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Clinical Development

LCZ696B

Clinical Trial Protocol CLCZ696B2317 / NCT02226120

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

RAP Module 3 – Detailed Statistical Methodology

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Document History – Changes compared to previous version of RAP module 3.

Version	Date	Changes
Amendment 1	Apr 13, 2016	Imputation algorithm for missing study drug stop date
Amendment 1	Dec 30, 2016	New AE outputs are added to address current HA data disclosure requirements (EudraCT and CT.gov)
Amendment 1	Jun 8, 2017	Updated PDs and exclusion criteria

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9 Investigational plan

9.7 Statistical methods planned in the protocol and determination of sample size

This document contains details of the statistical methods which will be used in the phase IIIb clinical trial CLCZ696B2317. The purpose of this study is to collect safety and tolerability data on LCZ696 in former PARADIGM-HF patients receiving open-label investigational drug. For each country, the study has a minimum duration of 12 months.

9.7.1 Statistical and analytical plans

The planned analysis is described in section 9 of the study protocol. All data analyses will be performed using SAS® statistical software (Version 9.3) unless otherwise noted. To ensure consistency across studies within the project, the RAP refers to the CSU harmonization MAP for heart failure (version number Final 1.0) and can be found in Novartis Clinical Research Documentation and Information system (CREDI)

9.7.1.1 Analysis sets

The following analysis populations will be defined for statistical analysis:

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

All cases of prospectively defined protocol deviations will be identified prior to clinical database lock and entered into a dedicated data panel as part of the locked database.

All exceptional cases and problems and the final decisions on the allocation of patients to populations will be fully defined and documented before database lock and will be fully identified and summarized in the clinical study report according to ICH E9.

Criteria defining protocol deviations are referenced in the Data Review Plan (DRP).

Table 9-1 Rules for subject classification in the analysis sets based on protocol deviations and non-protocol deviation classification criteria

Analysis set	PD severity codes that cause a subject to be excluded	Non-PD criteria that cause a subject to be excluded
Enrolled set	INCL01 Written informed consent missing	NA
Safety set	WITH01 Subject withdrew consent but continued to receive study medication. Data after withdrawal date will be excluded from SAF.	Subject did not receive study medication

9.7.1.2 Subject disposition, background and demographic characteristics

9.7.1.2.1 Subject disposition

Patients who signed the CLCZ696B2317 study informed consent but do not meet all of the enrollment requirements at Visit 1 are considered screening failures.

The number and percent of patients in the enrolled set who discontinue the study will be summarized. Discontinuations will be further summarized by reasons.

The reason for screen failure will be tabulated and listed. For patients who have re-screening visits, the reason for screen failure in the last screening visit will be reported.

The patients' center and patient numbers in this study and their corresponding center and patient numbers in PARADIGM-HF study (i.e., LCZ696B2314) will be listed.

9.7.1.2.2 Patient demographics and other baseline characteristics

Demographics and baseline data at baseline (defined below) will be summarized in the safety set (SAF). Continuous variables will be summarized by using n, mean, median, standard deviation, minimum, maximum, and categorical variables will be summarized by using frequency and percentage.

Summary statistics will be provided for demographics and other baseline characteristics including:

- (continuous) Age (years)
- (categorical) Age group: <65 years, >=65 years, <75 years, >=75 years at Visit 1
- (categorical) Sex
- (categorical) Race
- (categorical) Ethnicity
- (continuous) Height (cm)
- (continuous) Body weight (kg)
- (continuous) BMI (kg/m**2)
- (continuous) Systolic blood pressure (SBP) mm/Hg
- (continuous) Diastolic blood pressure (DBP) mm/Hg
- (continuous) Pulse (beats/min)

Body mass index (BMI) will be calculated from the measurements of height (m) and body weight (kg) measured at Visit 1: BMI = weight / height^2.

Relevant medical history will be summarized by primary system organ class and preferred term using frequency tables for the safety set.

Demographic, background, and medical histories data will be listed for the safety set.

The above analyses will also be performed for the ENR.

9.7.1.3 Definitions of baseline, post-baseline, and unscheduled visit

Baseline

In general, based on the principle described in the protocol, the baseline measurement is defined as the available measurement at Study start/Visit 1.

Post-baseline

Any measurements taken after baseline will be considered as post-baseline measurements.

Unscheduled visit

Unscheduled visit measurements will be taken into account for the analysis of safety laboratory evaluation

9.7.1.4 Missing date handling

All patients with imputed date will be listed for date imputation validation.

9.7.1.4.1 Event date missing or partially missing

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

a) If the day of the event is unknown, then the 15th day of this month will be imputed for a missing day;

b) If only the month is unknown, then July will be used for imputation of the missing;

c) If only the year of the event is known, then the 1st of July will be imputed for a missing day and month;

d) The above rules are only for general case. If there is additional information available for the missing date, then the information should be used and the imputation of missing date should be treated differently. For example, if an event occurs between two visits and its date is missing, then the date in the middle of these visits may be used.

9.7.1.4.2 Study drug stop date missing

If study drug stop date is unknown or is incomplete, the imputation rules are:

a) If only the day field of the drug stop is missing, then the missing date is imputed by using the 15th of the month;

b) If year and month are missing, then use the date of completion/discontinuation of the open-label treatment epoch if it is non-missing and no earlier than the start date of treatment;

c) If the drug stop date is completely missing, then:

    a. If patient had fatal AE (identified as either start or end date is equal to the date of death and the AE is flagged as an SAE), handling rules are (in the specified order):

        i. AE end date is not missing: use the AE end date to replace the missing drug stop date;

ii. AE end date is completely missing but AE onset date not missing: use the AE onset date to replace the missing drug stop date;

iii. AE end date is partially missing (only day field is missing): use Novartis standard procedure to impute the AE end date, and then use the imputed AE end date to replace the missing drug stop date;

iv. AE end date is completely missing and AE onset date is partial missing (missing the date field only): impute the AE onset date using Novartis standard procedure, and then use the imputed AE onset date to replace the missing drug stop date;

v. If both the AE onset and end dates are completely missing then use the last previous non-missing visit date plus 35 days to replace the missing drug stop date.

b. If patients had no fatal AE, handling rules are the same with the case that year and month are missing.

9.7.1.5 Study medication

9.7.1.5.1 Duration of treatment exposure

Duration of the treatment exposure (in days) will be summarized by using n, mean, standard deviation, minimum, Q1, median, Q3, maximum for the safety set.

The duration of the treatment exposure for a patient, regardless of temporary interruptions of usage of the study drug, is defined as

date of last study drug intake – first study drug date + 1.

The durations on each dose level, time from Visit 1 to the first dose of each dose level, and time from the first dose intake to the final top dose will also be summarized.

Duration of 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*.

The duration of total exposure to study drug will be summarized by using n, mean, standard deviation, minimum, Q1, median, Q3, maximum for the safety set.

9.7.1.5.2 Doses and Dose levels

Table 9-2 Dose and dose level

i	Dose level i	Level i dose
0	0	0 mg
1	1	50 mg
2	2	100 mg
3	3	200 mg

Average dose and dose level will be summarized by visit and overall study (n, mean, standard deviation, minimum, Q1, median, Q3, maximum).

Average dose at a given visit will be calculated as the sum of reported doses (including zero doses for interruption) / Total number of patients.

The formula for the average dose level will be calculated as the sum of reported dose levels (including dose level 0 for interruption) / Total number of patients.

The overall average (daily) dose will be calculated as:

1. Daily dose for each patient will be calculated as

$$\frac{\sum_{i=0}^{3}(\text{no. of days on taking dose level } i)\times(\text{level } i \text{ dose})}{\sum_{i=0}^{3}(\text{no. of days on taking dose level } i)},$$

   The definitions of dose level *i* and level *i* dose are described in Table 9-1. If a patient takes two different dose levels in one day (e.g., drug titrations or discontinuations due to safety concern), then 0.5 day will be counted for the patient on both two dose levels in the day.

2. Average daily dose for each patient over patients.

For the average overall dose level, the formula is similar to that for overall average (daily) dose by using "dose level *i*". to replace "level *i* dose*"*

Frequency and percentage of patients at each dose level will be summarized by visit.

The last recorded treatment on the drug administration form will be presented with the number and percentage of patients on each dose level, including dose level 0.

The average dose related to the last recorded treatment will also be summarized, for both cases of including all patients in the SAF and excluding dose level 0 patients.

9.7.1.5.3 Treatment exposure in subgroups

The above treatment exposure analyses will be repeated for the following subgroups:

- Age group <65, ≥65 years
- Age group <75, ≥75 years

- Gender (male, female)
- Race (Caucasian, Black, Asian, Other)

9.7.1.5.4 Concomitant heart failure medications

Concomitant heart failure medications are defined as any HF medications administered after the enrollment date into the study. Concomitant HF medications will be summarized by ATC and preferred term using frequency tables for the safety set.

9.7.1.6 Analysis of the primary variable

The primary objective of this study is to evaluate the safety and tolerability of LCZ696 and to provide heart failure patients from PARADIGM-HF with open-label access to this investigational drug. The safety evaluation will include:

- Adverse events
- Vital signs

9.7.1.6.1 Adverse events

Any adverse events (AEs) occurred during the study period will be assessed, overall, by primary system organ class, by preferred term, by maximum severity, by relationship to the investigational drug according to the Medical Dictionary for Regulatory Activities (MedDRA).

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

Within each AE report, the following rules are applicable. If a subject reported more than one adverse events 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 the following AEs will be summarized by primary system organ class, preferred term.

- Overall AEs
- Serious adverse events (SAEs)
- AE of special interests (AESIs), i.e. AEs of hypotension, hyperkalemia or renal dysfunction
- Angioedema/angioedema-like events
- Deaths
- AEs leading to study drug dose adjustment/temporary interruption or permanent discontinuation
- AEs leading to study drug permanent discontinuation including deaths
- AESIs leading to study drug permanent discontinuation with patients starting rescue medication(s) (ACEI/ARB)

The most common adverse events reported (≥ 1% for each preferred term in the SOC-PT table) will be presented in descending frequency according to its incidence starting from the most common event.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective

9.7.1.6.2 Vital Sign

Sitting systolic blood pressure, sitting diastolic blood pressure, and sitting pulse rate will be summarized by visit with standard summary statistics (n, mean, standard deviation, minimum, Q1, median, Q3, maximum), including changes from baseline. Baselines are defined in Section 9.7.1.3. Graphical mean plots for these vital signs will also be provided.

The descriptive summaries will be presented by vital sign and visit. Change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as:

- change from baseline = post-baseline value – baseline value

9.7.1.7 Analysis of the secondary variable

No secondary variable defined in this study.

9.7.1.8 Supportive analyses

For supportive purposes, the analysis of the primary variable described in Section 9.7.1.6 will be applied in the following subgroups:

- Age group <65, ≥65 years
- Age group <75, ≥75 years
- Gender (male, female)
- Race (Caucasian, Black, Asian, Other)

9.7.2 Interim analyses

No interim analysis was planned.

9.7.3 Sample size calculation

All surviving patients randomized in PARADIGM-HF can be considered for eligibility in this open-label study (CLCZ696B2317). It is estimated that 5,000 patients (about 59% of the core study population and approximately 72% of surviving patients) will meet the eligibility criteria and be enrolled into this open-label trial; however, since there is only one treatment arm in the study and treatment-related statistical comparisons are not planned, a specific sample size for the study is not required.

9.8 Changes in the conduct of the study or planned analyses

The following changes from the planned analyses according to the study protocol were performed.