patients from 1 month to < 18 years of age with heart failure due to systemic left ventricle systolic dysfunction
Brief title	Pharmacokinetics (PK), pharmacodynamics (PD), safety and efficacy study of LCZ696 in children (1 month to < 18 years) with heart failure due to systemic left ventricle systolic dysfunction
Sponsor and clinical phase	Novartis; Phase 2/3
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine whether pediatric heart failure (HF) patients (1 month to < 18 years old) will derive greater clinical treatment benefit with LCZ696 compared to enalapril over 52 weeks treatment duration. This study includes two parts. Part 1 will determine the dose for Part 2. Part 2 will assess the efficacy and safety of LCZ696 compared to enalapril.
Primary objective(s)	• Part 1: The primary objective is to determine the pharmacokinetics (PK) and pharmacodynamics (PD) of LCZ696 in pediatric HF patients • Part 2: The primary objective is to determine whether LCZ696 is superior to enalapril for treatment of heart failure as assessed using a global rank endpoint in pediatric HF patients
Secondary objectives	• Part 1: To assess the safety and tolerability of LCZ696 in pediatric patients with HF • Part 2: To determine whether LCZ696 is superior to enalapril in delaying time to first occurrence of the composite of either Category 1 or 2 events (e.g. death, worsening HF) • Part 2: To determine whether LCZ696 is superior to enalapril for improving NYHA (New York Heart Association)/Ross functional class • Part 2: To determine whether LCZ696 is superior to enalapril for improving the Patient Global Impression of Severity (PGIS) score • Part 2: To characterize the population PK of LCZ696 exposure in pediatric patients with HF, including an assessment of steady-state sparse PK data in a subset of Group 2 patients • Part 2: To assess the safety and tolerability of LCZ696 compared to enalapril in pediatric patients with HF
Study design	This is a multi-center study in pediatric patients (1 month to <18 years) with HF (i.e. LVEF/fractional shortening criteria as described in Inclusion Criterion Number 5). This study uses a seamless design which consists of two parts:

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	• Part 1: This is a multi-center, open-label study to characterize the PK and PD of LCZ696. This information will enable the prediction of multiple dose PK exposure and support dosage determination for Part 2 of this study • Part 2: This is a 52-week randomized, double blind, parallel-group, active controlled, study to evaluate the efficacy, safety, and tolerability of LCZ696 compared to enalapril in addition to conventional HF treatment in pediatric patients with HF
Population	The study population consists of pediatric HF patients 1 month to <18 years, inpatient or outpatient, with systemic left ventricle systolic dysfunction; and includes at least 18 patients in Part 1; and randomizes 360 patients in Part 2 at centers worldwide. For Part 1 and Part 2, the patients will be divided across three groups based on age: Group 1: 6 to <18 years; Group 2: 1 to <6 years; Group 3: 1 month to < 1 year.
Key inclusion criteria	1. Written informed consent by parent(s)/legal guardian(s) for the pediatric patient must be obtained before any study-specific assessment is performed. A consent or assent may also be required for some patients depending upon their age and local requirements 2. Male or female, inpatient or outpatient, 1 month to < 18 years of age 3. Chronic heart failure resulting from left ventricular systolic dysfunction, and receiving chronic HF therapy (if not newly diagnosed) 4. NYHA classification II-IV (older children: 6 to <18 years old) or Ross CHF classification II-IV (younger children: < 6 years old) any time prior to screening 5. Systemic left ventricular ejection fraction (EF) ≤ 45% or fractional shortening ≤22.5% (assessed by most recent echocardiography, MRI, MUGA or left ventricular angiogram). For Part 2, this assessment must be within 1 month from screening.[Note: The study will target enrollment of approximately 80% patients with a systemic left ventricular ejection fraction (EF) ≤ 40% or fractional shortening ≤20% for Part 2 only]. 6. Biventricular physiology with systemic left ventricle 7. For Part 1 PK/PD, patients must be treated with an ACEI (Angiotensin converting enzyme inhibitor) or ARB (Angiotensin receptor blockers) prior to screening. For Part 1 PK/PD, patients in Group 1 and 2 must be currently treated with a daily dose equivalent of at least enalapril 0.2 mg/kg (Table 3-1) prior to the LCZ696 3.1 mg/kg single dose assessment. For Part 1 PK/PD, patients in Group 3 must be currently treated with a daily dose equivalent of at least enalapril 0.1 mg/kg (Table 3-1) prior to the LCZ696 1.6 mg/kg single dose assessment For additional information, refer to Section 4.1
Key exclusion criteria	1. Patients with single ventricle or systemic right ventricle 2. Patients listed for heart transplantation as United Network for Organ Sharing (UNOS) status 1A or hospitalized waiting for transplant while on inotropes or with ventricular assist device at time of entry into the study 3. Sustained or symptomatic dysrhythmias uncontrolled with drug or device therapy 4. For Part 2 only, patients that have had cardiovascular surgery or percutaneous intervention to palliate or correct congenital

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	cardiovascular malformations within 3 months of the screening visit. Patients anticipated to undergo corrective heart surgery during the 12 months after entry into Part 2. 5. Patients with unoperated obstructive or severe regurgitant valvular (aortic, pulmonary, or tricuspid) disease, or significant systemic ventricular outflow obstruction or aortic arch obstruction 6. Patients with restrictive or hypertrophic cardiomyopathy 7. For Part 2 only, active myocarditis (diagnosed with presumed or acute myocarditis within 3 months of enrollment) 8. Symptomatic hypotension or blood pressures (BPs) below the calculated 5th percentile systolic BP (SBP) for age at screening visit and as described in Appendix 4 9. Renal vascular hypertension (including renal artery stenosis) 10. Severe pulmonary hypertension (defined by pulmonary vascular resistance (PVR) index >6 Wood units-m2) unresponsive to vasodilator agents (such as oxygen, nitroprusside or nitric oxide). Note measurement of PVR is not a requirement for study eligibility. 11. History or current clinical evidence of moderate-to severe obstructive pulmonary disease or reactive airway diseases (e.g. asthma) 12. Serum potassium >5.3 mmol/L at Visit 1 or at Visit 301 13. Patients with significant renal (eGFR calculated using the modified Schwartz formula < 30% mean GFR for age, Appendix 10, Table 22-1); 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) 14. Concurrent terminal illness or other severe disease (e.g. acute lymphocytic leukemia) or other significant laboratory values that, in the opinion of the Investigator, precludes study participation or survival 15. Patients with history of angioedema 16. Patients with allergy or hypersensitivity to ACEI/ARB For additional information, refer to Section 4.2
Study treatment	LCZ696 Part 1: single dose 0.8 mg/kg, 3.1 mg/kg (age Groups 1 and 2) and 0.4 mg/kg, 1.6 mg/kg (age Group 3), (using 3.125 mg granules or liquid formulation) Part 2: projected target dose 3.1 mg/kg bid for age Groups 1 and 2 (Dose Level 4 for Groups 1 and 2) (actual dose dependent on Part 1; using 3.125 mg granules, 50 mg tablets, 100 mg tablets, 200 mg tablets or liquid formulation). For age Group 3, the target dose will be 2.3 mg/kg bid (Dose Level 4x for Group 3 patients). In addition, Group 3 patients who turn 1 year old during the study, may be further up-titrated to a dose of 3.1 mg/kg bid (Dose Level 5x for Age Group 3 patients). See Appendix 14 for details. Enalapril Part 1: open-label enalapril (tablet or liquid) and Part 2: target dose 0.2 mg/kg bid for Groups 1 and 2, (Dose Level 4 for Groups 1 and 2); using liquid formulation, 2.5 mg tablets, 5 mg tablets, 10 mg tablets. For Group 3, the target dose will be 0.15 mg/kg bid (Dose Level

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	4x for Group 3 patients). In addition, Group 3 patients who turn 1 year old during the study, may be further up-titrated to a dose of 0.2 mg/kg bid (Dose Level 5x for Group 3 patients). See Appendix 14 for details All study treatment in Part 2 will be bid dosing.
Efficacy assessments	The primary global rank endpoint will be derived based on 5 categories ranking worst outcome to best outcome: 1. Category 1: Death; UNOS status 1A listing for heart transplant or equivalent; VAD/ECMO/mechanical ventilation/intra-aortic balloon pump requirement for life support at end of study 2. Category 2: Worsening HF (WHF); defined by signs and symptoms of WHF that requires an intensification of HF therapy 3. Category 3: Worsened; worse NYHA/Ross or worse Patient Global Impression of Severity (PGIS); and further ranking by PedsQL physical functioning domain 4. Category 4: Unchanged; unchanged NYHA/Ross and unchanged PGIS; and further ranking by PedsQL physical functioning domain 5. Category 5: Improved; improved NYHA/Ross or improved PGIS (neither can be worse); and further ranking by PedsQL physical functioning domain)
Key safety assessments	• Adverse events (AEs) and serious adverse events (SAEs) • Blood pressure, heart rate • Height, weight and head circumference (≤ 3 years) • Laboratory values (including potassium & serum creatinine) • Angioedema surveillance • Electrocardiogram (ECG) changes
Other assessments	• NYHA/Ross class • Patient Global Impression of Severity (PGIS) [redacted] [redacted] • PK of LCZ696 analytes • Plasma NTproBNP, BNP • Urine and plasma cGMP
Data analysis	Part 1 PK and PD variables • The PK and PD parameters of LCZ696 will be summarized descriptively by age group (Group 1: 6 to < 18 years; Group 2: 1 to < 6 years; Group 3: 1 month to < 1 year), and dose. Part 2 efficacy variables • To characterize the effects of LCZ696 and enalapril on whether the patients were improved or not improved using the global rank endpoint. The endpoint will be assessed using a stratified Wilcoxon rank-sum analysis (Kawaguchi 2011), stratifying by modified age group (Group 1: 6 to < 18 years; Group 2a: 2 to < 6 years; Group 3a: 1 month to < 2 years) and NYHA/Ross class group (Class I/II, Class III/IV)

[redacted]

	[redacted]
Key words	Pediatric, heart failure, pharmacokinetics, pharmacodynamics, safety, efficacy, multicenter, systemic left ventricle systolic dysfunction, global rank endpoint

[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 2009a). HF can develop or exacerbate in childhood, during adolescence and also later in adulthood as made evident by the growing number of adults with congenital heart disease. Congenital heart disease and cardiomyopathy are the two most common causes of pediatric HF (Sharma 2003, Andrews 2008).

The largest HF burden comes from children born with congenital malformations. Congenital heart disease occurs in approximately 8 per 1,000 live births of which 1-2 per 1,000 develop HF (Kay 2001). A wide variety of congenital abnormalities may be present including ventricular or atrial septal defect, patent ductus arteriosus, aorto-pulmonary window, hypoplastic left heart, aortic or pulmonary vein stenosis, anomalous origin of the left coronary artery, and coarctation of the aorta. Most of these children are diagnosed before ages 1 and many have early surgical intervention, usually before age 2.

The other main cause of pediatric HF is cardiomyopathy, with an estimated annual incidence of 1 per 100,000 children in the US, Australia, United Kingdom and Ireland (Lipshultz 2003, Nugent 2003, Andrews 2008). Dilated cardiomyopathy (usually diagnosed as idiopathic, familial, or myocarditis) is the most common type. Hypertrophic cardiomyopathy due to familial isolated cardiomyopathy, an inborn error of metabolism, or a malformation syndrome is the next most common type. Cardiomyopathy can also be associated with muscular dystrophies such as Duchenne's muscular dystrophy and myotonic dystrophy. In developing countries, rheumatic heart disease, nutritional deficiencies, and other tropical diseases such as Chagas disease can also be a substantial cause of pediatric HF.

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 2009). Furthermore, nearly 40% of children in the US with symptomatic cardiomyopathy either undergo heart transplantation or die within 2 years (Lipshultz 2003).

In contrast to HF in adults, there is very limited research in pediatric HF. Consequently, treatment of HF in children is based on information and results provided by adult studies (Kantor 2010). Pediatric HF treatment is outlined in the recent guidelines published by the International Society of Heart and Lung Transplantation (ISHLT) (Kirk 2014). Respondents to the Diovan Pediatric Heart Failure Survey confirmed that 'efficacy shown in adult HF trials' and 'Consensus Statements and Guidelines' were the two most important factors they considered when making treatment decisions for pediatric patients with HF (CVAL489K2304

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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 this point, no trial has demonstrated an outcome benefit of any pharmacotherapy in children with HF. The largest pediatric HF trial done thus far is the randomized, double-blind, placebo-controlled, parallel-group trial of carvedilol in patients 8 months to 14 years with HF due to congenital heart disease or cardiomyopathy (Shaddy 2007). The primary endpoint for the pediatric carvedilol study was a composite measure of HF outcomes, assessing the response to treatment as worsening, improved or unchanged. While adult HF populations have shown benefit with β-blockade, this study did not meet its composite primary endpoint. This may have been attributable to the known issues related to pediatric HF trials in general including: varying causes of HF, uncertain natural history of HF in children, and trial design challenges unique to the pediatric population.

LCZ696 is sacubitril/valsartan and has the trade name ENTRESTO. In some countries where ENTRESTO is approved, it is available as 24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg sacubitril/valsartan, but will be subsequently referred to as LCZ696 50 mg, 100 mg, 200 mg in this study protocol. LCZ696 is a first-in-class, angiotensin receptor neprilysin inhibitor treatment for chronic HF (CHF). Neprilysin (NEP) inhibition with chronic oral administration of LCZ696 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. LCZ696, 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 (NP) 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), LCZ696 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, LCZ696 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 21% RRR ($p=0.00004$). PARADIGM-HF also showed that LCZ696 is generally safe and well tolerated in adult patients with HF (McMurray 2014).

In both pediatric and adult HF due to systolic dysfunction, there is a decrease in systemic cardiac output. The pathophysiologic adaptation to decreased cardiac output for both adult and pediatric HF involves increased sympathetic tone and activation of the renin-angiotensin system (RAS) (Momma 2006). In addition, also similar to adult HF, pediatric HF results in increased activation of the natriuretic peptide system (Favilli 2009). This pathophysiologic neurohumoral activation plays a key role in the progression of HF due to systolic dysfunction in adults and children, and this is why heart failure management in this pediatric HF subset with systemic left ventricular systolic dysfunction is similar to adult HFrEF.

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This protocol focuses on studying a subset of pediatric HF with systemic left ventricular systolic dysfunction. The rationale for studying this patient population is that it allows for examination of a more homogeneous pediatric HF population that also has pathophysiology similar to adult HFrEF where LCZ696 has demonstrated a significant mortality and morbidity benefit (McMurray 2014) compared to current standard of care (ACEI). In addition, for the Carvedilol Pediatric HF study using a related clinical endpoint as planned in this study, there was a potential treatment benefit in the subgroup of patients with systemic left ventricle morphology (Shaddy 2007).

The efficacy of LCZ696 over the standard of care enalapril for reducing mortality and morbidity in adult HFrEF patients provides strong rationale that LCZ696 may have clinically meaningful benefits for pediatric HF patients with reduced left ventricular ejection fraction (LVEF). Despite differences with regards to the etiology of pediatric and adult HF with systolic dysfunction (or reduced LVEF), there is overlap in the pathophysiology and clinical management between both populations. Thus, we are seeking to prospectively evaluate the effects of LCZ696 in pediatric patients with symptomatic systemic left ventricular systolic dysfunction.

1.2 Purpose

The purpose of this study is to determine whether pediatric HF patients will derive greater clinical treatment benefit assessed by a global rank endpoint with LCZ696 compared to enalapril over 52-week treatment duration. This study includes two parts. Part 1 will confirm the dose for Part 2. Part 2 will be used to assess the efficacy and safety of LCZ696 compared to enalapril.

2 Study objectives and endpoints

2.1 Primary objectives

Part 1:

- The primary objective is to determine the pharmacokinetics (PK) and pharmacodynamics (PD) of LCZ696 in pediatric HF patients

Part 2:

- The primary objective is to determine whether LCZ696 is superior to enalapril for the treatment of HF as assessed using a global rank endpoint (described in Section 6.4) in pediatric HF patients

2.2 Secondary objectives

Part 1:

- To assess the safety and tolerability of LCZ696 in pediatric patients with HF

Part 2:

- To determine whether LCZ696 is superior to enalapril in delaying time to first occurrence of the composite of either Category 1 or 2 events (e.g. death, worsening HF)

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- To determine whether LCZ696 is superior to enalapril for improving NYHA/Ross functional class
- To determine whether LCZ696 is superior to enalapril for improving the Patient Global Impression of Severity (PGIS) score
- To characterize the population PK of LCZ696 exposure in pediatric patients with HF, including an assessment of steady-state sparse PK data in a subset of Group 2 patients.
- To assess the safety and tolerability of LCZ696 compared to enalapril in pediatric patients with HF

2.4 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

OBJECTIVE	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Stat Analysis Section
Primary		
Part 1: The primary objective is to determine the pharmacokinetics (PK) and pharmacodynamics (PD) of LCZ696 in pediatric HF patients	*Title:* PK and PD of LCZ696 after single dose treatment *Unit of measure*: PK: C_{max} (ng/mL); T_{max} (h); AUC_{last}, $AUCi_{nf}$ (h▪ng/mL); Cl/F (L/h); $T_{1/2}$ (h); PD: plasma BNP, plasma NTproBNP, plasma cGMP, urine cGMP change from baseline geometric mean ratio (GMR) after single dose treatment *Description*: Part 1 PK assessment: The samples will be collected at the following intervals for the various age groups: • Patients ≥6 years of age: Blood samples are collected at pre-dose (pre-dose sample for all patients), 0.5, 1, 2, 4, 8, 10, and optional 24 hours post dosing • Patients <6 years of age: Blood samples are collected at pre-dose (pre-dose sample only from those patients who are on valsartan), 1, 2,	Section 9.4.1, Section 9.5.3 and, Section 9.5.4

[redacted]

OBJECTIVE	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Stat Analysis Section
	4, 10, and optional 24 hours post dosing Part 1 PD assessments: The blood samples will be collected at pre-dose, 4, 8 and optional 24 hours post dosing. The urine samples will be collected at pre-dose and once between 4 to 8 hours post dosing. *Time Frame*: Single dose PK/PD visit	
Part 2: The primary objective is to determine whether LCZ696 is superior to enalapril for the treatment of HF as assessed using a global rank endpoint in pediatric HF patients	*Title*: Global Rank endpoint through 52 weeks of treatment *Unit of Measure*: The mean global rank endpoint does not have a unit. Patients are ranked from worst to best. The ranking is based on clinical events such as death, listing for urgent heart transplant, mechanical life support requirement at end of study, worsening HF, NYHA/Ross, PGIS, PedsQL physical functioning domain. *Description*: The effects of LCZ696 and enalapril will be assessed using the Global Rank endpoint as outlined below through 52 weeks of double-blind treatment. The primary endpoint will be derived based on 5 categories ranking worst to best outcome: • Category 1: Death; UNOS status 1A listing for heart transplant or equivalent; VAD/ECMO/mechanical ventilation/intra-aortic balloon pump requirement for life support at end of study • Category 2: Worsening HF (WHF); defined by signs and symptoms of WHF that requires an intensification of HF therapy • Category 3: Worsened; worse NYHA/Ross or worse Patient Global Impression of Severity (PGIS); and further ranking by PedsQL physical functioning domain • Category 4: Unchanged; unchanged NYHA/Ross and unchanged PGIS; and further ranking by PedsQL physical functioning domain • Category 5: Improved; improved NYHA/Ross or improved PGIS (neither can be worse); and further ranking by PedsQL physical functioning domain	Section 9.4.1

[redacted]

OBJECTIVE	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Stat Analysis Section
	Within each category, patients are ranked from worst to best based on pre-defined criteria. *Time Frame*: 52 Weeks	
Secondary		
To determine whether LCZ696 is superior to enalapril in delaying time to first occurrence of the composite of either Category 1 or 2 events (e.g. death, worsening HF)	*Title*: Time to first occurrence of Category 1 or Category 2 event through 52 weeks of treatment *Unit of Measure*: Days *Description*: Time to first occurrence of Category 1 or Category 2 event will be compared for LCZ696 and enalapril through 52 weeks of double-blind treatment *Time Frame*: 52 Weeks	Section 9.5.1
To determine whether LCZ696 is superior to enalapril for improving NYHA/Ross functional class	*Title*: NYHA/Ross functional class change from baseline through 52 weeks of treatment *Unit of Measure*: NYHA/Ross classification *Description*: NYHA/Ross functional class will be compared through 52 weeks of double-blind treatment *Time Frame*: 52 Weeks	Section 9.5.1
To determine whether LCZ696 is superior to enalapril for improving the Patient Global Impression of Severity (PGIS) score	*Title*: PGIS score change from baseline through 52 weeks of treatment *Unit of Measure*: PGIS scale *Description*: PGIS scale will be compared for LCZ696 and enalapril through 52 weeks of double-blind treatment *Time Frame*: 52 weeks	Section 9.5.1
To characterize the population PK of LCZ696 exposure in pediatric patients with HF, including an assessment of steady-state sparse PK data in a subset of Group 2 patients.	*Title*: Population PK LCZ696 *Unit of Measure*: ng/mL/kg, ng*h/mL/kg, L/h/kg, L/kg, and 1 /h *Description*: During Part 2 Efficacy, population PK will be assessed with chronic dosing. Population PK allows us to estimate clearance and total exposure. *Time frame*: weeks 4, 12, 52 *Title:* Steady-state Sparse PK data *Unit of measure:* ng/mL, ng*h/mL, and L/h/kg *Description:* During Part 2 Efficacy, a sparse PK assessment at steady state will be done in a subset of Group 2 patients which allows for	Section 9.4.1 and Section 9.5.1

[redacted]

OBJECTIVE	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Stat Analysis Section
	an estimate clearance and total exposure to further confirm the target dose for this age group. Available BioMarker data will also be assessed. *Time frame*: week 8 or a subsequent visit	
To assess the safety and tolerability of LCZ696 in pediatric patients with HF	*Title:* Safety and tolerability of LCZ696 in Part 1 *Unit of Measure:* Multiple *Description:* Safety and tolerability including AEs, laboratory, vital signs *Time Frame:* Single dose PK/PD visit	Section 9.5.2
To assess the safety and tolerability of LCZ696 compared to enalapril in pediatric patients with HF	*Title:* Safety and tolerability through 52 weeks of treatment *Unit of Measure:* Multiple *Description:* Safety and tolerability including AEs, laboratory, ECG, vital signs data through 52 weeks of double-blind treatment *Time Frame:* 52 weeks	Section 9.5.2
[redacted]		

[redacted]

3 Investigational plan

3.1 Study design

This study uses a seamless design which consists of two parts (Figure 3-1):

Part 1: This is a multi-center, open-label, study in pediatric patients (1 month to <18 years) with HF (LVEF ≤ 45% or LV fractional shortening ≤ 22.5%).

A screening epoch of up to 3 weeks will be used to assess eligibility. Eligible patients who participate in this open-label PK/PD assessment will be placed into three Groups based on age (Group 1: 6 to < 18 years, Group 2: 1 to < 6 years, and Group 3: 1 month to < 1 year). To ensure that patients are enrolled in both high and low end of the 6 to < 18 years of age group, approximately 50% patients will be enrolled who are 6 to 11 years of age in Group 1.

The following stepwise recruitment will be utilized:

- Group 1 (6 to < 18 years): A sample size of at least 6 patients will be prospectively planned to be recruited to evaluate PK and PD of LCZ696 analytes following the single dose administration of LCZ696 0.8 mg/kg (N=6 observations) and then the single dose administration of LCZ696 3.1 mg/kg (N=6 observations). The patients who receive the LCZ696 single dose of 0.8 mg/kg treatment will also have an option to subsequently receive the LCZ696 3.1 mg/kg dose. If a patient who received the LCZ696 0.8 mg/kg does not qualify or declines to receive the LCZ696 3.1 mg/kg dose, an additional patient will be recruited to receive the LCZ696 3.1 mg/kg dose.
- Group 2 (1 to < 6 years): A sample size of at least 6 patients will be prospectively planned to be recruited to evaluate PK and PD of LCZ696 analytes following the single dose administration of LCZ696 0.8 mg/kg (N=6 observations) and then the single dose administration of LCZ696 3.1 mg/kg (N=6 observations). The patients who receive LCZ696 single dose of 0.8 mg/kg treatment will have an option to receive LCZ696 3.1 mg/kg dose subsequently. If a patient who received the LCZ696 0.8 mg/kg dose does not qualify or declines to receive the LCZ696 3.1 mg/kg dose, an additional patient will be recruited to receive the LCZ696 3.1 mg/kg dose.

[redacted]

- Group 3 (1 month to < 1 year): A sample size of at least 4 patients will be prospectively planned to be recruited to evaluate PK and PD of LCZ696 analytes following the single dose administration of LCZ696 0.4 mg/kg (N= approximately 4 observations) and then the single dose administration of LCZ696 1.6 mg/kg (N= approximately 4 observations). The patients who receive LCZ696 single dose of 0.4 mg/kg treatment will have an option to receive LCZ696 1.6 mg/kg dose subsequently. If a patient who received the LCZ696 0.4 mg/kg dose does not qualify or declines to receive the LCZ696 1.6 mg/kg dose, an additional patient will be recruited to receive the LCZ696 1.6 mg/kg dose.

Available PK/PD and safety data will be reviewed to confirm or modify the doses tested for each age group (Section 3.5 and Section 9.4.1).

If deemed necessary for dose determination for Part 2, additional age group 3 patients may be enrolled in Part 1.

Eligible patients will first receive the LCZ696 0.4 mg/kg single dose (Group 3) or 0.8 mg/kg single dose (Group 1 or 2). Patients must be currently treated with an ACEI or ARB (at any dose) at screening to be eligible for the LCZ696 0.4 mg/kg (Group 3) or 0.8 mg/kg (Group 1 and 2) single dose.

To be eligible for the subsequent LCZ696 3.1 mg/kg dose, patients in Group 1 or 2 must be currently treated with a daily dose equivalent of at least enalapril 0.2 mg/kg (Table 3-1) prior to the LCZ696 3.1 mg/kg (Group 1 and 2) single dose assessment.

To be eligible for the subsequent LCZ696 1.6 mg/kg dose, patients in Group 3 must be currently treated with a daily dose equivalent of at least enalapril 0.1 mg/kg (Table 3-1) prior to the LCZ696 1.6 mg/kg single dose assessment.

If a patient who has completed the LCZ696 0.4 mg/kg or 0.8 mg/kg single dose does not participate in the LCZ696 1.6 mg/kg or 3.1 mg/kg dose, the next eligible replacement patient may be enrolled to directly receive the LCZ696 1.6 mg/kg or 3.1 mg/kg dose, respectively.

The LCZ696 1.6 mg/kg or 3.1 mg/kg dose can be administered after a minimum of 5 days following the LCZ696 0.4 mg/kg or 0.8 mg/kg dose, respectively (to allow for washout of the LCZ696 analytes from the first dose).

Patients previously taking an ACEI are required to discontinue their ACEI at least 36 hours before the LCZ696 dose to minimize the potential risk of angioedema due to overlapping ACEI-NEP inhibition. Similarly, all patients who have taken LCZ696 should discontinue their LCZ696 at least 36 hours before taking an ACEI. Patients taking an ARB or renin inhibitor are required to discontinue the ARB or renin inhibitor the morning of the LCZ696 single dose visit.

After completion of the PK/PD assessment visit, patients can either be maintained on open-label enalapril or their standard of care HF medical regimen until Part 2 (Efficacy). Patients in each age group can enroll in Part 2 after the target dose for that age group is determined based on Part 1 data for the corresponding age cohort. Patients that discontinue from Part 1 (PK/PD) will be allowed to screen and enroll for participation in Part 2 (Efficacy).

Part 2: This is a randomized, double blind, parallel-group, active controlled, 52-week study to evaluate the efficacy, safety, and tolerability of LCZ696 compared to enalapril in pediatric HF patients (1 month to < 18 years). A screening epoch of up to 3 weeks will be used to assess

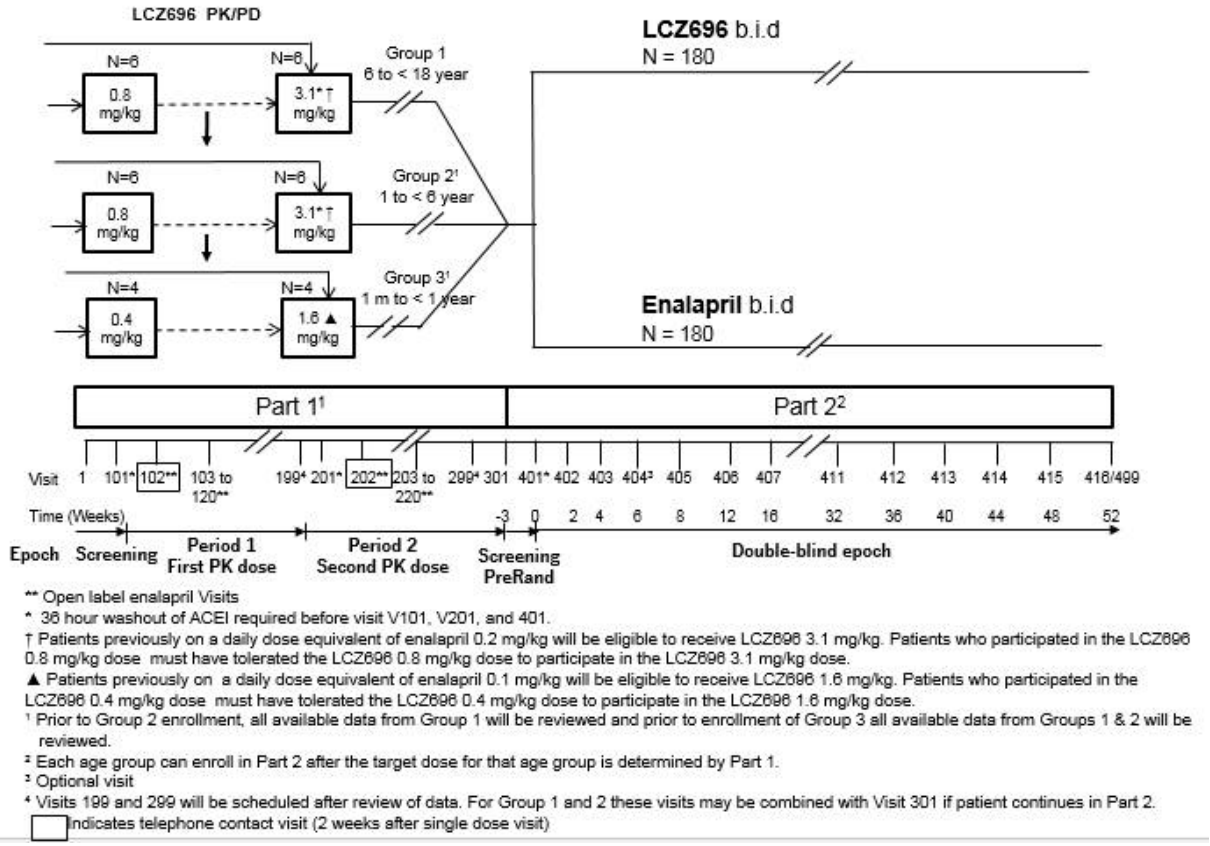
[redacted]

eligibility. 360 eligible patients will be randomized to one of the two treatment arms (LCZ696 vs. enalapril) and continue treatment for 52 weeks duration (see Appendix 15 for USM exception). Both hospitalized patients and outpatients are eligible. Chronic HF patients that are either previously treated for HF or newly diagnosed are eligible.

An interim efficacy analysis is planned to be performed when at least 180 patients (at least 36 patients from each age group) have completed the study (i.e., reached a terminal endpoint or completed the 1 year study visit), and at least 40 patients have had an event in Category 1 or 2. Further details about interim analyses are provided in Section 9.6.

Part 2 will stop when at least 360 patients have completed the study.

Figure 3-1 Study design



** Open label enalapril Visits
* 36 hour washout of ACEI required before visit V101, V201, and 401.
† Patients previously on a daily dose equivalent of enalapril 0.2 mg/kg will be eligible to receive LCZ696 3.1 mg/kg. Patients who participated in the LCZ696 0.8 mg/kg dose must have tolerated the LCZ696 0.8 mg/kg dose to participate in the LCZ696 3.1 mg/kg dose.
▲ Patients previously on a daily dose equivalent of enalapril 0.1 mg/kg will be eligible to receive LCZ696 1.6 mg/kg. Patients who participated in the LCZ696 0.4 mg/kg dose must have tolerated the LCZ696 0.4 mg/kg dose to participate in the LCZ696 1.6 mg/kg dose.
¹ Prior to Group 2 enrollment, all available data from Group 1 will be reviewed and prior to enrollment of Group 3 all available data from Groups 1 & 2 will be reviewed.
² Each age group can enroll in Part 2 after the target dose for that age group is determined by Part 1.
³ Optional visit
⁴ Visits 199 and 299 will be scheduled after review of data. For Group 1 and 2 these visits may be combined with Visit 301 if patient continues in Part 2.
Indicates telephone contact visit (2 weeks after single dose visit)

Part 1 (PK/PD) - Screening epoch

Part 1 will be conducted in selected countries and centers due to the limited number of patients required. At least 18 patients combining the three age groups will be enrolled. All eligible patients will be consented (parent/legal guardian ICF and if applicable, patient assent) at Visit 1. A screening period of approximately up to three weeks will be used to determine if patients

qualify to enter the Part 1 (PK/PD) epoch. No study medication will be administered during this time. Both hospitalized patients and outpatients are eligible for participation.

Qualifying LVEF or LV fractional shortening assessment will be based on a locally obtained echocardiogram (ECHO), MRI, MUGA, or left ventricular angiogram. If a qualifying LVEF or fractional shortening measurement is not available, a qualifying echocardiogram measurement must be obtained during screening before the patient receives study treatment. The preferred LV function assessment is by ECHO. A MUGA, MRI or ventriculogram that is done as part of standard of care can be used instead of ECHO.

Screening laboratory values will be assessed by sending blood and urine samples to the local laboratory. Only patients with the required values per the entry criteria will be eligible to continue in the study. It is recommended that at Visit 1 (Part 1 PK/PD – Screening), the site schedule the patient's next visit approximately one week after Visit 1.

In order to be eligible for Part 1, patients in Groups 1, 2 and 3 must be taking an ACEI/ARB (at any dose) prior to the single dose LCZ696 0.4 mg/kg (Group 3) or 0.8 mg/kg PK/PD assessment (Group 1 and 2) and meet all the inclusion/exclusion criteria at Visit 1.

Patients in Group 1 and 2 must be currently treated with the equivalent of at least enalapril 0.2 mg/kg daily dose (Table 3-1) prior to the single dose LCZ696 3.1 mg/kg and Group 3 patients must be treated with the equivalent of at least enalapril 0.1 mg/kg daily dose (Table 3-1) prior to the single dose LCZ696 1.6 mg/kg PK/PD assessment and meet all the inclusion/exclusion criteria at Visit 1.

Dosing will be performed with patient supine or sitting and under close observation. Enalapril 0.1 mg/kg and 0.2 mg/kg provides similar renin angiotensin system inhibition compared to the LCZ696 1.6 mg/kg and 3.1 mg/kg dose being examined, respectively. If a patient is not taking one of the commonly prescribed ACEI/ARBs shown in Table 3-1, the Investigator may use his/her judgment regarding the equivalent ACEI/ARB dose based on product information, medical literature, medical expertise, and/or consultation with Novartis.

Table 3-1 Part 1: PK/PD - Minimum required pre-study body-weight normalized daily doses of commonly prescribed ACEIs or ARBs that should be tolerated prior to the LCZ696 1.6 mg/kg and 3.1 mg/kg single dose PK/PD assessment

ACEI/ARB	Body weight normalized daily dose	Body weight normalized daily dose	Adult daily dose
Prior to the LCZ696 1.6 mg/kg (Group 3)		**Prior to the LCZ696 3.1 mg/kg (Group 1 and 2)**	
Captopril	0.3 mg/kg	0.6 mg/kg	37.5 mg
Enalapril	0.1 mg/kg	0.2 mg/kg	10 mg
Enalaprilat	0.01 mg/kg	0.02 mg/kg	-
Lisinopril	0.1 mg/kg	0.2 mg/kg	10 mg
Valsartan	1.25 mg/kg	2.5 mg/kg	160 mg
Losartan	0.75 mg/kg	1.5 mg/kg	100 mg
Candesartan	0.25 mg/kg	0.5 mg/kg	32 mg

[redacted]

A patient who enters screening, but is determined not to be eligible to enter Part 1 will be considered a screen failure. The Investigator may consider re-screening the patient for Part 1 at a later time if the patient's condition has changed and they may potentially be eligible. A patient may be re-screened for Part 1 up to two times. A minimum of 2 weeks must elapse between re-screenings. A patient not eligible for Part 1 (PK/PD) may also be re-screened for Part 2 (Efficacy) when Part 2 begins.

Part 1 (PK/PD) - Visits 101, 201, UNS PK/PD (if performed) – Period 1 and 2 epoch

Visit 101 will occur approximately up to three weeks after Visit 1. Visit 201 may occur approximately up to three weeks after Visit 1 if patient is directly going to second dose PK assessment from Visit 1.

Part 1 PK/PD assessment is conducted using three age groups (Groups 1, 2 and 3) enrolled into the study in a sequential and descending age group order. A single dose of LCZ696 0.4 mg/kg (Group 3) or 0.8 mg/kg (Groups 1 and 2) followed by a single dose of 1.6 mg/kg (Group 3) or 3.1 mg/kg (Groups 1 and 2) will be administered for PK and PD evaluations in participating patients.

All patients in Part 1 will be administered the single dose of LCZ696 using the 3.125 mg granules. Safety, tolerability, PK and PD data will be evaluated by Sponsor and an independent Data Monitoring Committee (DMC). This data will be used to guide and/or confirm the dose level for the other age groups in Part 1 (Groups 1, 2 and 3) and the same age group in Part 2.

Patients are required to discontinue their enalapril or other ACEI at least 36 hours before taking the single dose LCZ696 to minimize the potential risk of angioedema due to overlapping ACEI-NEP inhibition. Patients taking an ARB or renin inhibitor are required to discontinue their ARB or renin inhibitor the morning of their single dose LCZ696 PK/PD visit.

Patients should, if possible, fast for 2 hours prior to the PK/PD assessment at Visits 101, 201, and UNS PK/PD (if performed). Patients may eat starting at two hours after the patient is administered LCZ696. If the patient is not able to fast, this will be recorded and the PK/PD assessment will still be performed. The reason for collecting this information is to consider any food effect on the PK/PD assessments. All eligible patients will provide a blood sample for PK (Section 6.6.2) and biomarkers (Section 6.5.4.5) prior to taking any study medication. Additional blood and urine samples will be collected at pre-specified time points during Visit 101, 201, and UNS PK/PD (Table 3-2). Biomarker blood samples for plasma cGMP, plasma B-type natriuretic peptide (BNP) and plasma NTproBNP are scheduled to be collected based on Table 3-2. Details about blood volume drawing restrictions, blood biomarker prioritization (given blood volume restrictions), blood volume laboratory requirements for PK/PD samples, sample collection, processing and storage instructions are provided in the laboratory manual.

Abbreviated chemistry laboratory samples will be obtained at the end of Visit 101, 201 and Unscheduled PK/PD (if performed). The number of PK/PD samples collected is dependent on the age group and blood volume drawing restrictions (Table 18-1). Efforts to minimize patient discomfort should be used when possible. To minimize discomfort and multiple needle sticks, pre-existing venous access may be used. Where feasible, a temporary indwelling venous catheter will be inserted if not already present. Local anesthetic cream may also be considered

[redacted]

for use to reduce pain and discomfort from venipuncture, if possible. The collection of the 24 hour post-dose blood sample for PK and biomarkers is optional.

Table 3-2 Part 1 (PK/PD) - Visit 101, 201, and UNS PK/PD blood and urine sample collection

Time point	Blood (PK)		Plasma cGMP	Plasma BNP	Plasma NTproBNP	Urine cGMP
	Group 1 ≥6 yr	*Groups 2 and 3 <6 yr*				
Pre-dose	x	x[1]	x	x	x	x[3]
0.5 hours post-dose	x					
1 hour post-dose	x	x				
2 hours post-dose	x	x				
4 hours post-dose	x	x	x	x		x (4-8 h)[3]
8 hours post-dose	x		x[2]	x[2]		
10-hours post-dose	x	x				
24 hours post-dose (optional)	x[2]	x[2]			x[2]	

[1]Due to blood volume restrictions (dependent on patient weight), this sample will only be collected for patients taking valsartan. The sample will be used to measure the plasma concentration of the pre-dose valsartan, if valsartan is being used by the patient prior to the single dose PK.

[2]Patients with blood volume restrictions (dependent on patient weight) will not have this sample collected. See Laboratory manual for details about biomarker prioritization when blood volume that can be drawn is limited.

[3] A spot urine sample will be collected at pre-dose and at any time between 4 to 8 hours post-dose.

Additional information about LCZ696 liquid formulation preparation is available in the (Pharmacy Manual).

AEs and vital signs will be monitored throughout the PK/PD assessment visits. Other safety evaluations will include abbreviated physical exam and abbreviated laboratory tests (refer to Table 6-1).

For all age groups, additional single dose PK/PD assessments may be performed if deemed necessary for dose determination for Part 2. This will be a decision made by the Sponsor and the DMC (Section 9.6). Unscheduled PK/PD visits may be used for additional PK/PD assessments. Additional PK/PD assessments may involve new Part 1 patients, or patients who have completed a PK/PD assessment and agree to another PK/PD assessment.

[redacted]

Part 1 (PK/PD) - Open-label enalapril or standard of care HF medical regimen (Visits 102 to 199 and 202 to 299) – Period 1 and 2 epoch

Visits 101 through 199 and 201 through 299 are for first PK dose and second PK dose, respectively.

A telephone call (Visit 102 and/or Visit 202) will occur 2 weeks after Visit 101 (first PK dose visit) and/or Visit 201 (second PK dose visit) for safety evaluation (refer to Table 6-1).

Patients who have successfully completed Visit 101 and/or Visit 201 and will consent to participate in Part 2 (Efficacy) will take open-label enalapril or be maintained on their standard of care HF medical regimen (which may include captopril or other ACEI/ARB). Open-label enalapril visits will begin after Visit 101 and/or Visit 201 and continue until Part 2 (Efficacy) begins.

All patients will be seen at the site every 12 weeks (3 months) after Visit 101 and/or Visit 201 until Part 2 begins with monthly telephone visits in between the three month visits.

Patients taking the open-label enalapril adult formulation will come to the site for their scheduled visits and to receive open-label enalapril medication every 12 weeks (e.g. Visit 105/205, 108/208, etc.). Telephone visits will occur monthly for these patients between the every 3 month visits (e.g. 103/203, 104/204, 106/206, etc.). Refer to Table 6-1 and Table 6-2 for assessments performed by telephone.

If needed, based on the patient's age and/or inability to swallow tablets, liquid enalapril may be used. The liquid enalapril can be prepared at the site's pharmacy and can be commercially sourced such as Epaned (if available).

Patients receiving liquid enalapril must return to the site for resupply at intervals dependent on the storage life of liquid enalapril (every 1 month; or every 2 months if Epaned (enalapril) is available and used, which has a 2 month shelf life). Given the burden of traveling to the site for the study visit for patients and families, the parent/caregiver can come to the site without the patient for dispensation of study drug. Delivery of study drug to the patient can also be used where possible and allowed per local regulations. If the parent/caregiver comes to the visit without the patient, a telephone call to the patient (≥ 6 years old) can be used in conjunction with the parent/caregiver visit for the visit assessments that can be performed verbally.

Patients that discontinue from Part 1 (PK/PD) will be allowed to screen and enroll for participation in Part 2 (Efficacy).

Novartis or its representatives will notify Investigators once Part 1 is complete for each age group. At that time, patients in the completed age group will be scheduled for their final visit in Part 1 (PK/PD, for first dose Visit 199, for second dose Visit 299). For the patient who completed second dose PK/PD assessment, Visit 299 may occur on the same day as Visit 301 (Part 2 Pre-Randomization/Screening) if the patient will participate in Part 2. For the patient that only participated in first dose PK/PD assessment (and not second dose PK/PD assessment), the Visit 199 may occur on the same day as Visit 301, if the patient will participate in Part 2.

Part 2 (Efficacy) - Overview

All participating countries and centers will be eligible for Part 2 (Efficacy).

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Part 2 is a double-blind, randomized treatment epoch. Patients will receive either LCZ696 or enalapril, and matching placebo for enalapril or LCZ696, respectively. The target dose of LCZ696 for Groups 1 and 2 is dose level 4 and for Group 3 is dose level 4x, and was selected based on the Part 1 PK/PD results. Blinded study drug will be titrated to the target dose as tolerated per the safety monitoring criteria (Table 3-3) (e.g. if the patient does not experience adverse events that include symptomatic hypotension, worsening renal function, or hyperkalemia). AEs or conditions that preclude initiation or up-titration of study drug can include abnormalities in laboratory chemistry values based on local laboratory normal reference ranges and the Investigator's judgment. Additional safety monitoring will be required for Group 3 patients. Starting with the first dose of study medication, vital signs must be checked for up to 4 hours after the initial dose at each dose level (i.e. dose levels 1x through 4x, as applicable). Note: this does not apply for up-titrations following study drug interruptions or down-titrations up to the prior achieved maximal dose level). See Appendix 13 for details.

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

Parameter	Description
Potassium level	K ≤ 5.4 mmol/L (mEq/L)
Kidney function	eGFR (calculated using the modified Schwartz formula) ≥ 30% mean GFR for age (Appendix 10, Table 22-1)
Kidney function	eGFR reduction < 35% compared to randomization Visit 401 (Part 2).
Blood pressure	SBP > than the calculated 5th percentile SBP for age as described in Appendix 4
AEs or conditions	No conditions that preclude continuation according to Investigator's judgment, including hypotension.

Part 2 (Efficacy) - Pre-randomization/screening epoch, Visit 301

All patients will be consented for Part 2 efficacy (parent/legal guardian ICF and if applicable, patient assent) before any study-specific procedures are performed. All patients entering Part 2 must fulfill all inclusion criteria and none of the exclusion criteria at Visit 301 (Part 2 Efficacy-Pre-Randomization/Screening). Local laboratory evaluations are required to assess the patient's eligibility at Visit 301 (refer to Table 6-1, Table 6-2 and Section 6.5.4).

Patients may enter Part 2 (Efficacy) via two pathways:

- Patients participating in Part 1 will be re-evaluated to assess all inclusion and exclusion criteria. A repeat assessment of LVEF or fractional shortening is only required if the last assessment of LVEF or fractional shortening was > 1 month prior to Visit 301
- Patients that did not participate in Part 1 (PK/PD) will be evaluated to assess all inclusion and exclusion criteria for participation in Part 2 (Efficacy).

The screening period will be up to three weeks. No study medication will be administered during this time.

[redacted]

Qualifying LVEF or fractional shortening measurements will be based on a locally obtained echocardiogram, MRI, MUGA, or left ventriculogram. If these qualifying measurements are not available within 1 month of Visit 301 (Part 2 Efficacy- Pre-Randomization/Screening), then an echocardiogram should be obtained during the screening period.

Part 2 screening laboratory assessments should be performed locally. Only patients with the required values per the entry criteria will be eligible to continue in the study.

Both hospitalized patients and outpatients are eligible for participation in Part 2 (Efficacy). A hospitalized patient is defined as a patient who is being treated in the hospital at the time of Visit 401 (Part 2 Efficacy - Randomization). An outpatient is a patient who is screened in stable health status and can initiate study medication intake in an ambulatory setting.

Part 2 (Efficacy) - Randomized treatment epoch (Visit 401 to Visit 416/499)

The Part 2 randomized treatment epoch begins at Visit 401. Part 2 will enroll 360 patients. Patients are required to discontinue their enalapril or other ACEI at least 36 hours before taking blinded study drug at randomization to minimize the potential risk of angioedema due to overlapping ACEI-NEP inhibition. Patients taking an ARB or renin inhibitor are required to discontinue their ARB or renin inhibitor on the day of randomization (i.e. patient should not have taken ARBs, or renin inhibitor on the day of randomization).

At randomization (Visit 401), patients who meet eligibility and safety criteria will be randomized to 1 of 2 treatment arms: double-blind enalapril bid or LCZ696 bid. The initial study drug dose started at randomization for Group 1 and 2 is dose level 1 or 2 (Table 3-5), and for Group 3 is dose level 1x or 2x (Table 3-6). Patients who are ACEI/ARB naïve or on low dose ACEI/ARB (dose levels 1 or 2; Table 3-4) prior to randomization should start at dose level 1 or 1x at randomization, depending upon the age group (Table 3-5, Table 3-6). Patients who are on higher doses of ACEI/ARB (dose levels 3 or 4; Table 3-4) prior to randomization may start at dose level 2 or 2x, based on age group (Table 3-5, Table 3-6). Given the patient's condition is often dynamic, patients may start, depending upon the age group, on dose levels 1 or 1x or 2 or 2x at randomization based on Investigator judgement.

Patients will continue taking their background HF therapy except for ACEIs and/or ARBs, which are replaced by the study medication. The concomitant use of ACEIs, ARBs, or renin inhibitors with study medication is strictly prohibited.

Table 3-4 Part 2 (Efficacy): Total daily dose levels of commonly prescribed ACEI/ARBs to guide selection of the study medication starting dose

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

For age groups 1 and 2, the target dose for enalapril is 0.2 mg/kg bid (0.4 mg/kg total daily dose) with a maximum dose of 10 mg bid (20 mg total daily dose). For age groups 1 and 2, the target dose for LCZ696 is projected to be 3.1 mg/kg bid. Based on the PK/PD results from Part 1 for Group 3 patients, the target dose for LCZ696 (dose level 4x) will be 2.3 mg/kg bid. In addition, for Group 3 patients who turn 1 year old during the study, consideration should be given to up-titrate to a dose of 3.1 mg/kg bid (dose level 5x). See Appendix 14 for details. The LCZ696 dose is not to exceed 200 mg bid irrespective of the body weight (Table 3-5, Table 3-6). The actual target dose (dose level 4 or 4x, depending upon age group) and lower dose levels (1, 2, 3 or 1x, 2x, 3x, depending upon age group) of LCZ696 for Part 2 were determined based on PK and PD results from Part 1 of the study.

Study drug is titrated to target dose level 4 for Group 1 and 2, or to target dose level 4x for Group 3, as tolerated based on the safety monitoring criteria approximately every 2 weeks beginning at Visit 401 (Part 2 Efficacy – Randomization) and continuing at Visits 402 and 403 (Table 3-3). Investigators have the option to schedule a patient for an additional visit (Visit 404; 6 weeks post-randomization) in order to complete the titration to the target dose. Additional safety monitoring will be required for Group 3 patients. Starting with the first dose of study medication, vital signs must be checked for up to 4 hours after the initial dose at each dose level (i.e. dose levels 1x through 4x, as applicable). Note: this does not apply for up-titrations following study drug interruptions or down-titrations up to the prior achieved maximal dose level) See Appendix 13 for details. Unscheduled visits may be necessary to assess the patient and/or adjust study medication as needed. Group 3 patients who turn 1 year old during the study and for whom study drug is to be up-titrated based on the safety monitoring criteria, a scheduled or unscheduled visit may be used for these up-titration visits. See Appendix 14 for details.

Single PK samples will be collected during Part 2 (Efficacy) at the following visits: Visit 403, Visit 406, and Visit 416/499 (Week 52/End of Study) (see Appendix 15 for USM exception). Additional samples for PK may be considered if patient has an unscheduled visit.

In approximately 24 Group 2 patients, sparse PK blood samples will be collected at steady-state at 3 time-points on the same day, at Visit 405 or at a subsequent scheduled or unscheduled visit

[redacted]

(except visits 406 and 416/499), when the patient is on Dose-Level 4 or at his/her highest tolerated dose for at least 1 week. Refer to Section 6.6.2 for additional PK information.

To assess the patient's eligibility to titrate to the next dose level, local laboratories should be used.

Table 3-5 Part 2 (Efficacy): Study drug dose levels for double-blind enalapril and LCZ696 for age groups 1 and 2

Dose levels for pediatric formulation	Enalapril dose	LCZ696 dose †
Dose level 1	0.05 mg/kg bid.	0.8 mg/kg bid.
Dose level 2	0.1 mg/kg bid.	1.6 mg/kg bid.
Dose level 3	0.15 mg/kg bid.	2.3 mg/kg bid.
Dose level 4	0.2 mg/kg bid.	3.1 mg/kg bid.
Dose levels for adult formulation	**Enalapril dose**	**LCZ696 dose †**
Dose level 1	2.5 mg bid.	50 mg bid.
Dose level 2	5 mg bid.	100 mg bid.
Dose level 3	7.5 mg bid.	150 mg bid.
Dose level 4	10 mg bid.	200 mg bid.

†Note: LCZ696 target dose (dose level 4) and other dose levels shown in table are based on target dose of LCZ696 3.1 mg/kg bid. LCZ696 target dose has been verified by Part 1 PK/PD.

Table 3-6 Part 2(Efficacy): Study drug dose levels for double-blind enalapril and LCZ696 for age group 3

Dose levels for pediatric formulation	Enalapril dose	LCZ696 dose †
Dose level 1x	0.05 mg/kg bid.	0.8 mg/kg bid.
Dose level 2x	0.075 mg/kg bid.	1.2 mg/kg bid.
Dose level 3x	0.1 mg/kg bid.	1.6 mg/kg bid.
Dose level 4x	0.15 mg/kg bid.	2.3 mg/kg bid.

†Note: LCZ696 target dose 2.3 mg/kg (dose level 4x) is based on Part 1 PK/PD Safety data. The other dose levels for LCZ696 shown in table are based on target dose of LCZ696 2.3 mg/kg bid and Part 1 PK/PD Safety data. For Group 3 patients who turn 1 year old during the study, consideration should be given to up-titrate to a dose of 3.1 mg/kg bid (Dose Level 5x). See Appendix 14 for details.

Randomized, ongoing, Part 2 Age Group 3 patients (i.e. patients who are 1 month to <1 year old at randomization) who are safely tolerating Dose Level 4x (i.e. LCZ696/Placebo, 2.3 mg/kg bid / Enalapril/Placebo 0.15 mg/kg bid) for at least 2 weeks, and who turn 1 year old during the study, may be up-titrated to Dose Level 5x (LCZ696/Placebo, 3.1 mg/kg bid / Enalapril/Placebo 0.2 mg/kg bid), if it is the patient's best interest to be up-titrated based on the medical judgement of the investigator. See Appendix 14, Table 26-1 for Dose Level 5x up-titration information for Age Group 3 patients.

Study drug dose level adjustments should be based on overall safety and tolerability. Patients should be titrated to the next dose level if there is no symptomatic hypotension, hyperkalemia, worsening renal function, or other AEs per the Investigator's judgment as shown in Table 3-3.

[redacted]

Additional safety monitoring will be required for Group 3 patients with each initial dose level up-titration. See Appendix 13 for details.

Every attempt should be made to achieve and maintain patients on the target study drug dose level throughout Part 2 (Efficacy). If, in the opinion of the Investigator, the patient does not tolerate the assigned study medication, the Investigator should consider whether non-disease-modifying medication (e.g. calcium channel blockers, diuretics, α-blockers) can be reduced to rectify the situation. The Investigator may adjust doses of disease-modifying medications (e.g. beta-blockers, aldosterone antagonists) if it is believed that they are the most likely cause of the adverse effect. If adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern, the Investigator may down-titrate or interrupt the study drug. Refer to Section 5.5.5 for guidance on permitted study drug dose adjustments and interruptions. If the reason for a dose adjustment is due to an adverse event, an adverse event should be reported.

At each visit after randomization (Part 2 Efficacy - Visit 401), the patient's medication compliance, safety, and tolerability of the study medication are assessed. This will include, but not be limited to signs and symptoms of hypotension, serum potassium level, and renal function. Patients who experience angioedema as determined by the Investigator at any time during the double-blind epoch must be discontinued from the study.

Both scheduled and unscheduled visits can be utilized for up-titration/down-titration throughout the study based on Investigator judgment (Section 5.5.5) for re-evaluation of safety criteria parameters and study drug management.

3.2 Rationale for study design

The patient population will be described in more detail in Section 4 below.

The study is comprised of two parts combined into a seamless design:

- Part 1: PK and PD assessments to determine the LCZ696 dose for Part 2
- Part 2: 52-week efficacy and safety assessments

The purpose of this design is to improve study efficiency compared to a sequential approach involving two separate studies.

3.3 Rationale for Global Rank primary endpoint

There is no agreed upon, validated clinical efficacy endpoint for this patient population. In addition, the low prevalence of HF in children limits the possibility to conduct large outcome trials. The Global Rank primary endpoint is developed based on Packer's composite score to assess the totality of the interventions. Packer's composite score has been widely used in cardiovascular clinical trials (Packer 2001) including ularitide TRUE-AHF (Anker 2015, Chang 2015). Packer's composite score classifies patients into three categories: worsened, unchanged, and improved. Similarly, a clinical composite endpoint with three categories (worsened, neither worsened nor improved, and improved) was also used in the Carvedilol Pediatric HF study (Shaddy 2007).

The primary endpoint for this LCZ696 pediatric HF study uses a Global Rank endpoint that builds on Packer's composite score with a methodology that further differentiates patients

[redacted]

between treatment groups (Felker 2010, Sun 2012). The Global Rank endpoint rank orders patients from worst to best using: (a) objective outcome events of death, listing for urgent heart transplant or mechanical support; (b) events of worsening HF; and (c) measures of functional assessment (NYHA/Ross) and patient reported outcomes: Patient Global Impression of Severity (PGIS) and the PedsQL (physical functioning subgroup of questions). Thus, the global ranked endpoint encompasses important clinical events grouped into broadly agreed categories of severity from mortality to disease progression (worsening HF) to measures of symptoms and physical functioning. This global rank endpoint for this study has been developed with input and endorsement by world leading pediatric heart failure experts.

The effects of LCZ696 and enalapril will be assessed after 52 weeks of double-blind treatment using the Global Rank endpoint algorithm (as outlined in Table 6-3) (see Appendix 15 for USM exception). Clinical events that are potential endpoints for Categories 1 and 2 (described below) will be adjudicated by a blinded, external adjudication committee.

Classification of patients in the global rank endpoint according to severity

- Category 1: Death; UNOS status 1A listing for heart transplant or equivalent; VAD/ECMO/mechanical ventilation/intra-aortic balloon pump requirement for life support at end of study

Reducing Category 1 endpoints such as death is a major goal for treating pediatric HF. HF transplant is a major therapy and treatment of last resort for pediatric HF. Listing for urgent HF transplant instead of the heart transplant itself is used for the time to event analysis given the assumptions that these patients would die without an imminent heart transplant and that the duration waiting for a heart transplant is dependent on the availability of the donor heart. Urgent HF transplant is defined as UNOS status 1A or equivalent where the patient must be in the intensive care unit on intravenous inotropic medications and/or mechanical life support. The requirement for mechanical life support (VAD, ECMO, mechanical ventilation, intra-aortic balloon pump) at the end of the study is also Category 1. In this case, the patient would die or need a heart transplant if removed from this mechanical support to qualify for Category 1. Death and other Category 1 events should be modifiable by treatments that improve HF. Within Category 1, the patients will be ranked by time to first event.

- Category 2: Worsening HF (WHF); defined by signs and symptoms of WHF that requires an intensification of HF therapy

There is general agreement that reducing WHF is a major goal for treating pediatric HF. Inpatient and outpatient WHF events reflect disease-specific endpoints related to progressive worsening of the HF syndrome. These WHF events should be modifiable by treatments that improve this condition.

WHF is defined as new or worsening symptoms and signs of heart failure that requires intensification of HF therapy (Section 6.4.1). Within Category 2, the events will be classified into 3 subcategories from worst to best:

- Worsening HF hospitalization with intensive care unit (ICU) stay
- Worsening HF hospitalization without ICU stay

[redacted]

- Worsening HF without hospitalization

Within Category 2, the patients will be ranked first by event subcategory, and then by number of events within each subcategory. Further ranking will be performed by time to first event in the worst subcategory.

Patients who do not have a clinical event that qualifies for Categories 1 or 2 will be placed into Categories 3, 4, and 5 (refer to Table 6-3).

- Category 3: Worsened; worse NYHA/Ross or worse Patient Global Impression of Severity (PGIS); and further ranking by PedsQL physical functioning domain
- Category 4: Unchanged; unchanged NYHA/Ross and unchanged PGIS; and further ranking by PedsQL physical functioning domain
- Category 5: Improved; improved NYHA/Ross or improved PGIS (neither can be worse); and further ranking by PedsQL physical functioning domain

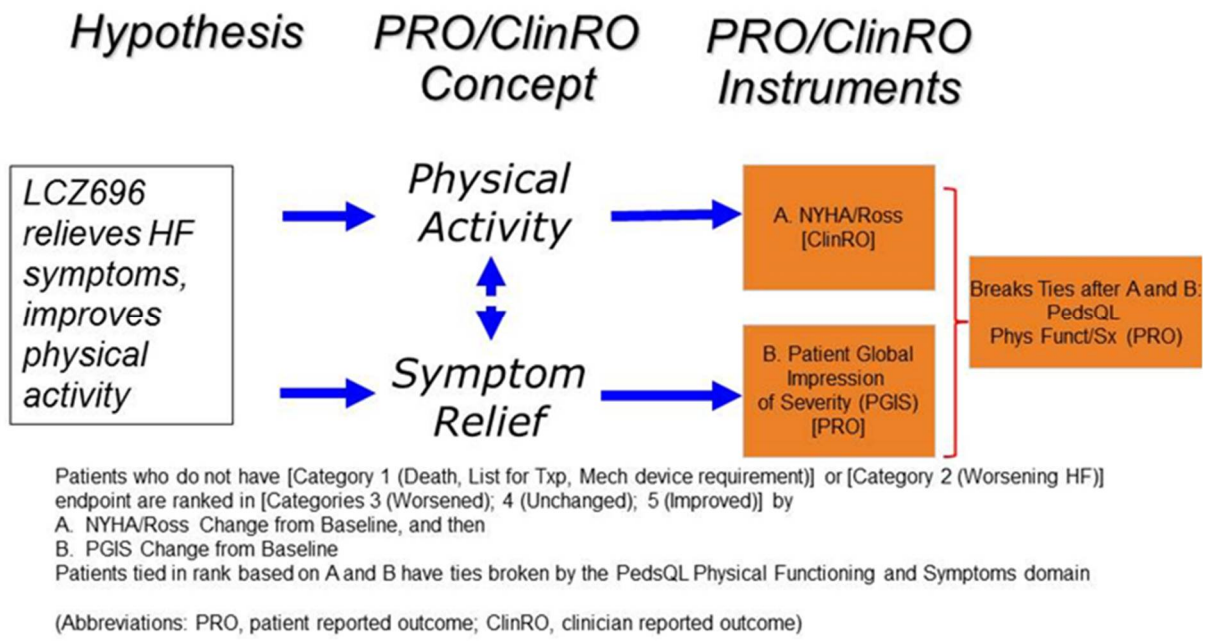
The hypothesis is that LCZ696 will improve functional capacity (NYHA/Ross) and HF symptoms (PGIS) and that these two phenotypic characteristics are interrelated (Figure 3-2).

NYHA/Ross

The impact of study drug on the patient's physical functional status will be assessed using the NYHA classification I-IV (older children: 6 to < 18 years old) or Ross HF classification I-IV (younger children: l month to < 6 old year). The NYHA and Ross functional class assessments are reliable instruments for rating HF patients' functionality (Criteria Committee NYHA 1994, Ross 1992, Packer 2001, Rosenthal 2004).

[redacted]

Figure 3-2 Global rank endpoint categories 3, 4, 5



Patient Global Impression of Severity (PGIS)

The impact of study drug on the patient's heart failure symptomatic status will be assessed using the PGIS which is a static global impression of severity question that will be used to capture the patients' current health status relative to their heart failure over a 7 days recall period.

- Patient (7 to < 18 years old): How would you describe the severity of your heart failure symptoms **over the past 7 days**? (None / Mild / Moderate / Severe / Very Severe) [5-point response scale]
- Parent (for < 5 years old patients): How would you describe the severity of your child's heart failure symptoms **over the past 7 days**? (None / Mild / Moderate / Severe / Very Severe) [5-point response scale]
- Patient (5 to < 7 years old): Point to the one face that best shows how your heart problems have been **over the last 7 days**? (Good / Neither Good nor Bad / Bad) [3-point scale]

The PGIS uses a 5-point patient evaluation scale for patients ≥ 7 years. A 5-point evaluation scale is used for parent/caregivers for patients < 5 years of age. A 3-point faces scale will be used for patient self-report by children 5 to < 7 years.

For the Global Rank primary endpoint, a one class change in the PGIS is considered to represent a clinically significant change. The parent/caregiver PGIS report will only be used for the Global Rank endpoint for patients < 5 years old. The patient PGIS report will be used for the Global Rank endpoint for patients ≥ 5 years old. For additional information, refer to Section 6.6.1.2 and Appendix 8.

Categories 3, 4, 5 are ranked first on a combination of two measures of efficacy: NYHA/Ross functional class and the PGIS. Both measures are simple, comprehensive, and complementary. Worsened is defined as worsening in heart failure functional class (NYHA/ Ross heart failure classification) at the last reported observation; **or** worsening of PGIS score at the last reported

[redacted]

observation. Improved is defined as a condition that is not worsening, and demonstrating improvement in heart failure functional class at the last reported observation, **and/or** improvement in PGIS score at last reported observation. Unchanged is defined as neither improving nor worsening for both NYHA/Ross and PGIS.

PedsQL physical functioning domain

Further ranking within Categories 3, 4, 5 as needed ('tie breaking') will be based on a subset of 5 physical functioning domain questions of the PedsQL score (for Group 1 patients 6 to < 18 years old). For example, patients who are equally ranked based on the NYHA/Ross and the PGIS will be further ordered from worst to best by the PedsQL physical functioning assessment. The physical functioning domain of questions from the PedsQL focuses on proximal effects of health-related quality of life related to heart failure (refer to Section 6.6.1.2 and Appendix 9). The PedsQL physical functioning domain will only be used for the primary endpoint for Group 1 since the same age-specific version of the patient-reported PedsQL will be collected for all patients in Group 1 (and this does not occur for Groups 2 and 3).

For the duration of Part 2, the same PedsQL, NYHA and Ross instruments based on the age at randomization should be used.

3.4 Rationale for patient population

Pediatric heart failure differs from adult HF as it is more heterogeneous and has a different etiology. Pediatric HF can be due to: volume overload of the ventricle with preserved systolic function (e.g. left to right shunt), pressure overload, persistent arrhythmias, dilated cardiomyopathy and systemic disorders that affect myocardial contractile function (Chaturvedi 2009). This study focuses on studying a subset of pediatric HF with systemic left ventricular dysfunction. The rationale for studying this patient population is that it allows for examination of a more homogeneous pediatric HF population that also has pathophysiology similar to adult HFrEF where LCZ696 has demonstrated a significant mortality and morbidity benefit (McMurray 2014) compared to current standard of care (ACEI). In addition, for the Carvedilol Pediatric HF study which uses a clinical endpoint similar to this study, there was a potential treatment benefit in the subgroup of patients with systemic left ventricle morphology (Shaddy 2007). When underlying ventricular morphology was taken into account in the Carvedilol Pediatric HF study, a significant interaction was seen between treatment and ventricular morphology (p=0.02) indicating a possible differential effect of treatment between patients with a systemic left ventricle (beneficial trend) and those whose systemic ventricle was not a left ventricle (non-beneficial trend) (Shaddy 2007).

Numerous small observational studies in children 1.5 days to < 18 years old have suggested that ACE inhibition benefits patients with HF caused by systemic ventricular systolic dysfunction, left to right shunt, congenital heart disease, and valvular regurgitation (Leversha 1994, Rosenthal 2004, Momma 2006). However, the use of ACEI and ARBs in infants with single-ventricle physiology and adults with systemic right ventricle resulted in no significant benefit (Hechter 2001, Dore 2005, Hsu and Pearson 2009b, van der Bom 2013).

In view of (1) a potential differential effect systemic ventricular morphology may have on outcomes (based on the Carvedilol Pediatric HF study) and (2) studies in children suggesting benefit from ACEI in HF due to systemic left ventricular systolic dysfunction but no benefit

[redacted]

from ACEI or ARB treatment in HF due to single ventricle or systemic right ventricle anatomy/physiology (Bengur 1991, Lewis 1993, Hechter 2001, Rosenthal 2004, Lipshultz 2003, Dore 2005, Duboc 2005 and 2007, Hsu and Pearson 2009b, van der Bom 2013), this study will examine a more homogeneous population with biventricular hearts and HF due to systemic left ventricle with decreased EF. Such an approach will result in a patient population that resembles more closely the adult HF population in which LCZ696 has been shown to be more effective than enalapril in reducing mortality, HF hospitalization and improving symptoms in patients with HF.

Given the concern that use of a RAS blocker may affect kidney development based on preclinical rat toxicity studies, children < 1 month old (full term infant) (or < 44 weeks post conception for pre-term infant) are excluded from the study. Thus, the study population is 1 month (or ≥ 44 weeks post conception for pre-term infants) to < 18 years old.

3.5 Rationale for dose/regimen, route of administration and duration of treatment

Rationale for dose selection

The approach for dose selection examines safety, PK, and PD responses following administration of two doses equivalent to adult LCZ696 50 mg (lowest) and 200 mg (highest) doses, respectively. The objective is to select a dose that provides similar exposures of LCZ696 analytes to that observed in adult heart failure patients and that maximizes neprilysin inhibition. The PD effect of neprilysin inhibition in children will be assessed through the measurement of urine and plasma biomarkers.

For the estimation of precision for pharmacokinetic parameters, data obtained from both dose levels will be pooled as pharmacokinetics of LCZ696 analytes is dose-independent (dose linearity has been established). Dose-exposure response for pharmacodynamics parameters will be compared with available adult data.

Rationale for dose/regimen

Part 1 (PK/PD)

Part 1 (PK/PD) was designed with safety of the trial subjects in mind, sequentially exposing older and then younger age groups to LCZ696:

- The dose of LCZ696 0.8 mg/kg corresponds to the LCZ696 50 mg dose for adult subjects with a body weight of 65 kg. Furthermore, the LCZ696 50 mg dose is the recommended starting dose for adult HF patients who are ACEI/ARB naïve, on a low dose of ACEI/ARB treatment, have severe renal impairment, or have moderate hepatic impairment. The LCZ696 0.8 mg/kg dose delivers valsartan exposure bioequivalent of 0.6 mg/kg valsartan which is below the starting dose for valsartan in pediatric hypertension (1.3 mg/kg). LCZ696 0.8 mg/kg is also expected to have similar tolerability as enalapril 0.05 mg/kg which is below the recommended daily starting dose of enalapril for pediatric heart failure. Note that enalapril doses ranging from 0.1 to 0.5 mg/kg/day are used in the treatment of pediatric HF.

[redacted]

- To further ensure patient safety, patients must be treated with an ACEI or ARB prior to screening. Patients in Group 1 and 2 must be currently treated with a daily dose equivalent of at least enalapril 0.2 mg/kg (Table 3-1) prior to the LCZ696 3.1 mg/kg single dose assessment, and patients in Group 3 must be currently treated with a daily dose equivalent of at least enalapril 0.1 mg/kg (Table 3-1) prior to the LCZ696 1.6 mg/kg single dose assessment. For those patients who participated, the LCZ696 0.4 mg/kg or 0.8 mg/kg single dose assessment must have been tolerated in order to participate in the LCZ696 1.6 mg/kg or 3.1 mg/kg single dose assessment.
- The LCZ696 3.1 mg/kg dose corresponds to the LCZ696 200 mg dose in adult subjects of 65 kg body weight. In adult HF patients, no significant impact of body weight on the PK of LCZ696 analytes was observed over a range of 41.5 kg to 157.3 kg. Therefore, for patients in this weight range, LCZ696 3.1 mg/kg is expected to have similar exposure to that observed in adult heart failure patients
- Furthermore, simulations using physiologically based PK (PBPK) models and allometric scaling techniques indicate exposure similarity between pediatric patients (6 to < 18 years old) and adult HF patients.
- The proposed maximum LCZ696 dose of 3.1 mg/kg delivers valsartan exposure similar to that observed with 160 mg valsartan marketed tablets which is the target dose administered twice daily in adult HF patients. Valsartan at a 2.0 mg/kg dose administered orally was studied in children 1 to 16 years old with hypertension (Blumer 2009). In this study, with patients (1 – 16 years old) valsartan exposure (C_{max} and AUC) did not vary significantly with age. The body weight-adjusted CL/F values were also comparable across the 1-16 year old children and were similar to those observed in adult subjects.
- It should be noted that the LCZ696 3.1 mg/kg single dose for Part 1 (PK/PD) is half the LCZ696 200 mg bid (or pediatric equivalent 3.1 mg/kg bid target dose) maximal daily dose in Part 2 (Efficacy).
- The dose for Group 2 (1 to < 6 years) may be adjusted depending on safety, PK, and PD information from Group 1. In Group 2 (1 to < 6 years), the projection is to similarly evaluate the LCZ696 0.8 mg/kg and 3.1 mg/kg doses.
- The dose for Group 3 (1 month to <1 year) may be adjusted depending on safety, PK, and PD information from Groups 1 and 2. Since the physiologically based pharmacokinetic modeling (PBPK) simulations predicts higher exposure in Group 3 (1 month to < 1 year) compared to older ages, the projection is to evaluate the LCZ696 0.4 mg/kg and 1.6 mg/kg dose in Group 3.

Safety will be closely monitored during Part 1 of the study. Dosing will be performed in an experienced pediatric clinical unit setting with close observation, and patient supine/sitting.

Part 2 (Efficacy)

For Part 2 randomization, patients are assigned in a blinded manner to enalapril or LCZ696. The target dose and dose regimens are outlined in Table 3-5 and Table 3-6. Based on Part 1 data, the target dose for Group 3 has been increased from the originally planned 1.6 mg/kg to 2.3 mg/kg as observed exposures in Part 1 Group 3 patients were lower than initially expected. The study drug is uptitrated to the target dose at 2 week intervals, as tolerated. Safety criteria

[redacted]

for dose escalation are provided in Table 3-3. The patient should achieve the target dose (dose level 4 or 4x, depending upon the age group) by Visit 403 or optional Visit 404 if tolerated. Additional safety monitoring for hypotension is required for Group 3 patients with each initial dose level up-titration. See Appendix 13 for details. Both scheduled and unscheduled visits can be utilized for up-titration/down-titration throughout the study based on Investigator judgment.

The rationale for the projected target dose of LCZ696 3.1 mg/kg bid for Groups 1 and 2 in Part 2 of the study are:

- LCZ696 3.1 mg/kg bid is expected to be consistent with the adult dose target of 200 mg bid
- Simulations using physiologically based PK models and allometric scaling techniques indicated that a dose of 3.1 mg/kg in pediatric patients of age > 2 years provides similar exposure to that observed in adult heart failure patients, therefore justifying administration of 3.1 mg/kg in 6 to <18 years age group

The LCZ696 doses used in Part 2 (Efficacy) will be confirmed based on the observed PK, PD and safety data obtained from Part 1 of the study.

Rationale for duration of treatment

The rationale for the 52-week treatment duration is based on the positive LCZ696 treatment effect for relevant clinical endpoints that were evident as early as 4 to 6 months treatment duration in the LCZ696 adult PARADIGM-HF study. The 52-week treatment duration will also increase the number of clinical events in Categories 1 and 2.

- There was a sustained separation of Kaplan-Meier survival curves as early as 6 months for the primary composite endpoint consisting of cardiovascular death and time to first HF hospitalization.
- At four months compared to baseline, there was less worsening of HF symptoms and physical limitations compared to enalapril as measured by the KCCQ (p=0.0423).
- At four months, there were more improved patients with the Global Assessment, and fewer worsened patients for both NYHA and the Global Assessment for the LCZ696 group compared to the enalapril group (NYHA, p=0.0028; Global Assessment, p=0.0039).

Safety areas of interest such as hypotension, hyperkalemia, renal impairment, angioedema, and liver toxicity can be assessed in the 52 week period based on experience from the adult LCZ696 HF studies.

The study duration will provide 1 year (52 weeks) growth and safety data in growing children.

3.6 Rationale for choice of comparator

Enalapril has been chosen as the comparator as it is the most commonly used renin angiotensin system (RAS) blocker in children with HF (The Report on the Expert Group Meeting of Pediatric Heart Failure, London, 29 November 2010 (EMA/112144/2011)). Additionally, enalapril is considered the standard of care in the treatment of chronic heart failure in most geographic areas. Enalapril doses ranging from 0.1 to 0.5 mg/kg/day are used in the treatment of pediatric HF.

[redacted]

The dose of 0.4 mg/kg/day was the target dose in the "Enalapril in infants with single ventricle" study published (Hsu 2010), and is the target dose in the ongoing "The labeling of enalapril from neonates up to adolescents", or LENA Study (http://www.lena-med.eu).

In addition, enalapril has a twice daily dosing regimen similar to LCZ696. Two other commonly used ACEIs in pediatric HF are captopril and lisinopril. However captopril is typically dosed three times daily and lisinopril is typically dosed once daily.

3.7 Purpose and timing of interim analyses/design adaptations

In Part 1, a review of PK/PD and safety data will be performed for Group 1 and 2 after both doses (LCZ696 0.8 mg/kg and 3.1 mg/kg) are administered. For Group 3, this analysis will be conducted after both doses (LCZ696 0.4 mg/kg and 1.6 mg/kg) are administered.

The dosing of each corresponding age group can begin in Part 2 after the dose has been confirmed from Part 1 for that age group. Based on Part 1, these dose regimens may also be adjusted. To determine the LCZ696 dose for Part 2: (1) the exposure normalized to dose/body weight of pharmacologically active LCZ696 analytes (LBQ657, valsartan) will be compared between pediatric patients and adult HF patients; and (2) the exposure-response will be examined for neprilysin pharmacodynamic effect.

Interim efficacy analysis of the global rank endpoint

In Part 2 (Efficacy), an interim efficacy analysis and futility analysis is planned when at least 180 patients (at least 36 patients from each age group) have completed the study (i.e., reached a terminal endpoint or completed the 1 year study visit), and at least 40 patients have had an event in Category 1 or 2. This interim analysis will be done to allow for early stopping of the study in the event that efficacy is observed at the time of the interim analysis or in the event that the study is unlikely to demonstrate a benefit for patients.

In addition, an analysis of sparse PK data collected in a subset of patients in Part 2 Age Group 2, is planned (see Section 9.6 for details).

[redacted]

3.8 Risks and benefits

The study will assess the efficacy of LCZ696 in pediatric HF patients. To date no trial has demonstrated an outcome benefit of any pharmacotherapy in children with HF. Little progress has been made in improving the significant mortality and morbidity associated with symptomatic heart failure. In the 1980s, 1-year mortality rates in pediatric HF rates were 20%

[redacted]

to 30%, reaching 40% by 5 years. The advent of pediatric heart transplantation has decreased mortality in the first year after presentation but only where available (Hsu and Pearson 2009b).

The mortality and morbidity benefit of LCZ696 compared to the standard of care enalapril for the treatment of adult HF with reduced systolic function (HFrEF) is evident from the PARADIGM-HF study. Clinical trial data in adults demonstrate that LCZ696 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 LCZ696 studies. While the incidence rate of hypotension in study CLCZ696B2314 was higher for LCZ696 compared with enalapril, hypotension assessed as severe or serious was not higher in the LCZ696 group compared to the enalapril group. Also, 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 LCZ696 group compared to the enalapril group in study CLCZ696B2314.

In the PANORAMA-HF study, two patients in the high dose group (1.6 mg/kg) of Part 1 Age Group 3 experienced AEs of hypotension. While the risk for hypotension may be lower for this age group in Part 2 of the study where study drug will be up-titrated in a step-wise manner compared to the single, high-dose setting in Part 1, additional safety measures have been implemented in an effort to decrease the risk of, and to monitor for, hypotension in Part 2 Age Group 3 patients: (1) lower target dose compared to Age Groups 1 and 2 despite similar observed exposures adjusted for dose in Part 1; (2) smaller up-titration steps compared to Age Groups 1 and 2; (3) a 4 hour observation period following the initial dose at each dose level to monitor vital signs; and (4) an additional phone call at 3 days (+/- 1 day) after each initial dose level up-titration step in order to check for symptoms of hypotension.

Results of juvenile studies with valsartan in rats have identified kidney and bone as potential targets for adverse effects associated with LCZ696 administration. Renal changes observed in rats treated with valsartan are consistent with those observed for other compounds which interact with RAAS, and occurred as a result of valsartan administration during a critical period of renal development (i.e. completed by post-natal weeks 4-6 weeks) (Zoetis 2003). Corresponding renal development is complete in the human by ~35-36 weeks of gestation, occasionally extending to 44 weeks.

Results of juvenile rat studies with sacubitril demonstrated minimal bone changes that are considered possibly due to associated body weight reductions. These changes were not associated with any changes in bone strength, matrix or growth plate. These findings also did not adversely affect the health of the animal. The non-clinical findings described do not demonstrate safety findings that preclude studying LCZ696 in the proposed pediatric HF population.

In addition, neprilysin is one of multiple pathways involved in the clearance of amyloid β peptide from the brain and CSF. In a study in young cynomolgus monkeys, administration of LCZ696 for 2 weeks resulted in increased total cerebrospinal fluid levels of amyloid β 1-42, 1-40 and 1-38. In this study, there were no changes in amyloid β levels in brain tissue. There was also no evidence for brain amyloid β deposition and plaque formation in a 39-week study in cynomolgus monkeys with a dose of LCZ696 that was 6-fold higher than the dose used in the 2-week study.

[redacted]

In contrast to the non-clinical study, administration of LCZ696 400 mg once daily for 14 days in healthy subjects did not result in changes in cerebrospinal fluid concentrations of amyloid β 1-40 and 1-42, although there was an increase in amyloid β 1-38. The clinical relevance of the small increase in CSF Aβ1-38 observed with LCZ696 is unknown. These observations suggest that enzymes and disposition pathways other than neprilysin appear to be more important in clearance of CSF Aβ in humans. There was also no increased incidence of cognition- or dementia-related AEs in the LCZ696 clinical program with up to 5 year LCZ696 exposure in the PARADIGM-HF study. The clinical implication of pharmacological changes in CSF amyloid β metabolism is unknown (Ryman 2014). Increased CSF amyloid β levels found in Down's syndrome patients (Schupf 2002) and associated with specific familial Alzheimer's disease mutations are not associated with dementia symptoms until late in life (> 40 – 50 years old) (Wang 2006).

Given the significant morbidity and mortality of pediatric HF patients and the context of the current data and knowledge of this issue, the benefit risk assessment is considered to be positive. To mitigate potential risks in pediatric study participants, safety parameters will be monitored closely, and these parameters will include vital signs, physical exam (including height and weight), biomarkers, hematology, blood chemistry, urinalysis tests and ECG.

4 Population

The study population consists of pediatric HF patients 1 month to < 18 years, inpatient or outpatient, with systemic left ventricle systolic dysfunction (LVEF ≤45% or a fractional shortening ≤ 22.5%). For inclusion criteria details regarding LVEF and fractional shortening, refer to Section 4.1. The study will enroll at least 18 patients in Part 1 and 360 patients in Part 2 (Efficacy) at centers worldwide. With an expected screen failure rate of 35% for both Part 1 (PK/PD) and Part 2 (Efficacy), it is estimated that approximately 46 patients will have to be screened for Part 1 and 554 patients will have to be screened for Part 2.

For Part 1, at least 18 subjects will be divided across three groups based on age: **Group 1**: 6 to < 18 years (6 observations for the LCZ696 0.8 mg/kg dose and 6 observations for the LCZ696 3.1 mg/kg dose); **Group 2**: 1 to < 6 years (6 observations for the LCZ696 0.8 mg/kg dose and 6 observations for the LCZ696 3.1 mg/kg dose); **Group 3**: 1 month to < 1 year (approximately 4 observations for LCZ696 -0.4 mg/kg dose and approximately 4 observations for the LCZ696 1.6 mg/kg dose). Eligible patients will participate in the LCZ696 0.8 mg/kg and 3.1 mg/kg doses in Groups 1 and 2 and in the LCZ696 0.4 mg/kg and 1.6 mg/kg doses in Group 3. Patients who do not participate in the LCZ696 3.1 mg/kg (Group 1 or 2) or 1.6 mg/kg (Group 3) dose will be replaced. To ensure that patients are enrolled in both high and low end of the 6 to < 18 years of age group, approximately 50% patients will be enrolled who are 6 to 11 years of age in Group 1.

For Part 2, patients will be stratified by age (Age Groups 1, 2 and 3) and NYHA/Ross class group (Class I/II, Class III/IV) at randomization to ensure a balanced distribution of treatment allocation within each age group. Patients who discontinue from Part 2 will not be replaced.

[redacted]

4.1 Inclusion criteria

Patients eligible for inclusion in this study (Part 1 and Part 2) must fulfill all of the following criteria:

1. Written informed consent by parent(s)/legal guardian(s) for the pediatric patient must be obtained before any study-specific assessment is performed.* A consent or assent may also be required for some patients depending upon their age and local requirement.
2. Male or female, inpatient or outpatient, 1 month (≥44 weeks post-conception for pre-term infants) to < 18 years of age.
3. Chronic heart failure resulting from left ventricular systolic dysfunction, and receiving chronic HF therapy (if not newly diagnosed)..
4. NYHA classification II-IV (older children: 6 to less than 18 year old) or Ross HF classification II-IV (younger children: less than 6 year old) any time prior to screening. [Note: Age Group 1 patients may be NYHA class I at time of screening if there is a prior history of NYHA class II-IV. Age Group 2 patients must be Ross class II or higher at time of randomization].
5. Systemic left ventricular ejection fraction (EF) ≤ 45% or fractional shortening ≤22.5% (assessed by echocardiogram, MRI, MUGA or left ventricular angiogram within 1 month before patient begins Part 2). [Note: The study will target enrollment of approximately 80% patients with a systemic left ventricular ejection fraction (EF) ≤ 40% or fractional shortening ≤20% for Part 2 only].
6. Biventricular physiology with systemic left ventricle.
7. For Part 1 PK/PD, patients must be treated with an ACEI or ARB prior to screening. For Part 1 PK/PD, patients in Group 1 and 2 must be currently treated with a daily dose equivalent of at least enalapril 0.2 mg/kg (Table 3-1) prior to the LCZ696 3.1 mg/kg single dose assessment. For Part 1 PK/PD, patients in Group 3 must be currently treated with a daily dose equivalent of at least enalapril 0.1 mg/kg (Table 3-1) prior to the LCZ696 1.6 mg/kg single dose assessment
8. HF etiologies include: Congenital Cardiac Malformation with systemic ventricular systolic dysfunction; Idiopathic Cardiomyopathy; Familial/Inherited and/or Genetic Cardiomyopathy; History of Myocarditis; Neuromuscular Disorder; Inborn Error of Metabolism; Mitochondrial Disorder; Acquired (Chemotherapy, Iatrogenic, Infection, Rheumatic, Nutritional); Ischemic (e.g. Kawasaki Disease, post-operative); Left ventricular noncompaction

*Assessments of HF (e.g. ECHO) in patients that are done according to current local institutional/hospital standard protocol or that are part of routine clinical care can be used to support patient screening and may have taken place before signing informed consent. An informed consent must be obtained from a patient once they become 18 years old during the study.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study (Part 1 and Part 2). No additional exclusions may be applied by the Investigator, in order to ensure that the study population will be representative of all eligible patients.

[redacted]

1. Patients with single ventricle or systemic right ventricle
2. Patients listed for heart transplantation as United Network for Organ Sharing (UNOS) Status 1A or hospitalized waiting for transplant while on inotropes or with ventricular assist device at time of entry into the study
3. Sustained or symptomatic dysrhythmias uncontrolled with drug or device therapy
4. For Part 2 only, patients that have had cardiovascular surgery or percutaneous intervention to palliate or correct congenital cardiovascular malformations within 3 months of the screening visit. Patients anticipated to undergo corrective heart surgery during the 12 months after entry into Part 2.
5. Patients with unoperated obstructive or severe regurgitant valvular (aortic, pulmonary, or tricuspid) disease, or significant systemic ventricular outflow obstruction or aortic arch obstruction
6. Patients with restrictive or hypertrophic cardiomyopathy
7. For Part 2 only, active myocarditis (diagnosed with presumed or acute myocarditis within 3 months of enrollment)
8. Symptomatic hypotension or blood pressures (BPs) below the calculated 5th percentile systolic BP (SBP) for age at screening visit and as described in Appendix 4
9. Renal vascular hypertension (including renal artery stenosis)
10. Severe pulmonary hypertension (defined by pulmonary vascular resistance (PVR) index >6 Wood units-m^2) unresponsive to vasodilator agents (such as oxygen, nitroprusside or nitric oxide). Note measurement of PVR is not a requirement for study eligibility
11. History or current clinical evidence of moderate-to severe obstructive pulmonary disease or reactive airway diseases (e.g. asthma)
12. Serum potassium >5.3 mmol/L at Visit 1 or at Visit 301
13. Patients with significant renal (eGFR calculated using the modified Schwartz formula < 30% mean GFR for age, Appendix 10, Table 22-1); 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)
14. Concurrent terminal illness or other severe disease (e.g. acute lymphocytic leukemia) or other significant laboratory values that, in the opinion of the Investigator, precludes study participation or survival
15. Patients with a history of angioedema
16. Patients with allergy or hypersensitivity to ACEI or ARB
17. 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
18. Pregnant or nursing (lactating) women
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of investigational drug and for 7 days after study drug discontinuation. Highly effective contraception methods include:

[redacted]

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject and if acceptable by the local regulation). 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 investigational drug. 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 (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 investigational drug

20. Use of other investigational drugs within 5 half-lives or within 30 days of enrollment, whichever is shorter
21. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes
22. Any major solid organ transplant recipient
23. History of malignancy of any organ system, treated or untreated, within the past year with a life expectancy less than 1 year
24. Any advanced severe or unstable disease that may interfere with the primary or secondary study outcome evaluations or put the patient at special risk
25. Any other medical conditions that may put the patient at risk or influence study results in the Investigator's opinion, or that the Investigator deems unsuitable for the study
26. Patient breastfed by a mother taking ACEI

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

The sponsor will provide the following study drugs:

Part 1 - PK/PD treatment epoch

All eligible patients that enter Part 1 will receive LCZ696.

The LCZ696 study medication is available as granules or liquid formulation based on age, weight, dosing, and patient's ability to take study medication (Pharmacy Manual).

The following study drug will be provided:

[redacted]

- LCZ696 3.125 mg granules (packaged in capsules containing 4 or 10 granules)

Sites will be provided with study drug to administer for single dose Part 1 PK/PD to all eligible patients at that site. LCZ696 granules can be ingested after removing from the capsule. The liquid formulation can be compounded at the site / pharmacy [Pharmacy Manual].

Patients will be instructed to not use an ACEI for 36 hours after taking the single dose of LCZ696 to minimize the potential risk of angioedema due to overlapping ACEI-NEP inhibition. Patients should not use an ARB or renin inhibitor on the day of the single dose PK assessment visit.

At the completion of the single dose PK assessment visit (Visit 101 and/or 201), patients will be provided with open-label enalapril or will be instructed to resume their usual care as deemed necessary by the Investigator. The open-label enalapril will be obtained from a local commercial source by the site and provided to the patient. If needed, based on the patient's age and/or inability to swallow tablets, liquid enalapril may be used. The liquid enalapril is prepared at the site's pharmacy as per local regulations, and can be commercially sourced such as Epaned (if available). Patients receiving enalapril liquid formulation must return to the site for resupply at intervals dependent on the storage life of enalapril liquid formulation (every 1 month; or every 2 months if Epaned (enalapril) which has 2 month shelf life, is available and used).

Part 2 (Efficacy) - Randomized treatment epoch

The LCZ696 study medication is available in three formulations: tablets, granules (mini-tablets) or liquid formulation (if patient cannot swallow granules) (refer to Table 5-1).

The enalapril study medication is available in two formulations: tablets or liquid formulation (refer to Table 5-2).

Patients will be randomized to initiate study medication at dose levels 1 or 2 for Groups 1 and 2, and 1x or 2x for Group 3, depending on whether they are ACEI/ARB naïve or depending on their ACEI/ARB dose prior to randomization (refer to Table 3-4, Table 3-5, Table 3-6). The study medication will be titrated at subsequent visits to the target dose. In addition to study medication, patients will continue to take optimal background HF therapy as considered appropriate by the Investigator and in accordance with standard HF treatment guidelines. The exception is that ACEI or ARB will be replaced by study drug. The use of open-label ACEI, ARB, or renin inhibitor in addition to randomized study drug is strictly prohibited.

The following study drugs will be provided for Part 2 (Efficacy):

- LCZ696 12.5mg (bottle will contain capsules, each capsule contains 4 granules of LCZ696 3.125mg)
- Placebo to match LCZ696 12.5mg (bottle will contain capsules, each capsule contains 4 granules of LCZ696 3.125mg matching placebo)
- LCZ696 31.25mg (bottle will contain capsules, each capsule contains 10 granules of LCZ696 3.125mg)
- Placebo to match LCZ696 31.25mg (bottle will contain capsules, each capsule contains 10 granules of LCZ696 3.125mg matching placebo)
- LCZ696 50mg tablets

[redacted]

- Placebo to match LCZ696 50mg tablets
- LCZ696 100mg tablets
- Placebo to match LCZ696 100mg tablets
- LCZ696 200mg tablets
- Placebo to match LCZ696 200mg tablets
- Enalapril 2.5mg tablets
- Placebo to match enalapril 2.5mg tablets
- Enalapril 5mg tablets
- Placebo to match enalapril 5mg tablets
- Enalapril 10mg tablets
- Placebo to match enalapril 10 mg tablets

All study medications will be supplied in bottles or blister cards. Capsules of LCZ696/matching placebo containing 4 granules or 10 granules per capsule will be provided for oral use. The granules can be swallowed (after the removal of the outer capsule) by the patient. LCZ696/matching placebo liquid formulation will be compounded by the site / pharmacy [Pharmacy Manual]. Patients taking < 8 granules (< 25 mg) for a dose will use the liquid formulation. The appropriate aliquot of liquid medication corresponding to the patient's dose will be given to the patient. Appropriate oral syringes will be provided to facilitate study drug administration as a liquid.

Sufficient medication will be provided for the treatment according to the study protocol (Table 5-1 and Table 5-2). 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 patient.

Patients taking the liquid formulation of LCZ696/matching placebo or enalapril/matching placebo must return to the site every 4 weeks for resupply. The enalapril or enalapril placebo - liquid formulation will be prepared at the site / pharmacy based on the patient's age and ability to swallow adult tablets. The site personnel or the pharmacy at the sites is responsible for preparing enalapril liquid formulation (Pharmacy Manual). Given the burden of traveling to the site for study visits for patients and families, the parent/caregiver can come to the site without the patient for dispensation of study drug. Delivery of study drug to the patient can also be used where possible and allowed per local regulations.

Instructions for preparation of the liquid study drugs are provided in the Pharmacy Manual.

Table 5-1 LCZ696 drug supply for Part 1 (PK/PD) and Part 2 (Efficacy)

Study drug – Part 1 PK/PD open-label	**Strength**	**Formulation**
LCZ696	3.125 mg	Granules packaged in capsules of 4 or 10 granules in bottle
Study drug – Part 2 Efficacy double blind	**Strength**	**Formulation**
LCZ696 or matching placebo	3.125 mg	Granules packaged in capsules of 4 or 10 granules in bottle

[redacted]

Study drug – Part 1 PK/PD open-label	Strength	Formulation
LCZ696 or matching placebo	50 mg	Tablets in bottle
LCZ696 or matching placebo	100 mg	Tablets in bottle
LCZ696 or matching placebo	200 mg	Tablets in bottle

Table 5-2 Enalapril drug supply for Part 2 (Efficacy)

Study drug – Part 2 Efficacy double blind	Strength	Formulation
Enalapril or matching placebo	2.5 mg	Tablets in bottle/blister
Enalapril or matching placebo	5 mg	Tablets in blister
Enalapril or matching placebo	10 mg	Tablets in blister

Part 1:

The LCZ696 study medication is available as granules or liquid formulation based on age, dosing, and patient's ability to take study medication (Pharmacy Manual).

Part 2:

The LCZ696 study medication is available in three formulations: tablets, granules (mini-tablets) or liquid formulation (refer to Pharmacy Manual) (if patient cannot swallow granules) (refer to Table 5-1).

The enalapril study medication is available in two formulations: tablets or liquid formulation.

All pediatric formulations of study medication (LCZ696 granules or liquid, enalapril liquid) will be made available to all age groups. The adult tablet formulations of LCZ696 and enalapril will be available to patients based on the patient's dosing and ability to swallow adult tablets (refer to Pharmacy manual).

Dispensing of medication to the subjects will be controlled by an Interactive Response Technology (IRT) system.

5.1.2 Additional treatment

No additional treatment beyond investigational drug (LCZ696) and active comparator drug (enalapril) are included in this trial.

5.2 Treatment arms

Part 1 (PK/PD): All patients will receive open-label LCZ696. Patients completing Part 1 and who are willing to participate in Part 2 will be provided open-label enalapril (or their standard of care HF regimen) by the study site.

Part 2 (Efficacy): Patients are assigned to one of the following two double blind treatment arms in a ratio of 1:1 at the randomization Visit 401:

- LCZ696
- Enalapril

[redacted]

5.3 Treatment assignment and randomization

At Visit 401, all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. Patients will be stratified by age group (Age Groups 1, 2 and 3) and NYHA/Ross class group (Class I/II, Class III/IV) at randomization to ensure a balanced distribution of treatment allocation within each age strata. The Investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients/subjects and Investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The randomization scheme for patients will be reviewed and approved by a member of the Randomization Group.

5.4 Treatment blinding

Part 1 (PK/PD) involves open-label LCZ696.

Part 2 (Efficacy) is a randomized, double-blind, active controlled study. Patients, Investigator and staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock using the following methods:

- Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone involved in the study with the following exceptions:

1. The independent and unblinded statistician, programmer and data personnel who are involved in preparing safety and efficacy interim analysis reports for the DMC. These personnel will not be involved in any other trial conduct related activities
2. The DMC members
3. An unblinded team, which is not involved in the conduct of the study, will evaluate the steady-state sparse PK blood samples collected from approximately 24 patients (approximately half of whom are expected to be randomized to LCZ696) in Part 2 Group 2 (Section 9.5.1).
4. [redacted]

- A double-dummy design is used because the identity of the investigational treatment cannot be disguised, as the drug products are visibly different

[redacted]

- The identity of the treatments will be concealed by the use of investigational treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor

Unblinding will only occur in the case of patient emergencies (Section 5.5.9), at the time of interim analyses (Section 9.6), and at the conclusion of the study.

The randomization codes associated with patients/subjects from whom Part 2 PK samples are taken will be disclosed to PK analysts who will keep Part 2 PK results confidential until data base lock.

An assessment will be done by the appropriate site personnel and the Medical Lead (or designee) for any patient whose treatment code has been broken inadvertently or for any nonemergency reason to assess whether or not study treatment/investigational treatment should be discontinued and, if applicable, whether the patient can continue in the trial.

5.5 Treating the patient

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

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the Investigator. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number by the Investigator. The Investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the CRF book with a matching Subject Number from the EDC system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the Screening epoch Study Disposition case report form (CRF).

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique randomization number is printed on each part of this label which corresponds to one of the two treatment arms and dose level. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, Investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient’s unique subject number.

[redacted]

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

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

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

At the conclusion of the study, and as appropriate during the course of the study, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

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

5.5.3.2 Handling of additional treatment

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

The patient should be receiving optimal standard of care medical and surgical treatment for their HF and comorbidities. In Part 2 of the study, study drug (LCZ696 vs. enalapril) will be used instead of ACEI or ARB.

5.5.4 Instructions for prescribing and taking study treatment

Novartis will supply the Investigators with all study medications required for the course of the study. Patients will be provided with bottles and blisters containing study drug corresponding to their assigned treatment arm and dose level, sufficient to last until the next scheduled visit.

Part 1:

- LCZ696 granules: 3.125 mg (packaged in capsule containing either 4 or 10 granules) supplied in a bottle

[redacted]

- LCZ696 liquid formulation (compounded by site / pharmacy) (refer to Pharmacy Manual)

Part 2:

Patients will be taking the following as provided in blinded packaging:

- LCZ696 tablets: 50 mg or matching placebo, 100 mg or matching placebo, 200 mg or matching placebo
- LCZ696: 3.125 mg granules or matching placebo, supplied in a bottle containing capsules with granules. Each capsule will contain either 4 or 10 granules
- LCZ696 liquid formulation (compounded by site / pharmacy) (refer to Pharmacy Manual) Enalapril liquid formulation(compounded by site / pharmacy) (refer to Pharmacy Manual) or matching placebo, 2.5 mg tablets or matching placebo, 5 mg tablets or matching placebo, 10 mg tablets or matching placebo

The above Part 2 supplies are provided in blinded packaging.

Details regarding preparation of liquid formulation for LCZ696 and enalapril are provided in the [Pharmacy Manual].

For Part 1 (PK/PD), the site will provide the single dose open-label LCZ696 to the patient for administration. For Part 2 (Efficacy), patients 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. The LCZ696 granules can be administered as solid or mixed with soft food. LCZ696 can also be administered as a liquid form [Pharmacy Manual]. If the patient misses taking any study drug dose, s/he should take it as soon as possible, unless it is almost time for the following scheduled dose. In this case, the patient should skip the missed dose and return back to his/her regular study drug administration schedule.

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

The Investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the Investigator if he/she is unable for any reason to take the study treatment as prescribed.

5.5.5 Permitted dose adjustments and interruptions of study treatment

The study drug is up-titrated every 2 weeks as tolerated to target dose (level 4 for Group 1 and 2, and 4x for Group 3) as outlined in (Table 3-5 and Table 3-6) based on the safety monitoring criteria (Table 3-3). Additional safety monitoring will be required for Age Group 3 patients with each initial dose level up-titration. See Appendix 13 for details. 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/down-titration throughout the study based on Investigator judgment.

[redacted]

For patients who are unable to tolerate the protocol-specified dosing scheme, dose level adjustments and interruptions of study treatment are permitted in order to keep the patient on study drug. The following guidelines should be followed:

- The Investigator should adjust doses of concomitant medications if it is believed that they are the most likely cause of an adverse effect
- If adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern, the Investigator may down titrate to the next lower study drug dose level down (Table 3-5 and Table 3-6) to temporary or permanent discontinuation of study drug
- The patient should be rechallenged with 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 temporarily or permanently discontinued, then the patient should continue to attend the study visits and be followed until the completion of the study

Patients may be seen at any time for unscheduled visits during the randomized treatment epoch for reevaluation 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. Local laboratory assessments of serum sodium, potassium, creatinine, and eGFR (calculated based on the modified Schwartz formula (Schwartz 2009) will be utilized. Refer to Appendices 15, 16, and 17 for treatment guidelines for renal dysfunction, management of hypotension and hyperkalemia, respectively.

Adjustment of study drug dose level

During the double-blind treatment epoch, down titration of the study drug at any time is allowed based on the safety and tolerability criteria defined in (Table 3-3). If down titration is necessary, the patient should be down titrated to a lower study drug dose level (Table 3-5 and Table 3-6).

The Investigator may down titrate to the next lower study drug dose level. If the tolerability issues are not alleviated despite down titration by multiple dose levels, the Investigator may temporarily discontinue study drug. Once the patient's condition is stable, s/he can be up-titrated to the next higher dose level every 1 to 4 weeks in an attempt to bring back the patient gradually to the target study drug dose level (dose level 4 for Group 1 and 2, and 4x for Group 3). The Investigator may choose the next dose level for down- or up-titration according to his or her judgment (Table 3-5 and Table 3-6).

All changes should be recorded on the DAR CRF. In addition, IRT should be contacted to register any changes in the patient'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

Patients who have temporarily discontinued study drug should be restarted as soon as possible as deemed appropriate by the Investigator. The Investigator should restart the patient on the study drug at the most appropriate dose level (Table 3-5 and Table 3-6) as per the Investigator's clinical judgment. Patients must discontinue their ACEI medication(s) 36 hours prior to re-starting study drug to allow for an ACEI-free washout period. If the patient does not tolerate

[redacted]

the newly restarted study drug dose level, s/he may be down titrated again (if appropriate) or the study medication may be temporarily discontinued again.

Patients restarted on the study drug will retain their original randomization and study identification numbers.

Investigators may discontinue the study drug due to serious or intolerable AEs suspected to be causally related to study drug. If study drug is discontinued for any reason, the exact time and date of study drug discontinuation must be recorded on the DAR CRFs. In addition, patients who discontinue study drug should continue to be followed at all study visits as defined in the protocol (Table 6-1 and Table 6-2).

The use of an open-label ACEI, ARB or a renin inhibitor during a period in which the patient may be off study drug is discouraged. However, if a patient off study drug has started open-label treatment with an ACEI, the ACEI must be discontinued ≥36 hours prior to restarting study drug. Patients 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 started. These changes must be recorded on the DAR and Concomitant Medication CRFs.

If the patient is discovered to be pregnant during the course of the study, the patient should discontinue study drug immediately. Meanwhile, the patient should continue to attend scheduled study visits.

Refer to (Section 6.5.7 and Section 7.7) for further details on pregnancies and reporting guidelines.

5.5.6 Rescue medication

If in the opinion of the Investigator, the patient does not tolerate the assigned study medication, the Investigator should consider whether non disease-modifying medication (e.g. CCBs, diuretics, α-blockers) can be reduced to rectify the situation.

Guidance on handling renal dysfunction, hypotension, and hyperkalemia are provided to Investigators in (Appendix 3, Appendix 4, and Appendix 5) respectively.

The Investigator may prescribe any medications and/or supportive care during the study based on clinical needs. Use of rescue medication and/or supportive care must be recorded on the Concomitant medications CRF.

5.5.7 Concomitant medication

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

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 randomizing a patient or allowing a new medication to be started.

[redacted]

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-3 is NOT allowed while taking study drug after randomization due to safety reasons. If the medications displayed in Table 5-3 must be used, study drug must be discontinued and the actions specified below must be taken.

Table 5-3 Prohibited treatment by medication class

Medication	Action taken
Any ACEI	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 patient 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 should be stopped 36 hours prior to starting open-label ACEI. Study drug should be stopped prior to starting open-label ARB or renin inhibitor.

Similarly, if study drug is to be restarted, the open-label ACEI should be stopped >36 hours prior to resuming study drug. Open-label ARB or renin inhibitor should be stopped prior to resuming study drug.

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the Investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The Investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

It is the Investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The Investigator will provide:

- protocol number
- study drug name (if available)
- patient number

[redacted]

In addition, oral and written information to the subject must be provided on how to contact the investigator's backup in cases of emergency, or when the investigator is unavailable, to ensure that un-blinding can be performed at any time.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol.

Continuing care should be provided by Investigator and/or other caring physician. The patient should be placed on an ACEI or ARB for HF treatment as determined by the caring physician.

5.6.2 Discontinuation of study treatment

Patients may voluntarily discontinue study treatment for any reason at any time.

The emergence of the following circumstances will require permanent study drug discontinuation:

- Withdrawal of informed consent
- Investigator believes that continuation would be detrimental to the patient's well-being
- Suspected occurrence of angioedema; a patient with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the Investigator

The emergence of the following circumstances will require temporary or permanent discontinuation (study drug may be restarted once these circumstances no longer exist):

- Use of an open-label ACEI, ARB or renin inhibitor
- Pregnancy and post-pregnancy during lactation period (Section 7.7)

Study drug may be discontinued at the Investigator's discretion if any of the following occurs:

- Any severe or suspected drug-related AE
- Any other protocol deviation that results in a significant risk to the patient's safety

The appropriate personnel from the site and Novartis will assess whether study drug should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

If permanent discontinuation of study treatment occurs and the patient/parents/guardians have not withdrawn consent, the patient should NOT be considered withdrawn from the study. The patient should return to the clinic as soon as possible, after discontinuation of study drug, for a study treatment discontinuation visit. Treatment discontinuation visit assessments detailed in the "unscheduled treatment discontinuation visit" (UNS) in Table 6-1 and Table 6-2 should be completed and recorded in the CRF. The Investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the Dosage Administration CRF.

After study treatment discontinuation, the following minimum data should to be collected at clinic visits or via telephone visits:

- new / concomitant treatments

[redacted]

- adverse events/serious adverse events

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, caregiver/parent, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

The Investigator must also contact the IRT to register the patient's discontinuation from study treatment.

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9.

5.6.3 Withdrawal of informed consent

Parents/guardians may voluntarily withdraw consent for their child to participate in the study for any reason at any time. Withdrawal of consent occurs only when a parent/guardian:

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

In this situation, the Investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the parent/guardian's decision to withdraw his/her consent for their child and record this information in the CRF.

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in Table 6-1 and Table 6-2.

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

For 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 and Rest of World: 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. Any child's request to be withdrawn from the study should be respected and discussed in detail with parents/guardians and the local Investigator before acting upon the request.

5.6.4 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator should show "due diligence" by

documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

An assessment of the child's well-being must be made if the family is non-compliant with study visits. Appropriate referral to local social services should be considered based on safety concerns for the child.

5.6.5 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. Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely discontinued patient. 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 patient's interests. The Sponsor will be responsible for informing the Investigator, the national competent authority and Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial as per local regulations. In some countries and based on local regulations, the sponsor may delegate to the Investigator the duty to inform the ECs about the early termination.

6 Visit schedule and assessments

Table 6-1 and Table 6-2 lists all of the assessments and indicates with an "x" when the visits are performed.

After identifying a potential patient, an informed consent form (ICF) and assent (if applicable) must be signed by the parent(s)/legal guardian(s) and by the patient (as applicable) before performing any study-related procedures that are not considered standard of care for pediatric HF patients at that site. Procedures that are part of a site's standard of care for a pediatric patient may pre-date the signed ICF. The AE and SAE reporting period will begin at the time the ICF is signed.

Part 1 of the study consists of Visits 1 to 299. After screening (Visit 1), there are two LCZ696 single dose PK/PD assessments (Visit 101 and Visit 201). There are telephone visits (Visit 102 and 202) followed by a sequence of telephone visits monthly in between the in person visits every 3 months (Visits 103 to 120, Visits 203 to 220).

Patients taking open-label liquid enalapril should obtain study drug from the site monthly until Part 2 begins (due to the 1 month storage life of liquid enalapril). If the patient is taking Epaned liquid enalapril that has a 2 month storage life, patients must obtain open-label enalapril every 2 months until Part 2 begins. If the parent/caregiver comes to the site without the patient to pick up the open label liquid enalapril, a telephone call to the patient (≥ 6 years old) can be used in conjunction with the parent/caregiver visit. At the telephone visits for Part 1, the following assessments **will not be** performed: vital signs, abbreviated physical exam, weight, abbreviated laboratories and urine pregnancy.

Visit 199 and 299 are end of LCZ696 PK/PD first dose visit and second dose visit, respectively. For the patient that only participates in the LCZ696 PK/PD first dose, the Visit 199 may occur

[redacted]

on the same day as Visit 301, if patient is going to participate in Part 2. For the patient that participates in the LCZ696 PK/PD first and second PK doses, Visit 199 may occur on the same day as Visit 201. For the patient that only participates in the LCZ696 PK/PD second dose, Visit 299 may occur on the same day as Visit 301, if patient is going to participate in Part 2. Visit 301 is a pre-randomization screening visit for Part 2.Part 2 of the study consists of Visits 301 to 499. Visit 401 (randomization) will be considered the reference visit for all study visits during Part 2 (Efficacy). Regardless of the occurrence of any unscheduled visits, scheduled visits should be performed within the specified timeframe in relation to Visit 401.

Patients must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients/subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

After Visit 406 (12 weeks), patients using the adult formulation will be seen at 12 week intervals. The liquid formulation of study drug (LCZ696/matching placebo or enalapril/matching placebo) and LCZ696 granules have a limited shelf life. Therefore, Visits 407, 408, 410, 411, 413, 414 are visits intended primarily to permit dispensation of study drug for patients who are using blinded liquid enalapril/matching placebo and/or LCZ696/matching placebo granules. Given the burden of traveling to study visits for patients and families, the parent/caregiver can come to the site for dispensation of study drug. If the parent/caregiver comes to the visit without the patient, a telephone call to the patient (≥ 6 years old) can be used in conjunction with the parent/caregiver visit for the visit assessments (all can be performed verbally). Delivery of study drug to the patient can also be used where possible and allowed per local regulations. At these visits (407, 408, 410, 411, 413, and 414), the following assessments are performed: concomitant medications, AE/SAEs, dosage administration record, study medication compliance, endpoint collection (for additional details refer to Table 6-2). Urine pregnancy testing will be done for females of childbearing potential (for additional details see Table 6-2). IRT will be contacted if study medications are dispensed.

Visits 407, 408, 410, 411, 413, 414 are telephone visits for patients using the adult formulation of study drug. The assessments listed for these visits (Table 6-2) can be performed by telephone.

Patients who prematurely discontinue the investigational treatment will remain in the study and should undergo all the assessments illustrated in Table 6-2. If a patient/parent(s)/legal guardian(s) withdraws from participation in the study, refuses to return for study assessments or is unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone and/or other measures to determine the patient's survival status 52 weeks from randomization (Visit 499).

Patients will be contacted for safety evaluations during the 30 days following the last administration of study treatment.

[redacted]

Table 6-1 Part 1 Assessment Schedule

Epoch	Screening	Period 1 First Dose PK					Period 2 Second Dose PK					Pre-Randomization
Visit	**1**	**101**	**102 (telephone visit)**	**103 to 120***	**UNS PK/PD**	**199****	**201**	**202 (telephone visit)**	**203 to 220***	**UNS PK/PD**	**299****	**301** (Part 2 Screening)**
Week	♦	♦	♦				♦	♦				**up to -3**
Obtain Informed Consent (parent (s)-legal guardian (s)/consent-assent (patient, as applicable)[13]	x, S											x, S
Demography	x											x[1]
Inclusion/Exclusion Criteria	x											x
Medical History	x											x[1]
Pediatric Heart Failure History	x											x[1]
Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x
Alcohol & Smoking History	x											x[1]
Vital Signs (BP and pulse)	x	x[2]		x[9]	x[2]	x	x[2]		x[9]	x[2]	x	x
Height	x					x					x	x
Weight[3]	x	x		x[9]	x	x	x		x[9]	x	x	x
Head Circumference (≤ 3 years old)	x					x					x	x
Physical Examination (complete)	S											S
Physical Exam (abbreviated)		S		S[9]	S	S	S		S[9]	S	S	
ECG	x					x					x	x
ECHO, LVEF or fractional shortening measurement[4]	x											x
Urinalysis	x					x					x	x
Serum/Urine Pregnancy Test[5]	x	x		x[9]	x	x	x		x[9]	x	x	x
Complete Laboratories[6]	x					x					x	x
Abbreviated Laboratories[7]		x		x[9]	x		x		x[9]	x		
PK Blood Samples		x			x		x			x		
Plasma Biomarkers/PD[8]		x			x		x			x		

[redacted]

Epoch	Screening	Period 1 First Dose PK					Period 2 Second Dose PK					Pre-Randomization
Visit	**1**	**101**	**102 (telephone visit)**	**103 to 120***	**UNS PK/PD**	**199****	**201**	**202 (telephone visit)**	**203 to 220***	**UNS PK/PD**	**299****	**301** (Part 2 Screening)**
Week	♦	♦	♦				♦	♦				**up to -3**
Urine cGMP[8]		x			x		x			x		
NYHA/ Ross Classification	x					X					x	x
AEs/SAEs		x	x	x	x	x	x	x	x	x	x	
Dosage Administration Record		x					x					
Study Medication Compliance[10]			S[11]	S		S		S[11]	S		S	
Contact IRT	x	x			x	x	x			x	x	x
Dose Open-Label LCZ (single dose)		x			x		x			x		
Dispense Open-Label Enalapril[12]		x		x	x		x		x	x		
Screening Disposition (Parts 1 and 2)	x											x
Part 1 Disposition						x					x	

UNS PK/PD = Unscheduled PK/PD visit. Only one unscheduled visit either in Period 1 or Period 2 should be conducted.

S = assessment to be recorded on source documentation only

♦ Visit 101 will occur approximately up to three weeks after Visit 1. Visit 201 may occur approximately up to three weeks after Visit 1 if patient is directly going to second dose PK assessment from Visit 1. The Visit 102/202 are telephone visits that occur 2 weeks after completion of Visit 101/201 respectively.

* Visits 103 to 120 / 203 to 220 are combination of in person and telephone visits. Telephone visits will occur monthly between the every 3 month in person visits. At these telephone visits the following assessments **will not be** performed: vital signs, abbreviated physical exam, weight, abbreviated laboratories and urine pregnancy

** For the patient that participates in the second PK/PD dose, Visit 299 may occur on the same day as Visit 301, if the patient is going to participate in Part 2. For the patient that only participates in the first dose PK/PD assessment, the Visit 199 may occur on the same day as Visit 301, if the patient is going to participate in Part 2. If the patient participates in both first and second PK/PD doses Visit 199 may occur on the same day as Visit 201.

[1] Demography, medical history, pediatric HF history alcohol & smoking history are only obtained at Visit 301 for patients who did not participate in Part 1.

[2] Patients who have PK done at Visit 101/201/ unscheduled PK/PD will have vital signs (blood pressure and heart rate/pulse) collected at 0, 30 min, 1 hr, 2 hrs, 3 hrs, 4 hrs, 5 hrs, 6 hrs, 7 hrs, 8 hrs, 9 hrs, 10 hrs, 11 hrs, 12 hrs, 18 hrs and 24 hours post-dose. Vital signs at 11 hrs, 12 hrs and 18 hrs are optional unless the patient physically stays on-site. The 24-hr post dose vital signs will be measured if the patient either stays on-site or returns to the site the next day.

[3] Weights are measured for safety and for dose administration at V101 and/or V 201 or UNS PK/PD (if this visit occurs).

[4] For Part 1, patients are to meet inclusion criteria regarding ECHO, LVEF or fractional shortening measurement (i.e. Systemic left ventricular ejection fraction (EF) ≤ 45% or fractional shortening ≤22.5%), by history at any time prior to screening (V1). If there is no history of LVEF or fractional shortening measurements an ECHO can be performed at screening (Visit 1). (see Section 4.1, Inclusion criteria).

[redacted]

Epoch	Screening	Period 1 First Dose PK					Period 2 Second Dose PK					Pre-Randomization
Visit	1	101	102 (telephone visit)	103 to 120*	UNS PK/PD	199**	201	202 (telephone visit)	203 to 220*	UNS PK/PD	299**	301** (Part 2 Screening)
Week	♦	♦	♦				♦	♦				up to -3

[5] For child bearing potential females (CHBP) only. Urine pregnancy test is analyzed locally and done at all visits on all female patients ≥11 years of age and all female patients who are <11 years of age if they are menstruating. In addition, a serum pregnancy test is performed and analyzed locally at Visit 1 and Visit 301.

[6] Complete laboratory evaluations will be performed by local lab for Part 1.

[7] Abbreviated laboratories will be collected and sent to the local lab at specified visits for all patients. Abbreviated laboratories consist of sodium, potassium, creatinine, eGFR (modified Schwartz formula). Abbreviated laboratories may be performed at any visit based on the Investigator's clinical judgement. At Visit 101, 201 or/and UNS PK/PD (if occurs) the abbreviated labs will be collected at the end of the visit.

[8] At Visit 101, 201, or/and UNS PK/PD (if this visit occurs), samples will be collected for plasma NTproBNP, plasma and urine cGMP, and plasma BNP. Central laboratory will be used for these biomarkers.

[9] For Visits 103 -120 / 203 – 220 vital signs, abbreviated physical exam, weight, abbreviated laboratories and urine pregnancy test are performed every 3 months when the patient comes to the site for a visit.

[10] For Part 1, only applicable for patients taking open-label enalapril. For Parts 1 and 2, dosage administration record and compliance will be performed when the study drug is dispensed and when the last dispensed study drug is presented to the site for tablet/granule count or liquid assessment.

[11] Patients will be asked via telephone if they completed a 36-hour washout period after the single dose LCZ696 PK and prior to starting enalapril (or ACEI). This information will be captured in the source document.

[12] Patients who are taking open-label enalapril will be provided enalapril medication at the completion of visit 101 or/and 201. Patient will be instructed to take it after 36 hour washout period. Compliance will be evaluated at Visit 102 or/and 202 via telephone call.

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

[redacted]

Table 6-2 Part 2 Assessment Schedule

Epoch	Pre-Randomiza-tion	Double-blind																		
Visit	301** (Part 2 Screening)	401	401JPN[J]	402	403	404 Optional	405	406	407†	408†	409	410†	411†	412	413†	414†	415	UNS/ TD	UNS	416/ 499(PSD)
Week	up to -3	0	1	2	4	6	8	12	16	20	24	28	32	36	40	44	48			52
Obtain Informed Consent (parent (s)-legal guardian (s)/consent-assent (patient, as applicable)[2]	x, S																			
Demography	x[1]																			
Inclusion/Exclusion Criteria	x																			
Medical History	x[1]																			
Pediatric Heart Failure History	x[1]																			
Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Alcohol & Smoking History	x[1]																			
Vital Signs (BP and pulse)[17]	x	x	x	x	x	x	x	x			x			x			x	x	x	x
Height	x																			x
Weight[3]	x	x	x	x	x	x	x	x			x			x			x	x	x	x
Head Circumference (≤ 3 years old)	x																			x
Physical Examination (complete)	S																			S
Physical Exam (abbreviated)		S	S	S	S	S	S	S			S			S			S	S	S	
ECG	x																			x
ECHO, LVEF or fractional shortening measurement[4]	x																			
Urinalysis	x	x									x									x
Serum/Urine Pregnancy Test[5]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Complete Laboratories[6, 13]	x	x									x									x

[redacted]

Epoch	Pre-Randomiza-tion	Double-blind																		
Visit	301** (Part 2 Screening)	401	401JPN[J]	402	403	404 Optional	405	406	407†	408†	409	410†	411†	412	413†	414†	415	UNS/ TD	UNS	416/ 499/(PSD)
Week	up to -3	0	1	2	4	6	8	12	16	20	24	28	32	36	40	44	48			52
Abbreviated Laboratories[7]				(x)	x	(x)	x	x						x			x	(x)[18]	(x)[18]	
Population PK Blood Samples[13, 15]					x			X[15]											(x)[18]	X[15, 19]
Sparse PK blood Samples (Group 2 Subset of patients)[13, 14]							x[14]												(x)[14]	
Plasma Biomarkers/PD[8, 13]		x			x			x											(x)[18]	X
Plasma Biomarker/PD (Sparse PK Group 2 Subset of patients) [13, 16]							x[16]												(x)[16]	
NYHA/ Ross Classification	x	x			x			x			x			x				(x)[18]		x
PGIS (Global Impression of Severity): Patient[9]		x			x			x			x			x				(x)[18]		x
PGIS: Parent/Care-giver[9]		x			x			x			x			x				(x)[18]		x
[redacted]																				
PedsQL: Patient[10]		x						x			x			x				(x)[18]		x
[redacted]																				

Epoch	Pre-Randomiza-tion	Double-blind																		
Visit	301** (Part 2 Screening)	401	401JPN[J]	402	403	404 Optional	405	406	407†	408†	409	410†	411†	412	413†	414†	415	UNS/ TD	UNS	416/ 499(PSD)
Week	up to -3	0	1	2	4	6	8	12	16	20	24	28	32	36	40	44	48			52
[redacted]																				
AEs/SAEs		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dosage Administration Record[11]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)	(x)	x
Study Medication Compliance[11]		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	(S)	(S)	S
Contact IRT	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dispense Double-Blind Study Medications		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		(x)	
Screening Disposition (Parts 1 and 2)	x																			
Endpoints		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Efficacy Study Treatment Disposition (Part 2)																				x
End of Study Treatment Discontinuation (Part 2)																		x		

UNS = Unscheduled visit
S = assessment to be recorded on source documentation only
TD = Study treatment discontinuation and patient continues study visits;
PSD = Premature subject/patient discontinuation
(x) / (S) = optional assessment
Visit 404 Optional = Investigators have the option to schedule a patient for an additional visit (Visit 404) for up titration.
** A patient may be screened and randomized the same day for Part 2. Visits 299 and 301 (for patient in second dose PK) and Visits 199 and 301 (for patient only going to take first dose PK) may occur on the same day if patient is participating in Part 2. Any assessments should not be repeated if visits occur on the same day.

[redacted]

Epoch	Pre-Randomiza-tion	Double-blind																		
Visit	301** (Part 2 Screening)	401	401JPN[J]	402	403	404 Optional	405	406	407[†]	408[†]	409	410[†]	411[†]	412	413[†]	414[†]	415	UNS/ TD	UNS	416/ 499(PSD)
Week	up to -3	0	1	2	4	6	8	12	16	20	24	28	32	36	40	44	48			52

[†] Visits 407, 408, 410, 411, 413, 414 are telephone visits. Patients who are dispensed LCZ696 liquid formulation/matching placebo, liquid enalapril/matching placebo and LCZ696/matching placebo granules will come to the site for dispensation of study drug. If the parent/caregiver comes to the site without the patient, a telephone call to the patient (≥ 6 years old) can be used in conjunction with the parent/caregiver visit for the visit assessments. IRT will be contacted only if study drug is dispensed.

[J] Visit 401JPN (week 1) is applicable only to patients enrolled at sites in Japan.

[1] Demography, medical history, pediatric HF history alcohol & smoking history are only obtained at Visit 301 for patients who did not participate in Part 1.

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

[3] Weights are measured for safety. For patients 1 month to < 1 year old, last available study weight measurement will be used to ascertain dose. For patients 1 to < 6 years old, weight measurements every 3 months will be used for dose determination. For patients who are ≥ 6 years old, weight measurement every 6 months will be used for dose determination.

[4] This must be performed within 1 month of Visit 301 (Part 2). Patients who have participated in Part 1 (PK) and remain in study for Part 2 (efficacy) need a repeat assessment of LVEF or fractional shortening to determine eligibility for Part 2 if the assessment is greater than 1 month prior to Visit 301 (see Section 4.1, Inclusion criteria).

[5] For child bearing potential females (CHBP) only. Urine pregnancy test is analyzed locally and done at all visits on all female patients ≥11 years of age and all female patients who are <11 years of age if they are menstruating. In addition, a serum pregnancy test is performed and analyzed locally at Visit 301 and centrally at Visit 416/499 respectively. Urine pregnancy tests will not be done at visit 401JPN (i.e. week 1 visit, which is applicable only to patients enrolled at sites in Japan). Note: In addition to the testing done in the clinic, all female subjects ≥11 years of age and all female subjects who are <11 years of age if they are menstruating, will be given a urine pregnancy test kit for each month between in-person study visits and will be instructed to do a urine pregnancy test at home, for each visit designated to be a telephone visit (i.e. Visits 407, 408, 410, 411, 413 and 414). Patients will be instructed to save the pregnancy test kits in a container (e.g. plastic) and bring them to the next in-person clinic visit. Study site personnel are to review the pregnancy test kits the patients bring to the clinic and record the results in the source documentation and on the appropriate CRF. If, according to local requirements, pregnancy tests cannot be done at home, the patient can have the test done at the study site or an alternative venue (additional details are included in the Central Lab Manual). Patients will be instructed to come to the clinic for a serum pregnancy test if the urine pregnancy test is positive.

[6] Local laboratories should be used for all laboratory tests at Visit 301. Central lab should only be used for Visit 301, if local lab is unavailable using unscheduled visit. Central laboratory should be used at Visits 401, 409, and 416/499 for all patients, where possible.

[7] Abbreviated laboratories will be collected and sent to the local lab at specified visits for all patients. Abbreviated laboratories consist of sodium, potassium, creatinine, eGFR (modified Schwartz formula). Abbreviated laboratories may be performed at any visit based on the Investigator's clinical judgement. Central lab should only be used for abbreviated lab testing only if local lab is unavailable, using unscheduled visit. Note: The Abbreviated laboratories scheduled at Visit 402 (week 2) and Visit 404 (week 6) are optional if it is considered safe and where the patient is not being up-titrated (applicable to Visit 402 and 404). For Age Group 3 patients who turn 1 year old during the study and who are up-titrated to Group 3 Dose Level 5x (if applicable) at a scheduled visit or at an unscheduled visit, abbreviated labs are to be done at the additional up titration visit.

[redacted]

Epoch	Pre-Randomiza-tion	Double-blind																		
Visit	301** (Part 2 Screening)	401	401JPN[J]	402	403	404 Optional	405	406	407[†]	408[†]	409	410[†]	411[†]	412	413[†]	414[†]	415	UNS/TD	UNS	416/499(PSD)
Week	up to -3	0	1	2	4	6	8	12	16	20	24	28	32	36	40	44	48			52

[redacted]

[9] Patient or parent/caregiver will complete the PGIS , depending on the age of patient.

[redacted]

[11] For Part 1, only applicable for patients taking open-label enalapril. For Parts 1 and 2, dosage administration record and compliance will be performed when the study drug is dispensed and when the last dispensed study drug is presented to the site for tablet/granule count or liquid assessment.

[redacted]

[13] For countries where blood samples cannot be shipped out of the country due to local regulations, the PK blood samples and Plasma Biomarkers/PD are not required. In these countries, complete laboratories at visit 401, 409 and 416/499 will be collected and sent to the local lab.

[14] In approximately 24 patients in Age Group 2, sparse PK blood samples will be collected at steady-state, at 3 time-points on the same day, at Visit 405 or at a subsequent scheduled or unscheduled visit (with the exception of Visit 406 and 416/499), Please refer to Section 6.6.2 and Table 6-5 for instructions regarding sample collection.

[15] For the subset of patients who participate in the sparse PK sampling visit, blood samples for Population PK will NOT be required to be collected at Visits 406 and 416/499.

[16] For the subset of patients who participate in the sparse PK sampling visit, [redacted] (e.g. visit 405 or a scheduled or unscheduled visit with the exception of visits 406 and 416/499).

[17] For Part 2 Group 3 patients, starting with the first dose of study medication, vital signs need to be checked for up to 4 hours after the initial dose at each dose level. Patients are to remain in the study site clinic for this 4-hour post-dose Vital Sign monitoring period. Vital signs (i.e. blood pressure and heart rate) are to be measured pre-dose (time 0), and post-dose at 0.5, 1, 2, 3 and 4 hours for the initial study medication dose at each dose level. See Appendix 13 for details.

[18] For patients impacted by the urgent safety measure (USM), additional evaluations are to be done at the visit that is used to discontinue study medication (see Appendix 15 for details). PK [redacted] must be collected, and NYHA/Ross Classification and all PROs (PedsQL, PGIS, [redacted]) must be completed, at this visit.

[19] For patients impacted by the USM and who transitioned to SOC before the EoS visit, a sample for Population PK should NOT be collected.

[redacted]

6.1 Information to be collected on screening failures

All patients who have signed informed consent for Part 1 (PK/PD) and/or Part 2 (Efficacy), but have not entered into the next epoch will have the study completion page for the screening epoch, demographics, inclusion/exclusion, and SAE data collected. Adverse events that are not SAEs will be followed by the Investigator and collected only in the source data.

A patient who has failed screening may have abnormal test findings that occurred prior to the informed consent. Investigators have the discretion to record these abnormal test findings on the CRF.

Re-screening

A patient who enters screening but is determined not to be eligible for the study will be considered a screen failure. The Investigator may consider rescreening the patient at a later time if he/she believes that the patient's condition has changed and they may potentially be eligible. In this case, a new patient number will be allocated to the subject and he/she will need to perform all screening Visit 1 (Part 1- PK/PD) or Visit 301 (Part 2 Efficacy-Pre-randomization/Screening) procedures again. A patient may be rescreened up to two times. A minimum of 2 weeks must elapse between rescreening. The parent(s)/legal guardian(s) for the pediatric patient must provide new written informed consent before each time the patient is rescreened. Patients required to provide assent must also provide new assent before being rescreened.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: year of birth, age, sex, race, ethnicity, concomitant medications, alcohol/smoking history, NYHA/Ross class, pediatric heart failure history, vital signs, weight and height. Relevant medical history/current medical condition data includes data until the start of study drug.

Rationale for collecting race and ethnicity data: Race and ethnicity data are collected for patients in this study, as available. The rationale for this is noted in a 2016 FDA Guidance document "Collection of Race and Ethnicity Data in Clinical Trials," which states "…evidence must be reviewed to establish whether or not there are potentially clinically important sex-and racial/ethnic-based differences in the anticipated effects of the intervention." ICH E5 is also cited in this Guidance document and states that the "Question and Answer Addendum to E5 introduces the multi-regional clinical trial study design as one means to evaluate treatment response heterogeneity and extrapolation. Multi-regional clinical trials may present special situations for the collection and self-reporting of race and ethnicity." (FDA 2016)

6.3 Treatment exposure and compliance

This information should be captured in the source document at each visit and specific CRFs. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Compliance will be assessed by the Investigator and/or study personnel using pill counts, liquid study medication assessment and information provided by the caregiver. This information

should be captured in the source document and specific CRFs. All study treatment dispensed and returned must be recorded in the Drug Accountability Log. The Investigator and/or study personnel should counsel the patient and his/her parent(s)/legal guardian-caretaker(s), as appropriate, if compliance is below 80% at any time during the study. Study drug accountability will be determined by the site monitor while performing routine site visits and at the completion of the study.

The duration of randomized treatment exposure will be calculated based upon the start and stop dates recorded in the CRF.

6.4 Efficacy

6.4.1 Efficacy assessment

The efficacy of LCZ696 compared to enalapril after 52-week of double-blind treatment is assessed using a global rank endpoint as outlined below (Table 6-3) (see Appendix 15 for USM exception). Clinical events (Categories 1 and 2) are adjudicated by an external independent adjudication committee. The NYHA/Ross classification (Criteria Committee NYHA 1994, Ross 1992, Rosenthal 2004), PGIS, and PedsQL are conducted at randomization and end of study (and during the study as shown in Table 6-2 assessment schedule).

Table 6-3 Primary endpoint algorithm using ranked analysis

Category	Sub-category	Description	Ranking algorithm
1	Death; UNOS status 1A listing for heart transplant or equivalent; VAD/ECMO/mechanical ventilation/intra-aortic balloon pump requirement for life support at end of study.		
	A	Category 1: Death; UNOS status 1A listing for heart transplant or equivalent; VAD/ECMO/mechanical ventilation/intra-aortic balloon pump requirement for life support at end of study.	Rank within this category by time to first event. All Category 1 events are considered equal.
2	Worsening HF (WHF); defined by signs and symptoms of WHF that requires an intensification of HF therapy.		

[redacted]

Category	Sub-category	Description	Ranking algorithm
	B	Worsening heart failure hospitalization with intensive care unit stay (HFH-ICU).	Within Category 2, the patients will be ranked first by event subcategory, and then by number of events within each subcategory. Further ranking by time to first event in the worst subcategory.
	C	Worsening heart failure hospitalization without intensive care unit stay (HFH-No ICU).	Within Category 2, the patients will be ranked first by event subcategory, and then by number of events within each subcategory. Further ranking by time to first event in the worst subcategory.
	D	Worsening heart failure without hospitalization (WHF-No Hosp).	Within Category 2, the patients will be ranked first by event subcategory, and then by number of events within each subcategory. Further ranking by time to first event in the worst subcategory.
3	Worsened; worse NYHA/Ross or worse Patient Global Impression of Severity (PGIS); and further ranking by PedsQL physical functioning domain.		
	E	NYHA/Ross or Patient Global Impression of Severity (PGIS) worsened based on last available assessment compared to baseline.	Rank by combination of NYHA/Ross and PGIS degree of change. Within a group of the same degree of NYHA/Ross and PGIS change, further rank by PedsQL (physical functioning domain) change from baseline.
4	Unchanged; unchanged NYHA/Ross and unchanged PGIS; and further ranking by PedsQL physical functioning domain.		

[redacted]

Category	Sub-category	Description	Ranking algorithm
	F	NYHA/Ross and PGIS unchanged based on last available assessment compared to baseline.	Worst baseline combination of NYHA/Ross functional class and PGIS without change is ranked worse than a better baseline NYHA/Ross functional class and PGIS. Within a group of the same baseline NYHA/Ross and PGIS, further rank by PedsQL (physical functioning domain) change from baseline.
5	Improved; improved NYHA/Ross or improved PGIS (neither can be worse); and further ranking by PedsQL physical functioning domain).		
	G	NYHA/Ross or PGIS improved based on last available assessment compared to baseline	Rank by combination of NYHA/Ross and PGIS degree of change. Within a group of the same degree of NYHA/Ross and PGIS change, further rank by PedsQL (physical functioning domain) change from baseline.

Changes in heart transplant status should be documented by completing a new 'Heart Transplant Listing Endpoint' CRF.

Worsening HF is defined as new or worsening symptoms and signs of HF that require an intensification of HF therapy. The symptoms of WHF include but are not limited to: dyspnea on exertion; dyspnea at rest; orthopnea; paroxysmal nocturnal dyspnea; decreased exercise tolerance due to fatigue; abdominal bloating/discomfort; tachypnea with feeding; diaphoresis with feeding; fatigue with feeding; feeding intolerance/emesis/weight loss and fluid retention. The signs of WHF include but are not limited to: pulmonary edema or rales; tachypnea or rapid respiration rate; increased jugular venous pressure; peripheral hypoperfusion; radiographic evidence of pulmonary edema, radiographic evidence of pulmonary vascular congestion, radiographic evidence of pleural effusion; hypoxemia; growth failure or failure to thrive; peripheral edema; hepatomegaly and any other sign consistent with heart failure.

Treatments for worsening heart failure include intravenous diuretics, intravenous vasodilators, intravenous vasopressors, intravenous inotropes, mechanical fluid removal (e.g., ultrafiltration or dialysis), ventricular assist device, extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump, mechanical ventilation, non-invasive ventilation, surgical or catheter-based interventions. Treatment for worsening heart failure with oral medication includes the initiation or intensification of standing oral diuretics. Intensification of oral diuretics must be a 50% increase or more of the daily maintenance dose for at least 2 weeks duration. For worsening heart failure characterized by growth failure or failure to thrive, treatments can include feeding

[redacted]

tube placement or parenteral nutrition (Section 3.3). Further details are documented in the Clinical Endpoint Committee (CEC) charter.

Primary endpoint Categories 3, 4 and 5 are ranked by NYHA/Ross class and PGIS score. The combined change from the end of study compared to baseline for both the NYHA/Ross class and the PGIS score will be used to rank patients from worst to best within categories 3, 4 and 5. Within a group of patients with the same degree of combined NYHA/Ross and PGIS change, the PedsQL (physical functioning domain) change from baseline will be used to further rank these patients from worst to best. Further ranking within Categories 3, 4, 5 as needed ('tie breaking') will be based on a subset of 5 physical functioning domain questions of the PedsQL score (for patients 6 to < 18 years old). The PedsQL will not be used for the youngest two age strata (1 month to < 1 year and 1 to < 6 years), as the patient reported PedsQL data will not be collected for all patients in these strata. (Note: Patient < 5 years old only have a parent report for the PedsQL).

6.4.2 Secondary efficacy endpoints

The secondary efficacy endpoints include:

- To determine whether LCZ696 is superior to enalapril in delaying time to first occurrence of the composite of either Category 1 or 2 events (e.g. death, worsening HF)
- To determine whether LCZ696 is superior to enalapril for improving NYHA/Ross functional class
- To determine whether LCZ696 is superior to enalapril for improving the Patient Global Impression of Severity (PGIS) score
- To characterize the population PK of LCZ696 exposure in pediatric patients with HF. Also to further confirm the LCZ696 target dose for Age Group 2 using a population PK approach with steady-state sparse PK blood samples (i.e. 3 samples per patient drawn on the same day) collected from approximately 24 patients, approximately half of whom are expected to be randomized to LCZ696. Therefore, blood samples from approximately 12 patients randomized to LCZ696 will be used in the PK analysis.

[redacted]

6.5 Safety

Novartis may request additional information on specific AEs or laboratory events of interest and may make requests to perform additional diagnostic tests to further assess the safety profile of the study drugs. Such information may include diagnostic procedure reports, discharge

[redacted]

summaries, autopsy reports, and other relevant information that may help in assessing the reported AE. All additional information is de-identified prior to collection by Novartis or its agents. In addition to AE/SAEs, the following safety related data will be collected:

- Physical examinations
- Vital signs
- Height, weight, and head circumference (head circumference is only collected in patients ≤3 years of age at enrollment)
- Laboratory evaluations
- Electrocardiograms (ECG)
- Pregnancy
- Angioedema

6.5.1 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, and extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A complete physical examination will be performed at the screening visits for Part 1 (Visit 1) and Part 2 (Visit 301), and also the end of study Visit 416/499. An abbreviated physical examination will be performed at other in person visits as shown in Table 6-1 and Table 6-2. An abbreviated physical exam will include the examination of general appearance and vital signs (BP and pulse) as well as other examinations based on Investigator discretion.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to signing informed consent must be included in the Medical History part of the patient's CRF. Significant findings made after signing the informed consent which meet the definition of an AE must be recorded on the AE section of the CRF.

6.5.2 Vital signs

Vital signs include BP and pulse measurements and are assessed when a complete or abbreviated physical examination is performed. BP will be measured in the sitting position after 5 minutes of rest using an automated validated device (e.g. OMRON) or a standard sphygmomanometer with an appropriate size cuff on the non-dominant arm. Supine BP instead of sitting BP will be measured in patients who are infants or who cannot sit comfortably. Guidelines for the management of hypotension are provided in Appendix 4.

Vital signs (blood pressure and heart rate/pulse) will be collected at Visit 101, 201 during PK assessment (and unscheduled PK/PD visit if it occurs) at: 0, 30 min, 1 hr, 2 hrs, 3 hrs, 4 hrs, 5 hrs, 6 hrs, 7 hrs, 8 hrs, 9 hrs, 10 hrs, 11 hrs, 12 hrs, 18 hrs, and 24 hours post-dose LCZ696. Vital signs at 11 hrs, 12 hrs and 18 hrs are optional unless the patient physically stays on-site. The 24-hr post dose vital signs will be measured if the patient either stays on-site or returns to the site the next day. The vital signs will be collected in Part 1 and Part 2 of the study as depicted in the assessment schedule (Table 6-1 and Table 6-2).

For Part 2 Age Group 3 patients, starting with the first dose of study medication, vital signs need to be checked for up to 4 hours after the initial study medication dose at each dose level. Patients are to remain in the study site clinic for this 4-hour post-dose Vital Sign monitoring period. Vital signs are to be measured pre-dose (time 0), and post-dose at 0.5, 1, 2, 3 and 4 hours for the initial study medication dose at each dose level.

Clinically notable vital signs for this patient population are defined in Appendix 1.

6.5.3 Height/length, head circumference and weight

Height/length in centimeters (cm) will be measured using a standard device at Visit 1 (Part1 PK/PD- Screening), Visit 199 and/or Visit 299, Visit 301 (Part 2 Efficacy- Pre-randomization/Screening), and Visit 416/499 (Week 52/Final Visit). Use of a stadiometer for standing height measurements is recommended.

For patients ≤ 3 years, head circumference in centimeters (cm) is measured at Visit 1 (Part 1 PK/PD-Screening), Visit 199 and/or Visit 299, Visit 301 (Part 2 Efficacy-Pre-randomization/Screening), and Visit 416/499 (Week 52/Final Visit).

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) is measured at every in-person visit. Body weight during hospitalization is to be recorded only if available as per standard of care. For patients 1 month to < 1 year old, last available study weight measurements will be used to ascertain dose. For patients who are 1 to < 6 years old, weight measurements every 3 months will be used for dose determination. For patients who are ≥6 years old, weight measurement every 6 months will be used for dose determination.

6.5.4 Laboratory evaluations

Complete laboratory evaluations (hematology, blood chemistry, and urine) as outlined in Table 6-4 are performed in Part 1 at Visit 1 (Screening), Visit 199 and/or 299, and in Part 2 at Visit 301 (Screening), Visit 401 (Randomization), Visit 409 and Visit 416/499 (Week 52/Final Visit). Local laboratory should be used for Visit 1, 199, 299 and 301 for complete laboratory evaluations. Central laboratory should only be used for Visit 301, if local lab is unavailable using unscheduled visit. Central laboratory must be used for Visit 401, 409 and 416/499 for complete laboratory evaluations for all patients. 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. Patient can be randomized based on safety laboratory results from Visit 199/299/301 unless the Investigator feels the need to wait for laboratory results from Visit 401.

Abbreviated safety laboratory evaluation consists of serum sodium, potassium, creatinine, and eGFR. Abbreviated safety laboratories should be performed locally. If the local laboratory is unavailable (either for abbreviated or complete labs), the central laboratory should be used as an unscheduled visit. Abbreviated laboratory evaluations are to be performed at Part 1 PK/PD Visits 101, 201, 103 to 120 (when patient comes to the site for a visit about every three months), 203 to 220 (when patient comes to the site for a visit about every three months), UNS PK/PD; and Part 2 (Efficacy) Visits 402 (Abbreviated labs are optional if considered safe and where patient is not being up-titrated), 403, 404 (optional visit; Abbreviated labs are optional if considered safe and where patient is not being up-titrated), 405, 406, 412, 415 and as an optional assessment at UNS TD, and UNS. For those patients who have Visits 299 and 301 on the same

[redacted]

day (for second PK dose patient) or Visits 199 and 301 on the same day (for the first PK dose only patient), laboratories will be performed only once. Local laboratory results will allow Investigators to proceed with study visit procedures without the need to wait for central laboratory results. The local laboratory results must be recorded in the appropriate CRF. Given limitations of blood volume, the local laboratory assessments will be a priority for urgent medical decision making (including for study drug dose titration).

Local and central laboratory results need not agree in order for the Investigator to qualify a patient for the trial or make a dose titration decision. A patient enrolled in the study based on local laboratory results and subsequently determined to be above an exclusion criteria based on central laboratory results may be continued or discontinued from the study at the discretion of the Investigator. The Investigator should use his/her clinical judgment on how best to manage the study drug dose level in the event a dose titration decision based on a local laboratory results is subsequently found to be discrepant with central laboratory results. If the central laboratory is used, it may take up to 72 hours or more to obtain the results.

For child bearing potential females only, serum pregnancy testing will be performed at Visit 1 (Part 1 PK/PD - Screening), Visit 301 (Part 2 Efficacy- Pre-Randomization/Screening) and Visit 416/499 (Part 2 Week 52/End of Study). Child-bearing potential females (CHBP) are defined as all female patients ≥ 11 years of age and all female patients who are <11 years of age if they are menstruating. Patients with a positive urine/serum pregnancy at any time in the study must be excluded. Urine pregnancy test is analyzed locally and done at all visits on all CHBP female patients (for additional details regarding urine pregnancy testing requirements for visits 407, 408, 410, 411, 413, and 414, please see Table 6-2). Serum pregnancy test will be analyzed centrally (for Visit 416/499) or locally (for Visits 1 and 301). A positive urine pregnancy test should be confirmed with a serum pregnancy test.

Table 6-4 Laboratory examinations

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

[redacted]

Hematology	Biochemistry	Urine measurements**
	Bicarbonate	Granular casts
	Total bilirubin (TBL)	Waxy casts
	Fractionated bilirubin (if total bilirubin >2x ULN)	WBC casts
	Total protein	RBC casts
	Uric acid	
	eGFR*	

*Abbreviated laboratory evaluations must include these parameters

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

Study procedures may be performed without restriction while the central laboratory results are pending. In these cases, the Investigator or his/her designee should review the central laboratory results as soon as they become available to decide on whether any adjustments in the patient's study drug or non-study drug regimen are needed.

Abnormal laboratory values (as defined in Appendix 1) may require additional laboratory evaluations be performed, as judged appropriate by the Investigator. If the laboratory abnormality induces clinical signs or symptoms, or requires therapeutic intervention, then the diagnosis or medical condition must be entered on the AE page of the patient's CRF. 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 from the study drug (temporarily or permanently), the patient 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 Novartis medical monitor.

A table which provides the maximum, allowable blood-draw volumes by weight can be found in Appendix 6.

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 5, can be converted to plasma potassium thresholds for the study by subtracting 0.4 mmol/L from the serum potassium threshold (Hartland 1999).

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, MCV, MCHC, RDW, white blood cell count with differential counts, and platelet count are to be measured as part of the complete laboratory assessments (Table 6-4) at scheduled study visits (Table 6-1 and Table 6-2). Results from the local laboratory are to be recorded in the CRF.

[redacted]

6.5.4.2 Clinical chemistry

Blood urea nitrogen (BUN), serum creatinine, total bilirubin, fractionated bilirubin (if total bilirubin >2x ULN (upper limit of normal)), AST, ALT, alkaline phosphatase, sodium, potassium, chloride, calcium, phosphate, magnesium, bicarbonate, total protein, albumin, uric acid, glucose are measured as part of complete laboratory assessments (Table 6-4) at scheduled study visits (Table 6-1 and Table 6-2). Results from local laboratory are to be recorded in the CRF.

6.5.4.3 Estimated GFR

Estimated glomerular filtration rate (eGFR) as per Schwartz formula (Schwartz 2009) will be calculated and reported by the central laboratory whenever a serum creatinine is performed by the central laboratory. eGFR must be calculated by the laboratory or the Investigator for local labs.

The calculation is based on the following formula:

eGFR (ml/min/1.73m^2) = 0.413 x height (cm) / serum creatinine (mg/dl)

Height will be provided by the site to the local and/or central lab.

For eGFR, baseline value for the decrease from baseline criterion for the analysis will be calculated from screening for local labs and from randomization for central labs.

6.5.4.4 Urinalysis

Urinalysis with dipstick includes specific gravity, pH, glucose, total protein, bilirubin, ketones, urobilinogen, leukocyte esterase, nitrite and hemoglobin (blood). If a urine dipstick is positive, other urine measurements such as a qualitative microscopic determination of WBC and RBC sediments (and casts) will also be measured.

Urinalysis will be performed for all patients at Visit 1 (Part 1 PK/PD - Screening), Visit 199 and/or 299 and Part 2 (Efficacy) Visit 301, Visit 401, Visit 409, and Visit 416/499 (Week 52/End of Study). For those patients who have visits 299 and 301 (for second dose PK), or Visit 199 and Visit 301 (for the first dose PK) on the same day, urinalysis will be performed only once.

6.5.4.5 Biomarkers

[redacted]

In Part 1 (PK/PD) (in the absence of the above-mentioned collection / sample handling issues): plasma BNP, plasma and urine cGMP and plasma NTproBNP samples are collected at Visits 101, 201 and UNS PK/PD (if performed). Plasma BNP and plasma cGMP are collected at pre-dose, 4 hour and 8 hour time points post-dose. Plasma NTproBNP is collected at pre-dose and 24 hours post-dose (optional). Urine cGMP is collected at pre-dose and between 4-8 hours.

[redacted]

At Visit 101, 201 or UNS PK/PD (if performed), infants who weigh < 15.5 kg will only have plasma cGMP and BNP collected; infants who weigh ≥ 15.5kg, will have three biomarker (plasma BNP, cGMP and plasma NTproBNP) samples collected as long as blood volume restriction allows.

Urine cGMP should be collected in Part 1 (PK/PD) at Visit 101, 201 and UNS PK/PD (if performed) at pre-dose and once at any time between 4 to 8 hours after LCZ696 single dose administration.

Details about biomarker prioritization when blood volumes are restrictive; blood volume requirements for each of the biomarkers; sample collection, processing and storage are provided in the laboratory manual.

Details about blood sample collection for biomarkers in Part 1 are also provided in Table 3-2.

[redacted]

6.5.5 Electrocardiogram (ECG)

ECGs are conducted at Visit 1 (Part 1 PK/PD - Screening), Visit 199 and/or 299, and Visit 301 (Part 2 Efficacy - Pre-Randomization/Screening) and Visit 416/499 (Week 52/End of Study). ECGs are interpreted locally for study entry and for purpose of safety assessment. For those patients who have Visit 299 and Visit 301 (for second dose PK) or Visit 199 and Visit 301 (for the first dose PK) on the same day, ECG will be performed only once.

ECGs must be recorded in the supine position, after at least 10 minutes rest if possible to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling The Fridericia QT correction formula ($QTcF = (QT/[RR]^{0.33})$) should be used for clinical decisions.

Single 12 lead ECGs are collected. The original ECGs, appropriately signed by the ECG reader, must be collected and archived at the study site.

Each ECG tracing must be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs must be performed to confirm the safety finding. Clinically significant ECG findings at baseline must be discussed with the sponsor before administration of study treatment.

Clinically significant ECG abnormalities must be recorded on the relevant section of the medical history or adverse event CRFs as appropriate.

6.5.6 Left ventricular ejection fraction (LVEF) or fractional shortening assessments

All patients entering Part 1 (PK/PD) will require a qualifying LVEF or fractional shortening assessment by echocardiogram, MRI, MUGA or left ventricular angiogram. If a qualifying LVEF or fractional shortening assessment is not available, the patient may enter the study based on a qualifying echocardiogram performed during the screening epoch between Visit 1 and

[redacted]

before patient receives the first dose of open label LCZ696 (Visit 101or V 201). Patients who have participated in Part 1 (PK/PD) and continue to Part 2 (Efficacy) need a repeat assessment of LVEF or fractional shortening in order to determine eligibility for Part 2 (Efficacy) unless the most recent assessment is within 1 month prior to Visit 301 (Part 2 Pre-Randomization/Screening).

Patients entering directly into Part 2 (Efficacy) will require a LVEF or fractional shortening assessment obtained within 1 month prior to Visit 301 (Part 2 Pre-Randomization/Screening). If a qualifying LVEF or fractional shortening assessment (echocardiogram, MRI, MUGA, or left ventricular angiogram) within 1 month of Visit 301 is not available, the patient may enter the study based on a qualifying echocardiogram performed during screening before the patient receives study treatment.

6.5.7 Pregnancy and assessments of fertility

Pregnancy test (urine) is analyzed locally and done at all visits on all female patients ≥11 years of age and all female patients who are <11 years of age if they are menstruating (for additional details regarding urine pregnancy testing requirements for visits 407, 408, 410, 411, 413, and 414, see Table 6-2). In addition, serum pregnancy test is only conducted at Visit 1 (Part 1 PK/PD - Screening), Visit 301 (Part 2 Efficacy-Pre-Randomization/Screening) and Visit 416/499 (Part 2 at Week 52/End of Study); and serum pregnancy test will be analyzed centrally (for Visit 416/499) or locally (for Visits 1 and 301). A positive urine pregnancy test should be confirmed with a serum pregnancy test.

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 with the patient and her parents/caregivers are therefore best performed by Investigators familiar with the pediatric patient 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 patient and her parents/caregivers. The privacy of the patient should be considered in accordance with the local law and ethics.

Any patient with a positive pregnancy test must discontinue study drug immediately and the patient should remain in study and continue to attend scheduled study visits.

6.5.8 Angioedema

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 patients. 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

[redacted]

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 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 to an external independent Angioedema Adjudication Committee by Novartis for assessment.

Information regarding this committee is outlined in Section 8.4. Details on the procedures for reporting angioedema events will be provided to Investigators in a manual.

6.5.9 Appropriateness of safety measurements

The safety assessments selected for this trial are standard assessments for demonstrating safety in this pediatric patient population, based on safety data from adult LCZ696 studies (Investigator Brochure), and in accordance with guidelines (ICH E11 Clinical Investigation of Medicinal Products in the Pediatric Population).

6.6 Other assessments

6.6.1 Clinical outcome assessments (COAs)

6.6.1.1 Clinician reported outcomes (ClinRO)

The impact of study drug on the patient's physical functional status will be assessed using the NYHA classification I-IV (older children: 6 to < 18 years old) or Ross HF classification I-IV (younger children: l month to < 6 years old). The NYHA and Ross functional class assessments are reliable instruments for rating HF patients' functionality (Criteria Committee NYHA 1994, Ross 1992, Packer 2001, Rosenthal 2004).

The NYHA functional class system is commonly used and is a clinically important system for staging the severity of HF (Spertus 2005). Similar to NYHA, the Ross classification system is a common system for grading the severity of HF in infants (Ross 1992). The most recent pediatric HF Guidelines from the International Society of Heart and Lung Transplant (ISHLT) mention both NYHA and Ross as Heart Failure Severity Classifications (Kirk 2014). A one class change in the NYHA or Ross functional class scale is considered to represent a clinically significant change (Ross 1992, Madsen 1994) based on the fact that the four stages in each classification differ considerably in severity.

Assessment of NYHA/Ross class will be conducted at screening visits for Part 1 (Visit 1) and Part 2 (Visit 301); randomization for Part 2 (Visit 401); end of study for Part 2 (Visit 416/499), and other visits as per Table 6-1 and Table 6-2.

For the duration of Part 2, the same PedsQL, NYHA and Ross instruments based on the age at randomization should be used.

[redacted]

6.6.1.2 Patient reported outcomes (PRO)

The impact of HF on the patient's status will be assessed by the following measures:

- Patient global impression of severity (PGIS)
- Pediatric quality of life inventory (PedsQL) 4.0 generic scales
- [redacted]

All questionnaires will be completed in the language most familiar to the respondent, and at the scheduled study visit prior to the patient seeing the Investigator for any clinical assessment or evaluation. The patient should be given sufficient instruction, space, time and privacy to complete the questionnaire. The study coordinator should check the responses to the questionnaire for completeness and encourage the patient to complete any missing responses.

A detailed training manual relating to the administrative procedures of the questionnaires will be provided to the sites. The Investigator enters the data from the questionnaire into the CRFs. The original questionnaire will be kept with the patient's file as the source document.

In Part 2 the patient or parent/caregiver will complete the patient reported outcome (PGIS, [redacted] and PedsQL) evaluations based on age at randomization.

Patient global impression of severity (PGIS)

The patient global impression of severity (PGIS) is a static global impression of severity question that will be used to capture the patients' current health status relative to their heart failure over 7 days recall period.

- Patient (7 to < 18 years old): How would you describe the severity of your heart failure symptoms **over the past 7 days**? (None / Mild / Moderate / Severe / Very Severe)
- Parent (for < 5 years old patients): How would you describe the severity of your child's heart failure symptoms **over the past 7 days**? (None / Mild / Moderate / Severe / Very Severe)
- A 3-point faces scale (corresponding/coded to Good / Neither Good nor Bad/ Bad) will be used for patient self-report by children 5 to < 7 years (Appendix 8).

For the global rank primary endpoint, a one class change in the PGIS is considered to represent a clinically significant change. The patient PGIS report will be used for the Global Rank endpoint for patients ≥ 5 years old.

Given the nature of heart failure symptoms, the PGIS will be performed when the patient is at rest and at the same location during the study visit. Additionally, instructions will be provided to the child and/or parent/caregiver that describe several symptoms of heart failure for consideration while responding to the PGIS. When the pediatric patient is completing the PGIS, the parent/caregiver will be instructed to not interfere with the child's response. There will be standardized instructions for patient and parent/caregiver to complete the PGIS. If a child is unable to complete the PGIS, this will be noted. If a patient 5 years and older is unable to complete the assessment, the assessment will be considered not done. The parent/caregiver PGIS report will only be used for the Global Rank endpoint for patients < 5 years old because patients < 5 years old are not considered mature enough to complete the patient PGIS self-report.

[redacted]

Parents and caregivers should be instructed to minimize any interaction, assistance and influence on the patient while the patient is completing the PGIS.

Patient or parent/caregiver will complete the PGIS at randomization for Part 2 (Visit 401); end of study for Part 2 (Visit 416/499), and other Part 2 visits as per Table 6-1 and Table 6-2.

Pediatric quality of life inventory (PedsQL)

The PedsQL is a patient-reported outcome instrument that evaluates health related quality of life in healthy children and adolescents and in pediatric patients with acute and chronic health conditions (Varni 2003, 2011). The PedsQL has published data in over 25,000 children and adolescents in multiple disease areas including pediatric cardiology (Varni 2003; Uzark 2008). The PedsQL has been validated in multiple pediatric disease populations and has demonstrated responsiveness to meaningful clinical change (Uzark 2008, Uzark 2013, Desai 2014). The PedsQL is the most widely used pediatric patient reported outcome assessment, and it is currently being used in the PEDIMACS (pediatric mechanical circulatory support devise) registry (INTERMACS protocol 2014) and in an observational study of pediatric solid organ transplant recipients (ClinicalTrials.gov 2008).

[redacted] The physical functioning domain of questions that focuses on proximal effects of health-related quality of life related to heart failure will be used for the Global Rank primary endpoint. The responsiveness of the PedsQL physical functioning domain in pediatric patients with cardiovascular disease has been demonstrated in several studies. In a prospective study of 475 families including 347 children with cardiovascular disease, the PedsQL score for physical functioning by patient self-report was significantly lower than the norms for healthy children (Uzark 2008). In this study, PedsQL physical functioning scores were also significantly lower for patients with more severe cardiovascular disease compared to milder cardiovascular disease. In a study of 126 families from Sweden with congenital heart disease, the PedsQL physical functioning scores were significantly lower for patients with more severe compared to mild/moderate congenital heart disease; and PedsQL physical functioning scores were also significantly lower comparing non-operated to operated congenital heart disease (Sand 2013). PedsQL physical functioning scores were significantly lower for children who received a heart transplant compared to healthy peers and children who received curative heart surgery (Uzark 2012). Another study demonstrated that children with the more severe condition of hypoplastic left ventricle had significantly lower PedsQL physical functioning scores compared to the less clinically severe tetralogy of Fallot pediatric patients (Eagleson 2013).

The PedsQL is administered to both the patient via child self-report and the patient's parent/legal guardian-caretaker via parent proxy-report. The PedsQL requires on average 5 minutes for completing. A 5-point response scale is used for 8-18 years old patients; while a 3-point scale is used for 5-7 years old patients. [redacted] The patients' self-report will be used for the primary endpoint for patients ≥ 6 years. [redacted]

[redacted]

Parents and caregivers should be instructed to minimize any interaction, assistance and influence on the patient while the patient is completing the PedsQL. The patient's age at randomization (Part 2 Efficacy - Visit 401) will be utilized to determine the corresponding PedsQL questionnaire to be administered at that visit and all subsequent visits.

The PedsQL will be completed at randomization for Part 2 (Visit 401); end of study for Part 2 (Visit 416/499), and other Part 2 visits as per Table 6-2.

[redacted]

6.6.2 Pharmacokinetics

Part 1 (PK/PD)

At Visit 101, 201 and UNS PK/PD the PK samples will be collected at the following intervals for the various age groups:

- Patients ≥6 years of age: Blood samples are collected at pre-dose (pre-dose sample for all patients) 0.5, 1, 2, 4, 8, 10, and optional 24 hours post dosing
- Patients <6 years of age: Blood samples are collected at pre-dose (pre-dose sample only from those patients who are on valsartan) 1, 2, 4, 10, and at an optional 24 hours post dosing

The exact time of the treatment administration, dose of LCZ696, sample number, and time of sample collection are recorded for each sample collected in the CRF. Sampling problems are to

[redacted]

be documented in the CRF and may include but are not limited to hemolyzed samples, insufficient sample volumes, and/or a lack of sample collections.

The plasma levels of LCZ696 analytes are determined using a validated LCMS/MS method with a lower limit of quantitation (LLOQ) of 1 ng/mL for sacubitril, 20 ng/mL for LBQ657, and 10 ng/mL for valsartan. The detailed method description of analysis will be included in bioanalytical report.

The following PK parameters will be determined for LCZ696 analytes (sacubitril, LBQ657, and valsartan) using Phoenix version 6.2 or higher using non-compartmental methods: C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $T_{1/2}$, Cl/F, and other relevant PK parameters (data permitting). In case of data limitations for estimating PK parameters using non-compartmental methods, a population PK approach will also be used to estimate exposure of LCZ696 analytes.

The information about pharmacodynamic parameters (biomarkers) is provided in Table 3-2 and Section 6.5.4.5.

Part 2 (Efficacy)

Population PK data collection:

Pre-dose PK blood samples will be collected at Visit 403, Visit 406, and Visit 416/499 for population PK analysis (see Appendix 15 for USM exception). Every effort should be made to collect PK samples at all three visits. If a PK sample is not obtained at Visit 403 or 406, the PK sample can be collected at a subsequent scheduled or unscheduled visit. A population PK blood sample should only be obtained if permissible by blood volume limits (Appendix 6).

Steady-state sparse PK data collection (Group 2 patients only):

In approximately 24 patients (approximately half of whom are expected to be randomized to LCZ696) in Group 2 (1-<6 years old), sparse PK blood samples will be collected at steady-state, at approximately 3 time-points on the same day, at Visit 405 or at a subsequent scheduled or unscheduled visit (with the exception of Visit 406 and 416/499), when the patient is on Dose-Level 4 or at his/her highest tolerated dose for at least 1 week. The study site personnel are to confirm that blood volume restrictions for each patient are not an issue for the patient before blood sampling for steady-state sparse PK Visit is started. Patients will be instructed to hold their morning dose the day of the steady-state, sparse PK Visit to enable the collection of a pre-dose blood sample. The time of the last dose taken the day before the sparse PK visit will be recorded in the CRF. Patients will take their morning dose at the study site after the pre-dose blood sample is collected. Two additional blood samples will be collected at 2 hours post dose and 6 hours post dose. In this sub-set Age Group 2 patients, collection of additional PK blood samples for Population PK at Visits 406 and 416/499 will not be required.

Table 6-5 Sparse PK Assessment Schedule Part 2 Group 2 Subset

Timepoint	Visit 405 (week 8)	# Visit 409,412,415, UNS
Pre-dose	X	X#
2 hours post-dose	X	X#
6 hours post dose	X	X#

[redacted]

If sparse PK blood samples cannot be collected at V405 than one of the following visits can be used for collection of the sparse PK samples: Visit 409, Visit 412, Visit 415 or an UNS visit.

Steady state concentrations of valsartan, sacubitril, and LBQ657 will be analyzed by graphical methods to determine an appropriate structural PK model to fit the data. Data obtained from Part 1 will also be included in this PK modeling. Following this, a population PK model will be developed using the data obtained from this study and/or in combination with PK data obtained from other studies to quantify PK of valsartan, sacubitril, and LBQ657. Significant covariates that influence PK properties of these analytes will also be examined.

Patients/caregivers should be instructed not to take their morning dose of study treatment during the PK blood sample collection visits.

For the Population PK blood samples that are to be collected at Visits 403, 406, and 416/499, if a patient takes his or her morning study drug dose prior to obtaining the PK blood sample, the PK blood sample must still be collected and the actual time of study drug dosing and sample collection time must be recorded.

For the sparse PK samples that are to be collected at the sparse PK Visit for Age Group 2 patients, if a patient takes his or her study drug dose the morning of this sparse PK Visit, the patient will be asked to return at a later date to complete the sparse PK blood sample collection Visit.

All samples are given a unique sample number and a collection number (laboratory manual). The exact time of the treatment administration, study drug dose, sample number, and time of sample collection are recorded for each sample collected on the CRF. Whether the patient fasted prior to the single dose PK assessment should also be collected in the CRF. Sampling problems may include but are not limited to hemolyzed samples, insufficient sample volumes, and/or a lack of sample collections are to be documented in the CRF. PK samples are to be collected when the patient is expected to be at steady state, i.e., patient has been receiving the study drug regularly on the same dose levels as prescribed for at least 1 week.

PK blood sample handling

The PK section of the (Laboratory Manual) for this study will provide details regarding sample handling including collection, labeling, processing, storage and shipping. The Laboratory Manual will also provide details regarding which samples to exclude if blood volume is an issue.

7 Safety monitoring

7.1 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 until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

[redacted]

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

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 patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the AE CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- 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

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

- no action taken (e.g. further observation only)
- investigational treatment dosage adjusted/temporarily interrupted
- investigational treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (refer to Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB

[redacted]

updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The Investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the Investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

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:

- is fatal or life-threatening
- 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:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - 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
  - 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
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient 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 (refer to Annex IV, ICH-E11D Guideline).

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 patient or might require intervention to prevent one of the other outcomes listed above. 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 (refer to Annex IV, ICH-E11D Guideline).

[redacted]

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

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient 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.). Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis if the Investigator suspects a causal relationship to study treatment.

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.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation

Follow-up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Drug Safety and Epidemiology 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. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

[redacted]

7.3 Protocol specific unblinding rules

7.3.1 Adverse events that are commonly seen in the study population

Investigators will report AEs or SAEs that are commonly seen in the study population, but they will not be unblinded and will not be reported as SUSARs to regulatory agencies, ethics committees (ECs), or Investigators during the study (Table 7-1).

These SAEs will be reviewed by an external independent DMC (Section 8.3) appointed to monitor the safety of study participants. If the DMC observes a clinically important imbalance in the AEs or SAEs, it will inform Novartis. Novartis will then inform all health authorities, ECs, and Investigators in an expedited manner and implement any additional actions required.

These events will be presented in the clinical study report (CSR) at the end of the study.

Table 7-1 Adverse events (AEs) 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

Study-specific unblinding rules for SUSARs that are disease related and present efficacy endpoints

The integrity of this study may be compromised, if the blind is systematically broken for SUSARs that could also be efficacy endpoints [for relevant EU guidance please refer to the European Commission ENTR/CT 12 Guideline (2006), FDA Guidance 2012]. Therefore, the rules for unblinding will apply as follows.

- A SUSAR will not be unblinded, if it could represent one of the following pre-specified disease related endpoints:
  - Death (All cause, Cardiovascular, Non-cardiovascular), Ventricular Assist Device/ECMO/Mechanical Ventilation/Intra-aortic Balloon Pump requirement, Worsening HF (with and without hospitalization)

In addition, no report to competent authorities and relevant EC and no issuance of an Investigator Notification (IN) will occur. An external independent DMC (Section 8.3) has been previously appointed and will review efficacy and safety data of the ongoing trial on a regular basis. DMC opinion and recommendations will be notified by Novartis as soon as possible to the competent authorities and the ECs where they qualify for expedited reporting.

If specifically requested by a local Health Authority (HA), pre-specified endpoints (see above) that also meet the criteria for SUSARs will be expedited to this HA as blinded reports. INs will not be issued for these events.

[redacted]

Any other SUSAR that will not meet the pre-specified disease related endpoints as mentioned above will be unblinded and a report to competent authorities and relevant ethics committees and issuance of an IN will occur.

7.4 Liver safety monitoring

To ensure patient 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/AEs have to be considered during the course of the study:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 14-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 14-1 of Appendix 2 should be followed up by the Investigator or designated personal at the trial site as summarized below. Follow up information is outlined in Table 14-2 in Appendix 2.

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory should then be performed at the central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate

For the liver events:

- repeating the LFT to confirm elevation as appropriate
- discontinuation of the investigational drug if appropriate
- hospitalization of the patient if appropriate
- a causality assessment of the liver event via exclusion of alternative causes (e.g. disease, co-medications)
- an investigation of the liver event which needs to be followed until resolution

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultation. These investigations can be performed based on Investigator's discretion. All follow-up information, and the procedures performed should be recorded on appropriate CRF pages, including the liver event CRF pages.

[redacted]

7.5 Renal safety monitoring

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

The following two categories of renal AEs have to be considered during the course of the study:

1. Serum event:
   - Confirmed (after ≥ 24h) decrease in estimated glomerular filtration rate (eGFR) of ≥ 25% compared to baseline during normal hydration status as estimated by Schwartz equation AND eGFR <90 mL/min/1.73m^2
2. Urine event:
   - New onset (≥ 1+) proteinuria, hematuria or glucosuria
   - New onset of proteinuria should be confirmed by urinary protein creatinine ratio

Every renal laboratory trigger or renal event as defined in Table 15-1 in Appendix 3 should be followed up by the Investigator or designated personnel.

7.6 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, patient or consumer (EMA definition).

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE (Table 7-2). Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Table 7-2 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) CRF (Yes/No)	Document in AE CRF	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.

7.7 Pregnancy reporting

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

[redacted]

the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications (with up to 12 months follow up after the birth of the baby, where consent is provided).

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the Investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

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

8 Data review and database management

Site monitoring

Before study initiation, at a site initiation visit, or at an Investigator's meeting, a Novartis representative will review the protocol and CRFs with the Investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to GCP, 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 CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. 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 patients/subjects will be disclosed.

[redacted]

8.1 Data collection

Designated Investigator staff will enter the data required by the protocol into the clinical database system. Designated Investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated Investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the Investigator will receive copies of the patient data for archiving at the investigational site.

8.2 Database management and quality control

Novartis staff review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated Investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the Investigator site.

Concomitant 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. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples processed centrally will have results sent electronically to Novartis.

Randomization codes and data about all study drug(s) dispensed to the patient 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 database will be sent electronically to Novartis (or a designated Clinical Research Organization (CRO)).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded 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.

8.3 Data monitoring committee (DMC)

An external and independent DMC will evaluate the unblinded data during the course of study, which will be provided by an independent and external Statistical Data Analysis Center. Data

[redacted]

may also be provided to Health Authorities, if required for an ongoing marketing authorization application regulatory review and Novartis will inform the DMC should this occur.

In addition, the DMC will review efficacy data from one prespecified interim efficacy and futility analysis when at least 180 patients and at least 36 patients from each age group have completed the study (i.e. reached a terminal endpoint or completed the 1 year study visit), and at least 40 patients have had an event in Category 1 or 2. Further details about interim analyses are provided in Section 9.6.

As necessary, the DMC may also review the data associated with the analysis of sparse PK steady state data from a subset of patients in Part 2 Group 2 (Section 9.5.1).

Both the DMC and Novartis (Section 8.5) will be responsible for the review of Part 1 PK/PD data and dose determination for Part 2 (Efficacy). Any major recommendation from the DMC will be communicated to the study Executive Committee and must be reviewed and ratified by the study Executive Committee in consultation with Novartis prior to its enactment. Further information is provided in the DMC Charter.

8.4 Adjudication committee

Clinical endpoint committee

All clinical events, which could potentially fulfill the Category 1 or 2 endpoints will be assessed during the study and reported to the Clinical Endpoint Committee for adjudication.

The CEC will review and adjudicate events including but not limited to deaths (CV and non-CV death), circulatory and/or respiratory mechanical assistance for life support, listing for heart transplantation, and clinical worsening of heart failure (with or without hospitalization) for endpoint determination. The detailed definitions of the endpoints, required documentation, and the adjudication process will be included in a separate CEC Manual.

Sites are instructed to take a conservative approach when reporting endpoints. If the Investigator suspects an endpoint may have occurred, it is best to report the event in the endpoint CRF.

Angioedema adjudication committee

If an angioedema or angioedema-like event occurs, the Investigator will complete case report forms for angioedema adjudication. 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 report 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.

8.5 Part 1 PK/PD data review

As described in Section 3.1, the age groups will be enrolled sequentially from Group 1 to Group 3. For the oldest age group (Group 1: 6 to < 18 years), the PK, PD, and safety data obtained from all 12 observations will be reviewed by the DMC prior to starting Group 2 in Part 1 and

[redacted]

to support the dose recommendation before patients will be enrolled into Part 2 of the same age group. Similarly, for Group 2 (1 to < 6 years), the PK, PD, and safety data obtained from all 12 observations will be reviewed by the DMC prior to starting Group 3 in Part 1 and to support the dose recommendation for Part 2 of the same age group. For Group 3 (1 month to < 1 years) the PK, PD, and safety data obtained from approximately 8 observations will be reviewed by the DMC to support the dose recommendation for Part 2 in the same age group. All suspect abnormalities will be discussed before enrollment into the next dose group/age group is allowed. The decision on the dosing for Part 2 (Efficacy) for each age group will be made jointly by Novartis and the DMC.

Data review is anticipated to include the following, when available:

- AEs and SAEs and their causal relationship to the study drug
- Evidence of pharmacodynamic interactions between LCZ696 and co-medications
- Vital signs
- Blood chemistry and hematology
- PK and PK/PD response

9 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

9.1 Analysis sets

For Part 1: All subjects with at least one dose of study drug will be included in safety analysis set. All subjects with evaluable PK/PD data will be included in the PK/PD data analysis.

For Part 2 (Efficacy), the following populations will be used for the statistical analyses

The full analysis set (FAS) will consist of all randomized patients with the exception for those patients who have not been qualified for randomization and have not received study drug, but have been inadvertently randomized into the study. Following the intent-to-treat principle, patients will be analyzed according to the treatment to which they were assigned at randomization. Efficacy variables will be analyzed based on the FAS as the primary population.

The Safety Population (SAF) will consist of all patients who received at least one dose of study drug and have at least one post-baseline safety assessment. Of note, the statement that a patient had no AEs also constitutes a safety assessment. Patients will be analyzed according to the treatment actually received. The safety population will be used for the analyses of safety variables.

The Per-Protocol (PP) population will be a subset of the FAS which will consist of the patients who do not have major deviations from the protocol procedures in the double-blind study stage. Major protocol deviations will be pre-specified prior to unblinding treatment codes for analyses. This supplemental efficacy population will be used to support the primary analysis results.

[redacted]

9.2 Patient demographics and other baseline characteristics

Summary statistics for Part 1 (PK/PD) and Part 2 (Efficacy) will be provided by treatment group for demographics and baseline characteristics, including age, age group (Group 1: 6 to < 18 years; Group 2: 1 to < 6 years; Group 3: 1 month to < 1 year), modified age group (Group 1: 6 to < 18 years; Group 2a: 2 to < 6 years; Group 3a: 1 month to < 2 years), sex, race, ethnicity, weight, height, body mass index (BMI), category of prior HF medication, HF etiology, prior HF hospitalization, NYHA/Ross class, [redacted] and vital signs. BMI will be calculated as weight (kg) / height^2 (m^2) from the collected height and weight at the Screening visit. Continuous variables will be summarized using n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency and percentage. Additionally, summary statistics will be provided by treatment and age group, and by treatment and modified age group, for demographics and baseline characteristics for both Part 1 and Part 2.

For Part 2 (Efficacy), baseline value is defined as the last non-missing assessment prior to the first dose of randomized study medication unless specified otherwise.

For Part 1 (PK/PD), all subjects with at least one dose of study drug will be included in the above analyses. For Part 2 (Efficacy), the FAS set will be the patient population for the above analyses.

9.3 Treatments

Part 1 (PK/PD)

The study drug administration (single dose of LCZ696 in mg/kg) will be summarized for subjects who received study drug during Part 1 (PK/PD). The summary will be conducted by age group and overall; and the summary will use mean, standard deviation, median, minimum, and maximum. The number and percentage of patients will be summarized by age group and dose levels (mg/kg).

Concomitant medications will be summarized by therapeutic class, preferred term (PT) and dose level for each age group and overall for all subjects who received study drug in Part 1 (PK/PD).

Part 2 (Efficacy)

The overall duration of the double-blind study drug will be summarized for the SAF population by treatment group using mean, standard deviation, median, minimum, and maximum. Additionally, the number and percentage of patients will be summarized by treatment group for duration category.

Concomitant medications will be summarized by therapeutic class, preferred term (PT), treatment group for the SAF population.

Additionally, all analyses conducted above for Part 2 (Efficacy) will be summarized by modified age group.

[redacted]

9.4 Analysis of the primary variable(s)

9.4.1 Variable(s)

Part 1 (PK/PD)

The objective of Part 1 of the study is to characterize PK and PD of LCZ696 in pediatric patients and compare PK, PD, and exposure-response with observed data in adult heart failure patients in order to determine the dose for Part 2 (Efficacy) of the study. In Part 1 (PK/PD) of the study, the pediatric patient population is divided into three age groups; Group 1: 6 to < 18 years old, Group 2: 1 to < 6 years old, and Group 3: 1 month to < 1 year old.

Considering various factors including factors such as ontogeny of enzymes/transporters, the variability in PK parameters is assumed to be similar between adult and pediatric HF patients (>3 months). Since LBQ657 is a metabolite, clearance and volume of distribution were not estimated in earlier clinical trials and coefficient of variation% (CV%) of total exposure was considered for sample size estimation. From previous clinical study in adult HF patients, the observed CV% for body-weight normalized LBQ657 exposure was 37.1% and the observed CV% for body-weight normalized clearance and volume of distribution of valsartan was 39.4% and 49.6%, respectively (CLCZ696A2117). Therefore 49.6% of CV% was assumed for sample size estimations. The sample size is up to 12 observations per age group (except Group 3 where N= 8 observations) to achieve 95% CI for geometric mean of PK parameters to fall between 60% and 140% range (95% CI: 71 – 141%) with 80% coverage probability.

A population PK model will be developed to describe incoming data from pediatric patients based on an established model developed for the adult HF population. The fidelity of the developed PK model will be cross validated for its robustness and precision to the observed data. The steady state population PK parameters including clearance, volume of distribution, Ka, T1/2, Cmax, Cmin, and AUC will be estimated. The impact of covariates such as eGFR, age, body weight, NYHA/Ross class, TBL, and AST levels will be evaluated.

Pharmacodynamic evaluations will include analysis of change in plasma cGMP, plasma BNP, plasma NTproBNP and urine cGMP. Dose and exposure-response relationship will be evaluated based on changes in plasma cGMP levels (and also plasma NTproBNP, plasma BNP, urine cGMP).

PKPD modeling of Part 1 data may be carried out, depending on the robustness of both the PK and biomarkers to be used to inform the dose justification for Part 2.

Part 2 (Efficacy)

The global rank primary endpoint is constructed through 2 steps:

- Step 1: Patients are classified into the 5 ordinal categories based on the logic described in Table 6-3 in Section 6.4.1.
- Step 2: Within each category, patients are ranked from worst to best based first on the subcategory if applicable, and then the ranking algorithm as explained in Table 6-3.

[redacted]

9.4.2 Statistical model, hypothesis, and method of analysis

The primary endpoint comparing the distributions for patients receiving LCZ696 and patients receiving enalapril will be assessed using a stratified Wilcoxon rank-sum analysis (Kawaguchi 2011), stratifying by modified age group (Group 1: 6 to < 18 years; Group 2a: 2 to < 6 years; Group 3a: 1 month to < 2 years) and NYHA/Ross class group (Class I/II; Class III/IV). The overall significance level (Type 1 error) of 0.05 (2-sided) will be used. In addition, the proportion of patients falling into each of the 5 ordered categories of the primary endpoint will be presented by treatment group. These proportions will be provided both hierarchically (only worst category counted for each patient), as the endpoint is defined, and overall, not accounting for whether a patient also had a worse event. Full analysis set will be used for these analyses.

In addition, the number and percentage of patients in each category will be provided by treatment group for each age group, each modified age group, and for overall.

Due to unresolvable technical reasons in study drug supply, the unforeseen intercurrent events of the USM leading to study treatment discontinuations are not related to disease progression, are not related to the assigned study treatment, and do not reflect a real-world setting. The exposure to the study treatment and study follow-up are reasonably long. Therefore, the on-treatment approach is considered to be more appropriate for the handling of USM-impacted patients in the primary analysis, utilizing the relevant components of the global rank endpoint including Category 1 and Category 2 status at the time of treatment discontinuation.

9.4.3 Handling of missing values/censoring/discontinuations

Part 1 (PK/PD)

All concentrations below the lowest limit of quantitation (LLOQ) or missing data will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics and for the calculation of PK parameters.

The statistical analysis will include all subjects with valid PK parameters.

Part 2 (Efficacy)

All efforts should be made to collect all information including vital status for all patients at the 52 week visit, or the last on-treatment assessment visit for the USM impacted patients.

For the primary efficacy endpoint, missing information will be handled as follows.

Patients will be classified into the worst possible category, based on available and retrievable information for the patient. Within Categories 1 and 2, patients will be further ranked according to the day of the last reliable information (for example, last day of contact). If the patient is not classified as Categories 1 or 2 (e.g. patient is alive and is documented to not have any WHF events), the same principle will be followed for ranking the patient.

If the 52 weeks measurements, or the last on-treatment assessment visit for the USM impacted patients, of NYHA classification or Ross classification and the PGIS score are missing then the last-observation-carried-forward (LOCF) technique will be used to impute the missing post-randomization values (for patients who do not experience any events in Category 1 or 2). Only post-randomization values will be used for imputation.

[redacted]

Categories 3, 4, and 5 will be determined based on available information if the NYHA/Ross, PGIS, and PedsQL physical functioning domain are not complete. When ranking these patients, the ranking algorithm will place the patients at the median for the missing assessment component(s).

9.4.4 Sensitivity analyses

In addition to the primary analysis, the primary efficacy endpoint will also be analyzed using the same primary analysis model in the PP population.

For the USM-impacted patients, the full data, including the off-treatment part, from the impacted patients will be included as a sensitivity analysis.

[redacted]

9.4.5 Supportive analyses

To characterize the treatment difference between LCZ696 compared to enalapril, an ordered categorical endpoint with 5 categories, as used for deriving the primary endpoint variables, will be analyzed using a stratified Wilcoxon rank-sum test. The number and percent of patients within each individual category will be summarized by treatment group.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

Part 1 (PK/PD)

The objective of this part is to characterize the PK and PD of LCZ696 in pediatric patients with HF. Primary variables are described in Section 9.4.1. There are no specific secondary variables in Part 1.

Part 2 (Efficacy)

To determine whether LCZ696 is superior to enalapril, Part 2 (Efficacy) variables include

- Time to first Category 1 or 2 event
- Change from baseline (randomization visit) for NYHA/Ross class
- Change from baseline (randomization visit) for PGIS
- Population PK of LCZ696 exposure in pediatric patients with HF, including an assessment of steady-state sparse PK data in a subset of Group 2 patients, to further confirm the LCZ696 target dose for Group 2.

The full analysis set will be used in analyses for secondary endpoints.

With the same reasons described for the primary analysis, for the USM-impacted patients, the relevant assessments at the time of treatment discontinuation will be utilized in the secondary analyses (on-treatment approach).

For the USM-impacted patients, the full data, including the off-treatment part, from the impacted patients will be included as the sensitivity analyses.

[redacted]

The time to event endpoints will be analyzed using Cox's proportional hazards model with treatment as fixed-effect factor stratified by modified age group (Group 1: 6 to < 18 years; Group 2a: 2 to < 6 years; Group 3a: 1 month to < 2 years). The estimated hazards ratio and the corresponding two-sided confidence interval will be provided.

NYHA/Ross class and PGIS will be compared for LCZ696 and enalapril at week 52, respectively. Change from baseline at week 52 for these assessments will be analyzed based on a proportional cumulative odds model, stratified by modified age group (Group 1: 6 to < 18 years; Group 2a: 2 to < 6 years; Group 3a: 1 month to < 2 years) in which treatment will be included as fixed-effect factors and baseline value as a covariate. The treatment comparison between LCZ696 and enalapril for the secondary objective is to be made at week 52. This model assumes that the treatment effect sizes across measurement categories are the same. The effect size estimates and their 95% confidence intervals will also be provided.

Part 2 Age Group 2 (PK)

The population PK Model will be updated with sparse PK data from a subset of Part 2 Group 2 patients for the purpose of further confirming the target dose for Age Group 2. This will be performed prior to database lock and requires unblinding, and as such will be done by an unblinded team who is not involved in the conduct of the study.

9.5.2 Safety variables

Safety data from Part 1 (PK/PD) and Part 2 (Efficacy) will be presented separately.

The assessment of safety will be based primarily on the frequency of AEs, SAEs, and laboratory abnormalities. Other safety data, such as specific adverse events of interest (i.e. hypotension, hyperkalemia, renal impairment, angioedema), will be summarized as appropriate.

The incidence of treatment-emergent AEs (new or worsened) will be summarized by primary system organ class, preferred term, severity, and relationship to study drug. In addition, the incidence of death, SAEs, and AEs leading to discontinuation will be summarized separately by primary system organ class and preferred term.

Laboratory data will be summarized by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (mean, medians, standard deviations, ranges) and by the flagging of notable values in data listings.

Data from other tests (e.g. vital signs) will be descriptively summarized as appropriate by presenting absolute values and change from baseline at each assessment time point. Any other information collected will be listed as appropriate.

Safety analyses will be performed based on all patients who received study drug during Part 1 and the safety population for Part 2 (Efficacy). There will be no formal statistical inference analysis.

[redacted]

9.5.3 Biomarkers

Data for each biomarker will be summarized by treatment group and time point using descriptive statistics (n, mean, median, SD, min, max, n below LLOQ, n above ULOQ, geometric mean and 95% confidence interval around the geometric mean). Summary statistics for change from baseline at each time point will also be presented.

[redacted]

In addition, as a supportive analysis, the same MMRM analysis as above will be performed using data from all post-baseline scheduled visits (Week 4, Week 8, Week 12 and Week 52).

9.5.4 PK/PD

The relationship between LBQ657 exposure to changes in plasma BNP, plasma NTproBNP and plasma cGMP will be explored using exposure-response models.

[redacted]

[redacted]

9.6 Interim analyses

An external DMC will monitor patient safety data during the course of the study. For this study, the DMC will review safety data on a regular frequency, e.g. every six months. DMC may request additional safety data review. Such safety analyses do not inflate the type I error for the primary efficacy hypothesis testing and thus require no multiplicity adjustments.

Part 1 (PK/PD)

The available PK, PD and safety data from each age group will be analyzed to confirm the dose for that age group in Part 2 and to start the next younger age group in Part 1. A sample size of up to 12 observations per age group for Groups 1 and 2 is prospectively planned to evaluate the PK and PD of LCZ696 analytes following single dose administration of LCZ696 0.8 mg/kg (N=6 observations) and LCZ696 3.1 mg/kg (N=6 observations). For Group 3 a sample size of up to 8 observations is prospectively planned to evaluate the PK and PD of LCZ696 analytes following single dose administration of LCZ696 0.4 mg/kg (N= approximately 4 observations) and LCZ696 1.6 mg/kg (N= approximately 4 observations). Since the pharmacokinetics of LCZ696 is demonstrated to be dose independent, dose-normalized PK parameters from both dose cohorts will be combined. If no age effect on PK is observed, then data from two different groups may be pooled.

Part 2 (Efficacy)

Interim efficacy analysis of the global rank endpoint

It is planned to have a formal interim efficacy analysis. The interim efficacy analysis is planned when at least 180 patients (at least 36 patients from each age group) have completed the study (i.e., reached a terminal endpoint or completed the 1 year study visit), and at least 40 patients have had an event in Category 1 or 2. Some adjustment to the time of interim analysis may be made to coincide with the regular DMC meetings. One-sided tests will be performed and appropriate statistical adjustments for the interim efficacy analysis actually performed will be made to ensure the overall one-sided type I error of 0.025 (Lan-DeMets spending function to match an O'Brien-Fleming stopping boundary). For the interim efficacy analysis, the analysis dataset will comprise all patients who completed the study by the cut-off date.

The trial may only be concluded early for efficacy, if a significant difference between two treatment arms for the primary efficacy endpoint is achieved by crossing the pre-specified boundary at the interim efficacy analysis and the overall risk/benefit profile is considered positive. A futility analysis will also be incorporated into the interim analysis plan, whereby the study can be stopped if there is evidence that the study is unlikely to have a positive outcome. Details of the stopping rules for the futility analysis will be described in the interim analysis statistical plan.

[redacted]

The interim analysis will be performed by an external independent statistician at an external data analysis center, who will not be involved in the study conduct. The results will be reviewed by the independent DMC. Investigators and others who are involved in the conduct of the trial and in the analysis of the final trial results, or who have contact with study centers, will remain blinded to the treatment codes and interim analysis results until all monitoring decisions have been made and the database has been unblinded for final analysis. Additional details of the interim analysis plan for efficacy and safety will be described in the [DMC charter].

If the study is stopped early at interim analysis due to overwhelming efficacy, then the pre-specified percentage of patients will be used for this analysis. Additional sensitivity analysis for the primary global rank endpoint (and components) will be performed at time points of 30 days, 90 days, and 180 days. For time to event endpoints, annualized event rates will be calculated.

[redacted]

9.7 Sample size calculation

Part 1 (PK/PD)

From a prior clinical study in adult HF patients, the observed CV% for body-weight normalized LBQ657 exposure was 37.1%, and the observed CV% for body-weight normalized clearance and volume of distribution of valsartan was 39.4% and 49.6%, respectively (Study CLCZ696A2117). Therefore, 49.6% of CV% was assumed for sample size estimations. A sample size of 12 observations (except Group 3 where N=–approximately 8 observations) is expected to have 80% probability that the 95% CI of the point estimate for the geometric mean estimates of clearance and volume of distribution will be between 60% and 140% range (95% CI: 71 – 141%).

[redacted]

Part 2 (Efficacy)

In the Carvedilol Pediatric HF study (Shaddy 2007) for the subgroup of systemic left ventricle patients, the improvement rate of the placebo group was 51%, while the improvement rate in the carvedilol group was 64%. This was a 13% increase in absolute improvement rate over 8 month treatment period. Most of the patients in the carvedilol and placebo groups received ACEI treatment.

Table 9-1 presents the assumed underlying probabilities for each category of the primary endpoint in Part 2 (Efficacy) using data from the Carvedilol Pediatric HF study data (Shaddy 2007). It is assumed that the probability for patients receiving LCZ696 and enalapril who will have an event of death, circulatory and/or respiratory mechanical support or UNOS 1A heart transplant listing (Category 1) is similar to what was observed for the carvedilol and placebo groups in the Carvedilol Pediatric HF study. It is also assumed that the probability of patients experiencing Worsening HF (Category 2) is similar to Hospitalization for HF observed in the Carvedilol Pediatric HF study. Thus, for Categories 1 and 2, the events percentages are based on the Carvedilol Pediatric HF study (Shaddy 2007). The probability of an improved outcome for enalapril patients is assumed to be the same as for the placebo group in the carvedilol study, and the probability for the LCZ696 patients is assumed to be the same as observed for carvedilol patients in the Carvedilol Pediatric HF study. The probabilities for the worsened and unchanged categories are formed by splitting the remaining probability approximately equally for these two categories.

Table 9-1 Assumed percentage of patients in each category of the primary efficacy endpoint in Part 2 by treatment group at Month 8 (Week 32)

Category	LCZ696 (%)	Enalapril (%)
1. Clinical event – death / heart transplant listing / mech. support	6	9
2. Clinical event – WHF	10	13
3. Worsened functional class: NYHA/ Ross Classification or worsened PGIS	9	14
4. Unchanged functional class: NYHA/ Ross Classification and unchanged PGIS	11	13
5. Improved functional class: NYHA/ Ross Classification or Improved PGIS	64	51

The projected event percentages presented in Table 9-1 are based on the 8 month treatment period estimates. For a 52 weeks treatment period (Table 9-2), for Categories 1 and 2, the anticipated events percentages are calculated based on an exponential distribution assumption, extending from Month 8 to Month 12; and the remaining percentages within each treatment group are shared by Categories 3, 4, 5 according to their corresponding proportions at Month 8 (i.e. according to Table 9-1, 9 : 11 : 64 for the LCZ696 group, and 14 : 13 : 51 for the enalapril group). The treatment difference represented in Table 9-2 represents a Mann-Whitney-Wilcoxon Odds of 0.753.

[redacted]

Table 9-2 Assumed percentage of patients in each category of the primary efficacy endpoint in Part 2 by treatment group at Month 12 (Week 52)

Category	LCZ696 (%)	Enalapril (%)
1. Clinical event – death / heart transplant listing / mech. support	9	13
2. Clinical event – WHF	15	19
3. Worsened functional class: NYHA/ Ross Classification or worsened PGIS	8.1	12.2
4. Unchanged functional class: NYHA/ Ross Classification and unchanged PGIS	10.0	11.3
5. Improved functional class: NYHA/ Ross Classification or Improved PGIS	57.9	44.5

The primary efficacy analysis will be a stratified Wilcoxon rank-sum test with alpha level of 0.05%, (two-sided). For the analysis of an ordered categorical endpoint with an underlying distribution as presented in Table 9-2, there is approximately 70% power with a sample size of 177 patients per group (354 total patients). Sample size calculations for the ordered categorical test (ordered categorical Mann-Whitney/Wilcoxon rank sum test) were determined using nQuery. Using a global ranked endpoint, the power under the same assumptions is expected to increase. While the exact increase in power is dependent on the distribution of the ranking within each category, simulation studies have demonstrated that the power for the global rank endpoint increases 10-20% more than with the ordered categorical analysis when the power of the ordered categorical endpoint is more than 50% (Sun 2012). Based on the assumptions stated, the power is estimated to be at least 80% for this study.

The sample size is further increased to account for a single planned interim analysis to be performed when approximately 50% of the patients (and at least 36 patients from each age group) have completed the study (50% information fraction). This interim analysis will be done to allow for early stopping of the study in the event that overwhelming positive efficacy is observed at the time of the interim analysis. Using the Lan-DeMets alpha spending function of the O'Brien-Fleming stopping boundary, a sample size of 180 patients per group (360 patients total) will provide at least 80% power for a test of the primary endpoint including a planned interim analysis. Further simulations will be performed to ensure that the estimated sample size maintains the targeted power when accounting for the interim analysis.

10 Ethical considerations

10.1 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 Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

[redacted]

10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing written (witnessed, where required by law or regulation), 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 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. all of the procedures described in the protocol). The process of obtaining informed consent and 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 ICH 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 and for 7 days after study drug discontinuation. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 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 patients/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 monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, 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 immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

[redacted]

11 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 patients/subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an Investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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.

11.1 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 intended to eliminate an apparent immediate hazard to patients/subjects 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 patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

12 References

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13 Appendix 1: Clinically notable laboratory values and vital signs

Table 13-1 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

[redacted]

Parameter	Conventional Alert Value	Conventional Units	SI Alert Value	SI Units
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

Table 13-2 Criteria for clinically notable vital signs

Age	HR [min^{-1}]	SBP [mmHg]	DBP [mmHg]	RR [min^{-1}]
1-<3 months	<90, >160	<60, >95	<40, >50	<25, >60
3-<6 months	<80, >130	<60, >100	<40, >60	<20, >50
6-<12 months	<70, >130	<60, >110	<45, >70	<15, >45
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]

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

Table 14-1 Liver event and laboratory trigger definitions

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

*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 14-2 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 CRF	ALT, AST, TBL, 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 CRF	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 CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at Investigator discretion)
> 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 CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at Investigator discretion)

[redacted]

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	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 CRF	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 CRF	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 CRF	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 • Complete liver CRF	Investigator discretion

[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]

15 Appendix 3: Specific renal alert criteria and actions

Table 15-1 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	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

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 CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed.

[redacted]

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.

15.1 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 randomization.

Two types of response to serum creatinine increase are described:

1. Surveillance situation

If, at any time after randomization, eGFR%* decreases by ≥ 50% from baseline (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.

2. Action situation

If a patient eGFR* decreases by ≥ 50% from baseline (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

[redacted]

16 Appendix 4: American heart association (AHA) pediatric advanced life support (PALS) guidelines

Table 16-1 5th percentile systolic blood pressure 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

[redacted]

16 years	5th	90
17 years	5th	90

* AHA PALS guidelines 2010 (Kleinman 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 BP percentile up to 10 years. For children 1 month to < 1 year and >10 years, the AHA PALS guidelines 2010 5th percentile is set at 70 mmHg and 90 mmHg respectively. NOTE: This formula approximates the population-based 5th percentile BP data; however, the margin of error increases with increasing age, with the PALS formula value generally providing a lower value.

16.1 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. The dose re-challenge and medications adjust guidelines described in Section 5.5.5 should be adhered to as much as possible.

[redacted]

17 Appendix 5: Treatment guidelines for elevated potassium and hyperkalemia (serum potassium greater than or equal to 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 less than or equal to 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 greater than or equal to 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.

[redacted]

18 Appendix 6: Reference table - blood volume by weight

Table 18-1 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
20	1600	40	80
20.5	1640	41	82
21	1680	42	84

[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)
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 PK, biomarker and 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

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

[redacted]

19 Appendix 7: NYHA/Ross classification

For older children 6 to less than 18 years old, the Investigator will determine the appropriate NYHA class of heart failure. Classification criteria are as follows:

- NYHA Class I: No limitation - ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation
- NYHA Class II: Slight limitation of physical activity - comfortable at rest, ordinary physical activity results in fatigue, palpitation, dyspnea, or angina
- NYHA Class III: Marked limitation of physical activity - comfortable at rest, less than ordinary activity will lead to symptoms
- NYHA Class IV: Inability to carry on any physical activity without discomfort - symptoms of congestive failure present even at rest; with any physical activity, increased discomfort is experienced

For younger children less than 6 years old, the Investigator will determine the appropriate Ross class of heart failure. Classification criteria are as follows:

- Ross Class I: No limitation or symptoms.
- Ross Class II: No growth failure.
  Mild tachypnea with feeds in infants and/or
  Mild diaphoresis with feeds in infants and/or
  Dyspnea on exertion in older children.
- Ross Class III: Growth failure. Prolonged feeding time in infants.
  Marked tachypnea with exertion or with feeding.
  Marked diaphoresis with exertion or with feeding.
- Ross Class IV: Symptomatic at rest with the following sign/symptom(s):
  Tachypnea and/or
  Retractions and/or
  Grunting and/or
  Diaphoresis.

[redacted]

20 Appendix 8: Patient global impression of severity (PGIS)

For patients 7 to < 18 years old:

- How would you describe the severity of your heart failure symptoms **over the past 7 days**? (None / Mild / Moderate / Severe / Very Severe)

For parents/caregivers of patients < 5 years of age:

- How would you describe the severity of your child's heart failure symptoms **over the past 7 days**? (None / Mild / Moderate / Severe / Very Severe)

For patients 5 to < 7 years old:

- Point to the one face that best shows how your heart problems have been **over the past 7 days**?

[redacted]

[redacted]

21.1 Teen report (ages 13-18)

DIRECTIONS

On the following page is a list of things that might be a problem for you.
Please tell us **how much of a problem** each one has been for you during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

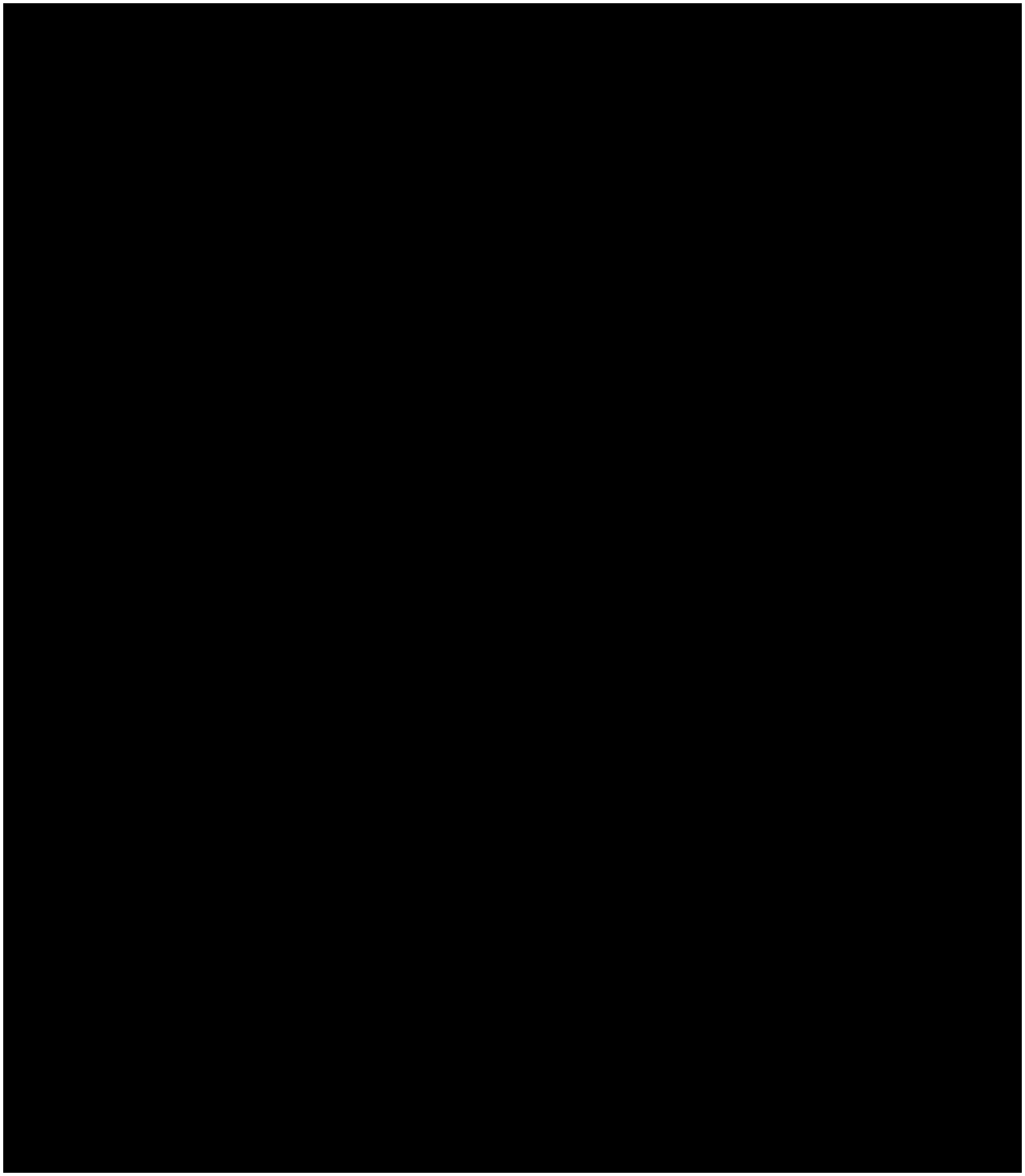
[redacted]

*In the past **7 days**, how much of a **problem** has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

PedsQL 4.0 - (13-18) Acute
03/00
PedsQL-4.0-Core-Acute – United States/English – Original version
PedsQL-4.0-Core-Acute-A_AU4.0_eng-USori

[redacted]



21.3 Child report (ages 8-12)

DIRECTIONS

On the following page is a list of things that might be a problem for you.
Please tell us **how much of a problem** each one has been for you during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

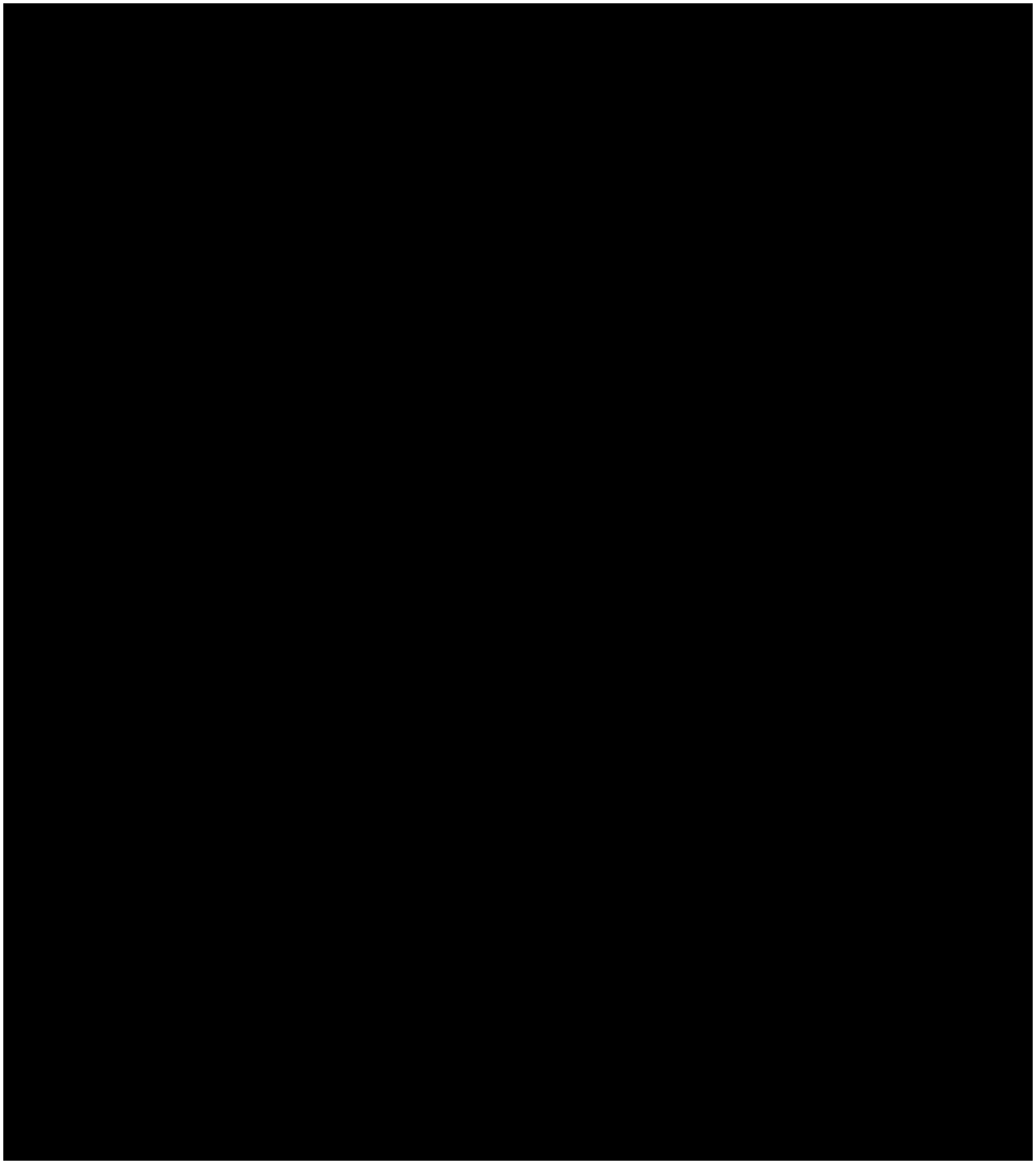
[redacted]

*In the past **7 days**, how much of a **problem** has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

[redacted]

[redacted]



21.5 Young child report (ages 5-7)

Instructions for interviewer:

I am going to ask you some questions about things that might be a problem for some children. I want to know how much of a problem any of these things might be for you.

Show the child the template and point to the responses as you read.

If it is <u>not at all</u> a problem for you, point to the smiling face

If it is <u>sometimes</u> a problem for you, point to the middle face

If it is a problem for you <u>a lot</u>, point to the frowning face

I will read each question. Point to the pictures to show me how much of a problem it is for you. Let's try a practice one first.

	Not at all	Sometimes	A lot
Is it hard for you to snap your fingers	☺	😐	☹

Ask the child to demonstrate snapping his or her fingers to determine whether or not the question was answered correctly. Repeat the question if the child demonstrates a response that is different from his or her action.

[redacted]

Think about how you have been doing for the past 7 days. Please listen carefully to each sentence and tell me how much of a problem this is for you.

After reading the item, gesture to the template. If the child hesitates or does not seem to understand how to answer, read the response options while pointing at the faces.

PHYSICAL FUNCTIONING *(problems with…)*	Not at all	Some-times	A lot
1. Is it hard for you to walk	0	2	4
2. Is it hard for you to run	0	2	4
3. Is it hard for you to play sports or exercise	0	2	4
4. Is it hard for you to pick up big things	0	2	4
5. Is it hard for you to take a bath or shower	0	2	4
6. Is it hard for you to do chores (like pick up your toys)	0	2	4
7. Do you have hurts or aches (***Where?*** _____)	0	2	4
8. Do you ever feel too tired to play	0	2	4

How much of a problem is this for you?

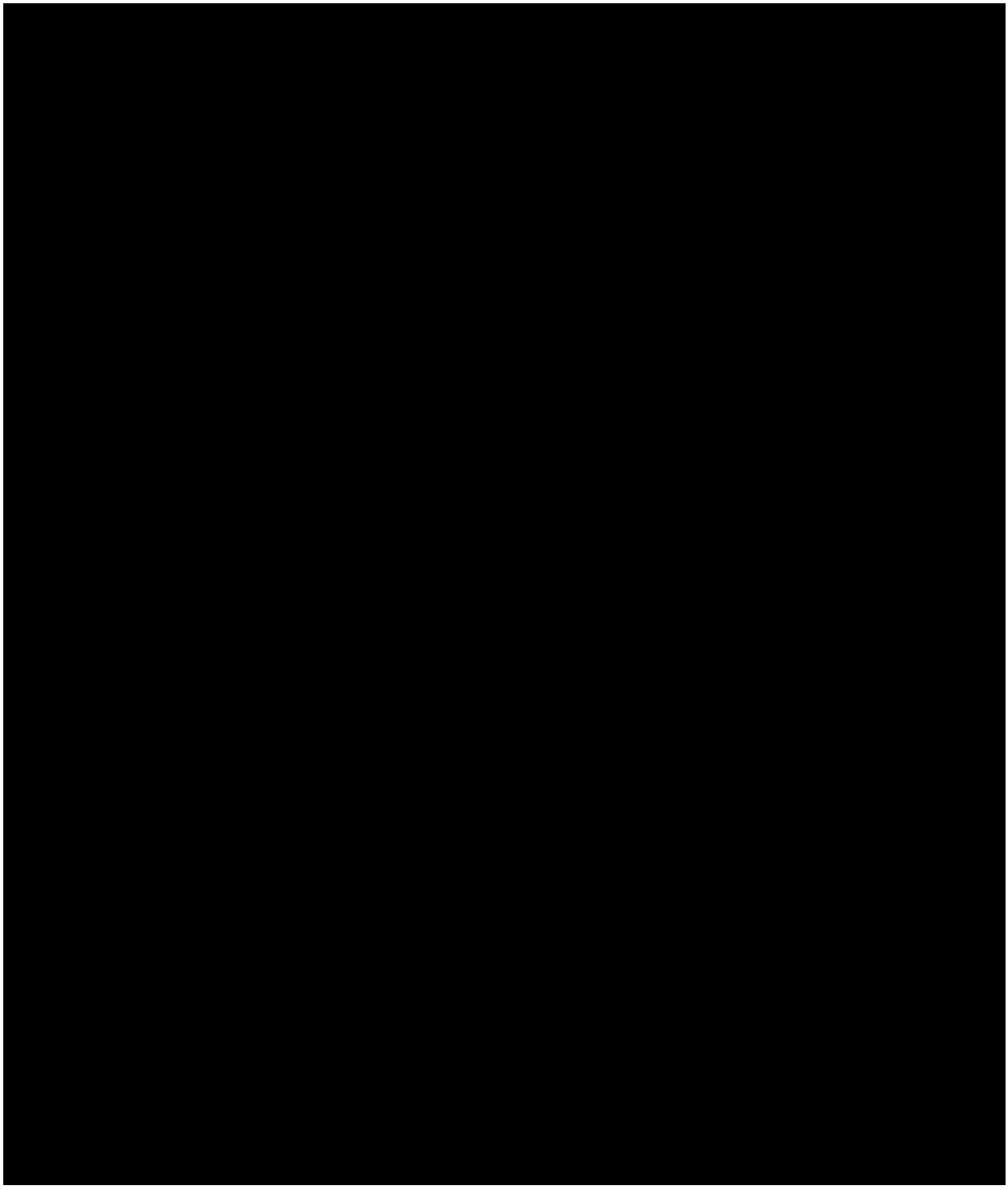
Not at all

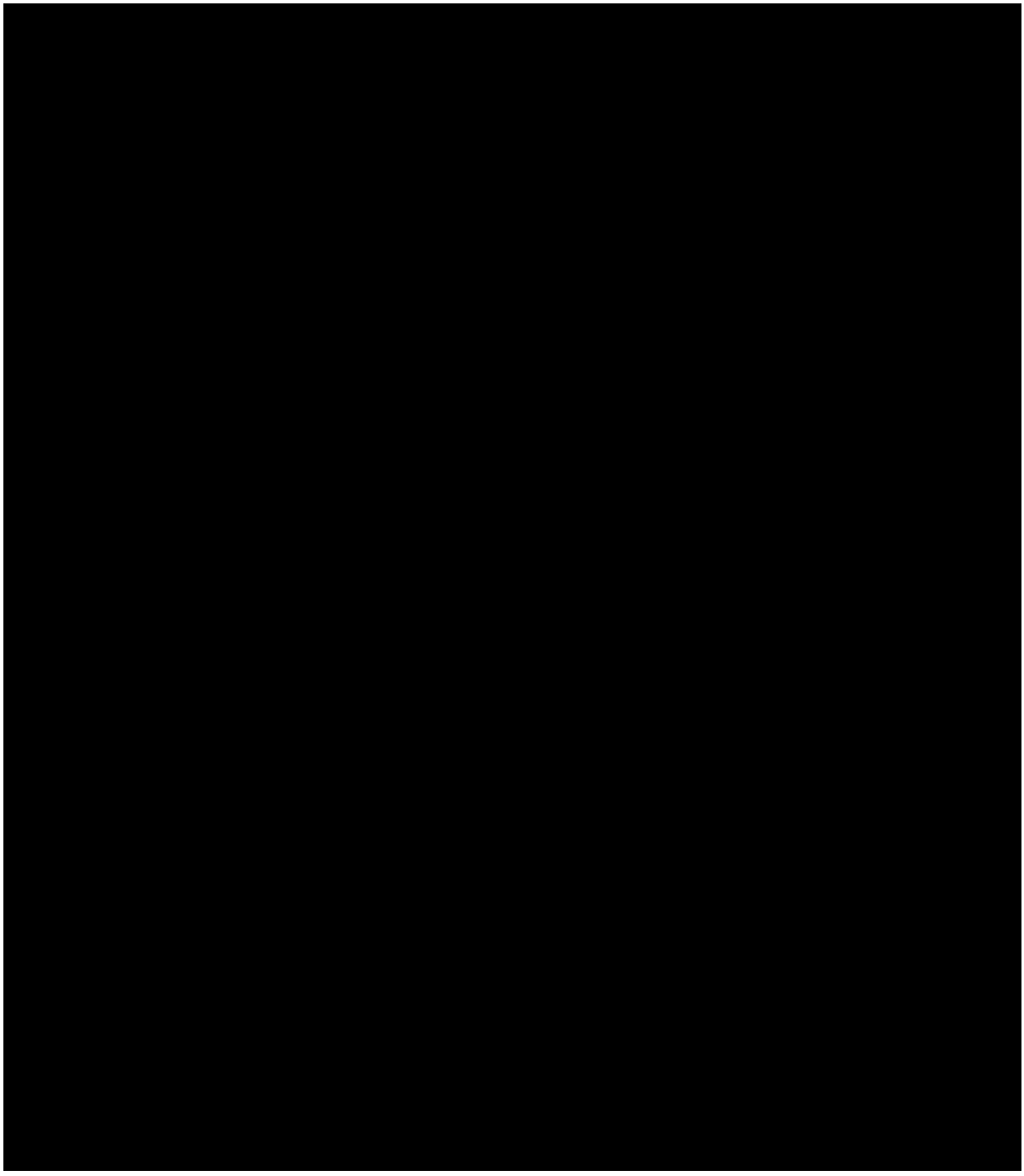
Sometimes

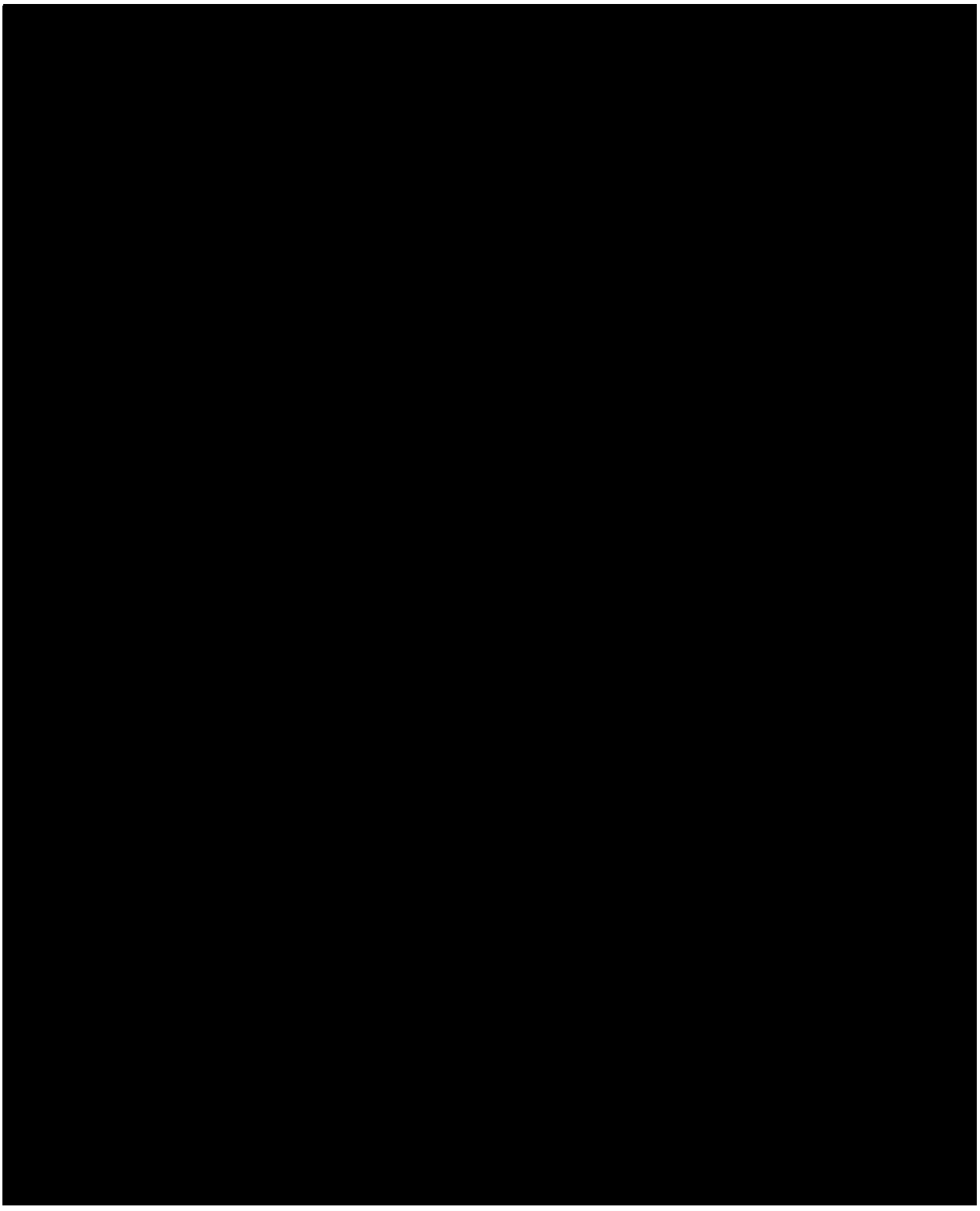
A lot

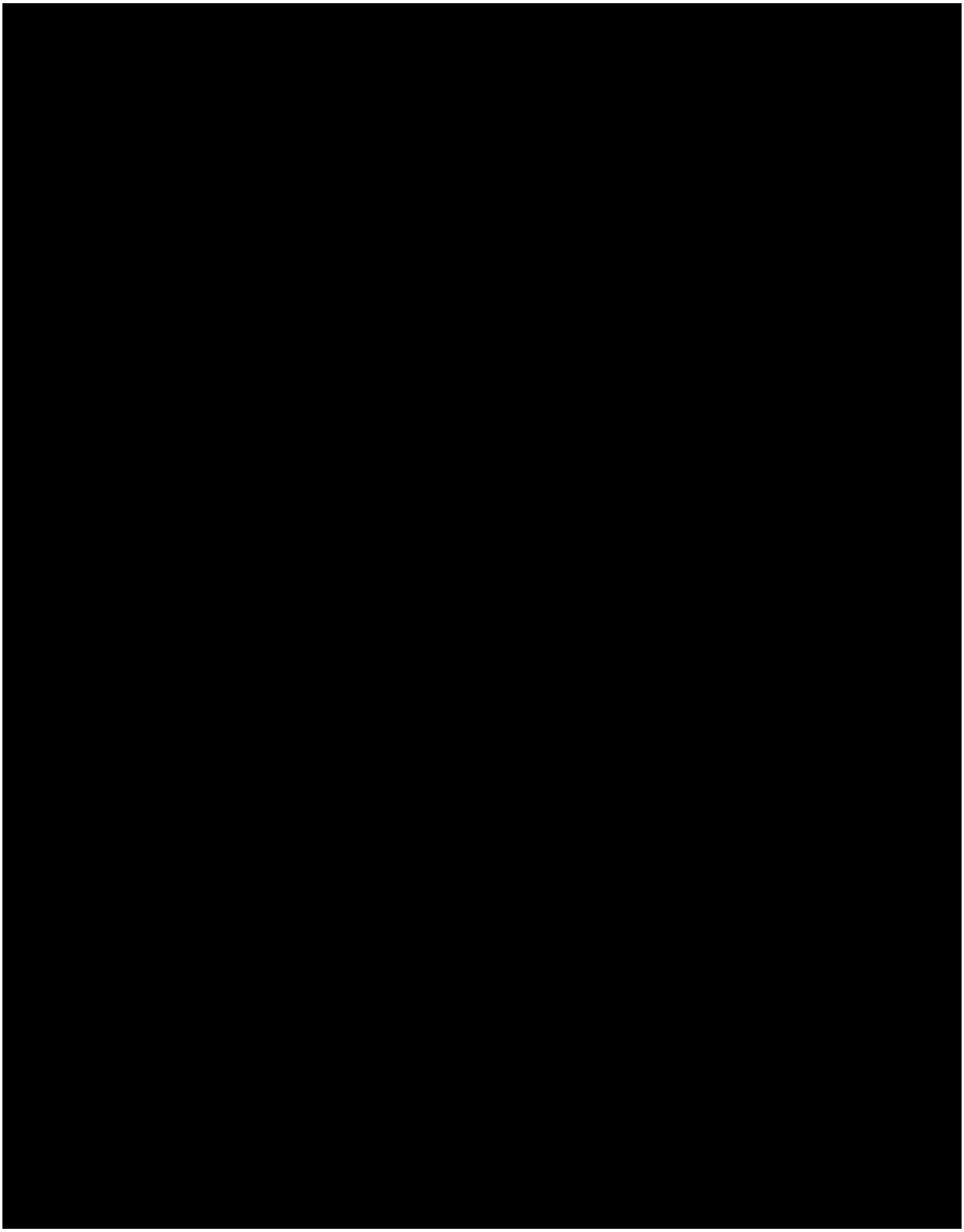
[redacted]

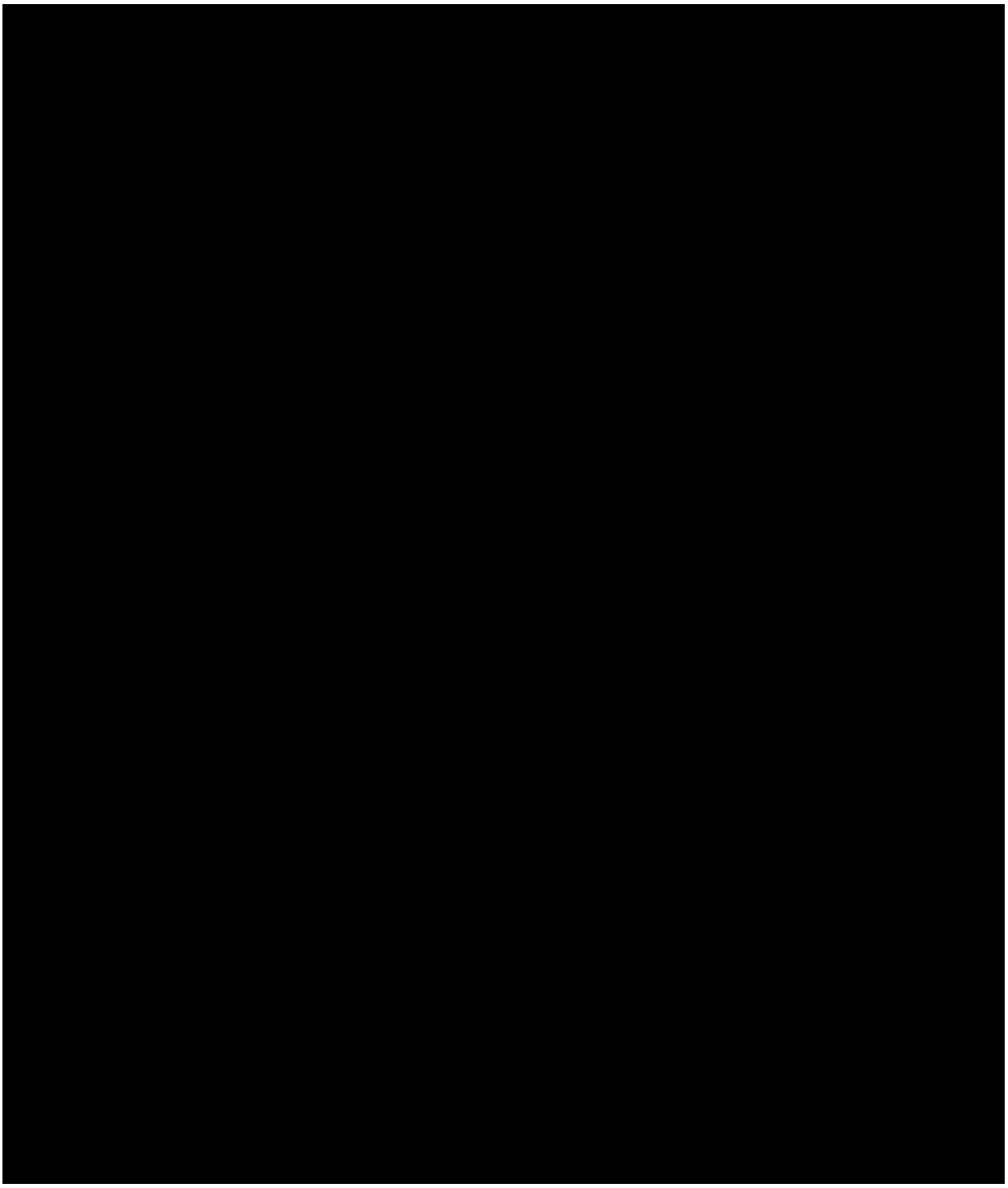
[redacted]

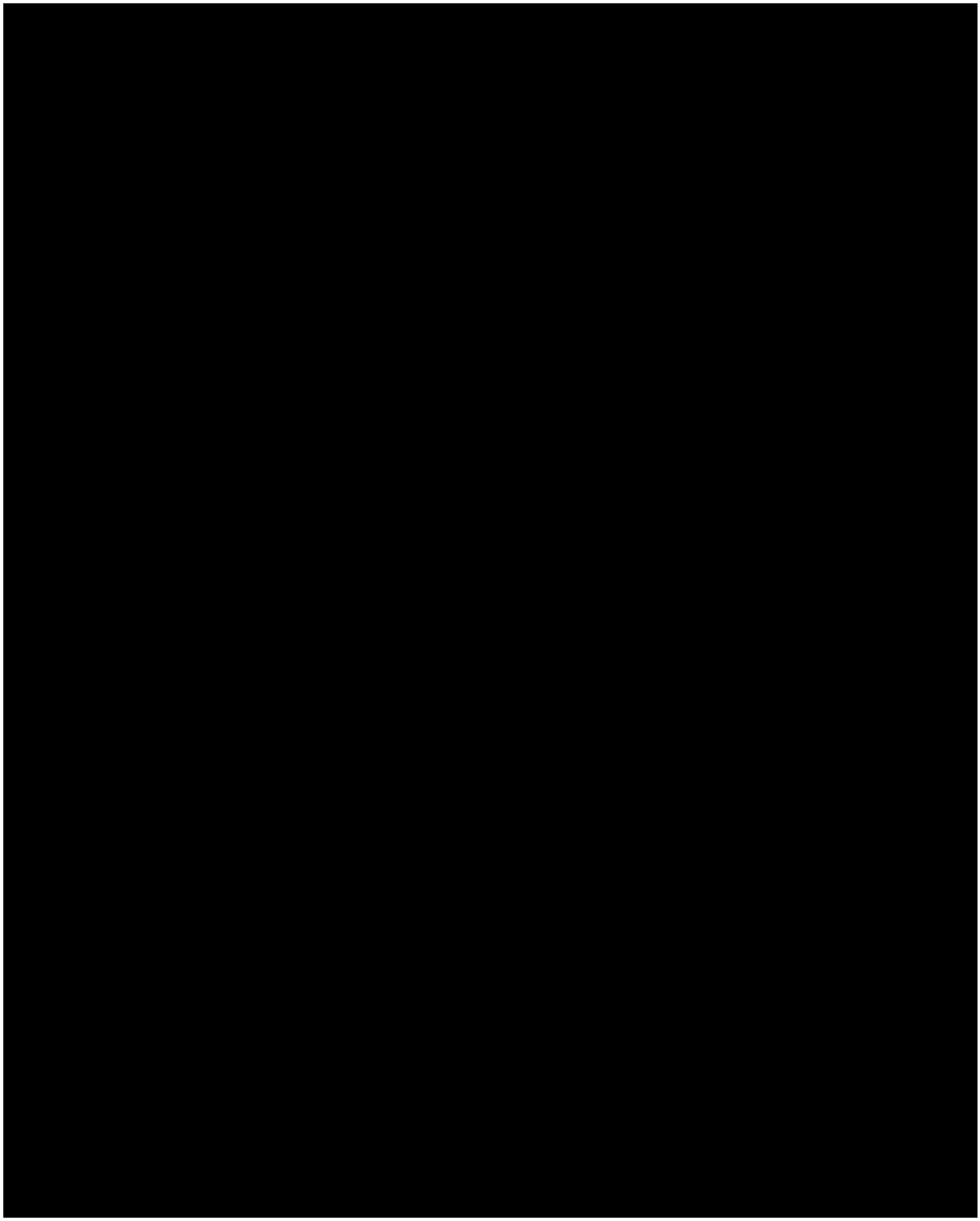












22 Appendix 10: GFR by age

Table 22-1 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)***
1 month to < 3 months	≥ 14	< 14
3 months to < 6 months	≥ 17	< 17
6 months to < 12 months	≥ 23	< 23
12 months to < 19 months (1 year, 7 months)	≥ 31	< 31
19 months to < 18 years	≥ 38	< 38

* Age rounded to nearest whole number
** Initiation/up-titration criteria
*** Exclusion criteria

Source: (Peters 1999)

[redacted]

[redacted]

[redacted]

25 Appendix 13: Safety Monitoring for Age Group 3 patients

This Appendix applies only to Part 2 Age Group 3 patients (i.e. patients who are 1 month to <1 year old at randomization) and provides Safety Monitoring requirements for the initial up-titration portion of the study for Part 2 Age Group 3 patients.

25.1 Safety Monitoring for Age Group 3 patients:

Starting with the first dose of study medication, vital signs must be checked for up to 4 hours after the initial dose at each study drug dose level (i.e. dose levels 1x through 4x, as applicable). (Note: This does not apply for up-titrations following study drug interruptions or down-titrations, up to the prior achieved maximal dose level.) Patients are to remain in the study site clinic for this 4-hour post-dose Vital Sign monitoring period. Vital signs (i.e. blood pressure and heart rate) are to be measured pre-dose (time 0), and post-dose at 0.5, 1, 2, 3 and 4 hours. These data are to be recorded on the CRFs as well as in the source documentation.

The Investigator is to follow up with the parents of the Part 2 Group 3 patient by phone, 3 days (+/- 1 day) after the initial dose of the study medication at each dose level, checking for symptoms of hypotension. This does not apply for up-titrations following study drug interruptions or down-titrations. up to the prior achieved maximal dose level.

Examples of signs and/or symptoms of hypotension in infants:

- Not feeding or eating as they usually do
- Not breast-feeding or drinking milk from a bottle (as it applies) as they usually do
- Acting more fussy or tired than usual
- More difficult than usual to arouse from a nap or sleep
- Breathing faster than normal
- Unusually cold arms, legs, hands and/or feet: change from how they usually are
- Change in appearance of skin: pale or mottled skin (spotted, blotchy, varicolored skin)
- Decrease in amount of urine made; producing very little urine or not at all

If any signs and/or symptoms of hypotension are reported by the parents/guardians, the parents/guardians should be instructed to have their child seen by their local provider or at the study site as quickly as possible, so their vital signs can be assessed.

[redacted]

26 Appendix 14: Up-titration dosing instructions for patients in Age Group 3 (1 month to <1 year at randomization) who turn 1 year old during Part 2

This Appendix applies only to Part 2 Age Group 3 patients (i.e. patients who are 1 month to <1 year old at randomization) and provides Up-titration instructions for patients randomized into Age Group 3. who turn 1 year old during Part 2 of the study.

26.1 Up-titration instructions for Age Group 3 patients who turn one year old during Part 2

Randomized, ongoing, Part 2 Age Group 3 patients who are safely tolerating Age Group 3 Dose Level 4x (i.e. LCZ696/Placebo, 2.3 mg/kg bid / Enalapril/Placebo 0.15 mg/kg bid) for at least 2 weeks, and who turn 1 year old during the study, may be up-titrated, if it is the patient's best interest to be up-titrated based on the medical judgement of the investigator. Under these circumstances, the patient may be further up-titrated to Age Group 3 Dose Level 5x (i.e. LCZ696/Placebo, 3.1 mg/kg bid / Enalapril/Placebo 0.2 mg/kg bid).

See Table 26-1 for dose level up-titration information for Age Group 3 patients who have turned 1 year old during Part 2 of the study.

Table 26-1 Part 2 (Efficacy): Study drug dose level for double-blind enalapril and LCZ696 for Age Group 3 patients who turn 1 year old during the study

Dose levels for pediatric formulation	Enalapril dose^	LCZ696 dose^
Dose Level 5x for Age Group 3 patients who turn 1 year old during the study	0.2 mg/kg bid.	3.1 mg/kg bid.

^Note: The maximum LCZ696 dose and enalapril dose allowed for patients who turn 1 year old during the Part 2 study, is Dose Level 5x (3.1 mg/kg bid and 0.2 mg/kg bid, respectively).

A subsequent planned study visit or an unscheduled visit (see Table 6-2 Part 2 Assessment Schedule) can be utilized for the additional up-titration visit for the Age Group 3 patients that turn 1 year old during the study. The timing of the up-titration visit, where applicable, will vary from patient to patient.

Abbreviated safety labs: For Age Group 3 patients who are ≥1 year old and who are further up-titrated to Dose Level 5x, at a scheduled visit or at an unscheduled visit, abbreviated safety labs are to be done at this up-titration visit for Dose Level 5x.

All safety requirements for dose up-titration (and down titration), that are outlined in the protocol in Section 5.5.5, Permitted dose adjustments and interruptions of study treatment, apply to the above described dose up-titration for patients that have turned 1 year old during part 2.

[redacted]

27 Appendix 15: Urgent safety measure (USM)

This appendix describes the USM implemented in consideration of a quality event affecting the active comparator used in this study, effective 26 October 2021. An out of specification (OOS) result for an unspecified degradation product (observed: 0.3% vs. requirement: ≤ 0.2%) for both enalapril maleate 5 mg and 10 mg, packaged in alu-alu blisters by Novartis for this clinical trial, was observed in representative batches during supportive stability testing. As a result, the assigned shelf-life of 24 months of enalapril 5 mg and 10 mg in alu-alu blisters can no longer be supported for the current batches in use in the study and only a shelf-life of 12 months and 18 months, respectively, is supported. This finding impacts the batches currently in use in the trial of enalapril 5 mg and 10 mg as well as one batch of enalapril 5 mg and 10 mg used earlier in the study. The current clinical trial supply of enalapril 5 mg is beyond the revised supported 12-month shelf-life (expiry date was 31 March 2021). The current supply of enalapril 10 mg has a revised supported expiry date of 18 months lasting up to 31 October 2021. The finding only relates to enalapril 5 mg and 10 mg in alu-alu blister packs. The placebo of enalapril 5 mg and 10 mg, as well as all LCZ696/placebo and Enalapril/placebo 2.5 mg, are not impacted.

What follows outlines the safety measures that have been implemented for the 31 patients who were ongoing and receiving study medication at the time the USM was initiated.

The USM includes the following:

- Investigational medicinal product (IMP) dispensation was blocked in the IRT system by Novartis
- All patients who were receiving study medication at the time the USM was initiated, had to discontinue study treatment by 31 October 2021 and change to local standard of care, respecting any required washout periods. These patients were to attend an unscheduled visit at the site by 31 October 2021, or as soon as possible thereafter, for safety and efficacy assessments (see Section 27.1 for additional details).
- It was requested for all patients to return IMP in their possession by 31 October 2021.
- All IMP is to be removed from the sites for destruction per local practices.

27.1 Instructions for patients impacted by the USM

For patients who discontinued study treatment for other reasons before the USM was implemented but were being followed in the study at the time the USM was initiated, instructions are as follows:

- Patients to remain off study medication permanently and continue to be treated with SOC
- Patients to be followed to their originally planned EOS visit (week 52 ± 2 weeks).

For patients who were receiving study medication, with an EOS visit originally planned for a date up to and including 14 November 2021, instructions are as follows:

- Patients to have an EOS visit by 31 October 2021 enabling visit to be within 2 weeks of their originally planned EOS visit.

[redacted]

For patients who were receiving study medication with an EOS visit originally planned for after 14 November 2021, instructions are as follows:

- Patients to come to the study site for an unscheduled visit (or regularly scheduled visit) by 31 October 2021 and perform the following:
  - Discontinue study medication
  - Transition to local SOC, respecting the required washout period
  - Complete the following additional assessments with all data maintained in source documentation (see Table 6-2 Part2 Assessment schedule, visits UNS/TD and UNS and footnotes 18 and 19 for details):
    - [redacted]
    - Unscheduled PK
    - Unscheduled abbreviated labs
    - NYHA/ROSS class evaluation
    - PGIS patients or parent/caregiver
    - [redacted]
    - [redacted]
- These patients should continue to be followed in the trial until the planned EOS visit (week 52 ± 2 weeks).
- Full EOS visit assessments (with the exception of PK) are to be conducted at the planned EOS visit (week 52 ± 2 weeks)

27.2 USM implications regarding data collection and study results

As described in the sections above, due to unresolvable technical reasons regarding study drug supply, all patients on study medication at the initiation of the USM will have to discontinue study drug treatment by 31October2021, which is up to two months prior to the scheduled study end for the last patient. This early study drug discontinuation is not expected to compromise the scientific integrity of the study due to the limited number of patients impacted.

The early study drug discontinuation affects a maximum of 31 patients, who were on-treatment as of 26 October 2021, with a current follow-up between 297 days to 395 days. The total on-treatment follow-up time lost is expected to be <1%.

Regarding CRF documentation, the reason for the treatment discontinuation is to be reported on the End of Treatment (EOT) CRF as ‘Technical problems’. If a patient withdraws from study participation after the study drug discontinuation due to the USM and before they have completed 52 weeks (± 2 weeks) of follow up, the reason for the study phase discontinuation on the EOS CRF, is also be documented as ‘Technical problems’.

Every effort is to be made to keep patients in the study until the planned 52-week follow up and to ensure study integrity. While the current statistical analysis plan (SAP) includes off-treatment

[redacted]

data after treatment discontinuations in the primary analysis (reflecting a real-world setting), this does not seem appropriate for the study drug discontinuations in the context of this USM. The unforeseen intercurrent events of the USM leading to study treatment discontinuations are not related to disease progression, are not related to the assigned study treatment and do not reflect a real-world setting. The exposure to the study treatment and study follow-up are reasonably long. Therefore, an on-treatment approach is considered to be more appropriate for the handling of USM-impacted patients in the primary analysis, utilizing the relevant components of the global rank endpoint including Category 1 and 2 status at the time of treatment discontinuation. The full data, including the portion off-treatment from the impacted patients, will be included in a sensitivity analysis. The SAP will be amended to reflect this.

[redacted]