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LCZ696

Clinical Trial Protocol CLCZ696B2401 / NCT02661217

A multicenter, randomized, open label, parallel group study comparing pre-discharge and posT-discharge tReatment initiation with LCZ696 in heArt failure patieNtS with reduced ejectIon-fracTion hospItalized for an acute decOmpensation eveNt (ADHF) (the TRANSITION study)

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List of abbreviations

ACEI	Angiotensin Converting Enzyme Inhibitor
AE	Adverse Event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ARB	Angiotensin II Receptor Blocker
ARNI	Angiotensin II Receptor Neprilysin Inhibitor
ADHF	Acute Decompensated Heart Failure
b.i.d.	twice a day
CCB	Calcium Channel Blocker
CFR	US Code of Federal Regulations
CRF	Case Report/Record Form (electronic)
CRO	Contract Research Organization
CSF	Cerebrospinal Fluid
CTC	Common Toxicity Criteria
CT scan	Computerized Tomography scan
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
eCRF	electronic Clinical Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
GCP	Good Clinical Practice
[redacted]	[redacted]
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
LFT	Liver function test (raised serum transaminases and/or bilirubin levels)

LLN	Lower limit of normal
MRA	Mineralocorticoid Receptor Antagonists
MRI	Magnetic Resonance Imaging
MUGA scan	MUltiGated Acquisition scan
MedDRA	Medical dictionary for regulatory activities
OC/RDC	Oracle Clinical/Remote Data Capture
o.d.	once a day
p.o.	oral(ly)
PARADIGM-HF	Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure – Study CLCZ696B2314
RAN	Randomized Population
SAE	serious adverse event
SAF	Safety Analysis Set
SUSAR	Suspected Unexpected Serious Adverse Reactions
ULN	Upper Limit of Normal

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical Epochs are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication

Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Period	A subdivision of a cross-over study
Premature subject/patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

Amendment 2

Purpose of this amendment is to address the following changes:

- Section 3.1 (Study design) minor wording changes were entered to clarify:
  - the duration of hemodynamic stabilization (i.e., no need for IV diuretics in the past 24 hours prior to signing ICF) with respect to the timing of ICF administration (first bullet under "ICF should be administered");
  - a redundant statement on Randomization was deleted on page 18;
  - for patients randomized to Pre-discharge group, with a prolonged hospital stay, details on the Discharge visit (Visit 102) assessments are edited on page 20 (bullet No. 1).
- Section 4.1 Inclusion criteria number 7: clarification for the 24-hour duration of hemodynamically stable conditions at Screening prior to signing ICF.
- Section 5.4: Editorial changes were made to clarify that the sponsor clinical team blinding status during the study will not be compromised.
- Section 6, Assessment table (Table 6-1) a missing check was added under Discharge, visit 102, to clarify that IRT should be notified of the visit date.
- Section 6.5.7.3: Clarifying text has been added on the parameters of local laboratory dipstick assessment to consistently reflect the CRF page.
- Section 6.5.8: Clarification on Screening ECG data have been added.
- Additional minor editorial changes have also been added to address typographical errors and inaccuracies.

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

Amendment 1

Amendment rationale

The purpose of this amendment is to address the inquiry by the Health Authorities from Germany. This change will apply to Germany only.

- Section 10.2 of the protocol [Informed consent procedure], will indicate an asterisk for the first paragraph of the Section. The modified version of the first paragraph is located at the end of the Section. The text clarifies that the procedure should be limited to patients capable to provide written informed consent.

Protocol summary

Protocol number	CLCZ696B2401
Title	A multicenter, randomized, open label, parallel group study comparing pre-discharge and pos**T**-discharge t**R**eatment initiation with LCZ696 in he**A**rt failure patie**N**t**S** with reduced eject**I**on-frac**T**ion hosp**I**talized for an acute dec**O**mpensation eve**N**t (ADHF) (the TRANSITION study)
Brief title	Study to compare Pre-discharge and Post-discharge treatment initiation with LCZ696 therapy in heart failure patients with reduced ejection fraction (HF-rEF) after an acute decompensation event.
Sponsor and Clinical Phase	Novartis Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Purpose of this trial is to explore two modalities of treatment initiation (Pre-discharge, and Post-discharge) with LCZ696 in HFrEF patients following stabilization after an acute decompensated heart failure (ADHF) episode.
Primary Objective	Evaluate the proportion of patients in the Pre- and Post-discharge treatment initiation groups achieving the target dose of 200 mg LCZ696 twice daily at the end of the week-10 after randomization (Treatment Epoch), regardless of previous temporary dose interruption or down-titration.
Secondary Objectives	1. Assess the proportion of patients that, regardless of previous dose interruption or down-titration during the Treatment Epoch, achieved and maintained either the 2 highest doses of LCZ696 bid for at least 2 weeks leading to week 10 after randomization. 2. Assess the proportion of patients that, regardless of previous dose interruption or down-titration during the Treatment Epoch, achieved and maintained any dose of LCZ696 for at least 2 weeks leading to week 10 after randomization. 3. Assess the proportion of patients permanently discontinued from study drug, due to Adverse Events, during the 10-week Treatment Epoch.
Study design	The TRANSITION study is a Phase IV randomized, multicenter, open-label study, testing two treatment-modalities of LCZ696 initiation in hemodynamically stabilized HFrEF patients hospitalized due to ADHF episode. The study consists of three Epochs (phases): the Screening Epoch; the Treatment Epoch defined as 10 weeks after Randomization; and 16-week Follow-up Epoch. Patient will be stratified based on the pre-admission type: - on RAAS-inhibition therapy with ACEI (any dose); - on RAAS-inhibition therapy with ARB (any dose); - ACEI/ARB treatment-naïve patients, defined as patients either without any previous treatment with ACEI or ARBs,or without ACEI/ARB therapy for at least 4 weeks before hospital

	admission due to ADHF. Within each stratum, patients will be randomized 1:1 to start LCZ696 either Pre-discharge or Post-discharge, and Randomization should occur no later than 48 hours prior to the planned discharge date. Patients are expected to be continuously treated with optimized standard of care therapy, as per HF guidelines. Therapy with LCZ696 is intended to replace the ACEI/ARB-inhibition therapy: all ongoing ACEI and ARB treatment will be stopped before LCZ696 initiation. Prior to starting treatment with LCZ696, a mandatory 36 hours wash-out period between last dose ACEI and first dose of LCZ696 must be observed. Patients randomized to Pre-discharge treatment initiation could receive first dose of LCZ696 at any point after the investigator deemed the patient to be stable for at least 24 h, relatively to the ongoing acute HF-therapy. Patients randomized to Post-discharge treatment initiation could receive the first LCZ696 dose at any point between the day after discharge and up to 14 days after Discharge.
Population	The study population will consist of adult male or female patients (18 years of age or older), hospitalized for an episode of acute decompensation of heart failure who are diagnosed with CHF NYHA class II-to-IV and reduced ejection fraction (LVEF ≤ 40%). Patients can be either with first HF presentation (de novo), or acute decompensation of HF due to deterioration in patients with a prior history of chronic HF.
Inclusion criteria	1. Patients hospitalized due to acute decompensated HF episode (ADHF) as primary diagnosis) and consistent Signs & Symptoms 2. Diagnosis of HF New York Heart Association class II-to-IV and reduced ejection fraction: Left ventricular ejection fraction ≤ 40% at Screening 3. Patients did not receive any IV vasodilators (except nitrates), and/or any IV inotropic therapy from the time of presentation for ADHF to Randomization 4. Stabilized (while in the hospital) for at least 24 hours leading to Randomization defined as: • No need for IV diuretics in the past 24 hours prior to signing ICF • Systolic blood pressure (SBP) ≥ 110 mm Hg for at least 6 h prior to Randomization 5. Meeting one of the following criteria: • Patients on any dose of ACEI or ARB at screening • ACEI/ARB naïve patients and patients not on ACEI or ARB for at least 4 weeks before screening.
Exclusion criteria	1. History of hypersensitivity to the sacubitril, valsartan, or any ARBs, NEP inhibitors or to any of the LCZ696 excipients. 2. Symptomatic hypotension and/or a SBP < 110 mm Hg or SBP > 180 mm Hg prior to randomization 3. End stage renal disease at Screening; or estimated GFR < 30 mL/min/1.73 m^2 as measured by the simplified Modification of Diet in Renal Disease (MDRD) formula at Randomization.

	4. Serum potassium > 5.4 mmol/L at Randomization. 5. Current hospitalization where patient does not receive treatment for decompensated HF. 6. Known history of hereditary or idiopathic angioedema or angioedema related to previous ACE inhibitor or ARB therapy 7. Severe hepatic impairment, biliary cirrhosis and cholestasis
Investigational therapy	LCZ696 therapy only (no reference therapy)
Efficacy assessments	Efficacy variables will not be assessed in this study
Safety assessments	Adverse events; angioedema; hyperkalemia; hypotension; liver and renal dysfunction
Other assessments	[redacted]
Data analysis	The primary endpoint will be analyzed using the stratified Cochran-Mantel-Haenszel method with treatment group and randomization stratification variable (ACEI stratum, ARB stratum, or naïve patient stratum) as stratification factor. The risk ratio (of the Pre-discharge initiation of LCZ696 arm versus the Post-discharge initiation of LCZ696 arm) will be estimated with a 2-sided 95% CI along with the estimated rate and 95% CI for each treatment arm. The above analyses will be performed based on safety analysis set (SAF). The secondary variables will be analyzed in an identical fashion to the primary variable (using the stratified Cochran-Mantel-Haenszel method A sample size of 1000 randomized patients (about 930 patients for ARB and ACEI, and about 70 in the naïve group) provides reasonable precision across a range of possible outcomes. For instance, when the observed rate 10-weeks up-titration, success is 80% in both pre- and post-discharge arms, it will provide an estimated risk ratio and 95% CI of 1.00 (0.94, 1.06).
Key words	Acute decompensated heart failure, reduced ejection fraction, pre-discharge treatment, post-discharge treatment, LCZ696, angiotensin receptor neprilysine inhibitor, safety and tolerability.

1 Introduction

1.1 Background

Chronic heart failure (CHF) is a major public health problem characterized by significant mortality, frequent hospitalization, and poor quality of life, with an overall prevalence that is increasing throughout the world (Hunt SA, 2009; McMurray JJ, 2012).

Although most patients improve symptomatically during the first 24 hours with current medical treatment (Follath F, 2011), their prognosis remains poor with over 15% to 20% mortality and 30% to 40% readmission rate in the first year after discharge (Maggioni AP, 2013a). Compared with ambulatory outpatients with heart failure, those hospitalized for AHF have >10-fold increase in the risk of dying, and although this risk decreases exponentially after discharge, it remains twofold to fourfold higher 12 to 18 months later (Gheorghiade M, 2005; Lassus JP, 2013). These outcomes have not changed in the last decade, making AHF one of the most severe clinical conditions leading to hospitalization.

Despite the changes in treatment during the last decades, where ACE inhibitor therapy reduces mortality in patients with HFrEF and has been the standard of care in this disease since the 1990s following publications of trials like CONSENSUS in 1987, and SOLV-D in 1991, although ARBs may be substituted if ACE inhibitors are poorly tolerated. Beta-blockers and aldosterone antagonists have further improved survival, but mortality remains high.

LCZ696 exhibits the novel mechanism of action of an Angiotensin Receptor Neprilysin Inhibitor (ARNI) by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type-1 (AT_1) receptor via valsartan.

The complementary cardiovascular benefits of LCZ696 in heart failure patients are attributed to the enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), by LBQ657 and the simultaneous inhibition of the effects of angiotensin II by valsartan. NPs exert their effects by activating membrane-bound guanylyl cyclase-coupled receptors, resulting in increased concentrations of the second messenger cyclic guanosine monophosphate (cGMP), which could result in vasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity, and anti-hypertrophic and anti-fibrotic effects. Valsartan inhibits detrimental cardiovascular and renal effects of angiotensin II by selectively blocking the AT_1 receptor, and also inhibits angiotensin II-dependent aldosterone release. This prevents sustained activation of the renin-angiotensin-aldosterone system that would result in vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation, and subsequent maladaptive cardiovascular remodeling.

LCZ696 contains a salt complex of the anionic forms of sacubitril and valsartan. Following oral administration, LCZ696 dissociates into the pro-drug sacubitril (also known as AHU377), which is further metabolized to the neprilysin inhibitor LBQ657, and valsartan.

Dosing in clinical trials was based on the total amount of both components of LCZ696, i.e. 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg of as sacubitril/valsartan sodium salt complex and is referred to as LCZ696 50 mg, 100 mg, and 200 mg respectively.

The PARADIGM-HF was a multinational, randomized, double-blind study of 8,442 patients comparing LCZ696 (200 mg twice daily) to enalapril (10 mg twice daily) in adult patients with chronic heart failure, NYHA class II-IV and reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤40%, amended later to ≤35%) in addition to other heart failure therapy. The primary endpoint was the composite of cardiovascular (CV) death or hospitalization for heart failure (HF).

Prior to study participation, patients were well treated with standard of care therapy which included ACE inhibitors/ARBs (>99%), beta blockers (94%), mineralocorticoid antagonists (58%) and diuretics (82%). The median follow-up duration was 27 months and patients were treated for up to 4.3 years. In addition, patients were allowed to receive treatment for other comorbid conditions (McMurray, JJV, 2014b).

A total of 8442 patients were randomized and prospectively included in the intention-to-treat analysis (4187 to LCZ696 and 4212 to enalapril). The trial was stopped early, according to pre-specified rules, after a median follow-up of 27 months, because the boundary for an overwhelming benefit with LCZ696 had been achieved. The study showed that risk for death from cardiovascular causes or hospitalization for heart failure (the composite primary end point) was reduced by 20% in the LCZ696 group, compared with the enalapril group. LCZ696 was associated with a statistically significant 20% reduction of risk for CV death and 21% reduction of risk of first hospitalization for heart failure. For the secondary endpoint, the risk of death for *any* reason, had a 16% reduction in the LCZ696 group, compared with the enalapril group. In addition to a benefit in mortality reduction, LCZ696 was also superior to enalapril in reducing symptoms and physical limitations of heart failure assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ). Fewer patients on LCZ696 (5.4%) had worsened NYHA functional class (≥1 class) from baseline to 8 month of treatment compared to enalapril (7.0%) (Packer M, 2015). The LCZ696 group had higher proportions of patients with hypotension and non-serious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group (McMurray JJV, 2014b).

When compared with enalapril, 16% fewer LCZ696-treated patients required intensification of outpatient therapy for worsening of heart failure or 34% fewer patients were evaluated and treated in emergency department for worsening heart failure but discharged without hospital admission. The patients in the LCZ696 group had 18% fewer stays in intensive care and were 31% less likely to receive intravenous positive inotropic agents, and 22% less likely to have implantation of a heart failure device or cardiac transplantation. The reduction in HF-hospitalization with LCZ696 was evident within the first 30 days after randomization (Packer M, 2015).

Current acute decompensated HF episode was an exclusion criterion in PARADIGM-HF study and only limited evidence is currently available on safety and tolerability of LCZ696 initiation in recently hospitalized due to acute decompensated HF-rEF episode patients.

The simultaneous inhibition of neprilysin and blockade of the AT_1 receptors with LCZ696 was more effective than the ACE inhibitor enalapril in reducing all-cause mortality, cardiovascular mortality, and HF hospitalizations. In addition, treatment with LCZ696 was delaying the clinical progression of surviving patients with a reduced ejection fraction (Packer M, 2015). It is expected that starting the LCZ696 therapy closer to the ADHF event will be safe and tolerated and may exert favorable effects on the clinical course in stabilized HF-rEF patients.

1.2 Purpose

The purpose of this trial is to explore two modalities of treatment initiation (Pre-discharge, and Post-discharge) with LCZ696 in HFrEF patients following stabilization after an ADHF episode.

2 Study objectives

2.1 Primary objective

Evaluate the proportion of patients in the Pre- and Post-discharge treatment initiation groups achieving the target dose of 200 mg LCZ696 bid at the end of the week-10 after randomization (Treatment Epoch), regardless of previous temporary dose interruption or down-titration.

2.2 Secondary objectives

- Assess the proportion of patients that, regardless of previous dose interruption or down-titration during the Treatment Epoch, achieved and maintained either the dose of 100 mg and/or 200 mg LCZ696 bid for at least 2 weeks leading to week 10 after randomization.
- Assess the proportion of patients that, regardless of previous dose interruption or down-titration during the Treatment Epoch, achieved and maintained *any dose* of LCZ696 for at least 2 weeks leading to week 10 after randomization.
- Assess the proportion of patients permanently discontinued from study drug, due to Adverse Events, during the 10-week Treatment Epoch.

3 Investigational plan

3.1 Study design

The CLCZ696B2401 study is a Phase IV randomized, multicenter, open-label study, testing two treatment-modalities of LCZ696 in the ADHF population. Data from the study will provide information regarding the safety and tolerability of LCZ696 therapy in HF-rEF patients when initiated Pre- and Post-discharge following stabilization of patients hospitalized due to an ADHF episode.

Patient will be stratified based on the **pre-admission** type of RAAS-inhibition therapy:

- ACEI
- ARB
- ACEI/ARB treatment naïve patients
  defined as patients either without any previous treatment with ACEI or ARBs, or without ACEI/ARB therapy for at least 4 weeks before hospital admission due to ADHF.

The study consists of three Epochs (phases): the Screening Epoch; the Treatment Epoch defined as 10 weeks after Randomization; and 16-week Follow-up Epoch.

In the attempt to minimize screen failures at the time of Informed Consent Form (ICF) administration, patient could be identified/pre-screened at the time of admission for ADHF, bearing in mind that patients are severely ill and conditions may changes rapidly. The investigator could conduct a pre-screening assessment based on the patient's chart information compared to the eligibility criteria.

The **Screening Epoch** is defined as the time from administration of ICF and up to the time of Randomization. It is expected to range between 1 and 3 days.

When admitted for acute decompensated HF, conventional therapy is started or continued at the discretion of the treating physician and is performed until hemodynamic stability is achieved.

Randomization will occur *only* after a minimum of 24 h stabilization interval is completed.

The **Treatment Epoch** is identified as the initial 10 weeks after Randomization.

The **Follow-up Epoch** is identified as the continuation of open-label LCZ696 treatment for additional 16 weeks after the Treatment Epoch to further evaluate safety and tolerability.

All patients must provide written informed consent prior to start any study-related activities. Upon signing the ICF, patients give access to the treatment received and medical information

starting from the time of admission for ADHF to verify eligibility criteria i.e.,: acute treatment received, sign and symptoms consistent with admission for ADHF, local laboratory values, conditions confirming achievement of hemodynamic stability.

ICF should be administered:

- *At least 24 hours after achieving hemodynamic stabilization* (i.e., no need for intravenous diuretics in the past 24 hours prior to signing ICF, as described in the inclusion criteria No. 7, first bullet) following the acute treatment for ADHF.
- Upon achieving stabilization, but *not later than 48 h prior to the planned discharge date*, to enable the required 36 h wash-out from ACEI therapy if the patient is randomized to the Pre-discharge initiation of LCZ696 therapy.

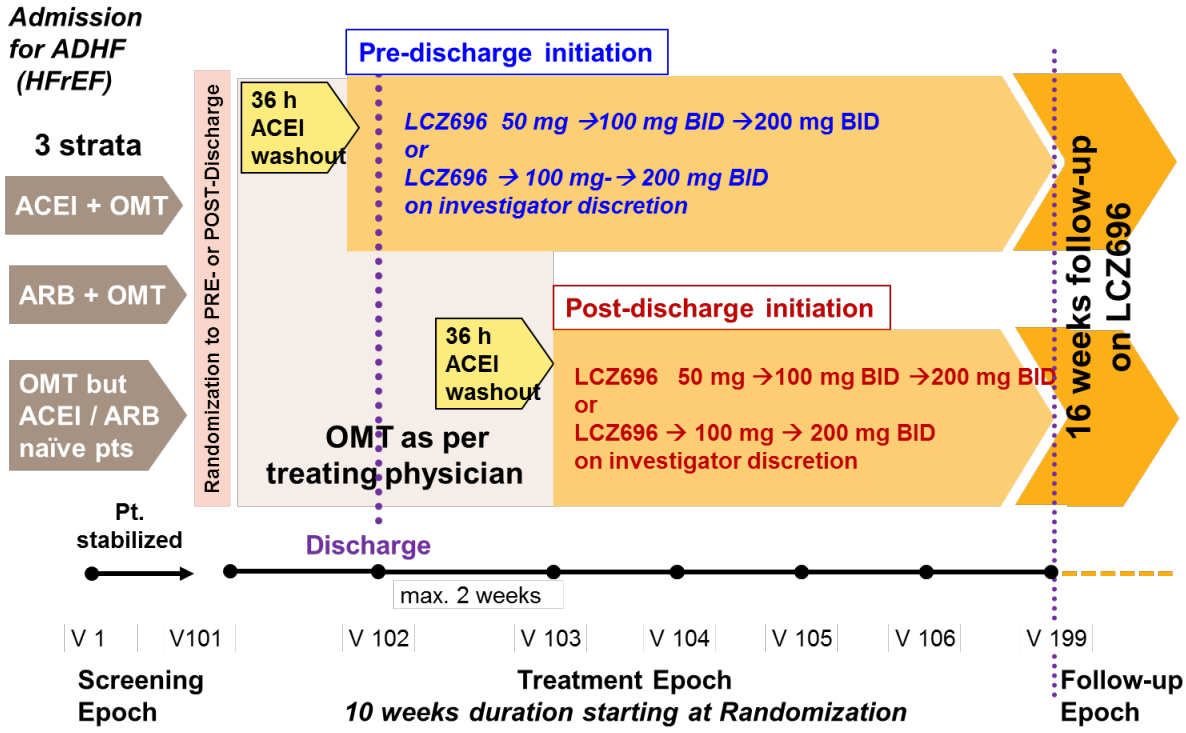
Patients will be randomized 1:1 to start LCZ696 either Pre-discharge or Post-discharge. In this study the **duration of the Treatment Epoch starts from the date of Randomization**.

Patients are expected to be continuously treated with optimized standard of care therapy, as per HF guidelines. The investigator will prescribe to the patient the required HF-medications (i.e., locally commercially available ACEI or ARB, beta-blockers, and other HF-guidelines recommended treatments) that will be acquired by the patient. Only LCZ696 will be provided through this study to the investigator/patient.

Therapy with LCZ696 is intended to replace the ACEI/ARB-inhibition therapy: all ongoing ACEI and ARB treatment will be stopped before LCZ696 initiation. Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, LCZ696 must not be started for at least 36 hours after discontinuing ACE inhibitor therapy.

LCZ696 should not be co-administered with another ARB due to the angiotensin II receptor blocking activity of valsartan. The investigator must train the patient to stop the current ARB therapy to ensure the first dose of LCZ696 will replace the routine dose of ARB at the next standard time point (usually next day).

Figure 3-1 Study design



OMT = optimized medical treatment
Total study duration = 26 weeks

Patients randomized to treatment initiation **Pre-**discharge initiation could receive first dose of LCZ696 at any time during their hospitalization after the investigator deemed the patient to be stable for at least 24 h, relatively to the ongoing acute HF-therapy. The first dose administration should occur no later than 12 h *before* discharge, and no later than 7 days after Randomization. The goals are (1) to administer at least one LCZ696 dose before discharge, bearing in mind that, if a patient is receiving ACEI therapy, a 36 h washout is mandatory prior to starting LCZ696 therapy; and (2) to initiate LCZ696 treatment adequately close to the Randomization event.

Patients randomized to treatment initiation **Post-**discharge will continue to be treated with optimized standard of care HF-medications (i.e., locally commercially available ACEI or ARB, beta-blockers, and other HF-guidelines therapy at the discretion of the treating physician). They could receive the first LCZ696 dose at any point between the **day after discharge** and **up to 14 days after Discharge** (i.e., Discharge occurred on 01-Oct-2016: Post-discharge treatment may start at any time *between the day after Discharge and 15-Oct-2016*), implementing the required mandatory 36 hours wash-out if a patient is on current ACEI therapy.

Prolonged hospital stay

Duration of hospitalization in the various countries may vary broadly. Across the globe, the average length of hospital stay is about 5–10 days (Ponikowski P, 2014). However, some patients may prolong their hospital stay for reasons **other than worsening of HF conditions**,

and the investigator must document the details for the prolongation in the source documentation. To allow for the variability and unplanned lengthening of hospital stay, provisions are made to enable initiation of the LCZ696 therapy, as indicated below.

1. If assigned to **Pre-**discharge treatment, patients *will continue* LCZ696 treatment as per investigator's directions.

   The date for the Discharge visit (Visit 102) assessments will be calculated as the date of Randomization + 1 week (i.e., Randomization on 07-Mar-2016; Visit 102 will be on 14-Mar-2016). All assessment will be completed and entered in the CRF page for Visit 102.

   Visit 103 (2 weeks after-Randomization) will be calculated as the date of Randomization + 2 weeks (i.e., Randomization on 07-Mar-2016; Visit 103 will be on 21-Mar-2016). All subsequent visit dates will be derived from the date of Visit 103 (i.e., visit 104 = Visit 103 + 2 weeks).
2. If assigned to **Post-**discharge AND in the hospital on day 10 AFTER Randomization:

   All the **assessments indicated for the Discharge visit** (Visit 102) should be carried out **at least 2 days before** starting LCZ696 treatment. All the results will be reported in the Discharge page of the CRFs. Also, the mandatory 36 h washout for ACEI must be completed.

   Patients may start LCZ696 treatment, *as early as 12 days but no later than 21 days after the RANDOMIZATION date,* while remaining in the hospital.

   The date when such patient starts LCZ696 treatment will represents Visit 103 and all assessment related to that visit must also be completed. All subsequent visit dates will be derived from the date of Visit 103 (i.e., visit 104 = Visit 103 + 2 weeks).

If a patient is Randomized but not treated with LCZ696 within the windows provided:

- For the **Pre-discharge** group within 7 days after Randomization;
- For the P**ost-discharge** group either
  a. within 2 weeks after discharge
  b. or, if due to prolonged hospital stay, between 12 and 21 days after Randomization

the patient should be withdrawn.

For more details on study treatment, please refer to Section 5, and refer to the Assessment Schedule for the visit frequency during the study.

To identify early in the course of the study any potential safety or tolerability issues, two interim safety analyses will be carried out by an internal independent DMC when 30% and 60% of the patients have completed the visit at 10-weeks after Randomization (Visit 199) to assess if the study should be terminated early.

3.2 Rationale of study design

The study population of hemodynamically stabilized patients, while hospitalized due to ADHF episode, was chosen to complement safety and tolerability data from the PARADIGM-HF study which investigated chronic HF patients with reduced ejection fraction.

The TRANSITION study is designed to provide information whether pre- discharge or post-discharge initiation of LCZ696 would be effective strategy to support treatment management in patients admitted to the hospital due to ADHF, treated and stabilized hemodynamically for at least 24-hour.

Stratification of admitted patients based on their HF therapy prior to admission (i.e., ACEI, ARBs, ACEI/ARB naïve treatment) will ensure that within a stratum the distribution between Pre- and Post-discharge is similar. Representation is pre-set only for the patients, who are ACEI/ARB-naïve, which are expected to represent at least 7% of the total patient population (see Section 5.3 for details). In the ASTRONAUT trial the patient population was similar to that expected to participate in this trial (LVEF<40 and admitted for ADHF), with 15.1% of patients not taking ACEI or ARBs at baseline (Gheorghiade M, 2013). As the use of ACEI and ARBs has recently increased, compared to the time when recruitment for the ASTRONAUT study occurred (2009-2011), a conservative assessment for the enrollment of ACEI/ARB treatment-naïve was taken, leading to the expectation of a minimum of 70 patients (7% of total) in this study.

The open-label treatment is considered to be operationally pragmatic, as the type and number of HF treatments are numerous and it would be cumbersome to implement a double-blind double dummy treatment plan. In PARADIGM-HF study fewer patients stopped their study medication overall or because of an adverse event in the LCZ696 group than in the enalapril group. It is expected that early withdrawal rate due to intolerance or AEs should be the same between the Pre- and Post-discharge groups, thus reducing bias.

Re-hospitalization rates in European countries range from 24% at 12 weeks to 44% at 1 year after discharge (Du XJ, 2014; Dar O and Cowie MR, 2008). It is then important for the study to capture the totality of hospitalizations for the study duration, given that: 1) hospitalization is an independent risk factor for mortality; 2) hospitalization is an independent risk factor for future hospitalizations; 3) one of the main goals of treatment of HF is to reduce risk of hospitalizations, as per current guidelines.

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

Starting dose, target dose, regimen, titration scheme, and tapering-off scheme for LCZ696 all are in accordance with approved product labeling.

The target dose of 200 mg LCZ696 bid used in this protocol is the dose studied in the CLCZ696B2314/PARADIGM-HF trial that demonstrated superiority over enalapril 10 mg bid. A dose of 200 mg LCZ696 bid delivers similar exposures of valsartan (assessed by AUC) as valsartan 160 mg bid, the maximal approved valsartan dose for HF and the dose recommended in international guidelines for the treatment of HF. In addition, biomarker analysis (increase in levels of ANP and cGMP) indicates that this dose delivers approximately 90% of its maximal neprilysin inhibition (Gu J, 2010).

The duration of the Treatment Epoch for 10 weeks after Randomization is deemed adequate to enable the assessment of the study endpoints: number of patients in the Pre-discharge treatment initiation group and number of patients in the Post-discharge treatment initiation

group achieving the target dose of 200 mg LCZ696 twice daily, as well as the safety and tolerability of LCZ696 treatment. The Follow-up Epoch for 16 weeks is deemed adequate to evaluate maintenance of either target- or tolerated dose in both treatment groups (Pre- and Post-discharge).

With respect to oral HF treatments, the proportion of patients treated with ACE inhibitors and ARBs, beta-blockers, and mineralocorticoid-receptor-antagonists (MRA) significantly increases at discharge after the index admission. This practice is supporting the event of an admission for HF as an opportunity to optimize the patient's background therapy, for a relevant number of patients (Maggioni A, 2013b). Pre-discharge initiation may be one approach to optimize evidence-based treatments in this population. In the IMPACT-HF study, Pre-discharge initiation of the beta-blocker carvedilol in stabilized patients hospitalized for HF, did not increase side effects or length of stay and was not associated with an increased risk of serious adverse events up to 60 days after discharge (Gattis WA, 2004).

Pre-discharge initiation of LCZ696 is expected to provide patients with the benefits of novel therapeutic approach of simultaneous neprilysin inhibition and angiotensin type 1 (AT_1) receptor blockade as early as possible.

3.4 Rationale for choice of comparator

No comparator is used in this study. The comparison is carried out between two different modalities of treatment with LCZ696, Pre- and Post-discharge treatment initiation.

3.5 Purpose and timing of interim analyses

Two interim analyses of tolerability and safety will be carried out during the study when 30% and 60% of the patients have completed the visit at 10-weeks after Randomization (Visit 199). Details will be pre-specified in the Charter of the DMC .

The results of the interim analyses will be reviewed by the internal independent DMC. Apart from investigators and pharmacists, all Novartis employees and others, who are involved in the conduct of the trial, in the analysis of the final trial results, or who have contact with study centers, should remain blinded to the treatment codes as much as possible. The CRF does allow accidental systematic unblinding, with treatment assignment only indirectly apparent. Interim analysis results should also not be divulged until all monitoring decisions have been made and the database has been locked for either of the final analyses.

3.6 Risks and benefits

Risks associated with participation in this study are primarily associated with potential side effects of the study drug LCZ696, which are comparable to other proven HF treatments, such as ACEI, ARBs, and MRA, including events like hypotension, renal impairment, hyperkalemia, angioedema.

To date, over 15,000 subjects have taken LCZ696 in studies that have been performed in healthy subjects and patients with hypertension, heart failure with preserve ejection fraction, and heart failure with reduced ejection fraction.

In PARADIGM-HF study the overall incidence of adverse drug reactions to LCZ696 in heart failure patients was comparable to that seen with enalapril. During PARADIGM-HF LCZ696 up-titration run-in phase (median drug exposure 29 days), 10.4% of patients permanently discontinued, 5.9% because of an adverse event, most commonly renal dysfunction (1.8%), hypotension (1.7%) and hyperkalemia (1.3%). However, discontinuation of therapy due to an adverse event in the double-blind period of the PARADIGM-HF study occurred in 10.7% LCZ696-treated patients and in 12.2% enalapril-treated patients. The events most commonly associated with dosage adjustment or treatment interruption were hypotension, hyperkalemia and renal impairment.

Risk of hypotension

Cases of symptomatic hypotension have been reported in patients treated with LCZ696 during clinical trials, especially in patients ≥ 65 years old, patients with renal disease and patients with low SBP (< 112 mmHg). Patients with SBP < 100 mmHg were not studied, therefore LCZ696 therapy should not be initiated until SBP is ≥ 110 mmHg.

A higher rate of symptomatic hypotension was observed with LCZ696 than with enalapril in the CLCZ696B2314/PARADIGM-HF trial. However, there was no increase in the rate of discontinuation because of possible hypotension-related adverse effects. Other hypotension-related SAEs, including syncope, dizziness, loss of consciousness, and orthostatic hypotension, were infrequent and occurred at a comparable incidence with enalapril. Hypotension was reversible and manageable with dose adjustment or temporary treatment interruption.

Symptomatic hypotension is more likely to occur if the patient has been volume-depleted, e.g., by diuretic therapy, dietary salt restriction, diarrhea or vomiting. Sodium and/or volume depletion should be corrected before starting treatment with LCZ696, however, such corrective action must be carefully weighed against the risk of volume overload.

When initiating therapy or during dose titration with LCZ696, blood pressure should be monitored at an appropriate interval, in accordance with normal clinical practice.

If hypotension occurs, dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g. hypovolemia) should be considered. If hypotension persists despite such measures, the dosage of LCZ696 should be reduced or temporarily discontinued. Permanent discontinuation of therapy is usually not required.

Risk of renal impairment

As for any drug that acts on the renin-angiotensin-aldosterone system, use of LCZ696 may be associated with decreased renal function. In PARADIGM-HF, the incidence of clinically relevant renal impairment was low and associated treatment discontinuation was observed less frequently in patients receiving LCZ696 (0.65%) compared to enalapril (1.28%).

There is very limited clinical experience in patients with severe renal impairment (estimated GFR <30 ml/min/1.73 m^2), these patients may be at greater risk of hypotension and therefore will be excluded from the study participation. There is no experience in patients with end-

stage renal disease, LCZ696 is not recommended in these patients and should be permanently discontinued if such condition should develope during the study.

Assessments of patient's renal function will be performed during routine study visits (i.e., serum creatinine and eGFR).

In patients with moderate renal impairment (eGFR 30-60 ml/min/1.73 m^2), the starting dose will be 50 mg twice daily. Down titration of LCZ696 should be considered in patients who develop a clinically significant decrease in renal function

Concomitant administration of LCZ696 with ACEI, ARBs or direct renin inhibitor aliskiren is prohibited.

In elderly patients, volume-depleted patients (including those on diuretic therapy), which is more representative of the TRANSITION-study population, concomitant use of LCZ696 and NSAIDs may lead to an increased risk of worsening of renal function. Monitoring of renal function will be carrying out during the study in all study subjects.

The occurrence of a clinically significant renal dysfunction event must be reported using the appropriate CRF pages.

The risk of renal impairment can be adequately managed by complying with the entry criteria, frequent renal function laboratory assessments during the study, as well as following Appendix 5 "Guidelines for the management of renal dysfunction".

Risk of hyperkalemia

Similar to other RAAS-blockade agents, the use of LCZ696 may be associated with an increased risk of hyperkalemia, although hypokalemia may also occur.

In PARADIGM-HF, the incidence of hyperkalemia adverse events was 11.6% in the LCZ696 treated patients compared to 14% in the enalapril treated patients. Clinically relevant hyperkalemia that resulted in treatment discontinuation was observed in 0.26% of LCZ696 treated patients compared to 0.35% of enalapril treated patients. (McMurray, JJV, 2014b)

Therapy with LCZ696 should not be initiated if serum potassium level is above 5.4 mmol/L.

Medications known to raise potassium levels (e.g. potassium-sparing diuretics, potassium supplements) should be used with caution when co-administered with LCZ696, especially in patients who have risk factors such as renal impairment, diabetes mellitus, hypoaldosteronism, or patients on a high potassium diet or on mineralocorticoid antagonists.

Monitoring of serum potassium will be performed during all routine study visits.

If patients experience clinically significant hyperkalemia, adjustment of concomitant medications, or temporary down–titration or discontinuation of LCZ696 is recommended. If serum potassium level is above 5.4 mmol/L temporary discontinuation of LCZ696 should be considered.

The risk of hyperkalemia can be adequately managed by the described in Appendix 3 "Treatment guidelines for hyperkalemia" and frequent laboratory assessments of potassium levels starting before LCZ696 initiation and continuing during treatment. An option for

stopping potassium supplements or reducing dietary potassium or adjusting the dose of concomitant medications, as well as down-titrating and temporary discontinuation of LCZ696 is also provided.

Risk of angioedema

Angioedema has been reported in patients treated with LCZ696. In PARADIGM-HF, during the randomized treatment, angioedema was reported in 19/4187 (0.5%) patients treated with LCZ696, compared with 10/4212 (0.2%) patients treated with enalapril (McMurray JJV, 2014a).

Black patients have an increased susceptibility to develop angioedema and a higher incidence of adjudicated angioedema was observed in Black patients treated with LCZ696 (2.4%) compared with enalapril (0.5%). However, there were no severe cases of angioedema involving airway compromise or requiring mechanical support in this study.

Simultaneous inhibition of the ACE and NEP breakdown pathways of bradykinin is thought to significantly increase the risk of occurrence of angioedema (Sulpizio AC, 2002). Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, the co-administration of the LCZ696 with ACEI is contraindicated and LCZ696 must not be started for at least 36 hours after discontinuing ACE inhibitor therapy.

Patients with a known history of angioedema were not studied. As they may be at higher risk for angioedema, related exclusion criteria for patients with a history of hereditary or idiopathic angioedema or a known history of angioedema related to previous ACE inhibitor or ARB therapy is included in this protocol.

Concomitant use of LCZ696 with ACEIs is contraindicated during the whole duration of the study to minimize the risk of angioedema. A washout period of 36 hours is required between taking the last dose of ACEI therapy and initiating LCZ696 to reduce the risk of angioedema due to otherwise overlapping ACE/neprilysin inhibition. The 36-hour washout is generalizable for most ACE-inhibitors, which have half-lives comparable to enalapril. For the few ACEIs that have longer half-lives than enalapril, those agents will have a 2-4 times decrease in plasma levels at 36 hours, which is considered a good compromise between avoiding the overlap of simultaneous inhibition of both ACEI and neprilysin inhibition and the withdrawal of ACEI therapy. This 36-hour washout period is expected to present minimal risk to patients, especially since all patients will continue using their other background HF medications during this period.

Similarly, a 36 hours washout period will be implemented any time when LCZ696 is discontinued and patients resume the use of an ACEI. This 36-hour ACEI/LCZ696-free washout period is consistent with other LCZ696 studies, as well as the CLCZ696B2314/PARADIGM-HF study (McMurray JJV, 2014a; Solomon SD, 2012).

If angioedema occurs, LCZ696 should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. LCZ696 must not be re-administered. The occurrence of an angioedema-like event must be reported using the appropriate CRF pages including the narrative of the event.

The risk of angioedema is considered to be adequately managed by exclusion criteria, warnings and precautions that recommend permanent discontinuation of LCZ696 and symptomatic treatment and monitoring in case angioedema occurs.

Other risks

Other risks may be associated with general study procedures, such as pain and infection potentially associated with needle pricks required for blood draws. All of these risks are no different from ones associated with similar studies.

Risks to patients in this trial will be minimized by compliance with the entry criteria, close clinical monitoring.

Benefits of LCZ696

LCZ696 offers an innovative approach to the treatment of patients with heart failure through enhancement of the beneficial effects of the endogenous natriuretic peptides (NP) system and other vasoactive peptides while simultaneously limiting the detrimental effects of RAAS over-activation. It has been shown that treatment with LCZ696 translated into a clinically meaningful benefit over current evidence-based guideline recommended ACEI therapy for reduction in CV death, all-cause mortality, HF hospitalization, including first and total hospitalization, and improvement in symptoms and patient-reported outcomes in patients with NYHA Class II-IV HF with systolic dysfunction (HFrEF) when LCZ696 has been taken for an average of 27 months (McMurray JJ, 2014).

When compared with enalapril, 16% fewer LCZ696-treated patients required intensification of outpatient therapy for worsening of HF defined as addition of a new HF drug, intravenous therapy, or an increase in the daily dose of diuretic for more than one month. When all (including repeat) emergency department evaluations for heart failure were considered, the LCZ696 group had 30% lower rate of such visits than the enalapril group. The patients in the LCZ696 group had 23% fewer hospitalizations for HF ($P<0.001$). In addition, the reduction in heart failure hospitalization with LCZ696 was evident within the first 30 days after randomization (Packer M, 2015). In this study, treatment is planned for 26 weeks, and there are limited information on a short term treatment.

Benefits associated with participation in the study include receiving a potentially efficacious treatment for a currently unmet medical need in the treatment of HF, as suggested by results of previous studies. Also, all medical monitoring/tests associated with the study will be provided to closely observe the patients' health status in a manned that may be stricter than the conventional standard of care, and thus eliciting compliance with medical treatments and potentially eliciting the feeling to have more control over their condition, which can lead to a more positive outlook and better quality of life. In addition, the contribution to the diseases knowledge attained from this study may lead to more effective treatment in the future for HF patients.

4 Population

The study population will consist of patients hospitalized for an episode of acute decompensation of heart failure who are diagnosed with CHF NYHA class II-to-IV and reduced ejection fraction (LVEF ≤ 40%). Patients can be either with first presentation (*de novo*), or acute decompensation of HF due to deterioration in patients with a prior history of chronic HF.

The goal is to randomize approximately 1000 patients in approximately 200 centers worldwide. Approximately, 1250 patients will be screened. Considering that a 20% screening failure rate is expected, approximately 1000 patients are expected to be included in the primary analysis.

4.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed
2. Male or female patients 18 years of age or older
3. Patients hospitalized due to acute decompensated HF episode (**ADHF as primary diagnosis)**, including Signs and Symptoms evaluation at admission.
4. Diagnosis of HF New York Heart Association class II-to-IV and reduced ejection fraction at Screening
5. Left ventricular ejection fraction ≤ 40% at Screening (if not assessed at Screening, any local measurement made within the past 12 months using echocardiography, MUGA, CT scanning, MRI, or ventricular angiography is acceptable, provided the latest assessment indicates values ≤40%
6. Patients **did not** receive ***any*** IV vasodilators (except nitrates), and/or ***any*** IV inotropic therapy from the time of presentation for ADHF to Randomization
7. Stabilized (while in the hospital) for *at least 24 hours leading to Randomization defined as:*
   - No need for IV diuretics in the past 24 hours prior to signing ICF
   - Systolic blood pressure (SBP) ≥ 110 mm Hg for at least 6 h prior to Randomization
8. Meeting one of the following criteria:
   - Patients on any dose of ACEI or ARB before admission.
   - ACEI/ARB **naïve** patients and patients **not** on ACEI or ARB for at least 4 weeks before admission.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. 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 or allergy to the sacubitril, valsartan or any ARBs, or any of the LCZ696 excipients.

2. Symptomatic hypotension and/or a SBP of (1) < 100 mmHg at Screening, and (2) symptomatic hypotension and/or a SBP < 110 mm Hg or SBP > 180 mm Hg prior to Randomization.
3. End-stage renal disease at Screening; or estimated GFR < 30 mL/min/1.73 m^2 as measured by the simplified Modification of Diet in Renal Disease (MDRD) formula at Randomization.
4. Serum potassium > 5.4 mmol/L at Randomization.
5. Uses of other investigational drugs within 5 half-lives of enrollment, or within 30 days and until the expected pharmacodynamic effects have returned to baseline, whichever is longer.
6. Current hospitalization where patient does not receive treatment for decompensated HF.
7. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study such as:
   - Concomitant clinically relevant cardiac arrhythmias, e.g., sustained ventricular tachycardia, symptomatic bradycardia or clinically significant second degree AV block, or third degree AV block without a pacemaker;
   - Documented untreated ventricular arrhythmia with syncopal episodes within the 3 months prior to Screening;
   - History of familial long QT syndrome; or
   - Known family history of Torsades de Pointes
8. Known history of hereditary or idiopathic angioedema or angioedema related to previous ACE inhibitor or ARB therapy.
9. Requirement of concomitant treatment with both ACEIs and ARBs, or with aliskiren.
10. Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid or other major CV surgery, percutaneous coronary intervention (PCI) or carotid angioplasty within the 3 months prior to Visit 1 (Screening).
11. Coronary or carotid artery disease likely to require surgical or percutaneous intervention within the 3 months after Visit 1 (Screening).
12. Implantation of a pacemaker, implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy pacemaker / defibrillator (CRT-P/D), or upgrade of an existing device or revision of device leads within 1 month of Visit 1 (Screening).
13. Heart transplant or ventricular assistance device (VAD) or intent to transplant (on transplant list) or implant a VAD.
14. History of severe pulmonary disease (i.e., treatment with oral steroid for their pulmonary disease, or with inhaled oxygen on an out-patient basis).
15. History or evidence of drug or alcohol abuse within the last 12 months.
16. Diagnosis of peripartum or chemotherapy induced cardiomyopathy within the 12 months prior to Screening.
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. 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 at Screening (Visit 1):
    - History of active inflammatory bowel disease during the 12 months before;
    - Current duodenal or gastric ulcers during the 3 months prior to Visit 1;
    - Gastric bypass;
    - Severe hepatic impairment, biliary cirrhosis and cholestasis;
    - History of hepatic encephalopathy, history of esophageal varices, or history of portacaval shunt
      OR evidence of hepatic disease as determined by any one of the following: AST or ALT values exceeding 5 x ULN or total bilirubin > 3 x ULN at Screening;
    - Active treatment with cholestyramine or colestipol resins;
20. Presence of any other disease with a life expectancy of < 90 days.
21. Presence of bilateral or unilateral renal artery stenosis.
22. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
23. Any surgical or medical condition, which in the opinion of the investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study.
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 after discontinuation of LCZ696 treatment**.

    Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject.
      - Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal **are not acceptable methods** of contraception;
    - Male sterilization (at least 6 months prior to Visit 1). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject;
    - Combination of any two of the following (a+b or a+c, or b+c):
      a. use of oral, injected or implanted hormonal methods of contraception (combined estrogen and progestogen or progestogen only) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
      b. placement of an intrauterine device (IUD) or intrauterine system (IUS)
      c. barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with the appropriate hormonal profile, or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks prior to study treatment administration. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment she is considered not of child bearing potential.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

The sponsor will provide the following study medications:

- 50 mg LCZ696 film-coated tablet that contains 24 mg sacubitril and 26 mg valsartan (as sacubitril valsartan sodium salt complex).
- 100 mg LCZ696 film-coated tablet that contains 49 mg sacubitril and 51 mg valsartan (as sacubitril valsartan sodium salt complex).
- 200 mg LCZ696 film-coated tablet that contains 97 mg sacubitril and 103 mg valsartan (as sacubitril valsartan sodium salt complex).

Patients will be required to take the study medication twice daily in addition to their daily therapies, possibly at 12 hour interval (i.e., at 7:00 in the morning and 19:00 in the evening). Tablets should be taken with a glass of water, and may be administered with or without food.

5.1.2 Additional study treatment

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

5.2 Treatment groups

Patients will be assigned in a ratio of 1:1 within each stratum to one of the following treatment groups

- **Pre-discharge** initiation of LCZ696 treatment, where treatment is started prior to Discharge (see study design for timing);
- **Post-discharge** initiation of LCZ696 treatment, where treatment should be started AFTER Discharge but within two (2) weeks after Discharge (see study design for timing).

5.3 Treatment assignment, randomization

Stratification will occur *prior to* Randomization and it will be based on the patient's HF-therapy prior to admission (i.e., ACEI, ARBs, or 'ACEI/ARB-inhibition-naïve treatment'). Stratification will ensure that within a stratum the distribution between Pre- and Post-discharge is similar. It is expected that the naïve patients will represent *at least* 7% of the total number of patients (i.e., 70 patients from in total 1000 randomized patients).

For the samples size of 1000 patients, a maximum of 930 of ACEI or ARB-treated patients will be randomized, to ensure achieving the minimum target of 70 ACEI/ARB-naïve patients. However, more than 70 RAAS inhibition-naïve treatment patients could be included if during the study conduct a higher number is enrolled. Stratification will be performed at the country level.

Randomization/treatment assignment will be accomplished through the Interactive Response Technology (IRT).

5.4 Treatment blinding

This is an open-label study, therefore, after randomization, the investigator, pharmacist and subject will be aware of which treatment is administered to the subject. If the investigator interacts with the Novartis clinical team, he/she should not disclose treatment assignment to the Novartis team, where avoidable. The independent statistician, programmer and data manager coordinator, who need to be unblinded to review interim analysis reports for the DMCs, will not be involved in any other trial activities. Due to the nature of the CRF, accidental systematic unblinding is possible for anyone involved in ongoing data review. However, as treatment assignment is not openly apparent, and it would need a combination of data from different panels to ascertain, it is assumed that the scientific credibility of the study will not be compromised.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third patient is assigned patient number 3). The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT.

For this study using eCRFs, only the assigned patient number should be entered in the field labeled "Patient ID" on the EDC data entry screen (e.g. enter '1', '2', etc.). Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient was not randomized. The

reason for not being randomized will be enter on Screening phase disposition electronic Case report form (eCRF).

The following eCRF must be completed for **subjects who screen fail**: The demography eCRF, Informed consent eCRF; Inclusion/ Exclusion eCRF; the adverse event eCRF paper serious adverse event (SAE) form should be complete for any SAE that occurred during the screening period; Death eCRF (only in case of death during the screening period) and Withdrawal of informed consent eCRF (if consent was withdrawn during the screening period before the patient was randomized).

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with investigational treatment. The investigational treatment packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the two treatment groups 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

The target dose of LCZ696 is 200 mg twice daily.

The recommended starting dose of LCZ696 is 100 mg twice daily.

A **starting dose of 50 mg LCZ696** twice daily should be considered for:

(1) patients not currently taking an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB);
(2) patients previously taking low doses of these agents;
(3) patients with moderate hepatic impairment (Child Pugh B classification), or with AST/ALT values more than twice the upper limit of the normal range;
(4) patients with moderate renal impairment (eGFR 30-60 ml/min/1.73 m^2).

The dose of LCZ696 should be doubled every 2-4 weeks to achieve the target dose of 200 mg twice daily, as tolerated by the patient.

If a dose of LZC696 is missed, the patient should take the next dose at the scheduled time.

Investigator judgment will be the basis for up-titration toward the target dose taking into consideration tolerability (i.e., incidence of hypotension, renal or hepatic impairment and hyperkalemia) based on clinical evaluation and laboratory assessment. In case of patients experiencing tolerability issues, the investigator should consider (a) adjusting concomitant medications, or (b) temporary down–titration, or (c) temporary or permanent discontinuation of LCZ696.

All therapy dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF. Similarly, if any adverse events is reported, the appropriate eCRF page must be completed.

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

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 LCZ696 as prescribed.

5.5.5 Permitted dose adjustments and interruptions of study treatment

At the discretion of the investigator, patients could be initiated and may be maintained on either 50 or 100 mg LCZ696 bid, if they are unable to tolerate up-titration to higher doses of LCZ696 in this open-label study.

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

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

a) hyperkalemia (Appendix 3: treatment guidelines for hyperkalemia);
b) symptomatic hypotension (Appendix 4: guidelines for management of BP);
c) clinically significant decrease in eGFR/increase in serum creatinine (Appendix 5: guidelines for management of renal dysfunction).
d) worsening hepatic function. (Appendix 2: Liver event and laboratory trigger definitions and follow up requirements).

If, in the opinion of the investigator, the patient does not tolerate the assigned dose level, the investigator should consider the following:

1. Whether non-disease-modifying medication (e.g., diuretics, nitrates, CCBs, α-blockers) can be reduced to rectify the situation, before reducing the dose of the study drug to a lower dose level (100 mg bid or 50 mg bid LCZ696).
2. 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.
3. If adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern, the investigator may down-titrate the dose of the LCZ696 to:
    a. the next lower level

       The patient should be re-challenged with a higher dose when the investigator feels it is appropriate to do so per the directions provided below in this section.
    b. temporary or permanent withdrawal of the study drug

       If the study drug is temporarily discontinued, it should be reintroduced as soon as medically justified in the opinion of the investigator.

Any changes in the LCZ696 dose level must be recorded on the Dosage Administration Record eCRF and registered in the IRT system. Similarly, if any adverse events is reported, the appropriate (AEV) eCRF page must be completed.

Adjustment of LCZ696 dose level

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

If down-titration is necessary, the patient should be down-titrated to the next lower dose level. The patient may continue to receive the lower dose level for a recommended period of 1 to 4 weeks, or longer based on the investigator's judgment, before re-challenging the patient with the next higher dose level. For example, a patient who encounters tolerability problems at the target dose of 200 mg LCZ696 bid could be down-titrated to the dose of 100 mg LCZ696 bid for 1 to 4 weeks.

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, if feasible, or to temporary discontinue the study drug (see next paragraph for details).

In some instances, according to the safety and tolerability criteria and the investigator's judgment, LCZ696 dose level of 50 or 100 mg bid can be maintained if he/she considers that

the patient's condition would not allow any further up-titration to the target dose of 200 mg LCZ696 bid. In this case it would be acceptable to maintain the patient at the highest tolerated dose level.

At each up- or down-titration, IRT should be contacted to register any changes in the patient's LCZ696 dose level, including cases of temporary and permanent withdrawal of the study drug, and to obtain the medication numbers of the LCZ696 supplies required for the new dose level.

Study drug restart after temporary treatment interruption

Once the investigator considers the patient's condition appropriate for receiving LCZ696, the investigator should re-start the patient on the study drug at the most appropriate and allowable dose level per his/her medical judgment. If tolerated, the dose of LCZ696 should be doubled every 2 to 4 weeks to the target dose of 200 mg twice daily, as tolerated by the patient and as per the investigator's judgment.

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

Study visits should occur as close as possible to the time points indicated in the Assessment Schedule. The time interval between the regular visits should be maintained as scheduled, irrespective of the number of unscheduled visits that may be performed in between, according to the visit and time schedule described in the Assessment Table.

In case of pregnancy discovered during the study, the patient should be instructed to stop taking the study drug immediately. See Section 7.7 for further details on pregnancies and reporting guidelines.

Upon permanent discontinuation of LCZ696 treatment, **a minimum of 36 h between last dose LCZ696 and first dose of ACEI** should be completed. Any changes in the study drug dose level, including temporary/permanent withdrawal or re-start of the study drug, must be recorded on the Dosage Administration Record eCRF and registered in the IRT system.

5.5.6 Rescue medication

Guidance on handling liver event, hyperkalemia, hypotension, and renal dysfunction are provided to investigators in Appendix 2, 3, 4, and 5, respectively. Based on reported tolerability events, changes/lowering in LCZ696 dose levels or temporary discontinuation are allowed during the study and must be recorded in the eCRF page.

In case of concomitant medication administration, please record them in the appropriate eCRF page, and in the occurrence of an adverse event refer to the safety section of this protocol for reporting procedures.

ONLY if LCZ696 has been permanently discontinued, patients may resume the ACEIs and/or ARBs treatment. Se Section 5.5.9 for discontinuation of study treatment.

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 (i.e., after signing ICF) into the study must be recorded in the CRFs.

Medication to be recorded in the CRFs:

- Prior medications: Medications taken BEFORE hospital admission will be reported in the CRFs (also needed for stratification).
- Treatment administered **after signing ICF** will be recorded in the CRFs.

Medications administered during the acute treatments of the decompensated heart failure event (from admission to the time of signing ICF) will NOT be included in the CRFs but will remain as source documentation.

5.5.7.1 Heart failure medications for chronic therapy and other cardiovascular medications

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

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

5.5.7.2 Medications known to raise potassium levels

Concomitant use of potassium-sparing diuretics (triamterene, amiloride), mineralocorticoid antagonists (e.g. spironolactone, eplerenone), potassium supplements, and salt substitutes containing potassium or other agents (such as heparin) may lead to increases in serum potassium, and to increases in serum creatinine.

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 if LCZ696 is co-administered with these agents.

5.5.7.3 Phosphodiesterase-5 (PDE-5) inhibitors

PDE-5 inhibitors (e.g., sildenafil, vardenafil and tadalafil) should be used with caution while the patient is receiving LCZ696 due to the increased possibility of occurrence of hypotension.

5.5.7.4 Intravenous neseritide, nitroprusside and nitrates

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

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

5.5.7.5 Atorvastatin and other statins

In vitro data indicates that sacubitril inhibits OATP1B1 and OATP1B3 transporters. LCZ696 may therefore increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins.

In vivo, at steady state, the levels of atorvastatin increased when co-administered with LCZ696. Co-administration of LCZ696 increased the Cmax of atorvastatin and its metabolites by up to 2-fold and AUC by up to 1.3-fold. Therefore, caution should be exercised upon co-administration of LCZ696 with statins.

However, steady state pharmacokinetics of LBQ657 (neprilysin component of LCZ696) were not changed, valsartan levels decreased slightly when administered with atorvastatin. The effect of LCZ696 on other statins has not been examined.

Based on these results, caution is recommended when LCZ696 is co-administered with atorvastatin or other statins that are substrates of the organic anion transporters, OATP1B1 and OATP1B3.

5.5.8 Prohibited treatment

ACEIs, ARBs and direct renin inhibitors such as aliskiren

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

Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, LCZ696 must not be started for at least 36 hours after discontinuing ACE inhibitor therapy.

LCZ696 should not be co-administered with an ARB due to the angiotensin II receptor blocking activity of valsartan.

The concomitant use of any ACEIs or ARBs is strictly prohibited while the patient is receiving LCZ696. If the investigator believes that addition of an ACEI or ARB is necessary, then LCZ696 must be discontinued. If treatment with LCZ696 is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of LCZ696.

Concomitant administration of direct renin inhibitors, such as aliskiren is also prohibited in this study.

Other medications

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

5.5.9 Discontinuation of study treatment

During the **Treatment Epoch** (up to 10 weeks after Randomization), *permanent* discontinuation of LCZ696 treatment should NOT be considered withdrawn from the study. The patient should return for the assessments indicated for Visit 199 (10-weeks after Randomization), if discontinued before that visit, and Visit 199 will be also the End of Study visit for that patient. 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.

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

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

The emergence of the following circumstances will require LCZ696 discontinuation:

- Withdrawal of informed consent
- Failure to follow study-related instructions
- Pregnancy (Section 7.7)
- Use of prohibited treatment
- Investigator thinks that continuation would be detrimental to the patient's well-being

LCZ696 may be permanently discontinued **at the investigator's discretion** if any of the following occurs:

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

Depending on the serum potassium, blood pressure, or eGFR, patients may need to have their LCZ696 dose or the dose of another concomitant medication reduced or discontinued, or, if appropriate, have potentially contributing agents adjusted. Please refer to Appendices 3, 4, and 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. Treatment with LCZ696 must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require 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, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

5.5.12 Emergency breaking of assigned treatment code

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

5.5.13 Study completion and post-study treatment

Patients who reach Visit 299/EoS while taking study medication will be considered completers. Patients already in screening at the time planned enrollment is met will be allowed to continue in the study based only on approval from Novartis. Otherwise, these patients will be screen-failed.

The investigator must provide follow-up medical care for all study completers and all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care may include continuation of treatment with commercially available LCZ696 treatment or, if this will be not feasible, switching patients to ACEI/ARBs in addition to other guidelines recommended HF medications. Due to the potential risk of angioedema when LCZ696 used concomitantly with an ACE inhibitor, ACE inhibitor therapy must not be re-started until 36 hours after discontinuing of LCZ696. The type of treatment administered after End of study with regard to HF treatment (i.e., ACEI, ARBs, LCZ696) will be also included in the Concomitant Medication page.

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. The trial could also be terminated prematurely at the recommendation of the DMC if they decide any safety issues require trial termination.

6 Visit schedule and assessments

The assessment table (Table 6-1) lists the assessments schedule by study visit. All data obtained from the assessments listed, and described in detail in the subsections below, must be supported in the patient's source documentation (e.g., medical charts or patient notes). In the table it is and indicates with an "X" when the visits are performed, and identified which data remain in source documents only (S), or are entered into the database from separate source documents, i.e. outside vendors (D).

The investigator should remember to implement the mandatory 36 hours washout for ACEI prior to starting treatment with LCZ696, although it is not clearly indicated in the table of assessment.

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

[redacted]

Since this study will compare two initiation regimens for LCZ696 that may differ in their duration, it will be important for patient visits to be maintained within the visit windows specified in the protocol.

Up to the time of 10 weeks after Randomization (Visit 199), if one visit is changed with either an earlier or later date outside of the range provided, that should not result in a rescheduling of the next visit. In fact, the next visit, if at all possible, should adhere to the original time schedule.

Visits occurring after discharge but before 10 weeks after Randomization (Visit 199) should occur **within a window of +/- 3 days of the designated calendar day according to Table 6-1. Visits** occurring during the Follow-up Epoch should occur within a window of +/- 7 days of the designated calendar day

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

For patients who permanently discontinue LCZ696 during the Treatment Epoch (up to visit 199), irrespective of the treatment assignment group, the last date of LCZ696 administration will be entered in the drug administration records (DAR) page of the CRFs. However, the patient will be followed-up and should return to the site for all remaining visits up to Visit 199 (10 weeks after Randomization) but will not return for the Follow-up epoch.

Enrolled patients withdrawing from the study for any reasons during the Follow-up Epoch should be scheduled for a visit as soon as possible, at which time all of the assessments listed

for End of Study visit (EoS, Visit 299) will be performed. At this final visit all dispensed medication supplies should be reconciled and the Adverse Events and Concomitant Medications updated on their respective CRFs.

Documentation of attempts to contact the patient who do not report for the EoS visit, and are lost to follow-up, should be recorded in the source documentation.

Table 6-1 Assessment table

Epoch	**Screen-ing**	**Treatment**									**Follow-up**			
Visit	1	101 Random-ization	Start date of **Pre-** discharge treatment	102 Discharge ¤	Start date of **Post-** discharge	103	104	105	106	**199** & TD and/or PPW	201	202	203	End of Study Visit 299 & TD and/or PPW
Day	-3-to-1	1				14§	28§							
Weeks AFTER Randomization						2§	4§	6§	8§	**10**§	14 Φ	18 Φ	22 Φ	26 Φ
Weeks of follow-up											4	8	12	16
Obtain informed consent	X													
Entry criteria review	X													
Demography	X													
Medical History	X													
Alcohol and smoking history	X													
ECG	S	X		X						X				X
Signs & Symptoms	S	X		X						X				X
NYHA class		X		X						X				X
Prior & Concomitant HF Medications	X ⊥	X ⊥⊥		XΔ		XΔ	XΔ	XΔ	XΔ	XΔ	XΔ	XΔ	XΔ	XΔ
Physical Exam	S													S
Height	X													

Epoch	**Screen-ing**	**Treatment**									**Follow-up**			
Visit	1	101 Random-ization	Start date of **Pre-**discharge treatment	102 Discharge ¤	Start date of **Post-**discharge	103	104	105	106	**199** & TD and/or PPW	201	202	203	End of Study Visit 299 & TD and/or PPW
Day	-3-to-1	1				14§	28§							
Weeks AFTER Randomization						2§	4§	6§	8§	**10**§	14 Φ	18 Φ	22 Φ	26 Φ
Weeks of follow-up											4	8	12	16
Weight	S	X		S						S				S
Vital signs	X	X ₪		X		X	X	X	X	X	X	X	X	X
Blood hematology	L, S	C								C				C
Blood biochemistry, Local Laboratory	S													
*Blood biochemistry **Central** laboratory*		C		C			C			C				C
Serum creatinine, potassium, ALT, AST, total bilirubin - Local Laboratory	Ł	L		L		L	L	L	L	L	L	L	L	L
*Serum creatinine, potassium, ALT, AST, total bilirubin - **Central** laboratory*						C		C	C		C	C	C	
Urine dipstick		L				L	L	L	L	L	L	L	L	L
Urine albumin &		C		C		C	C	C	C	C	C	C	C	C

Epoch	**Screen-ing**	**Treatment**									**Follow-up**			
Visit	1	101 Random-ization	Start date of **Pre-**discharge treatment	102 Discharge ¤	Start date of **Post-**discharge	103	104	105	106	**199** & TD and/or PPW	201	202	203	End of Study Visit 299 & TD and/or PPW
Day	-3-to-1	1				14§	28§							
Weeks AFTER Randomization						2§	4§	6§	8§	**10**§	14 Φ	18 Φ	22 Φ	26 Φ
Weeks of follow-up											4	8	12	16
*creatinine-**Central** laboratory*														
[redacted]														
Pregnancy test *	X									X	X	X	X	X
Contact IRT	X	X		X		X	X	X	X	X	X	X	x	X
Dispense Study Medication / DAR			A		B	X**	X**	X**	X**	X**	X**	X**	X**	
Drug accountability						D	D	D	D	D	D	D	D	D
Adverse events	X													
Study Completion														X

TD = study discontinuation
PPW = Premature patient withdrawal
X = assessment to be recorded on clinical data base

Epoch	**Screen-ing**	**Treatment**									**Follow-up**			
Visit	1	101 Random-ization	Start date of **Pre-** discharge treatment	102 Discharge ◘	Start date of **Post-** discharge	103	104	105	106	**199** & TD and/or PPW	201	202	203	End of Study Visit 299 & TD and/or PPW
Day	-3-to-1	1				14§	28§							
Weeks AFTER Randomization						2§	4§	6§	8§	**10**§	14 Φ	18 Φ	22 Φ	26 Φ
Weeks of follow-up											4	8	12	16

S = assessment to be recorded on source documentation only

[redacted]

L = assessment carried out through the Local laboratory (and entered manually in the data base)

D = These assessments are source documentation only and will not be entered into the CRF, but collected and transferred to the database

* Please, see Section 6.5.7 for details.

** dispensing study medication depending upon change of dose level, or refilling the same dose

§ Visit should occur within a window of +/- 3 days of the designated calendar day

Φ Visit should occur within a window of +/- 7 days of the designated calendar day

◘ For patients with '*prolonged hospital stay*' (see Section 3.1 Study design) the assessments assigned to the Discharge visit should be carried out BEFORE starting LCZ696 treatment

₪ Values of BP over the preceding 24 h leading to confirmation of hemodynamic stabilization and leading to Randomization must be entered in the CRFs.

A start of LCZ696 treatment if assigned to the PRE-discharge treatment initiation

B start of LCZ696 treatment if assigned to the POST-discharge treatment initiation, and no later than 2 weeks after Discharge, or the date of stabilization as indicated by the physician.

Ł Values for [Serum creatinine, potassium, ALT, AST, total bilirubin] obtained from the local full biochemistry assessment should be entered in the CRFs.

Epoch	**Screen-ing**	**Treatment**									**Follow-up**			
Visit	1	101 Random-ization	Start date of **Pre-**discharge treatment	102 Discharge ¤	Start date of **Post-**discharge	103	104	105	106	**199** & TD and/or PPW	201	202	203	End of Study Visit 299 & TD and/or PPW
Day	-3-to-1	1				14§	28§							
Weeks AFTER Randomization						2§	4§	6§	8§	**10**§	14 Φ	18 Φ	22 Φ	26 Φ
Weeks of follow-up											4	8	12	16

[redacted]

Δ Review and update ConMeds as therapies may change/be optimized or titrated

⅄ Concomitant medications taken BEFORE admission, to enable stratification

⅄⅄ Concomitant medications/therapy provided at the time of achieving hemodynamic stability (24 h prior to Randomization)

[redacted]

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the Treatment Epoch will have the study completion page for the screening epoch, demographics, inclusion/exclusion, reason for failing screening, 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.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: year of birth, age, sex, race, ethnicity, smoking habit and alcohol use, relevant medical history/current medical condition present before signing informed consent, where diagnoses and not symptoms will be recorded.

Concomitant medication prior to admission will be collected at Screening to enable allocation of stratum. No acute therapy to treat ADHF will be collected up to the time of stabilization. Records of concomitant medications/therapy will resume (entered in the CRFs) at the time of achieving hemodynamic stability (24 h prior to Randomization), when concomitant medications are expected to be stable after the acute event treatment. Concomitant medications provided to treat AEs will be entered all the time when administered.

6.3 Treatment exposure and compliance

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

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the care giver, where feasible. Study drug accountability will also be determined by the site monitor while performing routine site visits and at the completion of the study.

6.4 Efficacy

Efficacy variables will not be assessed in this study.

6.5 Safety

6.5.1 Assessment or primary endpoint

The primary endpoint for this trial will be assessing the proportion of patients who achieve 10 weeks up-titration success, which is defined as achieving the target dose of LCZ696 200 mg bid at 10 weeks after randomization (Visit 199) regardless of previous dose interruption or down-titration (Yes/no).

6.5.2 Assessment of secondary endpoints

One of the secondary endpoints for this trial will be assessing the proportion of patients achieving and maintaining either the dose of 100 mg and/or 200 mg LCZ696 bid for at least 2

weeks leading to week 10 after randomization (Visit 199), regardless of previous dose interruption or down-titration during the 10-week after Randomization (Yes/no)

A further secondary endpoint for this trial will be assessing the proportion of patients achieving and maintaining any dose of LCZ696 for at least 2 weeks leading to week 10 after randomization (Visit 199), regardless of previous dose interruption or down-titration during the 10-week after Randomization (Yes/no)

The other secondary endpoints for this trial will be assessing the proportion of patients permanently discontinuation from study drug, at any time between randomization and week 10 (Visit 199), as well as during Follow-up Epoch, due to either AEs or any reasons (Yes/no).

6.5.3 Safety assessments

The following safety assessments will be collected throughout the study in all patients:

- Physical examinations
- Vital signs
- Height, weight
- Laboratory evaluations
- Electrocardiogram (ECG)
- All adverse events

For specific adverse events of interest (Angioedema, Hyperkalemia, Renal Impairment, Hypotension, Pregnancy), relevant data will be collected as described in the safety section and/or the appendices.

A Data Monitoring Committee (DMC) will perform interim analyses of tolerability and safety with a pre-specified charter in place that outlines potential stopping rules that will be agreed upon in advance by the sponsor.

6.5.4 Physical examination

A complete physical examination will be conducted at Screening and at End of Study visit (Visits 1, and 299) and 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.

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

6.5.5 Vital signs

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

At Screening the values of SBP must be ≥ 100 mm Hg.

During the 24 hours stabilization interval leading to Randomization, the values of BP must be documented. At least 6 BP measurements should be made, where the initial and last measurement should cover the interval of about 24 h (± 1 h). In particular, during the last 6 hours prior to Randomization, 3 BP measurements should be made and SBP must be equal or above 110 mm Hg for all of them. For example, if the first measurement is done at 18:00 on Tue. 02-Feb-2016, the last measurement should be around 18:00 on Wed. 03-Feb-2016 (± 1 h). During the last 6 hours (between 12:00 noon and 18:00 on Wed. 3 measurements must be recorded and all should be equal or above 110 mm Hg.

During the out-patient visits (e.g., after discharge), vital signs include BP and pulse measurements assessed after the patient has been sitting for five minutes, with back supported and both feet placed on the floor. If a repeat sitting measurements is deemed appropriate, as the patient may display a 'white coat effect', the measurement should be taken after 10-15 minute after the preceding one.

Clinically notable vital signs requiring review of ongoing therapeutic management are defined in Appendix 4.

6.5.6 Height and weight

Height in centimeters (cm) will be measured at Screening (Visit 1) if feasible, otherwise it could be assessed at any time before Discharge (Visit 102).

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing without shoes) will be measured at Screening (Visit 1, source documentation), at Randomization (Visit 101, to be entered in the CRF). All subsequent assessments at Discharge (Visit 102), at the Visit at 10 weeks after Randomization (Visit 199), and End of Study visit (Visit 299) will be part of source documentation.

6.5.7 Laboratory evaluations

Laboratory samples will be analyzed at the central and local laboratories. Local laboratory results will allow investigators to proceed with study visit procedures without the need to wait for central laboratory results, which may take several days to arrive.

Central and local laboratory results need not agree in order for the investigator to qualify a patient for the trial or make a dose titration decision. Local laboratory assessments will be done *in addition to* central laboratory assessments, not instead of them.

It is the responsibility of the investigator to review all laboratory results and make an assessment of whether an abnormal or notable value is clinically significant, whether additional evaluations should be performed as judged appropriate, and whether the patient may continue in the trial. Sample collection should be conducted according to the standards and requirements of the local laboratory.

- Laboratory values that exceed the boundaries of a *notable laboratory abnormality of interest* (refer to Appendix 1) must be commented on by the investigator and additional laboratory evaluations should be performed, as judged appropriate by the investigator.

- If the laboratory abnormality induces clinical signs or symptoms, or requires therapeutic intervention, and satisfies the criteria defined in Section 7.1, then the diagnosis or medical condition must be entered on the AEs page of the patient's eCRF and any treatment necessary should be documented. If the laboratory abnormality is the primary reason for an unforeseen *prolongation* of hospitalization, or unforeseen hospitalization during the out-patient period, or otherwise fulfills the seriousness category of an AE, then the procedure for rapid notification of SAEs must be followed.
- Likewise, if the laboratory abnormality leads to LCZ696 dose changes or discontinuation of LCZ696 , the patient must be followed until the abnormality resolves or until it is judged to be permanent. Any dose changes must be recorded in the DAR eCRF page. This investigation may include continued monitoring by repeat laboratory testing or by performing additional laboratory tests as deemed necessary by the investigator or the Sponsor's medical monitor.

If laboratory assessments must be repeated to confirm laboratory values or due to spoiled samples, such repeat assessments must occur *within two days* from the original assessment/study visit. If the dose of study medication was changed, IRT should be contacted, and an update to the Drug Administration Record page of the eCRFs should be entered indicating the end of the previous dose level and the start date and new dose level.

6.5.7.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential counts, and platelet count will be reported as per Table 6-2.

6.5.7.2 Clinical chemistry

A full biochemistry laboratory assessment is provided in the table below. Assessments will be carried out at Central and local laboratory as indicated in Table 6-2. Central laboratory assessments are carried out in addition to local laboratory assessment to provide a consistent platform and enable comparisons between different centers where different laboratories may use different methodologies for the analysis.

Local laboratory facilities may be used for screening and for safety monitoring supporting the evaluation of any dose changes (increase or decrease in the LCZ696 dose). Local laboratory results will allow investigators to proceed with study visit procedures, instead of waiting for central laboratory results, which may take several days to deliver the results. In addition, there will be no reconciliation of data between central and local laboratory results, and the investigator will base the decision to qualify a patient for the next step in the trial based on local laboratory data.

If a patient experiences liver function test (i.e. ALT, AST, ALP, TBL) values upper limit of normal during the study, please refer to Appendix 2 for the reporting of liver dysfunction events.

The assessment of eGFR, is based on levels of **serum creatinine** and should be provided by the laboratory of analysis and should be carried out using the simplified MDRD formula (Stenens LA, 2006).

Please, refer to Table 6-2 for the laboratory (central and/or local) and timing of collection.

Table 6-2 List of laboratory tests

Hematology *	**Biochemistry ****	**Urine assessments**
Hematocrit Hemoglobin Platelet Count Red Blood Cells count WBC Differential White Blood Cells count	Alanine amino-transferase (ALT) *** Albumin Alkaline phosphatase Aspartate amino-transferase (AST) *** Blood urea nitrogen (BUN) (OR urea ONLY for local laboratory unable to assess BUN) Calcium Chloride *Creatinine* *** *eGFR* *** Fractionated bilirubin (if total bilirubin > 2x ULN) Glucose Lipid profile (total cholesterol, LDL, HDL, and triglycerides) *Potassium* *** Sodium *Total Bilirubin** Total protein Uric Acid	Albumin ¥ Creatinine ¥ Urine dipstick §

* Timepoints of hematology assessments performed at

LOCAL laboratory	Visit No.	1, **S**

S to be kept as source documentation

CENTRAL laboratory	Visit No.	101	199	299 EoS

** Timepoints of complete list blood biochemistry assessments including those marked with ***, performed at

LOCAL laboratory	Visit No.	1, **S**

S to be kept as source documentation, with only 'selected' values to be entered in the CRFs (see below "Ł")

CENTRAL laboratory	Visit No.	101	102	104	199	299 EoS

*** Timepoints of 'selected' blood biochemistry, to be entered in the CRFs, performed at

LOCAL laboratory												
Visit No.	**1** Ł	101	102	103	104	105	106	199	201	202	203	299 EoS

Ł values obtained at Screening for 'selected' assessments from the Local full biochemistry should be entered in the CRFs

CENTRAL laboratory	Visit No.	103	105	106	201	202	203

§ Urine dipstick performed at

LOCAL laboratory	Visit No.	101	103	104	105	106	199	201	202	203	299 EoS

¥ Urine albumin and creatinine (spot urine sample) to be assessed at

CENTRAL laboratory	Visit No.	101	102	103	104	105	106	199	201	202	203	299 EoS

6.5.7.3 Urinalysis

First morning void urine samples should be collected from patients for the **dipstick assessment**. Dipstick measurements for specific gravity, pH, protein, glucose, bilirubin, ketones, WBC, and blood will be performed. WBC sediments will also be measured in case of an abnormal dipstick test.

A spot urine sample could be collected for the assessment of albumin and creatinine to be sent to the Central laboratory.

Please, refer to Table 6-2 for the laboratory (central or local) and timing of collection.

6.5.8 Electrocardiogram (ECG)

ECGs must be recorded after 10 minutes rest to ensure a stable baseline. The preferred sequence of CV data collection during study visits is ECG collection first, followed by vital signs, and blood sampling.

Standard 12 lead ECG will be performed at Screening (Visits 1), at Randomization (Visit 101)if more than 48 h after Screening, Discharge (Visit 102), at 10-weeks after Randomization (Visit 199), and End of Study visit (Visit 299).

The original ECGs should be on non-heat sensitive paper and appropriately signed. The assessment at Screening (Visit 1) will be archived at the study site as part of the Source documentation. If Randomization (Visit 101) occurs within 48 hours from Screening, and a new ECG is not performed, the ECG data from Visit 1 may be entered in the Randomization CRF set, to be used as baseline. All subsequent ECG assessments will be performed on the visit date and entered into the CRFs.

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

6.5.9 HF Signs & Symptoms and New York Heart Association Class

Heart failure signs and symptoms and NYHA functional class score will be collected at Screening (visit 1, but kept at source) to verify admission for ADHF conditions, Randomization (Visit 101), Discharge (Visit 102), at 10-weeks after Randomization (visit 199), and End of Study (Visit 299).

6.5.10 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile, as well as women of childbearing potential will have pregnancy tests performed locally as **serum** test at Screening (Visits 1), and End of Study visit (Visit 299). A pregnancy **urine test** will be performed at 10-weeks after Randomization (Visit 199), and monthly during the Follow-up Epoch (Visits 201, 202, 203). Se see assessment schedule for visit number reference.

A positive pregnancy test at Visit 1 constitutes a screen failure unless the serum β-hCG test is performed and found to be negative. In case of pregnancy discovered at any time during the treatment with LZC696, the patient should be instructed to stop taking LCZ696 immediately. A follow-up serum pregnancy test can be perform at the discretion of the patient and investigator but restarting LCZ696 treatment can be considered only if the test is negative.

6.5.11 Appropriateness of safety measurements

The safety assessments selected are appropriate for this indication/patient population, as well as assessing safety for a treatment with the mechanism of action of LCZ696 (angiotensin receptor antagonist and neprilysin inhibitor). For further details, see appendices 1-through 4 in this document.

[redacted]

7 Safety monitoring

7.1 Adverse events

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

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

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for labs and other test abnormalities are included in Appendix 1.

Adverse events should be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information.

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
  - its relationship to the study treatment (no/yes)
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE - See section 7.2 for definition of SAE)

- action taken regarding study treatment

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 Angioedema-like events

Angioedema

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

If angioedema occurs, LCZ696 should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. LCZ696 must not be re-administered. The procedure for reporting angioedema-like events is outlined in Section 8.4 of this document.

In the event of angioedema reporting, the treatment with **LCZ696 must be immediately and permanently interrupted** (i.e., do not wait for the adjudication outcome).

7.3 Serious adverse events

7.3.1 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.

7.3.2 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 is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship to study treatment, complete the SAE Report Form in English, and **send the completed, signed form by fax within 24 hours after 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

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.

7.4 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of LCZ696, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Liver events are divided into two categories:

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

Please refer to the table in Appendix 2 for complete definitions of liver events. In case of a Liver Event reporting is needed, please remember to fill out the appropriate CRF pages (Liver-Events CRF).

Any liver event which meets the criteria for "**medically significant**" event as outlined in the table of Appendix 2 should follow the **standard procedures for SAE reporting** as described in Section 7.3 of this protocol.

Every liver event as defined in the table of Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below.

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of LCZ696 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 the investigator's discretion. All follow-up information, and the procedures performed should be recorded on appropriate CRF pages, including the liver event overview CRF pages.

7.5 Serum potassium safety monitoring (hyperkalemia)

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

7.6 Renal safety monitoring

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

7.7 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 the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to LCZ696 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 analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

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

Novartis staff *[or CRO working on behalf of Novartis]* 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.

In addition, for laboratory samples are analyzed centrally, 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 (or a designated CRO).

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.3 Data Monitoring Committee

An internal and independent data monitoring committee (DMC) will be formed for this trial to monitor the study conduct, to review the results from the interim analyses, 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 or recommendation to stop the trial for safety or tolerability.

The DMC will include experts in cardiovascular disease, nephrology, clinical trials, and statistics; the members will review the results confidentially and will have no other roles in the study.

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 the data flow, purpose, 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.

8.4 Angioedema Adjudication Committee – program-wide

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

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. Submission of an angioedema report is not a substitution for the submission of an SAE report.

The membership and responsibilities of the Angioedema Adjudication Committee are defined in a separate document (entitled "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 is not specific to this study, but reviews all angioedema events in the LCZ696 program.

The procedure for reporting angioedema-like events

It is important that the investigator pays special attention to any swelling or edema that may resemble angioedema that may be reported by patients.

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

If such an event occurs, the investigator will **complete a Questionnaire for an Angioedema Event form** (provided by the Sponsor in the eCRFs) to summarize the event, its treatment, and its ultimate outcome and communicate this report to the Sponsor as soon as possible. Follow up reports must be communicated to the Sponsor as soon as new information regarding the event becomes available. All hospital records related to the event must be communicated to the Sponsor.

All Angioedema Questionnaire for an Angioedema Event **will be forwarded to an angioedema adjudication committee by the Sponsor for assessment.**

If an angioedema event satisfies the definition of an SAE, the investigator must also submit an SAE report, as outlined in the next section. Submission of an angioedema questionnaire report is not a substitution for the submission of an SAE report.

9 Data analysis

9.1 Analysis sets

The following populations will be used for the statistical analyses:

Randomized Population (RAN) will consist of all patients randomized.

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

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

9.2 Patient demographics and other baseline characteristics

The baseline value for any analysis variable in general is defined as the value measured at Visit 101 for all analyses except that a specific definition or reason is provided. For information which is not collected at Visit 101, e.g. NYHA class, physical exam, demography, local laboratory assessment, etc., the information collected at Visit 1 will be used for baseline evaluations.

Summary statistics for demographics and baseline characteristics will be provided by treatment group. The summary will be provided in mean, standard deviation, median, minimum and maximum for continuous variables or in frequency and percentage for categorical variables.

Treatment group comparability at baseline will be examined using a chi-squared test for the categorical variables and using a t-test for the continuous variables as appropriate. These p-values are provided for descriptive purposes, and are not to be considered to define any formal basis for determining factors that should be included in statistical models.

In addition, the patient relevant medical history and/or continuing medical conditions recorded at Visit 1 or Visit 101 will be summarized by primary system organ class, preferred term and treatment group.

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

9.3 Treatments

The duration on the treatment period will be summarized by treatment group (i.e., n, mean, standard deviation, median, minimum, and maximum).

Prior concomitant medications and concomitant medications used during the double-blind treatment period will be summarized by therapeutic class, preferred term and treatment group.

The SAF population will be used for the above analyses.

9.4 Analysis of the primary variable(s)

9.4.1 Variable

The primary variable is 10 weeks up-titration success, and is defined as: "achieving the target dose of LCZ696 200 mg bid at 10 weeks after randomization (Visit 199) regardless of previous dose interruption or down-titration (Yes/no)".

9.4.2 Statistical model, hypothesis, and method of analysis

The primary endpoint will be analyzed using the stratified Cochran-Mantel-Haenszel method with treatment group and randomization stratification variable (ACEI stratum, ARB stratum, or naïve patient stratum) as stratification factor; although randomization is stratified at the country level, country will not be used here as an additional stratification factor due to the expected small cell counts in some countries, in particular in the naïve patient stratum. The risk ratio (of the Pre-discharge initiation of LCZ696 arm versus the Post-discharge initiation of LCZ696 arm) will be estimated with a 2-sided 95% CI along with the estimated rate and 95% CI for each treatment arm. The above analyses will be performed based on SAF.

In addition, a supplementary analysis will be carried out, based on evaluable patients where patients with administrative discontinuations (non-AE or non-death reasons) will be considered as non-evaluable, and thus excluded.

9.4.3 Handling of missing values/censoring/discontinuations

In the primary analysis, no imputation will be used for any patients, who discontinue study therapy due to adverse events or abnormal laboratory values. All patients who prematurely discontinue, and do not achieve and maintain the target dose of LCZ696 200 mg bid at 10 weeks after randomization will be regarded as 10 week up-titration failures. Information of patients discontinuing study drug or participation in trial visits will be collected whenever possible and will be used in the analysis. In patients who could not be followed up for the primary endpoint, it is aimed to at least determine the vital status of the patients at the final visit. For the supplementary analysis, patients who prematurely discontinue due to administrative reasons (non-AE or non-death) will defined as non-evaluable, and thus be excluded from the analysis.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

Efficacy variables will not be assessed in this study

9.5.2 Safety variables

The following secondary variables will be used in the analyses:

- Achieving and maintaining either the dose of 100 mg and/or 200 mg LCZ696 bid for at least 2 weeks leading to week 10 after randomization, regardless of previous dose interruption or down-titration during the 10-week after Randomization (Yes/no)
- Achieving and maintaining any dose of LCZ696 for at least 2 weeks leading to week 10 after randomization, regardless of previous dose interruption or down-titration during the 10-week after Randomization (Yes/no)
- Permanently discontinuation from study drug (Yes/no),
    1. at any time between Randomization and week-10 after randomization, and
    2. during Follow-up Epoch, due to
        i. either AEs and
        ii. any reasons

These secondary variables will be analysed in an identical fashion to the primary variable (using the stratified Cochran-Mantel-Haenszel method – see 9.4.2 for details). Further safety and tolerability assessments are listed below:

- AEs and SAEs
- Angioedema
- Laboratory values
- Liver safety
- Vital signs: Systolic and diastolic blood pressure, pulse, heart rate, and body weight
- ECG changes
- Physical examination
- Pregnancy and assessments of fertility

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 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.

The characteristics of angioedema will be summarized as appropriate, using relative frequencies.

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.

Liver safety analyses include frequencies of treatment-emergent elevations, a shift table of baseline and worst post-baseline values, respective narrow and broad "Possible drug related hepatic disorders - comprehensive search" SMQ and preferred term frequencies, eDISH plots, and narratives for any patients discontinued due to liver function abnormalities.

Data from vital signs including body weight will be summarized as appropriate, , using both descriptive summary statistics, and various threshold flags; incidences of notable values will be presented in the tables and notable values will be flagged in the listings.

The following ECG variables will be summarized as appropriate, using both descriptive summary statistics and qualitative changes will be described.

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

9.5.4 Pharmacokinetics

Not applicable

9.5.6 PK/PD

Not Applicable

9.6 Sequence of planned analyses

9.6.1 Interim analyses

Two interim analyses are planned to be conducted when 30% and 60% of the patients have completed the visit at 10-weeks after Randomization (Visit 199) to detect early safety signals. The review will include the following analyses:

- AEs leading to permanent discontinuation of LCZ696
- AEs reported leading to down-titration of LCZ696 or temporary discontinuation
- Incidence of AEs of interest
- Concomitant medication changes when down-titration was implemented
- Compliance with the washout from ACEi or discontinuation of ARBs

The unblinded interim analysis results will be reviewed with other safety data by an unblinded DMC. At their discretion, the DMC will make a recommendation regarding trial continuation/amendment/termination. No stringent stopping boundaries are pre-specified. The details of the interim analyses will be defined in the DMC Charter.

9.6.2 Final analyses and reporting

The clinical database will be locked twice. The first database lock will occur when all subjects have completed 10 weeks after Randomization evaluation period of the study (Visit 199) and all data has been monitored, is query-clean and final. All follow-up data between 10 weeks after Randomization (Visit 199) and 26 weeks after Randomization (End of study Visit 299) will be included in the 26 weeks database. All planned analyses summarizing results by treatment group will be performed after the last subject has completed the 10 weeks after Randomization evaluation period of the study. For this analysis, group summaries will be presented. Individual subject treatment assignments (e.g. listing) will be provided prior to the 26 weeks after Randomization lock only if the required for regulatory submission(s); if required, these will be provided only to personnel identified by the Sponsor, who have no direct role in study operations. These results will be shared with a limited group of people to be identified by the Sponsor.

A second database lock will occur after all subjects have reached 26 weeks after Randomization of the study. Analyses of subject accountability and length of following, and subject status will be updated. Listings of individual subject data, and other information regarding individual subjects' treatment assignments, will be provided only after the 26 weeks after Randomization database is locked, unless required for regulatory submission(s).

9.7 Sample size calculation

The purpose of this study is to explore two modalities (Pre-discharge, and Post-discharge) of treatment initiation with LCZ696 in HFrEF patients following stabilization after an ADHF episode.

A sample size of about 1000 patients provides reasonable precision across a range of possible outcomes. When the observed rate of 10-weeks up-titration treatment success is 80% in both pre- and post-discharge, it will provide estimated risk-ratio and 95% CI of 1.00 (0.94, 1.06).

Observed rate of uptitration success at week 10 after Randomization		**Risk ratio** (Pre-discharge / Post-discharge)	**2-sided 95% CI**	**Total sample size** without adjustment
Late initiation	**Early initiation**			
75%	70%	0.93	0.87, 1.01	1000
75%	75%	1.00	0.93, 1.07	1000
75%	80%	1.07	1.00, 1.14	1000
80%	75%	0.94	0.88, 1.00	1000
80%	**80%**	**1.00**	**0.94, 1.06**	**1000**
80%	85%	1.06	1.00, 1.13	1000

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.

[*] For **Germany only**, the first paragraph will read as follows:
Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation) IRB/IEC-approved informed consent. He/she should indicate assent by personally signing and dating the written informed consent document. 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.

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.

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13 Appendix 1: Clinically notable laboratory values

Guidelines for the treating physician on clinically notable laboratory abnormalities for selected tests based on a percent change from either Screening or Randomization:

Hematology

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

Blood Chemistry

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

14 Appendix 2: Guidelines for the management of liver laboratory: Trigger definitions, liver event reporting, and follow-up requirements

General principles

Guidance is provided, based on the changes of liver function tests, to adequately and monitor report the changes in case of the occurrence during the study.

Therapy with LCZ696 should be immediately interrupted if severe hepatic impairment is developed during the study.

A special set of CRF pages should be completed at the time of reporting, to account medical history potential contributing to liver dysfunction, details on the event(s) reported, and laboratory tests.

Table 14-1 Liver event definitions

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

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

Table 14-2 Liver event follow up requirements

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

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

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

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

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

15 Appendix 3: Guidelines for the management of hyperkalemia (for serum potassium greater than 5.4 mmol/L)

General principles

Use of LCZ696 may be associated with an increased risk of hyperkalemia, although hypokalemia may also occur.

Therapy with LCZ696 should **not be initiated** if serum potassium level is above 5.4 mmol/L.

Monitoring of serum potassium will be performed during all routine study visits by both local and central laboratories.

If patients experience clinically significant hyperkalemia adjustment of concomitant medications, temporary down–titration or discontinuation of LCZ696 is recommended. If serum potassium persists at levels above 5.4 mmol/L temporary discontinuation of LCZ696 should be considered.

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

Any patient with a serum potassium above 5.4 mmol/L after enrollment into the study requires regular, repeated checks of potassium concentration (beyond that prescribed in the protocol) until it is clear that the potassium concentration is stable and not rising into the range of concern (≥ 5.5 and < 6.0 mmol/L) or potential danger (≥ 6.0 mmol/L).

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

Corrective action for management of hyperkalemia

Serum potassium above 5.4 and less than or equal to 5.5 mmol/L

- Confirm potassium concentration in a non-hemolyzed sample
- Reinforce low potassium diet and restriction of food/drinks with high potassium content (e.g. orange juice, melon, bananas, low-salt substitutes etc.)
- Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia. Consider reduction in dose or discontinuation of these agents:
  - Aldosterone antagonists (if they are believed to be the most likely cause of hyperkalemia)
  - Potassium-sparing diuretics (e.g. amiloride and triamterene) including in combination products with thiazide or loop diuretics
  - Potassium supplements, e.g., potassium chloride
  - Salt substitutes
  - Non-steroidal anti-inflammatory drugs (NSAIDs)
  - Cyclo-oxygenase-2 (COX-2) inhibitors

- Trimethoprim and trimethoprim-containing combination products, such as Bactrim® and Septra® (trimethoprim/sulfamethoxazole fixed combination)
- Herbal Supplements:
  - For example, Noni juice, alfalfa (*Medicago sativa*), dandelion (*Taraxacum officinale*), horsetail (*Equisetum arvense*), nettle (*Urtica dioica*), milkweed, lily of the valley, Siberian ginseng, hawthorn berries

- Repeat serum potassium measurement within 3 to 5 days
- If serum potassium remains above 5.4 and equal or less than 5.5 mmol/L, regularly monitor serum potassium levels to ensure stability
- Consider down-titration of LCZ696, according to investigator's medical judgment.

Serum potassium above 5.5 and less than 6.0 mmol/L

- Confirm potassium concentration in a non-hemolyzed sample
- Consider down-titration or temporarily discontinue study drug according to investigator medical judgment.
- Apply all measures outlined for serum potassium > 5.4 and ≤ 5.5 mmol/L
- Repeat serum potassium measurement after 2-3 days
- If serum potassium < 5.5 mmol/L, consider resumption of study drug at lower dose with repeat potassium within 5 days

Serum potassium greater than or equal to 6.0 mmol/L

- Immediately discontinue LCZ696
- Confirm potassium concentration in a **non-hemolyzed sample**
- Urgently evaluate patient and treat hyperkalemia as clinically indicated
- Apply all measures outlined for serum potassium > 5.4 and < 6.0 mmol/L

Notification to the sponsor of a potassium level equal to- or above 6 mmol/L should be done within 48 h. No resumption of LCZ696 without individualized case discussion with and permission from the Sponsor's Medical Monitor or his/her designee.

16 Appendix 4: Guidelines for the management of blood pressure

Symptomatic hypotension is more likely to occur if the patient has been volume-depleted, e.g., by diuretic therapy, dietary salt restriction, diarrhea or vomiting. Sodium and/or volume depletion should be corrected before starting treatment with LCZ696, however, such corrective action must be carefully weighed against the risk of volume overload.

If hypotension occurs, dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g. hypovolemia) should be considered.

If hypotension persists despite such measures, the dosage of LCZ696 should be reduced or temporarily discontinued.

Permanent discontinuation of therapy is usually not required.

The dose re-challenge and medication adjustment 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:

The recommendations that follow have been developed to guide investigators in managing patients with renal dysfunction during the course of the study.

If patients experience clinically significant decrease in renal function, adjustment of concomitant medications, temporary down–titration or discontinuation of LCZ696 is recommended.

In elderly patients, volume-depleted patients (including those on diuretic therapy), or patients with compromised renal function, concomitant use of LCZ696 and NSAIDs may lead to an increased risk of worsening of renal function.

The use of LCZ696 in end-stage renal disease patients is not recommended and LCZ696 should be immediately discontinued if patient develops this condition during the study.

If a clinically significant renal event is reported during the study, the investigator must ensure completion of the CRF pages for 'Renal events reporting'.

Two types of response to serum creatinine increase are described:

Surveillance situation

If, at any time after enrollment, eGFR decreases by ≥ 25% from baseline (Visit 1) (or if serum creatinine concentration increases to 2.5 mg/dL [221 µmol/L]), the investigator will check for potentially reversible causes of renal dysfunction such as:

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

Action situation

If a patient eGFR decreases by ≥ 40% from baseline (Visit 1) (or if serum creatinine concentration rises above 3 mg/dL (265 µmol/L), the investigator will check for potentially reversible causes of renal dysfunction (see above).

If the investigator judges that study medication has to be stopped, he/she should do so and also notify the Sponsor's Medical Monitor or his/her designee.

Thereafter, serum creatinine assessments will have to be **repeated at least each week** until levels return to acceptable values. If able to resume study drug treatment, renal function must be periodically monitored to ensure stability of eGFR.