NOVARTIS

Global Clinical Development - General Medicine

LCZ696

Clinical Trial Protocol CLCZ696B2317 / NCT02226120

A multicenter study to evaluate safety and tolerability in patients with chronic heart failure and reduced ejection fraction from PARADIGM-HF receiving open label LCZ696

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List of abbreviations

ACEI	Angiotensin converting enzyme inhibitor
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANP	Atrial natriuretic peptide
ARB	Angiotensin receptor blocker (antagonist)
AST	Aspartate aminotransferase
AT1	Angiotensin type 1 receptor
AUC	Area under the curve
β-hCG	Beta-human chorionic gonadotropin
bid	Bis in die, twice daily
BP	Blood pressure
BUN	Blood urea nitrogen
CCB	Calcium channel blocker
CFR	Code of Federal Regulation
CHF	Chronic heart failure
CPK	Creatine phosphokinase
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CV	Cardiovascular
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
FSH	Follicle-stimulating hormone
GFR	Glomerular filtration rate

[redacted]

γGT	Gammaglutamyl-transpeptidase
HF	Heart failure
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator notification
IRB	Institutional Review Board
IRT	Interactive Randomization Technology
ITD	Investigational treatment discontinuation
i.v.	Intravenous
LFT	Liver function test
MDRD	Modification of Diet in Renal Disease
NEP(i)	Neutral endopeptidase (inhibitor)
NPs	Natriuretic peptides
p.o.	Per os, oral
PARADIGM-HF	Clinical study CLCZ696B2314
PPW	Premature patient withdrawal
RAS	Renin-angiotensin system
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total bilirubin
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. 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.”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
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 with established disease and in those with newly-diagnosed disease.
Period	A subdivision of a cross-over study
Premature subject/patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
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), active drug run-ins or background therapy

[redacted]

Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject Number	A number assigned to each patient who enrolls into the study
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

Amendment 2

Amendment rationale

This is the second amendment to be released for protocol CLCZ6962317 and is of administrative type. Below is a list of items that have been addressed.

- Correction of Figure 3-1, indicating study duration and visit number consistent with the main text
- Clarification of recommended starting doses with addition of table title (Table 5-1)
- Additional editorial changes addressing typographical errors

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

Amendment 1

Amendment rationale

The purpose of this amendment is to clarify the patient population from the CLCZ696B2314 (PARADIGM-HF) study who is eligible for enrolment in this study, as well as facilitate tracking of those patients. Below is a list of items that have been addressed.

- This amendment will extend the collection of all AEs and subsequently Section 7, safety reporting, has been updated to enable collection of all AEs reported.
- Section 9.4 is updated with respect to safety data collection and analysis plan
- Clarification of patients who have been enrolled in the PARADIGM-HF study is provided in Section 4. Only patients who have been treated with study medication are eligible. Those patients who were discontinued during the PARADIGM study due to an event are eligible, assuming they are fully recovered, the event has resolved and no longer represents a risk for the patient and, in the investigator opinion, and the patient can safely tolerate the administration of LCZ696.
- Unlike what was stated in the original protocol, patients will be assigned a new identification (ID) number that is going to be similar to that previously assigned during the PARADIGM-HF study (CLCZ696B2314) at the time of Visit 1 (the exact identical

number will not be used, due to a change in the database system). Section 5.5.1 has been updated.

- A clarification about safety reporting, which will include Adverse Events arising from notable laboratory abnormalities: The actual laboratory data will not be reported as the values are not in the database but as source data.
- [redacted]
- Section 4.2, exclusion criterion No. 12 has been updated in response to the Health Authorities from the UK.
- In the Assessment Schedule, Table 6-1, the database visit number for the 6-months visit was updated; additional pregnancy tests were added for safety monitoring.
- Additional editorial changes have also been included to clarify processes and procedures, and also to clarify minimal duration of initial treatment with 50 and 100 mg LCZ696 bid.

[redacted]

Protocol summary

Protocol number	CLCZ696B2317
Title	A multicenter study to evaluate safety and tolerability in patients with chronic heart failure and reduced ejection fraction from PARADIGM-HF receiving open label LCZ696
Brief title	Safety and tolerability during open-label treatment with LCZ696 in patients with chronic heart failure and reduced ejection fraction
Sponsor and Clinical Phase	Novartis, Phase IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to collect safety and tolerability data on LCZ696 in eligible PARADIGM-HF patients receiving open-label investigational drug.
Primary Objective(s) and Key Secondary Objective	The primary objective of this study is to continue to evaluate the safety and tolerability of LCZ696 in heart failure patients from PARADIGM-HF receiving open-label investigational drug.
Secondary Objectives	There are no secondary objectives for this study.
Study design	This trial is a multicenter, open-label follow-up to PARADIGM-HF, which evaluated the morbidity, mortality and safety of LCZ696 compared to enalapril in patients with chronic heart failure and reduced ejection fraction. Prior to enrollment in this trial, all patients must have been randomized and received double-blind study medication in the PARADIGM-HF study and most will have transitioned to an ACEI or ARB. Investigators will be offered the option to initiate open-label treatment with LCZ696 for any PARADIGM-HF patient that meets the eligibility criteria. Consenting patients will undergo a washout period, if necessary (36 h for patients on ACEIs only), be up-titrated to the maximally tolerated dose of LCZ696 and scheduled for visits to dispense study drug and assess safety and tolerability at 6-month intervals until the conclusion of the trial.
Population	All surviving patients that were randomized in PARADIGM-HF can be considered for eligibility in this open-label study (CLCZ696B2317). It is estimated that 5,000 patients (about 59% of the core study population and approximately 72% of the surviving patients) who meet the eligibility criteria will be

[redacted]

	enrolled into this open-label trial.
Inclusion criteria	1. Written informed consent for the extension must be obtained before any assessment is performed. 2. Patients who have been enrolled and treated with double blind study medication in PARADIGM-HF and are able to safely enroll into the open-label study as judged by the investigator.
Exclusion criteria	1. Any condition that in the opinion of the investigator is likely to prevent the patient from safely tolerating LCZ696 or complying with the requirements of the study.
Investigational and reference therapy	LCZ696 (open-label); most patients titrated to 200 mg bid or lower doses of 50 or 100 mg bid depending on tolerability
Efficacy assessments	There will be no efficacy assessments in this study.
Safety assessments	All Adverse events reported will be recorded in the e-CRFs (including angioedema-like events).
Other assessments	Not applicable
Data analysis	Number and frequency of all AEs will be summarized by primary system organ class and preferred term. Narratives will be prepared for all Serious Adverse Events and AESIs. Vital signs will be reported as summary statistics.
Key words	LCZ696, chronic heart failure, open-label study, ARNI

[redacted]

1 Introduction

1.1 Background

Chronic heart failure (CHF) is a major public health problem characterized by significant mortality, frequent hospitalization, and poor quality of life, with an overall prevalence that is increasing throughout the world. In the United States (US) alone, approximately 5 million patients have heart failure (HF) and there are over half a million newly diagnosed cases annually (Hunt et al 2009, McMurray et al 2012). In Europe, the prevalence of HF is between 2 and 3%, and in the elderly is estimated between 10 to 20% (McMurray et al 2012). Medical therapies targeted at improving outcomes in HF with a low EF have been well studied over the past two decades, leading to an improvement in survival as well as a decrease in morbidity, mostly in the form of decreased re-hospitalization for HF. These medical therapies include angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β-blockers and mineralocorticoid antagonists (CONSENSUS Trial Study Group 1987, Cohn and Tognoni 2001, SOLVD Investigators 1991, SOLVD Investigators 1992, RALES Investigators 1996, Pitt et al 1999, MERIT-HF Study group 1999, CIBIS II Investigators 1999, Packer et al 2002, Pfeffer et al 2003, Flather et al 2005; Zannad et al 2011). However, despite advances in pharmacological (and device therapies), the outlook remains poor. Overall, 50% of patients die within 4 years and 40% of patients admitted to the hospital with HF die or are readmitted within 1 year (McMurray et al 2012). Thus, HF still represents a major cause of cardiac mortality and morbidity with a clear need for better therapy.

LCZ696 is a first-in-class, angiotensin receptor neprilysin inhibitor (ARNI) being developed for the treatment of heart failure. Following ingestion, LCZ696 provides systemic exposure to AHU377, a neprilysin (neutral endopeptidase 24.11, NEP) inhibitor (NEPi) and valsartan, an angiotensin receptor blocker (ARB). [redacted] Neprilysin degrades biologically active natriuretic peptides (NPs), including atrial natriuretic peptide (ANP), B-type natriuretic peptide and C-type natriuretic peptide. The effects of NEP inhibition are attributed to the enhanced effects of biologically active NPs. NPs, acting through the second messenger cyclic GMP, have potent natriuretic and vasodilator properties, inhibit the activity of the RAS, lower sympathetic drive and have antifibrotic and antihypertrophic effects (Levin et al 1998, Gardner et al 2007, Pandey 2008). NEP also inactivates other vasodilators including bradykinin, adrenomedullin, enkephalins, substance P, calcitonin gene-related peptide and vasoactive intestinal polypeptide; however, the role of these peptides in mediating the beneficial effects of NEP inhibition is not known.

Angiotensin receptor blockade is specific and competitive at the angiotensin type 1 (AT1) receptor, which mediates the deleterious effects of angiotensin II on the CV system. LCZ696, through its dual mode of action, potentiates NPs via NEP inhibition while inhibiting the RAS via AT1 receptor blockade. Both of these mechanisms are considered to act in a complementary and additive manner to improve the morbidity and mortality of HF patients.

The PARADIGM-HF study (protocol CLCZ696B2314) was a randomized, double-blind, Phase III outcome trial that evaluated the efficacy and safety of LCZ696 versus enalapril (an

[redacted]

ACEI) in 8,436 heart failure patients with reduced ejection fraction (McMurray et al 2013). The primary endpoint was time to first occurrence of either cardiovascular (CV) death or heart failure hospitalization, and the trial was also designed to be able to detect a significant difference in CV death alone (McMurray et al 2013).

The protocol and statistical analysis plan for PARADIGM-HF included a third interim efficacy analysis when approximately 2/3 of the total number of primary patient events occurred. In addition, the CV death component was also analyzed at each interim efficacy analysis. As pre-specified in the protocol, the study could be concluded early with a compelling claim of efficacy superiority for LCZ696 versus enalapril, if statistically significant results exceed the planned boundary ($p \leq 0.001$ one sided for the third interim analysis) for, (1) cardiovascular mortality by itself and also, (2) the primary composite endpoint (first occurrence of cardiovascular death or heart failure hospitalization).

On March 28, 2014 the Data Monitoring Committee (DMC) for PARADIGM-HF reviewed efficacy and safety data for the third interim analysis with approximately 1,027 CV death events and concluded that LCZ696 was superior to enalapril in delaying the time to first occurrence of the primary composite endpoint and most importantly, in delaying the time to the CV death component as well. Based on these results and an acceptable safety profile, the DMC unanimously recommended early closure of the study, which was agreed by the study Executive Committee and Sponsor of the trial.

In order to provide patients the opportunity to receive life-saving treatment with LCZ696 and to collect safety data, this open-label, safety and tolerability study will offer enrollment to all surviving, eligible patients that had been randomized in PARADIGM-HF.

1.2 Purpose

The purpose of this study is to collect safety and tolerability data on LCZ696 in eligible PARADIGM-HF patients receiving open-label investigational drug. For each country, the study has a minimum duration of 12 months and is expected to continue until marketing authorizations have been received in the participating countries and the drug product becomes commercially available which is anticipated to be approximately 30 months.

For the specific study duration in Denmark, the UK and in Germany, please see Section 3.3 of this document.

2 Study objectives

2.1 Primary objective

The primary objective of this study is to continue to evaluate the safety and tolerability of LCZ696 in heart failure patients from PARADIGM-HF receiving open-label investigational drug.

2.2 Secondary objectives

There are no secondary objectives for this study.

[redacted]

2.3 Exploratory objectives

Not applicable

3 Investigational plan

3.1 Study design

This trial is a multicenter, open-label follow-up to PARADIGM-HF, which was a double-blind parallel treatment study that evaluated the morbidity, mortality and safety of LCZ696 compared to enalapril in patients with chronic heart failure and reduced ejection fraction.

Investigators for PARADIGM-HF have been informed of the study's early closure and will be offered the option to initiate treatment with LCZ696 for eligible patients by enrolling them in this study (CLCZ696B2317). Only patients who were randomized in PARADIGM-HF and received study medication (i.e., either enalapril or LCZ696) are eligible (i.e., screen- or run-in-fail are not eligible). For all consenting patients, visits to dispense study drug and assess safety will be conducted at baseline and at 6-month intervals (except for Visits 2 and 3 required for the up-titration step and the 3-month visit [Visit 4]) until conclusion of the trial.

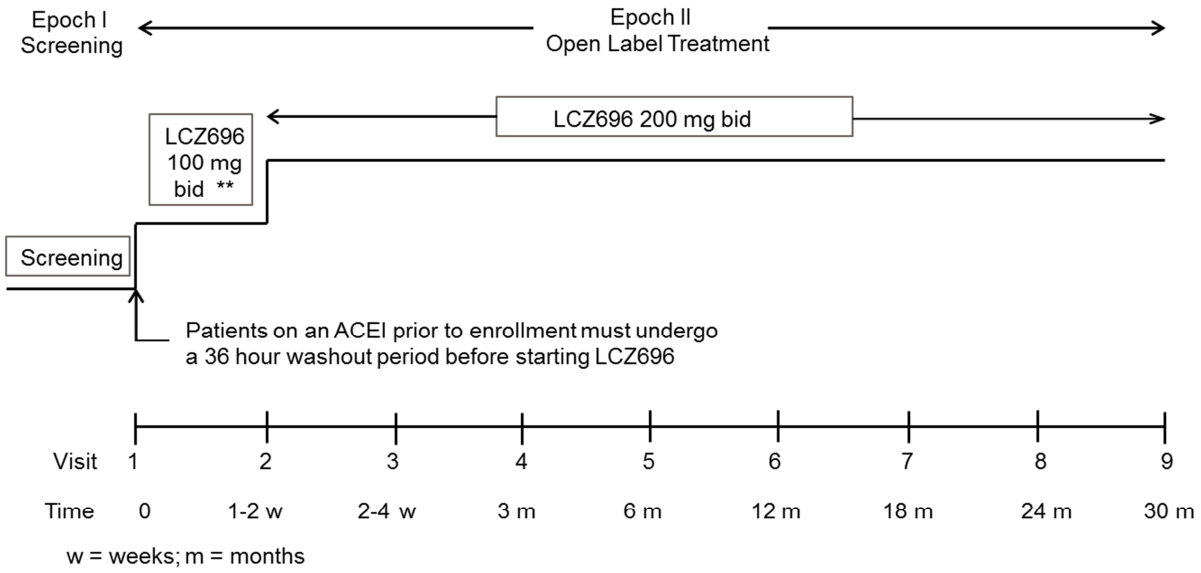
If the patient is taking an ACEI at the time of enrollment, a **36-hour washout** period is required before starting treatment with LCZ696. Patients will be up-titrated to the target oral dose of LCZ696 200 mg bid, as tolerated. At the discretion of the investigator, patients may be maintained on LCZ696 50 mg bid or 100 mg bid, if that was the highest dose-level (dose-level 1 or 2) tolerated in the PARADIGM-HF study, or if they are unable to tolerate up-titration to higher doses of LCZ696 in this open-label study.

Similarly, while the starting dose is recommended to be 100 mg LCZ696 bid, at the investigator's discretion patients could start at 50 mg LCZ696 bid. More details are provided in Section 5.5.5 of this document.

An outline of the study design with recommended dose levels is presented in Figure 3-1 with the overall duration. However, duration will be different for Denmark, Germany, and the UK, as per Section 3.3 of this document.

[redacted]

Figure 3-1 Overall study design and time interval between study visits



** While the starting dose is recommended to be 100 mg LCZ696 bid, at the investigator's discretion patients could start at 50 mg LCZ696 bid.

3.2 Rationale of study design

The DMC for PARADIGM-HF reviewed efficacy and safety data for the third interim analysis and concluded that LCZ696 was superior to enalapril for the primary composite endpoint of CV death or hospitalization for HF as well as CV death alone. Based on these results, the DMC recommended early closure of the study and Novartis has initiated processes to close-out the trial.

The open-label design of the current study is appropriate to provide patients the opportunity to receive treatment with LCZ696 until marketing authorizations are received and the drug product becomes commercially available, and to enable the collection of safety and tolerability data for the investigational drug.

[For the **United Kingdom only** the above paragraph will read as follows**:**
The purpose of this study is to collect safety and tolerability data on LCZ696 in eligible PARADIGM-HF patients receiving open-label investigational drug. Study duration in the UK is specified in Section 3.3]

Enrollment will be available to all surviving, eligible patients who were randomized in PARADIGM-HF.

3.3 Rationale of dose/regimen, route of administration and duration of treatment

Based on safety data from the PARADIGM-HF single-blind, sequential design run-in period, LCZ696 was well-tolerated, with over 90% of patients achieving the target dose.

[redacted]

A strong rationale exists for the target dose of LCZ696 in HF-rEF patients. A p.o. dose of LCZ696 200 mg bid delivers similar exposures of valsartan (assessed by AUC) as Diovan® 160 mg bid, the highest approved Diovan® dose for HF and the dose recommended in international guidelines for the treatment of HF. In addition, biomarker analysis (increase in ANP and cGMP) indicates that this dose delivers approximately 90% of its maximal NEP inhibition.

Most importantly, this study will target the oral dosing regimen for LCZ696 identical to that which showed a mortality and HF hospitalization benefit superior to that of enalapril in PARADIGM-HF.

[*] The study will continue in an individual country for a minimum of 12 months and until a marketing authorization has been received and the drug product becomes commercially available in that country (which is expected to be up to 30 months) from the date of the first eligible patient enrolled in that country, or until the study is terminated, whichever comes first. Within the study period, the duration of treatment for an individual patient will be at the discretion of the investigator.

[* For **Denmark only**, the above paragraph will read as follows:
From the date of the first eligible patient enrolled in Denmark, the study will have a duration of 12 months. The treatment duration may be re-evaluated and an amendment issued to adjust the treatment duration.]

[* For the **United Kingdom only** the above paragraph will read as follows**:**
From the date of the first eligible patient enrolled in the UK, the study has a minimum duration of 12 months and a maximum duration of 20 months. The treatment duration may be re-evaluated and an amendment issued to adjust the treatment duration.].

[* For **Germany only**, the above paragraph will read as follows:
From the date of the first eligible patient enrolled in Germany, the study will have a maximum duration of 24 months. The treatment duration may be re-evaluated and an amendment issued to adjust the treatment duration.]

3.4 Rationale for choice of comparator

Not applicable

3.5 Purpose and timing of interim analyses/design adaptations

No interim analysis is planned.

3.6 Risks and benefits

PARADIGM-HF (protocol CLCZ696B2314) was a randomized, double-blind, Phase III outcome study that evaluated the efficacy and safety of LCZ696 versus enalapril in patients with heart failure with reduced ejection fraction. The primary endpoint was a composite of time to first occurrence of either CV death or heart failure hospitalization, and the trial was also designed to be able to detect a significant difference in CV death alone.

[redacted]

On March 28, 2014 the Data Monitoring Committee (DMC) for PARADIGM-HF reviewed efficacy and safety data for the third interim analysis and disclosed that LCZ696 was superior to enalapril in delaying the time to first occurrence of both the primary composite endpoint (CV death or hospitalization for HF) as well as CV death alone. Based on these results and an acceptable safety profile, the DMC unanimously recommended early closure of the study.

As a consequence of the DMC's recommendation, the Sponsor believes that the results of PARADIGM-HF demonstrate superior efficacy over enalapril as well as a positive benefit/risk ratio and has initiated closure of the study. In order to provide patients the opportunity to receive open-label treatment with LCZ696 and to collect safety data, this open-label study (CLCZ696B2317) will offer enrollment to all surviving, eligible patients who were randomized in PARADIGM-HF. The risk to patients in the open-label trial will be minimized by rigorous compliance with the inclusion/exclusion criteria and study procedures, and careful clinical monitoring during this study. These risks (e.g., hyperkalemia, hypotension, renal impairment) are well known to investigators who have gained experience managing them in PARADIGM-HF.

4 Population

All surviving patients who safely tolerated study drug in PARADIGM-HF can be considered for eligibility in this open-label study (CLCZ6962317). Following discussions amongst the Sponsor's Clinical and Regulatory Departments and consultation with the PARADIGM-HF Executive Committee, is estimated that up to 5,000 patients (about 59% of the core study population and approximately 72% of the surviving patients) who meet the eligibility criteria will be enrolled into the trial.

1. Patients who were randomized and received study medication (LCZ696 or enalapril) in PARADIGM-HF will be considered for enrollment if they fulfill all entry criteria (screen- or run-in-failures in PARADIGM-HF will not be eligible for this study).
2. Patients who discontinued study drug treatment during PARADIGM-HF due to an event intercurrent illness/event are eligible, assuming they meet all entry criteria, the event has resolved and no longer represents a risk for the patient and, in the investigator opinion, and the patient can safely tolerate the administration of LCZ696.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent for the extension must be obtained before any assessment is performed.
2. Patients who have been enrolled and treated with double-blind study medication in the PARADIGM-HF study (protocol CLCZ696B2314) and are able to be safely enrolled into the open-label trial as judged by the investigator.

4.2 Exclusion criteria

1. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer

2. History of hypersensitivity or allergy to any of the study drugs, drugs of similar chemical classes, ACEIs, ARBs, or NEP inhibitors as well as known or suspected contraindications to LCZ696
3. Known history of **angioedema**
4. Requirement of simultaneous treatment with both ACEIs and ARBs
5. Current acute decompensated HF (exacerbation of chronic HF manifested by signs and symptoms) that may require intravenous therapy
6. Symptomatic hypotension and/or a SBP < 100 mmHg at Visit 1 (screening)
7. Estimated GFR < 30 mL/min/1.73m^2 as measured by the simplified MDRD formula at Visit 1 (screening)
8. Presence of bilateral renal artery stenosis
9. Serum potassium > 5.2 mmol/L at Visit 1 (screening)
10. Evidence of hepatic disease as determined by any one of the following: AST or ALT values exceeding 3 x ULN at Visit 1, history of hepatic encephalopathy, history of esophageal varices, or history of porta-caval shunt
11. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
12. 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 and for **7 days after discontinuation of LCZ696 treatment**.

    Highly effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject).
        - Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal **are not acceptable methods** of contraception;
    - Male sterilization (at least 6 months prior to Visit 1). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject;
      [*For the United Kingdom ONLY*: Male sterilization (at least 6 months prior to Visit 1): Prior to starting dosing of the female subject, medical assessment of the surgical success of the partner's vasectomy must be provided.]
    - Combination of any two of the following (a+b or a+c, or b+c):
        a. use of oral, injected or implanted hormonal methods of contraception (combined estrogen and progestogen or progestogen only) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
        b. placement of an intrauterine device (IUD) or intrauterine system (IUS)
        c. barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
    - In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

[redacted]

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

13. Any condition, not identified in the protocol that in the opinion of the investigator is likely to prevent the patient from safely tolerating LCZ696 or complying with the requirements of the study.

If a patient has experienced a significant cardiovascular (e.g., acute coronary syndromes, stroke, transient ischemic attack) or non-cardiovascular event in the interim between the end of PARADIGM-HF and the start of CLCZ696B2317, the investigator should ensure that the individual is appropriately stable before enrolling them in the open-label study. If there is uncertainty about a patient's eligibility, the investigator should consult the study medical monitor to determine if the individual should be enrolled.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

All eligible patients will receive LCZ696 in addition to optimal CHF therapy, as considered appropriate by the investigator and in accordance with standard therapy guidelines, but with the exception of an ACEI or ARB as this will be replaced by LCZ696. The use of an ACEI or an ARB in addition to LCZ696 is strictly prohibited.

The Sponsor will provide the following open-label study medication in bottles:

- LCZ696 50 mg film-coated tablets (LCZ696 dose level 1)
- LCZ696 100 mg film-coated tablets (LCZ696 dose level 2)
- LCZ696 200 mg film-coated tablets (LCZ696 dose level 3)

Sufficient medication will be provided for treatment according to the study protocol, including additional medication to allow for delayed visits.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug.

The target p.o. dose of LCZ696 is 200 mg bid. For patients not tolerating the target dose, LCZ696 will be titrated down to a lower dose level twice a day, at the investigator's discretion, based on the defined safety and tolerability criteria (Appendix 3, Appendix 4 and Appendix 5).

[redacted]

For the initial treatment doses (50 or 100 mg bid) administered up to visit 2 and 3, the protocol indicates that the dose could be administered 1-to-2 weeks prior to the next visit. However, treatment should last for **a minimum of 1 week** before up-titrating to the next dose strength.

Recommended starting LCZ696 dose

For patients who tolerated **dose level 3** (either 200 mg LCZ696 bid or 10 mg enalapril bid) in the PARADIGM-HF study, the recommended starting dose is 100 mg LCZ696 bid. Similarly, for patients who maximally tolerated **dose level 2** (either 100 mg LCZ696 bid or 5 mg enalapril bid) in the PARADIGM-HF study, the recommended starting dose could be 100 mg LCZ696 bid. These patients can be up-titrated to 200 mg LCZ696 bid at a later time at the discretion of the investigator.

If, in the investigator's judgment, the patient may not tolerate the proposed starting dose of 100 mg LCZ696 bid, the patient could start with 50 mg LCZ696 bid and be up-titrated at the time of subsequent visits.

The starting dose of 50 mg bid is also recommended for patients who previously only tolerated dose level 1(either LCZ696 50 mg bid or enalapril 2.5 mg bid) in the PARADIGM-HF study.

Table 5-1 Recommended starting dose

Dose levels used in CLCZ696B2314	Study treatment in CLCZ696B2314	Corresponding starting dose in this study LCZ696, mg bid
1	50 mg LCZ696bid or 2.5 mg enalapril bid	50
2	100 mg LCZ696bid or 5 mg enalapril bid	50 or 100
3	200 mg LCZ696bid or 10 mg enalapril bid	50 or 100

If the patient is taking an ACEI at the time of enrollment, a **36-hour washout** period is required before starting treatment with LCZ696.

If LCZ696 is *permanently* discontinued, treatment with an appropriate dose of an ACEI and/or ARB should be initiated. A 36-hour washout period is also required before starting treatment with an ACEI after discontinuation of LCZ696.

5.1.2 Additional study treatment

No additional treatment beyond investigational treatment is requested for this trial.

5.2 Treatment arms

There is one treatment arm in this open-label study.

[redacted]

5.3 Treatment assignment

Patients will not be randomized to treatment in this study; all patients previously treated with LCZ696 or enalapril in PARADIGM-HF will be treated with LCZ696 at maximally tolerated doses with a target dose of 200 mg bid.

An Interactive Response Technology (IRT) system will be used to enroll patients into the study and dispense study drug. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all of the inclusion/exclusion criteria. The IRT system will prompt the investigator to enter the patient's Subject Number into the system and then assign a uniquely numbered medication kit for the first investigational treatment to be dispensed to the patient (at the time of successfully completing Visit 1).

The IRT will be used to assign additional uniquely numbered medication kits at Visits 2 through 8 of the trial.

5.4 Treatment blinding

Treatment is not blinded to either investigators or patients during the course of the study (i.e., it is "open-label"). All patients will receive LCZ696 at maximally tolerated doses with a target dose of 200 mg bid.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Identification (ID) Number. Patient will be assigned an ID number *similar* to that assigned in PARADIGM-HF at the time of Visit 1 (the exact identical number will not be used, due a change in the database system). More details for the patient ID number assignment are included in the eCRF completion guide (eCCG).

Upon signing the informed consent form, the investigator or his/her staff will contact the IRT and provide the requested identifying information (including the current subject ID and the original subject ID from PARADIGM-HF) to register the patient into the IRT system.

If the patient fails the first attempt to qualify for the study at Visit 1, the patient will have two (2) more opportunities to undergo screening with a minimum of 2 weeks between visits, as indicated in Section 6.1 of this protocol. IRT must be contacted at each screening attempt.

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 Disposition CRF.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by the Sponsor with investigational treatment in packaging of identical appearance.

The investigational treatment packaging has a 2-part label that includes the medication kit number. The site staff will identify the investigational treatment package(s) to dispense to the

patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package(s) to the patient, the site 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.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

Investigational 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 investigational treatment should 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 Sponsor‘s 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 investigational treatment but no information about the patient except for the medication number. This study will be conducted as an open-label study, with no treatment blinding.

The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a Drug Accountability Log. Monitoring of drug accountability will be performed by the field monitor during site visits and at completion of the trial. Patients will be asked to return all unused investigational treatment and packaging at the end of the study or at the time of discontinuation of investigational treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational treatment, packaging, drug labels, and a copy of the completed Drug Accountability Log to the Sponsor's monitor or to the Sponsor's address provided in the investigator folder at each site.

5.5.3.2 Handling of other study treatment

Not applicable

5.5.4 Instructions for prescribing and taking study treatment

The Sponsor will supply the investigators with LCZ696 for the course of the study. Patients will be provided with bottles of medication sufficient to last until the next scheduled visit.

Open-label study medication will be dispensed at

Visit 1 upon fulfilling entry criteria,

Visit 2 (at 1 to-2 weeks after starting treatment with LCZ696),

Visit 3 (at 2-to-4 weeks),

Visit 4 (3 months),

Visit 5 (at 6 months),

[redacted]

Visit 6 (at 12 months),

Visit 9 (at 18 months),

Visit 8 (at 24 months) and longer if required.

LCZ696 will be supplied as film-coated tablets provided in the 50 or 100 or 200 mg strength.

All dosages prescribed and dispensed to the patient must be recorded in the IRT and on the Dosage Administration Record eCRF.

Visit 1

All patients must provide informed consent before any study-specific procedure is performed.

At Visit 1, patients' eligibility for enrollment will be assessed by the investigator. Laboratory values obtained within the last 5 days from visit 1 can be used to establish eligibility. If results from a recently drawn sample are not available, samples will be obtained during visit 1 to assess eligibility.

Patients **not on current ACEI therapy**: Patients will complete the tests required for visit 1 and, if fulfilling the entry criteria, they can be enrolled.

Patients on **current ACEI therapy**: Patients will complete the tests required for visit 1, and if fulfilling the entry criteria must complete a **36 h ACEI-free period** prior to beginning LCZ696 treatment.

Following completion of the study procedures for the visit 1, IRT will be contacted to enter the patient as screened. If the patient is eligible to enroll into the study, IRT will be contacted again to dispense LCZ696. The patient will start with 100 mg LCZ696 bid, unless the investigator decides that the patient should start with 50 mg bid. The patient will be instructed to take the bid p.o. dose for 1 to 2 weeks before returning to the study center for Visit 2.

The patients will be instructed to take their morning study drug p.o. dose at approximately 08:00 (8:00 AM) and their evening study drug p.o. dose at approximately 19:00 (7:00 PM). The study medication should be taken with a glass of water with or without food. If the patient misses taking any study drug dose, he/she 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.

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

Visit 2 (at 1-to-2 weeks after staring LCZ696 treatment)

Study procedures will be completed, including an assessment of the patient's tolerability to LCZ696 50 mg bid (dose level 1) or LCZ696 100 mg bid (dose level 2).

[redacted]

IRT will be contacted and the patient dispensed bottles of LCZ696 for the target dose appropriate for each patient (depending on the dose-level tolerated in PARADIGM-HF and the judgment of the investigator). The recommended steps to up-titrate the dose are indicated below.

- For those who maximally tolerated **dose level 1** in PARADIGM-HF, additional tablets for a dose of LCZ696 50 mg bid will be dispensed at Visit 2 (if the investigator chooses not to administer a higher dose to the patient) and taken for 1-to-2 weeks before returning to the study center for Visit 3.
- For patients that maximally tolerated **dose level 2** in PARADIGM-HF, additional tablets for a dose of LCZ696 100 mg bid will be dispensed at Visit 2 (if the investigator chooses not to administer a higher dose to the patient) and taken for 1-to-2 weeks before returning to the study center for Visit 3.
  - However, if a patient tolerated dose level 3 in PARADIGM-HF, they will receive additional tablets for a dose of LCZ696 200 mg bid, which will be taken for 1-to-2 weeks before returning to the study center for Visit 3.
- Any patient at dose level 1 or 2 can be up-titrated to a higher dose of LCZ696 at Visit 2 or any time thereafter at the discretion of the investigator.

LCZ696 tablets should be taken p.o. in the morning at approximately 08:00 (8:00 AM) and again in the evening at approximately 19:00 (7:00 PM). The instructions provided at Visit 1 for taking the tablets and compliance should again be reviewed with each patient.

Visit 3 (at 2-to-4 weeks), Visit 4 (at 3 months), Visit 5 (at 6 months), Visit 6 (at 12 months), Visit 7 (at 18 months) and Visit 8 (at 24 months)

Study procedures will be completed before contacting the IRT to dispensed bottles of LCZ696 50 mg, 100 mg or 200 mg tablets to patients. The instructions provided at Visits 1 and 2 for taking the tablets and compliance should again be reviewed with each patient.

Visit 9 (at 30 months)

Study procedures will be completed before contacting the IRT to record the patient's attendance for this visit but not to dispense study drug.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Every attempt should be made to maintain patients on the target LCZ696 dose level of 200 mg bid throughout the trial.

If in the opinion of the investigator, the patient does not tolerate the target dose of 200 mg LCZ696 bid (dose level 3), the investigator should consider the following:

1. whether non-disease-modifying medication (e.g., CCBs, diuretics, nitrates, α-blockers) can be reduced to rectify the situation, before reducing the dose of the study drug to a lower dose level (100 mg bid or 50 mg bid LCZ696).
2. may adjust doses of disease-modifying medications (e.g., β-blockers, aldosterone antagonists) if it is believed that they are the most likely cause of the adverse effect.

[redacted]

3. If adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern, the investigator may down-titrate the dose of the LCZ696 to:
    a. the next lower level
       The patient should be re-challenged with a higher dose when the investigator feels it is appropriate to do so per the directions provided below in this section.
    b. complete withdrawal of the study drug
       If the study drug is temporarily discontinued, it should be reintroduced as soon as medically justified in the opinion of the investigator.

If needed, LCZ696 may be discontinued in favor of starting the patient on an ACEI or ARB (minimum of 36 h between last dose LCZ696 and first dose of ACEI; 12 h between last dose LCZ696 and first dose of ARB).

Study drug dose level adjustments should mainly be based on overall safety and tolerability with special focus on:

a) hyperkalemia (Appendix 3: treatment guidelines for hyperkalemia);

b) symptomatic hypotension (Appendix 4: guidelines for management of BP);

c) clinically significant decrease in eGFR/increase in serum creatinine (Appendix 5: guidelines for management of renal dysfunction).

Any changes in the LCZ696 dose level must be recorded on the Dosage Administration Record eCRF and registered in the IRT.

Adjustment of study drug dose level

If despite adjustment of concomitant medications per the guidance provided above does not rectify the situation, the investigator may consider adjusting the dose of LCZ696 according to the following instructions.

If down-titration is necessary, the patient should be down-titrated to the next lower dose level (Table 5-2 below). The patient may continue to receive the lower dose level for a recommended period of 1 to 4 weeks, or longer based on the investigator's judgment, before re-challenging the patient with the next higher dose level. For example, a patient who encounters tolerability problems at the target dose of 200 mg LCZ696 bid (dose level 3), should receive the study drug at dose of 100 mg LCZ696 bid (dose level 2) for 1 to 4 weeks. Then, based on the investigator's judgment, he/she should be re-challenged with up-titration back to dose level 3.

[redacted]

Table 5-2 LCZ696 dispensed during the open-label treatment period

Study visit	Dose level	LCZ696
Dispensed at Visit 2 and all subsequent visits	3[a]	200 mg bid
Dispensed at Visit 1 and available for any visit after Visit 1	2[b]	100 mg bid
Dispensed at Visit 1 for patients that tolerated only dose level 1 in PARADIGM and available for any visit after Visit 1	1[c]	50 mg bid

a. This dose level should be maintained for as long a duration as possible. If down-titration is necessary due to side effects, the patient should be re-challenged as soon as medically possible per the investigator's judgment.
b. Only if dose level 3 is not tolerated despite modification of other non-disease-modifying HF medications.
c. Only if dose levels 2 and 3 are not tolerated despite modification of other non-disease-modifying HF medications.

If the tolerability issues are not alleviated despite down-titration by one dose level, the investigator may lower the study drug dose further to the next lower level for 1 to 4 weeks, up to temporary or permanent withdrawal of the study drug. Again, once stable, the patient should be re-challenged with up-titration 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 3).

The investigator may choose the next dose level for down- or up-titration according to his or her judgment (Table 5-2). As discussed in Section 5.5.5, the IRT should be contacted to register any changes in the patient's LCZ696 dose level, including cases of temporary and permanent withdrawal of the study drug, and to obtain the medication numbers of the LCZ696 supplies required for the new dose level.

In some instances, according to the safety and tolerability criteria and the investigator's judgment, LCZ696 dose level 1 or 2 can be maintained if he/she considers that the patient's condition would not allow any further up-titration to the target dose of study medication (level 3). In this case it would be acceptable to maintain the patient at dose level 1 or level 2, whichever is the higher and tolerated dose level for the patient.

Study drug restart after temporary treatment interruption

LCZ696 should be reintroduced in those who temporarily discontinue it as soon as medically justified in the opinion of the investigator.

Once the investigator considers the patient's condition appropriate for receiving LCZ696, the investigator should re-start the patient on the study drug at the most appropriate and allowable dose level (Table 5-2) per his/her medical judgment. If tolerated, the patient should be up-titrated up-to dose level 3 every 1 to 4 weeks, as per the investigator's judgment.

Should the patient not tolerate the re-started study drug at a particular dose level, he/she may be down-titrated again (if appropriate) or the study medication discontinued again and a new attempt to up-titrate or reintroduce the study drug could be considered by the investigator if justified in his/her medical judgment.

Study visits should occur as close as possible to the time points indicated in the Assessment Schedule (Table 6-1). The time interval between the regular visits should be maintained as

scheduled, irrespective of the number of unscheduled visits that may be performed in between, according to the visit and time schedule described in Table 6-1.

Any changes in the study drug dose level, including temporary/permanent withdrawal or re-start of the study drug, must be recorded on the Dosage Administration Record eCRF and registered in the IRT.

In case of pregnancy discovered during the open-label treatment period, the patient should be instructed to stop taking the study drug immediately.

See Section 7.6 for further details on pregnancies and reporting guidelines.

5.5.6 Rescue medication

Guidance on handling hyperkalemia, hypotension, and renal dysfunction are provided to investigators in Appendix 3, Appendix 4 and Appendix 5, respectively. Patients may receive open-label ACEIs and/or ARBs during the study **ONLY** if LCZ696 has been discontinued. Resuming ACEI therapy requires a 36 h washout from the last LCZ696 dose.

5.5.7 Concomitant treatment

The investigator should instruct the patient to notify the study site staff of any changes in concomitant medications (new medications or changes in dose regimens of existing medications). All concomitant medications for heart failure must be listed on the Heart Failure Medications eCRF.

5.5.7.1 Heart failure medications and other cardiovascular medications

Patients should be on an optimal medical regimen of background HF medications. The use of an aldosterone antagonist and a β-blocker should be considered in patients eligible for this study. In self-identified black patients, the use of isosorbide dinitrate/hydralazine hydrochloride (e.g., BiDil®) should be considered. Every effort should be made to keep the dose level of these background HF medications stable throughout the entire study. However, if the patient's condition warrants a change in any of these medications (for example, if the investigator believes a medication is causing an adverse event), it is allowed at the discretion of the study investigator.

Diuretics may be used and may be adjusted throughout the length of the study at the discretion of the investigator.

5.5.7.2 Medications known to raise potassium levels

Potassium-sparing diuretics, potassium supplements, aldosterone antagonists, and any other medications known to raise potassium levels should be used with caution while the patient is receiving the study medication due to the increased possibility of occurrence of hyperkalemia. The investigator is encouraged to assess patients' potassium levels regularly, especially in those who are receiving these medications.

[redacted]

5.5.7.3 Phosphodiesterase-5 (PDE-5) inhibitors

PDE-5 inhibitors (e.g., sildenafil, vardenafil and tadalafil) should be used with caution while the patient is receiving study medication due to the increased possibility of occurrence of hypotension.

5.5.7.4 Intravenous neseritide, nitroprusside and nitrates

The concomitant administration of LCZ696 with intravenous (i.v.) nitrates has been studied in healthy volunteers. There was no significant difference in the magnitude, dose or time-course of the decrease in systolic and diastolic blood pressure when nitroglycerin was given alone compared to the co-administration of nitroglycerin and LCZ696.

In these healthy volunteers, the administration of LCZ696 and nitroglycerin was safe and well tolerated when given alone or in combination.

The concomitant administration of LCZ696 with i.v. neseritide or nitroprusside has not been studied. In the event a study patient requires the concomitant administration of neseritide and/or nitroprusside with LCZ696, the investigator should consider starting them at a lower dose or a slower infusion rate while monitoring the patient's blood pressure carefully.

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 in the source documents.

5.5.7.5 Atorvastatin and other statins

The concomitant administration of LCZ696 and atorvastatin was evaluated in healthy Chinese subjects. At steady state, the levels of atorvastatin increased when co-administered with LCZ696. [redacted] valsartan levels decreased slightly when administered with atorvastatin. The effect of LCZ696 on other statins has not been examined. Based on these results, caution is recommended when LCZ696 is co-administered with atorvastatin or other statins that are substrates of the organic anion transporters, OATP1B1 and OATP1B3.

5.5.8 Prohibited treatment

5.5.8.1 ACEIs, ARBs and renin inhibitors

In this clinical trial, patients' pre-study ACEIs/ARBs will be replaced with LCZ696.

The concomitant use of open-label ACEIs or ARBs is strictly prohibited while the patient is receiving LCZ696. If the investigator believes that addition of an ACEI or ARB is necessary, then LCZ696 must be discontinued. In order to safely transition from LCZ696 to an ACEI, a period of 36 hours must transpire between the start of the last dose of LCZ696 and the start of the first dose of the ACEI (this is also true if transitioning from an ACEI to LCZ696). However, if the investigator discontinues LCZ696 and replaces it with an ARB, only 12 hours

[redacted]

must transpire between the start of the last dose of LCZ696 and the start of the first dose of the ARB (i.e., the next regularly scheduled dose).

Concomitant administration of renin inhibitors, such as aliskiren, is also prohibited.

5.5.8.2 Other medications

Bile acid sequestering agents, such as cholestyramine and colestipol are prohibited to avoid interference with study drug absorption.

5.5.9 Discontinuation of study treatment

Permanent discontinuation of LCZ696 constitutes withdrawal from the study. Under these circumstances, the patient should be evaluated at a final study visit but will not undergo assessments thereafter unless additional follow-up is required due to prior occurrence of an adverse event.

The investigator must also notify the IRT of the patient's discontinuation of LCZ696 and record it on the Drug Administration Record of the eCRFs.

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

- Withdrawal of informed consent
- Pregnancy (Section 6.5.6 and Section 7.6)
- Investigator thinks that continuation would be detrimental to the patient's well-being

Study medication may be discontinued at the investigator's discretion if any of the following occurs:

- Any severe suspected drug-related AE
- Suspected occurrence of angioedema. A patient with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator and constitute a reason for discontinuation of study medication.

Depending on the serum potassium, blood pressure, or eGFR, patients may need to have their LCZ696 dose or the dose of another concomitant medication reduced or discontinued, or, if appropriate, have potentially contributing agents adjusted. Please refer to Appendix 3, Appendix 4 and Appendix 5 for treatment guidelines for hyperkalemia, hypotension, or renal dysfunction, respectively.

5.5.10 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a patient does not want to participate in the study anymore and does not want any further visits or assessments and does not want any further study related contacts and does not allow analysis of already obtained biological material.

If a patient withdraws consent, the investigator should make every effort to determine the primary reason for this decision and record this information. Treatment with LCZ696 must be

discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communication or follow-up.

5.5.11 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

5.5.12 Emergency breaking of assigned treatment code

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

5.5.13 Study completion and post-study treatment

Patients who do not fulfill the eligibility criteria should not be enrolled in the study and only baseline characteristics, demographic information and the Screening Log entry should be completed on the eCRF.

When a patient has completed all scheduled study assessments, the investigator must call the IRT within 3 days to record the patient's completion in the IRT. At the EOS visit (Visit 9) patients will be asked to return all remaining LCZ696.

5.5.14 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated for a prematurely withdrawn 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 investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Following start of LCZ696 treatment (at Visit 1, or at the time of successfully complete the rescreening visits), initial visits up to the visit at 3 months (Visit 4) are set a relatively short interval. The subsequent visits will occur at intervals of 6 months beginning at Visit 6.

Visits 2 should be conducted between 1-to-2 weeks after starting treatment with LCZ696. Visit 3 should be conducted between 2-to-4 weeks and at least 1 week after Visit 2.

Visits 4 through 9 within +/- 7 days of the designated calendar day according to Table 6-1 or as close to it as possible. Specific circumstances surrounding missed or rescheduled visits

[redacted]

must be discussed with the study monitor. Missed or rescheduled visits SHOULD NOT LEAD automatically to patient discontinuation.

Patients should take their scheduled dose of LCZ696 in the morning of their study visits. Patients are not required to fast overnight on the day prior to or the day of the study visit.

The Assessment Schedule (Table 6-1) lists the assessments to be conducted at each of the study visits (indicated with an "x").

For patients, who discontinue LCZ696, the discontinuation visit will be Visit 9 (EOS). Enrolled patients who withdraw from the study for any reason, should be scheduled for a visit as soon as possible, at which time all of the assessments listed for Visit 9 (EOS) will be performed. At this final visit all dispensed medication supplies should be reconciled and the Adverse Events and Heart Failure Medications updated on their respective CRFs.

All data obtained from the assessments listed in Table 6-1 must be supported in the patient's source documentation. The table indicates which data are entered into the CRF from the source data (D), remain in the source documents only (S)or are loaded into the database from separate source documents, i.e. outside vendors (DS). Assessments that generate data for database entry and which are recorded on CRFs are listed using the CRF name.

Table 6-1 Assessment schedule

Epoch		**Epoch I Screening**	**Epoch II Open-label Treatment**							
Database visit numbering		**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**199**
Visit[1]		**1 ***	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9** [2] **EOS and ITD**
Time	**Category**	**0**	**1-2 w** after start dose	**2-4 w**	**3 m** §	**6 m** §	**12 m** §	**18 m** §	**24 m**	**30 m** §
Informed consent	D/S	X								
Previous subject identifiers used in PARADIGM-HF (CLZC696B2314) study	D/S	X								
Inclusion/Exclusion criteria	D/S	X								
Demography/Medical history (including alcohol and smoking history)	D/S	X								
IRT[3]	DS	X	X	X	X	X	X	X	X	X
Physical examination	S	X	X	X	X	X	X	X	X	X
Vital signs	D/S	X	X	X	X	X	X	X	X	X
Height (1st visit only)/ Weight	D/S	X[4]	X	X	X	X	X	X	X	X
Blood sample for abbreviated laboratory assessments [5] (locally)	S		X	X	X	X	X	X	X	X
Blood sample for full laboratory assessments (locally) [7]	S	X								

[redacted]

Epoch		**Epoch I Screening**	**Epoch II Open-label Treatment**							
Database visit numbering		**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**199**
Visit[1]		**1 ***	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**[2] **EOS and ITD**
Time	**Category**	**0**	**1-2 w** after start dose	**2-4 w**	**3 m** §	**6 m** §	**12 m** §	**18 m** §	**24 m**	**30 m** §
Pregnancy test (urine dipstick)[6]	S	X				X	X	X	X	
Pregnancy test (serum)[6]	S	X								X
Prior/Concomitant heart failure medications	D/S	X	X	X	X	X	X	X	X	X
Adverse events	D/S		X	X	X	X	X	X	X	X
Dispense study medications	D/S	X	X	X	X	X	X	X	X	
Drug accountability	S		X	X	X	X	X	X	X	X

EOS = end of study; ITD = investigational treatment discontinuation; D = assessment to be recorded on clinical data base; S = assessment to be recorded in source documentation; DS = data transferred from vendor

§ Within +/- 7 days of the designated calendar day

[1] Unscheduled visits may occur if a safety issue develops

* if a patient fails screening to qualify for the study at Visit 1, s/he may repeat Visit 1 up to two times in order to participate in the study.

[2] Visit 9 (End of Study visit) will be completed at approximately 30 months or if the patient permanently discontinues LCZ696 or withdraws early from the study between Visit 1 and Visit 8 or when marketing authorizations are obtained and the product becomes commercially available in the patient's country.

[3] IRT will be used to enroll patients into the study, dispense open-label medication, track visit dates and record completion or early withdrawal from the trial.

[4] Height will be measured at Visit 1 only.

[5] Abbreviated laboratory assessments (performed locally) include serum sodium, potassium and creatinine measured at Visits 2, 3, 4, 7 and 9. At Visits 5, 6 and 8 local labs will include serum sodium, potassium, creatinine, ALT, AST, alkaline phosphatase and total bilirubin.

[6] Pregnancy testing performed in women of child-bearing potential only, see Section 6.5.6.

[7] Laboratory values obtained from a sample collected either on the day of Visit 1, or within the last 5 days from Visit 1

[redacted]

6.1 Information to be collected on screening visit (Visit 1)

Please refer to Table 6-1 Assessment Table for the information to be collected during the Screening visit. If a patient is not eligible for enrollment, the investigator may consider re-screening the patient at a later time if he/she believes that the patient's condition has changed and may potentially be eligible. In this case, a completely **new patient number will be allocated to the subject** and he/she will need to re-perform all Visit 1 assessments. A patient may be **re**-screened for enrollment in this protocol up to two additional times with a minimum of 2 weeks between re-screening visits. The patient must provide new written informed consent before each time they are to be re-screened.

For these patients that are considered screening failures only baseline characteristics, demographic information, and the Screening Log entry with the reason for screen failure should be completed on the eCRF.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data will be collected including: year of birth, age, sex, race and ethnicity, as well as the Identification Number (ID No.) the subject was formerly assigned in the PARADIGM-HF study (CLCZ696B2314). Relevant medical history/current medical condition data includes data until the start of study drug. When possible, diagnoses and not symptoms will be recorded. HF medications will be recorded on the prior/concomitant Heart Failure Medications eCRF.

6.3 Treatment exposure and compliance

Dosing information for study medication will be collected on corresponding Dosage Administration Record eCRFs. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient. This information should be captured in the source document at each visit. All investigational treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.4 Efficacy

Efficacy variables will not be assessed in this study.

6.5 Safety

The Sponsor may request additional information on specific adverse events or laboratory events of interest and may make requests to perform additional diagnostic tests to further assess the safety profile of LCZ696. Such information may include diagnostic procedure reports, discharge summaries, autopsy reports, and other relevant information that may help in assessing the reported adverse event. All additional information will be de-identified prior to collection by Novartis or its agents.

[redacted]

6.5.1 Physical examination

A physical examination will be performed at every visit through the End of Study visit (Visit 9). It will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

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

6.5.2 Vital signs

Vital signs will be assessed at every visit. This will include SBP/DBP and pulse measurements. SBP/DBP will be measured by using a standard sphygmomanometer with an appropriate size cuff and the non-dominant arm in the sitting position after 5 minutes of rest.

6.5.3 Height and weight

Height in centimeters (cm) will be measured at Visit 1.

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing without shoes) will be measured every visit through the End of Study visit (Visit 9).

6.5.4 Laboratory evaluations

Laboratory samples will be analyzed locally. Values outside the normal ranges and notable values should be flagged on the report. It is the responsibility of the investigator to review all laboratory results and make an assessment of whether an abnormal or notable value is clinically significant, whether additional evaluations should be performed as judged appropriate, and whether the patient may continue in the trial. Sample collection should be conducted according to the standards and requirements of the local laboratory.

- Laboratory values that exceed the boundaries of a notable laboratory abnormality (refer to Appendix 1) must be commented on by the investigator in the source documents and additional laboratory evaluations should be performed, as judged appropriate by the investigator.
- If the laboratory abnormality induces clinical signs or symptoms, or requires therapeutic intervention, and satisfies the criteria defined in Section 7.1, then the diagnosis or medical condition must be entered on the AEs page of the patient's eCRF and any treatment necessary should be documented. If the laboratory abnormality is the primary reason for an unforeseen hospitalization or otherwise fulfills the seriousness category of an AE, then the procedure for rapid notification of SAEs must be followed.
- Likewise, if the laboratory abnormality leads to discontinuation of the study drug, the 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

[redacted]

testing or by performing additional laboratory tests as deemed necessary by the investigator or the Sponsor's medical monitor.

Clinically notable laboratory findings are defined in Appendix 1.

Full laboratory clinical chemistry (Table 6-2) will be performed locally at Visit 1 and abbreviated laboratory evaluations (sodium, potassium, creatinine) will be performed locally at Visits 2, 3, 4, 7 and 9. At Visits 5, 6 and 8 local labs will include sodium, potassium, creatinine, ALT, AST, alkaline phosphatase and total bilirubin.

Full laboratory tests will include the following:

Table 6-2 Full laboratory evaluations

Biochemistry
Sodium
Potassium
BUN
Creatinine
Total bilirubin
AST
ALT
γ GT
Alkaline phosphatase
Creatine phosphokinase (CPK)
Uric acid
Total protein
Albumin

6.5.4.1 Hematology

Hematology will not be performed in this study unless requested by the investigator as part of the patient's Standard of Care (conducted locally).

6.5.4.2 Clinical chemistry

Sodium, potassium, BUN, creatinine, total bilirubin, AST, ALT, γGT, alkaline phosphatase, CPK, uric acid, total protein, and albumin and will be measured as full laboratory evaluations at Visit 1 (Table 6-1).

The eGFR to determine eligibility of the patient for screening into the trial will be calculated at Visit 1 from the serum creatinine concentration. Estimated GFR will only be calculated using the following formula:

Estimated GFR (mL/min/1.73 m^2) = 175 × (standardized S_{Cr} in mg/dL)$^{-1.154}$ × (age in years)$^{-0.203}$ × (0.742 if female) × (1.212 if black), where S_{Cr} is the standardized serum creatinine value

Abbreviated laboratory evaluations (sodium, potassium and creatinine) will be performed at Visits 2, 3, 4, 7 and 9. At Visits 5, 6 and 8 the abbreviated laboratory evaluations will

[redacted]

include sodium, potassium, creatinine, ALT, AST, alkaline phosphatase and total bilirubin. Fasting is not required prior to the blood sampling for assessment of these laboratory parameters.

If a patient experiences liver function test (i.e. ALT, AST, ALP, TBL) values greater than three times the upper limit of normal during the study, additional information may be collected. See Appendix 2 for the follow-up requirements.

6.5.4.3 Urinalysis

Not applicable

6.5.5 Electrocardiogram (ECG)

ECG measurements are not required per protocol but are recommended as part of the patient's Standard of Care.

6.5.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have urine pregnancy tests performed locally at Visits 1, 5, 6, 7 and 8 and serum pregnancy tests performed locally at Visit 1 and the End of Study visit (Visit 9). A positive urine pregnancy test at Visit 1 constitutes a screen failure unless the serum β-hCG test is performed and found to be negative. In case of pregnancy discovered at any time during the open-label treatment period, the patient should be instructed to stop taking LCZ696 immediately. If the urine pregnancy test at Visit 6 or 8 is positive, LCZ696 must be stopped immediately. A follow-up serum pregnancy test can be perform at the discretion of the patient and investigator but restarting LCZ696 treatment can be considered only if the test is negative.

6.5.7 Appropriateness of safety measurements

The safety and clinical laboratory assessments performed in this study are similar to those used in the core study PARADIGM-HF (CLCZ696B2314). These assessments are appropriate for an investigational drug with the mechanism(s) of action of LCZ696 (angiotensin receptor antagonist and neprilysin inhibitor), the safety profile described in the LCZ696 Investigator Brochure, and the indication/patient population under study.

6.6 Other assessments

No additional tests will be performed on patients enrolled into this study.

7 Safety monitoring

7.1 Adverse events

All Adverse events reported will be recorded in the e-CRFs regardless of seriousness, causality, or actions (including angioedema-like events). An AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory

[redacted]

findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should 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, laboratory tests, 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 should 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 patients with the underlying disease. Investigators have the responsibility of managing the safety of individual patients and identifying adverse events. Alert ranges for labs and other test abnormalities are included in Appendix 1.

Adverse events should be recorded in the Adverse Events 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
- its relationship to the investigational treatment (no/yes)
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes an SAE
- action taken regarding investigational treatment
- whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); investigational treatment dosage adjusted/temporarily interrupted; study drug(s) permanently discontinued; concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

[redacted]

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

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

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The investigator should 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 should be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE, it must be reported to the Sponsor.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is any adverse event with the 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
    - 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, i.e. defined as an event that jeopardizes the patient or may require

[redacted]

medical or surgical intervention to prevent one of the outcomes listed above.

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

Life-threatening in the context of an 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 more severe (see Annex IV, ICH-E2D 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 (see Annex IV, ICH-E2D Guideline).

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

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.2.

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 following the last administration of study treatment must be reported to the Sponsor within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 days period should only be reported to the Sponsor if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow up information) is collected and recorded in English on the paper Serious Adverse Event Report Form or the electronic Serious Adverse Event Form within the EDC system (where available). The investigator must assess the relationship to each specific component of the study treatment (if the study treatment consists of several components).

SAEs (initial and follow-up) that are recorded *on the paper SAE form* should be faxed within 24 hours of awareness of the SAE to the Sponsor's local Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up

[redacted]

information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE

SAEs (initial and follow-up) that are recorded *electronically* in the EDC system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to the Sponsor's Drug Safety & Epidemiology immediately after investigator signature or 24 hours after entry, whichever occurs first.

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not (not applicable in this study) and whether the patient continued or withdrew from study participation. 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.

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 investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. The Sponsor may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational 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 Directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.3 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.

Liver events are divided into two categories:

- Liver events of special interest (AESI) which consist of LFTs elevations
- Medically significant liver events which are considered as serious adverse events (SAEs) and which consist of marked elevations of LFTs and / or pre-specified adverse events.

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

Any liver event which meets the criteria for "**medically significant**" event as outlined in Table 14-1 of Appendix 2 should follow the **standard procedures for SAE reporting** as described in Section 7.2.2.

Every 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. Detailed information is outlined in Table 14-2 in Appendix 2.

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of LCZ696 if appropriate
- Hospitalization of the patient if appropriate

[redacted]

- 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 consultancy, based on the investigator's discretion. All follow-up information, and the procedures performed should be recorded on appropriate CRF pages, including the liver event overview CRF pages.

7.4 Serum potassium safety monitoring (hyperkalemia)

To ensure patient safety, a standardized process for identifying, monitoring, and managing hyperkalemia is summarized in Appendix 3.

7.5 Renal safety monitoring

To ensure patient safety, a standardized process for identifying, monitoring, and managing renal dysfunction is summarized in Appendix 5.

7.6 Pregnancy reporting

In case a patient becomes pregnant, or plans to become pregnant, LCZ696 must be discontinued permanently. To ensure patient safety, each pregnancy occurring while the patient is on LCZ696 treatment must be reported to the Sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the Sponsor's local 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 LCZ696 treatment.

Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.7 Reporting angioedema events

It is important that the investigator pays special attention to any swelling or edema that may resemble angioedema that may be reported by patients. If such an event occurs, the investigator will complete a Questionnaire for an Angioedema Event form (provided by the Sponsor in the eCRFs) to summarize the event, its treatment, and its ultimate outcome and communicate this report to the Sponsor as soon as possible. Follow up reports must be communicated to the Sponsor as soon as new information regarding the event becomes available. All hospital records related to the event must be communicated to the Sponsor.

Occasionally, the investigator may be contacted by the Sponsor regarding AEs that were reported on behalf of patients that may resemble an angioedema event. The investigator or his/her delegated staff must complete the required report forms and supply the required

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medical records for such events, regardless of whether the investigator views the event in question as angioedema or not.

All angioedema reports will be forwarded to an angioedema adjudication committee by the Sponsor for assessment.

Submission of an angioedema report is not a substitution for the submission of an SAE report. If an angioedema event satisfies the definition of an SAE, the investigator must submit an SAE report (as described in Section 7.2.2) in addition to the Adjudication Questionnaire for an Angioedema Event.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an Investigator's Meeting, the Sponsor's representative will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will regularly check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice, and ensure that investigational treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor.

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. The Sponsor's 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 will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the EDC 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

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database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

The Sponsor's 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 the Sponsor's staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant heart failure medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be analyzed locally. The data will be recorded in source documents but will not be entered into the clinical database.

Data about LCZ696 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 CRO).

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 made available for data analysis. Any changes to the database after that time can only be made after written agreement by the Sponsor's Development management.

8.4 Data Monitoring Committee

A Data Monitoring Committee will not be used in this study.

8.5 Adjudication Committee

If swelling or edema that resembles angioedema occurs, the investigator will complete a Questionnaire for an Angioedema Event form (provided by the Sponsor in the eCRFs) to summarize the event, its treatment, and its ultimate outcome and communicate this report to the Sponsor as soon as possible. An angioedema AE will be recorded in the Adverse Event eCRFs if the criteria described in Section 7.1 are fulfilled. All angioedema reports will be forwarded to an angioedema adjudication committee for assessment.

[redacted]

9 Data analysis

9.1 Analysis sets

The following analysis populations will be defined for statistical analysis:

- Enrolled set (ENR) – All patients who signed the open-label study informed consent.
- Safety set (SAF) - All patients who received at least one dose of open-label study medication.

9.2 Patient demographics and other baseline characteristics

Demographics and baseline data will be collected in CLCZ696B2317. Summary statistics will be provided for demographics and other baseline characteristics including age, age group (<65, ≥65, <75, and ≥75 years), sex, race, ethnicity, weight, height, Body Mass Index (BMI), and vital signs. BMI will be calculated as weight (kg) / height^2 (m^2) from the collected height and weight. Continuous variables will be summarized using n, mean, median, standard deviation, minimum, maximum, and categorical variables will be summarized using frequency and percentage.

The ENR set will be used for the above analyses.

9.3 Treatments

Summary statistics for duration (in days) of exposure to LCZ696 will be provided for the Safety set.

Concomitant heart failure medications are defined as any HF medications administered after the enrollment date into the study. Concomitant HF medications will be summarized by therapeutic class and preferred term for the Safety Set.

Upon discontinuation of a patient from treatment, s/he is expected to resume ACEI or ARB therapy and those HF-related medications must be reported in the Concomitant Medication page of the eCRF.

9.4 Analysis of the primary variable(s)

The primary objective of this study is to evaluate the safety and tolerability of LCZ696 and to provide heart failure patients from PARADIGM-HF receiving open-label investigational drug. The primary assessment for safety will be based on the frequency of adverse events (AE) including:

- Overall AEs
- Serious adverse events (SAEs)
- adverse events of special interest (AESI),i.e., hypotension, hyperkalemia, or renal dysfunction
- Angioedema/angioedema-like events
- Deaths

[redacted]

- AEs leading to study drug dose adjustment/temporary interruption or permanent discontinuation
- AEs leading to study drug permanent discontinuation, including deaths
- AESIs leading to study drug permanent discontinuation with patients starting rescue medication(s) (ACEI/ARB)

AEs will be summarized as appropriate by resenting the number and percentage of patients reporting AEs by primary system organ class, by preferred term, by maximum severity, and by relationship to the investigational treatment.

In addition, the primary assessment for safety is the reporting of vital signs (i.e., sitting systolic blood pressure, sitting diastolic blood pressure, and heart rate) by visit with standard summary statistics (n, mean, standard deviation, minimum, Q1, median, Q3, maximum), including changes from baseline.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

There are no efficacy data being collected in this study.

9.5.2 Safety variables

Safety and tolerability are primary variables in this study; see Section 9.4.

9.5.3 Statistical model, hypothesis, and method of analysis

The number and frequency of adverse events will be summarized by primary system organ class, and preferred term. Serious adverse events and adverse events of special interest will be summarized in Clinical narratives.

9.5.4 Supportive analyses

For supportive purposes, the above analysis of number and frequency of adverse events will be summarized by demographic subgroups of age (<65 years, ≥65 years and <75 years, ≥75 years), sex, and race.

9.6 Interim analyses

No interim analysis will be performed.

9.7 Sample size calculation

All surviving patients randomized in PARADIGM-HF can be considered for eligibility in this open-label study (CLCZ6962317). It is estimated that 5,000 patients (about 59% of the core study population and approximately 72% of surviving patients) will meet the eligibility criteria and be enrolled into this open-label trial; however, since there is only one treatment arm in the study and treatment-related statistical comparisons are not planned, a specific sample size for the study is not required.

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10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented 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.

10.2 Informed consent procedures

Eligible patients 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 should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should 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 (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

The Sponsor will provide to investigators in a separate document a proposed informed consent form that complies 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 the Sponsor before submission to the IRB/IEC, and a copy of the approved version must be provided to the Sponsor's monitor after IRB/IEC approval.

Women of child bearing potential should 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. If there is any question that the patient will not reliably comply, they should not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should 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. 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 the Sponsor's monitors, auditors, the Sponsor's Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an

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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

Novartis assures that 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.

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 should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

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. All significant protocol deviations will be recorded and reported in the CSR.

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 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 should be followed.

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[redacted]

13 Appendix 1: Clinically notable laboratory values

Clinically notable laboratory abnormalities for selected tests based on a percent change from baseline:

Hematology

RBC count	>50% increase, >20% decrease
Hemoglobin	>50% increase, >20% decrease
Hematocrit	>50% increase, >20% decrease
WBC count	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease

Blood Chemistry

ALT (SGPT)	>150% increase
AST (SGOT)	>150% increase
BUN	>50% increase
Creatinine	>50% increase
Total bilirubin	>100% increase
CPK	>300% increase
Alkaline phosphatase	>100% increase
Sodium	>5% decrease
Potassium	>20% increase, >20% decrease
Uric acid	>50% increase

[redacted]

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

Table 14-1 Liver event definitions

	Definition/ threshold
AE of special interest	
Laboratory values	ALT or AST > 3 x ULN
	ALP > 2 x ULN
	TBL > 1.5 x ULN
Medically significant event (SAE)	
Laboratory values	ALT or AST > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction])
	ALP > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction])
	TBL > 3 x ULN
	Potential Hy's Law cases (defined as ALT/AST > 3 x ULN and TBL > 2 x ULN [mainly conjugated fraction] without notable increase in ALP to > 2 x ULN)
AEs	Any clinical event of jaundice (or equivalent term)
	ALT or AST > 3 x ULN accompanied by general malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any event that links to a preferred term (PT) in the MedDRA dictionary falling under the SMQ sub-module "Drug-related hepatic disorders – severe events only"* or any "Hy's law case" PT

* 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

Table 14-2 Liver event follow up requirements

Criteria	Event type	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	Medically significant	Discontinue the study drug immediately Hospitalize, if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST			
> 8 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Event type	Actions required	Follow-up monitoring
> 5 to ≤ 8 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists for *more than 2 weeks*, discontinue the study drug Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 x ULN accompanied by symptoms[b]	Medically significant	Discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 x ULN (patient is asymptomatic)	AESI	Laboratory to report to Investigator and Investigator to Novartis Repeat LFT once or twice in the week If elevation persists, establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 3 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
ALP (isolated)			
> 5 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, report to Novartis as an SAE Establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
> 2 to ≤5 x ULN (patient is asymptomatic)	AESI	Laboratory to report to Investigator and Investigator to Novartis Repeat LFT once or twice in the week. If elevation persists, establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 2 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
TBL (isolated)			
> 3 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 3 x ULN	AESI	Laboratory to report to	investigator discretion

[redacted]

Criteria	Event type	Actions required	Follow-up monitoring
(patient is asymptomatic)		Investigator and Investigator to Novartis Repeat LFT once or twice in the week. If elevation persists, establish causality	Monitor LFT within 1 to 4 weeks or at next visit
≤ 1.5 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
Preferred terms			
Jaundice	Medically significant	Discontinue the study drug immediately Hospitalize the patient Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
"Drug-related hepatic disorders - severe events only" SMQ AE	Medically significant	Discontinue the study drug Hospitalization if clinically appropriate Report to Novartis as an SAE Establish causality	Investigator discretion

[a] Elevated ALT/AST > 3 x ULN and TBL > 2 x ULN but with no notable increase in ALP to > 2 x ULN

[b] General malaise, fatigue, abdominal pain, nausea, or vomiting, rash with eosinophilia

[c] Resolution is defined as an outcome of one of the following: return to baseline values, stable values at three subsequent monitoring visits at least 2 weeks apart, remain at elevated level after a maximum of 6 months, liver transplantation, and death.

[redacted]

15 Appendix 3: Treatment guidelines for hyperkalemia (serum potassium greater than or equal to 5.3 mmol/L)

General principles

Elevation of potassium levels above the predefined values should be repeated and confirmed before any action is taken.

Any patient with a serum potassium > 5.3 mmol/L after enrollment into the study requires regular, repeated checks of potassium concentration (beyond that prescribed in the protocol) until it is clear that the potassium concentration is stable and not rising into the range of concern (≥ 5.5 and < 6.0 mmol/L) or potential danger (≥ 6.0 mmol/L).

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

Corrective action for management of hyperkalemia

Serum potassium > 5.3 and less than or equal to 5.5 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 > 5.3 and ≤ 5.5 mmol/L, regularly monitor serum potassium levels to ensure stability (suggested once monthly)

[redacted]

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

Serum potassium > 5.5 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 > 5.3 and ≤ 5.5 mmol/L
- Repeat serum potassium measurement after 2-3 days
- If serum potassium < 5.5 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

- Immediately discontinue study drug
- Confirm potassium concentration in a **non-hemolyzed sample**
- Urgently evaluate patient and treat hyperkalemia as clinically indicated
- Apply all measures outlined for serum potassium > 5.3 and < 6.0 mmol/L

Notification to the sponsor of a potassium level equal to- or above 6 mmol/L should be done within 48 h. No resumption of study drug without individualized case discussion with and permission from the Sponsor's Medical Monitor or his/her designee.

[redacted]

16 Appendix 4: Guidelines for the management of blood pressure

Guidelines

1. Investigator should monitor blood pressure closely
2. If symptomatic hypotension occurs:
   a. Correct any treatable cause, e.g. hypovolemia
   b. If hypotension persists, any antihypertensive drug and non-disease-modifying drugs, such as diuretics, 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 medication adjustment guidelines described in Section 5.5.5 should be adhered to as much as possible.

[redacted]

17 Appendix 5: 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 study medication. Moreover, renal dysfunction may develop or may deteriorate in some patients after study drug administration. The recommendations that follow have been developed to guide investigators in managing patients with renal dysfunction during the course of the study.

Two types of response to serum creatinine increase are described:

Surveillance situation

If, at any time after enrollment, eGFR decreases by ≥ 25% from baseline (Visit 1) (or if serum creatinine concentration increases to 2.5 mg/dL [221 μmol/L]), 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 affect creatininemia
- Volume decrease, including that resulting from excessive dosing of diuretics
- Urinary infection
- Urinary tract obstruction
- Study medication

Action situation

If a patient eGFR decreases by ≥ 40% from baseline (Visit 1) (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 should do so and also notify the Sponsor's 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 able to resume study drug treatment, renal function must be periodically monitored to ensure stability of eGFR.

[redacted]