NOVARTIS

Clinical Development

LCZ696B

LCZ696B1301OLE / NCT02468232

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

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)
14-Dec-2018	Prior to first patient first visit	Creation of final version	n.a.	
11-Jul-2019	Prior to DBL at month 4	Core SAP amended	Amendment 1 created.	
			Scope of Protocol deviation added.	Section 2.3.1
			Definition of baseline, at screening or OLE baseline, clarified.	Section 2.3.2, 2.3.3
			FAS-Ext is used in place of EXT population for medical history.	Section 2.3.3
			Formula for mean daily dose corrected.	Section 2.4.1
			Use of TEAEs instead of all AEs clarified.	Section 2.8.1
			Scope of urinalysis analysis clarified.	Section 2.8.3
			Specifications for the liver enzyme abnormality analysis clarified to be consistenet with CLCZ696B2314.	Section 2.8.3
			Baseline visit corrected for analyses based on LCZ-Ext set.	Section 2.8.3, 2.8.4.1, 2.8.4.2.
			An irrelevant imputation rule removed.	Section 5.1.2
			Several obvious mistakes and scope of month 4 analysis corrected.	
11-Mar-2021	Prior to DBL	Minor update	Amendment 2 created.	
			Unnecessary KM plot for permanent discontinuation deleted.	Section 2.4.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			% for selection of most common AEs updated	Section 2.8.1
			Definition of core baseline clarified.	Section 2.8.3, 2.8.4.1, 2.8.4.2
			Descriptive summary statistics for ECG clarified.	Section 2.8.4.1

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List of abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
b.i.d.	Twice a day
BMI	body mass index
BNP	B-type natriuretic peptide
BP	Blood pressure
Bpm	beats per minute
BUN	Blood urea nitrogen
cGMP	Cyclic guanosine monophosphate
CHF	Chronic heart failure
CI	Confidence interval
CRT	Cardiac resynchronization therapy
CRT-D	Cardiac resynchronization therapy defibrillator
CRT-P	Cardiac resynchronization therapy pacemaker
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	estimated glomerular filtration rate
EOS	end of study
HDL	high density lipoprotein
HF	heart failure
ICD	implantable cardioverter defibrillator
LA	left atrial
LBB	left bundle branch
LDL	low density lipoprotein
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRA	mineralocorticoid antagonist
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PD	Pharmacodynamics
OLE	Open-label extension
PK	Pharmacokinetics
RBB	right bundle branch
RBC	red blood cell
SAE	Serious adverse event
SBP	systolic blood pressure
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase

TBL	total bilirubin
ULN	upper limit of normal
WBC	white blood cell

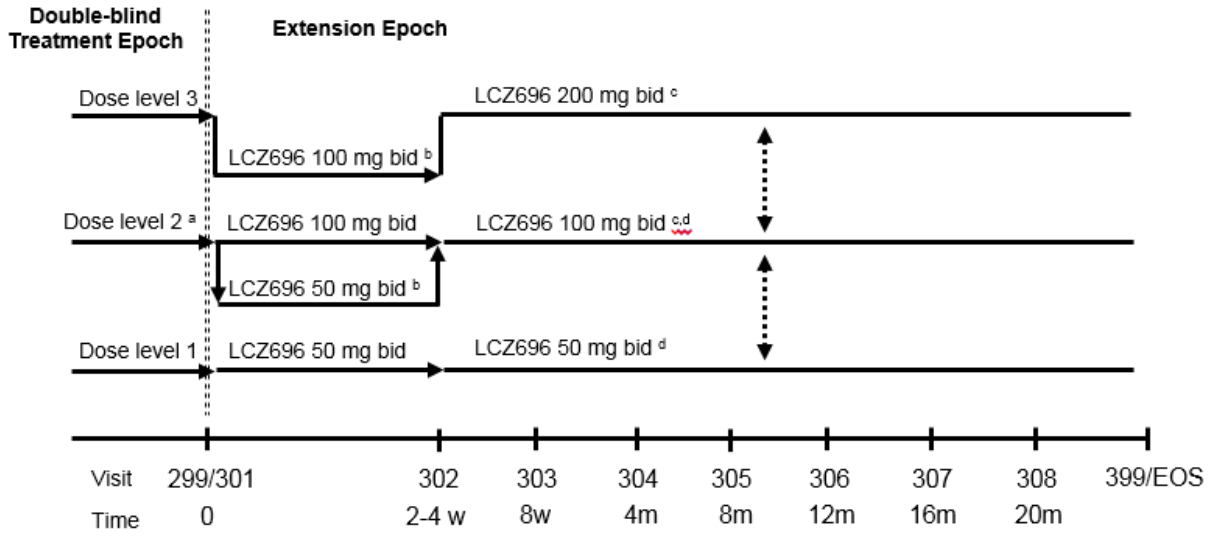
1 Introduction

An open-label extension (OLE) to the study will be conducted following the completion of the core part in which patients are treated with open-label LCZ696. All participants of the core part who are eligible to receive study drug will be offered the option to enter the OLE. The purpose of this OLE is to provide access to LCZ696 for the eligible patients until marketed product is available in Japan or approximately 2 years from the date of the first patient enrolled in the OLE epoch, whichever occurs first, and also to assess the safety, tolerability and efficacy of the treatment with LCZ696.

Data will be analyzed according to the data analysis section 9 of the study protocol. Descriptive statistics for continuous variables will be n, mean, standard deviation, median, minimum, the first quartile, the third quartile, and maximum. For in-text tables, the first quartile and the third quartile will not be presented. Categorical variables will be described using frequency and percentage.

1.1 Study design

An open-label extension to the study will be conducted following the completion of the core part.



w = week; m = month

a. Patients receiving double-blind study drug at dose level 2 have options to start with either the open-label LCZ696 100 mg b.i.d. (dose level 2) or LCZ696 50 mg b.i.d. (dose level 1) at the investigator's discretion.
b. Dosage should be up-titrated at Visit 302 if tolerated in accordance with Table 1-1, and follow the general protocol guidance regarding maintenance dose (Protocol section 5.5.5).
c. Dose adjustment is permitted if not tolerated at the dose during the OLE epoch following the general protocol guidance regarding maintenance dose (Protocol section 5.5.5).

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

Table 1-1 Safety monitoring criteria for up-titration at Visit 302 (Week 2 to 4)

Parameter	Visit 302 (Week 2 to 4)
Serum potassium level	K ≤ 5.4 mmol/L (mEq/L) (local assessment)
Kidney function	eGFR ≥ 30 mL/min/1.73m2 eGFR reduction ≤ 35% compared to Visit 301 (local assessment)
Blood pressure	No symptomatic hypotension and SBP ≥ 95 mmHg.
AEs or conditions	No postural symptoms or any AEs that preclude continuation according to the investigator's judgment

Every consenting trial participant who is eligible to receive study drug will start the OLE epoch. Informed consent will be obtained before any study-specific procedure for OLE epoch is performed. The last dose of study medication that the patient is taking during the core part should be considered in determining the starting dose level of LCZ696. For all patients, the first visit of the OLE epoch will occur on the same day as the EOS visit of the core part. At Visit 301, patients will be switched to an open-label LCZ696 from double-blinded study drug. Dose adjustments and temporary interruptions of study treatment are permitted if not tolerated during OLE epoch following the pre-specified protocol guidance (Protocol section 5.5.5).

Table 1-2 Starting dose levels of open-label LCZ696 at the start of the OLE

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

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

1.2 Study objectives and endpoints

Below are the objectives during the open-label extension.

- To evaluate the safety and tolerability of LCZ696 treatment during the OLE epoch
- To assess the proportion of patients reaching target dose level 3 of LCZ696 at Week 8 and maintained at Month 4
- To assess the effect of LCZ696 on change in NYHA classification from OLE baseline (Visit 301) at Month 12

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

2 Statistical methods

2.1 Data analysis general information

In addition to analyses at study completion, a cut-off data analysis will be carried during the OLE epoch after all patients have been enrolled into the OLE, and completed Visit 304 (Month 4) or discontinued.

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

2.1.1 General definitions

Physical exam, vital signs, Weight, NYHA classification, ECG and lab data at Visit 299 will be utilized as the data at Visit 301(Protocol Table 6-2). OLE baseline is Visit 301. If not specified otherwise, baseline is OLE baseline.

2.2 Analysis sets

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

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

Patients from FAS-Ext who were randomized in LCZ group in randomized epoch (LCZ-Ext): All patients in the FAS-Ext who receive at least one dose of the extension study drug and were randomized to LCZ in randomized epoch. The LCZ-Ext population is used to assess the effects of long-term treatment with LCZ696 on the safety and tolerability throughout the study period.

2.2.1 Subgroup of interest

Subgroups listed below will be formed for the analyses to explore the consistency of treatment effects and safety profiling between the subgroups and the overall population.

1. Treatment arms in the double blind treatment epoch
   LCZ696, Enalapril

2. Age subgroups
   <65, ≥65 at OLE baseline
   <75, ≥75 at OLE baseline
3. Gender
   Male, Female
4. Baseline eGFR (mL/min/1.73m2)
   <60, ≥60 at OLE baseline

Note that only important parameters or variables in these analyses will have subgroup analyses. The details about the parameters having subgroup analyses will be presented in the corresponding sections below. In principle, there will be no adjustment for multiple comparisons for subgroup analyses.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number and percentage of subjects successfully enrolled in OLE epoch, receive at least one dose of the study drug in OLE epoch, completed/discontinued the OLE epoch, and the reason for discontinuation will be presented for total, and by the treatment arm in the double blind treatment epoch based on EXT population.

All PDs are specified in the "Protocol Deviations" of Data Review Plan(SSD3). Number and percentage of subjects with protocol deviation during OLE epoch will be tabulated by deviation category for total, and by the treatment arm in the double blind treatment epoch based on EXT population.

2.3.2 Demographics and other baseline characteristics

Baseline characteristics will be summarized according to OLE baseline. In OLE epoch, value at Visit 301 is defined as OLE baseline. Core baseline value is defined as the available measurement at screening visit.

Summary statistics will be provided for total, and by the treatment arm in the double blind treatment epoch based on the EXT population for the demographic, disease characteristics, heart failure and cardiovascular diseases parameters listed below.

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

Demographics

- Age (years) at visit 301
- Age group 1 [<65 years, ≥65 years] at visit 301
- Age group 2 [<75 years, ≥75 years] at visit 301
- Gender [Male, Female]
- Race [Caucasian, Black, Asian, Native American, Pacific Islander, Unknown, Other]
- Ethnicity [Hispanic or Latino, Chinese, Japanese, Korean, Other East Asian, Southeast Asian, South Asian, West Asian, Mixed ethnicity, Unknown, Other]

- Weight (kg) at visit 301
- Height (cm) at screening visit in core part
- Body Mass Index (BMI) (kg/m^2) – calculated as weight/height^2 from the collected height at screening visit in core part and weight at visit 301
- BMI group [<25, ≥25 & <30, ≥30 (kg/m2)]
- SBP (mmHg) at visit 301
- DBP (mmHg) at visit 301
- Pulse pressure (mmHg) at visit 301
- eGFR (mL/min/1.73m^2) at visit 301
- eGFR group [< 60, ≥60 (mL/min/1.73 m2)] at visit 301

Disease characteristics

- NYHA class [Class I, Class II, Class III, Class IV] at visit 301
- Hypertension [No, Yes] at screening
- Diabetes mellitus [No, Yes] at screening

2.3.3 Medical history from core part of the study

Medical history data are captured in the core part of the study with the following eCRF pages: Medical History, Heart Failure and Diabetes History, Cardiovascular Medical History, Protocol Solicited Medical History, Medical History Possibly Contributing to Liver Dysfunction, Alcohol History, Smoking History, Vaccination Medical History, which are collected at screening visit.

Heart failure and cardiovascular disease history

Summary statistics will be provided for total, and by the treatment arm in the double blind treatment epoch based on FAS-Ext population for the parameters listed below.

- Prior HF hospitalization [No, Yes]
- Number of hospitalization for HF within 12 months prior to screening [0, 1 ,2 , >2]
- Time from diagnosis of CHF (years)
- Time from diagnosis of CHF group [>0 to 3 months, >3 to 6 months, >6 to 12 months, >1 to 2 years, >2 to 5 years, >5 years]
- Primary HF etiology [Ischemic, Non-ischemic]
- Prior MI [No, Yes] at screening
- Prior stroke [No, Yes] at screening
- Prior TIA [No, Yes] at screening
- Atrial Fibrillation [No, Yes] at screening
- Prior coronary artery bypass graft [No, Yes] at screening
- Prior percutaneous coronary intervention [No, Yes] at screening
- Prior angina pectoris [No, Yes] at screening
- Angina class [Class I, Class II, Class III, Class IV] at screening
- CRT [No, Yes] at screening
- CRT-P [No, Yes] at screening
- CRT-D [No, Yes] at screening
- CRT/ICD [No, Yes] at screening
- ICD only [No, Yes] at screening

Protocol Solicited Medical History, Medical History Possibly Contributing to Liver Dysfunction

Protocol solicited medical history/Medical History Possibly Contributing to Liver Dysfunction will be summarized by occurrence (No, Yes, Unknown) and ongoing status (No, Yes, NA) based on FAS-Ext population.

Alcohol History and Smoking History

Alcohol History will be summarized by amount consumed on average for each substance based on FAS-Ext population.

Vaccination Medical History

Vaccination Medical History will be summarized by occurrence of each vaccination based on FAS-Ext population.

Medical History

Any condition entered on the eCRF pages of Medical History will be coded using the most updated version of MedDRA dictionary.

Number of subjects with medical history will be summarized by primary system organ class and preferred term based on FAS-Ext population.

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

2.4.1 Study treatment / compliance

Duration of treatment (including interruptions) for each subject will be computed regardless of temporary interruptions of usage of the study drug as follows.

- date of last study drug intake in OLE epoch – date of first study drug intake in OLE epoch + 1.

Duration of exposure to study drug (excluding interruptions) for each subject will be computed as follows.

- date of last study drug intake in OLE peoch – date of first study drug intake in OLE epoch + 1 – number of days of no treatment.

The duration of treatment (including interruptions) and the duration of exposure to study drug (excluding interruptions) will be descriptively summarized for total, and by the treatment arm in the double blind treatment epoch as well as frequencies per duration category defined below.

- <4 weeks
- 4 to <8 weeks
- 8 weeks to < 4 months
- 4 to < 8 months
- 8 to < 12 months
- ≥12 months

Additionally, above analyses will be repeated for throughout the period from run-in epoch to OLE epoch for LCZ-Ext population.

Dose level

Doses and dose levels in the OLE epoch are summarized in Table 2-1.

Table 2-1 Study drug dose levels during OLE

Dose level	LCZ696
0	0 mg bid
1	50 mg bid
2	100 mg bid
3	200 mg bid

Mean daily dose and mean daily dose level for each subject will be computed as follows.

$$\text{Mean daily dose (mg)} = \frac{\sum_{i=0}^{3}(number\ of\ days\ on\ dose\ level\ i)\times(dose\ level\ i\ )\times 2}{number\ of\ days\ upto\ end\ of\ treatment}$$

$$\text{Mean daily dose level} = \frac{\sum_{i=0}^{3}(number\ of\ days\ on\ dose\ level\ i)\times i}{number\ of\ days\ upto\ end\ of\ treatment}$$

Number and percentage of subjects classified by dose level will be presented for total, and by the treatment arm in the double blind treatment epoch at OLE baseline, Week 2-4, Week 8, Month 4, Month 8, Month 12, Month 16, Month 20 and end of study visit. Same analysis will be done for cut-off data analysis at month 4.

Mean daily dose per subject and mean daily dose level per subject will be summarized for total, and by the treatment arm in the double blind treatment epoch and visit. Same analysis will be done for cut-off data analysis at month 4.

Mean daily dose per subject and mean daily dose level per subject will also be summarized for throughout the period from run-in epoch to OLE epoch for LCZ-Ext population.

Number and percentage of subjects on each dose level at last available record will be presented for total, and by the treatment arm in the double blind treatment epoch. Mean dose level at last available record will be summarized for total, and by the treatment arm in the double blind treatment epoch. Same analysis will be repeated for the subjects who are alive at the last visit.

A treatment exposure interruption episode is defined as any interval during which the treatment is stopped (i.e. Dispensing Level=No treatment on Dosage Administration

Record CRF). Any treatment interruption episodes, any treatment interruption episodes >7 days and any treatment interruption episodes >14 days will be classified into the followings: “None”, “At least once”, “1”, “2”, “3”, “4”, “5”, ”6”, “7”, “>7”. This categorical variable will be summarized for total, and by the treatment arm in the double-blind treatment epoch.

The reasons for all treatment interruptions (As per protocol, Adverse event, Dosing error, Dispensing error, Technical problems, Subject/guardian decision, Physician decision, Hyperkalemia, Hypotension, Renal dysfunction, Angioedema/angioedema-like event, Cough) will be also summarized for total, and by the treatment arm in the double-blind treatment epoch. Same analysis will be repeated for cut-off data analysis at month 4.

A treatment down titration is defined as any dose reduction from dose level 3 to 2, 3 to 1, 3 to 0, 2 to 1, 2 to 0 or 1 to 0 (i.e. a lower Dispensing Level in the subsequent administration record). Treatment down titrations will be summarized by reason for total, and by the treatment arm in the double-blind treatment epoch. Subjects experienced treatment down titration will be summarized with the number and percentage of subjects by reason for study treatment dose reduction. Same analysis will be repeated for cut-off data analysis at month 4.

Number and percentage of subjects will be summarised for medication exposure time categories “1-30 days”, “31-60 days”, “61-90 days”, “91-180 days”, “181 days- 1 year, “>1 year” by last received drug dose level.

2.4.2 Prior, concomitant and post therapies

Medications will be identified using Novartis Drug and Therapy Dictionary (NovDTD) including Anatomical Therapeutic Chemical (ATC) code. Medications will be presented in alphabetical order, by ATC codes and grouped by anatomical main group (the 1st level of the ATC codes). Tables will show the overall number and percentage of subjects receiving at least one drug of a particular ATC code and at least one drug in a particular anatomical main group.

Prior or concomitant medications will be identified based on recorded or imputed start and end dates of taking medication. The rules for imputing incomplete (start and end) dates are described in section 5.1.3.

Prior medications are defined as drugs taken prior to first dose of run-in study medication in core part of study(i.e. End date on Concomitant Medications eCRF < first run-in study drug date). Selected prior medications will be listed based on FAS-Ext population.

Any medication given at least once during the OLE epoch will be a OLE concomitant medication, including those which were started before OLE epoch and continued into the OLE epoch.

The OLE concomitant medication information will be summarized for total, and by the treatment arm in the double-blind treatment epoch based on the FAS-Ext population.

All OLE concomitant medications and heart failure/cardiovascular OLE concomitant medications will be summarized separately in the same way.

More specifically, the following classes of medications will be summarized separately from general medications:

HF medications

- Calcium channel blocker (CCB)
- Diuretics
- Beta blockers
- Mineralocorticoid receptor antagonists (MRAs)
- Digitalis glycosides
- Oral anticoagulants
- Antiarrhythmic agents
- Aspirin
- Other antiplatelet agents(excluding Aspirin)
- Statins
- Nitrates
- Other(non-statin) lipid lowering agents

Medications for heart failure/cardiovascular diseases at the start of OLE study drug will be summarized.

General medications newly added after the start of OLE study drug will be summarized. Medications for heart failure/cardiovascular diseases newly added after the start of OLE study drug will be summarized.

Number and percentage of subjects treated with heart failure/cardiovascular medications upto month 18 in OLE epoch will be presented for total, and by the treatment arm in the double blind treatment epoch and ATC class.

Surgical and medical procedures during OLE epoch by primary system organ class, preferred term will be summarized.

All concomitant medication, surgical and medical procedures will be summarized for cut-off data analysis at month 4.

2.5 Analysis of the primary objective

2.5.1 Efficacy endpoints

Below endpoints will be analyzed based on FAS-Ext poplulation.

- NYHA classification
- Echocardiographic parameters
- Biomarkers
- Association between NT-proBNP and echocardiographic parameters

2.5.2 Statistical hypothesis, model, and method of analysis

NYHA classification

Change of NYHA functional class from OLE baseline will be grouped into 3 categories: improved, unchanged, or worsened. A shift table from OLE baseline to each post-baseline visit in NYHA class will be provided by the treatment arm in the double blind treatment epoch. FAS-Ext will be used. Number and percentage of subjects in each category will be provided. Same analysis will be repeated for cut-off data analysis at month 4.

To assess the magnitude of change in NYHA class throughout the period from run-in epoch to OLE epoch, shift table will be provided for LCZ-Ext population, using Visit 101 as baseline.

Echocardiographic parameters

The echocardiogram will be performed at Visit 301 before administration of study medication and also at Visit 306. Cardiac parameters related to LV and LA structure, LV systolic and diastolic function etc. (including LV end systolic and diastolic volume indices, LVEF, and LA volume index) will be assessed. Summary statistics for change from OLE baseline of echo parameters will be presented. FAS-Ext will be used, and analyses will be done by the treatment arm in the double-blind treatment epoch.

Biomarkers

In the OLE epoch, biomarker measurements will be obtained from plasma and spot urine samples at Visits 301, 302, 303, 304, and 306 to determine effects of LCZ696 treatments on biomarkers. Descriptive summary statistics (mean, median, standard deviation, min, max, Q1, Q3, geometric mean, 95% CI for geometric mean) for the changes from OLE baseline to each post-baseline visit will be presented by treatment arm in the double blind treatment epoch for BNP, NT-proBNP, and urine cGMP. Same analysis will be repeated for cut-off data analysis at month 4.

Descriptive summary statistics for NT-proBNP will be presentd for LCZ-Ext population, throughout the period from run-in epoch to OLE epoch using Visit 101 as baseline.

Graph for geometric mean and 95% confidence interval for total, and by treatment arm in the double blind treatment epoch will be presented for BNP, NT-proBNP, and urine cGMP.

Association between NT-proBNP and echocardiographic parameters

Pearson's and Spearman's correlation coefficient and their two-sided 95% confidence interval between change in log transformed NT-proBNP and change in structural cardiac measurements (LV end systolic and diastolic volume indices, LVEF, and LA volume index) from OLE baseline to Month 12 will be analyzed. FAS-Ext will be used, and analyses will be done for total, and by the treatment arm in the double-blind treatment epoch.

2.5.3 Handling of missing values/censoring/discontinuations

No imputation for missing.

2.6 Analysis of the key secondary objective

No key secondary objectives are analyzed.

2.7 Analysis of secondary efficacy objective(s)

No secondary efficacy objectives are analyzed.

2.8 Safety analyses

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

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

Proportion of patients reaching target dose level 3 of LCZ696 at Week 8 and maintained at Month 4 will be presented. Additionally, proportion of patients in each dose level category upto month 12 will be presented.

2.8.1 Adverse events (AEs)

All AEs during OLE epoch including on-going AEs at Visit 301 will be recorded on the *Adverse Event* eCRF page. AEs starting on or after the first dose of OLE epoch study medication or events present prior to the first dose of OLE epoch study medication but increased in severity based on preferred term will be classified as **treatment-emergent AEs(TEAE)**.

The following rules are applied. 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.

Number and percentage of subjects reporting any treatment-emergent AE during OLE epoch, reporting an AE in each primary system organ class and reporting individual AE (preferred term) will be summarized for the followings.

- all treatment-emergent AEs, all treatment-emergent SAEs
- drug-related treatmentemergent AEs, drug-related treatment-emergent SAEs
- most common treatment-emergent AEs (≥3% in total)
- most common drug-related treatment-emergent AEs (≥2% in total)
- treatment-emergent AEs requiring dose adjustment or temporary interruption
- treatment-emergent AEs causing study drug discontinuation

Similarly, summaries for following will be presented for cut-off data analysis upto month 4.

- treatment-emergent AEs, treatment-emergent SAEs upto month 4
- drug-related treatment-emergent AEs, drug-related treatment-emergent SAEs upto month 4

- treatment-emergent AEs requiring dose adjustment or temporary interruption upto month 4
- treatment-emergent AEs causing study drug discontinuation upto month 4

The most common adverse events reported will be presented in descending frequency of total. Summaries will also be presented by severity for all treatment-emergent AEs in OLE epoch and treatment-emergent AEs upto month 4 for cut-off data analysis.

Number and percentage of subjects reporting any AE throughout the period from run-in epoch to OLE epoch, reporting an AE in each primary system organ class and reporting individual AE (preferred term) for LCZ-Ext population will be summarized for the followings.

- all AEs, all SAEs
- drug-related AEs, drug-related SAEs
- most common AEs (≥5%)
- most common drug-related AEs (≥3%)
- AEs requiring dose adjustment or temporary interruption
- AEs causing study drug discontinuation

The most common adverse events reported will be presented in descending frequency. Summaries will also be presented by severity for all AEs throughout the period from run-in epoch to OLE epoch for LCZ-Ext population.

2.8.1.1 Adverse events of special interest / grouping of AEs

AEs of special interest will also be summarized. AEs of special interest and their further specified events include the followings.

Hypotension

- SBP <90 mmHg
- SBP decline by ≥30 mmHg
- Simultaneous SBP <90 mmHg and SBP decline by ≥30 mmHg

Hyperkalemia

- serum potassium ≥5.5 mmol/L
- serum potassium >6.0 mmol/L
- serum potassium >6.5 mmol/L

Renal impairment

- Serum creatinine level >176.8 µmol/L
- Serum creatinine level >221.0 µmol/L
- Serum creatinine level >265.2 µmol/L
- Serum creatinine increase by >50%
- eGFR decline by ≥25%
- eGFR decline by ≥40%
- eGFR decline by ≥50%

Angioedema (adjudicated)

- No treatment or antihistamines only
- Treated with catecholamines or steroids
- Hospitalized but no mechanical airway protection, without airway compromise
- Hospitalized but no mechanical airway protection, with airway compromise
- Mechanical airway protection or death from airway compromise

Drug-related hepatic disorders

- all preferred terms listed in the Standardized Med-DRA Query(SMQ) module "drugrelated hepatic disorders – comprehensive search SMQ code 20000006 - broad search"

Cough

Summary tables that summarize the numbers and percentages of subjects experienced the above events at least once during OLE epoch will be presented by event or SMQ (when drug-related hepatic disorders). Same summary analysis will be repeated for cut-off data analysis at month 4.

Summary tables that summarize the numbers and percentages of subjects experienced the above events at least once throughout the period from run-in epoch to OLE epoch for LCZ-Ext population will be presented by event or SMQ (when drug-related hepatic disorders).

The search paths for the related preferred terms (PTs), high level group term (HLGT), high level term (HLT), in Standard Medical Queries (SMQs), or NMQ in MedDRA for hypotension, hyperkalaemia, renal impairment and cough are based on LCZ696 used in core part.

Numbers and percentages of subjects with adjudicated angioedema events with the adjudicated maximum severity and angioedema-like (i.e. investigator-reported) events will be presented in OLE epoch.

Numbers and percentages of subjects with adjudicated angioedema events with the adjudicated maximum severity and angioedema-like (i.e. investigator-reported) events throughout the period from run-in epoch to OLE epoch for LCZ-Ext population will be presented.

2.8.2 Deaths

Summaries for death will be provided by the investigator-reported primary cause in OLE epoch. Summaries for death will also be presented for cut-off data analysis at month 4. Additionaly, summaries for death will be provided by the investigator-reported primary cause throughout the period from run-in epoch to OLE epoch for LCZ-Ext population.

2.8.3 Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests.
Hematology

- Hemoglobin

- Hematocrit
- RBC count
- WBC count
- WBC differential
- Platelet count

Biochemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Estimated glomerular filtration rate (eGFR)
- Total bilirubin
- AST (SGOT)
- ALT (SGPT)
- Alkaline phosphatase
- Sodium
- Potassium
- Chloride
- Calcium
- Glucose
- Total protein
- Albumin
- Uric acid
- Total cholesterol
- LDL
- HDL
- Triglycerides
- Hemoglobin A1c

Urinalysis

- Specific gravity
- pH
- Blood
- Total protein
- Bilirubin
- Ketones
- Leukocytes

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

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

where serum creatinine is in μmol/L (SI unit) and age at the time of the laboratory sample in years.

For continuous laboratory parameters, descriptive summary statistics for the change from OLE baseline to each post-baseline visit will be presented. These descriptive summaries will be presented by laboratory parameter. 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 – OLE baseline value. Similarly, summary statistics for hematology and biochemistry lab parameters(including eGFR) will be presented for cut-off data analysis at month 4.

In addition, shift tables will be provided for all parameters to compare a subject's OLE baseline laboratory evaluation relative to the visit's observed value and the most extreme value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the OLE baseline value was normal, low, or high. These summaries will be presented by laboratory parameter and treatment arm in the double-blind treatment epoch.

The number and percentage of subjects with clinically notable laboratory results at each post baseline visit will be presented by laboratory parameter. An additional section will be included for abnormalities occurring at any visit. The denominator for each visit is based on subjects with values at both OLE baseline and corresponding post-baseline visit; the denominator for any visit is based on subjects with values at both OLE baseline and any post-baseline visit. Number and percentage of subjects with clinically notable laboratory results will also be presented for cut-off data analysis at month 4.

Clinically notable criteria, for those parameters where ranges are available, are given in appendix 5.3.
Specific gravity of urinalysis will be summarized by visit with standard summary statistics, including change from baseline. 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 – OLE baseline value.
Other categorical urinalysis laboratory parameters (blood, total protein, bilirubin, ketones, Leukocytes, pH) will be described using frequency and percentage by visit and treatment arm in the double blind treatment epoch.

Liver function test data
Liver events and triggers, defined in Appendix 2 of protocol, should be based on central laboratory results. The details of every liver event should be provided on *Liver Event* eCRF pages.

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

- ALT or AST >3x upper limit of normal range (ULN)
- ALT or AST >5x ULN
- ALT or AST >8x ULN
- ALT or AST >10x ULN
- ALT or AST >20x ULN

- ALT or AST >3x ULN and TB >1.5x ULN
- ALT or AST >3x ULN and TB >2x ULN
- ALT or AST >5x ULN and TB >2x ULN
- ALT or AST >8x ULN and TB >2x ULN
- ALT or AST >10x ULN and TB >2x ULN
- ALT or AST >20x ULN and TB >2x ULN
- ALP >2x ULN
- ALP >3x ULN
- ALP >5x ULN
- TBL >1.5x ULN
- TBL >2x ULN
- TBL >3x ULN
- ALP >3x ULN and TBL >2x ULN
- ALP >5x ULN and TBL >2x ULN
- (AST or ALT >3x ULN) and (TBL >2x ULN) and (ALP ≤2x ULN)
- (AST or ALT >3x ULN) and (TBL >2x ULN) and (ALP ≤2x ULN) or reported Hy's Law case
- (ALT or AST >3x ULN) and reported symptoms of (nausea or vomiting or fatigue or malaise or abdominal pain or (rash and eosinophilia))
- (TBL >3x ULN) and (AST or ALT ≤3x ULN) and (ALP ≤1.5x ULN)
- (ALP >3x ULN) and (AST, ALT, TBL are within normal range)

Liver enzyme abnormalities will also be summarized for cut-off data analysis at month 4.

The event which combines lab information and signs/symptoms information is derived using central laboratory results and the *Liver Event* eCRF. A case will be considered as newly occurring if a criterion is not met at baseline but is met thereafter.

All analyses in this section will be repeated for LCZ-Ext population, throughout the period from run-in epoch to OLE epoch using screening as baseline. As applicable, all visits will be presented.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Heart rate and QRS duration will be summarized. Descriptive summary statistics for the change from OLE baseline to each post-baseline visit will be presented. FAS-Ext will be used, and analyses will be done by the treatment arm in the double-blind treatment epoch.

In addition, shift tables comparing OLE baseline overall ECG interpretation (normal, clinically abnormal) will be provided for each post-baseline visit.

In the case where any new clinically significant abnormalities are present, more detailed abnormalities should be specified: atrial fibrillation, atrial flutter, LBB block, RBB block, pathological Q waves, left ventricular hypertrophy, paced rhythm. The numbers and percentages of subjects with these specific abnormalities will be shown by visit.

All analyses in this section will be repeated for LCZ-Ext population, throughout the period from run-in epoch to OLE epoch using screening visit as baseline. As applicable, all visits will be presented.

2.8.4.2 Vital signs

Sitting systolic blood pressure, sitting diastolic blood pressure, sitting pulse rate and body weight will be summarized by post-baseline visit with standard summary statistics, including changes from OLE baseline. 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. Same analysis will be repeated for cut-off data analysis at month 4.

Graphical mean plots with 95% CIs for these vital signs will also be provided. The number and percentage of subjects with clinically notable vital signs changes from baseline will be presented. Number and percentage of subjects with clinically notable vital signs change from baseline will also be presented for cut-off data analysis at month 4. The clinically notable criteria are provided in Table 2-2 below.

Table 2-2 Clinically notable changes in vital signs

Vital Sign (unit)	Clinically notable criteria
Weight (kg)	decrease > 7% from baseline
	increase > 7% from baseline
Sitting systolic blood pressure (mmHg)	<90 and decrease from baseline of >20
	>180 and increase from baseline of >20
Sitting diastolic blood pressure (mmHg)	<50 and decrease from baseline of >15
	>105 and increase from baseline of >15
Pulse (bpm)	<50 and decrease from baseline of > 15
	>120 and increase from baseline of >15

All analyses in this section will be repeated for LCZ-Ext population, throughout the period from run-in epoch to OLE epoch using Visit 101 as baseline. As applicable, all visits will be presented.

2.8.4.3 Patients reaching target dose level

Proportion of patients reaching target dose level 3 of LCZ696 at Week 8 and maintained at Month 4 will be presented. FAS-Ext will be used, and analyses will be done for total, and by the treatment arm in the double-blind treatment epoch. Proportions of patients by visit upto month 12 will be presented for dose levels of open-label LCZ696. FAS-Ext will be used, and analyses will be done for total, and by the treatment arm in the double-blind treatment epoch.

2.9 Pharmacokinetic endpoints

PK samples will not be collected during the OLE epoch.

2.10 PD and PK/PD analyses

None.

2.11 Patient-reported outcomes

None.

2.12 Biomarkers

Described in section 2.5.2

2.13 Other Exploratory analyses

None.

2.14 Interim analysis

Not planned.

3 Sample size calculation

Sample size calculation is not done for open label extension epoch.

4 Change to protocol specified analyses

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

If medication 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 next scheduled visit date (using the protocol specified visit schedule) from the previous last non-missing visit date to replace the missing drug stop date;
c) If the drug stop date is completely missing, then:

a. If subject had fatal AEs (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 day 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 subjects had no fatal AEs, handling rules are the same with the case that year and month are missing.

5.1.2 AE date imputation

If the start/stop 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;

5.1.3 Concomitant medication date imputation

If the start/stop date of concomitant medication is not known or is incomplete, same imputation method as described above in section 5.1.1 will be used.

5.2 AEs coding/grading

AEs will be coded using MedDRA (Medical Dictionary for Regulatory Activities Terminology). The MedDRA version used for reporting the study will be described in a footnote.

5.3 Laboratory parameters derivations

Table 5-1 Clinical notable criteria for selected laboratory tests

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
Biochemistry	
ALT (SGOT)	>150% increase
AST (SGPT)	>150% increase
BUN	>50% increase >14.28 mmol/L
Creatinine	>50% increase >136.8 µmol/L
Total bilirubin	>100% increase
Alkaline phosphatase	>100% increase

Sodium	>5% decrease
Potassium	>20% increase, >20% decrease
	≥6.0 mmol/L
	≥5.5 mmol/L
	<3.5 mmol/L
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease
Uric acid	>50% increase

In the above table increase and decrease are defined as compared to the baseline value.

5.4 Statistical models

5.5 Rule of exclusion criteria of analysis sets

Table 1 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses
INCL07	Informed consent missing	Excluded form EXT, FAS-Ext and LCZ-Ext analysis

Table 2 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
EXT	INCL07	
FAS-Ext	INCL07	No open-label study drug taken
LCZ-Ext	INCL07	Not in FAS-Ext

6 Reference