Clinical Development

LCZ696B

Clinical Trial Protocol CLCZ696BDE01 / NCT02768298

A randomized, double-blind, active-controlled study to assess the effect of LCZ696 compared with enalapril to improve exercise capacity in patients with heart failure with reduced ejection fraction (HFrEF).

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List of abbreviations

ACE	angiotensin converting enzyme
ACEI(s)	angiotensin converting enzyme inhibitor(s)
AE(s)	adverse event(s)
AF	atrial fibrillation
AHU377	pro-drug that is metabolized to the active moiety LBQ657
ALT	alanine aminotransferase
ANCOVA	analysis of covariance model
ANP	atrial natriuretic peptide
APP	aminopeptidase P
ARB(s)	angiotensin receptor blocker(s)
ARNi(s)	angiotensin receptor neprilysin inhibitor(s)
AST	aspartate aminotransferase
AT_1	angiotensin type 1
AUC	area under the curve
bid	twice a day
BP	blood pressure
CCB	Calcium channel blockers
CHF	chronic heart failure
CPET	cardiopulmonary exercise testing
CPO	Country Pharma Organization
CRF	Case Report/Record Form
CRO	Contract Research Organization
CRT-D	cardiac resynchronization therapy defibrillator
CRT-P	cardiac resynchronization therapy pacemaker
CSR	Clinical Study Report
CV	cardiovascular
DBP	diastolic blood pressure
DS&E	Drug Safety and Epidemiology
EC(s)	Ethics Committee(s)
ECG	electrocardiogram
eCRF	electronic case report form

EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
EOS	end of study
[redacted]	[redacted]
ER	emergency room
ESRD	end stage renal disease
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
[redacted]	[redacted]
IA	interim analysis(es)
ICD	implantable cardioverter defibrillator
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	intensive care unit
IEC	Independent Ethics Committee
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IRB(s)	Institutional Review Board(s)
IRT	Interactive Response Technology
i.v.	intravenous(ly)
IVRS	Interactive Voice Response System
[redacted]	[redacted]
LBW	Lean Body Weight
LCZ696	Novartis compound code
LFT	Liver function test
LVEF	left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease
MET	metabolic equivalent of task
mg	milligram
MI	myocardial infarction
mmHg	millimeter mercury
mph	mile per hour
MRI	magnetic resonance imaging

MUGA	multiple gate acquisition scan
NEP	neutral endopeptidase
NODM	new onset diabetes mellitus
NP(s)	natriuretic peptide(s)
NYHA	New York Heart Association
o.d.	once a day
PK	pharmacokinetic(s)
p.o.	oral(ly)
PCI	percutaneous coronary intervention
PRA	plasma renin activity
RAAS	renin angiotensin aldosterone system
REB	Research Ethics Board
RER	respiratory exchange ratio
SAE(s)	serious adverse event(s)
SBP	systolic blood pressure
[redacted]	[redacted]
SHF	systolic heart failure
UACR	urinary albumin to creatinine ratio
ULN	upper limit of normal
V	visit
VAD	ventricular assistance device
VAT	Ventilatory anaerobic threshold
VO_2	respiratory oxygen uptake
VO_{2max}	respiratory oxygen uptake (max.)
VO_{2peak}	respiratory oxygen uptake (peak)
WBC	White blood cell

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	The planned stage of the subjects' participation in the study. Each epoch serves a purpose in the study as a whole. Typical epochs are: determination of subject eligibility, wash-out of previous treatments, exposure of subject to treatment or to follow-up on subjects after treatment has ended.
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* other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Subject Number	A number assigned to each patient who enrolls into the study
Part	A subdivision of a single protocol into major design components. These parts often are independent of each other and have different populations or objectives. For example, a single dose design, a multiple dose design that are combined into one protocol, or the same design with different patient populations in each part.
Period	A subdivision of a cross-over study
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all investigational/study treatment administration and all assessments (including follow-up)
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study/investigational treatment was discontinued whichever is later
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
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
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

Protocol synopsis

Protocol number	CLCZ696BDE01
Title	A randomized, double-blind, active-controlled study to assess the effect of LCZ696 compared with enalapril to improve exercise capacity in patients with heart failure with reduced ejection fraction (HFrEF).
Brief title	Exercise capacity study of LCZ696 vs. enalapril in patients with chronic heart failure and reduced ejection fraction
Sponsor and Clinical Phase	Novartis Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Patients with chronic heart failure (CHF) with impaired cardiac function and peripheral deconditioning experience a significantly reduced ability to exercise, reduced daily physical activity and a diminished quality of life. Current pharmacological treatment for CHF has so far substantially improved symptoms, hospitalization and clinical outcomes but most patients remain symptomatic experiencing shortness of breath during daily activity. Therefore, there is a demand for therapeutic interventions showing improvement in symptoms and exercise capacity with subsequent improvement of quality of life in CHF patients. Studies have demonstrated that cardiopulmonary exercise testing (CPET) could reliably evaluate the exercise tolerance of heart failure patients. In addition, parameters attained by CPET have shown to provide very reliable parameters for predicting prognosis. There is sound evidence including VO_{2peak} in stratifying the risk in patients with CHF. In addition, exercise parameters assessed by CPET are not only associated with prognosis, but are all associated with the severity of CHF symptoms and quality of life in CHF patients. LCZ696 is an angiotensin receptor neprilysin inhibitor (ARNI) being developed for the treatment of CHF. The clinical efficacy of LCZ696 in patients with heart failure with reduced ejection fraction (HFrEF) has been assessed previously and showed a significant benefit over enalapril in reducing cardiovascular death and hospitalizations due to HF. [redacted] We therefore hypothesize that LCZ696 will also improve exercise capacity and daily physical activity in

	HF patients, parameters of immediate relevance to patients suffering from HF.
Primary Objective(s) and Key Secondary Objective	To assess the effect of LCZ696 versus enalapril regarding improvement of exercise tolerance (VO_{2peak}, adjusted to body weight) as assessed by cardiopulmonary exercise testing (CPET) in patients with chronic heart failure (NYHA class III, left ventricular ejection fraction (LVEF ≤40%). Key secondary objective: To assess the early effect (6 weeks) of LCZ696 versus enalapril regarding improvement of exercise tolerance (VO_{2peak}, adjusted to body weight) as assessed by cardiopulmonary exercise testing (CPET) in patients with chronic heart failure (NYHA class III, LVEF ≤40%).
Secondary Objectives	To assess the long-term effect of LCZ696 versus enalapril on the following CPET parameters: • Change of VE/VCO_2 slope after 6 weeks and 3 months • Change in exercise capacity (Watt) at ventilatory anaerobic threshold (VAT) after 6 weeks and 3 months • Change in rate of perceived exertion during exercise (Borg Scale) after 3 months
Study design	This is a randomized, double-blind, active-controlled parallel grouped study to assess the effect of LCZ696 compared with enalapril to improve exercise capacity, daily physical activity and quality of life in patients with stable chronic heart failure (NYHA class III) with reduced ejection fraction (LVEF ≤ 40 %), within a duration of 3 months.
Population	Patients with CHF (NYHA class III) and reduced ability to exercise, evidenced by VO_{2peak} ≤ 18 ml/min per kg, aged 18 years or older with LVEF ≤ 40%. The target projected sample size is 200 patients (100 patients in each arm). It is estimated that approximately 400 patients will be screened at up to approximately 40 study sites because a screen failure rate of approximately 50 % is anticipated based on previous experience.
Inclusion criteria	▪ Patients must give written informed consent before any assessment is performed and must be willing and capable to comply with all study procedures. ▪ Outpatients ≥ 18 years of age, male or female. ▪ Patients with a diagnosis of CHF NYHA class III and reduced ejection fraction (LVEF ≤ 40%) ▪ Reduced ability to exercise, evidenced by VO_{2peak} ≤ 18 ml/min per kg

	▪ Patients must be on an ACEI or an ARB at a stable dose of at least enalapril 10 mg/d or equivalent for at least 4 weeks before Visit 1
Exclusion criteria	▪ 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 the study drugs ▪ Previous history of intolerance to recommended target doses of ACEIs or ARBs ▪ Known history of angioedema ▪ Requirement of treatment with both ACEIs and ARBs ▪ Current acute decompensated HF (exacerbation of chronic HF manifested by signs and symptoms that may require intravenous therapy) ▪ Symptomatic hypotension and/or a SBP < 100 mmHg at Visit 1 (screening) or at Visit 3 (randomization) ▪ Estimated GFR < 30 mL/min/1.73m^2 as measured by the simplified MDRD formula at Visit 1 (screening), or Visit 3 (randomization) ▪ Serum potassium > 5.2 mmol/L at Visit 1 (screening) or at Visit 3 (randomization) ▪ Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid or other major CV surgery, percutaneous coronary intervention (PCI) or carotid angioplasty within the 3 months prior to Visit 1 ▪ Coronary or carotid artery disease likely to require surgical or percutaneous intervention within the 6 months after Visit 1 ▪ Patients with severe obesity (Adipositas permagna – BMI ≥ 40) ▪ Pregnant or nursing (lactating) women
Investigational and reference therapy	• LCZ696 200 mg bid • Enalapril 10 mg bid
Efficacy assessments	Primary assessment: • change of VO_{2peak} compared to baseline measurements (adjusted to body weight) after 3 months Secondary assessments: • change of VO_{2peak} compared to baseline measurements (adjusted to body weight) after 6 weeks of treatment

	• Change of VE/VCO_2 slope after 6 weeks and 3 months of treatment • Change in exercise capacity (Watt) at ventilatory anaerobic threshold (VAT) after 6 weeks and 3 months of treatment • Change in rate of perceived exertion during exercise (Borg Scale) after 3 months of treatment
	[redacted]
Safety assessments	• AEs and SAEs • Sitting systolic (SBP) and sitting diastolic BP (DBP) • Symptomatic hypotension • Angioedema • Laboratory values • Hyperkalemia • Renal dysfunction
Other assessments	[redacted]
Data analysis	Conservatively assuming a standard deviation of 3 ml/min/kg and a two-sided alpha of 0.05, 86 patients per arm would confer a 90% power to detect a treatment difference of 1.5 ml/min/kg. Correcting for expected drop-out of patients, approximately 100 patients per treatment group (200 in total) will need to be enrolled in the trial.

Key words	Heart failure, NYHA class III, VO_{2peak}, Exercise capacity, ventilatory anaerobic threshold, VE/VCO_2 slope, ergospirometry, cardiopulmonary exercise testing (CPET), [redacted]

Amendment 4

Amendment Rationale

This amendment was implemented to improve comparability of the primary and secondary endpoints with other studies using cardiopulmonary exercise testing (CPET) as an outcome measure in heart failure trials (Keteyan et al., 2016; Akbulut et al., 2006; Arena and Sietsema, 2011).

1) Substituting "VO_{2peak} adjusted by lean body weight (VO_{2peak}/LBW)" by "VO_{2peak} adjusted by whole body weight" (VO_{2peak}/kg):

   This amendment affects the primary endpoint "Change of VO_{2peak} compared to baseline measurements (adjusted to body weight) after 3 months" and the secondary endpoint "Change of VO_{2peak} compared to baseline measurements (adjusted to body weight) after 6 weeks of treatment". As most of the heart failure trials investigated VO_{2peak}/kg instead of VO_{2peak}/LBW, we changed this accordingly.

[redacted]

3) Substituting RER = 1 by ventilatory anaerobic threshold (VAT):

   This amendment affects the secondary endpoint "Exercise capacity (Watt) at RER = 1 (RER=VCO_2/VO_2)" [redacted]. VAT is the gold standard of submaximal exercise capacity comparable to daily activities and therefore more valid and reliable than RER=1. Furthermore, it is a strong prognostic marker to identify patients at high risk for adverse events (Gitt et al. 2002).

In addition, minor changes were made to correct inconsistencies within the study protocol.

Changes to the protocol

- The term "lean body weight" was changed to "body weight" throughout the protocol and therefore the primary (adjusted VO_{2peak} after 3 months of treatment) and secondary endpoint (adjusted VO_{2peak} after 6 weeks of treatment) are altered
- RER=1 was exchanged to VAT for the secondary endpoint "Exercise capacity (Watt)" [redacted]
- Minor changes to other sections (pages 8, 12, 27, 29, 30, 31, 67 and 69)

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

References:

- Keteyian SJ, Patel M, Kraus WE, et al. (2016). Variables Measured During Cardiopulmonary Exercise Testing as Predictors of Mortality in Chronic Systolic Heart Failure. *J Am Coll Cardiol*., 67(7):780–789. doi:10.1016/j.jacc.2015.11.050
- Akbulut T, Akgöz H, Dayi ŞÜ, Çelik SE, Gürkan U, & Tayyareci G (2006). Evaluation of Enalapril+Losartan Treatment with Cardiopulmonary Exercise Test in Patients with Left Ventricular Dysfunction. *Angiology*, 57(2):181–186. https://doi.org/10.1177/000331970605700207
- Arena R and Sietsema KE (2011). Cardiopulmonary Exercise Testing in the Clinical Evaluation of Patients With Heart and Lung Disease. *Circulation*, 123:668-680. https://doi.org/10.1161/CIRCULATIONAHA.109.914788
- Gitt AK, Wasserman K, Kilkowski, C, Kleemann T, Kilkowksy A, Bangert M, Schneider S, Schwarz A & Senges J (2002). Exercise Anaerobic Threshold and Ventilatory Efficiency Identify Heart Failure Patients for High Risk of Early Death. Circulation, 103:3079-3084.

Amendment 3

Amendment Rationale

This Amendment was introduced as consequence of changes in the drug supply, so that enalapril 5 mg and 10 mg tablets which were provided in blister packs, will be provided in HDPE bottles, as enalapril 2.5 mg tablets already were. There will be a transition time where both versions of packaging are possible, thus both versions are reflected in this protocol version.

Changes to the protocol

In section 5.1.1 'Investigational treatment', the primary packaging of enalapril 5 mg and 10 mg tablets is updated.

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

Amendment 2

Amendment Rationale

This Amendment was introduced as consequence of experiences made during the recruitment period of the first patients. Recruitment of patients eligible for the study is slow and patients are hard to identify. The specific patients with more severe chronic heart failure (NYHA III) mostly have a number of comorbidities that fulfill exclusion criteria. Thus, all inclusion and exclusion criteria were reviewed.

More symptomatic patients (NYHA III) tend to more often have a device (ICD/CRT) or are treated with amiodarone which both artificially prolong the QT interval without posing pathology or qualifying as true long QT syndrome. From the LCZ696 program it is known, that in a thorough QTc clinical study in healthy male subjects, single doses of 400 mg and 1200 mg LCZ696 had no effect on cardiac repolarization. Additionally, the SmPC of the marketed product does not include any specific effects or warnings of LCZ696 on QTc time. Therefore, the respective exclusion criterion was modified excluding only patients with long QT syndrome.

Patients for whom a heart transplantation or a ventricular assist device implantation is planned are excluded, since this significant procedure would considerably impact the study endpoint. However, patients need only to be excluded if it is very likely that these procedures are necessary throughout the study. Since the study duration of 14 weeks (including screening period) is rather short this exclusion criterion was reworded to account for this.

To assess the efficacy endpoints investigated in this study, it is necessary to evaluate the chronic HF patients and its baseline characteristics and to perform baseline assessments in a stable state of the chronic disease. Thus, all medications prescribed for treatment of HF are to be stable 4 weeks prior to inclusion of the patient, more specifically, prior to the baseline assessments. Throughout the study, to evaluate the effect of LCZ696 vs. comparator, all other disease modifying agents should be kept on a stable dose, if possible. Thus, those medications have to be stable 4 weeks prior to the screening visit and until randomization visit. After randomization, all efforts should be made to keep the dose stable, This is clarified in the protocol.

Additionally, minor changes are made to be consistent throughout the protocol.

Changes to the protocol

The described changes in the amendment rationale are implemented throughout the protocol:

- Exclusion criterion 13 is adapted to clarify that only a planned transplantation of heart or VAD during the expected study duration of 14 weeks is excluded.
- Exclusion criterion 31 is updated to only exclude a diagnosed long QT syndrome.
- In Section 5.5.8 ‘Other concomitant medication’, it is explicitly stated that concomitant HF medication should be stable 4 weeks prior to screening Visit 1 and until randomization Visit 3.
- In Section 3, investigational plan, it is clarified, that 36 hour wash-out period is necessary for ACEI, but not for ARB. This is to be consistent throughout the protocol.

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

Amendment 1

Amendment Rationale

CLCZ696BDE01 Protocol Amendment 1 clarifies that if during the double-blind treatment period the initiation of prohibited concomitant medication is necessary, study drug has to be discontinued. Especially due to increased risk of angioedema, concomitant application of ACEI is strictly prohibited and an at least 36 hour wash-out period is mandatory. Thus, the protocol is amended to clearly define that as long as the discontinued study medication is blinded in any case the 36 hours washout with regard to contraindicated concomitant medication ACEI must be followed. It is clarified that for prohibited treatment ARBs study drug has to be discontinued but no additional wash-out period is necessary. This is now consistent throughout the protocol and in line with current safety data.

Changes to the protocol

The described changes in the amendment rationale are implemented throughout the protocol:

- Section 5.5.8 Other concomitant treatment –ACEIs and ARBs – is reworded to clearly state that both ACEI and ARB are prohibited during treatment with double-blind study medication. If ACEI and/or ARB are initiated, study medication has to be discontinued. It is clarified, that 36 hour wash-out period is necessary for ACEI, but not for ARB.
- In Section 5.5.10, the use of prohibited treatment during the study will now require to stop study medication. The mandatory wash-out period for ACEI is explicitly mentioned.

1 Introduction

1.1 Background

The prevalence of chronic heart failure (CHF) is steadily increasing and remains a major cause of morbidity and mortality in the Western world. Because of impaired cardiac function and peripheral deconditioning patients with CHF experience a significantly reduced ability to exercise, directly leading to reduced daily physical activity and a dramatically diminished quality of life. Long before clinical outcomes, patients with CHF experience inability to perform exercise without discomfort as one of the first clinical symptoms. It is often the initial reason for seeking medical care and a central target for treatment. Current pharmacological treatment for CHF has so far substantially improved symptoms, hospitalization and clinical outcomes. However, most patients remain symptomatic particularly experiencing shortness of breath during daily activity. This issue remains an urgent challenge in the development of future therapeutic strategies in these patients. Therefore, given this background, there is a definite and high demand for therapeutic interventions showing improvement in symptoms and exercise capacity with subsequent improvement of quality of life in these patients (Belardinelli et al. 1999).

Cardiopulmonary exercise testing (CPET) is an established method to reliably evaluate the exercise tolerance of heart failure patients by evaluating the cardio-pulmonary system using the measurement of respiratory gases during physical (exercise) stress. In addition, parameters attained by this test have shown to provide very reliable parameters for predicting prognosis. The most important measurements acquired during cardiopulmonary exercise testing are respiratory oxygen uptake (VO_2), carbon dioxide production (VCO_2), and ventilatory measures (Albouaini et al. 2007). Respiratory oxygen uptake reflects the cellular O_2 demand up to a level that equates to maximal rate of O_2 transport limited by cardiocirculatory, pulmonary and peripheral function. As response to increasing exercise load VO_2 increases reaching a plateau, called VO_{2max}. In a clinical setting, patients are often unable to reach this plateau because of symptom limitation. Then peak VO_{2max} is termed VO_{2peak}. There is sound evidence for VO_{2peak} in stratifying the risk in patients with CHF and prognostic value for patients with CHF (Corrà et al. 2004; Mancini et al. 1991). An adjustment of VO_{2peak} to body weight could provide an even better prognostic value in these patients (Osman et al. 2000). Moreover of significant prognostic value seem to be the ventilatory expired gas parameters, namely minute ventilation (VE) to carbon dioxide output slope (VE/VCO_2). Likewise, various studies have demonstrated that an abnormally high VE/VCO_2 ratio resembling the inability to eliminate CO_2 by respiration is associated with a poor outcome in patients with CHF. In addition, these exercise parameters are not only associated with prognosis, but are all associated with the severity of CHF symptoms and quality of life in CHF patients. The Weber classification for CHF (Table 1-1) indicates increasing disease severity from Class A through Class D and correlates subjective symptom severity levels with the measure of oxygen consumption VO_{2max}. Data suggest a moderate risk of cardiac events in patients with VO_{2peak} between 10 and 18 mL/kg/min.
CPET will be performed to assess $VO_{2peak.}$ The test protocol was selected according to the purpose of testing and the patient population in the current study. CPET is evaluated according to the modified Naughton protocol as recommended for treadmill exercise in patients with CHF (Fletcher et al. 2013) which provides a moderate increase in workload between stages and is thus a useful choice for elderly, deconditioned patients like patients with CHF and NYHA class

III. Based on this protocol, the workload will start at 10W and will be increased by 10W for each 1-minute stage.

LCZ696 is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI) being developed for the treatment of patients with CHF. The clinical efficacy of LCZ696 in heart failure with reduced ejection fraction (HFrEF) patients has been assessed in the LCZ696B2314 PARADIGM-HF study (McMurray et al. 2013). LCZ696 showed a significant benefit over enalapril in reducing cardiovascular death and hospitalizations due to HF as well as all-cause mortality (McMurray et al. 2014). [redacted] We therefore hypothesize that LCZ696 will also improve exercise capacity and daily physical activity in HF patients, parameters of immediate relevance to patients suffering from HF.

Table 1-1 Weber classification of CHF

Class	Severity level	$VO_{2\ max}$ (ml/min/kg)	CI max (l/min/m^2)
A	Mild/none	>20	>8
B	Mild to moderate	16-20	6-8
C	Moderate to severe	10-16	4-6
D	Severe	6-10	2-4
E	Very severe	<6	<2

1.2 Purpose

The purpose of this study is to evaluate the effect of LCZ696 on daily physical activity and quality of life by improving exercise capacity in patients with stable CHF and reduced ejection fraction. Data from this study are intended to provide further understanding of the early impact of LCZ696 treatment on CHF patients with regard to other patient related outcomes. Data are also intended for publication.

2 Study objectives

2.1 Primary objectives

The primary objective of this study is to demonstrate the superiority of LCZ696 200 mg bid compared to enalapril 10 mg bid in improving exercise tolerance (VO_{2peak}, adjusted to body weight) as assessed by cardiopulmonary exercise testing (CPET) in patients with stable chronic heart failure (NYHA class III) and reduced ejection fraction (LVEF $\leq$ 40%) after 3 months treatment.

2.2 Secondary objectives

Secondary objectives of this study are

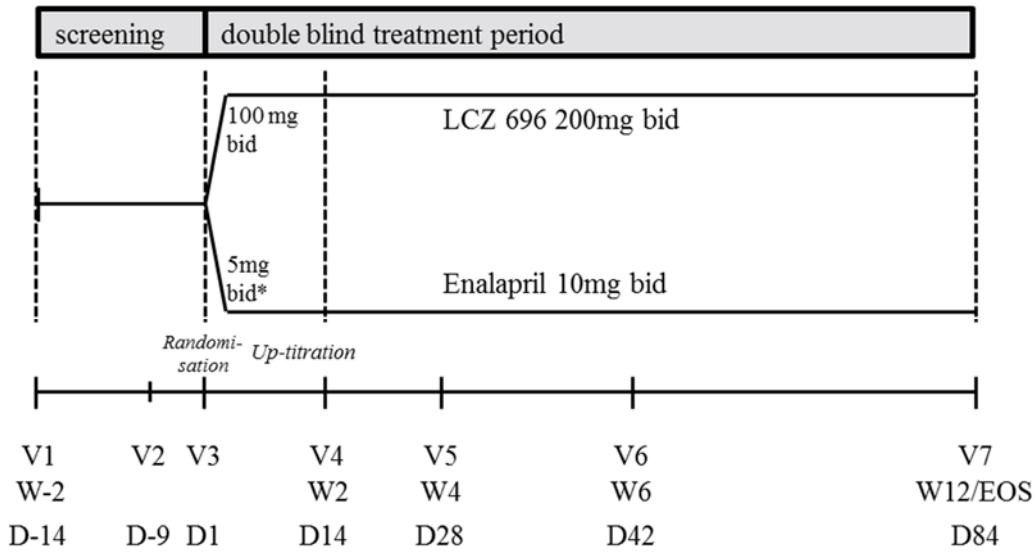
- To demonstrate the superiority LCZ696 versus enalapril regarding improvement of exercise tolerance (VO_{2peak}, adjusted to body weight) as assessed by cardiopulmonary exercise testing (CPET) in patients with chronic heart failure after 6 weeks treatment.

- To compare LCZ696 versus enalapril on the following CPET parameters:
  - Change of VE/VCO_2 slope after 6 weeks and 3 months
  - Change in exercise capacity (Watt) at VAT after 6 weeks and 3 months
  - Rate of perceived exertion during exercise (Borg Scale) after 3 months
- To assess the safety and tolerability of LCZ696 in patients with stable chronic heart failure with NYHA class III and reduced ejection fraction (LVEF $\leq$ 40%)

3 Investigational plan

3.1 Study design

Figure 3-1 Study design



* Patients at a stable daily dose of enalapril above 10 mg per day (or corresponding doses of other ACEI/ARB) prior to Visit 1 should start at a dose of enalapril 10mg bid.

This study is a randomized, double-blind, double-dummy, parallel-group, active-controlled, two-arm trial to compare LCZ696 200 mg bid to enalapril 10 mg bid in improving exercise capacity, daily physical activity and quality of life in patients with stable CHF (NYHA III) and reduced ejection fraction (LVEF ≤ 40%).

Eligible patients at stable dose of at least enalapril 10 mg/d or equivalent for at least 4 weeks before Visit 1 and LVEF ≤ 40% can be randomized at Visit 3. β-blocker, ivabradine and aldosterone antagonist therapy should be at a stable dose for 4 weeks prior to Visit 1. Please refer to Section 4 Population for a full list of inclusion and exclusion criteria.

VO_{2peak} inclusion criterion will only be checked after assessment of patients' eligibility according to all other inclusion and exclusion criteria. Thus, ergospirometry will be performed on Visit 2 to get a complete assessment of CPET (for screening), [redacted]

Once patients' eligibility has been ascertained, they will attend Visit 3 for randomization approximately two weeks after Visit 1 to start enalapril 5 mg bid versus LCZ 100 mg bid for 2 weeks. All efficacy assessments collected at Visit 2 will be used as baseline values.

Before dispensing of study treatment, a valid baseline efficacy assessment of CPET must be performed including central plausibility and quality check.

At baseline, all eligible patients will be randomized to receive either LCZ696 or enalapril in a 1:1 allocation during the double-blind period.

Treatment will be initiated with enalapril 5 mg bid (enalapril 10 mg bid for patients with a dose above enalapril 10 mg/d or equivalent prior Visit 1) or LCZ696 100mg bid, respectively. Dose

will be up-titrated after 2 weeks to the final dose of enalapril 10mg bid or LCZ696 200mg bid. For allowed investigational treatment dose adjustments during double-blind period refer to Section 5.5.5.

Patients should continue to take their background medications for CHF during the study, with the exception of ACEI or ARBs which are replaced by investigational treatment and must be discontinued before first application of study drug (washout period of 36 hours applies to ACEI, compare Section 5.5.8). First application of study drug is planned on the day after Visit 3; last intake of ACEI or ARB before study drug application thus will be in the evening prior to Visit 3 (randomization) (If Visit 3 is scheduled for Wednesday e.g., last ACE or ARB medication should be taken by the patient on Tuesday evening. The patient will then start to take the first dose of LCZ696 or enalapril double blind medication on Thursday morning.).

Tolerability to study treatment will be checked at every visit after randomization. Please refer to Section 5.5.5 for allowed study drug adjustments during the study. Non-disease modifying medications (such as nitrates, CCBs, α-blockers, and diuretics) may be changed (dose reduced or discontinued) in response to the occurrence of adverse events, if they are believed to be the cause of the AE such as hyperkalemia, hypotension, and renal dysfunction, in an attempt to allow patients to meet the safety criteria in Table 3-2. The dose of background disease modifying drugs, such as β-blockers, ivabradine and aldosterone antagonists, may be reduced to facilitate maintenance of study drug if they are believed to be the cause of the adverse effect in question. If necessary, in doubt patients will be titrated down to the next lower dose level of study medication twice a day as described in Section 5.5.5, at the investigator's discretion, based on the defined safety and tolerability criteria (Appendix 1, Appendix 2, Appendix 3, and Appendix 4). The reason for medication modification must be carefully documented in the appropriate eCRFs. Any changes in the study drug dose level, including temporary/permanent withdrawal or restart of the study drug, must be recorded on the Dosage Administration Record eCRF.

After randomization, temporary study drug discontinuation for any reason does not automatically constitute withdrawal from the study and should not lead to the patient being withdrawn from the study. Patients should be re-challenged to receive study treatment according to guidance in Section 5.5.5.

Please refer to Table 6-1 for a detailed list of study procedures and assessment to be performed at each double-blind period visit. Regardless of the occurrence of any unscheduled visits, scheduled visits must occur within the timeframe of -3/+3 days to the visits outlined in Table 6-1.

Of note, all appointments shall be scheduled in the morning if possible. Otherwise all appointments at all study days shall be performed at about same time.

All laboratory evaluations for planned visits and also for unscheduled visits will be performed by the central laboratory. Thus, at Visit 3 and 4, patients should come to the site 3 to 4 days prior to the scheduled visit date for blood draw only so that results from central laboratory are available and enable a competent decision on randomization or up-titration at the respective visits.

Visit 1 (Screening)

At Visit 1 (day -14) patients will be checked for eligibility. Inclusion and exclusion criteria will be checked for all patients. Eligible patients at least at a stable dose of enalapril 10 mg (or equivalent ACE or ARBs according to Table 3-1) 4 weeks prior to Visit1 can be randomized at Visit 3 (day 1).

Table 3-1 Minimum required pre-study daily doses of commonly prescribed ACEIs and ARBs

ACEIs	Minimum dose	ARBs	Minimum dose
Enalapril	10 mg	Candesartan	16 mg
Benazepril	20 mg	Eprosartan	400 mg
Captopril	100 mg	Irbesartan	150 mg
Cilazapril	2.5 mg	Losartan	50 mg
Fosinopril	20 mg	Olmesartan	10 mg
Lisinopril	10 mg	Telmisartan	40 mg
Moexipril	7.5 mg	Valsartan	160 mg
Perindopril	4 mg		
Quinapril	20 mg		
Ramipril	5 mg		
Trandolapril	2 mg		
Zofenopril	30 mg		

Table 3-2 Safety monitoring criteria that must be met at Visit 1 (screening) and Visit 3 (randomization)

Parameter	Visit 1 (screening) and Visit 3 (randomization)
Potassium level	K ≤ 5.2 mmol/L
Kidney function	eGFR ≥ 30 mL/min/1.73m^2
Blood pressure	No symptomatic hypotension and SBP ≥ 100 mmHg
Adverse events (AEs) or conditions	No postural symptoms or any conditions that preclude continuation according to the investigator's judgment

Patients will be asked to sign an informed consent form prior to performing any study-related procedures. For a full list of inclusion and exclusion criteria see Section 4 Population.

Complete physical examination is required at Visit 1. Any local measurement of LVEF made within the past 6 months using echocardiography, multiple-gated acquisition (MUGA), CT scanning, MRI or ventricular angiography will be acceptable, provided no subsequent measurement above 40%. If a patient has an implanted cardiac resynchronization therapy device, the LVEF values used to qualify for the study must be obtained after the implantation of that device by at least three months. Screening potassium levels and eGFR will be assessed by sending blood samples to the central laboratory and only patients with the required values per entry criteria will be eligible for entering the study. Since it may take up to 72 hours to

obtain the results of the clinical laboratory assessments to evaluate the patient's eligibility for the study, it is recommended that at Visit 1 the site schedules Visit 2 approximately 5 days after Visit 1 and Visit 3 approximately two weeks after Visit 1.

Detailed HF history and other relevant CV medical history will be recorded on eCRFs separately from other medical history.

Screening ECG performed within the 6 months before Visit 1 is accepted, otherwise ECG evaluation must be performed at Visit 1 for safety reasons.

Visit 2 (-9 d)

Visit 2 is performed to get a complete laboratory assessment by the central lab and assessment of CPET to verify inclusion criterion of VO_{2peak} including a quality evaluation of CPET in time before randomization. All efficacy assessments will be collected at this visit as well to ascertain a similar schedule of all visits with efficacy assessments.

Blood draw for lab assessments will be done.

[redacted]

Ergospirometry will be performed at Visit 2 for assessment of eligibility of VO_{2peak} according to provided separate manual. The details of the procedure will be outlined in a manual provided to all participating sites. Patients will be under continuous ECG and frequent blood pressure monitoring.

[redacted]

Plausibility and quality checks of the ergospirometry data will be done by a reading center. If ergospirometry data acquisition fails for any reason, it may be repeated one day later. Study medication dispense at Visit 3 can only be done with a valid ergospirometry measurement.

[redacted]

Patients should be reminded to come without taking their usual ACEI or ARB to Visit 3 to ascertain a wash-out period of 36 hours for ACEI before first application of investigational treatment.

[redacted]

Visit 3 (Randomization)

At Visit 3 all patients who meet all entry criteria, including the required clinical laboratory values, and meet the safety criteria in Table 3-2, will be randomized to one of the two treatment arms enalapril bid or LCZ bid add on to their current heart failure therapy.

Patients should have discontinued their ACE/ARB medical therapy in the evening before Visit 3 in order to start study drug in the morning one day later. (If Visit 3 is scheduled for e.g. Wednesday, last ACE or ARB medication should be taken by the patient on Tuesday evening. The patient will then start to take the first dose of LCZ696 or enalapril double blind medication on Thursday morning.). If the patient continued to take their usual ACEI, the start of study drug has to be postponed to assure a 36 hour washout before first application of study drug.

Patients will start study treatment at dose level 2 or 2a according to their ACE/ARB-treatment prior to study (refer to Section 5.5.4 for details) and must be stabilized on this dose for 2 weeks.

To ascertain patient's eligibility, study drug should not be dispensed unless laboratory assessments of potassium and eGFR are available and meet the safety criteria (see Table 3-2).

Study medication dispense can only be done with a valid ergospirometry measurement.

[redacted]

Visit 4 (+ 2 weeks; up-titration visit)

After 2 weeks of treatment at Visit 4, patients will be checked for tolerability and will be up-titrated to target dose level 3 (LCZ 200 mg bid; enalapril 10 mg bid). Therefore symptomatic hypotension, renal dysfunction and/or hyperkalemia are considered to be safety parameters and should be handled according to respective guidelines for management (Appendix 1, Appendix 2 Appendix 3, and Appendix 4).

Blood draw for lab assessments has to be done. In case of lab deviations an unscheduled visit may be scheduled at the discretion of the investigator to re-assess lab parameters and evaluate the efficacy of taken measures. Please refer to Appendix 1, Appendix 2, Appendix 3, and Appendix 4, respectively, for guidance on handling hyperkalemia, hypotension, and renal dysfunction.

Visit 5 (+4 weeks)

After 2 weeks of treatment on level 3 study medication, patients will be checked for tolerability at Visit 5. Every attempt should be made to keep the patients stable on level 3 throughout the whole study in accordance with all safety parameters (e.g. symptomatic hypotension, renal dysfunction and /or hyperkalemia).

[redacted]

Blood draw for lab assessments (abbreviated chemistry panel) has to be done. In case of lab deviations an unscheduled visit may be scheduled at the discretion of the investigator to re-

assess lab parameters and evaluate the efficacy of taken measures. Please refer to Appendix 1, Appendix 2, Appendix 3, and Appendix 4, respectively, for guidance on handling hyperkalemia, hypotension, and renal dysfunction.

Visit 6 (+6 weeks)

After 6 weeks of treatment, patients will be checked for tolerability at Visit 6. Every attempt should be made to keep the patients stable on level 3 in accordance with all safety parameters (e.g. symptomatic hypotension, renal dysfunction and /or hyperkalemia).

[redacted]

Ergospirometry will be performed at Visit 6 (according to a separate manual). Patients will be under continuous ECG and frequent blood pressure monitoring.

[redacted]

Plausibility and quality checks of the ergospirometry data will be done by a reading center. If ergospirometry data acquisition fails for any reason, it may be repeated one day later.

[redacted]

Blood draw for lab assessments (abbreviated chemistry panel) has to be done. In case of lab deviations an unscheduled visit may be scheduled at the discretion of the investigator to re-assess lab parameters and evaluate the efficacy of taken measures. Please refer to Appendix 1, Appendix 2, Appendix 3, and Appendix 4, respectively, for guidance on handling hyperkalemia, hypotension, and renal dysfunction.

Visit 7 (+3 months; EOS)

After 3 months of treatment, a final assessment of patients for tolerability at Visit 7 is performed.

[redacted]

Ergospirometry will be performed at Visit 7 (according to separate manual). Patients will be under continuous ECG and frequent blood pressure monitoring.

[redacted]

Plausibility and quality checks of the ergospirometry data will be done by a reading center. If ergospirometry data acquisition fails for any reason, it may be repeated one day later.

[redacted]

Blood draw for final laboratory assessments has to be done.

Unscheduled visits

In addition to the protocol-required visits, patients may be seen at any time throughout the study at the discretion of the investigator to follow any new lab abnormalities or AEs. All randomized patients, including any patient who has experienced a health event, should continue to receive double-blind treatment until the trial is completed. Unscheduled visits may also be performed throughout the study at the discretion of the investigator for up-titration of the study medication.

3.2 Rationale of study design

There is a general agreement that apart from reducing the major fatal and non-fatal consequences of HF with a reduced LVEF, i.e., CV death and hospitalization for worsening HF, improving exercise capacity, daily physical activity and quality of life is crucial in patients with CHF. Thus, measurement of VO_{2peak} (adjusted to body weight) as assessed by cardiopulmonary exercise testing (CPET) in patients with chronic heart failure will be the primary endpoint of this study. This endpoint is established for assessing activity levels of patients. Moreover, the study design is reasonable and adapted from recent studies in treatment of patients with CHF in terms of investigational treatment, duration of assessment period and the comparator is established as standard of care in those patients. The study design is also in line with all required safety assessments and follow-ups for patients with CHF and for the treatment with LCZ696 and in compliance with the effective risk management plan for the product. Thus, events of angioedema, liver events, statin related events, and events of cognitive impairment are followed up by targeted questionnaires. Pregnancies during the study are also followed to capture outcome. Please refer to Section 6.5 (safety assessments) for further details. Known risks of hypotension, renal impairment, and hyperkalemia are closely monitored to prevent severe events and are subject to separate guidance should such events occur. Please refer to Sections 6.5.2 and 6.5.4 for assessments of blood pressure and laboratory assessments, respectively; and to Sections 14, 15, and 16 for guidance to manage these risks.

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

A strong rationale from the PARADIGM data (McMurray et al. 2014) exists for the selection of LCZ696 200 mg bid as the target dose. Importantly, a dose of LCZ696 200 mg bid delivers similar exposures of valsartan (assessed by AUC) as Diovan® 160 mg bid, the maximal 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. The biomarker data are also consistent with results obtained in a dose ranging study in hypertension, which demonstrated additive effects of the ARB moiety and the NEPi moiety with LCZ696 400 mg and 200 mg once daily, with a minimal incremental BP reduction from LCZ696 200 mg/d to LCZ696 400 mg/d. LCZ696 400 mg/d and 200 mg/d were well tolerated in this study.

LCZ696 will be dosed at 200 mg twice daily to ensure sustained NEP inhibition over 24 hours, which is thought to be critical for patients with HF. Furthermore, twice daily dosing will also mitigate the likelihood of hypotension, particularly in those with more severe HF impairment (NYHA class III as chosen in this study).

The dose regimen is also in accordance with the label of LCZ696.

With the purpose of this study to demonstrate the superiority of LCZ696 compared to enalapril in improving exercise capacity, daily physical activity and quality of life, in patients with CHF (NYHA class III) and LVEF $\leq$ 40 %, we assume an measurable effect of VO_{2peak} (adjusted to body weight) after 3 months of treatment.

3.4 Rationale for choice of comparator

Major clinical trials have established ACEI treatment as the standard of care for RAAS blockade and to date, treatment guidelines recommend ACEI as the treatment of choice for all patients with CHF and reduced LVEF, unless ACEI-intolerant. Since LCZ696 is tested in this study according to its label in treatment of patients with CHF, a standard-of-care comparator is thought to be most appropriate. As a well-studied ACEI in HF, enalapril is used as the comparator in this study. Enalapril was studied in a number of previous large, outcome-driven studies, such as OVERTURE (Packer et al. 2002), CONSENSUS (CONSENSUS Trial Study Group 1987), SOLVD-Treatment (SOLVD Investigators 1991), and SOLVD-Prevention (SOLVD Investigators 1992).

An enalapril dose of 10 mg bid has been selected as the comparator target dose for this study based on its ability to reduce the risk of death or hospitalization as demonstrated in the SOLVD-Treatment study (SOLVD Investigators 1991).

The comparator is standard of care in HF indication with established efficacy and safety profile. Dose for comparator is according to label and established treatment practice.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

Both treatments LCZ696 and Enalapril are approved in the indication investigated within this study. Please refer to the corresponding Summary of Product Characteristics (SmPC) of the corresponding products as well as the Investigator's Brochure (IB) for LCZ696 for known adverse reactions, or special precautions on both IMPs (provided to all participating sites).

Patients will be instructed to discontinue any RAAS blockade medications (ACEI or ARB) with a 36 hours washout for ACEI before study start treatment with study drug to avoid excess RAAS

blockade. The risk of discontinuation of concomitant ACEIs or ARBs will be minimal as it will be reflective of the typical dosing schedule of most ACEIs and ARBs.

All patients will be allowed to continue receiving their other background CV medications.

The risk to patients in this trial will be minimized by compliance with the eligibility criteria and close clinical monitoring.

In women of child-bearing potential, a possible risk of developmental toxicity cannot be excluded. Women of child-bearing potential should therefore use a highly effective method of contraception during dosing and for 7 days off study medication as described under Section 4.2 on page 35.

If there is any question that the patient will not reliably comply, they should not be entered in the study. Participating patients will benefit from careful monitoring and follow-up during the entire study duration.

4 Population

This is an outpatients multi-center clinical study to be conducted in Germany. It is expected that 400 patients will be screened in order to randomize 200 patients in about 40 centers in Germany. The study population will consist of a representative group of patients with NYHA class III and LVEF ≤ 40%. Eligible patients should be on a stable dose of an ACEI or an ARB for at least 4 weeks before entering into the study. The required minimum doses of pre-study ACEIs and ARBs are listed in Table 3-1.

Patients from up to approximately 40 research sites in Germany will be randomized in a 1:1 ratio to either LCZ696 200 mg bid or enalapril 10 mg bid.

The investigator must ensure that all patients who meet the inclusion criteria and do not fulfill any of the exclusion criteria are offered enrollment in the study. No additional parameter can be applied by the investigator.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill **all** of the following criteria:

1. Patients must give written informed consent before any assessment is performed and must be willing and capable to comply with all study procedures.
2. Outpatients ≥ 18 years of age, male or female.
3. Patients with a diagnosis of CHF NYHA class III and reduced ejection fraction:
    - LVEF ≤ 40% at Visit 1 (any local measurement, made within the past 6 months using echocardiography, MUGA, CT scanning, MRI or ventricular angiography is acceptable, provided no subsequent measurement above 40%)
4. Reduced ability to exercise, evidenced by $VO_{2peak} \leq 18$ ml/min per kg
5. Patients must be on an ACEI or an ARB at a stable dose of at least enalapril 10 mg/d or equivalent for at least 4 weeks before Visit 1, which have to be discontinued before randomization.

- For this protocol doses of other ACEIs considered to be equivalent to enalapril 10 mg/d include benazepril 20 mg/d, captopril 100 mg/d, cilazapril 2.5 mg/d, fosinopril 20 mg/d, lisinopril 10 mg/d, moexipril 7.5 mg/d, perindopril 4 mg/d, quinapril 20 mg/d, ramipril 5 mg/d, trandolapril 2 mg/d, and zofenopril 30 mg/d.
- For this protocol doses of ARBs considered to be equivalent to enalapril 10 mg/d include candesartan 16 mg/d, eprosartan 400 mg/d, irbesartan 150 mg/d, losartan 50 mg/d, olmesartan 10 mg/d, telmisartan 40 mg/d, and valsartan 160 mg/d.

6. Patients must be treated for CHF according to local guideline recommendations and should be stable on treatment and dose for at least 4 weeks prior to Visit 1. Treatment according to guideline should include:
   - A β-blocker, unless contraindicated or not tolerated, (reason should be documented for patients not on CHF target doses per local guidelines, or in absence of that medication).
   - An aldosterone antagonist should also be considered in all patients, taking account of renal function, serum potassium and tolerability. If given, the dose of aldosterone antagonist should be optimized according to guideline recommendations and patient tolerability.
   - Ivabradine should also be considered in all patients with heart rates above 70 beats per minute. If given, the dose of ivabradine should be optimized according to guideline recommendations and patient tolerability.
   - Other evidence-based therapy for heart failure should also be considered e.g. cardiac resynchronization therapy and an implantable cardioverter-defibrillator in selected patients, as recommended by guidelines.

4.2 Exclusion criteria

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study:

1. Use of other investigational drugs at the time of enrolment, or within 30 days or 5 half-lives of enrolment, 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 the study drugs
3. Previous history of intolerance to recommended target doses of ACEIs or ARBs
4. Known history of angioedema
5. Requirement of treatment with a dual RAAS blockade, e.g. a treatment with both ACEIs and ARBs or concomitant treatment with aliskiren
6. Current acute decompensated HF (exacerbation of chronic HF manifested by signs and symptoms that may require intravenous therapy)
7. Symptomatic hypotension and/or a SBP < 100 mmHg at Visit 1 (screening) or at Visit 3 (randomization)

8. Estimated GFR < 30 mL/min/1.73m^2 as measured by the simplified MDRD formula at Visit 1 (screening), or Visit 3 (randomization)
9. Serum potassium > 5.2 mmol/L at Visit 1 (screening) or Visit 3 (randomization)
10. Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid or other major CV surgery, percutaneous coronary intervention (PCI) or carotid angioplasty within the 3 months prior to Visit 1
11. Coronary or carotid artery disease likely to require surgical or percutaneous intervention within the 6 months after Visit 1.
12. Implantation of a cardiac resynchronization therapy pacemaker (CRT-P) or a cardiac resynchronization therapy defibrillator (CRT-D) or upgrading of an existing conventional pacemaker or an implantable cardioverter defibrillator (ICD) to CRT device within 3 months prior Visit 1 or intent to implant such a device. Also, patients who had implantation of a conventional pacemaker or an ICD or had a revision of a pacemaker or other device leads within 1 month before Visit 1 are excluded.
13. Heart transplant or ventricular assistance device (VAD) or intent to transplant within the 14 week study duration (on transplant list with high urgency (HU) status) or to implant a VAD.
14. History or current diagnosis of severe pulmonary disease, including chronic obstructive pulmonary disease (COPD).
15. Diagnosis of peripartum or chemotherapy induced cardiomyopathy within the 12 months prior to Visit 1
16. Documented untreated ventricular arrhythmia with syncopal episodes within the 3 months prior to Visit 1
17. Symptomatic bradycardia or second or third degree heart block without a pacemaker
18. Presence of hemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation secondary to left ventricular dilatation
19. Presence of other hemodynamically significant obstructive lesions of left ventricular outflow tract, including aortic and sub-aortic stenosis
20. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs, including but not limited to any of the following:
    - History of active inflammatory bowel disease during the 12 months before Visit 1.
    - Current duodenal or gastric ulcers during the 3 months prior to Visit 1
21. Evidence of hepatic disease as determined by any one of the following: AST or ALT values exceeding 2 x ULN at Visit 1, severe hepatic insufficiency (classification Child-Pugh C), biliary cirrhosis, cholestasis (current or anamnestic evidence), history of hepatic encephalopathy, history of esophageal varices, or history of portocaval shunt
22. Active treatment with cholestyramine or colestipol resins

23. Presence of any other disease with a life expectancy of < 5 years
24. 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 (> 5 mIU/mL)
25. 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 further 7 days. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - 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 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 hormonal contraception (oral, injected, implanted or IUS) women should have been stabile on the same treatment for a minimum of 3 months before taking study treatment.
    - Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
26. Presence of bilateral renal artery stenosis.
27. Patients with thyroidal dysfunction which have not been on a stable dosing of L-thyroxin within the last 3 months
28. Patients with Basedow disease
29. Patients with severe adipositas (Adipositas permagna – BMI ≥ 40)

30. Based on the judgement of the investigator unable to undergo a CPET
31. Long QT syndrome.
32. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Double blind treatment

All eligible patients will be randomized to receive either LCZ696 or enalapril 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 investigational treatment. The use of an ACEI or an ARB in addition to investigational treatment after randomization is strictly prohibited.

The following study drugs will be provided:

- LCZ696 50 mg film-coated tablets (LCZ696 dose level 1)
- Placebo to match LCZ696 50 mg film-coated tablets (placebo matching LCZ696 dose level 1)
- LCZ696 100 mg film-coated tablets (LCZ696 dose level 2; dose level 2a)
- Placebo to match LCZ696 100 mg film-coated tablets (placebo matching LCZ696 dose level 2; dose level 2a)
- LCZ696 200 mg film-coated tablets (LCZ696 dose level 3)
- Placebo to match LCZ696 200 mg film-coated tablets (placebo matching LCZ696 dose level 3)
- Enalapril 2.5 mg film-coated tablets (enalapril dose level 1)
- Placebo to match enalapril 2.5 mg tablets (placebo matching enalapril dose level 1)
- Enalapril 5 mg film-coated tablets (enalapril dose level 2)
- Placebo to match enalapril 5 mg tablets (placebo matching enalapril dose level 2)
- Enalapril 10 mg film-coated tablets (enalapril dose level 3; dose level 2a)
- Placebo to match enalapril 10 mg tablets (placebo matching enalapril dose level 3, dose level 2a)

Target doses: LCZ696 200 mg bid and enalapril 10 mg bid

All tablets (LCZ696 50 mg, LCZ696 100 mg, LCZ696 200 mg, enalapril 2.5 mg, enalapril 5 mg, enalapril 10 mg) have different shapes and colors. Therefore, the study will be designed as a double-blind, double-dummy trial to ensure the blinding during the entire course of the study.

To maintain the blinding, patients will be required to take their assigned active treatment tablet along with placebo matching the opposite treatment twice daily (morning and evening dose) in addition to their conventional concomitant therapy.

LCZ696 and its matching placebo will be provided in HDPE bottles. Enalapril 2.5 mg and its matching placebo will be provided in HDPE bottles, while enalapril 5 mg and 10 mg and its matching placebo will be provided in either blister packs or HDPE bottles.

5.1.2 Additional study treatment

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

5.2 Treatment arms

Patients who are eligible for randomization at Visit 3 will be assigned to one of the following two treatment arms in a 1:1 ratio bid:

- LCZ696 bid and placebo to match enalapril bid
- Enalapril bid and placebo to match LCZ696 bid

5.3 Treatment assignment, randomization

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff.

A randomization list will be produced by or under the responsibility of Novartis Randomization Office using a validated system ensuring assignment of treatment arms to randomization numbers in the specified ratio.

At Visit 3, all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

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

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using

the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study and (2) the identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor. Unblinding will only occur in the case of patient emergencies (see Section 5.5.11) and at the conclusion of the study.

A double-dummy design is used because the identity of the investigational treatment cannot be disguised due to their different forms.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number (XXXXYYY). The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a sequential number by the investigator. At each site the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g., the second patient is assigned patient number 2, the third patient is assigned patient number 3).

The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site should select the CRF book with a matching Subject Number from the EDC system to enter data.

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

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with study drug in identically-appearing packaging for each medication (LCZ696 or enalapril).

The investigational treatment packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to a specific material type. Investigator 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 to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

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.

Medication labels will be in German and comply with the legal requirements of Germany. They will include storage conditions for the investigational treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by the field monitor during site visits and at the 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 Novartis monitor or to the Novartis 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

Novartis will supply the investigators with all medications sufficient for the course of the study. Patients will be provided with medication packs containing study drug corresponding to their assigned treatment arm and dose level, sufficient to last until the next scheduled visit. In order to adequately blind the study, patients will be required to take a total of two tablets (one tablet from the LCZ696/LCZ696 matching placebo pack and one tablet from the enalapril/enalapril matching placebo pack) twice a day for the duration of the study. Table 5-1 summarizes the study drug that will be taken during the double-blind period.

Patients will begin treatment with dose level 2 or 2a for 2 weeks. Patients at a stable daily dose of enalapril 10 mg (or equivalent ACE or ARBs according to Table 3-1) 4 weeks prior to Visit1will start treatment at dose level 2. Patients at a stable daily dose of enalapril above 10 mg once daily (or equivalent ACE or ARBs according to Table 3-1) 4 weeks prior to Visit1will start treatment at dose level 2a. Dose level 2a is for initial up-titration only and will not be available for down-titration for safety reasons during the course of the study.

At Visit 4, patients will be up-titrated to dose level 3 unless safety monitoring criteria (Table 3-2) prevent up-titration.

Table 5-1 Study drug dispensed during the double-blind period

Study visit	Dose level	LCZ696	Enalapril
Visit 4 and all subsequent visits	3*	200 mg or matching placebo bid	10 mg or matching placebo bid
Available for Visit 3 and any visit after Visit 3	2§	100 mg or matching placebo bid	5 mg or matching placebo bid
Available for Visit 3	2a$	100 mg or matching placebo bid	10 mg or matching placebo bid
Available for any visit after Visit 3	1&	50 mg or matching placebo bid	2.5 mg or matching placebo bid

* This dose level must 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.

§ Available for Visit 3 and thereafter, if dose level 3 is not tolerated despite modification of other non-disease-modifying HF medications. See also Section 5.5.5

$ Available for up-titration (Visit 3) only. If dose level 3 is not tolerated despite modification of other non-disease-modifying HF medications, down-titration to dose level 2 is to be done.

&. Only if dose levels 3 and 2 are not tolerated despite modification of other non-disease-modifying HF medications.

Patients will be instructed to take their morning study drug doses at approximately 08:00 (8 AM) and their evening study drug doses at approximately 19:00 (7 PM). The study medications 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 if it is almost time for the following scheduled dose. In this case, the patient should skip the missed dose and return back to his/her regular study drug administration schedule.

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

All kits of investigational treatment assigned by the IRT will be recorded/databased in the IRT.

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 treatment as prescribed for any reason.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Every attempt should be made to maintain patients on the target study drug dose level for as long a duration as possible throughout the trial. If, however, in the opinion of the investigator, the patient does not tolerate the target dose of study drug, the investigator should consider whether non-disease-modifying medication (e.g., CCBs, diuretics, nitrates, α-blockers) can be reduced to rectify the situation, before considering to reduce the dose of the study drug to the next lower dose level.

Also, the investigator may adjust doses of disease-modifying medications if it is believed that they are the most likely cause of the adverse effect. If adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern, the investigator may down-titrate the dose of the study drug to the next lower level, up to complete withdrawal of the investigational treatment if necessary. The patient should be re-challenged with the higher dose when the investigator feels it is appropriate to do so per the directions provided below in this section. If needed, the study drug may be stopped completely, but the patient should continue to attend the study visits and be followed until the completion of the study. Ultimately,

the goal is to keep the patient on the highest study drug dose possible for as long as possible and to follow the patient in the study as long as possible.

Study drug dose level adjustments should mainly be based on overall safety and tolerability with special focus on a) hyperkalemia; b) symptomatic hypotension; and c) clinically significant decrease in eGFR/increase in serum creatinine (see Appendix 1, Appendix 2, Appendix 3, and Appendix 4 for treatment guidelines for hyperkalemia, management of BP, and renal dysfunction, respectively).

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

Adjustment of study drug dose level

If despite adjustment of concomitant medications per the guidance provided above the situation is not rectified, the investigator may consider adjusting the study medication according the following instructions.

During the double-blind treatment period down-titration of the study drug at any time will be allowed based on the safety and tolerability criteria defined in Appendix 1, Appendix 2, Appendix 3, and Appendix 4. If down-titration is necessary, the patient should be down-titrated to the next dose level (see Table 5-1; Dose level 2a is for initial up-titration only and will not be available for down-titration for safety reasons.). The patient may continue receiving the lower dose level for a recommended period of 1 to 2 weeks before re-challenging the patient with the next higher dose level. For example, a patient who encounters tolerability problems at the target dose level (dose level 3), should receive the study drug at dose level 2 for 1 to 2 weeks. Then, he/she should be re-challenged with up-titration back to dose level 3.

If the tolerability issues are not alleviated, the investigator may lower the study drug dose further to the next lower level for 1 to 2 weeks, up to temporary 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 2 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 5-1).

In some cases, according to the safety and tolerability criteria and the investigator's judgment, dose level 2 could be maintained if he/she considers that the patient's condition would not allow an 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 2 (or lower), to assure treatment with the higher dose level tolerated by the patient.

Study drug restart after temporary treatment interruption

Study drug should be reintroduced after 1-2 weeks in those who temporarily discontinue as soon as medically justified in the opinion of the investigator.

Once the investigator considers the patient's condition appropriate for receiving the study drug, the investigator should re-start the patient on the study drug at the most appropriate and allowable dose level (Table 5-1) per his/her medical judgment. If tolerated based on the safety

and tolerability criteria in Appendix 1, Appendix 2, Appendix 3, and Appendix 4 the patient should be up-titrated to the next dose level (up to dose level 3) every 1 to 2 weeks, as per the investigator's judgment. Dose level 2a is for initial up-titration only and will not be available for down-titration for safety reasons during the course of the study.

Patients re-started on the study drug will retain their original randomization and study identification numbers. Should the patient not tolerate the re-start study drug dose level, he/she may be down-titrated again (if appropriate) or discontinue the study medication. Up-titration or reintroducing the study drug could be considered by the investigator as soon as medically justified in his/her medical judgment.

Study visits should occur as close as possible to the time points indicated in Table 6-1. The timeframe 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 CRF.

In case of pregnancy discovered during the double-blind treatment period, the patient should be instructed to stop taking the study drug immediately. The patient should be followed until birth according to guidelines for pregnancies and reporting in Section 7.4.

5.5.6 Rescue medication

Guidance on handling hyperkalemia, hypotension, and renal dysfunction are provided to investigators in Appendix 1, Appendix 2, Appendix 3, and Appendix 4 respectively. Patients may receive open-label ACEIs and/or ARBs during the study **ONLY** if the study medication has been discontinued either temporarily or permanently. A 36 hours washout phase of study drug is needed before start of an ACEI.

Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies Record in the CRF.

5.5.7 Concomitant treatment

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

5.5.8 Other 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 and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with the study medication must be listed on the Concomitant Medications/Significant Non-Drug Therapies eCRF.

ACEIs and ARBs

Patients' pre-study ACEIs/ARBs will be replaced by the study medications.

The concomitant use of open-label ACEIs or ARBs is strictly prohibited while the patient is receiving study medication. If the investigator believes that addition of an ACEI or ARB is necessary, then study drug must be discontinued. **Study medication should be stopped 36 hours prior to addition of open-label ACEI**. If not already treated with an aldosterone antagonist, consideration should be given to adding this therapy rather than an ACEI or ARB.

Similarly, if study medication is to be restarted, the open-label ACEI should be discontinued 36 hours prior to resuming study medication.

Heart failure medications and other cardiovascular medications

The patient should be on an optimal medical regimen of background HF medications which have to be stable 4 weeks prior to screening at Visit 1 and during the screening period until randomization at Visit 3. Background HF medication must include an individually optimized dose of a β-blocker (i.e., maximally tolerated dose) at a stable dose for at least 4 weeks prior to study entry, unless contraindicated or not tolerated. This also includes the use of ivabradine according to guideline recommendations. Use of an aldosterone antagonist 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 **with caution**.

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

Every effort should be made to keep the dose level of these background disease-modifying HF medications stable throughout the entire study including screening period. However, if the patient's condition warrants a change in any of these medications (for example, if the investigator believes a disease-modifying medication is causing an adverse event), it is allowed at the discretion of the study investigator.

If a patient experiences any AEs that may be contributed to the study drug, other HF medication, or other CV medications, the investigator should adjust non-disease-modifying medications (e.g., CCBs, nitrates, α-blockers, and diuretics) first in an attempt to alleviate the AEs.

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.

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

Phosphodiesterase-5 (PDE-5) inhibitors

PDE-5 inhibitors should be used with caution while the patient is receiving study medication due to the increased possibility of occurrence of hypotension.

Neseritide and intravenous nitrates

Nesiritide and intravenous nitrates should only be used as the last choice as vasodilators are known to modulate VO_{2max}. The concomitant administration of LCZ696 with neseritide and intravenous (i.v.) nitrates has not been studied. In the event a study patient requires the concomitant administration of neseritide and/or i.v. nitrates with the study medications, the investigator should consider starting them at a lower dose or a slower infusion rate while monitoring the patient's blood pressure carefully.

Statins

Caution should be exercised upon co-administration of LCZ696 and statins such as atorvastatin, simvastatin, pravastatin, and/or pitavastatin. The co-administration of LCZ696 increased the Cmax (maximum plasma concentration) of atorvastatin and its metabolites by 68% -108%, although the AUC was not significantly changed (<34%).

L-thyroxin

The patient should be on an optimal medical regimen of L-thyroxin medication in case of thyroidal dysfunction. This must include an individually optimized dose at a stable dose for at least 3 months prior to study entry. All changes administered after the patient starts treatment with the study medication must be listed on the Concomitant Medications/Significant Non-Drug Therapies eCRF.

Other medications

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

5.5.9 Prohibited Treatment

Use of the treatments displayed in Table 5-2 is NOT allowed after the start of investigational treatment. Treatment with an investigational drug other than study treatment is also prohibited.

Table 5-2 Prohibited treatment

Medication	Action to be taken
Any ACEI	Discontinue study drug. The open label ACEI must be stopped for ≥36 hours prior to re-initiation of study drug
Any ARB	Discontinue study drug. The open label ARB must be stopped prior to re-initiation of study drug and stop ARB
Renin inhibitors (confounding safety: increased likelihood of occurrence of hyperkalemia)	Discontinue study drug. The open label renin inhibitor must be stopped prior to re-initiation of study drug
bile acid sequestering agents (cholestyramine, colestipol; potential interference with study drug absorption)	none

5.5.10 Discontinuation of study treatment and premature patient withdrawal

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

- Withdrawal of informed consent
- Pregnancy (see Section 7.4 Pregnancy reporting)
- Investigator thinks that continuation would be detrimental to the patient's well-being
- Suspected occurrence of angioedema. A patient with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator and constitute a reason for temporary or permanent discontinuation of study treatment.
- Use of prohibited treatment as per Table 5-2. In case of initiation of open-label ACEI during the double blind treatment period, study medication must be stopped for ≥36 hours prior to initiation of open-label ACEI. The open label ACEI must be stopped for ≥36 hours prior to re-initiation of study drug.

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

- Any severe suspected drug related AE
- Depending on the serum potassium, blood pressure, or eGFR, patients may need to have their study drug dose or the dose of another concomitant medication reduced or discontinued, or, if appropriate, have potentially contributing agents adjusted. Please refer to Appendix 2, Appendix 3, and Appendix 4 for treatment guidelines for hyperkalemia, hypotension, or renal dysfunction, respectively.
- Any other protocol deviation that results in a significant risk to the patient's safety

In the case of study drug discontinuation, the patient should continue to complete all scheduled study visits and procedures. If the patient refuses, he/she should be contacted by telephone in place of protocol-specified visits unless the patient expressly refuses such contacts.

The investigator must also record it on the drug administration form of the eCRF.

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information.

The investigator should discontinue study treatment for a given patient and/or withdraw the patient from study if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Patients who discontinue study drug before completing the study or who prematurely withdraw from the study for any reason, should be scheduled for a visit as soon as possible at which time all (safety) assessments listed for the final end of study visit (EOS) will be performed.

The investigator must also contact the IRT to register the patient's discontinuation from investigational treatment. For patients who are lost to follow-up (i.e. those 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 documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

Patients who are prematurely withdrawn from the study **will not be replaced** by an equal number of newly enrolled patients.

5.5.11 Emergency breaking of treatment assignment

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, investigational treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient. The system will automatically inform the Novartis monitor for the site and the Clinical Trial Head (CTH) that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, investigational treatment name if available, patient number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case an emergency treatment code break is required at a time when the investigator and backup are unavailable.

5.5.12 Study completion and post-study treatment

The study will be considered completed when the patient completes the EOS visit (Visit 7). Patients will be asked to return the remaining study drug. The study as a whole will be considered completed when the last visit of last subject occurred.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.5.13 Early study termination

The study can be terminated at any time for any reason specified in the clinical trial study contract, by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated for a prematurely withdrawn patient. The sponsor will be responsible for informing IRBs and/or ECs of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" which assessments are performed at each visit.

Patients should be seen for all visits on the designated day with an allowed "visit window" of "+/-3" days.

Patients who discontinue study drug before completing the study or who prematurely withdraw from the study for any reason, should be scheduled for a visit as soon as possible at which time all (safety) assessments, listed for the final EOS visit will be performed.

These patients should return for the assessments indicated by three asterisks (***) in Table 6-1. If they refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone. Documentation of attempts to contact the patient should be recorded in the patient's record.

At a minimum, patients will be contacted for safety evaluations during the 30 days following the last study visit or following the last administration of study treatment if there are post-treatment follow-up visits (whichever is later), including a final contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the source documentation.

All data obtained from the assessments listed in Table 6-1 and described in detail in the subsections below must be supported in the patient's source documentation (e.g., medical charts or patient notes). Table 6-1 indicates which data remain in source documents only (S), or may be entered directly into the database (D; i.e., these data are considered source documentation and do not require separate source documentation), or are entered into the database from separate source documents (DS). Assessments that generate data for database entry and are recorded on eCRFs are listed using the eCRF name.

If one visit is postponed or brought forward, it should not result in the next visit being postponed or brought forward (except Visit 2 must be repeated for ergospirometry). The next visit, if at all possible and with the latter mentioned exceptions, should adhere to the original time schedule.

Patients will also be instructed to take study drug, as usual, on the morning of their site visits, with or without food. If a patient did not take his/her study drug on the morning of his/her scheduled visit, the study visit could nevertheless be conducted.

Table 6-1 Assessment schedule

Phase		Screening		Double blind treatment**				
Visit	**D/S***	**1**	**2****	**3****	**4****	**5****	**6****	**7/EOS*****
Days(D)/ Weeks (W)		**D-16 to -12 W-2**	**D-9**	**D1**	**D14 W2**	**D28 W4**	**D42 W6**	**D84 W12**
Screening log	DS	x						
Informed consent form	DS	x						
Inclusion/Exclusion criteria	DS	x	x	x				
Demography	DS	x						
Medical history (including alcohol and smoking history)	DS	x						
Heart Failure History	DS	x						
Cardiovascular disease History	DS	x						
NYHA Classification (HF signs and symptoms)	DS	x	x	x	x	x	x	x***
Heart Failure and CV Medications	DS	x	x	x	x	x	x	x***
Concomitant Medications	DS	x	x	x	x	x	x	x***
Randomization	DS			x				
Physical Exam[1]	S	x	x	x	x	x	x	x***
Height (H) / Weight (W)	DS	H / W	W	W	W	W	W	W***
Vital signs	DS	x	x	x	x	x	x	x***
Waist/hip circumference	DS		x					x***
Echocardiography[2]	DS	x						
Serum Pregnancy tests[3]	DS	x						x***
Urine Pregnancy tests[3]	DS		x					x***
AEs / SAEs	DS	x	x	x	x	x	x	x***
Complete laboratory assessments	DS	x	x					x***
Abbreviated chemistry panel[4]	DS			x[9]	x[9]	x	x	

Phase		Screening		Double blind treatment**				
Visit	**D/S***	**1**	**2****	**3****	**4****	**5****	**6****	**7/EOS*****
Days(D)/ Weeks (W)		**D-16 to -12 W-2**	**D-9**	**D1**	**D14 W2**	**D28 W4**	**D42 W6**	**D84 W12**
12-lead ECG evaluation	S	x[5]						
Ergospirometry	DS		x				x	x
Borg Scale documentation	DS		x				x	x
[redacted]								
Double blind medication dispense	DS			x	x	x	x	
Contact IRT	S	x		x	x	x	x	x
Drug accountability	S			x	x	x	x	x
Treatment completion form	DS							x****
Study completion form	DS							x***

* DS: assessment to be documented in the clinical database, S: assessment to be recorded in the source data
** Visits marked with ** can be followed by unscheduled visits that may be performed at the investigator's discretion due to chemistry panel evaluation or up-titration.
*** Patients who prematurely discontinue study treatment should also return for the end of study (EOS) to collect at least safety assessments indicated by three asterisks (***).
**** To be documented at Visit 7 or at the time of premature discontinuation
1 Complete physical examination required at Visits 1, 2 and 7 (end-of-study visit). Short physical exam is sufficient at Visit 3 -6.
2 Qualifying LVEF measurements/documentation of structural heart disease will be based on obtained measurements (e.g. echocardiograms (echo)) performed ≤ 6 months prior to Visit 1. If an assessment performed ≤6 months prior to Visit 1 is not available, an echo must be performed during the screening epoch.
3 Women of childbearing potential only. At Visit 1 and 7 and in case of a positive urine pregnancy result, a confirmatory serum pregnancy test has to be performed at the central laboratory. A urine pregnancy test will be performed locally at Visit 2 and 7 and every time this is clinically indicated or a contraception gap has been reported.
4 Abbreviated chemistry panel including potassium, BUN, and serum creatinine will be measured at interim visits at the central laboratory.
5 Screening ECG performed within the 6 months before Visit 1 is accepted.
[redacted]

Phase		Screening		Double blind treatment**				
Visit	**D/S***	**1**	**2****	**3****	**4****	**5****	**6****	**7/EOS*****
Days(D)/ Weeks (W)		**D-16 to -12 W-2**	**D-9**	**D1**	**D14 W2**	**D28 W4**	**D42 W6**	**D84 W12**

[redacted]

9 At Visit 3 and 4, patients should come to the site 3 to 4 days prior to the scheduled visit date for blood draw only so that results from central laboratory are available and enable a competent decision on randomization or up-titration at the respective visits.

6.1 Information to be collected on screening failures

Patients may discontinue from the study prior to randomization from Visit 3, prior to any double-blind medication being administered.

Patients discontinuing at Visit 1, Visit 2 or Visit 3 (were never randomized and never received active study drug) are considered screening failures

All patients who have signed informed consent but not entered into the next epoch will have the study completion page for the screening epoch, demographics, inclusion/exclusion, and SAE data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

Re-screening

If a patient is not eligible to enter the double blind treatment period (Visit 3) and screen-fails, 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.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: year of birth, age, sex, race, and source of patient referral. Relevant medical history/current medical condition data includes data until the start of study drug. Where possible, diagnoses and not symptoms will be recorded. HF medications and other CV medications will be recorded in eCRFs separately from other medications. Likewise, detailed HF history and other relevant CV medical history will be recorded on eCRFs separately from other medical history.

6.3 Treatment exposure and compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the care giver. This information should be captured in the source document at each visit. Patient compliance should be at least 80% during the double-blind treatment period. The investigator and/or study personnel will counsel the patient if compliance is below 80%. Study drug accountability will also be determined by the site monitor while performing routine site visits and at the completion of the study.

Duration of double-blind study drug exposure will be calculated based upon the start and stop dates recorded in the eCRF.

6.4 Efficacy

6.4.1 Peak respiratory oxygen uptake (VO_{2peak})

Cardio-pulmonary-exercise testing (CPET) is an examination of the cardio-pulmonary system using the measurement of respiratory gases during exercise stress. The result provides an overview of cardiopulmonary function, including the measurement of peak oxygen uptake ($VO_{2\,peak}$).

CPET to assess VO_{2peak} will be performed at a cycle ergometer during screening (Visit 2) and after 6 weeks and 3 months (Visit 6 and Visit 7). It will be evaluated by the modified Naughton protocol as recommended for treadmill exercise in patients with CHF. The workload will start at 10W and will be increased by 10W for each 1-minute stage. Patients will be under continuous ECG and frequent blood pressure monitoring. During ergospirometry, a physician should be available in case of an emergency situation where immediate medical intervention is necessary.

[redacted]

The details of the procedure will be outlined in a manual provided to all participating sites.

The primary endpoint is change of VO_{2peak} compared to baseline measurements (adjusted to body weight) after 3 months of treatment.

Further efficacy parameters assessed during CPET are

- Change in VO_{2peak} (adjusted to body weight) after 6 weeks of treatment
- Change in VO_{2peak} (unadjusted) after 6 weeks and 3 months
- Change of VE/VCO_2 slope after 6 weeks and 3 months
- [redacted]
- Change in exercise capacity (Watt) at VAT after 6 weeks and 3 month
- Change in rate of perceived exertion during exercise (Borg Scale) after 6 weeks and 3 months

[redacted]

[redacted]

[redacted]

[redacted]

6.4.4 Appropriateness of efficacy assessments

VO_{2max} is the peak oxygen uptake achieved during the performance of dynamic exercise involving a large part of total muscle mass. It is considered the best measure of cardiovascular fitness and exercise capacity (Fletcher et al. 2013). Patients with CHF usually cannot achieve this plateau due to limiting factors caused by the presence of heart disease, LV dysfunction, myocardial ischemia, and associated symptomatology. Thus, it is common to refer to assessed VO_{2max} as the VO_{2peak} attained during volitional incremental exercise. Method and protocol for the assessment of VO_{2peak} is defined as recommended in current guidelines (Fletcher et al. 2013).

[redacted]

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.

6.5.1 Physical examination

A complete physical examination will be performed at visit 1, 2 and 7. 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.

A short physical exam will include the examination of general appearance and vital signs (BP and pulse). A short physical exam will be at all visits starting from Visit 3 to 6 and at all unscheduled visits, except where a complete physical exam is required (see above).

Information about the all physical examinations must be present in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's eCRF. Significant findings made after the start of study drug which meet the definition of an AE must be recorded on the AE screen of the patient's eCRF.

6.5.2 Vital signs

Vital signs will be assessed at every visit. This will include BP and pulse measurements. BP 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. During ergospirometry patients will be under frequent blood pressure monitoring.

Guidelines for the management of BP are provided in Section 15 Appendix 3.

6.5.3 Height and weight and waist hip circumference

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 at all visits, until the EOS visit.

Waist/hip circumference (to the nearest centimeter [cm] in indoor clothing) will be measured at Visit 2 and at the EOS visit.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all collected specimens. Details on the collections, shipment of samples and reporting of results by the central laboratory will be provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

Full laboratory evaluations (hematology, blood chemistry, and urine for pregnancy assessment in child-bearing women; Table 6-2) for the assessment of safety in this study will be performed at Visits 1, 2 and 7. Electrolyte laboratory evaluations will be included in the abbreviated laboratory assessments at Visits 4 to 6.

The investigator or his/her designee should review the central laboratory results as soon as they become available to decide on whether any adjustments in the patient's study drug or non-study

drug regimen are needed. Therefore unscheduled visit are possible based on investigator's discretion.

All central laboratory results will be communicated to the investigators and the sponsor. Details on the collection, shipment of samples and reporting of results by the central laboratory will be provided to investigators in the laboratory manual.

Laboratory values that exceed the boundaries of a notable laboratory abnormality must be commented on by the investigator in the Comments screen of the patient's eCRF 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, then the diagnosis or medical condition must be entered on the AEs screen of the patient's eCRF. If the laboratory abnormality is the primary reason for an unforeseen hospitalization or otherwise fulfills the seriousness category of an AE, then the procedure for rapid notification of SAEs must be followed. Likewise, if the laboratory abnormality leads to discontinuation from the study drug (temporarily or permanently), the patient must be followed until the abnormality resolves or until it is judged to be permanent.

Table 6-2 Routine laboratory examination

Hematology*	Biochemistry*	Urine measurements
Red Blood Cells count	Glucose	Urine pregnancy test at Visit 2 and 7 and when clinically indicated or a contraception gap has been reported
White Blood Cells count	Sodium	
Platelet Count	Potassium **	
Hemoglobin	Chloride	
Hematocrit	Calcium	
WBC differential	Blood urea nitrogen (BUN) **	
	Creatine kinase (CK)	
	Creatinine **	
	Total Bilirubin	
	Aspartate amino-transferase (AST)	
	Alanine amino-transferase (ALT)	
	Alkaline phosphatase	
	Total protein	
	Albumin	
	Uric Acid	
	Serum Pregnancy Test[a]	
	Lipid profile (total cholesterol, LDL, HDL, and triglycerides)	
	Hemoglobin A1C	
	Thyroid-stimulating hormone (TSH)[b]	

* List of laboratory assessments performed at Visits 1, 2 and 7(EOS)

** Laboratory assessments for the abbreviated biochemistry test performed at visits where the complete laboratory test is not performed.

a. Serum pregnancy test is performed at Visit 1, 7, and in case of positive urine pregnancy test only.

b. TSH is assessed at Visit 1 only.

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured at Visits 1, 2, and 7 (Table 6-2).

6.5.4.2 Clinical chemistry

Blood urea nitrogen (BUN), glucose, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), alkaline phosphatase, sodium, potassium, chloride, calcium, hemoglobin A1C, total protein, albumin, uric acid, and lipid profile will be measured at Visits 1, 2, and 7.

BUN, serum potassium, and serum creatinine value for eGFR calculation will be obtained from patients at every visit when a complete laboratory test is not done (i.e., Visits 3-5).

The latter is true for all unscheduled visits done with up-titration intention.

6.5.4.3 Urinalysis

Urine pregnancy measurement is performed as dipstick measurement at Visit 2, and 7.

6.5.5 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed at screening (Visit 1, unless an ECG performed within the last 6 months is available) to assess the eligibility of patients regarding inclusion and exclusion criteria. Interpretation of the tracing must be made by a qualified physician. Each ECG tracing should be labeled with the study number, patient number, and date and kept in the source documents at the study site. Clinically significant abnormalities according to the judgment of the investigator should also be recorded on the relevant medical history/current medical conditions or AE eCRF page.

During ergospirometry, patients will be under continuous ECG evaluation.

6.5.6 Pregnancy and assessments of fertility

All female patients of childbearing potential will have a serum pregnancy test performed at Visit 1 and Visit 7. Additionally, at Visit 2 and 7 a urine pregnancy test will be performed, and whenever this is clinically indicated or a contraception gap has been reported.

If during the study, the patient provides information which suggests that contraception might be impaired (e.g. due to of diarrhea and/or vomiting), the investigator should perform an additional urine pregnancy test to assure that the patient is not pregnant.

In case of a positive urine pregnancy result, a confirmatory serum pregnancy test has to be performed at the central laboratory, and the study drug should be temporarily withdrawn until the result confirms no pregnancy.

See Section 5.5.5 and 7.4 for details on pregnancies.

6.5.7 Angioedema

Angioedema is a type of abrupt swelling that occurs under the skin and/or mucous membranes and is often localized to the head, neck, throat, and/or tongue, but may occur elsewhere, including the genitalia and intestines. Severe cases may be associated with airway compromise. Although, the mechanism is not fully understood, bradykinin has been implicated as the putative mediator. Therefore, medications that raise the levels of endogenous bradykinin by inhibiting the enzymes responsible for its breakdown, such as ACE, aminopeptidase P, and NEP, may result in this potentially dangerous side effect.

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

The investigator may be also be contacted by Novartis regarding AEs that may resemble an angioedema-like event. A list of terms that are considered “angioedema-like” (e.g., periorbital swelling) will be provided to sites in a manual. The investigator or his/her delegated staff must

complete the required forms and provide the required medical records for all such events, regardless of whether the investigator views the event in question as angioedema or not.

All angioedema reports will be forwarded to an Angioedema Adjudication Committee by Novartis for assessment. Information regarding this committee is outlined in Section 8.5. Details on the procedures for reporting angioedema events will be provided to investigators in a manual.

6.5.8 Cognitive impairment

Angiotensin receptor blockade has been suggested to improve cognitive function, as might overall improvement in cardiac and vascular function. Thus, improvements in cardiac function and cerebral blood flow by LCZ696 are hypothesized to potentially improve vascular effects and, thereby, cognition. However, neprilysin is one of multiple enzymes involved in the breakdown of amyloid β, a peptide linked to cognitive impairment. Thus, cognitive function resulting from combined angiotensin receptor blockade and neprilysin inhibition with LCZ696 is subject to standardized follow-up.

It is important that the investigator pays attention to any events of cognitive impairment or related events that may be reported by patients. If such an event occurs that meets criteria for serious adverse event, the investigator will complete a separate questionnaire for a Dementia-related Event form (provided by Novartis) to summarize the event, its further diagnostic tests performed, and its related information. A list of terms that are considered "dementia-like" (e.g., presenile dementia, memory impairment) will be provided to sites in a manual.

6.5.9 Statin-related Events

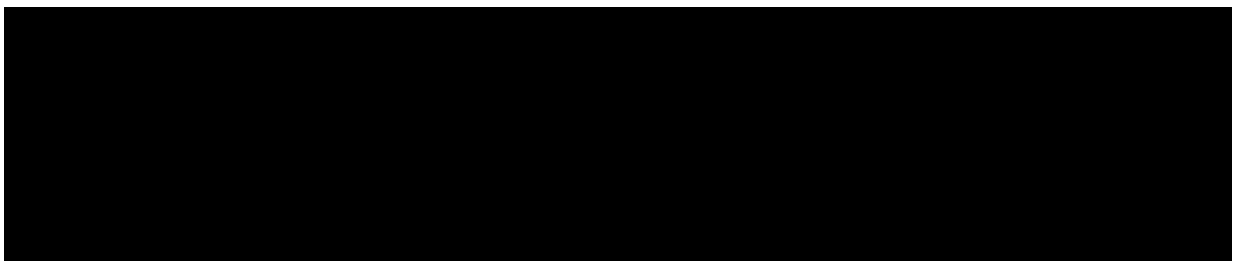
Statin-related events are subject to additional safety assessments and thus are followed with a standardized questionnaire. A list of terms that are considered "statin-related" (e.g., rhabdomyolysis, acute pancreatitis, myalgia and muscle spasm) will be provided to sites in a manual.

If such an event occurs that meets criteria for serious adverse event, the investigator will complete a separate questionnaire for a Hepatotoxicity and Statin-related Event form (provided by Novartis) to summarize the event, its further diagnostic tests performed, and its related information.

6.5.10 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

6.6 Other assessments



[redacted]

6.6.2 Blood pressure home measurements

Additionally to the assessment of vital signs at each visit, blood pressure will be self-monitored by the patient via home-measurement.

Therefore, at Visit 3, the use of a home blood pressure monitor should be explained. A home blood pressure monitor will be provided with all appropriate supplies. Blood pressure should be measured

- once daily until Visit 5
- each time the patient experiences symptoms which may be suggestive of hypotension, as well as other time points which may be recommended by the investigator

The review of the Standard Patient Diary should be done at every visit after Visit 3. Any time the patient experiences symptoms which he/she suspects are related to hypotension, the patient should be instructed to take a blood pressure measurement. Patients should record the event in the Standard Patient Diary, including:

- the blood pressure value. Any symptomatic blood pressure < 100 mmHg should be recorded in the Standard Patient Diary and the patient should be instructed to contact the study investigator directly
- any relevant associated information.

- time of occurrence in relation to the last medication.

Additionally, if a patient performs routine measurements of blood pressure, any asymptomatic blood pressure ≤ 95 mmHg should be recorded in the Standard Patient Diary and the patient should be instructed to contact the study investigator directly.

The patient should return the study diary at each next scheduled visit.

The home blood pressure monitor and Standard Patient Diary should be given to the patient at Visit 3.

6.6.3 Pharmacokinetics

Not applicable

6.6.4 Pharmacogenetics/pharmacogenomics

Not applicable.

6.6.5 Other biomarkers

Not applicable.

7 Safety monitoring

7.1 Adverse events

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

The 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 test, 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 patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient 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 study 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 a serious adverse event (SAE)
- action taken regarding study 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)

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for :
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - 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 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.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

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.

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 study treatment, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) 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 Novartis.

7.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 days period should only be reported to Novartis 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.

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 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. Novartis 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.

Hepatotoxicity-related events are subject to additional safety assessments and thus are followed with a standardized questionnaire. A list of terms that are considered "hepatotoxicity-related" (e.g., cholaemia, ascites, liver disorder) will be provided to sites in a manual.

If such an event occurs that meets criteria for serious adverse event, the investigator will complete a separate questionnaire for a Hepatotoxicity and Statin-related Event form (provided by Novartis) to summarize the event, its further diagnostic tests performed, and its related information.

Liver events are divided into two categories:

- Liver events of special interest (AESI) which consist of liver function tests (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 19-1 in Appendix 7 for complete definitions of liver events.

Any liver event which meets the criteria for "**medically significant**" event as outlined in Table 19-1 of Appendix 7 should follow the **standard procedures for SAE reporting** as described in Section 7.2.

Every liver event as defined in Table 19-1 of Appendix 7 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 19-2 in Appendix 7.

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on 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 Pregnancy reporting

In case a patient becomes pregnant, or plans to become pregnant, the study drug must be interrupted before contraception is discontinued (or, from the date the pregnancy becomes known) for the entire duration of the pregnancy and lactation period (or, for the entire duration that contraception is discontinued). To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary

termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis DS&E Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.5 Prospective suicidality assessment

Not applicable.

8 Data review and database management

8.1 Site monitoring

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

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

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

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that

the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

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

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a Novartis, who will also manage the database.

At the conclusion of a non-IRT study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused supplies to Novartis. The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Trial Statistician and Statistical Reporting and the Clinical Trial Leader.

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

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Angioedema Adjudication Committee

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

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

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

9 Data analysis

9.1 Analysis sets

The following populations will be used for the statistical analyses:

The full analysis set (FAS) will consist of all randomized patients who have received at least one dose of study drug. Following the **intent-to-treat principle**, patients will be analyzed according to the treatment to which they were assigned at randomization. Efficacy variables will be analyzed based on the FAS as the primary population.

The Safety Population (SAF) will consist of all randomized patients who received at least one dose of study drug. Patients will be analyzed according to the treatment actually received. The safety population will be used for the analyses of safety variables.

9.2 Patient demographics and other baseline characteristics

Baseline value is defined as the last non-missing assessment prior to the first dose of randomized study medication unless specified otherwise.

Summary statistics will be provided by treatment group for demographics and baseline characteristics, including age, age group (<65 years vs. ≥65 years), sex, race, weight, height, body mass index (BMI), category of prior CHF medication, prior HF hospitalization, NYHA class, and vital signs. BMI will be calculated as weight (kg) / height^2 (m^2) from the collected height and weight at Visit 1 (Screening Visit). Continuous variables will be summarized using n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency and percentage.

The FAS will be the patient population for the above analyses.

9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

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

Concomitant medications and significant non-drug therapies, prior to and after the randomization date respectively, will be summarized by therapeutic class, preferred term, and treatment group for the safety population.

The number and percentage of patients on different CHF background medications (aldosterone antagonists, β-blockers, ivabradine, diuretics, digoxin) will be tabulated by treatment at baseline and during the double-blind stage.

The FAS will be used for the above analyses.

9.4 Analysis of the primary and key secondary variable(s)

9.4.1 Variable(s)

The primary efficacy variable is the change from baseline in VO_{2peak} (adjusted to body weight) at month 3.

The key secondary variable is the change from baseline in VO_{2peak} (adjusted to body weight) at week 6.

9.4.2 Statistical model, hypothesis, and method of analysis

The trial aims to establish the (alternative) hypotheses of superiority of LCZ696 vs enalapril.

The primary analysis will be performed comparing treatments with respect to the primary efficacy variable in an analysis of covariance (ANCOVA) model with the factors treatment and center and baseline VO_{2peak} as a covariate. The raw- as well as the adjusted (LS) group means will be presented. Additionally, a 95% confidence interval and a p-value will be given for the treatment contrast.

The key secondary endpoint, the change from baseline in VO_{2peak} (adjusted to body weight) at week 6 will be analyzed using the same model. The significance level will not be adjusted for multiplicity, the result of the test for week 6 will be regarded as providing confirmatory evidence, only if the test of the primary hypothesis (month 3) is also significant (a-priori ordered hypotheses).

9.4.3 Handling of missing values/censoring/discontinuations

Missing values of VO_{2peak} will be replaced with the last observed value (LOCF). Since the trial aims to estimate which improvements are achievable under the respective treatment regimens, LOCF seems to provide meaningful estimates for this purpose.

9.4.4 Supportive analyses

In case of serious deviations from the normality assumptions, treatments may additionally be compared by a non-parametric test (Mann-Whitney-U-test). In case of a substantial rate of missing data (>15%) or strong imbalances between treatment groups, Multiple Imputation (MI) may be considered as a sensitivity analysis.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

Secondary efficacy variables are:

- Change in VE/VCO_2 slope after 6 weeks and 3 months

- Change in exercise capacity (Watt) at VAT after 6 weeks and 3 months
- Change in rate of perceived exertion during exercise (Borg Scale) after 6 weeks and 3 months

Secondary efficacy variables will be analyzed using ANCOVA models analogous to the analyses of the primary endpoint.

9.5.2 Safety variables

Safety assessments will be based mainly on the frequency of adverse events. Adverse events will be coded by primary system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). An adverse event related to study drug is defined as one considered by the investigator to have a suspected relationship with the study drug. The adverse events will be summarized by the number and percentage of patients in each primary system organ class and preferred term. For summaries by severity of event, the most severe occurrence for a particular preferred term will be used for a given patient. Summary tables of adverse events by treatment and severity will be provided.

Multiple occurrences of the same AE or SAE in the same patient will be counted only once, using the worst severity and drug relationship.

In the data listings of adverse events, the severity of an AE, whether or not an AE is study drug related, and whether or not it is a serious AE, will be indicated.

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy.

Laboratory data will be summarized by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges) and by presenting number and percentage of patients with notable laboratory abnormalities according to Appendix 1.

Data from other tests (vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

9.5.3 Resource utilization

Not required.

9.5.4 Health-related Quality of Life

See under 'secondary/ [redacted] endpoints' above.

9.5.5 Pharmacokinetics

Not applicable.

9.5.6 Pharmacogenetics/pharmacogenomics

Not applicable

9.5.7 Biomarkers

Not applicable

9.5.8 PK/PD

Not applicable

9.6 Interim analyses

Not applicable.

9.7 Sample size calculation

Existing data suggest that the difference between LCZ696 and enalapril in VO_{2peak} at month 3 may be about 1.5 mL kg^{-1} min^{-1} with a (common) SD of 3 (Guazzi et al. 1999; Lewis et al. 2007). Under these assumptions, 86 patients per treatment arm would be required to achieve 90% power on a 2-sided, 5% significance level. To compensate for some drop-out and other protocol deviations, 100 patients per treatment group (200 in total) will need to be enrolled into this trial. The above mentioned literature suggests that the treatment effect for the key secondary endpoint, VO_{2peak} after 6 weeks, might be of a similar magnitude, therefore, the sample size calculation above applies also for the key secondary endpoint.

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 Code of Federal Regulations Title 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 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.

Novartis will provide to investigators in a separate document an informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study.

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

The protocol and the informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

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

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as requests to approve deviations will not be granted.

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

If the 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 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. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. 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, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days or less, if required by local regulations.

12 References

Albouaini, K. et al., 2007. Cardiopulmonary exercise testing and its application. *Postgraduate medical journal*, 83(985), pp.675–82. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2734442&tool=pmcentrez&rendertype=abstract [Accessed September 28, 2015].

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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
Potassium	>20% increase, >20% decrease
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease
Uric acid	>50% increase

14 Appendix 2: 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 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 trimethoprim/sulfamethoxazole fixed combinations
  - 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)
- 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

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

15 Appendix 3: 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
   c. If hypotension persists, the study drug should be down-titrated or even temporarily withdrawn. The dose re-challenge and medications adjust guidelines described in Section 5.5.5 should be adhered to as much as possible.

16 Appendix 4: Guidelines for the management of renal dysfunction

General principles:

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

Two types of response to serum creatinine increase are described:

Surveillance situation

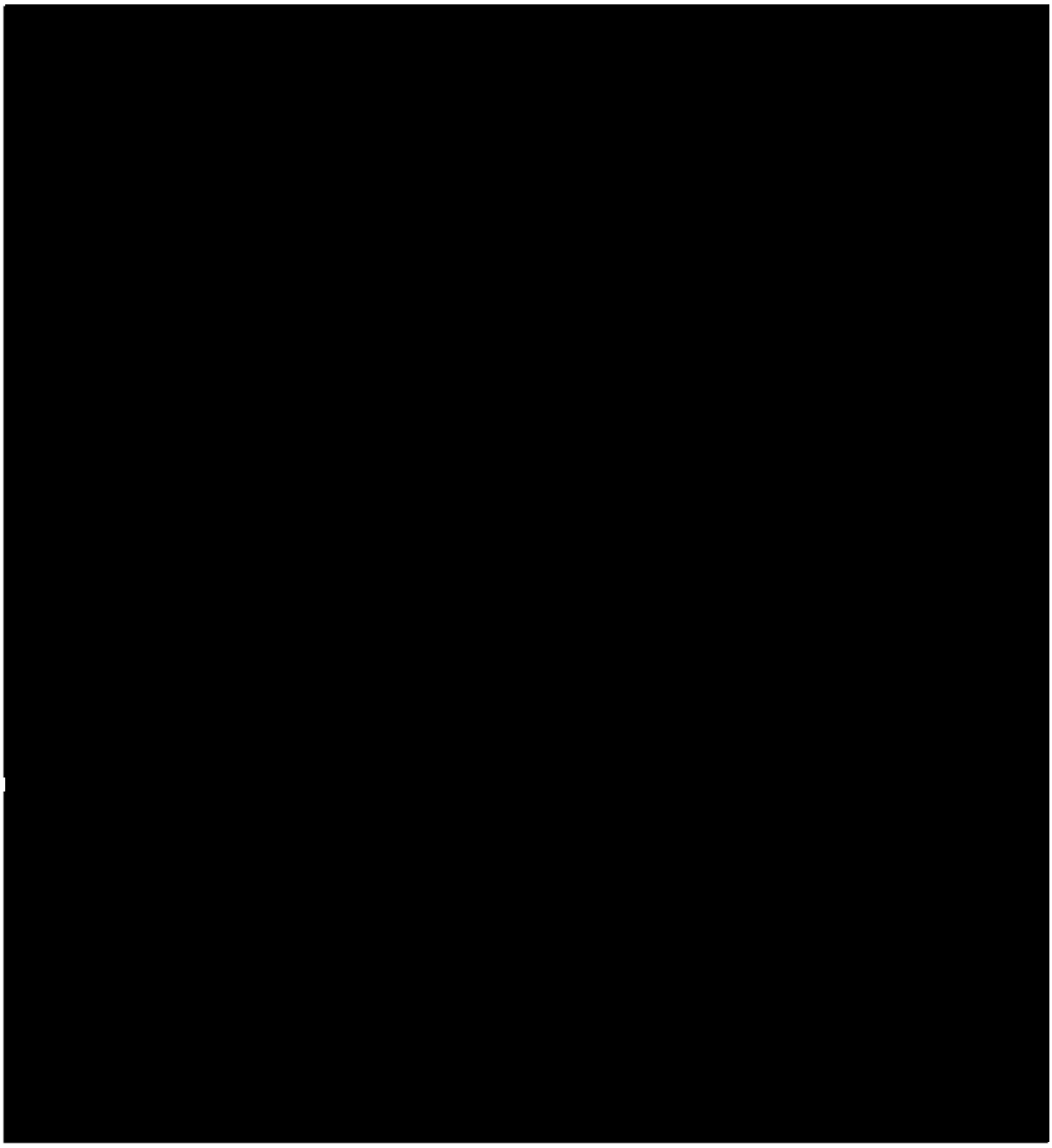
If, at any time after randomization, eGFR decreases by ≥ 25% from baseline (Visit 2) (or if serum creatinine concentration increase to 2.5 mg/dL [221 µmol/L]), the investigator will check for potentially reversible causes of renal dysfunction such as:

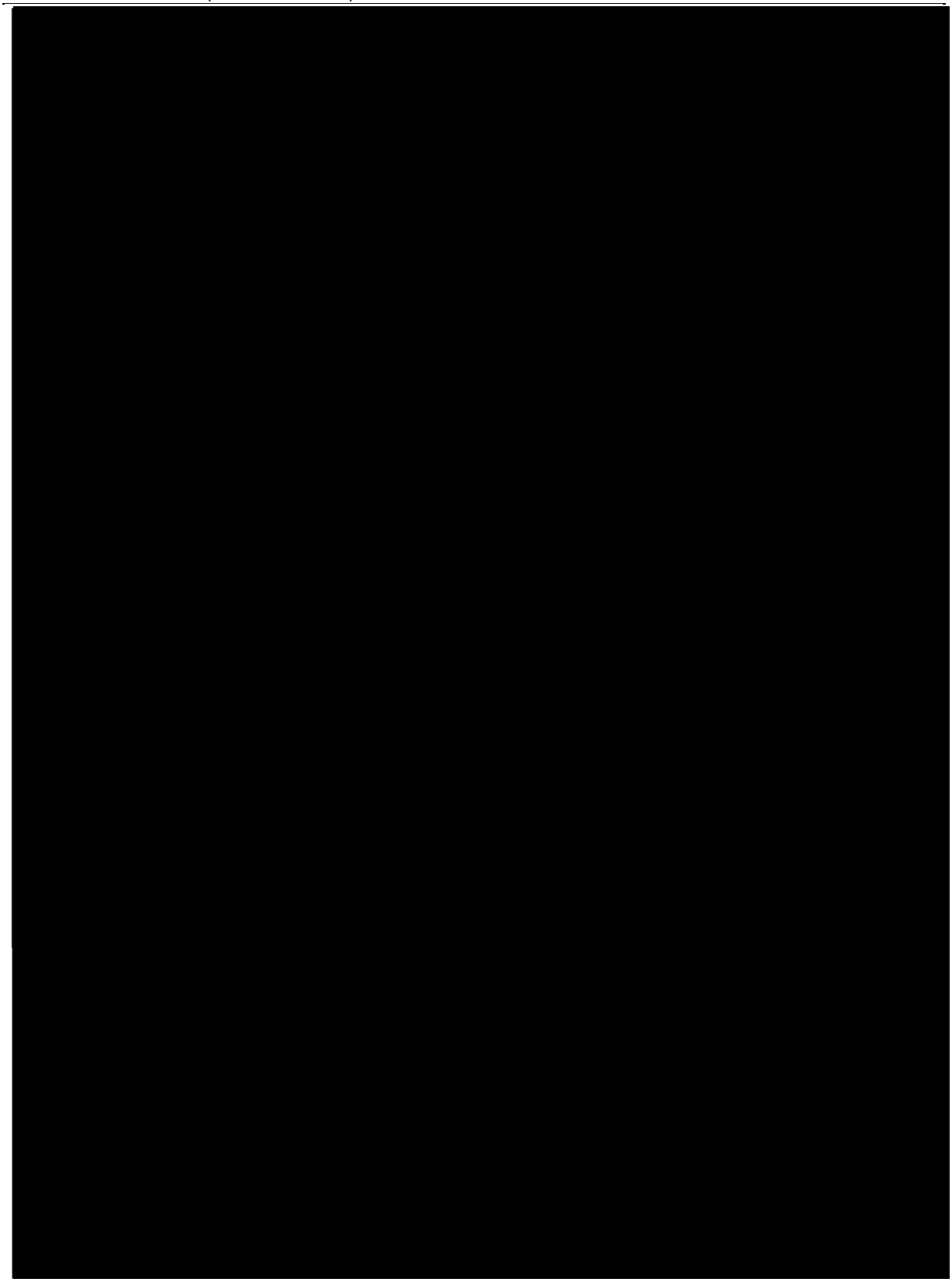
- Non-steroidal anti-inflammatory drug intake, antibiotics, or other treatments known to affect creatininemia
- Volume decrease, including that resulting from excessive dosing of diuretics
- Urinary infection
- Urinary tract obstruction
- Study medication

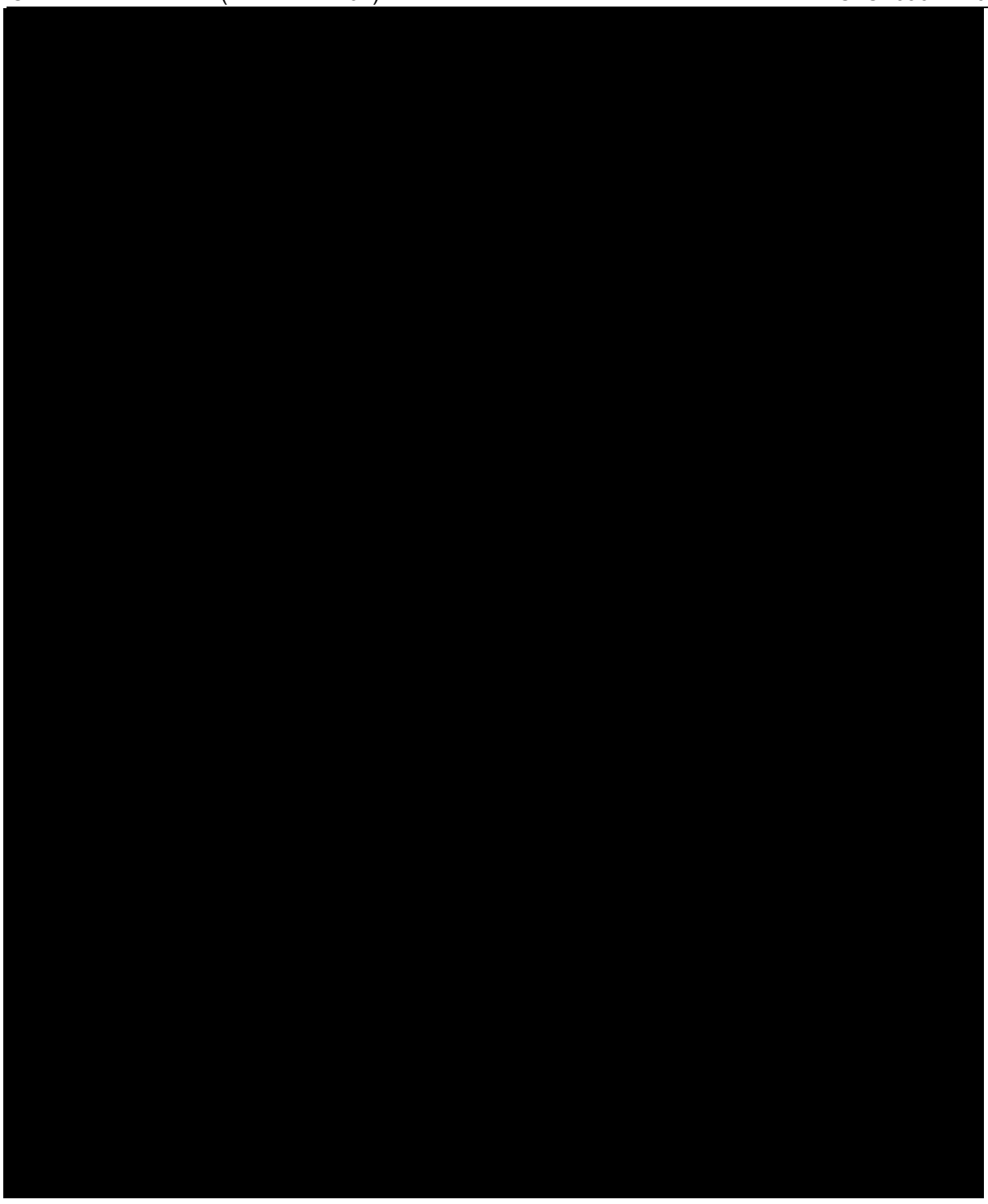
Action situation

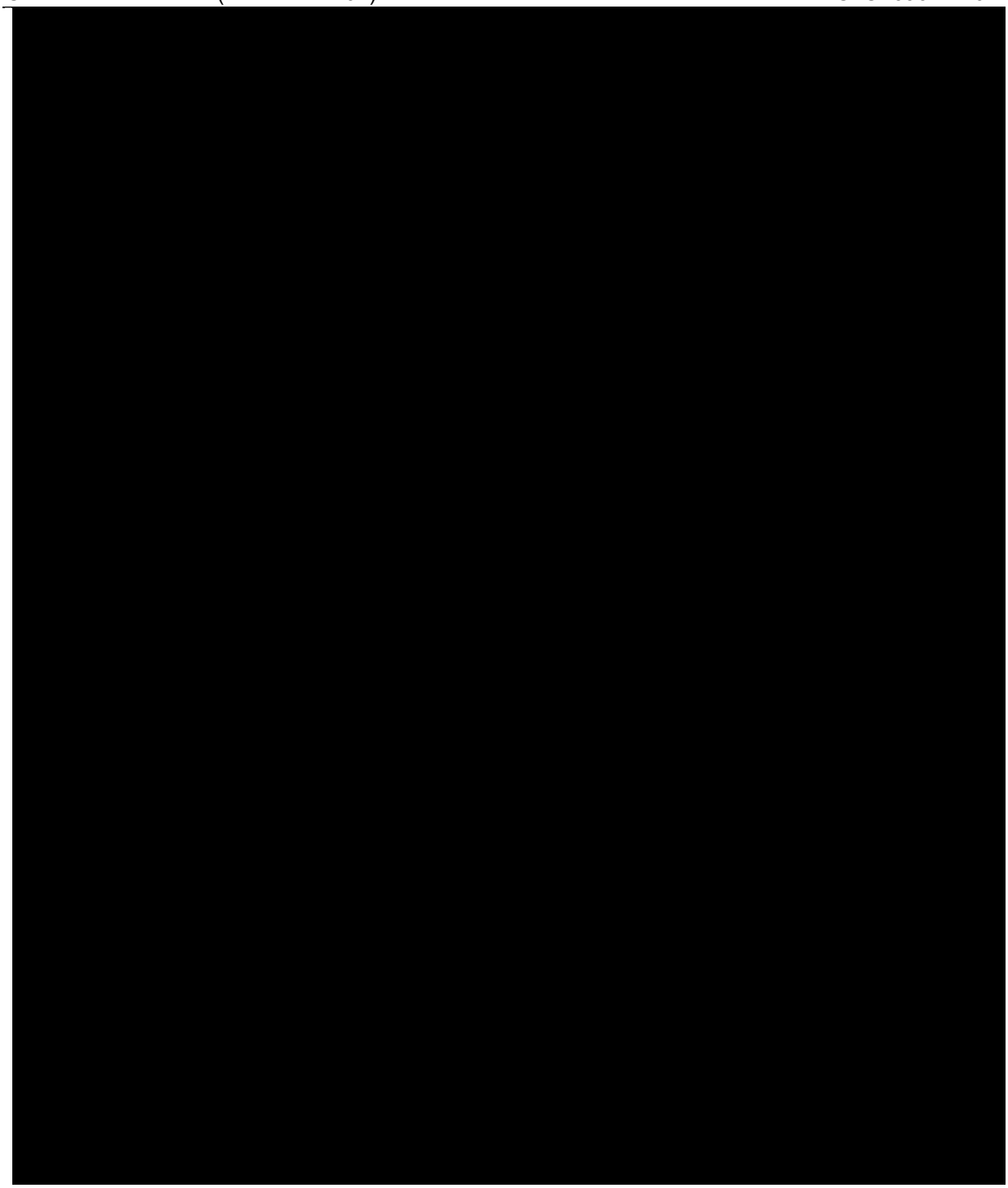
If a patient eGFR decreases by ≥ 40% from baseline (Visit 2) (or if serum creatinine concentration rises above 3 mg/dL (265 µmol/L)), the investigator will check for potentially reversible causes of renal dysfunction (see above).

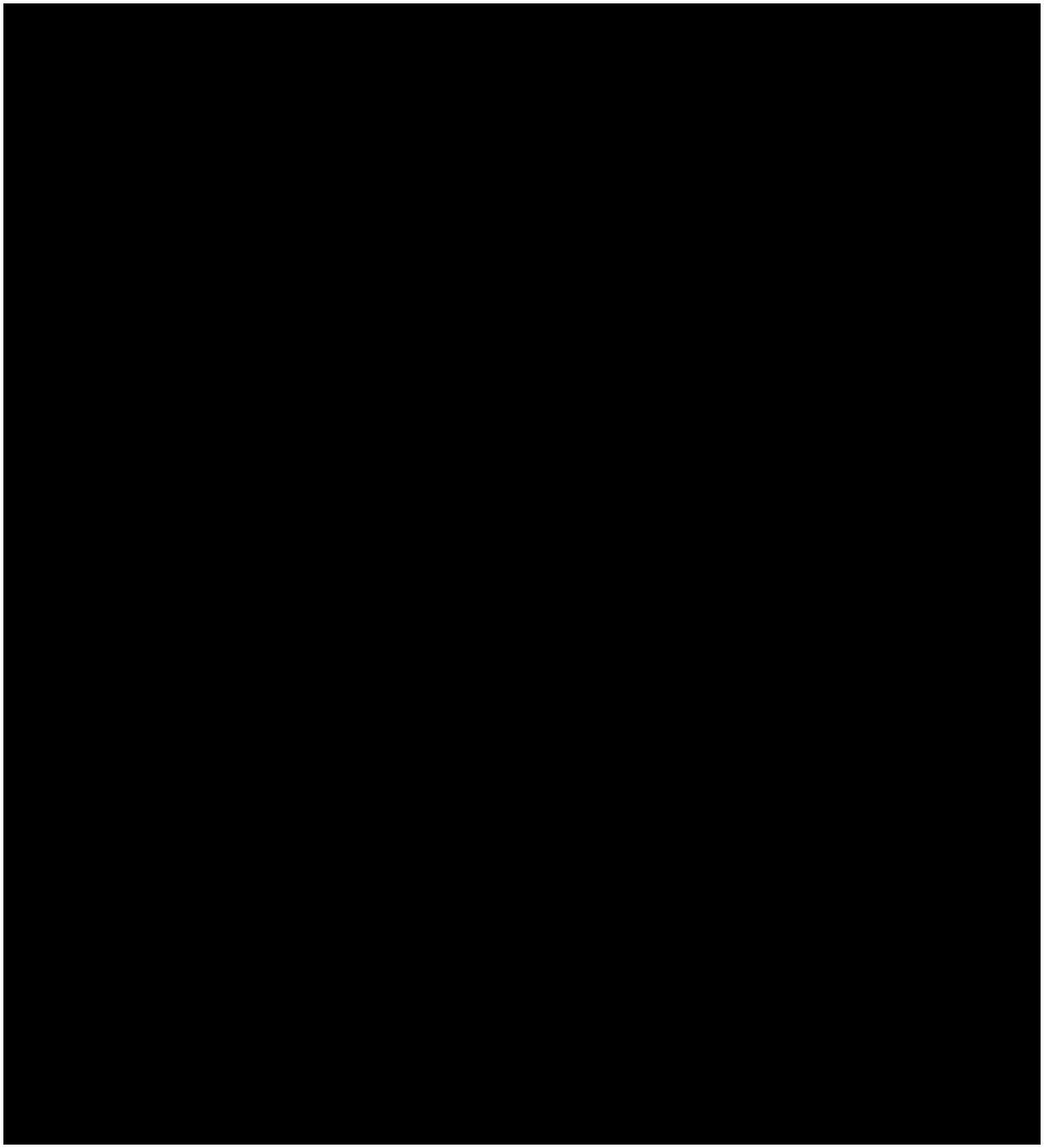
If the investigator judges that study medication has to be stopped, he/she will have to contact the Novartis medical monitor or his/her designee. Thereafter, serum creatinine assessments will have to be repeated at least each week until levels return to acceptable values. If study medication was stopped, every effort will be done to restart it again, according to clinical conditions.

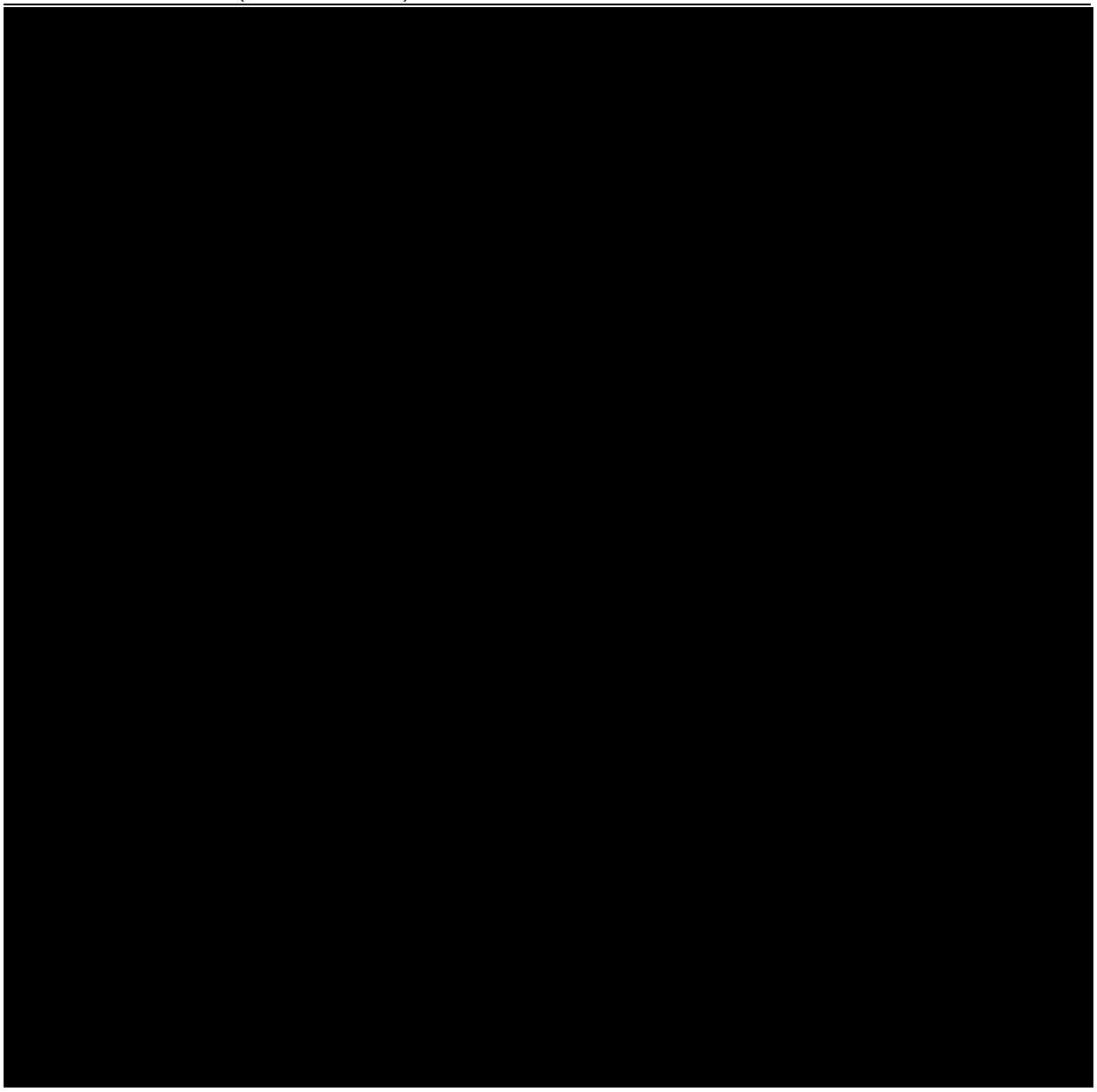












19 Appendix 7: Liver event definitions and follow-up requirements

Table 19-1 Liver event definitions

	Definition/ threshold
Adverse event 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)
Adverse events	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 19-2 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)
> 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	Central laboratory to report to Investigator & 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	Central laboratory to report to Investigator & 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	N/A	Repeat LFT at next visit	

Criteria	Event type	Actions required	Follow-up monitoring
(patient is asymptomatic)			
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 (patient is asymptomatic)	AESI	Central laboratory to report 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
≤ 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.