NOVARTIS

Clinical Development

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)

Statistical Analysis Plan (SAP)
Amendment 4

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10-Nov-2017	Prior to DB lock	Add SCR set Update the rehospitalization not-HF cause Update concomitant medication selection and imputation rules on dates Update the exposure cutoff to be consistent with protocol visit window Add liver toxicity criteria table and notable vital sign criteria Update PDs that excluded from populations Detail liver and renal events	Amendment 1	NA
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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		treatment within protocol specified windows. Patients with this PD to be excluded from FAS and included in SAF. Definition of FAS is updated accordingly due to this additional exclusion.		
18-Oct-2018	Prior to Final DBL	Definition of adverse events of special interest updated for hyperkalemia and renal dysfunction.	Amendment 4	2.8.8.1
		Updates in notable vital signs.		2.8.4.2
		Medical history date imputation added.		4.1.4
		Precision added for CM end date imputation.		5.1.3.1
		Clarification for the medications collected after end of study visit.		2.4.2
		Updates in wording terms used for the duration of treatment and the total exposure to study drug.		2.4.1
		Updates in clinically notable laboratory parameter definition and adding of imputation rule.		2.8.3
		Updated 'Change to protocol specified analyses' section.		4
		Precision added for the analysis of patients permanently discontinued from study drug, due to any reasons, at any time during the study.		1.2.5

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebrovascular accident
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
ICD	Implantable cardioverter defibrillator
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment emergent adverse event
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The TRANSITION study is 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).

This document outlines the Statistical Analysis Plan for TRANSITION. This detailed statistical analysis plan includes details of [redacted] table shells and data set specifications.

The two Interim Analysis Reports for the DMC, the First Interpretable Results (FIR), and the Clinical Study Report (CSR) will result from the analysis described in this SAP.

1.1 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, or ACEI/ARB treatment naïve patients.

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.

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 the 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 are given 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, either at least 24 hours after achieving hemodynamic stabilization following the acute treatment for ADHF, or 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, and Pre-discharge treatment should start no later than 48 h prior to the planned discharge date.

A sample size of approximately 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.

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).

The primary analysis time point is Week 10 after randomization. In the primary analysis, no imputation will be used for any patients who discontinue study therapy due to adverse events or abnormal laboratory values prematurely.

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 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, 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 lock. 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).

1.2 Study objectives and endpoints

1.2.1 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.

1.2.2 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.

1.2.4 Assessment of 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).

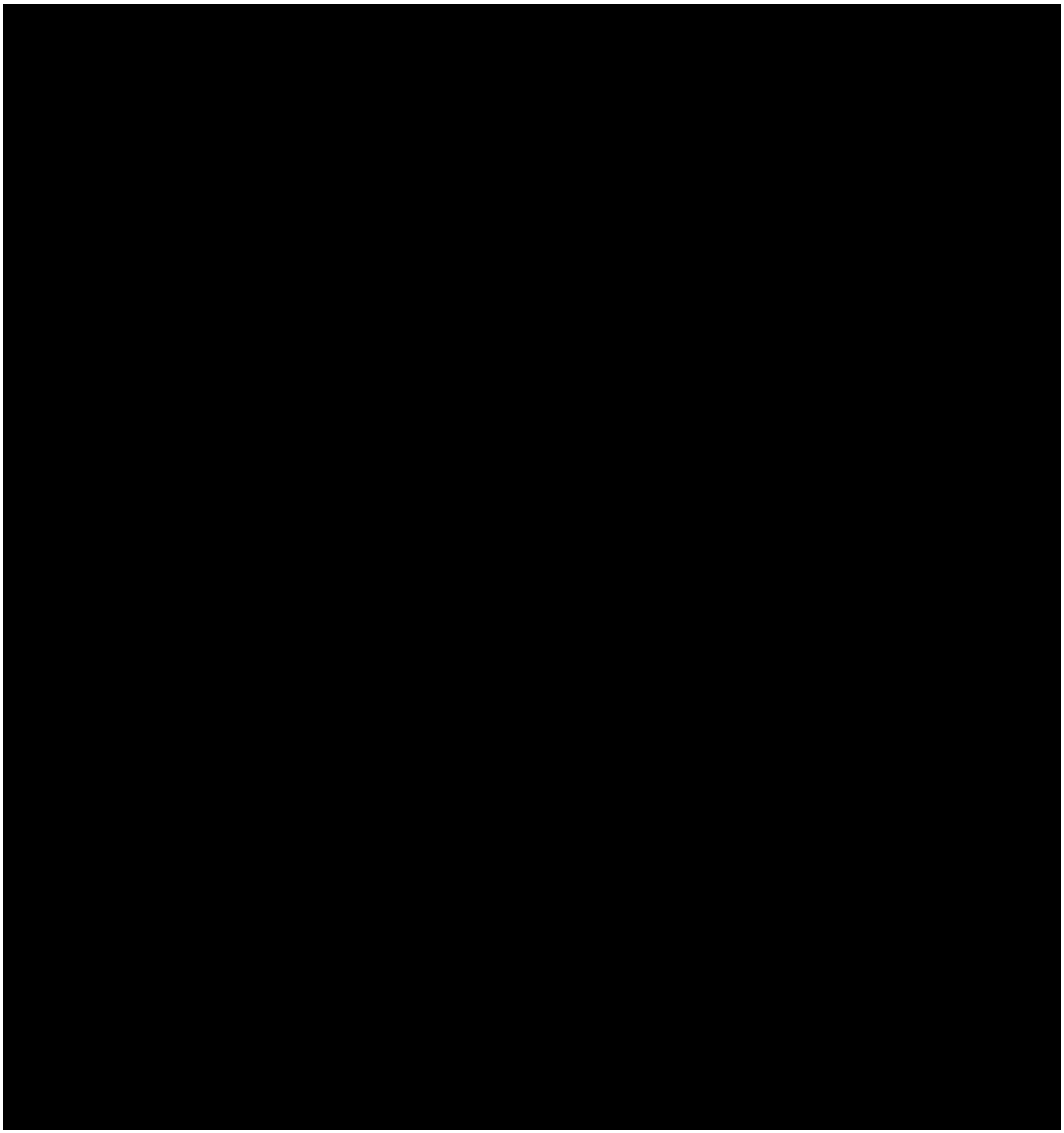
1.2.5 Assessment of secondary endpoints

There are three secondary objectives for this trial.

One endpoint will be 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).

One endpoint will be 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).

And the last endpoint will be the proportion of patients permanently discontinued 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). To analyze the proportion of patients who permanently discontinued from study drug, due to any reasons, at any time during the study, only the patients who stopped the study drug at least 7 days prior to the end of study will be considered as permanently discontinued.



2 Statistical methods

2.1 Data analysis general information

An external vendor (CRO), to which the statistical analysis is outsourced, will perfom the primary/final analysis. Data will be analyzed using SAS® version 9.4 (or higher).

Descriptive summary statistics for continuous variables include mean, median, standard deviation, Q1 (25th percentile), Q3 (75th percentile), minimum and maximum, and geometric mean (where appropriate), while for categorical variables frequencies and relative percentages will be reported.

Two interim analyses are planned, after 30% and 60% of the patients have completed the visit at 10-weeks after Randomization (Visit 199). These will be carried out by an independent statistician and independent programmer at the third-party vendor (details can be found in section 2.11) who will not be otherwise involved in the trial. Cut-off dates will need to be determined empirically; these will allow for all necessary activities (data cleaning, raising and resolution of all queries to the clinical sites, etc.) to be concluded. Details of the interim analyses are outlined in this document and in the DMC Charter

Specific descriptive analyses will be stratified by the randomization stratification factor HF therapy prior to admission (i.e. ACEI, ARBs, ACEI/ARB naïve treatment) and/or regions, countries, or centers, where deemed appropriate. The randomization stratification factor will be included in the primary endpoint analysis.

2.1.1 General definitions

In this study, patients are randomized to two Treatment groups:

- Pre-discharge initiation of LCZ696 treatment
- Post-discharge initiation of LCZ696 treatment

Thus *study treatment* in this document will refer to Pre-discharge and Post-discharge. *Study drug* will refer to LCZ696 film-coated tablets at doses of 50 mg, 100 mg, and 200 mg. *Treatment actually received* will refer to the *actual* treatment group, rather than the *randomized* treatment group.

The terms *date of first administration of study drug/treatment* and *date of last administration of study drug/treatment* are the first and last reported dates of administration of LCZ696 reported in the Drug Administration Record page of the eCRF.

The term *Study Day* in this document relates to the Analysis Relative Day, Relative Start Day or Relative End Day as applicable. *Study Day* is defined relative to the analysis reference date, which is the date of randomization; it is the number of days from the reference date to the analysis date. For all dates on or after the analysis reference date, the study day is the difference to the analysis reference date plus one day (ie for date ≥ reference date, study day = date - reference date + 1); for any dates prior to the analysis reference date, the study day is simply the difference to the reference date (ie for date < reference date, study day = date - reference date). Thus the Subject Reference Start Date is designated as Study Day 1, while the date directly prior to the reference date is defined as Study Day -1 (there is no Study Day 0).

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

The study consists of three Epochs (phases): the *Screening Epoch*, the *Treatment Epoch,* and the *Follow-up Epoch*. The *Screening Epoch* is defined as the time from administration of ICF and up to the time of *Randomization*, which 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 the 24h 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.

In this study, last contact with the subject will be the end of study visit, unless an SAE occurs (see below). However, to ensure patient safety, every SAE must be reported to Novartis:

- occurring until 30 days after the last study visit, regardless of causality
- occurring after the 30 days period, if a causal relationship to study treatment is suspected

The on-treatment period exposure is defined as:

- Date of last study drug intake – first study drug intake + 1

In general, treatment emergent AEs are defined as events starting after the first dose of study treatment that were absent pre-treatment, or events present prior to the first dose but increased in severity after the first dose. This assumes the same AE with increased severity is properly entered as a separate record in the database with start date being the date when severity increases and that a second AE with same severity won't be entered before the same AE is resolved.

For any other safety analyses based on abnormalities post-baseline compared to baseline (i.e. ECGs, vital signs, etc.), where either of the results is not available, the *missing* category will be included to avoid any abnormalities being overlooked.

The following regions will be defined:

Table 2-1 Region definition

Region	Country
North America	Canada
Latin America	Argentina
Western Europe	Belgium, France, Germany, Italy, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom
Eastern Europe	Czech Republic, Poland, Russia, Slovakia
Asia	Lebanon, Saudi Arabia, Turkey

2.2 Analysis sets

The following populations will be used for the statistical analyses:

- Screened set (SCR) – All patients who signed the informed consent. The SCR includes only unique screened patients.
- 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 inadvertently been randomized into the study. In addition, patients not starting treatment within protocol specified windows will be excluded from FAS. 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 with the exception of those patients who have inadvertently been randomized into the study. Patients will be analyzed according to treatment actually received. The safety population will be used for the analyses of safety variables.

The protocol deviation codes leading to exclusion from the analysis sets defined above are presented in the section 4.5 Rule of exclusion criteria of analysis sets.

2.2.1 Subgroup of interest

Here is a list of subgroups to be used in the analysis. They will be summarized descriptively. They will also be used to stratify the primary and secondary endpoint analyses both in descriptive tables, as well as graphically in forest plots.

Table 2-2 Subgroups to be used in the statistical analysis

	Subgroup
1	Age groups: (<65, ≥65; <75, ≥75 years)
2	Gender
3	Race (Caucasian, Black, Asian, Other)
4	eGFR (≥ 30 - <60 mL/min/1.73m^2, >= 60 mL/min/1.73m^2)
5	Patients on Beta-blocker before admission (yes, no)
6	Patients on MRA (aldosterone antagonist) before admission (yes, no)
7	Patients on diuretics at baseline (before admission) (yes, no)
8	ACEI or ARBs or Naïve prior to admission (ACEi, ARB, naive)
[redacted]	
10	Diabetes (yes, no)
11	History of implantable device (CRT or ICD) (yes, no)
12	Heart failure due to ischemic heart disease (yes, no)
13	Previous hospitalization within 12 months (yes, no)
14	Atrial Fibrillation (present, absent)
15	Systolic BP at baseline (<100, ≥100 - <120, ≥120 mmHg)
16	Region *

*Region is defined as outlined in Table 2-1

2.3 Patient disposition, 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, ECG, etc., the information collected at Visit 1 will be used for baseline evaluations.

Summary statistics for demographics (age, sex, child bearing potential, race, ethnicity, weight, height and BMI), baseline characteristics, and enrolment, will be provided by treatment group. The summary will be provided in mean, standard deviation, Q1, median, Q3, 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 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 RAN will be the patient population for the above analyses. If the SAF differs from the RAN population by more than 10 patients, summary statistics for demographics, baseline characteristics, and enrolment, will carried out on the SAF patient population additionally.

2.3.1 Patient disposition

The number and percentage of patients who completed, discontinued from the study, and the reason for discontinuation will be summarized by both epoch and treatment group. The SCR and RAN will be the patient population for the above analyses; additionally, relative frequencies for both SAF and FAS populations will also be reported.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Analysis will be performed for duration of treatment with interruptions and total exposure to study drug separately. The analysis will be based on the SAF. The following definitions will be computed in days:

Duration of treatment with interruptions is defined as:

- Date of last study drug intake – first study drug intake + 1

Duration of treatment with interruptions will be summarized by treatment group for the descriptively (i.e. n, mean, standard deviation, minimum, Q1, median, Q3, and maximum) and the number (percentage) of patients will be summarized by exposure category:

- <4 weeks
- 4 to < 10 weeks
- 10 to < 14 weeks
- 14 to < 18 weeks
- 18 to <22 weeks
- 22 to <26 weeks
- ≥26 weeks

The overall patient-years on-treatment and average patient years on-treatment will be computed based on the duration of the treatment exposure as follows:

Overall patient-years = $\sum_{i=1}^{n} duration\ of\ treatment\ with\ interruptions_i/365.25$

where *n* is the total number of patients in SAF. Average patient-years on-treatment = overall patient-years on-treatment/*n*. They will be summarized by treatment group.

The durations on each dose level, time from randomization to the first dose of each dose level, and time from first dose level to final top dose will be summarized by treatment group.

Total exposure to study drug (excluding interruptions) will be computed as:

- date of last study drug intake – first study drug date + 1 – number of days of treatment interruption.

Total exposure to study drug will be summarized by treatment group (mean, standard deviation, median, minimum and maximum) as well as frequencies per duration category defined below.

- <4 weeks
- 4 to < 10 weeks
- 10 to < 14 weeks
- 14 to < 18 weeks
- 18 to < 22 weeks
- 22 to <26 weeks
- ≥26 weeks

Percentage exposure for each patient is defined as the ratio of the total exposure to study drug divided by the duration of treatment with interruptions x 100. The percentage exposure to study drug will be summarized by treatment group (mean, standard deviation, median, minimum and maximum). Treatment compliance for the on-treatment period will also be presented. The compliance is reported in the eCRF page as assessed by the investigator at each visit. No overall compliance is collected.

For each patient overall compliance will be assessed by averaging over all visits with compliance data available.

2.4.2 Prior, concomitant and post therapies

Prior or concomitant medications will be summarized for the safety set in separate tabulations based on the coding dictionary used. Prior and concomitant medications used during the randomized phase will be summarized by therapeutic class, preferred term and treatment group.

The SAF population will be used for the above analyses.

Prior medications are defined as drugs taken prior to index hospital admission. Concomitant medication is any medication given at least once post-admission and the last day of the study, including those which were started pre-admission and continued post-admission. Prior or concomitant medication will be identified based on recorded or imputed start and end dates of medication taking. 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. Concomitant medication at discharge will be summarized separately.

Per protocol, HF-related therapy starting after the End of Study (to ensure adequate chronic treatment after conclusion of study participation) is also reported. This therapy is HF-specific and may start either on the same day of EoS or as late as 10 days later due to availablity in the country of the commercial product, and also considering the needed 36-h washout that may be

needed to resume ACEI treatment after ending study medication administration. A separate table will be compiled indicating the treatment started after End of study Visit.

Prior and concomitant heart failure and cardiovascular-related medications will be summarized separately at separate time points. To be consistent with LCZ696B2314, here are the medications that will be summarized:

- ACEi*
- ARBs*
- Beta-blocking agents*
- Diuretic*
- Loop diuretics
- Thiazide
- Other Potassium sparing diuretics
- Mineralocorticoid receptor antagonists (MRAs)*
- Digoxin
- Cardiac glycosides*
- Calcium Channel Blockers (CCB)/Calcium antagonist*
- Nitrates*
- Other vasodilators*
- Oral anticoagulant*
- Other antiplatelet agents*
- Aspirin*
- Antiarrhythmic agent*
- Statins*
- Other lipid lowering agents*
- Simvastatin
- Inotropic agents

Note: those with an asterisk will be included additionally in a figure

The classes of medications will be defined in a separate file with ATC preferred term and WHO drug code.

The compliance with 36-hour washout from ACEi strata will also be summarized.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

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)”. There is no primary efficacy analysis. The Safety Population (SAF) will be used for the primary endpoint analysis. The primary endpoint will also be investigated for its robustness across subgroups defined in section 2.2.1.

2.5.2 Statistical hypothesis, model, 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; patients will be analyzed according to treatment actually received, as well as the actual stratum (rather than randomized stratum).

2.5.3 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.

2.5.4 Supportive analyses

In addition to the primary analysis, a supportive analysis will be carried out, based on evaluable patients in the SAF population where patients with administrative discontinuations (non-AE or non-death reasons) will be considered as non-evaluable, and thus excluded.

As a further supportive analysis, the primary analysis, will be repeated using the FAS population instead of the SAF population,

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary efficacy objective(s)

There are no other secondary efficacy objectives to be analyzed.

2.8 Safety analyses

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) at any time between Randomization and week-10 after randomization due to Adverse Events

These secondary variables will be analyzed in an identical fashion to the primary variable (using the stratified Cochran-Mantel-Haenszel method; see 2.5.2 for details).

2.8.1 Adverse events (AEs)

The incidence of treatment emergent adverse events (events occurred between the first dose and the last dose of study medication, including those occurred on the first dose date or last dose date of study medication) will be summarized by primary system organ class and preferred term. Additional summaries will be provided by severity and relationship to study medication. As the analysis of treatment emergent AEs will most likely lead to a higher frequency in the pre-discharge group, due to the longer exposure duration as well as the early exposure in a well-monitored hospital setting, an additional analysis of AEs since randomization will be carried out in the FAS population; for this analysis, AEs are defined as events occurred between the randomization date and the last dose of study medication that were absent pre-randomization, or events present prior to randomization but increased in severity after randomization.

Adverse events occurring after the last dose of study medication will be summarized by primary system organ class and preferred term.

Adverse events will be reported by primary system organ class and preferred term and separately by SMQ according to the Medical Dictionary for Regulatory Activities (MedDRA).

The MedDRA version used for reporting the study will be described in a footnote.

If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

The number and percentage of subjects reporting any adverse event and adverse events adjusted for exposure during the double-blind period of the study will be summarized by primary system organ class, preferred term and treatment and also by SMQ and treatment. The most common adverse events reported (1 % in any group for each preferred term in the SOC-PT table or 1% in any group for each SMQ table) will be presented in descending frequency according to its incidence in <treatment group xxx > starting from the most common event.

Separate summaries will be provided for study medication related adverse events, death, serious adverse event, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment.

Three periods will be considered for the AEs analysis:

- 10 weeks of treatment epoch which is defined as the initial 10 weeks after randomization: all AEs started during the 10 weeks of treatment epoch will be included;
- 16-weeks follow-up epoch which is defined as the additional 16 weeks after the treatment epoch: all AEs started during the follow-up epoch will be included;
- 26 weeks duration which is defined as the whole study from the randomization date up to the end of study date.

2.8.1.1 Adverse events of special interest / grouping of AEs

The characteristics of the following adverse events of special interest will be summarized as appropriate, using relative frequencies.

Table 2-3 Adverse events of special interest

AE of special interest	Definition: MedDRA preferred term / eCRF form
Hypotension events	Hypotension
	Orthostatic hypotension
	Presyncope
	Dizziness
	Dizziness postural
	Syncope
	Blood pressure decreased
	Syncope vasovagal
	Vertigo
	Vertigo positional
Hyperkalemia events	Hyperkalaemia
	Serum potassium increased
	Blood potassium increased
Renal dysfunction events	All events captured in the renal questionnaire event pages of the CRF

Only the adjudicated angioedema (as adjudicated by the adjudication Committee) reported during treatment and follow-up periods will be presented.

The information is derived from the first page of the Angioedema questionaire, after the Adjudication committee has completed and the adjudication is = Yes.

For all events, please refer to the table for specific angioedema questionnaires details.

2.8.2 Deaths

Separate summaries will be provided for deaths, including flags for on-treatment or post-treatment follow-up.

2.8.3 Laboratory data

Central 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 absolute data and change from baseline values (mean, medians, standard deviations, ranges) at each visit for which assessments are available for the parameters as in Table 2-4, and by the flagging of notable values in data listings by the criteria defined in Table 2-5. Listings will be provided for local laboratory evaluations for hematology and biochemistry parameters, as available.

Any values below the limit of quantification will be analysed as 0.5* the lower limit. Any values above the limit of quantification will be analysed as 1.5*the upper limit.

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.

Table 2-4 List of laboratory tests

Hematology	Biochemistry	Urine assessments
Hematocrit	Alanine amino-transferase (ALT)	Albumin
Hemoglobin	Albumin	Creatinine
Platelet Count	Alkaline phosphatase	Urine dipstick
Red Blood Cells count	Aspartate amino-transferase (AST)	
WBC Differential	Blood urea nitrogen (BUN) (OR urea ONLY for local laboratory unable to assess BUN)	
White Blood Cells count	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	

Table 2-5 Clinically notable laboratory values

These laboratory abnormalities are 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
Alkaline phosphatase	>100% increase
Total bilirubin	>100% increase
BUN	>50% increase
Creatinine	>50% increase
Sodium	>5% decrease
Potassium	>20% increase, >20% decrease
Uric acid	>50% increase

To evaluate potential drug-induced liver injury, newly occurring liver enzyme abnormalities at any time post-baseline will also be summarized based on the event criteria in below table.

Table 2-6 Criteria for evaluating liver toxicity

Parameter	Criteria
ALT	ALT > 3x ULN
	ALT > 5x ULN
	ALT > 8x ULN
	ALT > 10x ULN
	ALT > 20x ULN
AST	AST > 3x ULN
	AST > 5x ULN
	AST > 8x ULN
	AST > 10x ULN
	AST > 20x ULN
ALT or AST	ALT or AST > 3x ULN
	ALT or AST > 5x ULN

	ALT or AST > 8x ULN
	ALT or AST > 10x ULN
	ALT or AST > 20x ULN
ALT/AST & TBL	ALT or AST > 3x ULN & TBL > 1.5x ULN
	ALT or AST > 3x ULN & TBL > 2x ULN
	ALT or AST > 5x ULN & TBL > 2x ULN
	ALT or AST > 8x ULN & TBL > 2x ULN
	ALT or AST > 10x ULN & TBL > 2x ULN
	ALT or AST > 20x ULN & TBL > 2x ULN
ALP	ALP > 1.5x ULN
	ALP > 2x ULN
	ALP > 3x ULN
	ALP > 5x ULN
TBL	TBL > 1.5x ULN
	TBL > 2x ULN
	TBL > 3x ULN
ALP & TBL	ALP > 3x ULN & TBL > 2x ULN
	ALP > 5x ULN & TBL > 2x ULN
ALT/AST & TBL & ALP	ALT or AST > 3x ULN & TBL > 2x ULN & ALP ≤ 2x ULN
	(ALT or AST > 3x ULN & TBL > 2x ULN & ALP ≤ 2x ULN) or reported Hy's Law case
ALT or AST & AEs	ALT or AST > 3x ULN & (nausea or vomiting or fatigue or general malaise or abdominal pain or (rash and eosinophilia)

ULN: upper limit of normal

In addition, laboratory results meeting criteria (ALT/AST > 5x upper limit, Biliruin > 2x upper limit, Creatinine > 265 umol, eGFR decrease >=25%, 40% from baseline, potassium > 5.5 but <6.0 mmol/L or >=6 mmol/L) specified in protocol appendix will be summarized.

2.8.4 Other safety data

2.8.4.1 ECG data

The ECG variables (Heart rate, QRS duration) will be summarized by reporting actual and change from baseline values using descriptive summary statistics and qualitative changes as shift from baseline will be described. Additionally, data will be listed, and any other information collected will be listed as appropriate.

2.8.4.2 Vital signs

Data from vital signs will be summarized by reporting descriptive summary statistics for both actual and change from baseline at each available visit with visit 101 as baseline; furthermore, various threshold flags will also be used to determine incidences of notable values, which will be presented in tables and notable values will be flagged in the listings.

Patients with notable vital signs as defined below will be summarized:

- Pulse rate:
  - Low: <= 50 bpm and decrease from baseline higher or equal to 15 bpm
  - High: >= 120 bpm and increase from baseline higher or equal to 15 bpm
- Systolic blood pressure (SBP):
  - Low: <= 90 mmHg and a decrease from baseline higher or equal to 20 mmHg
  - High: >= 180 mmHg and increase from baseline higher or equal to 20 mmHg
- Diastolic blood pressure:
  - Low: <= 50 mmHg and a decrease from baseline higher or equal to 15 mmHg
  - High: >= 105 mmHg and increase from baseline higher or equal to 15 mmHg.

2.8.4.3 Liver and renal events

Detailed information of liver and renal event is collected only if patients report any.

The following eCRF pages will be collected for the reported liver event.

- Acetaminophen/Paracetamol
- Liver event overview: details of clinical signs and symptoms, event related to study drug, other alternative diagnoses etc.
- Local laboratory liver function test
- Autoimmune
- Viral serology
- Medical history possibly contributing to liver dysfunction.
- Pathology
- Drugs of abuse history
- History of alcohol use
- Imaging

The following eCRF pages will be collected for renal events include:

- Diagnosis page
- Follow up pages: details of clinical signs and symptoms
- Overview: other alternative diagnoses
- Renal function tests
- Local lab results
- Pathology
- Imaging

2.11 Interim analysis

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 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 DMC will also monitor all adverse outcomes during the trial and weigh them against the potential benefits of treatment. The DMC will in particular monitor:

- Angioedema
- Hyperkalemia
- Liver and Renal Dysfunction
- Hypotension
- Pregnancy

When considering whether to stop any active treatment arm of LCZ696 for safety concerns the following points should be considered

- whether observed adverse trends are compelling in terms of the amount of evidence
- whether observed adverse trends outweigh the potential benefits of treatment.

If the study is terminated, all ongoing patients will be brought in for the end of study visits. Those incomplete patients which do not get to Week 10 (Visit 199) as a result of DMC study termination by the DMC, will be excluded from both the primary analysis and the supplementary primary analysis.

To ensure the DMC is provided all required information and to ensure the proper execution of the interim analysis an interim analysis plan will be prepared. This analysis plan will include a description of all statistical analyses to be conducted, specifications for the analysis data sets and the layout of tables, figures and listings. Analyses will be planned and conducted as specified in the Clinical Trial Protocol, unless specific monitoring requirements of the DMC necessitate a different approach. The Novartis trial team will be given the opportunity to provide comments and recommendations and the Novartis list of mandatory tables for a DMC safety report will be included.

The interim analysis will not bias the course of the trial. Firstly, the independent statisticians and programmer, as well as all DMC members, are not involved in the conduct of or decisions about the study. Secondly, the DMC deliberations remain confidential to members of the clinical trial team, as well as investigators and their staff. And finally, only the recommendation to terminate the trial, if at all, will be reported to the clinical trial team.

3 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 up-titration 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

4 Change to protocol specified analyses

- The definition of the full analysis set (FAS) was updated to exclude patients who have inadvertently been randomized, regardless the study medication intake.
- The definition of the safety analysis set (SAF) was updated to exclude patients who have inadvertently been randomized, regardless the study medication intake.
- Creatinine kinase parameter is not analyzed as the data have not been collected.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Start date and end date of study drug on the respective CRF panel are mandatory; thus no date imputation will be applied.

5.1.2 AE date imputation

5.1.2.1 Adverse Event End Date Imputation

Rules for imputing the AE end date

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (treatment follow-up period end date, 31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (treatment follow-up period end date, last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.

5.1.2.2 Adverse Event Start Date Imputation

Rules for imputing the AE start date

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.c) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min (informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date

Impute AE start date -

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
4. If the AE start date year value is equal to the treatment start date year value:
    a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
    b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
    c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.3 Concomitant medication date imputation

5.1.3.1 Concomitant medication end date imputation

Rules for imputing the CM end date:

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the earliest of treatment follow-up period end date, last day of the month, date of death.

2. If CM end day/month are missing and CM year is non-missing then impute CM day as the earliest of treatment follow-up period end date, 31DECYYYY, date of death.
3. If CM day/month/year is missing then use the treatment follow-up period end date as the imputed CM end date. No imputation is performed when the concomitant medication start date is on or after the end of study visit.
4. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

5.1.3.2 Concomitant medication start date imputation

Rules for imputing the CM start date:

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial CMD Start Date	Not used	MON	YYYY
Index Admission Date	Not used	ZHSTM	ZHSTY

Where ZHSTM and ZHSTY is the corresponding Month and Year part of Index Admission Date.

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < ZHSTM	MON = ZHSTM	MON > ZHSTM
YYYY MISSING	(1) Uncertain	(1) Uncertain	(1) Uncertain	(1) Uncertain
YYYY < ZHSTY	(2.a) Before Admission Date	(2.b) Before Admission Date	(2.b) Before Admission Date	(2.b) Before Admission Date
YYYY = ZHSTY	(4.a) Uncertain	(4.b) Before Admission Date	(4.a) Uncertain	(4.c) After Admission Date
YYYY > ZHSTY	(3.a) After Admission Date	(3.b) After Admission Date	(3.b) After Admission Date	(3.b) After Admission Date

1. If the CM start date year value is missing and month/day is not missing, the imputed CM start date is set to one day prior to index admission date.
2. If the CM start date year value is less than the index admission date year value, the CM started before index admission. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the index admission date year value, the CM started after index admission. Therefore:

a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).

b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).

4. If the CM start date year value is equal to the index admission date year value:

a. And the CM month is missing or the CM month is equal to the index admission date month, then the imputed CM start date is set to one day prior to index admission date.

b. Else if the CM month is less than the index admission date month, the imputed CM start date is set to the mid-month point (15MONYYYY).

c. Else if the CM month is greater than the index admission date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.1.3.3 Prior therapies date imputation

See above

5.1.3.4 Post therapies date imputation

See above

5.1.3.5 Other imputations

There are currently no other imputation rules.

5.1.4 Medical history date imputation

If the date is not known or is incomplete, the imputation rules are:

1. If only the day is unknown, then the 01th day of this month will be imputed for a missing day;
2. If only the month is unknown, then July will be used for imputation of the missing;
3. If only the year is known, then the 1st of Jan. will be imputed for a missing day and month
4. If AE year is missing or AE is ongoing, the end date will not be imputed.

5.2 The imputed medical history date cannot be later than the screening date.AEs coding/grading

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version available at database lock.

5.3 Laboratory parameters derivations

See section 2.8.3.

5.4 Statistical models

5.4.1 Primary 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; no statistical test will be performed. The above analyses will be performed based on SAF.

For a single 2 x 2 table within each stratum, the layout is

Treatment	Outcome present	Outcome Absent	Total
Post-discharge	A	b	a+b
Pre-discharge	C	d	c+d
Total	a+c	b+d	n

The risk ratio $\widehat{RR}_{\text{post vs pre}} = (a/(a+b))/(c/(c+d))$

The Cochran-Mantel-Haenzel (CMH) test is for a series of two-by-two tables, one for each stratum, and the risk ratio estimate is

$$\widehat{RR}_{CMH} = \frac{\sum \frac{a_i\,(c_i + d_i)}{n_i}}{\sum \frac{c_i\,(a_i + b_i)}{n_i}}$$

PROC FREQ is used to calculate the relative risk estimate and the 95% confidence interval, using the RELRISK option (Dmitrienko et al, 2005).

5.4.2 Key secondary analysis

The three secondary endpoints are analyzed in identical fashion to the primary analysis, defined in section 5.4.1.

5.5 Rule of exclusion criteria of analysis sets

Table 5-1 Protocol deviations that cause subjects to be excluded

The table below shows the selected PDs leading to exclusion of the subject from analysis:

Check condition	Protocol Deviation ID (DVSPID)	Description used to Report PDs to HA/IRBs (DVTERM)	PD category - text description (DVDECOD)	Exclusion form analysis
No informed consent signature.	INCL01	No informed consent signature.	SELECTION CRITERIA NOT MET	Exclude from all analysis
Patient randomized but no study medication taken.	TRT04	Patient randomized (who have completed Randomization Visit) but no study medication taken.	TREATMENT DEVIATION	Exclude from SAF analysis
Patient was randomized in error but did NOT receive any study medication.	*OTH10	Patient was randomized in error but did NOT receive any study medication.	OTHER	Exclude from FAS and SAF analysis
Not Hospitalized due to acute decompensated HF episode (ADHF primary diagnosis), including signs and symptoms evaluation at admission.	*INCL03	Not Hospitalized due to acute decompensated HF episode (ADHF primary diagnosis), including signs and symptoms evaluation at admission.	SELECTION CRITERIA NOT MET	Exclude from FAS and SAF analysis
Patient not starting treatment within protocol specified windows.	OTH13	Patient not starting treatment within protocol specified windows	OTHER	Exclude from FAS analysis

*Subjects with PDs INCL03 and/or OTH10 are considered to have been inadvertently randomized into the study.

Table 5-2 Subject classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
RAN	INCL01	Patients that did not sign ICF
FAS	INCL01, OTH10, INCL03, OTH13	Patients that did not sign ICF
		Patient was randomized in error but did NOT receive any study medication.
		Patients not hospitalized for acute decompensated heart failure as primary diagnosis (not the same population)
		Patient not starting treatment within protocol specified windows.
SAF	INCL01, TRT04, OTH10, INCL03	Patients that did not sign ICF
		Patient randomized but no study medication taken
		Patient was randomized in error but did NOT receive any study medication.
		Patients not hospitalized for acute decompensated heart failure as primary diagnosis (not the same population)

6 Reference

Dmitrienko, A, Molenberghs, G, Chuang-Stein, C, Offen, W (2005) *Analysis of Clinical Trials Using SAS® A Practical Guide*. SAS Institute Inc., Cary, NC, USA.