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LCZ696

CLCZ696I12201 / NCT04164732

A multi-center, randomized, placebo-controlled patient and investigator-blinded study to explore the efficacy of oral sacubitril/valsartan in adult patients with non-obstructive hypertrophic cardiomyopathy (nHCM)

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
10-Jun-2020	Prior to DB lock	Creation of initial version	N/A - First version	NA
29-Sep-2023	Prior to DB lock	Updated to reflect the impact of the protocol amendment v02 (PA02) on the statistical aspects of the study and to add/clarify/update other points.	Information about the latest study reference documentation was updated.	Sections 1.2 & 9
			[redacted]	[redacted]
			The wording for the completed Interim Analysis 1 was updated to past tense for clarity.	Section 3
			[redacted]	[redacted]
			[redacted]	[redacted]
			[redacted]	[redacted]
			Protocol deviation with code='TRT02' was added in table 4-1 and leads to exclusion from all analysis sets	Section 4
			In addition to boxplots, arithmetic mean and spaghetti plots were added for vital signs. An additional spaghetti plot was also added for biochemistry lab parameters.	Section 7.3

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			It was clarified that deaths will be listed, if any death occurs.	Section 7.2
			Spaghetti plots for the primary efficacy endpoint were removed.	Section 6.1.3
			[redacted]	[redacted]
			[redacted]	[redacted]
			It was clarified that baseline will be presented in any change from baseline and ratio to baseline plots.	Section 6.1.4.2, 6.1.5.2, 7 & 8
			Bar charts used for model-based graphs were replaced by line plots.	Section 6.1.4.2 & 6.1.5.2.
			The analysis of the time weighted average daily dose was added.	Section 7.2
			'Subject' was replaced with 'Patient' in line with the general document wording.	Section 7.2
			An additional sensitivity model analysis was added for the primary endpoint.	Section 6.1.5
			[redacted]	[redacted]
			NYHA class was added in the background and demographic summary table.	Section 7.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			It was clarified that any compliance values>100% will be set to and used as 100% in the corresponding summary statistics.	Section 7.2
			[redacted]	[redacted]

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CLCZ696I12201".***

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

Tables, Figures, Listings (TFL) detail the presentation of the data, including shells of summary tables, figures and listings, and Programming Datasets Specification **(**PDS) contains programming specifications e.g. for derived variables and derived datasets, to support the creation of CSR outputs.

1.2 Study reference documentation

Final study protocol, version v02, 08 Apr 2022 and final SOM, version v06, 26 Jan 2022 are available at the time of finalization of Statistical Analysis Plan.

1.3 Study objectives

1.3.1 Primary objective(s)

Primary objective(s)	Endpoints related to primary objectives
• To evaluate the effect of LCZ696 on cardiopulmonary exercise test (CPET) parameters in patients with non-obstructive HCM.	• Peak VO_2 after 50 weeks of treatment.

1.3.2 Secondary objective(s)

Secondary objective(s)	Endpoints related to secondary objectives
• To evaluate the safety and tolerability of LCZ696 in patients with non-obstructive HCM.	• Adverse events (AEs), vital signs, ECGs, physical examinations and safety labs.

[redacted]

[redacted]

1.4 Study design and treatment

This multi-center study of non-obstructive HCM patients includes a single-blind (i.e., patient-blinded) treatment run-in period aimed to ensure as large a proportion as possible of patients (1) have stable symptoms and can comply with study visits during the placebo run-in period, and (2) can tolerate at least low dose LCZ696. The treatment run-in period is followed by a randomized, placebo-controlled, parallel-group, patient and investigator-blinded treatment period. It is estimated that 44 patients will be randomized into the double-blind placebo-controlled part of the study in order to have approximately 40 patients complete the week 50 CPET assessment.

The study will be comprised of a $\leq$ 35 day screening/baseline period, a 4-week single-blind treatment run-in period, followed by a 46-week double-blind placebo-controlled treatment period (total treatment period of 50 weeks), and a follow-up period of approximately 30 days after the last dose. The maximum study duration, from initial screening to end of study (EOS) for each patient is approximately 58 weeks. More details are provided in the Site Operations Manual.

Screening/baseline period

Patients who sign informed consent and pass the initial screening/baseline evaluations will then have CPET and echocardiogram testing conducted. The 35 day screening/baseline period is designed to allow for scheduling and availability of results in order to establish patient's study eligibility and baseline status. All screening/baseline safety evaluation results must be available prior to dosing. Patients who enter screening/baseline but are determined not to be eligible to enter the treatment run-in period will be considered screen failures. See protocol Section 8.1 for permitted re-screening criteria.

Treatment run-in period

Patients who qualify for study eligibility will then enter a single-blind treatment run-in period, during which all patients will receive oral (p.o.) placebo b.i.d. for 2 weeks followed by 50 mg p.o. b.i.d. of active LCZ696 for 2 weeks. Patients who are unable to tolerate either placebo or

the 50 mg p.o. b.i.d. dose level (i.e. do not meet safety criteria as specified in Table 1-1), will be considered treatment run-in failures and will not be randomized into the double-blind, placebo-controlled study, nor included in the efficacy analysis. At the end of the 4-week treatment run-in period, patients who meet the safety criteria (Table 1-1) will be eligible for randomization.

Randomized treatment period

At randomization (week 4 visit), eligible patients will be randomized into the study to receive oral (p.o.) doses of LCZ696 or placebo in a 1:1 ratio in a double-blind, placebo-controlled treatment period. All randomized patients will be titrated up to the 100 mg p.o. b.i.d. dose.

All patients will return to the study center approximately 14 days later for assessment of tolerability of the 100 mg p.o. b.i.d. dose (i.e. must meet safety criteria as specified in Table 1-1). Patients whose assessments demonstrate that they tolerate the 100 mg p.o. b.i.d. dose will be up-titrated to 200 mg p.o. b.i.d. dose, whereas those who do not meet the safety criteria (Table 1-1) will be titrated back down to the 50 mg b.i.d. dose. Tolerance to the current dose (50 mg b.i.d. or 200 mg b.i.d.) will again be assessed ~14 days later, and those patients who demonstrate tolerance will remain on this dose throughout the remaining treatment period, unless a change in tolerance is noted as defined by the criteria in protocol Section 16.3 - Section 16.5. Those patients who do not tolerate the 200 mg p.o. b.i.d. dose will be titrated down to 100 mg p.o. b.i.d. as outlined in protocol Section 6.5.

Tolerability can be assessed at scheduled visits or at any time during an unscheduled visit throughout the study as deemed appropriate by the investigator. Investigators are encouraged to request patients who report intolerance to study medication shortly after dose titration, to return to the clinic as soon as possible for re-assessment and dose modification via an unscheduled visit. Those patients who do not tolerate higher doses will be adjusted down to the previous dose as outlined in protocol Section 6.5. Patients who no longer tolerate the 50 mg p.o. b.i.d. dose will be discontinued from study treatment.

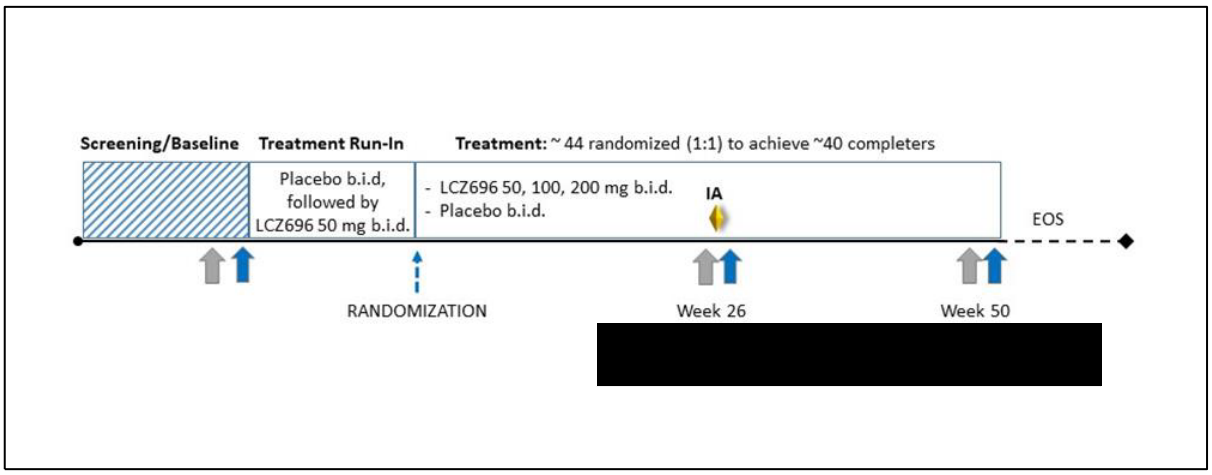
Table 1-1 Safety monitoring criteria that must be met for initial treatment and throughout all treatment periods

Parameter	Screening/baseline Period	Safety Monitoring during treatment run-in and randomized treatment periods
Potassium	≤ 5.2 mmol/L (mEg/L)	≤ 5.4 mmol/L (mEg/L)
eGFR	≥ 30 mL/min/1.73m^2	≥ 25 mL/min/1.73m^2
Blood Pressure	SBP ≥ 100 mmHg	No symptomatic hypotension as determined by the investigator and SBP ≥ 100 mmHg
AEs / Med History	No conditions that preclude continuation according to the eligibility criteria	No AEs that preclude continuation according to the investigator's judgment

Note that for abnormalities in potassium and eGFR, laboratory values should be repeated to confirm abnormality as outlined in protocol Section 16.3 and Section 16.4. For out-of-range blood pressure readings, measurement may be repeated up to two times as detailed in the Site Operations Manual and protocol Section 16.5.

Patients will receive study treatment for ~50 weeks, which includes the 4-week treatment run-in period, with dose tolerability being assessed at each visit as well as at unscheduled visits (as necessary) and through feedback that patients may provide between visits. Safety and tolerability assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology and blood chemistry), AE and SAE monitoring. At week 26 and week 50, patients will have follow-up CPET [redacted]. No further treatment will be provided after the week 50 visit, and patients will return to the study center ~30 days later for final safety and EOS evaluations.

Figure 1-1 Study design



2 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial at the IA and at the end of study (CSR).

The study FIR template (mock slides) can be found in SubWay in the study Statistics folder.

The template shows the analysis / results to be presented in the FIR. Study outputs required to be created at the time of the FIR will be highlighted in TFL shells document and marked as "Key" in the Programming Deliverables Tracker (PDT) output list.

3 Interim analyses

An interim analysis for safety and efficacy was performed when approximately 20 patients had completed the Week 26 [redacted]. [redacted] Unblinded results were reviewed by the clinical team. The clinical team may communicate the results (e.g., evaluation of PoC criteria or information needed for

planning/modifying another study) to relevant Novartis teams for information, consulting, and/or decision purposes. If early efficacy is demonstrated, enrollment of the study may be stopped. No other changes to the design of the study are anticipated as a result of the analysis.

Additional interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general, or in case of any safety concerns.

4 Statistical methods: Analysis sets

For all analysis sets, patients will be analyzed according to the study treatment(s) received.

Throughout this document, 'treatment' refers to one of the two randomized treatment arms assigned to each patient at the Day 29/Week 4 visit, i.e., LCZ696 or Placebo. For the safety analyses that will be presented separately for the treatment run-in period, 'treatment' refers to the corresponding treatments given during the treatment run-in period, i.e. placebo b.i.d. for 2 weeks followed by 50 mg p.o. b.i.d. of active LCZ696 for 2 weeks.

Unless specified otherwise, baseline will be defined as the last non-missing assessment prior to the first dose of study drug administered at the Day 1 visit.

The **safety analysis set** will include all patients that received any study drug.

The **randomized analysis set (RAS)** will consist of all randomized patients.

The **per-protocol analysis set (PPS)** will be a subset of the RAS that will consist of all randomized patients who have no major protocol deviations with relevant impact on PD/efficacy data and who are at least 80% compliant with the overall study drug administration.

The definition for the overall compliance to the study drug administration is provided in Section 7.2.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Patients are excluded from safety analysis in case of these PDs:		Exclude patient from safety analysis set
Patients are excluded from RAS analysis in case of these PDs:		Exclude patient from randomized analysis set
Patients are excluded from PD/efficacy analysis in case of these PDs:		Exclude patient from per-protocol analysis set

Category Deviation code	Text description of deviation	Data exclusion
INCL02	*Diagnosed with Hypertrophic Cardiomyopathy (hypertrophied and non-dilated left ventricle in the absence of any systemic cause) with a left ventricular wall thickness >13mm by the echocardiogram obtained during the screening/baseline period, based on local evaluation of echocardiographic images.*	
INCL03	*LVEF >50% by echocardiogram obtained during the screening/baseline period, based on local evaluation of echocardiographic images.*	
INCL04	*At the screening/baseline visit symptoms consistent with New York Heart Association (NYHA) Class II-III heart failure by physician assessment, or asymptomatic/NYHA Class I patients with:* • *NT-proBNP above 250 pg/ml and* • *peak VO2 of ≤80% of predicted based on age and gender.* *Refer to Protocol Section 16.6 for further details on screening patients who are asymptomatic/NYHA Class I.*	
INCL06	*Written informed consent must be obtained before any assessment is performed.*	
EXCL01	*Patients with a resting or provokable (i.e., exercise or valsalva-induced) left ventricular outflow tract gradient of ≥30mm Hg, based on local evaluation of echocardiographic images obtained during the screening/baseline period.*	
EXCL02	*Septal reduction procedure within 3 months of the screening/baseline visit.*	
EXCL03	*History of atrial fibrillation within 6 months of the screening/baseline visit, or secondary prevention implantable cardioverter-defibrillator device (ICD; primary prevention ICDs without a history of appropriate therapy, including shock or anti-tachycardia pacing, are allowable), or patients who are pacemaker dependent.*	
EXCL04	*Patients with a peak VO2 on the screening/baseline cardiopulmonary exercise test of > 80% of predicted based on age and gender.*	
EXCL06	*Treatment with sacubitril/valsartan within three months prior to screening.*	
EXCL07	*Known infiltrative or storage disorder causing cardiac hypertrophy that mimics hypertrophic cardiomyopathy, such as Fabry disease, or amyloidosis.*	
EXCL08	*Acute decompensated heart failure requiring augmented therapy with diuretics within 30 days of the screening/baseline visit.*	

Category Deviation code	Text description of deviation	Data exclusion
EXCL09	*Known or suspected symptomatic coronary artery disease or evidence of prior myocardial infarction based on symptoms or cardiac imaging history.*	
EXCL10	*More than moderate valvular heart disease or clinically significant congenital heart disease. Allowable conditions include systolic anterior motion of the mitral valve (SAM), bicuspid aortic valve without clinically significant stenosis or regurgitation; spontaneously closed ventricular septal defects; patent foramen ovale, small (≤ 2 mm) restrictive ventricular septal defects with normal ventricular size, and other minor defects following consultation with the sponsor's medical lead.*	
EXCL11	*Systolic blood pressure of <100 mmHg or symptomatic hypotension during the screening/baseline period or treatment run-in period.*	
EXCL12	*Persistent uncontrolled hypertension, defined as a systolic blood pressure (SBP) ≥150 mmHg, during the screening/baseline period, or a history of uncontrolled hypertension that could have led to cardiac hypertrophy.*	
EXCL14	*Contraindication to ARB administration, including hyperkalemia (serum potassium >5.2 mmol/L during screening/baseline period) or prior history of angioedema.*	
EXCL15	*Concomitant medical conditions that would preclude performance of exercise testing (e.g., lung disease, orthopedic/rheumatologic conditions).*	
*TRT02**	*Mis-randomized patient given study drug.*	

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

*NOTE: *TRT02* PD was raised for patients that were randomized and given study drug even though they should have been screen failures.

5 Statistical methods for Pharmacokinetic (PK) parameters

No PK endpoints will be analyzed in this study.

6 Statistical methods for Pharmacodynamic (PD)/Efficacy parameters

Unless specified otherwise, all patients within the per-protocol analysis set will be included in the PD/efficacy data analysis.

Note: If a patient experiences an episode of atrial fibrillation immediately before or during the CPET, as indicated on the CPET CRF page, the readings from that particular CPET will be excluded from all CPET summaries/analyses, but the patient will remain in all analysis sets.

6.1 Primary efficacy objective

To evaluate the effect of LCZ696 on cardiopulmonary exercise test (CPET) parameters in patients with non-obstructive HCM.

6.1.1 Variable

The primary efficacy variable/endpoint is the change from baseline in peak VO_2 (ml/kg/min) at Week 50.

6.1.2 Descriptive analyses

The raw peak VO_2 measurements, the change from baseline in peak VO_2 measurements and the ratio to baseline in peak VO_2 measurements will be listed by treatment, patient and visit/time.

Descriptive statistics will be provided for the raw peak VO_2 measurements, the change from baseline in peak VO_2 measurements and the ratio to baseline in peak VO_2 measurements by treatment and visit/time and will include sample size, mean (arithmetic), SD, median, minimum and maximum.

6.1.3 Graphical presentation

N/A.

6.1.4 Statistical model, assumptions and hypotheses

The effect of LCZ696 on the change from baseline in peak VO_2 over time (with Week 50 being of primary interest) will be analyzed using a longitudinal mixed effects model with change from baseline in peak VO_2 as the dependent variable. The model will include treatment, time (as a categorical variable relative to start of study treatment, i.e., Week 26 and Week 50), and the treatment-by-time interaction as fixed effects, patient as a random effect, and baseline peak VO_2 and the baseline-by-time interaction as covariates. Kenward-Roger method will be used for approximating the denominator degrees of freedom. The least-squares (LS) mean and associated 2-sided 90% confidence interval (CI) of the change from baseline in peak VO_2 for each treatment, and the estimated mean treatment difference, the p-value, and the corresponding 2-sided 80% CI will be extracted from the model at each time point.

6.1.4.1 Handling of missing data

There will be no imputation of missing data. The primary model implicitly imputes missing measurements under a missing at random assumption.

6.1.4.2 Graphical presentation of results

The least-squares (LS) arithmetic mean treatment estimates (+/- 90% CI) will be plotted over time and by treatment using line plots (all treatments in the same graph). Baseline will also be presented as 0 in this model-based plot for better visualization of the changes from baseline over time.

6.1.5 Sensitivity and supportive analyses

The following two supportive analyses will be performed to further assess the effect of LCZ696 on changes in peak VO_2:

(1) An analysis of the ratio to baseline in peak VO_2. A similar model to that described in Section 6.1.4 for the primary analysis will be used, but with ratio to baseline as the response, and all peak VO_2 measurements will be log transformed prior to analysis. In particular, ratio to baseline in peak VO_2 over time (with Week 50 being of primary interest) will be analyzed using a longitudinal mixed effects model with log-transformed ratio to baseline in peak VO_2 as the dependent variable. The model will include treatment, time (as a categorical variable relative to start of study treatment, i.e., Week 26 and Week 50), and the treatment-by-time interaction as fixed effects, patient as a random effect, and the log-transformed baseline peak VO_2 and the log-transformed baseline-by-time interaction as covariates. Kenward-Roger method will be used for approximating the denominator degrees of freedom. The LS mean and associated 2-sided 90% CI of the ratio to baseline in peak VO_2 for each treatment, on the log scale, will be extracted from the model at each time point, along with the estimated mean treatment difference, the p-value, and the corresponding 2-sided 80% CI. The means and CIs will be back transformed and reported as geometric mean ratios or ratios of geometric mean ratios on the original scale.

(2) The same model as described in Section 6.1.4 for the primary endpoint will be used, but it will be performed on the RAS.

(3) The same model as described in Section 6.1.4 for the primary endpoint will be used, but only patients who have RER > 0.95 at baseline, Week 26 and Week 50 time points will be analysed.

6.1.5.1 Handling of missing data

It is described in Section 6.1.4.1.

6.1.5.2 Graphical presentation of results

For the change from baseline model, i.e., supportive model (2), the model-based graphs are described in Section 6.1.4.2.

For the log-transformed ratio to baseline model, i.e., supportive model (1), the least-squares (LS) geometric mean treatment estimates (+/- 90% CI) will be plotted over time and by treatment using line plots (all treatments in the same graph). Baseline will also be presented as 1 in this model-based plot for better visualization of the ratios to baseline over time.

6.2 Secondary efficacy objectives

There are no secondary efficacy objectives for this study.

The secondary objectives of this study are related to the safety and tolerability of LCZ696 and are described in Section 7.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7 Statistical methods for safety and tolerability data

Unless specified otherwise, all safety analyses will be presented separately for the treatment run-in period and the double-blind placebo-controlled randomized treatment period, using the safety analysis set.

7.1 Variables

Adverse events, body height, body weight, BMI, vital signs (blood pressure, pulse rate and oral body temperature), ECG intervals (PR interval, QRS duration, heart rate, RR interval, QT interval and QTcF), laboratory measurements, as well as patient demographics, baseline characteristics, and treatment information.

7.2 Descriptive analyses

Patient demographics and other baseline characteristics

All data for background and demographic variables including disease characteristics (age, gender, race, ethnicity, height, weight, BMI, systolic blood pressure, diastolic blood pressure, NT-proBNP, peak VO_2, % of predicted peak VO_2 and NYHA class) will be listed by treatment and patient. Summary statistics will be provided by treatment for the RAS. Categorical data will be presented as frequencies and percentages. For continuous data, sample size, mean (arithmetic), SD, median, minimum and maximum will be presented. The same summary table will be created to compare the treatment run-in failure patients vs. the randomized patients for the safety analysis set.

Relevant medical history, current medical conditions, results of laboratory screens and any other relevant information will be listed by treatment and patient. Relevant medical histories and current medical conditions at baseline will be summarized by system organ class (SOC) and preferred term (PT), by treatment for the RAS. A patient with multiple relevant medical histories/current medical conditions within a system organ class (SOC) is only counted once towards the total of this system organ class (SOC).

Treatment

Data for study drug administration (rescue medication) as well as concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by treatment and patient.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized by Anatomical Therapeutic Chemical (ATC) class and treatment for the RAS. A patient with multiple concomitant medications/significant non-drug therapies within an Anatomical Therapeutic Chemical (ATC) class is only counted once towards the total of this Anatomical Therapeutic Chemical (ATC) class.

Overall compliance to the study drug administration

Overall compliance to the study drug administration* will be listed by treatment and patient and summarized by treatment for the RAS.

Note: Any compliance values >100% will be set to and used as 100% in summary statistics.

*For each patient, the overall compliance to study drug (%) will be calculated using the following formula:

$$100 * [\frac{\sum_{i=1}^{n}(Number\ of\ pills\ dispensed\ at\ V_{i-1} - Number\ of\ pills\ returned\ at\ V_i)}{\sum_{i=1}^{n}(\ (Study\ day\ at\ V_i - Study\ day\ at\ V_{i-1}) * 2\ pills\ per\ day\ )}]$$

$where,$

$V_0 = first\ visit\ of\ study\ drug\ administration,$
$V_1 = second\ visit\ of\ study\ drug\ administration,$
.
.
.
$V_{n-1} = second - to - last\ visit\ of\ study\ drug\ administration, and$
$V_n = last\ visit\ of\ study\ drug\ administration.$

Time weighted average daily dose

Time weighted average daily dose* will be listed by treatment and patient for the RAS and summarized by treatment for both the RAS and the PPS separately. Only patients randomized to the LCZ696 treatment will be included in this analysis.

*For each patient, the time weighted average daily dose will be calculated over the randomization period using the following formula:

$$[\frac{\sum_{i=1}^{n}(days\ of\ dosing_i^a * corresponding\ dose_i(in\ mg) * 2)}{days\ in\ the\ randomization\ period^b}]$$

$where,$

$a = Last\ study\ day\ of\ dose_i - \ first\ study\ day\ of\ dose_i + 1$
Note: During the transition from the previous dose to the next dose, we consider that the next dose starts one day after the end study day of the previous dose, i.e., if the previous dose ended on study day x, then the next dose is considered to start on study day x+1 even if the next dose started on study day x as per the data.

$b = Last\ study\ day\ of\ the\ randomization\ period - \ first\ day\ of\ the\ randomization\ period + 1$

Vital signs

All vital signs data will be listed by treatment, patient, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time and will include sample size, mean (arithmetic), SD, median, minimum and maximum.

ECG evaluations

All ECG data will be listed by treatment, patient, and visit/time, and abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time and will include sample size, mean (arithmetic), SD, median, minimum and maximum.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, patient, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing will be provided presenting all parameters in a patient with any abnormal values. Summary statistics will be provided by treatment and visit/time and will include sample size, mean (arithmetic), SD, median, minimum and maximum. Shift tables using the low/normal/high classification will be used to compare baseline to the worst on-treatment value.

Adverse events

All information obtained on adverse events will be listed by treatment and patient. If any death occurs, then all deaths will be listed by treatment and patient

The treatment emergent AEs are defined as follows for this study:

- For the **treatment run-in period**: Treatment emergent AEs will be the events that started at or after the first dose of study medication and before the start of the double-blind treatment period or events present prior to first dose of study medication but increased in severity during the treatment run-in period based on preferred term.
- For the **randomized treatment period**: Treatment emergent AEs will be the events that started at or after the start of the double-blind treatment period or events present prior to the start of double-blind treatment period but increased in severity based on preferred term.

The number and percentage of patients with treatment emergent AEs will be summarized in the following ways:

- by treatment, primary system organ class (SOC), and preferred term (PT).
- by treatment, primary system organ class (SOC), preferred term (PT), and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ), and preferred term (PT).

Separate summaries will be provided for study related adverse events, serious adverse events and adverse events leading to drug discontinuation.

A patient with multiple adverse events within a primary system organ class (SOC) is only counted once towards the total of the primary system organ class (SOC).

ClinicalTrials.gov and EudraCT
For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on <on-treatment/treatment emergent> adverse events which are not serious adverse events with an incidence greater than 5% and on <on-treatment/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 of study treatment relationship will be provided by SOC and PT.

7.3 Graphical presentation

A boxplot of the raw vital signs data (sitting pulse rate, sitting systolic blood pressure and sitting diastolic blood pressure) and an arithmetic mean (SE) plot of changes from baseline in vital signs data (sitting pulse rate, sitting systolic blood pressure and sitting diastolic blood pressure) to visualize trends in longitudinal safety data will be created by treatment and over time. Baseline will also be presented as 0 in the arithmetic mean (SE) plot for better visualization of the changes from baseline over time.

In addition, spaghetti plots of vital signs of interest (i.e., sitting systolic blood pressure and sitting diastolic blood pressure) and biochemistry lab parameters of interest (i.e., creatinine, eGFR, potassium and urea nitrogen) will be created by treatment. Note: Only the patients with at least one unscheduled assessment related to AE will be included in the spaghetti plots and all the measurements (scheduled, repeated & unscheduled) of these patients will be presented.

[redacted]

[redacted]

[redacted]

[redacted]

10 Reference list

1. Clinical Trial Protocol, CLCZ696I12201, Protocol Version 02, dated 08 Apr 2022.
2. Site Operations Manual for Protocol No. CLCZ696I12201, Version 06, dated 26 Jan 2022.

[redacted]