NOVARTIS

Global Clinical Development - General Medicine

LCZ696

Clinical Trial Protocol CLCZ696B1301 / NCT02468232

A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in Japanese patients with chronic heart failure and reduced ejection fraction

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List of abbreviations

ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
AE	adverse event
AF	atrial fibrillation
Alb	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
AST	aspartate aminotransferase
AT1	angiotensin II type 1
AUEC	area under the effect curve
b.i.d.	twice a day
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
BUN	blood urea nitrogen
CCB	calcium channel blocker
CEC	Clinical Endpoint Committee
cGMP	cyclic guanosine monophosphate
CHF	chronic heart failure
CI	confidence interval
C_{min}	minimum drug plasma (serum/blood) concentration
COPD	chronic obstructive pulmonary disease
COX-2	cyclo-oxygenase-2
CPO	Country Pharma Organization
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRT-D	cardiac resynchronization therapy defibrillator
CRT-P	cardiac resynchronization therapy pacemaker

CSR	clinical study report
CV	cardiovascular
DBP	diastolic blood pressure
DICOM	Digital Imaging and Communication in Medicine
DMC	Data Monitoring Committee
DS	assessment to be recorded in clinical database
DS&E	Drug Safety and Epidemiology
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
EOS	end of study
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FMV	first morning void
GCP	good clinical practice
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
HDPE	high density polyethylene
HF	heart failure
HF-pEF	heart failure with preserved left ventricular ejection fraction
HF-rEF	heart failure with reduced left ventricular ejection fraction
IA	interim analysis
IB	Investigator Brochure
ICD	implantable cardioverter defibrillator
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
INR	international normalized ratio

IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	left atrial
LDL	low density lipoprotein
LFT	liver function test
LVEF	left ventricular ejection fraction
MedDRA	Medical dictionary for regulatory activities
MRA	mineralocorticoid antagonist
MRI	magnetic resonance imaging
MUGA	multiple gate acquisition scan
NEP	neutral endopeptidase
NSAID	non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OC/RDC	Oracle Clinical/Remote Data Capture
OLE	open-label extension
PCI	percutaneous coronary intervention
PD	Pharmacodynamics
PDE-5	phosphodiesterase-5
[redacted]	[redacted]
PP	per protocol
PT/INR	international normalized ratio of prothrombin time
PINP	amino-terminal propeptide of type I procollagen
PIIINP	amino-terminal propeptide of type III procollagen
QOL	quality of life
RAS	renin angiotensin system
RBC	red blood cell
SAE	serious adverse event

SAF	safety
SBP	systolic blood pressure
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
ULN	upper limit of normal
UNS	Unscheduled visit
US	United States
VAD	ventricular assistance device
WBC	white blood cell
WHO	World Health Organization
γGT	gamma-glutamyltransferase

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical Epochs are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in subjects with established disease and in those with newly-diagnosed disease.
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Premature subject/patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

Amendment 04

Amendment rationale

This is the fourth amendment to the protocol. This amendment serves the following purpose;

Local laboratory assessments for serum potassium and eGFR at Visits 301 and 302 in the open-label extension (OLE) epoch are added to ascertain if patient meets safety monitoring criteria and ensure patient safety.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions. A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Summary of previous amendments

The first amendment of protocol CLCZ696B1301 (v01 of the protocol) was dated 27-Mar-2015. The main purpose of this amendment was to clarify study drug dose adjustments during the double-blind randomized treatment epoch and change some laboratory measurements.

The second amendment (v02) was dated 05-Nov-2015. The main purpose of this amendment was to correct the definition of 'worsening heart failure' events involved in the key secondary objectives, clarify the exclusion criteria related to heart block, change the action on the study treatment when emergency treatment code broken, and update the list of adverse events that are commonly seen in study population.

The third amendment (v03) was dated 11-Jun-2018. The main purpose of this amendment was to add the open-label extension epoch in the study design and provides details and the related changes in relevant sections of this protocol.

Protocol summary

Protocol number	CLCZ696B1301
Title	A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in Japanese patients with chronic heart failure and reduced ejection fraction
Brief title	Study of efficacy and safety of LCZ696 in Japanese patients with chronic heart failure and reduced ejection fraction
Sponsor and Clinical Phase	Novartis, Phase 3
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of the core part of this study is to assess the effect of LCZ696 compared to enalapril, in addition to the background HF treatment, on delaying time to first occurrence of either CV death or HF hospitalization events in Japanese patients with stable CHF, NYHA classes II-IV and reduced ejection fraction (LVEF ≤ 35%). Data from this core part are intended to be used to support registration of LCZ696 for treatment of HF patients in Japan. This study is designed to align with the guideline requirement for drug approval, to observe a similar trend of LCZ696 better than enalapril in reducing morbidity and mortality in Japanese HF patients and capture data of the efficacy variables of PARADIGM-HF so that the efficacy of LCZ696 over enalaprill in Japanese HF patients can be assessed in aspects comparing with PARADIGM-HF study outcomes. An open-label extension (OLE) to the study will be conducted following the completion of the core part. The purpose of this OLE is to provide access to LCZ696 for the eligible patients until marketed product is available in Japan or approximately 2 years from the date of the first patient enrolled in the OLE epoch, whichever occurs first, and also to assess the safety, tolerability and efficacy of the treatment with LCZ696.
Primary Objective(s)	To assess the effect of LCZ696 and enalapril on delaying time to first occurrence of the composite endpoint, which is defined as either CV death or HF hospitalization in patients with HF and reduced ejection fraction.
Secondary Objectives	Key secondary objectives • To assess the effect of LCZ696 on changes in NT-proBNP from baseline at predefined time points (Weeks 4, 8 and Month 6) • To assess the effect of LCZ696, compared to enalapril, on delaying the time to first occurrence of CV death, HF hospitalization, or intensification of treatments due to documented episode(s) of worsening HF defined as: worsening signs and symptoms of HF requiring addition of a new drug for HF treatment, initiation of IV treatment, increase of diuretic dose for persistent use for ≥ 4 consecutive weeks, or institution of mechanical or circulatory support such as mechanical ventilation, ultrafiltration, hemodialysis, intra-aortic balloon pump or ventricular assist device

	• To assess the effect of LCZ696, compared to enalapril, on changes in NYHA classification from baseline at predefined time points (Weeks 4, 8 and Month 6) • To assess the effect of LCZ696, compared to enalapril, on improving the clinical summary score for HF symptoms and physical limitations, as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) at predefined time points (Week 8 and Month 6) • To assess safety and tolerability of LCZ696 compared to enalapril Other secondary objectives • To assess the effect of LCZ696, compared to enalapril, on reducing the rate of the composite endpoint of CV death and total (first and recurrent) HF hospitalizations • To assess the effect of LCZ696, compared to enalapril, on the clinical composite score (as assessed by NYHA classification and patient global assessment) at predefined time point (Month 6) • To assess the effect of LCZ696, compared to enalapril, on delaying the time to all-cause mortality • To assess the effects of LCZ696, compared to enalapril, on reducing the number of patients hospitalized and number of hospital admission (all-cause and cause-specific) • To assess the effects of LCZ696, compared to enalapril, on reducing healthcare resource utilization, e.g., number of days/stays in ICU, number of rehospitalizations, and number of ER visits for HF • To assess the effects of LCZ696 and enalapril on changes in pre-specified and/or other relevant biomarkers (e.g., cardiac, vascular, renal, collagen, metabolism, and inflammatory biomarkers) from baseline to predefined timepoints (Weeks 2, 4, 8, Month 6 and 18) Objectives during the open-label extension • To evaluate the safety and tolerability of LCZ696 treatment during the OLE epoch • To assess the proportion of patients reaching target dose level 3 of LCZ696 at Week 8 and maintained at Month 4 • To assess the effect of LCZ696 on change in NYHA classification from OLE baseline (Visit 301) at Month 12 • To assess the effects of LCZ696 on change in cardiac measurements by echocardiography (LV end systolic and diastolic volume indices, LVEF, and LA volume index, etc.) from OLE baseline (Visit 301) at Month 12 • To assess the effects of LCZ696 on changes in pre-specified biomarkers from OLE baseline (Visit 301) to predefined timepoints (Weeks 2-4, 8, Month 4 and 12) • To assess the association between change in concentration of NT-proBNP and change in structural cardiac measurements (LV end systolic and diastolic volume indices, LVEF, and LA volume index) from OLE baseline (Visit 301) at Month 12 • To assess the effects of long-term treatment with LCZ696 on the safety and tolerability throughout the study period

Study design	This study is a multicenter, randomized, double-blind, double-dummy, parallel-group, active-controlled study to assess the effect of LCZ696 and enalapril on CV mortality and morbidity reduction in Japanese HF patients with reduced ejection fraction. The core part above is followed by the optional OLE in which patients are treated with open-label LCZ696 to assess the long-term safety and tolerability of LCZ696 treatment.
Population	Male or female patients with CHF (NYHA class II-IV), aged 20 years or older with LVEF ≤ 35%. Approximately 220 patients (110 patients in each arm) will be randomized. All participants of the core part who are eligible to receive study drug will be offered the option to enter the OLE. It is anticipated that approximately 180 patients will complete the core part of the study and that the majority of them will be enrolled into the OLE.
Key Inclusion criteria	Core part: Patients eligible for inclusion in the core part have to fulfill all of the following criteria: • Written informed consent must be obtained before any assessment is performed. • Outpatients ≥ 20 years of age (at the time of signing informed consent), male or female. • Patients with a diagnosis of CHF NYHA class II-IV and reduced ejection fraction: - LVEF ≤ 35% at Visit 1 (any local measurement, made within the past 6 months using echocardiography, MUGA, CT scanning, MRI or ventricular angiography is also acceptable, provided no subsequent measurement above 35%) - NT-proBNP ≥ 600 pg/ml at Visit 1 **OR** NT-proBNP ≥ 400 pg/ml at Visit 1 and a hospitalization for HF within the last 12 months (according to central laboratory measurements) • Patients must be on an ACEI or an ARB at a stable dose for at least 4 weeks before Visit 1. • Patients must be treated with a β-blocker, unless contraindicated or not tolerated, at a stable dose for at least 4 weeks prior to Visit 1 (reason should be documented if patients reported contraindications or intolerance). • 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, and should be stable for at least 4 weeks prior to Visit 1. Other evidence-based therapy for HF should also be considered e.g. cardiac resynchronization therapy and an implantable cardioverter-defibrillator in selected patients, as recommended by guidelines. Open-label extension (OLE) epoch: Patients eligible for inclusion into the open-label extension must fulfill the following criteria: • Written informed consent for the open-label extension must be obtained before any assessment is performed. • Patients who have completed the double-blind treatment epoch and are able to be safely enrolled into the OLE as judged by the

	investigator.
Key Exclusion criteria	Core part: Patients fulfilling any of the following criteria are not eligible for inclusion in the core part. • History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes, ACEIs, ARBs, NEP inhibitors as well as known or suspected contraindications to the study drugs. • Previous documented history of intolerance to 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 < 95 mmHg at Visit 199 (end of run-in). • Estimated GFR < 30 mL/min/1.73 m^2 as measured by the Japanese formula at Visit 1 (screening), or Visit 199 (end of run-in) or > 35% decline in eGFR between Visit 1 and Visit 199 (according to local measurements). • Serum potassium > 5.2 mmol/L (mEq/L) at Visit 1 (screening) or > 5.4 mmol/L (mEq/L) at Visit 199 (end of run-in) (according to local measurements). • 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. • 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 to 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. • Heart transplant or ventricular assistance device (VAD) or intent to transplant (on transplant list) or implant a VAD. • History of severe pulmonary disease. • Diagnosis of peripartum or chemotherapy induced cardiomyopathy within the 12 months prior to Visit 1. • Documented untreated ventricular arrhythmia with syncopal episodes within the 3 months prior to Visit 1. • Symptomatic bradycardia or second (except asymptomatic Wenckebach block) or third degree heart block without a pacemaker. • Presence of hemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation secondary to left ventricular dilatation. • Presence of other hemodynamically significant obstructive lesions of left ventricular outflow tract, including aortic and sub-aortic

	stenosis. • Presence of bilateral renal artery stenosis. • History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in-situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases. • Presence of any other disease with a life expectancy of < 3 years. Open-label extension (OLE) epoch: Patients fulfilling any of the following criteria at Visit 301, are not eligible for inclusion in the OLE epoch. • Patients who discontinued study drug treatment during the core part due to an event or intercurrent illness. Eligibility can be re-considered if the event has resolved and no longer represents a risk to the patient and the patient can safely tolerate the administration of LCZ696 per the investigator's assessment. • Any medical condition that in the opinion of the investigator is likely to prevent the patient from safely tolerating LCZ696 or complying with the requirements of the study. • Patients who have experience of angioedema event(s) which occurred and reported by the investigator during the core part of study.
Investigational and reference therapy	Core part: <u>LCZ696</u> 50 mg b.i.d.(dose level 1), 100 mg b.i.d.(dose level 2), 200 mg b.i.d.(dose level 3) <u>Enalapril</u> 2.5 mg b.i.d.(dose level 1), 5 mg b.i.d.(dose level 2), 10 mg b.i.d.(dose level 3) Open-label extension (OLE) epoch: LCZ696 50 mg b.i.d.(dose level 1), 100 mg b.i.d.(dose level 2), 200 mg b.i.d.(dose level 3)
Efficacy assessments	Core part: The primary composite endpoint consists of the following components: • CV death • HF hospitalization The key secondary endpoints are: • Changes in NT-proBNP from baseline • CV death, HF hospitalization or intensification of treatments due to documented episode(s) of worsening HF defined as: worsening signs and symptoms of HF requiring addition of a new drug for HF treatment, initiation of IV treatment, increase of diuretic dose for persistent use for ≥ 4 consecutive weeks, or institution of mechanical or circulatory support such as mechanical ventilation, ultrafiltration, hemodialysis, intra-aortic balloon pump or ventricular assist device • CV death • HF hospitalization

	• Intensification of treatments due to documented episode(s) of worsening HF • Changes in NYHA class from baseline • Clinical summary score (assessed by KCCQ) The other secondary endpoints are: • Composite of CV death and total (first and recurrent) HF hospitalizations • Clinical composite score (assessed by NYHA classification and patient global assessment) • All-cause mortality • Hospitalization (all-cause, cause-specific) • Changes in biomarkers from baseline • Health resource utilization Other endpoints during OLE epoch • Changes in NYHA class from OLE baseline (Visit 301) • Changes in echocardiographic parameters from OLE baseline (Visit 301) • Changes in biomarkers from OLE baseline (Visit 301)
Safety assessments	Core part: • AEs and SAEs • Sitting systolic, diastolic BP, and pulse pressure • Heart rate • Symptomatic hypotension and/or SBP < 90 mmHg • Angioedema • Hyperkalemia • Renal dysfunction • Cough • Drug-related hepatic disorders • Other relevant laboratory values • ECG changes Open-label extension (OLE) epoch: Same as the core part
Other assessments	[redacted]
Data analysis	Core part: The primary efficacy variable, the CEC adjudicated time to the first occurrence of the composite endpoint, which is defined as either CV death or HF hospitalization, will be analyzed using Cox proportional hazards model with treatment and the stratification factor of screening NT-proBNP (< 1,600 pg/mL, ≥ 1,600 pg/mL) as fixed-effect factors. The estimated hazards ratio and the corresponding two-sided 95% confidence interval and p-value will be provided. The frequency of patients with composite primary endpoint events and the treatment exposure adjusted event rate will be provided for individual treatment arm. The FAS will be used for the primary analysis. The primary objective of verifying the consistency between this study and PARADIGM-HF study is met when the hazard ratio (LCZ696 over enalapril) point estimate is less than 1. Above analysis will be repeated for the PP population as supportive analysis. Same analysis

	will be repeated for each of the components of the composite endpoint. The key secondary efficacy variables are: • Changes in NT-proBNP from baseline at pre-defined time points (Weeks 4 and 8, Month 6) • Time to the first occurrence of CV death, HF hospitalization or intensification of treatments due to documented episode(s) of worsening HF • Changes in NYHA classification from randomization to each of the post-randomization visits • Clinical summary score of KCCQ, computed as the mean of the available domain scores of total HF symptom and physical limitation Open-label extension (OLE) epoch: The assessment of safety will be based primarily on the frequency of adverse events, SAEs, and laboratory abnormalities. Other safety data will be summarized as appropriate.
Key words	Chronic heart failure and reduced ejection fraction, Japanese patients, Cardiovascular death, Heart failure hospitalization, NYHA, NT-proBNP, Kansas City Cardiomyopathy Questionnaire.

1 Introduction

1.1 Background

Heart failure (HF) is a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection. It is a major public health problem associated with high mortality rate, frequent hospitalizations, and poor quality of life. The overall prevalence of HF is increasing across the world due to population ageing and improvement in the treatment of acute conditions, such as acute coronary syndrome. Approximately 5.7 million persons in US (Roger et al. 2012) and 15 million persons in EU (Braunschweig et al. 2011) have HF. In Japan, there are currently 1-2 million CHF patients and the prevalence will continue to rise significantly since the elderly population (≥ 65 years) is expected to increase to 40% by 2050 and also due to precipitation by westernized dietary pattern, obesity, reduced physical activity, and increasing trend of cardiovascular/metabolic diseases (Shiba et al. 2011).

HF is a progressive disease characterized by increasing symptoms that lead to repeated hospitalizations and significantly greater risk of premature death. HF can be exhibited in patients with reduced left ventricular ejection fraction (HF-rEF) as well as preserved ejection fraction (HF-pEF). Therapies targeted at improving outcomes in HF-rEF patients have been well studied over the past few decades, leading to an improvement in survival as well as a decrease in morbidity, mostly in the form of decrease in HF hospitalization, with angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers and mineralocorticoid antagonists (MRAs) (CONSENSUS Trial Study Group 1987, SOLVD Investigators 1991, SOLVD Investigators 1992, RALES Investigators 1996, Pitt et al. 1999, MERIT-HF Study group 1999, CIBIS II Investigators 1999, Cohn and Tognoni 2001, Packer et al. 2002, Pfeffer et al. 2003, Flather et al. 2005). However, despite the advances in pharmacological (and device) therapies, the prognosis of HF patients remains poor. The absolute mortality rate for HF is approximately 50% within 4 years of diagnosis, and 40% of HF patients admitted to the hospital will either die or be readmitted within 1 year (Dickstein et al. 2008). Thus, HF represents a major cause of cardiac mortality and morbidity with a significant unmet medical need.

LCZ696 (sacubitril valsartan sodium hydrate) is a first-in-class angiotensin receptor neprilysin (neutral endopeptidase 24.11; NEP) inhibitor (ARNI). Following oral administration, LCZ696 dissociates into valsartan and the pro-drug AHU377, which is further metabolized to the NEP inhibitor LBQ657. LCZ696 exhibits the novel mechanism-of-action of an ARNI by simultaneously inhibiting NEP via LBQ657 and by blocking the angiotensin II type 1 (AT1) receptor via valsartan. The therapeutic effects of NEP inhibition by LBQ657 are attributable to increased levels of biologically active natriuretic peptides and/or other vasoactive peptides. The effects of AT1 receptor blockade by valsartan are related to inhibition of the deleterious effects of angiotensin II and its effectors on the cardiovascular system. The pharmacodynamic effects of LCZ696 include initial increased natriuresis and diuresis, vasodilation and subsequent blood pressure reduction, reduction of sympathetic tone, and inhibition of adverse cardiovascular remodeling, including anti-fibrotic and anti-hypertrophic effects. Therefore, LCZ696, through its unique dual mode of action, may fulfill the promise of providing a novel, more effective therapy for HF-rEF patients to address the high unmet medical need.

The phase III PARADIGM-HF study (CLCZ696B2314, n=8,442) was a large event-driven outcome study comparing LCZ696 at a target dose of 200 mg twice daily to enalapril 10 mg twice daily in patients with HF-rEF and was conducted globally in 47 countries. It demonstrated the superiority of LCZ696 over enalapril on the reduction of CV death and HF hospitalization (McMurray et al. 2014). When compared to enalapril, LCZ696 reduced the risk of composite of CV death or HF hospitalizations by 20% (one-sided p = 0.0000002), and it also significantly reduced the risk of CV death by 20% (one-sided p = 0.00004). LCZ696 200 mg b.i.d. was well tolerated in the PARADIGM-HF study, with the overall frequency of adverse events similar to enalapril, and no event of severe angioedema associated with airway compromise was reported.

There is no clinical study of LCZ696 conducted in HF patients in Japan. The PK of LCZ696 is similar between Japanese and Caucasian healthy subjects. Several studies have been conducted in Japanese hypertensive patients. In a Phase III pivotal study (CLCZ696A1306) comparing LCZ696 to an ARB olmesartan, a total of 1,161 hypertensive patients received LCZ696 (200 mg or 400 mg once daily, n=772) or olmesartan (20 mg once daily, n=389). This study showed LCZ696 was superior to olmesaltan in blood pressure lowering effect, and was safe and well tolerated in Japanese hypertensive patients.

The multicenter, randomized, double-blind, parallel group and active controlled study CLCZ696B1301 described here is planned to assess the efficacy/safety of LCZ696 on morbidity and mortality compared to enalapril, the current gold standard for RAS blockade in HF treatment, in Japanese HF-rEF patients.

1.2 Purpose

The purpose of the core part, which is comprised of screening epoch, single-blind active treatment run-in epoch and double-blind randomized treatment epoch, is to assess the effect of LCZ696 at a target dose of 200 mg b.i.d. compared to enalapril 10 mg b.i.d., in addition to the background HF treatment, on delaying time to first occurrence of either CV death or HF hospitalization events in Japanese patients with stable CHF, NYHA classes II-IV and reduced ejection fraction (LVEF $\leq$ 35%). Data from the core part are intended to be used to support registration of LCZ696 for treatment of HF patients in Japan.

The purpose of the open-label extension (OLE) is to provide access to LCZ696 for the eligible patients until marketed product is available in Japan or 2 years from the date of the first patient enrolled in the OLE epoch, whichever occurs first, and also to assess the safety, tolerability and efficacy of the treatment with LCZ696.

2 Study objectives

Unless specifically stated otherwise, the study objectives listed below apply only to the core part of this study, which ends at Visit 299 (the end visit of double-blind treatment epoch).

2.1 Primary objective(s)

To assess the effect of LCZ696 and enalapril on delaying time to first occurrence of the composite endpoint, which is defined as either CV death or HF hospitalization in patients with HF and reduced ejection fraction.

2.2 Secondary objectives

2.2.1 Key secondary objectives

- To assess the effect of LCZ696 100 mg b.i.d. and 200 mg b.i.d. on changes in NT-proBNP from baseline at predefined time points (Weeks 4, 8 and Month 6)
- To assess the effect of LCZ696, compared to enalapril, on delaying the time to first occurrence of CV death, HF hospitalization, or intensification of treatments due to documented episode(s) of worsening HF defined as: worsening signs and symptoms of HF requiring addition of a new drug for HF treatment, initiation of IV treatment, increase of diuretic dose for persistent use for ≥ 4 consecutive weeks, or institution of mechanical or circulatory support such as mechanical ventilation, ultrafiltration, hemodialysis, intra-aortic balloon pump or ventricular assist device
- To assess the effect of LCZ696, compared to enalapril, on changes in NYHA classification from baseline at predefined time points (Weeks 4, 8 and Month 6)
- To assess the effect of LCZ696, compared to enalapril, on improving the clinical summary score for HF symptoms and physical limitations, as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) at predefined time points (Week 8 and Month 6)
- To assess safety and tolerability of LCZ696 compared to enalapril

2.2.2 Other secondary objectives

- To assess the effect of LCZ696, compared to enalapril, on reducing the rate of the composite endpoint of CV death and total (first and recurrent) HF hospitalizations
- To assess the effect of LCZ696, compared to enalapril, on the clinical composite score (as assessed by NYHA classification and patient global assessment) at predefined time point (Month 6)
- To assess the effect of LCZ696, compared to enalapril, on delaying the time to all-cause mortality
- To assess the effects of LCZ696, compared to enalapril, on reducing the number of patients hospitalized and number of hospital admission (all-cause and cause-specific)
- To assess the effects of LCZ696, compared to enalapril, on reducing healthcare resource utilization, e.g., number of days/stays in ICU, number of rehospitalizations, and number of ER visits for HF
- To assess the effects of LCZ696 and enalapril on changes in pre-specified and/or other relevant biomarkers (e.g., cardiac, vascular, renal, collagen, metabolism, and inflammatory biomarkers) from baseline to predefined timepoints (Weeks 2, 4, 8, Month 6 and 18)

2.2.3 Objectives during the open-label extension

- To evaluate the safety and tolerability of LCZ696 treatment during the OLE epoch
- To assess the proportion of patients reaching target dose level 3 of LCZ696 at Week 8 and maintained at Month 4

- To assess the effect of LCZ696 on change in NYHA classification from OLE baseline (Visit 301) at Month 12
- To assess the effects of LCZ696 on change in cardiac measurements by echocardiography (LV end systolic and diastolic volume indices, LVEF, and LA volume index, etc.) from OLE baseline (Visit 301) at Month 12
- To assess the effects of LCZ696 on changes in pre-specified biomarkers from OLE baseline (Visit 301) to predefined timepoints (Weeks 2-4, 8, Month 4 and 12)
- To assess the association between change in concentration of NT-proBNP and change in structural cardiac measurements (LV end systolic and diastolic volume indices, LVEF, and LA volume index) from OLE baseline (Visit 301) at Month 12
- To assess the effects of long-term treatment with LCZ696 on the safety and tolerability throughout the study period

[redacted]

3 Investigational plan

3.1 Study design

The core part of this study is a multicenter, randomized, double-blind, double-dummy, parallel-group, active-controlled study to assess the effect of LCZ696 at a target dose of 200 mg b.i.d. and enalapril 10 mg b.i.d. on CV mortality and morbidity reduction in Japanese HF patients with reduced ejection fraction. Patients who qualify the eligibility criteria at screening will first enter a 2 week, single-blind, active treatment run-in epoch in which they will receive LCZ696 50 mg b.i.d. Patients who tolerate the LCZ696 50 mg b.i.d. for 2 weeks will be randomized in a 1:1 ratio to receive LCZ696 100 mg b.i.d. or enalapril 5 mg b.i.d. (Figure 3-1) for 4 weeks during the double-blind treatment epoch. The patient randomization is stratified by using NT-proBNP measured at the screening visit as a stratification factor. The patients will then be titrated up to the target dose of LCZ696 200 mg b.i.d. or enalapril 10 mg b.i.d. if they tolerate 4 weeks treatment of LCZ696 100 mg b.i.d. or enalapril 5 mg b.i.d. Dose adjustment (LCZ 50-100 mg b.i.d. & enalapril 2.5-5 mg b.i.d.) is permitted if not tolerated at the target dose of study drugs during the double-blind treatment epoch (Section 5.5.5).

An open-label extension to the study will be conducted following the completion of the core part (Figure 3-2).

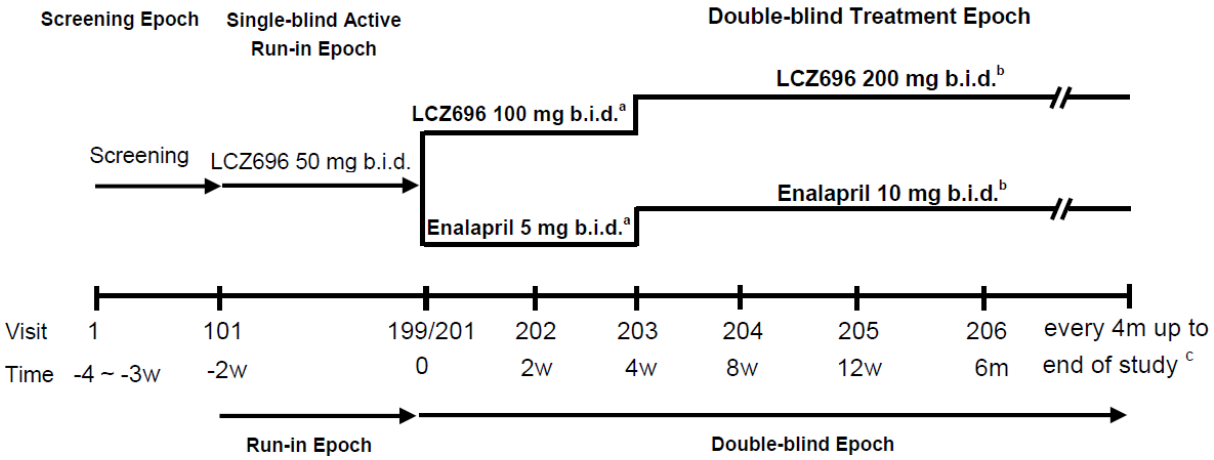
Every consenting trial participant who is eligible to receive study drug (refer to Section 4.1 and 4.2) will start the OLE epoch. For all patients, the first visit of the OLE epoch will occur on the same day as the EOS visit of the core part. At Visit 301, patients will be switched to an open-label LCZ696 from double-blinded study drug. Dose adjustments and temporary interruptions of study treatment are permitted if not tolerated during OLE epoch following the pre-specified protocol guidance (Section 5.5.5).

The core part will be event-driven in which patients will remain in the study (regardless of whether receiving investigational treatment) until the projected number of patients with primary events (approximately 57 events) has been reached.

It is planned that approximately 220 patients will be randomized and the total trial duration will be approximately 40 months, with a projected recruitment period of 22 months and a follow-up period of 18 months after the enrollment of the last patient into the trial. It is expected that the average follow-up time will be approximately 28.5 months.

The OLE epoch (Figure 3-2) is expected to continue until marketed product is available in Japan or for 2 years from the date of the first patient enrolled in the OLE epoch, whichever comes first.

Figure 3-1 Study design (Core)



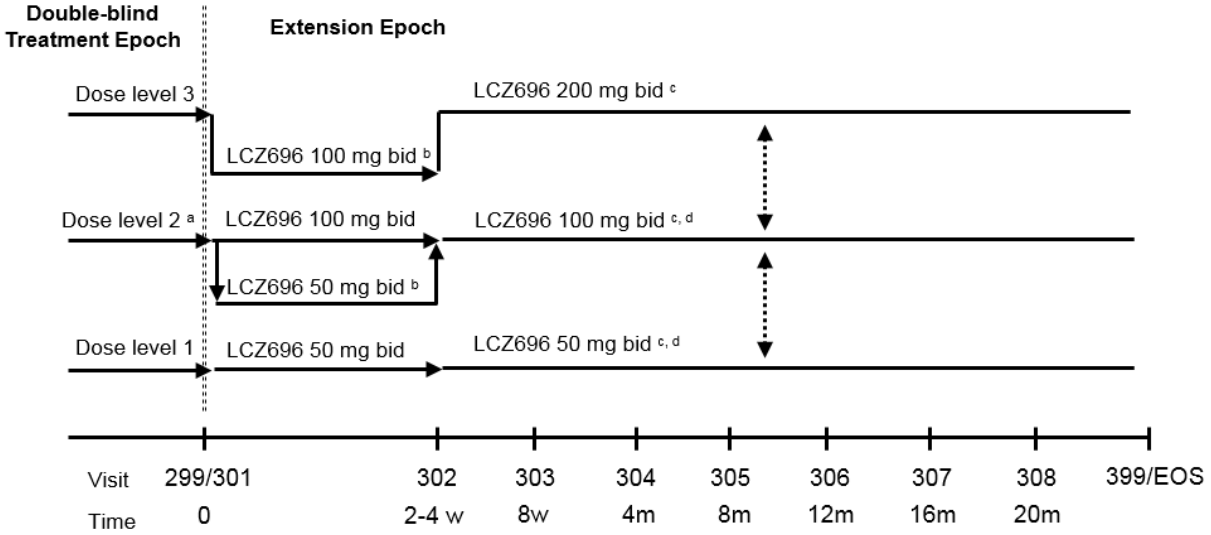
w = week; m = month

a Down-titration to lower dose level (LCZ 50 mg b.i.d. or enalapril 2.5 mg b.i.d.) is allowed if not tolerated during the first 4 weeks. Dosage should be up-titrated at Visit 203 if tolerated, and follow the general protocol guidance regarding maintenance dose (Section 5.5.5).

b Dose adjustment (LCZ 50-100 mg b.i.d. or enalapril 2.5-5 mg b.i.d.) is permitted if not tolerated at the target dose, ie, LCZ696 200 mg b.i.d. or enalapril 10 mg b.i.d., during the double-blind treatment epoch following the general protocol guidance regarding maintenance dose (Section 5.5.5).

c Projected duration of the trial is 40 months. Actual duration of the trial is event-driven.

Figure 3-2 Study design (OLE)



w = week; m = month

a Patients receiving double-blind study drug at dose level 2 have options to start with either the open-label LCZ696 100 mg b.i.d. (dose level 2) or LCZ696 50 mg b.i.d. (dose level 1) at the investigator's discretion.

b Dosage should be up-titrated at Visit 302 if tolerated in accordance with Table 3-3, and follow the general protocol guidance regarding maintenance dose (Section 5.5.5).

c Dose adjustment is permitted if not tolerated at the dose during the OLE epoch following the general protocol guidance regarding maintenance dose (Section 5.5.5).

d Attempt should be made to up-titrate and maintain the patient at the target LCZ696 dose (dose level 3) for as long as possible.

3.1.1 Study visits

3.1.1.1 Screening

Screening Visit (Visit 1)

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

At Visit 1, patients' eligibility for entering the active treatment run-in epoch will be assessed by the investigator. LVEF measurements required for eligibility will be based on locally obtained echocardiograms, MUGA scans, CT scans, MRIs, or ventricular angiographies performed within the last 6 months provided that no subsequent measurements were above 35%. If a LVEF measurement within the last 6 months is not available, the patient may enter the trial based on a LVEF $\leq$ 35% obtained during the screening epoch, i.e., before assigning any run-in study medication. If a patient has an implanted cardiac resynchronization therapy device, the LVEF values used to qualify for the study must be obtained at least three months after the implantation of that device. Screening NT-proBNP will be assessed by sending blood samples to the central laboratory and only patients with the required values per the entry criteria will be eligible for entering the treatment run-in epoch, which will begin at Visit 101. A patient may qualify for inclusion into the study based on a NT-proBNP value according to the inclusion criteria mentioned in Section 4.1.

Since it may take several days 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 101 approximately one to two weeks after Visit 1.

First morning urine void samples for biomarker assessments will be taken at Visit 101. Site should give the patient a urine collection container and instructions on how to collect the first morning urine void, which should be performed before returning to the site for Visit 101.

The site personnel should also instruct the patient not to take any ACEIs or ARBs on the day of Visit 101 and thereafter.

3.1.1.2 Single-blind active treatment run-in epoch

Patients who are successfully screened into the study at Visit 1 will enter the single-blind active treatment run-in epoch. Since this epoch will be a single-blind period, the site staff working with patients should exercise caution when discussing the study procedures and the study drug with patients to keep the patient blinded to the identity of the study drug.

Please refer to Table 6-1 for a detailed list of study procedures and assessment to be performed at each run-in epoch visit.

Visit 101

Once patients' eligibility has been ascertained, they will attend Visit 101 approximately one to two weeks after Visit 1 to start LCZ696 50 mg b.i.d. for 2 weeks. Patients should continue to take their background medications for CHF, with the exception of ACEIs or ARBs which must be discontinued at Visit 101.

If patients meet the criteria in Table 3-1, they will start to take the LCZ696 50 mg b.i.d. run-in medication the day after Visit 101. An approximately 36-48 hour wash-out period stopping concomitant ACEIs or ARBs should be included before the enrolled patients start taking the first dose of LCZ696. For example, if a patient's Visit 101 is on Wednesday, he/she must not take any doses of ACEIs or ARBs after the last dose on Tuesday. The patient will then start taking the first dose of LCZ696 50 mg b.i.d. run-in medication on Thursday morning.

End of treatment run-in visit (Visit 199)

A Visit 199 (end of treatment run-in visit) will be completed for all patients who enter the treatment run-in epoch. Patients not tolerating LCZ696 50 mg b.i.d. (Table 3-1) will be considered run-in failures and withdrawn from the study. For patients who discontinue during the treatment run-in epoch, Visit 199 will be their discontinuation visit.

Only patients who tolerate LCZ696 50 mg b.i.d. for 2 weeks will be eligible for randomization. For patients that are eligible to be randomized, Visit 199 will be their end of treatment run-in disposition visit and may be performed on the same day as Visit 201. Table 6-1 lists all procedures to be performed at Visit 199.

[redacted]

Safety and tolerability monitoring during the active treatment run-in epoch

Patients will be eligible for entering the run-in epoch at Visit 101, and for randomization at Visit 201 if they meet all the inclusion criteria and none of the exclusion criteria, including the serum potassium, eGFR, blood pressure, and postural symptoms listed in Table 3-1. Local laboratory assessments at Visits 1 and 199 are used to ascertain if patient doesn't meet the exclusion criteria of serum potassium and eGFR.

During the treatment run-in epoch, 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, such as hyperkalemia, hypotension, and renal dysfunction, in an attempt to allow patients to meet the safety criteria in Table 3-1. The doses of background disease modifying drugs, such as β-blockers or aldosterone antagonists, may be reduced to facilitate maintenance of study drug if in the opinion of the investigator they are believed to be the cause of the adverse effect in question.

The reason for patient discontinuation during the active treatment run-in epoch must be carefully documented in the appropriate eCRFs.

Patients who experience angioedema at any time during the treatment run-in epoch must be withdrawn from the study.

Table 3-1 Safety monitoring criteria that must be met at Visit 1 (screening) and Visit 199

Parameter	Visit 1 (screening)	Visit 199 (end of run-in)
Serum potassium level	K ≤ 5.2 mmol/L (mEq/L) (local assessment)	K ≤ 5.4 mmol/L (mEq/L) (local assessment)
Kidney function	eGFR ≥ 30 mL/min/1.73 m^2 (local assessment)	eGFR ≥ 30 mL/min/1.73 m^2 eGFR reduction ≤ 35% compared to Visit 1 (local assessments)
Blood pressure	No symptomatic hypotension and SBP ≥ 100 mmHg	No symptomatic hypotension and SBP ≥ 95 mmHg
Adverse events (AEs) or conditions	No postural symptoms or any conditions that preclude continuation according to the investigator's judgment	No postural symptoms or any AEs that preclude continuation according to the investigator's judgment

3.1.1.3 Double-blinded randomized treatment epoch

The randomized treatment epoch will begin at Visit 201. Patients who successfully complete the run-in and tolerate LCZ696 50 mg b.i.d. will be randomized to receive LCZ696 100 mg b.i.d. or enalapril 5 mg b.i.d. for 4 weeks and be up-titrated to the target dose of LCZ696 200 mg b.i.d. or enalapril 10 mg b.i.d. in a 1:1 ratio in a double-blind manner. Please refer to Table 6-1 for a detailed list of study procedures and assessment to be performed at each randomized treatment epoch visit.

The study medication will be added to the prescribed background HF therapy. Concomitant administration of ACEIs or ARBs with the study medication is strictly prohibited. Please refer to Section 5.5.7 for more information on co-administration of other medications.

Reported trial outcome endpoint events will be collected as they occur throughout the randomized treatment epoch. All laboratory evaluations for planned visits after randomization

will be performed through the central laboratory or other authorized laboratory. Unscheduled laboratory assessments can be performed locally as necessary.

Visit 201 will be considered the reference visit for all study visits during the randomized treatment epoch. Regardless of the occurrence of any unscheduled visits, scheduled visits should occur within the timeframe in relation to Visit 201 as outlined in Table 6-1.

Randomization Visit (Visit 201)

Patients who have met all the inclusion criteria and none of the exclusion criteria at the end of the active treatment run-in epoch will be randomized to either LCZ696 100 mg b.i.d. or enalapril 5 mg b.i.d. in a 1:1 ratio.

Site personnel should instruct the patient to refrain from taking their run-in medication on the day of Visit 201. Site personnel will document the date and time of the last dose of the LCZ696 run-in medication. This is necessary to ensure a 36-hour wash-out period to avoid overlapping of LCZ696 with enalapril and minimize the potential risk of occurrence of angioedema.

If appropriate, the patient will start to take the double-blind study medication (LCZ696 100 mg b.i.d. or enalapril 5 mg b.i.d.) the day after Visit 201. For example, if a patient's Visit 201 is on Wednesday, he/she must not take any doses of the LCZ696 50 mg b.i.d. run-in medication after Tuesday evening. The patient will then start taking the first dose of the double-blind study medication on Thursday morning.

Table 6-1 lists all procedures to be performed at Visit 201.

Visits 202 up to end visit for double-blind treatment epoch

In the first 6 months of the randomized treatment epoch, patients will return to the site for study visits at two, four, eight, twelve weeks and 6 months after randomization. Visits after the first 6 months of the randomized treatment epoch will be scheduled for every four months.

In addition to the protocol-required visits, patients may be seen at anytime throughout the study at the discretion of the investigator to follow any new laboratory abnormalities or AEs. All randomized patients should continue to receive double-blind treatment, if deemed appropriate by the investigator, until the trial is completed.

At Visit 203 (4 weeks after randomization), patients' medication compliance, safety, and tolerability of the study medication will be assessed, including signs and symptoms of hypotension, potassium level, and renal function. Dosage should be up-titrated to the target doses (LCZ696 200 mg b.i.d. or enalapril 10 mg b.i.d.) at Visit 203 if tolerated, and follow the general protocol guidance regarding maintenance dose (Section 5.5.5). Down-titration to lower dose level (LCZ 50 mg b.i.d. or enalapril 2.5 mg b.i.d.) is allowed if not tolerated during the first 4 weeks after randomization.

Monitoring of safety and tolerability will include: (1) hyperkalemia; (2) symptomatic hypotension; (3) increase in serum creatinine; (4) angioedema; and (5) AEs and SAEs. If, in the opinion of the investigator, the patient cannot 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 modified to rectify the situation before considering reducing the

dose of the study drug to the lower dose level. The dose of background disease modifying drugs, such as β-blockers and aldosterone antagonists, may be modified to facilitate maintenance of study drug if they are believed to be the cause of the adverse effect in question. If the situation is not rectified despite adjusting/discontinuing other concomitant medications or if adjusting other concomitant medications is not possible, patients who no longer tolerate the intermediate or target doses at any time during the double-blind treatment epoch of the trial can be down-titrated to the lower dose level at the investigator's discretion (please refer to Table 5-1 for dose levels available for titration). However, every attempt should be made to re-challenge the patients so that they are kept on the maximal tolerated dose of study drug for as long a duration as possible throughout the randomized treatment epoch of the trial. Please refer to Section 5.5.5 for guidance on study drug dose adjustment.

If the study drug is temporarily discontinued, it should be reintroduced as soon as medically justified in the opinion of the investigator. After randomization, study drug discontinuation for any reason does not constitute withdrawal from the study and should not lead to the patient being withdrawn from the study. On the contrary, even patients who have stopped taking study drug are expected to attend all the protocol specified study visits and perform all measurements as stipulated in the visit schedule. In case it is not possible for the patient to attend any visit(s), the site staff will keep in touch with the patient by means of regular phone contact with the patient himself/herself or with the person pre-designated by the patient accordance with the patient's study visit schedule. Data will continue to be collected about the patient's health status, including information on developing of cardiovascular complications and vital status. This information may be provided by either the patient himself/herself or patient's designee. Data, such as information on survival information and potential protocol-specified endpoint, might be also collected from a health care provider, or other sources as available as allowed by local regulation or restriction. These data will be collected until the conclusion of the study, even if the patient is no longer attending the study visits in person.

[redacted].

All randomized patients will remain in the trial until the projected number of primary endpoint (composite of CV death or HF hospitalization) is reached. Table 6-1 lists all procedures to be performed at Visit 202 and all the remaining visits in the study.

Patients will be instructed to take the last dose of the double-blind study drug on the day before the core part EOS visit (Visit 299), and visit the study sites without taking the study drug on the day of Visit 299.

3.1.1.4 Open-label extension (OLE) epoch

Upon completion of the core part of study, all eligible trial patients will be offered the option to enter the OLE epoch. Informed consent will be obtained at Visit 301, the start of the OLE epoch, and before any study-specific procedure for OLE epoch is performed. The last dose of study medication that the patient is taking during the core part should be considered in determining the starting dose level of LCZ696 (Table 3-2). The same principles of study drug monitoring for safety and tolerability during the core part must be applied during the OLE.

Treatment guidelines for hyperkalemia, management of BP and renal dysfunction are provided in Appendix 3, Appendix 4 and Appendix 5, respectively. Please refer to Table 6-2 for a detailed list of study procedures and assessment to be performed at each OLE epoch visit.

Attempt should be made to up-titrate and maintain the patient at the target LCZ696 dose (dose level 3) as soon as possible. At Visit 302 (Week 2-4), patients who meet the safety monitoring criteria (Table 3-3) and tolerate open-label LCZ696 should be up-titrated to the next higher level of daily dose. If patient does not meet the safety monitoring criteria, then investigator should try to modify background medication in line with Section 5.5.5 in order to re-challenge the patient with a higher dose level at the earliest possible opportunity.

The study medication will be added to the prescribed background HF therapy. Concomitant administration of ACEIs or ARBs with the study medication is strictly prohibited. Please refer to Section 5.5.7 for more information on co-administration of other medications.

Unlike the double-blind epoch, permanent discontinuation of study drug constitutes withdrawal from the study.

Visit 301 will be considered the reference visit for all study visits during the OLE epoch. Regardless of the occurrence of any unscheduled visits, scheduled visits should occur within the timeframe in relation to Visit 301 as outlined in Table 6-2.

Table 3-2 Starting dose levels of open-label LCZ696 at the start of the OLE epoch

Final dose level of study medication during the double-blind treatment epoch	Corresponding dose levels of open-label LCZ696 treatment upon entering OLE
3	100 mg b.i.d.
2	50 mg b.i.d. or 100 mg b.i.d. [a]
1	50 mg b.i.d.
No treatment	50 mg b.i.d.

a The patient receiving double-blind study drug at dose level 2 has options to start with either the open-label LCZ696 100 mg b.i.d. (dose level 2) or LCZ696 50 mg b.i.d. (dose level 1) at the investigator's discretion.

Table 3-3 Safety monitoring criteria for up-titration at Visit 302 (Week 2 to 4)

Parameter	Visit 302 (Week 2 to 4)
Serum potassium level	K ≤ 5.4 mmol/L (mEq/L) (local assessment)
Kidney function	eGFR ≥ 30 mL/min/1.73 m^2 eGFR reduction ≤ 35% compared to Visit 301 (local assessments)
Blood pressure	No symptomatic hypotension and SBP ≥ 95 mmHg.
AEs or conditions	No postural symptoms or any AEs that preclude continuation according to the investigator's judgment

OLE epoch initiation visit (Visit 301)

All patients must provide informed consent before any study-specific procedure for OLE epoch is performed. At Visit 301, patients' eligibility for entering the OLE epoch will be assessed by the investigator.

Patients will start the OLE epoch at this visit. This first visit of the OLE epoch will occur on the same day as the end of study (EOS) visit of the core part. Patients will be switched to an open-label LCZ696 at this visit. The patients receiving double-blind study drug at dose level 3 will start with open-label LCZ696 100 mg b.i.d. (dose level 2) (Table 3-2). The patients receiving double-blind study drug at dose level 2 will start with either open-label LCZ696 50 mg b.i.d. (dose level 1) or LCZ696 100 mg b.i.d. (dose level 2) at the investigator's discretion. The patients receiving double-blind study drug at dose level 1 will be also switched to an open-label LCZ696 but remain at same dose level (LCZ696 50 mg b.i.d.) up to Visit 302. Patients should continue to take their background medications for HF, with the exception of ACEIs or ARBs. The patients who have discontinued the double-blind study drug before this visit may be enrolled if eligible, however, should start with taking the LCZ696 50 mg b.i.d. (dose level 1).

Prior to Visit 301, site personnel should instruct the patient to refrain from taking their double-blind study drug or the open-label ACEIs received by those patients who are not on double-blind study drug treatment on the day of Visit 301. This is necessary to ensure a 36-hour wash-out period to avoid overlapping of LCZ696 with enalapril or the open-label ACEIs and minimize the potential risk of occurrence of angioedema. In case patient comes to visit after having taken the double-blind study drug or the open-label ACEIs at Visit 301, the assessments could nevertheless be conducted. In this case, patient should start taking open-label LCZ696 at least approximately 36 hours after the last dose of double-blind study drug or the open-label ACEIs.

The patients who have discontinued the double-blind study drug and are instead receiving open-label ARBs or renin inhibitors, are allowed to take these drugs on the day of Visit 301; however, approximately 12 hours should transpire between the first dose of open-label LCZ696 and the last dose of open-label ARB or renin inhibitor.

Site personnel will document the date and time of the last dose of the double-blind study drug or open-label ACEIs/ARBs/renin inhibitors prior to Visit 301 on source document at site.

The patient will start to take the open-label LCZ696 the day after Visit 301. For example, if a patient's Visit 301 is on Wednesday, he/she must not take any doses of the double-blind study drug after Tuesday evening. The patient will then start taking the first dose of the open-label LCZ696 on Thursday morning.

Table 6-2 lists all procedures to be performed at Visit 301.

Visits 302 up to end of study (EOS) visit for OLE epoch

In the first 4 months of the OLE epoch, patients will return to the site for study visits at two to four weeks, at eight weeks and 4 months. Visits after the first 4 months will be scheduled for every four months.

In addition to the protocol-required visits, patients may be seen at anytime throughout the study at the discretion of the investigator to follow any new laboratory abnormalities or AEs. All patients should continue to receive open-label LCZ696, if deemed appropriate by the investigator, until the trial is completed.

At Visit 302, patients' medication compliance, safety, and tolerability of the study medication will be assessed, including signs and symptoms of hypotension, potassium level, and renal function. The patients who meet the safety monitoring criteria (Table 3-3) and tolerate open-label LCZ696 should be up-titrated to the next higher level of daily dose and follow the general protocol guidance regarding maintenance dose (Section 5.5.5). If patient does not meet the safety monitoring criteria per Table 3-3, the investigator should try to modify background medication in line with Section 5.5.5 in order to re-challenge the patient with a higher dose level at the earliest possible opportunity.

The investigator should aim to up-titrate the open-label LCZ696 dose to the target dose level of 200 mg bid by 8 weeks, although a slower up-titration schedule is also allowed per patient's safety and tolerability.

The investigator should follow the same instructions for the double-blind treatment epoch on the monitoring of safety and tolerability, and the adjustments/discontinuation of concomitant medications when the patient cannot tolerate the dose of study drug. Please refer to Section 5.5.5 for guidance on study drug dose adjustment.

If the study drug is temporarily discontinued, it should be reintroduced as soon as medically justified in the opinion of the investigator. Meanwhile, permanent discontinuation of study drug during the OLE epoch constitutes withdrawal from the study.

Table 6-2 lists all procedures to be performed at Visit 302 and all the remaining visits in the study.

3.2 Rationale of study design

A randomized, double-blind, parallel group, active-controlled study is a well-established design to evaluate the efficacy and safety of investigational drugs for HF. The core part is comprised of three epochs, screening epoch, a single-blind active treatment run-in epoch and a double-blind randomized treatment epoch. A randomized treatment epoch is established to evaluate the effect of LCZ696 at a target dose of 200 mg b.i.d. compared to enalapril 10 mg b.i.d.

Requisite conditions for approval of CHF drugs in Japan are described in Japanese Guidelines for Clinical Evaluation of Drugs for Heart Failure (Ministry of Health, Labour and Welfare 2011). It indicates HF drug approval may be considered in case positive results of outcome study outside Japan are available and the results of clinical study in Japanese patients on morbidity show the same trends as overseas, even when it is impossible to conduct a clinical trial of a scale that can statistically investigate significant improvement in morbidity in Japan.

Recently, the superiority of LCZ696 over enalapril on the reduction of CV death and HF hospitalization in patients with HF-rEF was demonstrated in overseas outcomes study (PARADIGM-HF, CLCZ696B2314) (McMurray et al. 2014). Therefore, this study (CLCZ696B1301) is designed to align with the guideline requirement for drug approval, to observe a similar trend of LCZ696 better than enalapril in reducing morbidity and mortality in

Japanese HF patients and capture data of the efficacy variables of PARADIGM-HF so that the efficacy of LCZ696 over enalaprill in Japanese HF patients can be assessed in aspects comparing with PARADIGM-HF study outcomes.

Open-label study design is adopted for the OLE epoch because the main objective of this epoch is to provide access to LCZ696 for the eligible patients and also to obtain the safety and tolerability data of long-term treatment with LCZ696.

3.2.1 Rationale for primary endpoint

Apart from improving symptoms, there is general agreement that the major goal of treating HF with a reduced LVEF is to reduce the major fatal and non-fatal consequences of this illness, i.e., CV death and hospitalization for worsening HF. CV death accounts for approximately 80% of all deaths in HF patients and most CV deaths are due to either sudden (presumed arrhythmic) death or death due to worsening heart (i.e., pump) failure. Hospitalization for worsening HF is the single most common cause of hospital admission in this patient population and is an ominous development in that it portends high subsequent risk–both of readmission and of death. HF hospitalization is also the main driver of the huge economic burden of this syndrome.

As CV death and HF hospitalization both reflect disease-specific endpoints related to progressive worsening of the HF syndrome, they should both be modifiable by treatments improving this condition, which has generally proved to be the case with both drugs (ACEIs, aldosterone antagonists, and β-blockers) and devices (cardiac resynchronization therapy). This understanding of HF and its treatment has led to the disease-specific composite outcome of CV death or HF hospitalization becoming the most commonly used primary endpoint in current HF outcomes trials.

In Japan, it is referred in Japanese Guidelines for Clinical Evaluation of Drugs for Heart Failure that total mortality, cardiovascular morbidity, and subjective complaints are considered appropriate as the primary endpoints of HF studies (Ministry of Health, Labour and Welfare 2011).

3.2.2 Rationale for treatment run-in epoch

Patients start to receive LCZ696 50 mg b.i.d. in the single-blind active treatment run-in epoch. During the treatment run-in epoch, patients will continue their background HF medications except ACEI and ARB. Patients unable to tolerate LCZ696 50 mg b.i.d. during the treatment run-in will not be eligible for randomization, and will be discontinued from the study. This design will enable to maximize the number of patients who tolerate at least the lowest dose level (dose level 1) of LCZ696 throughout the double blind treatment epoch with long-term follow-up.

There are two short washout periods (approximately 36-48 hours for each) during the treatment run-in epoch to minimize the potential risk of angioedema due to overlapping ACE-NEP inhibition at Visit 101 and Visit 201 (Section 6.5.7): (1) after completing the screening epoch receiving conventional ACEIs or ARBs and prior to beginning the LCZ696 run-in at Visit 101, and (2) after completing the LCZ696 run-in and prior to starting randomized study drug at Visit 201.

On the other hand, the risk of HF deterioration associated with stopping concomitant ACEIs or ARBs for approximately 36-48 hours, the duration of the ACEI/ARB-free period, will be minimal, especially since all patients will be allowed to continue receiving their background HF and CV medications.

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

LCZ696 200 mg is associated with ~84% (95% CI, 64 - 100%) of maximum cGMP increase (AUEC), indicating near maximal neprilysin inhibition. The target dose of 200 mg b.i.d. has been examined in the completed PARADIGM-HF outcome trial evaluating the effect on morbidity and mortality in patients with HF-rEF (McMurray et al. 2014). The administration of LCZ696 200 mg b.i.d. demonstrated significantly greater effect on delaying time to first occurrence of morbidity and mortality events than enalapril 10 mg b.i.d. LCZ696 200 mg b.i.d. was also well tolerated in this study, with the frequency of overall adverse events similar to enalapril.

In addition, the efficacy and safety of LCZ696 400 mg once daily have been demonstrated in Japanese hypertensive patients. In a Phase III pivotal study (CLCZ696A1306) comparing LCZ696 to an ARB olmesartan, a total of 1,161 hypertensive patients received LCZ696 (200 mg or 400 mg once daily, n=772) or olmesartan (20 mg once daily, n=389) for 8 weeks. This study showed LCZ696 was superior to olmesaltan in blood pressure lowering effect in hypertensive patients. LCZ696 200 mg and 400 mg daily doses were shown safe and well-tolerated in hypertension clinical program, including the long-term treatment of 12 months in more than 150 Japanese hypertensive patients.

In order to adequately manage patient's safety and tolerability, optional titration design is adopted in this study, and dose adjustments and temporary interruptions of study treatment are also permitted during double blind treatment epoch following the pre-specified protocol guidance on maintenance dose.

Rather than 400 mg once daily dosing of LCZ696 that was used in the hypertension study, this dose will be split and LCZ696 will be dosed at 200 mg twice daily in the current HF-rEF study. This will ensure sustained NEP inhibition over 24 hours, which is thought to be critical for patients with HF. Furthermore, twice daily dosing regimen is anticipated to reduce the incidence of post-dose hypotension in HF patients, particularly in elderly patients.

This core part is an event driven, outcomes trial. The end of the core part will occur when the pre-specified number of patients achieves the primary composite endpoint of CV deaths or hospitalizations for HF (approximately 57 patients). As an event driven trial, the actual length of the trial will depend on the observed event rates, the patient accrual rate, and length of the accrual period. Patient should continue to attend the core part and receiving study drugs until the completion of the core part. As planned, it is expected to be up to 40 months: total study sample size of 220 patients with a recruitment period of approximately 22 months and a minimal follow-up of 18 months.

The main purpose of the OLE is to provide access to LCZ696 for the eligible patients and also to assess the safety and tolerability data of long-term treatment with LCZ696. The OLE epoch

will continue until marketed product is available in Japan or approximately for 2 years from the date of the first patient enrolled in the OLE epoch, whichever comes first.

The patients receiving double-blind study drug at dose level 3 will be switched to an open-label LCZ696 and start taking the open-label LCZ696 at the next lower dose level to ensure the patient's safety, then the dosage will be up-titrated to the original dose level after a short period if tolerated.

3.4 Rationale for choice of comparator

An ACEI has been selected as the active comparator in this study since major clinical trials have established ACEI treatment as the standard of care for RAS blockade and are recommended by treatment guidelines as the treatment of choice for all patients with HF-rEF, unless ACEI-intolerant. 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 CONSENSUS (CONSENSUS Trial Study Group 1987), SOLVD-Treatment (SOLVD Investigators 1991), and SOLVD-Prevention (SOLVD Investigators 1992).

Enalapril dose of 10 mg b.i.d. 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 compared to placebo (SOLVD Investigators 1991). Approved dosage of enalapril for CHF in Japan is 10 mg/day at maximum. While the clinical benefits at this dose level of enalapril in Japanese CHF patients was demonstrated by assessing the global improvement rating (Niitani et al. 1990), no study assessing the effect of enalapril on morbidity and mortality have been conducted in Japan. Enalapril dose of 10 mg b.i.d. was shown generally well tolerated in PARADIGM-HF study, which included more than 1,500 Asian HF-rEF patients participating in the trial. Considering these backgrounds, higher dosage of enalapril has been applied in this study to evaluate the potential effect of LCZ696 on morbidity and mortality in Japanese patients, compared to a standard-of-care enalapril at the dose associated with survival benefit.

3.5 Purpose and timing of interim analyses/design adaptations

Not planned.

3.6 Risks and benefits

Patients will be instructed not to take any open-label RAS blockade medications (eg., ACEIs or ARBs) once they enter the run-in, and also throughout the double-blind epochs and OLE epoch. The risk of wash-out of concomitant ACEIs/ARBs for 36-48 hours prior to the first dosing of LCZ696 for the run-in period or withholding the randomized medications and the open-label LCZ696 on the day entering the double-blind treatment epoch and the OLE epoch, respectively, to reduce the risk of angioedema will be minimal as all patients will still continue to receive the other background HF therapies such as β-blockers and/or MRAs during the course of study.

In addition, the risk to patients enrolled in this trial will be minimized by compliance with the eligibility criteria and close clinical monitoring comprising of the protocol-defined dose

adjustment and pre-specified criteria for drug-related adverse changes in blood pressure, potassium and/or renal function, etc.

Women of child bearing potential should be informed that taking the study drug 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.

Since this is a long-term outcome study, participating patients will benefit from careful clinical monitoring and follow-up during the entire study duration.

The OLE epoch following the double-blind core part allows the seamless availability of open-label LCZ696 to eligible patients which avoids the prolonged treatment interruption.

4 Population

The study population will consist of patients with CHF (NYHA class II-IV), aged 20 years or older with LVEF ≤ 35%. Eligible patients should also be on a stable dose of an ACEI or an ARB for at least 4 weeks before entering into the study. Patients from approximately 50 research sites will be randomized in a 1:1 ratio to either LCZ696 treatment arm or enalapril treatment arm. The patient randomization is stratified by using NT-proBNP measured at the screening visit as a stratification factor. In order to randomize approximately 220 patients (110 patients in each arm), it is estimated that approximately 370 patients will have to be screened as the screen or run-in failure rate is anticipated to be approximately 40%.

All participants of the core part who are eligible to receive study drug will be offered the option to enter the OLE. It is anticipated that approximately 180 patients will complete the core part of the study and that the majority of them will be enrolled into the OLE.

4.1 Inclusion criteria

Patients eligible for inclusion in the core part have to fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Outpatients ≥ 20 years of age (at the time of signing informed consent), male or female.
3. Patients with a diagnosis of CHF NYHA class II-IV and reduced ejection fraction:
   - LVEF ≤ 35% at Visit 1 (any local measurement, made within the past 6 months using echocardiography, MUGA, CT scanning, MRI or ventricular angiography is also acceptable, provided no subsequent measurement above 35%)
   - NT-proBNP ≥ 600 pg/ml at Visit 1 **OR** NT-proBNP ≥ 400 pg/ml at Visit 1 and a hospitalization for HF within the last 12 months (according to central laboratory measurements)
4. Patients must be on an ACEI or an ARB at a stable dose for at least 4 weeks before Visit 1.
5. Patients must be treated with a β-blocker, unless contraindicated or not tolerated, at a stable dose for at least 4 weeks prior to Visit 1 (reason should be documented if patients reported contraindications or intolerance).
6. 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, and should be stable for at least 4 weeks prior to Visit 1. Other evidence-based therapy for HF should also be considered e.g. cardiac resynchronization therapy and an implantable cardioverter-defibrillator in selected patients, as recommended by guidelines.

Patients eligible for inclusion into the open-label extension must fulfill the following criteria:

7. Written informed consent for the open-label extension must be obtained before any assessment is performed.
8. Patients who have completed the double-blind treatment epoch and are able to be safely enrolled into the OLE as judged by the investigator.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in the core part. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes, ACEIs, ARBs, NEP inhibitors as well as known or suspected contraindications to the study drugs.
2. Previous documented history of intolerance to ACEIs or ARBs.
3. Known history of angioedema.
4. Requirement of treatment with both ACEIs and ARBs.
5. Current acute decompensated HF (exacerbation of chronic HF manifested by signs and symptoms that may require intravenous therapy).
6. Symptomatic hypotension and/or a SBP < 100 mmHg at Visit 1 (screening) or < 95 mmHg at Visit 199 (end of run-in).
7. Estimated GFR < 30 mL/min/1.73 m^2 as measured by the Japanese formula at Visit 1 (Screening), or Visit 199 (end of run-in) or > 35% decline in eGFR between Visit 1 and Visit 199 (according to local measurements).
8. Serum potassium > 5.2 mmol/L (mEq/L) at Visit 1 (screening) or > 5.4 mmol/L (mEq/L) at Visit 199 (end of run-in) (according to local measurements).
9. 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.
10. Coronary or carotid artery disease likely to require surgical or percutaneous intervention within the 6 months after Visit 1.
11. 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 to 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.
12. Heart transplant or ventricular assistance device (VAD) or intent to transplant (on transplant list) or implant a VAD.
13. History of severe pulmonary disease.

14. Diagnosis of peripartum or chemotherapy induced cardiomyopathy within the 12 months prior to Visit 1.
15. Documented untreated ventricular arrhythmia with syncopal episodes within the 3 months prior to Visit 1.
16. Symptomatic bradycardia or second (except asymptomatic Wenckebach block) or third degree heart block without a pacemaker.
17. Presence of hemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation secondary to left ventricular dilatation.
18. Presence of other hemodynamically significant obstructive lesions of left ventricular outflow tract, including aortic and sub-aortic stenosis.
19. Presence of bilateral renal artery stenosis.
20. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in-situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
21. Presence of any other disease with a life expectancy of < 3 years.
22. 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
    - Evidence of hepatic disease as determined by any one of the following: AST or ALT values exceeding 3 × the upper limit of normal (ULN), bilirubin values exceeding 1.5 × the ULN at Visit 1, history of hepatic encephalopathy, history of esophageal varices, or history of portacaval shunt
    - Active treatment with cholestyramine or colestipol resins
23. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days, whichever is longer.
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.
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 7 days off study medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 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, 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*

  *: not approved in Japan, approved methods should be used.

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

  Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. , age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 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.

Patients fulfilling any of the following criteria at Visit 301, are not eligible for inclusion in the OLE epoch. No additional exclusions may be applied by the investigator.

26. Patients who discontinued study drug treatment during the core part due to an event or intercurrent illness. Eligibility can be re-considered if the event has resolved and no longer represents a risk to the patient and the patient can safely tolerate the administration of LCZ696 per the investigator's assessment.
27. Any medical condition that in the opinion of the investigator is likely to prevent the patient from safely tolerating LCZ696 or complying with the requirements of the study.
28. Patients who have experience of angioedema event(s) which occurred and reported by the investigator during the core part of study.
29. 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.
30. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment and for 7 days after stopping study treatment. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 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 Visit 301). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- Use of oral, injected* or implanted* hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception*.

  *: not approved in Japan, approved methods should be used.

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

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. , age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least 6 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.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Treatment run-in epoch

All eligible patients will enter an active treatment run-in epoch during which they will be exposed to LCZ696 treatment.

The following study drugs will be provided:

- LCZ696 50 mg film-coated tablets (LCZ696 dose level 1)
- Placebo to match enalapril 2.5 mg tablets (placebo matching enalapril dose level 1)

Patients will be required to take the single-blind LCZ696 50 mg and placebo to match enalapril 2.5 mg twice daily in addition to their conventional concomitant therapy (except for ACEI or ARB).

Randomized treatment epoch

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. The use of an ACEI or an ARB in addition to study drug 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)
- Placebo to match LCZ696 100 mg film-coated tablets (placebo matching LCZ696 dose level 2)
- 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 tablets (enalapril dose level 1)
- Placebo to match enalapril 2.5 mg tablets (placebo matching enalapril dose level 1)
- Enalapril 5 mg tablets (enalapril dose level 2)
- Placebo to match enalapril 5 mg tablets (placebo matching enalapril dose level 2)
- Enalapril 10 mg tablets (enalapril dose level 3)
- Placebo to match enalapril 10 mg tablets (placebo matching enalapril dose level 3)

Target doses: LCZ696 200 mg b.i.d. and enalapril 10 mg b.i.d.

Patients not tolerating the intermediate and target dose (LCZ696 100-200 mg b.i.d. or enalapril 5-10 mg b.i.d.) will be titrated down to the lower dose level twice a day, at the investigator's discretion, based on the defined safety and tolerability criteria (Appendix 3, Appendix 4 and Appendix 5).

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 high density polyethylene (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 blister packs. LCZ696 and enalapril will be packaged separately to limit the number of pack types which will allow more flexibility in the drug supply process to cover all the different treatment possibilities (treatment arm and medication level) (Section 5.5.4).

Open-label extension epoch

All eligible patients will receive open-label LCZ696 twice daily in addition to optimal background HF therapy, as considered appropriate by the investigator and in accordance with standard therapy guidelines. The use of an ACEI or an ARB in addition to the study drug throughout the OLE epoch is strictly prohibited.

The sponsor will provide the following open-label extension study drugs in bottles:

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

5.1.2 Additional study treatment

The patient should be on an optimal medical regimen of background HF medications. This must include an individually optimized dose of a β-blocker at a stable dose for at least 4 weeks prior to study entry, unless contraindicated or not tolerated. Use of an aldosterone antagonist should be considered if indicated in patients eligible for this study (see Section 5.5.7).

5.2 Treatment arms

At randomization visit, patients will be assigned to double-blind treatment groups in a ratio of 1:1 of either:

- LCZ696 200 mg b.i.d.: patients will start with 100 mg b.i.d. for 4 weeks at Visit 201, patients will then be up-titrated to 200 mg b.i.d. at Visit 203 if they are tolerant to 100 mg b.i.d.
- Enalapril 10 mg b.i.d.: patients will start with 5 mg b.i.d. for 4 weeks at Visit 201, patients will then be up-titrated to 10 mg b.i.d. at Visit 203 if they are tolerant to 5 mg b.i.d.

In the OLE epoch, all patients will receive open-label LCZ696 administered twice daily.

5.3 Treatment assignment, randomization

At Visit 201, 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 by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Randomization will be stratified by the level of NT-pro BNP obtained at Visit 1 (≥ or < 1600 pg/ml).

No randomization process will be applied to the OLE epoch. During the OLE, all patients will be treated with LCZ696. IRT system will be used to enroll patients into the OLE epoch and dispense study drug in the same manner as in the randomized treatment epoch described above.

5.4 Treatment blinding

Single-blind LCZ696 will be dispensed to patients during the active treatment run-in epoch. During the active treatment run-in epoch, patients will receive LCZ696 and placebo to match enalapril. 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 the core part 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 investigational treatment that are all identical in packaging, labeling, schedule of administration, appearance, and odor. A double-dummy design is used because the identity of the investigational treatment cannot be disguised, as the drug products are visibly different. Unblinding will only occur in the case of patient emergencies (see Section 5.5.12) and at the conclusion of the core part. [redacted]

In the OLE, the treatment will not be blinded to either the investigators or the patients.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused. The same Subject Number will be used throughout the core part and open label extension epoch of the study.

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site 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 Disposition CRF.

5.5.2 Dispensing the investigational treatment

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

The investigational treatment packaging has a 2-part label. A unique randomization number is printed on each part of this label which corresponds to one of the two treatment arms for the double-blind epoch or LCZ696 for the OLE epoch, and a dose level. 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. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

Medication labels will comply with the legal requirements of each country. They will include storage conditions for the investigational treatment but no information about the patient except for the medication number.

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 monitors during site visits or remotely 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 double-blind study drug, 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 double-blind treatment epoch. Patients participating the OLE epoch will be required to take one LCZ696 tablet twice a day for the duration of this epoch.

Patients will receive LCZ696 50 mg and placebo to match enalapril 2.5 mg (dose level 1) twice daily during the active treatment run-in epoch. Table 5-1 and Table 5-2 summarizes the study drug that will be taken during the randomized treatment epoch and the OLE epoch, respectively.

Table 5-1 Study drug dispensed during the randomized treatment epoch

Study visit	Dose level	LCZ696	Enalapril
Visit 203 and all subsequent visits	3[a]	200 mg or matching placebo b.i.d.	10 mg or matching placebo b.i.d.
Available for any visit after Visit 201	2[b]	100 mg or matching placebo b.i.d.	5 mg or matching placebo b.i.d.
Available for any visit after Visit 201	1[c]	50 mg or matching placebo b.i.d.	2.5 mg or matching placebo b.i.d.

a 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.

b Up to Visit 203 after randomization, or if dose level 3 is not tolerated despite modification of other non-disease-modifying or disease-modifying medications.

c Only if dose level 2 is not tolerated despite modification of other non-disease-modifying or disease-modifying medications.

Table 5-2 Study drug dispensed during the OLE epoch

Study visit	Dose level	LCZ696
Visit 302 and all subsequent visits	3 [a]	200 mg b.i.d.
Available for any visit after Visit 301	2	100 mg b.i.d.
Available for any visit after Visit 301	1	50 mg b.i.d.

a This dose level should be attempted and maintained for as long 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.

Patients will be instructed to take their morning study drug doses at approximately 8 AM and their evening study drug doses at approximately 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 in the IRT and on the Dosage Administration Record eCRF.

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

5.5.5 Permitted dose adjustments and interruptions of study treatment

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

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 (dose level 3), the investigator should consider whether non-disease-modifying medication (e.g., CCBs, diuretics, nitrates, α-blockers) can be modified 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 (e.g., β-blockers, aldosterone antagonists) if it is believed that they are the most likely cause of the adverse effect. If adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern, the investigator may down-titrate the dose of the study drug to the next lower level up to complete withdrawal of the study drug. 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 target dose level of study drug 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 3, Appendix 4 and Appendix 5 for treatment guidelines for hyperkalemia, management of BP, and renal dysfunction, respectively).

Adjustment of study drug dose level

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

Study drug dose adjustments during the single-blind treatment run-in epoch – There are no study drug dose adjustments in run-in epoch. Patients not tolerating LCZ696 50 mg b.i.d. will be considered run-in failures and withdrawn from the study.

Study drug dose adjustments during the double-blind randomized treatment epoch – During the randomized treatment epoch, down-titration of the study drug at any time will be allowed based on the safety and tolerability criteria defined in Appendix 3, Appendix 4 and Appendix 5. If down-titration is necessary, the patient should be down-titrated to the next lower dose level (Table 5-1). The patient may continue receiving the lower dose level for a recommended period of 1 to 4 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 4 weeks. Then, he/she should be re-challenged with up-titration back to dose level 3.

If the tolerability issues are not alleviated despite down-titration by one dose level, the investigator may lower the study drug dose further to the next lower level for 1 to 4 weeks, up to temporary withdrawal of the study drug. Again, once stable, the patient should be re-challenged with up-titration to the next higher dose level every 1 to 4 weeks in an attempt to bring back the patient gradually to the target study drug dose level (dose level 3). As discussed in Section 5.3, the IRT should be contacted to register any changes in the patient's study drug dose level, including in cases of temporary and permanent withdrawal of the study drug, and to obtain the medication numbers of the study drug supplies required for the new study drug dose level.

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

Study drug dose adjustments during the OLE epoch – The investigator should follow the same dosing instruction as the double-blind treatment epoch for the dose adjustment of open-label LCZ696 during the OLE epoch.

Study drug restart after temporary treatment interruption

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

Once the investigator considers the patient's condition appropriate for receiving 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 3, Appendix 4 and Appendix 5, the patient should be up-titrated up to the target dose level 3 every 1 to 4 weeks, as per the investigator's judgment. 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 again and a new attempt to up-titrate or reintroduce the study drug could be considered by the investigator as soon as medically justified in his/her medical judgment. This will also apply to the OLE epoch.

Study visits should occur as close as possible to the time points indicated in Table 6-1 (core part) or Table 6-2 (OLE epoch). 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 or Table 6-2. For example, if the patient's treatment needs to be adjusted between Visit 206 and Visit 207, Visit 207 will still be planned 4 months after Visit 206, irrespective of the number of unscheduled visits that may have occurred between these two visits or the additional period that the medication pack dispensed could have covered.

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 and registered in the IRT.

In case of pregnancy discovered during the treatment run-in epoch, the patient will be withdrawn from the study immediately.

In case of pregnancy discovered during the randomized treatment epoch, the patient should be instructed to stop taking the study drug immediately. Study drug intake should be resumed as soon as possible after the completion of the pregnancy and lactation period. Meanwhile, the patient should continue to attend scheduled study visits.

In case pregnancy is discovered during the OLE epoch, the patient should be instructed to stop taking the study drug immediately and must be withdrawn from the study.

See Section 7.4 for further details on pregnancies and reporting guidelines.

5.5.6 Rescue medication

Guidance on handling hyperkalemia, hypotension, and renal dysfunction are provided to investigators in Appendix 3, Appendix 4 and Appendix 5, respectively. Patients may receive open-label ACEIs and/or ARBs during the double-blind treatment epoch **ONLY** if the study medication has been discontinued either temporarily or permanently.

Patients may receive open-label ACEIs and/or ARBs during the OLE epoch **ONLY** if the study medication has been temporarily discontinued. Permanent discontinuation of study drug during the OLE epoch constitutes withdrawal from the study. In this case, patients may receive open-label ACEIs and/or ARBs after withdrawal from the study. Resuming ACEI therapy requires a 36 hours washout from the last LCZ696 dose.

Use of rescue medication must be recorded on the Concomitant medications in the eCRF.

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.

Heart failure medications and other cardiovascular medications

The patient should be on an optimal medical regimen of background HF medications. This must include an individually optimized dose of a β-blocker at a stable dose for at least 4 weeks prior to study entry, unless contraindicated or not tolerated. Use of an aldosterone antagonist should be considered in patients eligible for this study. Every effort should be made to keep the dose level of these disease-modifying background HF medications stable throughout the entire study. However, if the patient's condition warrants a change in any of these medications (for example, if the investigator believes a disease-modifying medication is causing an adverse event), it is allowed at the discretion of the study investigator.

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

If a patient experiences any AEs that may be contributed to by the study drug, other HF medications, or other CV medications, the investigator should adjust non-disease-modifying

medications (e.g., CCBs, nitrates, a-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.

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.

Intravenous nitrates

In the event a study patient requires the concomitant administration of 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.

5.5.8 Prohibited Treatment

Use of the treatments displayed below is NOT allowed after the start of investigational treatment.

ACEIs, ARBs and renin inhibitors

The concomitant use of open-label ACEIs, ARBs or a renin inhibitor is strictly prohibited while the patient is receiving investigational treatment, regardless of study epoch (active treatment run-in epoch, randomized treatment epoch or OLE epoch).

In case the study medication should be stopped and the investigator judges that and the replacement use of an open-label ACEI, ARB or renin inhibitor is necessary, ACEI should be started ≥ 36 hours after the last dose of study medication, and ARB or renin inhibitor should be started on and after the next day of stopping study medication. If not already treated with an aldosterone antagonist, consideration should be given to adding this therapy rather than an ACEI, ARB or renin inhibitor.

Similarly, if investigational treatment is to be restarted, the open-label ACEI should be discontinued ≥ 36 hours prior to resuming study medication and ARB or renin inhibitor should be discontinued the day prior to resuming study medication.

At the end of the randomized treatment epoch, patients who are not taking double-blind study medication but are taking an open-label ACEI must stop the ACEI ≥ 36 hours prior to initiating open-label LCZ696 treatment upon entering the OLE epoch. Similarly, patients taking open-label LCZ696 in the OLE epoch must stop LCZ696 ≥ 36 hours prior to initiating open-label ACEI instead. If the investigator discontinues LCZ696 and replaces it with an ARB or renin inhibitor, approximately 12 hours should transpire between the start of the last dose of LCZ696 and the start of the first dose of ARB or renin inhibitor (i.e., the next regularly scheduled dosing).

5.5.9 Discontinuation of study treatment

Patients may voluntarily discontinue study treatment for any reason at any time. The investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment discontinuation during the double-blind treatment epoch does not constitute withdrawal from the study, does not constitute withdrawal of consent and should not lead to the patient being withdrawn from the entire study unless the patient specifically withdraws his/her consent. Patients who have discontinued study drug are expected, and should be encouraged to, attend all the protocol specified study visits and perform all measurements as stipulated in the visit schedule (Table 6-1) and remain in follow up for the duration of the trial. If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, letter) should be made to contact them as specified in Section 5.5.11. The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

During the OLE epoch, permanent discontinuation of LCZ696 constitutes withdrawal from the study. Under these circumstances, the patient should be evaluated at a final study visit (Visit 399). The investigator must also notify the IRT of the patient's discontinuation of LCZ696 and record it on the Drug Administration Record of the eCRF.

If the patient does not attend the study visits, follow-up should continue according to the specified schedule by telephone to determine if any AEs/endpoints pre-specified in the protocol have occurred, except in the case that the patient **specifically** refuses such follow-up and withdraws his/her consent.

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

- Withdrawal of informed consent
- 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.

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

- Pregnancy and post-pregnancy during lactation period

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

- Any severe suspected drug-related AE
- Any other protocol deviation that results in a significant risk to the patient's safety
- 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 3, Appendix 4 and Appendix 5 for treatment guidelines for hyperkalemia, hypotension, or renal dysfunction, respectively.

5.5.10 Withdrawal of consent

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

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

If a patient withdraws consent, the investigator must make every effort (e.g., telephone, e-mail, letter) to determine the primary reason for this decision and record this information. Investigational treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

5.5.11 Loss to follow-up

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

5.5.12 Emergency breaking of assigned treatment code

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 and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a 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 Country Pharma Organization 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.

The patient must discontinue the study treatment after an emergency treatment code break.

An emergency breaking of treatment assignment is not applicable for the OLE epoch.

5.5.13 Study completion and post-study treatment

The core part will be completed when either: the target total number of endpoints is obtained **or** a recommendation is made by the DMC to prematurely stop the study.

At the end of the core part, all patients will return for the core part end of study (EOS) visit (Visit 299) and patients will be asked to return the remaining study drug.

The OLE epoch will be completed when 2 years from the date of the first patient enrolled or marketed product is available in Japan, whichever comes first.

When the patient has completed all scheduled study visits or permanently discontinued from the OLE epoch, the investigator must call the IRT to record the patient's completion within IRT. At the end of the OLE epoch, all patients will return for the OLE epoch EOS visit (Visit 399) and patients will be asked to return all remaining open-label LCZ696 tablets.

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.

5.5.14 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Core part

Table 6-1 lists all of the assessments for the core part and indicates with an "x" when the visits are performed. All patients, including those who discontinue the study medication before completing the core part, should continue attending the scheduled visits as outlined in Table 6-1 until the core part ends. At that point all patients will return to the study sites as soon as possible to undergo the core part EOS visit (Visit 299) assessments.

Patients should be seen for all visits on the designated day as close to it as possible. If one visit is postponed or brought forward, it should not result in the next visit being postponed or brought forward. The next visit, if at all possible, should adhere to the original time schedule.

A Visit 199 (end of treatment run-in visit) will be completed for all patients who enter the treatment run-in epoch. For patients who discontinue during the treatment run-in epoch, Visit 199 will be their discontinuation visit. For patients that are randomized, Visit 199 will be their end of treatment run-in disposition visit and may be performed on the same day as Visit 201. Inclusion/exclusion criteria, vital signs and laboratory evaluations for randomization (Visit 201) are reflected at Visit 199 in Table 6-1.

After randomization, study drug discontinuation (permanent or temporary) for any reason does not constitute withdrawal from the study and should not lead to the patient being

withdrawn from the study. Patients who discontinue study drug should be requested to return for all of the assessments outlined in Table 6-1 as scheduled. If any patient refuses to return for these assessments or is unable to do so, every effort should be made to contact him/her or knowledgeable informant by telephone to ask if any of the study endpoint events have occurred at the foreseen visit dates for the remaining duration of the study. Documentation of attempts to contact the patient should be recorded in the source documentation.

At a minimum, patients who not participating in the OLE epoch will be contacted for safety evaluations during the 30 days following the last study visit or following the last administration of investigational 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.

Patients should be instructed NOT to eat or drink anything (except water) for approximately 8 hours prior to each scheduled fasting laboratory evaluation (see Section 6.5.4). If the patient has not fasted, the study visit collection of samples for laboratory evaluations should still take place.

Patients will be instructed to take the last dose of the double-blind study drug on the day before the core part EOS visit (Visit 299), and visit the study sites without taking the study drug on the day of Visit 299.

Patients will also be instructed to take study drug, as usual, on the morning of their site visits (except for Visit 201 and Visit 299), 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. The only exception to this rule is for visits when the pre-study drug dose blood and urine samples for biomarker [redacted] are collected. In this case, the patient should not take the study drug before attending the study visit, but the study visit should be scheduled so that the biomarker [redacted] are obtained immediately before the time when the patient usually takes his/her study medication.

There are two short washout periods (approximately 36-48 hours for each) during the treatment run-in epoch to minimize the potential risk of angioedema due to overlapping ACE-NEP inhibition at Visit 101 and Visit 201 (Section 6.5.7): (1) after completing the screening epoch receiving conventional ACEI or ARBs and prior to beginning the LCZ696 run-in at Visit 101, and (2) after completing the LCZ696 run-in and prior to starting randomized study drug at Visit 201. For example, if a patient's Visit 101 is on Wednesday, he/she must not take any doses of ACEIs or ARBs after the last dose on Tuesday. The patient will then start to take the first dose of the single-blind LCZ696 run-in medication on Thursday morning. The same is true for Visit 201. If a patient's Visit 201 is on Wednesday, he/she must not take any doses of the LCZ696 run-in medication after the Tuesday evening dose. The patient will then start to take the first dose of double blind medication on Thursday morning.

Open-label extension epoch

Table 6-2 lists all of the assessments for the OLE epoch and indicates with an "x" when the visits are performed. At the study end, all patients will return to the study sites as soon as possible to undergo the EOS visit (Visit 399) assessments.

Patients should be seen for all visits on the designated day as close to it as possible. If one visit is postponed or brought forward, it should not result in the next visit being postponed or brought forward. The next visit, if at all possible, should adhere to the original time schedule.

First visit of OLE epoch at Week 0 (Visit 301) will occur on the same day as the core part EOS visit (Visit 299). For patients who discontinue the study during the OLE epoch, Visit 399 will be their discontinuation visit. Permanent discontinuation of study drug constitutes withdrawal from the study.

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 investigational 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.

Patients should be instructed NOT to eat or drink anything (except water) for approximately 8 hours prior to each scheduled fasting laboratory evaluation (see Section 6.5.4). If the patient has not fasted, the study visit collection of samples for laboratory evaluations should still take place.

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. The only exception to this rule is for visits when blood and urine samples for biomarker assessments are collected. At these visits, the patient should not take the study drug before attending the study visit, but the study visit should be scheduled so that the biomarker samples are obtained immediately before the time when the patient usually takes his/her study medication, except for Visit 301 as no double-blind study drug should be taken at this visit.

There is a short washout period (approximately 36 hours) during the start of OLE epoch after patients completing the double-blind treatment and prior to starting the first dose of open label LCZ696 to minimize the potential risk of angioedema due to overlapping ACE-NEP inhibition at Visit 301. The patient will start to take the open-label LCZ696 the day after Visit 301. For example, if a patient's Visit 301 is on Wednesday, he/she must not take any doses of the double-blind study drug after Tuesday evening dosing. The patient will then start taking the first dose of the open-label LCZ696 on Thursday morning. In case patient comes to visit after having taken the double-blind study drug or the open-label ACEIs at Visit 301, the assessments could nevertheless be conducted. In this case, patient should start taking open-label LCZ696 at least approximately 36 hours after the last dose of double-blind study drug or the open-label ACEIs.

Table 6-1 Assessment schedule (Core part)

Epoch		Screening	Treatment run-in		Randomized treatment*														
Visit	**DS/S**	**1**	**101**	**199†**	**201**	**202**	**203**	**204**	**205**	**206**	**207**	**208**	**209**	**210**	**211**	**212**	**213**	**214***	**UNS**	**299††(EOS)**
Weeks (w) / Months (m)		**−4 to −3w**	**−2w**	**-**	**0w**	**2w**	**4w**	**8w**	**12w**	**6m**	**10m**	**14m**	**18m**	**22m**	**26m**	**30m**	**34m**	**38m**	**-**	**EOS**
Informed consent form	S	x																		
Call to IRT[1]	DS	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Inclusion/Exclusion criteria[2]	DS	x		x																
Demography/Medical history (including alcohol and smoking history)	DS	x																		
Heart Failure and Diabetes History	DS	x																		
Cardiovascular disease History	DS	x																		
Concomitant Medications	DS	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Heart Failure and CV Medications	DS	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical Exam[3]	S	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs (BP and pulse)	DS	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Height	DS	x																		
Weight	DS	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Waist/hip circumference	DS			x																x
NYHA Classification (HF signs and symptoms)	DS	x	x		x[15]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
QOL questionnaire (KCCQ)	DS		x		x[15]			x		x			x			x				x
Patient Global Assessment [4]	DS				x[4, 15]			x		x			x			x				x
Echocardiography [5]	DS	x																		
12-lead ECG evaluation	DS	x[14]			x[15]					x			x			x			(x)	x
Plasma NT-proBNP (for eligibility assessment)	DS	x																		
Plasma / serum biomarkers (including NT-proBNP) and biobanking [6]	DS		x	x		x[16]	x	x		x			x[16]							

Epoch		Screening	Treatment run-in		Randomized treatment*															
Visit	**DS/S**	**1**	**101**	**199†**	**201**	**202**	**203**	**204**	**205**	**206**	**207**	**208**	**209**	**210**	**211**	**212**	**213**	**214***	**UNS**	**299††(EOS)**
Weeks (w) / Months (m)		**−4 to −3w**	**−2w**	**-**	**0w**	**2w**	**4w**	**8w**	**12w**	**6m**	**10m**	**14m**	**18m**	**22m**	**26m**	**30m**	**34m**	**38m**	**-**	**EOS**
1st Urine morning void[7]	DS		x	x			x	x		x										
[redacted]																				
Local laboratory assessments[9]	DS	x		x															(x)	
Complete laboratory assessments [10]	DS	x		x			x	x		x			x			x			(x)	x
Abbreviated chemistry panel [11]	DS					x			x		x	x		x	x		x	x	(x)	
Pregnancy tests (Serum / Urine) [12]	DS	x		x					x	x	x	x	x	x	x	x	x	x	(x)	x
AEs / SAEs	DS	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Screening epoch disposition	DS	x																		
Run-in medication dispensation	S		x																	
Drug accountability	S			x		x	x	x	x	x	x	x	x	x	x	x	x	x	(x)	x
Run-in epoch disposition [13]	DS			x																
Randomization	DS				x															
Double blind medication dispense	S				x[15]	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)	
Treatment epoch disposition	DS																			x
Endpoint information	DS			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

UNS = Unscheduled visit
EOS = End of Study
DS = assessment to be recorded in clinical database
S = assessment to be recorded on source document
(x) = optional assessment

† = Visit 199 (end of treatment run-in visit) will be completed for all patients who enter the treatment run-in epoch. For patients who discontinue during the treatment run-in epoch Visit 199 will be their discontinuation visit. For patients that are randomized, Visit 199 will be their end of treatment run-in disposition visit and may be performed on the same day as Visit 201. Inclusion/exclusion criteria, vital signs and laboratory evaluations for randomization (Visit 201) will be recorded at Visit 199.

†† = Visit 299 (end of randomized treatment visit: End Of Study [EOS]) will be completed for all patients that enter the randomized treatment epoch.

° UNS = Unscheduled visit. Assessments marked with (x) are optional procedures that may be performed at the investigator's discretion.

* If the trial is extended, Visits 215, 216, 217 and so forth to be performed at the same intervals and with same measurements as at visits 212, 213, 214 and so forth.

[1] Except for unscheduled visits when no dose changes will occur and only laboratory samples will be provided, phone calls to IRT have to be performed at all visits (including unscheduled visits) and when the patient is on study drug interruption.

[2] During the single-blind active treatment run-in at Visits 101 and 199, patient safety will be monitored to ensure eligibility to continue to the next phase until randomization at Visit 201. Reason for not qualifying for randomization must be documented in detail in the eCRFs.

[3] Complete physical examination required at Visits 1, 201, 203 and 206 and yearly thereafter up until Visit 299 (EOS visit). Short physical exam required at all interim visits.

[4] At Visit 201, the investigator should call the patient's attention to how he/she feels about his/her condition at that time and to explain that periodically the patient will be asked to rate how he/she feels compared to at this point in the study. No assessment is required at Visit 201.

[5] LVEF will be measured at Visit 1 unless local measurement was made within the past 6 months using echocardiography, MUGA, CT scanning, MRI or ventricular angiography, or in case the value of subsequent measurement was above 35%.

[6] Plasma/serum biomarkers samples will be taken before morning study drug dose.

[7] First morning urine void samples will be taken before morning study drug dose. Sites will give the urine collection containers and instructions at Visits 1, 101, 202, 203 and 205.

[redacted]

[9] Serum potassium and eGFR (estimated by using serum creatinine value).

[10] Complete laboratory evaluations (hematology, blood chemistry, and urine) will be collected in the fasting state and sent to the central laboratory.

[11] Abbreviated chemistry panel including serum potassium, blood urea nitrogen (BUN), and serum creatinine will be measured at interim visits at the central laboratory.

[12] Women of childbearing potential only. At Visit 1, 299 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 199, 205 and every 4 months up until Visit 299 (except for Visit 299). If positive with serum /urine pregnancy test during the screening or treatment run-in epoch, the patient must be discontinued from the trial. After randomization (Visit 201) a positive pregnancy test requires immediate interruption of study drug.

[13] Run-in disposition page to be completed for all patients who entered into the treatment run-in epoch.

[14] Screening ECG performed within the 6 months before Visit 1 is accepted.

[15] Procedure completed only for patients to be randomized at Visit 201

[16] At Visit 202, plasma sample for biomarkers such as NT-proBNP will be collected. At Visit 209, serum sample for selected biomarkers related to fibrosis/remodeling will be collected.

[redacted]

Table 6-2 Assessment schedule (OLE epoch)

Epoch		**Open-label extension**									
Visit	**DS/S**	**301†**	**302**	**303**	**304**	**305**	**306**	**307**	**308**	**UNS°**	**399††(EOS/ ITD)**
Weeks (w) / Months (m)		**0w**	**2 to 4w**	**8w**	**4m**	**8m**	**12m**	**16m**	**20m**	**-**	**EOS††**
Informed consent form	S	x									
Call to IRT [1]	DS	x	x	x	x	x	x	x	x	x	x
Inclusion/Exclusion criteria	DS	x									
Concomitant medications	DS	x	x	x	x	x	x	x	x	x	x
Physical Exam [2]	S	x [10]	x	x	x	x	x	x	x	x	x
Vital signs (BP and pulse)	DS	x [10]	x	x	x	x	x	x	x	x	x
Weight	DS	x [10]	x	x	x	x	x	x	x	x	x
NYHA Classification (HF signs and symptoms)	DS	x [10]	x	x	x	x	x	x	x		x
Echocardiography [3]	DS	x					x				
12-lead ECG evaluation	DS	x [10]					x			(x)	x
Complete laboratory assessments [4]	DS	x [10]			x		x			(x)	x
Abbreviated chemistry panel [5]	DS		x	x		x		x	x	(x)	
Local laboratory assessments [6]	S	x	x								
Pregnancy tests (Serum / Urine) [7]	DS	x			x	x	x	x	x	(x)	x
Plasma / Urine biomarkers [8]	DS	x	x	x	x		x				
AEs / SAEs	DS	x	x	x	x	x	x	x	x	x	x
Extension medication dispensation	S	x	x	x	x	x	x	x	x	(x)	
Drug accountability	S		x	x	x	x	x	x	x	(x)	x
OLE epoch disposition [9]	DS										x

UNS = Unscheduled visit
EOS = End of Study
ITD = investigational treatment discontinuation

DS = assessment to be recorded in clinical database
S = assessment to be recorded on source document
(x) = optional assessment

† = First visit of OLE epoch at Week 0 (Visit 301) will occur on the same day as the core part EOS visit (Visit 299).

†† = Visit 399 (end of OLE visit) will be completed for all patients that enter the OLE epoch. For patients who discontinue the study drug permanently during the OLE epoch, Visit 399 will be their study discontinuation visit. The OLE epoch will continue until marketed product is available in Japan or approximately for 2 years from the date of the first patient enrolled, whichever comes first.

° UNS = Unscheduled visit. Assessments marked with (x) are optional procedures that may be performed at the investigator's discretion.

[1] Except for unscheduled visits when no dose changes will occur and only laboratory samples will be provided, phone calls to IRT have to be performed at all visits (including unscheduled visits) and when the patient is on study drug interruption.

[2] Complete physical examination required at Visits 301, 304, 306 and Visit 399 (EOS visit). Short physical exam required at all interim visits.

[3] Echocardiograms will be recorded to digital media in DICOM format (CD, or Magneto-Optical Disc) and sent to the core laboratory for analysis. All echocardiographic measurements will be made at the core laboratory.

[4] Complete laboratory evaluations (hematology, blood chemistry, and urine) will be collected in the fasting state and measured at the central laboratory.

[5] Abbreviated chemistry panel including serum potassium, blood urea nitrogen (BUN), and serum creatinine will be measured at interim visits at the central laboratory.

[6] Serum potassium and eGFR (estimated by using serum creatinine value).

[7] Women of childbearing potential only. At Visit 399, 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 301 and every 4 months up until Visit 399 (except for Visit 399). A positive urine pregnancy result requires immediate interruption of study drug, and a confirmatory serum pregnancy test will be performed at the central laboratory. If serum pregnancy test result is positive, the patient must be discontinued from the trial.

[8] Plasma and urine biomarker samples will be taken before morning study drug dose.

[9] OLE epoch disposition page to be completed for all patients who entered into the OLE epoch.

[10] Procedure will not be required unless it has been done at Visit 299 (Completion of the core part). The data at Visit 299 will be utilized as the data at Visit 301.

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the run-in epoch will have the disposition page for the screening epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. These patients are considered screening failures.

All patients that sign informed consent and take treatment run-in study drug will have the visit specific CRFs and Run-in disposition (Visit 199) collected. The reason for patient discontinuation during the treatment run-in period must be carefully documented in the appropriate CRF. These patients are considered treatment run-in failures.

For all patients who have signed informed consent and receive study treatment all AEs occurring after informed consent is signed will be recorded on the Adverse Event CRF.

Re-screening

If a patient is not eligible to enter into the treatment run-in epoch 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 procedures.

A patient who is successfully screened and enters into the active treatment run-in epoch but is later found not to be eligible for randomization due to intolerance to LCZ696 50 mg b.i.d. may be re-screened at a future time if the investigator feels that the circumstances that may have contributed to the patient's intolerance are no longer present. In this case, a completely new patient number is to be allocated to the subject and he/she will need to re-perform all Visit 1 assessments.

For the core part, a patient may be re-screened up to two times. A minimum of 2 or 4 weeks must elapse between re-screenings if the patient was never exposed to study medication or if the patient was exposed to the run-in study medication, respectively. This is to ensure all the entry criteria are met, including the required minimum stability period on pre-study medications (refer to Section 4.1). Patient must provide new written informed consent before each time they are to be re-screened.

In the event of an extension, re-screening will not be allowed.

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 ethnicity, relevant medical history/current medical condition present before signing informed consent. 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 epoch and OLE epoch. 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 and extension study drug exposure will be calculated based upon the start and stop dates recorded in the eCRF.

6.4 Efficacy

6.4.1 Primary and secondary efficacy endpoints

The primary composite endpoint for the core part consists of the following components:

- CV death
- HF hospitalization

The key secondary endpoints for the core part are:

- Changes in NT-proBNP from baseline
- CV death, HF hospitalization or intensification of treatments due to documented episode(s) of worsening HF defined as: worsening signs and symptoms of HF requiring addition of a new drug for HF treatment, initiation of IV treatment, increase of diuretic dose for persistent use for ≥ 4 consecutive weeks, or institution of mechanical or circulatory support such as mechanical ventilation, ultrafiltration, hemodialysis, intra-aortic balloon pump or ventricular assist device
- CV death
- HF hospitalization
- Intensification of treatments due to documented episode(s) of worsening HF
- Changes in NYHA class from baseline
- Clinical summary score (assessed by KCCQ)

The other secondary endpoints for the core part are:

- Composite of CV death and total (first and recurrent) HF hospitalizations
- Clinical composite score (assessed by NYHA classification and patient global assessment)
- All-cause mortality
- Hospitalization (all-cause, cause-specific)
- Changes in biomarkers from baseline
- Healthcare resource utilization

Other endpoints during OLE epoch are:

- Changes in NYHA class from OLE baseline (Visit 301)
- Changes in echocardiographic parameters from OLE baseline (Visit 301)
- Changes in biomarkers from OLE baseline (Visit 301)

6.4.2 Endpoint committee

All of the following events, which could potentially fulfill the criteria for the primary or secondary endpoints will be assessed during the active treatment run-in epoch or the double-blind treatment epoch, and reported to the Endpoint Adjudication Committee for adjudication or assessment:

- All death events
- HF hospitalization
- Intensification of HF treatments due to documented episode(s) of worsening HF (regardless of hospital admission or not)

The Endpoint Adjudication Committee will be responsible for classifying all death events and for determining whether pre-specified endpoint criteria were met for the non-fatal events. Sites are instructed to take a conservative approach when reporting endpoints; if the investigator suspects an endpoint may have occurred, it is best to report the event to the Endpoint Adjudication Committee for the final determination.

Novartis' reporting guidelines for AE and SAE as outlined in Section 7.1 and Section 7.2 must be followed, independent from the circumstance that an event is also reported as a suspected study endpoint.

The OLE epoch will collect all safety events (serious and non-serious AEs), however, no clinical endpoint adjudication of these events, which occur during the OLE epoch, will be performed.

6.4.3 Heart failure symptoms reduction and reduction in physical limitation

The KCCQ is a self-administered questionnaire and requires, on average, 4-6 minutes to complete. It contains 23 items, covering physical function, clinical symptoms, social function, self-efficacy and knowledge, and Quality of Life (QoL), each with different Likert scaling wording, including limitations, frequency, bother, change in condition, understanding, levels of enjoyment and satisfaction. A change of 5 points on the scale scores, either as a group mean difference or an intra-individual change appears to be clinically significant. The KCCQ is a valid, reliable and responsive health status measure for patients with CHF and may serve as a clinically meaningful outcome in CV clinical research, patient management and quality assessment (Green et al. 2000).

The HF symptoms and physical limitation domains scores show the best the correlation for improvements following a CHF exacerbation (Green et al. 2000). Thus, one of the secondary endpoints is a clinical summary score based on the HF symptoms and physical limitation domains scores of the KCCQ at 6 months. The KCCQ questionnaire will be completed at Visits 201, 204, 206, 209, 212, and 299 (EOS).

In the OLE epoch, the KCCQ will not be assessed.

6.4.4 Biomarkers

Biomarkers related to cardiac and renal function/injury and associated comorbidities and their consequences in the HF-rEF population will be obtained from blood and first morning void (FMV) urine. Biomarkers will be used to elucidate the effect of study drugs. They may also be

used to determine which biomarkers are most predictive of event risk. Blood biomarkers of potential interest may include such as: NT-proBNP, aldosterone, Cystatin-C, high-sensitivity troponin T, amino-terminal propeptide of procollagen type I (PINP) and type III (PIIINP) or other biomarkers important in heart failure. FMV urine biomarkers may include markers such as cGMP, creatinine, and urine albumin to creatinine ratio (UACR). The list of blood and urine biomarkers may change during the course of the study as new or more relevant biomarkers are determined. Biomarker analysis may also occur retrospectively after study close with biomarker decisions dependent on study outcome and/or new biomarkers relevant to the HF-rEF patient population.

In the core part, NT-proBNP will be obtained in all patients by using a central laboratory at Visit 1 to determine eligibility for the trial. In addition, biomarker measurements will be obtained from serum, plasma, and first morning void (FMV) urine samples at Visits 101, 199, 202 (only selected biomarkers such as NT-proBNP), 203, 204, 206 and 209 (only selected biomarkers at Visit 209) to determine effects of treatments on biomarkers. Biomarkers related to fibrosis/remodeling such as PINP and PIIINP will be measured only at Visits 101 and 209. Values of selected biomarkers at Visit 101 may also be used to determine which biomarker best predicts risk of clinical events.

In the OLE, biomarker measurements will be obtained from plasma and spot urine samples at Visits 301, 302, 303, 304, and 306 to determine effects of LCZ696 treatments on biomarkers. BNP, NT-proBNP, and urine cGMP at these visits will be assessed.

These samples will be obtained before patients take their morning study drug dose.

The results of the biomarkers analyzed during the conduct of the core part, with the exception of the Visit 1 NT-proBNP results, will be blinded to the site and the Novartis clinical study team until the core part database lock. The Novartis clinical study team will only be unblinded to biomarker data following the core part database lock.

Unblinded (e.g. local) measurements of BNP or NT-proBNP after screening should be limited to cases requiring safety evaluations until the core part database lock.

6.4.5 Clinical composite score

The clinical composite score is one of the secondary endpoints of this study. It is derived from two instruments: the patient global assessment and the NYHA functional classification.

The patient global assessment is a seven-point patient self-evaluation scale. At Visit 201 (randomization), the investigator should call the patient's attention to how he/she feels about his/her condition at that time and to explain that periodically the patient will be asked to rate how he/she feels compared to at this point in the study. Subsequently, patients will be asked to rate how well they feel compared to Visit 201 (randomization/baseline) (Packer et al. 2002). This evaluation is combined with the NYHA functional class, one of the most reliable instruments for rating HF patients' functionality, and with occurrence of death and hospitalization for heart failure to arrive at an overall evaluation of whether a patient is considered to have improved, worsened, or unchanged after a pre-specified period of time (Packer 2001).

The patient global assessment will be conducted at Visits 204, 206, 209, 212 and 299 (EOS). HF signs and symptoms/NYHA classification will be conducted at all visits.

In the OLE epoch, the patient global assessment will not be conducted and clinical composite score will not be assessed.

6.4.6 Echocardiogram

In the core part, LVEF will be measured at Visit 1 unless local measurement was made within the past 6 months using echocardiography, MUGA, CT scanning, MRI or ventricular angiography, or in case the value of subsequent measurement was above 35% to assess the patient's eligibility.

In the OLE, echocardiograms will be performed at the sites by qualified echocardiographic personnel (technicians or physicians) in accordance with the details of procedures outlined in the manual provided to all participating sites.

The echocardiogram will be performed at Visit 301 and also before administration of study medication at Visit 306. Cardiac parameters related to LV and LA structure, LV systolic and diastolic function etc. (including LV end systolic and diastolic volume indices, LVEF, and LA volume index) will be assessed.

Echocardiograms will be recorded to digital media in DICOM format (CD, or Magneto-Optical Disc) and sent to the core laboratory for analysis. All echocardiographic measurements will be made at the core laboratory.

The echo data obtained during baseline (Visit 301) and Visit 306 will be sent to a core laboratory for evaluation and analysis. A detailed manual of all echo procedures will be provided to all sites.

6.4.7 Appropriateness of efficacy assessments

These measurements are standard and have been used in previous HF trials.

The definition of CV endpoints is consistent with the FDA CV endpoints draft guidelines (Hicks et al. 2012). It is referred in Japanese Guidelines for Clinical Evaluation of Drugs for Heart Failure that total mortality, cardiovascular morbidity, and subjective complaints are considered appropriate as the primary endpoints (Ministry of Health, Labour and Welfare 2011).

6.5 Safety

Novartis may request additional information on specific AEs or laboratory events of interest and may make requests to perform additional diagnostic tests to further assess the safety profile of the study drugs. Such information may include diagnostic procedure reports, discharge summaries, autopsy reports, and other relevant information that may help in assessing the reported AE. 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 Visits 1, 201, 203 and 206 and then at yearly intervals thereafter until the core part EOS visit, and also at Visits 301, 304, 306 and the OLE epoch EOS visit. 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 (blood pressure [SBP and DBP] and pulse). A short physical exam will be at all visits starting from Visit 101, except where a complete physical exam is required (see above).

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

6.5.2 Vital signs

Vital signs will be assessed at every visit. Vital signs include BP and pulse measurements. BP will be measured in the sitting position after 5 minutes of rest using an automated validated device (e.g., OMRON) or a standard sphygmomanometer with an appropriately sized cuff on the non-dominant arm. Guidelines for the management of BP (i.e., hypotension) are provided in Appendix 4.

Vital signs will also be assessed at every visit during the OLE epoch.

6.5.3 Height and weight

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

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at all visits, until the core part EOS visit. Body weight will be measured at all visits during the OLE epoch as well.

Waist/hip circumference (to the nearest centimeter [cm] in indoor clothing) will be measured at Visit 199 and at the core part EOS visit. Waist circumference is measured by horizontally positioning the tape measure on a bare abdomen, halfway between the lowest rib and the superior anterior iliac crest. In the OLE epoch, waist/hip circumference will not be measured.

6.5.4 Laboratory evaluations

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

Clinically notable laboratory findings are defined in Appendix 1.

In the core part, complete laboratory evaluations (hematology, blood chemistry, and urine; Table 6-3) for the assessment of safety will be performed in a fasting state at Visits 1, 199, 203, 204, 206 and then at yearly intervals until the end of the study and at Visit 299 (core part EOS visit). Abbreviated laboratory evaluations will be performed as indicated in Table 6-1.

In the OLE, complete laboratory evaluations will be performed in the same manner as the core part at Visits 301, 304, 306 and at Visit 399 (OLE EOS visit). Abbreviated laboratory evaluations will be performed as indicated in Table 6-2.

Local laboratory will be used for the assessment of serum potassium values and eGFR at Visits 1, 199, 301 and 302. In addition, local laboratory assessments may be performed on an as-needed basis to monitor tolerability to investigational treatment at unscheduled visits during the randomized treatment epoch and the OLE epoch.

All central laboratory results will be communicated to the investigators and the sponsor, with the exception of plasma/serum and urinary biomarkers, of which only the Visit 1 NT-proBNP will be reported to the investigator 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 patient's CRF 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 AE part of the 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 (Section 7.2). If the laboratory abnormality leads to study drug discontinuation (temporarily or permanently), the patient must be followed until the abnormality resolves or until it is judged to be permanent. This investigation may include continued monitoring by repeat laboratory testing or by performing additional laboratory tests as deemed necessary by the investigator or the Novartis medical monitor.

Table 6-3 Routine laboratory examinations

Hematology	Biochemistry	Urine measurements
Red Blood Cells count White Blood Cells count Platelet Count Hemoglobin Hematocrit WBC Differential	Glucose Sodium Potassium * Chloride Calcium Blood urea nitrogen (BUN) * Creatinine * Total Bilirubin Fractionated bilirubin (if total bilirubin > 2 × ULN) 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	Urinalysis

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

a. At Visits 1, 299, 399 and in case of positive urine pregnancy test only.

6.5.4.1 Hematology

In the core part, hemoglobin, hematocrit, red blood cell count, white blood cell count with differential counts, and platelet count will be measured at Visits 1, 199, 203, 204, 206 and then at yearly intervals until the end of the core part and at Visit 299 (core part EOS visit) (Table 6-1). In the OLE, the laboratory evaluations will be performed in the same manner as the core part at Visits 301, 304, 306 and at Visit 399 (OLE EOS visit).

6.5.4.2 Clinical chemistry

In the core part, 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, 199, 203, 204, 206 and then at yearly intervals until the end of the core part and at Visit 299 (core part EOS visit). In the OLE, the laboratory evaluations will be performed in the same manner as the core part at Visits 301, 304, 306 and at Visit 399 (OLE EOS visit). Fractionated bilirubin will be performed for all patients whose total bilirubin value is > 2 × ULN.

In the core part, BUN, serum potassium, and serum creatinine value for eGFR calculation will be obtained from patients at Visit 202 and at every visit when a complete serum chemistry test is not done (i.e., Visits 202, 205, 207, 208, 210, 211, 213 and 214). In the OLE, the laboratory evaluations will be performed in the same manner as the core part at Visits 302, 303, 305, 307, 308. Local laboratory assessments may be performed on an as-needed basis to monitor tolerability to investigational treatment at unscheduled visits during the randomized treatment epoch and the OLE epoch.

6.5.4.3 Potassium and Estimated glomerular filtration rate (eGFR) assessments by local laboratory

In addition to the central laboratory assessments, potassium and eGFR will be measured locally at Visit 1 and Visit 199 to determine eligibility of the patient into the trial. Local laboratory assessments at Visits 1 and 199 are used to ascertain if patient doesn't meet the exclusion criteria (Table 3-1). These parameters will also be measured locally at Visits 301 and 302 to monitor safety for up-titration at Visit 302. Local potassium and eGFR measurements may be performed during the randomized treatment epoch and the OLE epoch, mainly at the unscheduled visits, to monitor the tolerability to study medication dose administered and adjust medication dose if needed (according to Appendix 3 and Appendix 5).

Estimated GFR will only be calculated using the following formula for Japanese (Matsuo et al. 2009):

Estimated GFR (mL/min/1.73 m^2)
$= 194 \times (\text{serum creatinine in mg/dL})^{-1.094} \times (\text{age in years})^{-0.287} \times (0.739 \text{ if female})$

The results of the local laboratory during the active treatment run-in epoch and the OLE epoch will not be reconciled with the central laboratory measurements.

6.5.4.4 Urinalysis

In the core part, dipstick-test determination of specific gravity, pH, blood, total protein, bilirubin, ketones, and leukocytes will be measured at central laboratory at Visits 1, 199, 203,

204, 206 and then at yearly intervals until the end of the core part and at Visit 299 (core part EOS visit). Microscopic examination of red blood cell (RBC) and white blood cell (WBC) sediments will be also performed.

In the OLE, the laboratory evaluations will be performed in the same manner as the core part at Visits 301, 304, 306 and at Visit 399 (OLE EOS visit).

6.5.5 Electrocardiogram (ECG)

In the core part, a standard 12-lead ECG will be performed at screening (Visit 1, unless an ECG performed within the last 6 months is available), randomization (Visit 201), Visit 206, and at yearly intervals thereafter until the end of the study and at Visit 299 (core part EOS visit).

In the OLE epoch, a standard 12-lead ECG will also be performed at Visits 301, 306 and at Visit 399 (OLE epoch EOS visit).

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

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

Clinically significant abnormalities should be recorded on the relevant section of the medical history/AE eCRF page as appropriate.

6.5.6 Pregnancy and assessments of fertility

In the core part, all female patients of childbearing potential will have a serum pregnancy test performed at Visit 1 (central laboratory) and Visit 299 (core part EOS visit). Additionally, these patients will have urine pregnancy tests performed at the investigational sites at Visit 199, Visit 205 and all visits thereafter (except Visit 299). A positive urine pregnancy result requires immediate interruption of study drug, and a confirmatory serum pregnancy test will be performed at the central laboratory. If serum pregnancy test result is positive, the patient must discontinue study drug until after the pregnancy and lactation period.

In the OLE epoch, all female patients of childbearing potential will have urine pregnancy tests performed locally at Visit 301 and every 4 months up until Visit 399 (except for Visit 399). Additionally, these patients will have a serum pregnancy test performed at the central laboratory at Visit 399. A positive urine pregnancy result requires immediate interruption of study drug, and a confirmatory serum pregnancy test will be performed at the central laboratory. If serum pregnancy test result is positive, the patient must be discontinued the trial.

6.5.7 Angioedema

The occurrence of angioedema or angioedema-like events must be monitored and reported during this study. This procedure will also be applied to the OLE epoch.

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

It is important that the investigator pays special attention to any swelling or edema that may resemble angioedema or angioedema-like events that may be reported by patients. If such an event occurs, the investigator will complete 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 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 received during both the core part and OLE epoch will be forwarded to an Angioedema Adjudication Committee by Novartis for assessment.

Information regarding this committee is outlined in Section 8.5.2. Details on the procedures for reporting angioedema events will be provided to investigators in a manual.

6.5.8 Appropriateness of safety measurements

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

Bradykinin has been implicated as the putative mediator of angioedema. 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. Simultaneous inhibition of multiple breakdown pathways of bradykinin is thought to significantly increase the risk of occurrence of angioedema (Sulpizio et al. 2004). Therefore, cases of suspected angioedema will be collected and adjudicated by an independent angioedema adjudication committee in this study.

6.6 Other assessments

6.6.1 Resource utilization

Analyses will be undertaken, as appropriate, to assess the effects of treatment on Healthcare Resource Utilization (RU) parameters. These measures may include hospitalization (e.g.

number of hospital days), physician visits, other drugs used, and laboratory tests and procedures performed.

At Visit 202 and each subsequent scheduled visit, the level of healthcare resource utilization will be assessed through procedures during hospital stays. The frequency and duration of any inpatient hospitalization will be recorded along with the primary reason for the hospital admission and discharge. All attempts will be made to collect RU variables in all patients throughout the duration of the study to avoid selection bias. There may also be circumstances when the collection of such data after completion of the core part may be warranted.

The information of RU will not be collected in the OLE epoch.

[redacted]

6.6.3 Other biomarkers

The list of blood and urine biomarkers may change during the course of the study as new or more relevant biomarkers are determined. Biomarker analysis may also occur retrospectively after study close with biomarker decisions dependent on study outcome and/or new biomarkers relevant to the HF-rEF patient population. This will also be applied to the OLE epoch.

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.

An untoward medical occurrence may be a study endpoint as well as meeting the definition for an AE. Specific guidance on the appropriate recording and reporting of events that meet the criteria for both a study endpoint and an AE are provided in Section 7.2.3.

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 investigational treatment (no/yes)
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE)
- action taken regarding investigational treatment
- whether other medication or therapies have been taken (concomitant medication/non-drug therapy)

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

- no action taken (i.e. further observation only)
- study treatment dosage adjusted/temporarily interrupted
- study treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged

- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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 drug, the interventions required to treat it, and the outcome.

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

7.2.1 Definition of SAE

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

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

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

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

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to DS&E as per Section 7.2.2.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days 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.

Information about all SAEs (either initial or follow up information) is collected and recorded on the paper Serious Adverse Event Report Form or the electronic Serious Adverse Event Form within the Oracle Clinical/Remote Data Capture (OC/RDC) system (where available). The Investigator must assess the relationship to each specific component of the study treatment (if the study treatment consists of several components).

SAEs (initial and follow-up) that are recorded *on the paper SAE form* should be faxed within 24 hours of awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation

sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

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

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not 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 EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.2.3 Protocol specific unblinding rules for SUSARs that are also efficacy endpoints

In studies such as this one, where the efficacy endpoints potentially meet the requirements for SUSAR reporting, the integrity of the study may be compromised if the endpoints are systematically unblinded for expedited reporting to competent authorities/relevant ECs and investigators. In such cases, regulations allow an exemption from SUSAR unblinding and expediting aimed at ensuring the validity of an outcome study (European Commission ENTR/CT12 2006, FDA 2012). Therefore, the following rules for unblinding SUSARs during the study period will be applied.

The study specific exemption does not apply to the OLE epoch. During the OLE epoch, ALL adverse events will be reported as AEs following the procedures described in Section 7.1 and Section 7.2. No clinical endpoint adjudication of events during the OLE epoch will take place.

7.2.3.1 Primary and secondary endpoints

The primary endpoint (CV death and HF hospitalization) will not be unblinded even if they meet the definition of a SUSAR. Novartis will not expedite a report to competent authorities/relevant ECs and will not issue an IN. If specifically requested by a local Health Authority, these endpoints that also meet criteria for SUSARs will be expedited to this Health Authority as blinded reports. INs will not be issued for these events. Above will be also applied to CV hospitalization and prolongation of existing CV hospitalization. However, non-CV death will be unblinded if it meets the criteria for a SUSAR.

7.2.3.2 Adverse events that are commonly seen in the study population

Investigators will report AEs or SAEs that are commonly seen in the study population (Table 7-1) but they will not be unblinded and will not be reported as SUSARs to regulatory agencies, ECs, or investigators during the study. If specifically requested by a local Health Authority, these AE or SAEs that also meet criteria for SUSARs will be expedited to this Health Authority as blinded reports. INs will not be issued for these events. These events will be presented in the clinical study report (CSR) at the end of the study.

Table 7-1 Adverse events commonly seen in study population

Cardiovascular events		**Non-cardiovascular events**	
Unstable angina	Generalized edema	Arthralgia/Arthritis	COPD (including bronchitis and emphysema)
Arrhythmia	Hypertension	Constipation	Cough
Transient ischemic attack	Hypotension	Diarrhea	Fatigue
Renal impairment	Peripheral edema	Headache	Sepsis
Chest pain	Syncope	Nausea	Nasopharyngitis
Dizziness/vertigo	Angina pectoris	Anemia	Pneumonia
Cerebrovascular accident	Dyspnea	Upper respiratory infection/insufficiency	
Myocardial infarction	Stroke		

7.2.3.3 Other SAEs that meet the definition of SUSARs

All other SAEs that do not meet the criteria in Section 7.2.3.1 and Section 7.2.3.2 but do meet SUSAR criteria will be unblinded and reported to regulatory agencies and investigators during the study.

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.

The following two categories of abnormalities/adverse events have to be considered during the course of the study:

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

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

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

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation.

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

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

For the liver events:

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

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

7.4 Pregnancy reporting

To ensure patient safety, each pregnancy occurring while the patient is on study treatment 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 Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment.

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

8 Data review and database management

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, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)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. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization, additionally, a central analytics organization may analyse data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients 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 review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions.

Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis.

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

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

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked. The core and OLE data will be locked separately for each analysis, according to Data Management Plan. The treatment codes will be unblinded and made available at the core part database lock. Any changes to the database after each database lock can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

An external data monitoring committee (DMC) independent of Novartis will be appointed to monitor the study conduct and to determine if it is safe to continue the study according to the protocol. If applicable, the recommendation may include any new relevant safety issues(s) identified by the DMC during the evaluation.

The membership of the DMC and the responsibilities of the DMC and Novartis will be defined in a separate document entitled the ”Data Monitoring Committee Charter.” The DMC Charter will include information about data flow, purpose and timing of DMC meetings, guidance in the decision making process, communication strategy, procedures for ensuring confidentiality, procedures to address conflicts of interest and statistical monitoring guidelines.

The DMC will only cover the core part.

8.5 Adjudication Committee

8.5.1 Clinical Endpoint Committee

All events, which could potentially fulfill the criteria for the primary or secondary endpoints will be assessed during the core part and reported to the Clinical Endpoint Committee (CEC) for adjudication.

The CEC will be responsible for classifying all death events and for determining whether pre-specified endpoint criteria were met for the non-fatal events. Sites are instructed to take a conservative approach when reporting endpoints; if the investigator suspects an endpoint may have occurred, it should report the event to the CEC for the final determination. The membership and responsibilities of the CEC Committee will be defined in a separate document provided to the sites. This document will include definitions for endpoints and guidelines on the endpoint reporting process.

No adjudication of clinical endpoint events during the OLE epoch will take place.

8.5.2 Angioedema Adjudication Committee

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

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

All angioedema reports will be forwarded to an angioedema adjudication committee by Novartis for assessment. The membership and responsibilities of the Angioedema Adjudication Committee are defined in a separate document that will be provided to the sites.

The process above will also be applied to the OLE epoch.

9 Data analysis

9.1 Analysis sets

The following populations will be used for the core part statistical analyses:

The Screened Set (SCR) will consist of all patients who signed the informed consent. The screened set includes only unique screened patients, i.e., in the case of re-screened patients only the chronologically last screening data is counted.

The Enrolled Set (ENR) (run-in epoch) will consist of all patients who received at least one dose of run-in study medication.

The Randomized Set (RAN) will consist of all patients who received a randomization number, regardless of receiving double-blind investigational drug.

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

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

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

The following populations will be used for the OLE statistical analyses:

The Extension Population (EXT): All eligible patients who have completed the core part and have signed the informed consent for the OLE epoch.

The Full Analysis Set for OLE epoch (FAS-Ext): All patients who receive at least one dose of the extension study drug. The FAS-Ext population is the analysis set for both safety and efficacy analysis.

9.2 Patient demographics and other baseline characteristics

In the core part, baseline value is defined as the last non-missing assessment prior to the first dose of randomized study medication unless specified otherwise.

In the OLE epoch, value at Visit 301 is defined as OLE baseline.

Summary statistics will be provided by treatment group for demographics and baseline characteristics, including age, age group (< 65 years vs. ≥ 65 years; < 75 years vs. ≥ 75 years), sex, race, ethnicity, weight, height, body mass index (BMI), category of prior CHF

medication, prior HF hospitalization, NYHA class, LVEF, NT-proBNP, eGFR, 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 difference between treatment groups will be compared using the Chi-square test for categorical variables or using t-test for continuous variables. The p-values will be provided for descriptive purposes and will not be considered to define any formal basis for determining factors to be included in statistical models. If a substantial imbalance of treatment groups with respect to some variables does occur, supplemental analyses with addition of these variables in model may be performed to assess the potential impact on efficacy as appropriate.

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

Similarly, summary statistics as given above will be presented in the OLE epoch.

9.3 Treatments

The overall duration on the double-blind investigational treatment 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. Mean doses and dose levels will be summarized by treatment group and visit. The overall duration on the investigational product in the OLE epoch will be analyzed similarly.

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. Concomitant therapies used during the single-blind run-in epoch will also be similarly summarized. Concomitant medications in the OLE epoch will also be similarly summarized.

The number and percentage of patients on different CHF background medications (e.g., mineralocorticoid receptor antagonist, β-blockers, diuretics, digoxin) will be tabulated by treatment at baseline and during the double-blind stage. Similarly, the number and percentage of patients on different CHF background medications will be tabulated in the OLE epoch.

9.4 Analysis of the primary variable

9.4.1 Variable

The primary efficacy variable is time to the first occurrence of the composite endpoint, which is defined as either CV death or HF hospitalization. The confirmation of the primary composite events is based on an adjudication process by independent CEC (Section 8.5.1).

9.4.2 Statistical model, hypothesis, and method of analysis

The primary efficacy variable will be analyzed using Cox proportional hazards model with treatment and the stratification factor of screening NT-proBNP (< 1,600 pg/mL, ≥ 1,600 pg/mL) as fixed-effect factors. The primary hypothesis to be tested is H_{10}: $\lambda_2/\lambda_1 \geq 1$ versus H_{1a}: $\lambda_2/\lambda_1 < 1$, where λ_1 and λ_2 are hazards for enalapril treatment and LCZ696

treatment, respectively. The frequency of patients with composite primary endpoint events and the treatment exposure adjusted event rate will be provided for individual treatment arm.

The FAS will be used for the primary analysis.

The primary objective is met when the hazard ratio point estimate is less than 1.

9.4.3 Handling of missing values/censoring/discontinuations

The primary efficacy variable, the time to the first occurrence of either CV death or HF hospitalization, will be considered as censored for patients who have no event and at least one of the following applies:

- withdrawal of informed consent,
- loss to follow-up, or
- death from non-CV causes.

For those patients without events, the censoring date will be defined as the following (whichever occurs first):

- date when the patient withdrew informed consent,
- date of the patient's last visit,
- date of death from non-CV causes.

9.4.4 Supportive analyses

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

A supplemental log-rank test will be performed for both the FAS and the PP population. Survival function for each treatment group will be estimated by Kaplan-Meier method and the Kaplan-Meier curves will be presented for both the FAS and the PP populations.

The frequency and percentage of patients who reach the primary composite endpoint will be provided by treatment group for both the FAS and the PP population.

Additionally, similar analyses will be performed for each of the components of the composite endpoint with all events for that component that occurred during the double-blind treatment epoch of the study to quantify the strength of the effect for each component in the primary composite endpoint.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

In the core part, FAS will be used for the following key and other secondary analyses for efficacy endpoints.

A cut-off data analysis will be carried during the OLE epoch after all patients have been enrolled into the OLE, and completed Visit 304 (Month 4) or discontinued.

The cut-off date is defined as the latest of Visit 304 date or discontinuation date (the last visit prior to Visit 304). All data on or prior to this cut-off date during the OLE epoch will be used

for analysis. [redacted]

9.5.1.1 Changes in NT-proBNP from baseline at pre-defined time points (Weeks 4 and 8, Month 6)

Described in Section 9.5.1.10 Biomarkers.

9.5.1.2 Time to the first occurrence of CV death, HF hospitalization or intensification of treatments due to documented episode(s) of worsening HF

In the core part, it will be analyzed using the same Cox proportional hazards model used for the primary endpoint. Analysis will be repeated for each of the components of the composite endpoint.

The analysis above will not be applied for the OLE epoch.

9.5.1.3 NYHA classification

In the core part, the change from randomization to each of the post-randomization visits in NYHA classification will be analyzed using Cochran-Mantel-Haenszel test for different row (treatment) means, stratified for screening NT-proBNP classification, based on the modified ridit scores which are also referred to as the standardized mid-ranks.

In the OLE epoch, the change from baseline (Visit 301) to each of the post baseline visits in NYHA classification will be summarized. FAS-Ext will be used, and analyses will be done by the treatment arm in the double-blind treatment epoch. Additionally, analyses will be repeated for subset of FAS-Ext with only patients in the LCZ arm of the double-blind treatment epoch, throughout the period from run-in epoch to OLE epoch using Visit 101 as baseline.

9.5.1.4 KCCQ

The KCCQ instrument includes several domains. Only the domains that address HF symptoms and physical limitations will be analyzed. The clinical summary score of KCCQ is computed as the mean of the available domain scores of total HF symptom and physical limitation. The clinical summary score of KCCQ will be analyzed based on a repeated measures ANCOVA model in which treatment, screening NT-proBNP classification, visit, and treatment-by-visit interaction will be included as fixed-effect factors and baseline value as a covariate, with a common unstructured covariance for each treatment arm. The analysis will be performed based on all available data and based on likelihood method. The estimated treatment effect with the corresponding confidence interval will be provided. The primary treatment comparison between LCZ696 and enalapril is to be made at Week 8 and Month 6.

9.5.1.5 Composite of (total) HF hospitalizations and CV death

The composite endpoint of recurrent hospitalizations (including the first) due to HF and death due to CV during the double-blind period will be analyzed using a negative binomial model (McCullagh and Nelder 1989) with the count data as the dependent variable, treatment group and the stratification factor screening NT-proBNP as fixed-effect factors, and log(follow-up duration) as the off-set. The estimated event rates (intensities/risk rate) and their 95%

confidence intervals will be provided by treatment group. The treatment comparison will be performed through the estimated ratio of risk rates.

9.5.1.6 Clinical composite score

The clinical composite score will be analyzed at all time-points when both NYHA classification and Global Assessment are measured, using Cochran-Mantel-Haenszel (CMH) test for different row (treatment) means, stratified for screening NT-proBNP classification, based on the modified ridit scores which are also referred to as the standardized mid-ranks.

9.5.1.7 Time to all-cause death

It will be analyzed using the same Cox proportional hazards model used for the primary endpoint.

9.5.1.8 Hospitalizations (all-cause and cause-specific)

It will be analyzed using the same negative binomial model for the composite endpoint of total HF hospitalizations and CV death described in Section 9.5.1.5. Analysis will be performed for all-cause hospitalizations and cause-specific hospitalizations as well.

Time to the first occurrence of hospitalization will be analyzed using the same Cox proportional hazards model used for the primary endpoint. Analysis will be performed for all-cause hospitalizations and cause-specific hospitalizations as well.

9.5.1.9 Echocardiogram

Summary statistics for change from baseline (Visit 301) of echo parameters will be presented. FAS-Ext will be used, and analyses will be done by the treatment arm in the double-blind treatment epoch.

Pearson's correlation coefficient and its two-sided 95% confidence interval between change in NT-proBNP and change in structural cardiac measurements (LV end systolic and diastolic volume indices, LVEF, and LA volume index) from baseline (Visit 301) to Month 12 will be analyzed. Similarly spearman's correlation coefficient and its two-sided 95% confidence interval will be analyzed.

Above analysis is repeated for change in log transformed NT -proBNP.

9.5.1.10 Biomarkers

In the core part, for the treatment comparisons of LCZ696 vs enalapril, change from baseline (Visit 101) to the pre-defined time-points in logarithmic scale will be analyzed using a repeated measures ANCOVA model with treatment, the stratification factor screening NT-proBNP, visit and treatment-by-visit interaction as fixed effect factors and the logarithmic baseline biomarker value as a covariate, with a common unstructured covariance matrix among visits for each treatment. The estimated treatment effects in terms of ratios of geometric means, based on the least-squared means for within and between treatment groups from the ANCOVA model, and the corresponding two-sided 95% confidence intervals will be provided. The analysis will be performed based on all available data in the FAS and based on likelihood method with an assumption of missing at random for missing data. Descriptive

summary statistics (mean, median, standard deviation, min, max, Q1, Q3, geometric mean, 95% CI for geometric mean) for the change from Visit 101 to each post-baseline visit will be presented. Graphical mean plots with 95% CIs will also be provided.

Analysis will be conducted for all of the FAS population with relevant biomarker measures.

To characterize the effect of the two LCZ696 dosages (100 mg b.i.d., 200 mg b.i.d.) on NT-proBNP, the estimates of ratio from baseline (Visit 101) at Week 4 and Week 8 of LCZ696 treatment arm from the ANCOVA model described above are presented, and comparison of change from baseline at each dose level will be made using a t-test. Descriptive summary statistics for the changes from Visit 199 to post-randomization visits (Visits 202, 203, 204, 206) will be presented for LCZ696 treatment arm. In addition, descriptive summary for the change from Visit 199 to Visit 206 (Month 6) will be summarized by actual dose level immediately prior to Visit 206 for LCZ696 treatment arm. Graphical mean plots with 95% CIs will be provided as well. Analysis will be conducted for all of the FAS population with NT-proBNP measures. Same analysis will be conducted for the patients who did not require any dose adjustment(s) up to Week 8 in the FAS population with NT-proBNP measures. Analysis described above will be repeated for the subgroups, defined by the stratification for randomization – screening NT-proBNP (< 1,600 pg/mL, ≥ 1,600 pg/mL).

For reference, same analysis will be performed for enalapril treatment arm to characterize the effects of enalapril dosages (5 mg b.i.d., 10 mg b.i.d.).

In the OLE epoch, for biomarkers, descriptive summary statistics (mean, median, standard deviation, min, max, Q1, Q3, geometric mean, 95% CI for geometric mean) for the change from baseline (Visit 301) to each post-baseline visit will be presented. FAS-Ext will be used, and analyses will be done by the treatment arm in the double-blind treatment epoch. Additionally, analyses in NT-proBNP will be repeated for subset of FAS-Ext with only patients in the LCZ arm of the double blind treatment epoch, throughout the period from run-in epoch to OLE epoch biomarker visits (Visits 301, 302, 303, 304 and 306) using Visit 101 as baseline.

9.5.2 Safety variables

The safety and tolerability assessments are listed below:

- AEs and SAEs
- Sitting systolic, diastolic BP, and pulse pressure
- Heart rate
- Symptomatic hypotension and/or SBP < 90 mmHg
- Angioedema
- Hyperkalemia
- Renal dysfunction
- Cough
- Drug-related hepatic disorders
- Other relevant laboratory values
- ECG changes

The assessment of safety will be based primarily on the frequency of adverse events, SAEs, and laboratory abnormalities. Other safety data will be summarized as appropriate.

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

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

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

Safety analyses will be performed based on the safety population. There will be no formal statistical inference analysis.

In addition to the above safety analyses for the randomized double-blinded treatment epoch, the AEs, SAEs, and reasons for active run-in failures will be summarized for the active run-in epoch.

One cut-off data analysis will be carried during the OLE epoch after all patients have been enrolled into the OLE, and completed Visit 304 (Month 4) or discontinued.

The cut-off date is defined as the latest of Visit 304 date or discontinuation date (the last visit prior to Visit 304). All data on or prior to this cut-off date during the OLE epoch will be used for analysis. All specified safety analyses in this section will be performed for this cohort.

For AEs/SAEs, FAS-Ext will be used, and all analyses will be done for total, and by the treatment arm in the double-blind treatment epoch. Additionally, all analyses will be repeated for subset of FAS-Ext with only patients in LCZ arm of double blind treatment epoch, throughout the period from run-in epoch to OLE epoch.

Change from baseline (Visit 301) of lab parameters, vital signs and ECG will be summarized as given above. Shift from baseline of ECG data will be presented using shift table. FAS-Ext will be used, and all analyses will be done for total, and by the treatment arm in the double-blind treatment epoch. Additionally, all analyses will be repeated for subset of FAS-Ext with only patients in LCZ arm of double blind treatment epoch, throughout the period from run-in epoch to OLE epoch using Visit 201 as baseline.

Proportion of patients reaching target dose level 3 of LCZ696 at Week 8 and maintained at Month 4 will be presented. FAS-Ext will be used, and analyses will be done for total, and by the treatment arm in the double-blind treatment epoch.

9.5.3 Resource utilization

Data relating to resource utilization for the core part will be used for the purpose of economic evaluation which will be carried out and reported as a separate activity.

9.5.4 Health-related Quality of Life

Described in Section 9.5.1.4.

[redacted]

9.5.6 Biomarkers

See Section 9.5.1.1 and Section 9.5.1.10.

9.5.7 [redacted] D

See Section 9.5.5.

9.6 Interim analyses

Not planned.

9.7 Sample size calculation

The sample size for the core part is primarily based on feasibility considerations.

The target sample size is determined to ensure that there is at least 80% of probability in observing a hazard ratio (λ_2/λ_1) < 1 to verify the consistency between this study and PARADIGM-HF study, where λ_1 and λ_2 are hazards of enalapril treatment arm and LCZ696 treatment arm respectively. Assuming a hazard reduction of 20% for the primary endpoint (composite of CV death and HF hospitalization) in LCZ over enalapril, approximately 57 primary endpoint events will be required.

Assuming an annual event rate of 13% in the enalapril group, an enrollment period of 22 months and a minimum follow-up of 18 months, a total sample size of 220 patients will be required to obtain approximately 57 primary endpoint events.

The assumption of 13% annual event rate in enalapril for the primary endpoint of HF progression and 20% hazard reduction of LCZ over enalapril are based on the PARADIGM-HF study results (Table 9-1).

Table 9-1 Primary composite endpoint of PARADIGM-HF study

Variable	FAS entire population			Asia population (excluding India)		
	EAIR [95%CI]		Hazard ratio [95%CI]	EAIR [95%CI]		Hazard ratio [95%CI]
	LCZ696 N = 4187	Enalapril N = 4212		LCZ696 N = 424	Enalapril N = 427	
Primary composite endpoint	10.5 [9.81, 11.18]	13.2 [12.39, 13.95]	0.80 [0.731, 0.871]	11.9 [9.68, 14.44]	14.7 [12.17, 17.55]	0.82 [0.627, 1.065]

EAIR = Total number of events／100 patients years

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

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

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the

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

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

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

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

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

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this

study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring should be followed.

12 References

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13 Appendix 1: Clinically notable laboratory values and vital signs

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

Alkaline phosphatase	> 100% increase
ALT (SGPT)	> 150% increase
AST (SGOT)	> 150% increase
BUN	> 50% increase
Calcium	> 10% increase, > 10% decrease
Chloride	> 10% increase, > 10% decrease
Creatinine	> 50% increase
Potassium	> 20% increase, > 20% decrease
Total bilirubin	> 100% increase
Uric acid	> 50% increase

14 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 14-1 Liver Event and Laboratory Trigger Definitions

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

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

Table 14-2 Follow Up Requirements for Liver Events and Laboratory Triggers

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

Criteria	Actions required	Follow-up monitoring
	• Complete liver CRF	
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study drug immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study drug interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

*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

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

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

[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

15 Appendix 3: Treatment guidelines for hyperkalemia (serum potassium greater than 5.3 mmol/L[mEq/L])

General principles

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

Any patient who experiences a potassium level ≥ 5.5 mmol/L (mEq/L) confirmed by repeated testing at Visit 199 should be withdrawn from the study. Any patient with a serum potassium > 5.3 mmol/L (mEq/L) at any time after randomization requires the investigator to confirm the potassium concentration in a non-hemolyzed sample via an immediate repeat lab sample to both the clinic local lab and the study central lab. Regular, repeated checks of potassium concentration (beyond that prescribed in the protocol) should continue 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 [mEq/L]) or potential danger (≥ 6.0 mmol/L [mEq/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 (mEq/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, tomatoes, dried fruits, potatoes, low-salt substitutes, coffee, 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-containing combination products, such as Baktar® and Bactramin® (trimethoprim/sulfamethoxazole fixed combination)
    - Herbal Supplements:
        - For example, Noni juice, alfalfa (*Medicago sativa*), dandelion (*Taraxacum officinale*), horsetail (*Equisetum arvense*), nettle (*Urtica dioica*), milkweed, lily of the valley, Siberian ginseng, hawthorn berries

- Assess patient for dehydration or any condition that could lead to dehydration (e.g., diarrhea, vomiting) and/or hypovolemia and initiate appropriate corrective measures of rehydration.
- Repeat serum potassium measurement within 3 to 5 days
- If serum potassium remains > 5.3 and ≤ 5.5 mmol/L (mEq/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 (mEq/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 (mEq/L)
- Repeat serum potassium measurement after 2-3 days
- If serum potassium < 5.5 mmol/L (mEq/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 (mEq/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 (mEq/L)

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

16 Appendix 4: Guidelines for the management of blood pressure

Guidelines

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

17 Appendix 5: Guidelines for the management of renal dysfunction

General principles:

Glomerular filtration rate in HF patients depends on intrinsic renal function and on a balance between afferent and efferent glomerular arterial tonicity. This tonicity is partly regulated by a stimulation of angiotensin II and could be affected by 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.

Any patient who experiences a decline in eGFR > 35% from Visit 1 or an eGFR < 30 mL/min/1.73 m^2 at Visit 199 will be considered a run-in failure and withdrawn from the study.

Two types of response to serum creatinine increase are described:

Surveillance situation

Core part

If, at any time after randomization, eGFR decreases by ≥ 25% from baseline (Visit 199) (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

Open-label extension epoch

The same as above is applied to OLE epoch using OLE baseline (Visit 301).

Action situation

Core part

If a patient eGFR decreases by ≥ 40% from baseline (Visit 199) (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).

The investigator may consider down-titration of study drug. 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.

Open-label extension epoch

The same as above is applied to OLE epoch using OLE baseline (Visit 301).