NOVARTIS

Clinical Development

LCZ696

CLCZ696BCA02 / NCT02690974

PARASAIL - Prospective, multi-center, open lAbel, post-appRovAl Study AImed at characterizing the use of LCZ696 at 97 mg sacubitril / 103 mg valsartan bid in patients with HFrEF

Statistical Analysis Plan (SAP)

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Document type: SAP Documentation

Document status: Amendment 1

Release date: 4-Jul-2017

Number of pages: 28

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

Version	Date	Changes
Final 1.0	29-APR-2016	Initial draft
Amendment 1	27-Jul-2017	As per Protocol few amendment sections got updated Section 2.11 6MWT analysis updated; few sites won't be performing 6MWT twice [redacted] Section 2.2 Added definition of enrolled set Section 2.4.1 analysis regarding compliance [redacted] Section 5.5 Rule of exclusion criteria of analysis sets Section 5.6 Adverse event of special interest Section 5.7 Target dose of cardiovascular medication
Addendum 1	24-Apr-2018	Section 2.11 6 MWT analysis change, Observations with total distance walked >1000 m will be excluded from the analysis. Section 2.8.3 Laboratory data, handling unit coversion for creatinine and uric acid programmatically.

List of abbreviations

ACE	angiotensin converting enzyme
ACEI(s)	angiotensin converting enzyme inhibitor(s)
AE	Adverse event
ALT	alanine aminotransferase
ANP	atrial natriuretic peptide
APP	aminopeptidase P
ARB(s)	angiotensin receptor blocker(s)
ARNi(s)	Angiotensin Receptor Neprilysin Inhibitor(s)
AST	aspartate aminotransferase
AT1	angiotensin type 1bid twice a day
bid	bis in diem/twice a day
BP	blood pressure
CHF	chronic heart failure
CSR	Clinical Study report
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical Study Report
CRO	Contract Research Organization
CV	cardiovascular
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
EC(s)	Ethics Committee(s)
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
EOS	end of study
[redacted]	[redacted]
FAS	Full Analysis Set
HF	Hearth Failure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Randomization TechnologyLCZ696 Novartis compound code
LVEF	left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mg	milligram
NP(s)	natriuretic peptide(s)
NYHA	New York Heart Association
o.d.	once a day
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
p.o.	oral

QoL	Quality of Life
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SOC	System Organ Class
TFLs	Tables, Figures, Listings
ULN	upper limit of normal
WHO	World Health Organization

1 Introduction

The main purpose of this Statistical Analysis Plan (SAP) is to provide summary of the statistical methodology that will be used for this study; this includes a detailed description of data summaries. Analysis plans in this document refer to the related statistical analysis sections in clinical study reports.

This SAP module describes the statistical analysis according to Section 9 of the study protocol along with specifications or deviations planned.

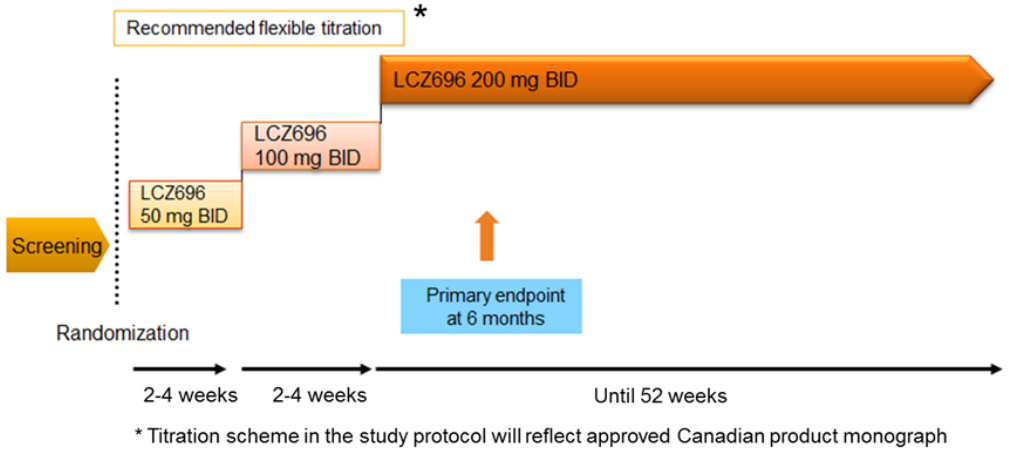
Data will be analyzed according to the data analysis section 9 of the study protocol which will be available in Appendix 16.1.1 of the CSR. Important information is given in the following sections 2.7 (Efficacy evaluation), 2.8 (Safety evaluation), 2.14 (Interim analysis) and 3 (power and sample size considerations).

1.1 Study design

This will be a multi-center, open label, prospective post-approval (phase IV) study. Patients with HFrEF that are eligible to be treated with LCZ696 as per the product monograph will be enrolled in the study. The study patients will be enrolled at Canadian community cardiologists and IM specialists that treat patients with HFrEF. Follow up will be for 12 months with assessments at baseline, week 2, week 4, month 3 (optional), month 6 and month 12. The primary endpoint will be assessed after 6 months of follow-up.

Treatment with ACEIs will be discontinued for 36 hours and then replaced with LCZ696 at 24 mg sacubitril / 26 mg valsartan bid. NO washout period is needed for patients previously treated on ARBs. The dose of LCZ696 will be increased to 49 mg sacubitril / 51 mg valsartan bid within 2-4 weeks of enrolment and to 97 mg sacubitril / 103 mg valsartan bid within 2-4 weeks from the first up titration to 49 mg sacubitril / 51 mg valsartan bid as tolerated by the patient and in accordance to the product monograph (Figure 1-1). Down titration of LCZ696 from the higher doses may be considered, as per the product monograph for patients that experience tolerability issues including, but not limited to, symptomatic hypotension or hyperkalemia.

Figure 1-1 Study design



* LCZ696 50 mg bid is the equivalent of 24 mg sacubitril / 26 mg valsartan bid
* LCZ696 100 mg bid is the equivalent of 49 mg sacubitril / 51 mg valsartan bid
* LCZ696 200 mg bid is the equivalent of 97 mg sacubitril / 103 mg valsartan bid

1.2 Study objectives and endpoints

1.2.1 Primary objective

The primary objective of this study is to describe the tolerability of LCZ696 at 97 mg sacubitril / 103 mg valsartan bid, after 6 months of treatment in patients with HFrEF.

1.2.2 Secondary objectives

In patients with HFrEF:

- To describe the tolerability of LCZ696 at 97 mg sacubitril / 103 mg valsartan bid, after 12 months of treatment.
- To evaluate the impact of the titration scheme on the tolerability of patients maintained on LCZ696 97 mg sacubitril / 103 mg valsartan bid at 6 and 12 months
- To describe the impact of LCZ696 on functional exercise capacity, as measured by the Six Minute Walk Test, at 6 and 12 months.
- To describe the time of up-titration for each dose (24 mg sacubitril / 26 mg valsartan bid / 49 mg sacubitril / 51 mg valsartan bid) of LCZ696.
- To describe the adherence to guideline recommended dosing of beta-blockers and MRAs at 6 and 12 months of treatment with LCZ696.
- To evaluate the overall safety profile of LCZ696 during 12 months of treatment.

2 Statistical methods

The data analysis for the current study will be primarily descriptive. Descriptive statistics will be produced for all study variables. The descriptive statistics will include mean, median, SD and 95% confidence interval of the mean for continuous scale variables and frequency distributions with 95% confidence intervals around the estimate of proportions will be reported for categorical scale variables.

For categorical data, percentages will be rounded up to 1 decimal place. For continuous data, mean, median and quartiles will be rounded up to 1 additional decimal place compared to the original data. Standard deviation will be rounded up to 2 additional decimal places. Minimum and maximum will be displayed with the same accuracy as in the original data. Wherever changes from baseline will be used, change will be calculated as "post-baseline value – baseline value". The number of decimal places for the "change from baseline" variables will be the same as for the original measurement.

2.1 Data analysis general information

Statistical Analysis System (SAS) version 9.4 or higher will be used to perform all the statistical analyses in the report.

The data analysis for the current study will be primarily descriptive. 95% confidence intervals will be calculated for the estimate of proportions in order to assess precision and make inferences to the target population.

Safety will be assessed with the incidence of treatment emergent adverse events.

2.1.1 General definitions

All patients who are eligible will be treated with the following:

- **Baseline:** Refers to the last measurement made prior to administration of the first dose of study medication.
- **Change from baseline**: post-baseline value – baseline value
- **Last contact:** last contact will be the last time a patient's study record has been taken. For a patient who is still alive and in study the last contact will be his/her last clinical

contact. For patient who died or is determined to be lost to follow-up before the analysis cut-off date, the last contact will be his/her death/lost-to-follow-up day.

- **Final Visit:** Final visit will be the last time a patient's study record has been taken. For a patient who is still alive and in the study the final visit will be his/her last clinical visit. For a patient who died or is determined to be lost to follow-up before the analysis cut-off date, the final visit will be his/her death/lost-to-follow-up day. For a patient who is alive but no longer has regularly scheduled clinic visits and whose study records only can be obtained by telephone or indirect contact, the final visit will be the day the study records being taken.
- **Incidence rate:** The incidence rate is the number of new cases per population at risk in a given time period . When the denominator is the sum of the person-time of the at risk population, it is also known as the incidence density rate or person-time incidence rate.
- **IDR per 100 person-month:** A rate of events per 100 patient months measures the intensity of the events over time for the underlying population events. Where event is defined as patient reaching 200 mg dose.

2.2 Analysis sets

The following analysis sets will be used for statistical analysis:

- Screened set (SCR) – Screened set will be comprised of all patients given informed consent.
- Enrolled set (ENR) – Patients who have met the eligibility criteria or has taken at least one dose of study medication.
- Full analysis set (FAS) – The Full Analysis Set (FAS) will be comprised of all patients that have received at least one dose of LCZ696. The primary analysis will be based on the FAS.
- Per protocol set (PPS) – The Per-Protocol Set will be comprised of the patients that complete the 6 month and 12 month follow up assessments depending on the time period analyzed. The analyses will be repeated for the PPS if there is a more than 10% difference between the FAS and PPS samples.
- Safety Set (SAF)- Safety set includes all the patients in FAS.

All analyses will be performed in both the FAS and PPS, unless otherwise specified. All Safety analysis will be performed on Safety Set.

2.2.1 Subgroup of interest

NYHA class will be used as subgroup of interest. Patient reported outcome will be provided by NYHA class II and NYHA class III.

2.3 Patient disposition, demographics and other baseline characteristics

Descriptive statistics will be reported for patient demographics and baseline characteristics. This will include the mean, median, standard deviation, minimum and maximum for continuous variables. Frequency distributions will be reported for categorical variables.

2.3.1 Patient disposition

The number and percentage of enrolled, completed, and discontinued in the study and reason for the discontinuation and screen failure will be provided. For patient who was screened more than once, the information from the last screen will be used in the summary. Data will be summarized using FAS.

The number and percentage of the patients with protocol deviations as well as the criteria leading to exclusion from analysis sets will be presented in separate table for the FAS.

2.3.2 Background and demographic characteristics

Descriptive statistics will be provided for patient demographics and baseline characteristics.

The following demographic and baseline parameters will be summarized at the visit 1 (day 1):

- **Demographics**
    - Age (Years)
    - Gender
    - Race (Caucasian, Black, Asian, Native American, Pacific Islander, Unknown, Other)
    - Ethnicity (Hispanic or Latino, east Asian, Southeast Asian, South Asian, West Asian, Russian, Mixed Ethnicity, Not reported, Unknown, Other)
    - Height (Cm)
    - Weight (kg)
    - Body Mass Index (BMI) (kg/m2)
    - Smoking history
    - Alcohol use history
- **Medical History**

Any condition entered on the relevant medical history / current medical conditions will be coded using the MedDRA dictionary. Medical history includes cardiovascular disease history in this study, which are collected prior to informed consent signature.

The number and percentage of subjects with each medical condition will be provided by system of organ class for the FAS.

The above medical conditions will also be listed.

- **Heart Failure History**

Heart failure history will be summarized by number and percent for following categories**.**

- Primary HF etiology (Ischemic /Non ischemic)
  - If Non ischemic:
    - Hypertensive (Yes/No)
    - Diabetic (Yes/No)
    - Alcoholic (Yes/No)
    - Viral cardiomyopathy (Yes/No)
    - Infectious cardiomyopathy (Yes/No)
    - Peripartum (Yes/No)
    - Drug induced (Yes/No)
    - Hypertrophic cardiomyopathy (Yes/No)
    - Idiopathic (yes/No)
    - Unknown (Yes/No)
- Prior heart failure hospitalization(yes/no)
- Number of hospitalization in the last 12 months
- Ejection Fraction (%) in last 12 months
- NYHA class at enrollement
- Timing since last ejection fraction (months)

The above demographic and heart failure history will also be listed based on FAS.

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

2.4.1 Study treatment / compliance

The duration of the study treatment exposure will be summarized (n, mean, standard deviation, minimum, median, and maximum). Descriptive statistics will be based on SAF.

The exposure duration categories are defined for each phase as:

- Day 1
- >= 2 Weeks
- >= 4 Weeks
- >= 12 Weeks
- >= 24 Weeks
- >= 52 Weeks (12 Months)

Treatment duration (days) = (date of last dose of LCZ696 – date of first dose of LCZ696) + 1

Compliance with treatment will be defined as the percentage of doses taken by the patient and will be calculated using the following formula:

Compliance (%) = 100 x (total number of capsules dispensed – total number of capsules returned) / total number of capsules dispensed.In addition listing for the total number of missed doses by each patient will be provided.

This information will be used as a measure of the number of tablets taken between study visits for compliance.

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

2.4.2 Prior, concomitant and post therapies

The concomitant medication information will be summarized based on the SAF.

Concomitant medications and significant non-drug therapies, prior to and after the study treatment will be summarized by therapeutic class, preferred term according to the WHO-DRL dictionary. Also, cardiovascular concomitant medication will be summarized separately.

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

The proportion of patients on guideline recommended dose of beta-blockers and MRAs at baseline ,6 and 12 months will also be summarized.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary outcome measure of the study will be the proportion of patients remaining on treatment with LCZ696 97 mg sacubitril / 103 mg valsartan at six months of follow up. The proportion will be calculated as the number of patients at 97 mg sacubitril / 103 mg valsartan over the total number of patients that received at least one dose of LCZ696.

2.5.2 Statistical hypothesis, model, and method of analysis

The data analysis will be primarily descriptive. Therefore, there is no a-priori hypothesis being tested.

The primary efficacy outcome will be assessed by the proportion of patients on LCZ696 97 mg sacubitril / 103 mg valsartan bid at 6 months of treatment. 95% confidence interval using binomial proportion will be calculated for the estimate of the proportion in order to assess precision and make inferences to the target population.

2.5.3 Handling of missing values/censoring/discontinuations

There will be no replacement or imputation of missing values. All analysis will be conducted on observed cases only. For patients lost to follow up after achieving the LCZ696 dose of 97 mg sacubitril / 103 mg valsartan bid, the conservative approach will be used, according to which they will be considered as not staying on treatment.

2.5.4 Supportive analyses

A sensitivity analysis will be conducted for PPS if there is a more than 10% difference between the FAS and PPS samples.

2.6 Analysis of the key secondary objective

There is no key secondary objective for this study.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

The following secondary outcome measures will be analyzed:

1. The proportion of patients who tolerate the LCZ696 dose of 97 mg sacubitril / 103 mg valsartan mg bid at 12 months of treatment.
2. The proportion of patients on LCZ696 who had required down-titration after reaching the 97 mg sacubitril / 103 mg valsartan
3. The number of down-titration changes from 97 mg sacubitril / 103 mg valsartan during 12 months of treatment.
4. Functional capacity as measured by the change from baseline to 6 months and 12 months in the Six Minute Walk Test.
5. Time to each up-titration to 49 mg sacubitril / 51 mg valsartan and 97 mg sacubitril / 103 mg valsartan.
6. Duration of treatment on each dose of LCZ696.
7. The proportion of patients on guideline-recommended doses and who are tolerant of beta-blockers and MRAs at baseline, 6 and 12 months.

2.7.2 Statistical hypothesis, model, and method of analysis

The data analysis will be primarily descriptive. For the secondary efficacy outcomes, the proportion of patients on LCZ696 97 mg sacubitril / 103 mg valsartan bid at 12 months, the proportion of patients requiring down titration, and the proportion of patients treated in accordance to guideline recommended doses of beta blockers and MRAs will be presented along with the 95% Confidence Intervals using binomial proportion to assess the precision.

The number of down titrations during the 12 month treatment periods will be described with a Poisson distribution and the incidence density rate (IDR) as the number of dose reductions per 100 person – month of follow up.

The change in the Six Minute Walk Test from baseline to 6 and 12 months of treatment will be assessed along with the 95% confidence intervals using Student's t-test for paired observations.

The time to LCZ696 up-titration to 97 mg sacubitril / 103 mg valsartan bid and the duration on treatment for each dose will be assessed with the Kaplan Meier estimator of the survival function.

Duration of treatment on each dose of LCZ696 will be summarized descriptively.

2.7.3 Handling of missing values/censoring/discontinuations

There will be no replacement or imputation of missing values. All analysis will be conducted on observed cases only. For patients lost to follow up after achieving the LCZ696 dose of 97 mg sacubitril / 103 mg valsartan bid, the conservative approach will be used according to which they will be considered as not staying on treatment.

A sensitivity analysis could be conducted for the PPS as required.

2.8 Safety analyses

2.8.1 Adverse events (AEs)

Adverse events (AEs) will be classified according to the latest MedDRA dictionary of terms and summarized using :

- The total number of AEs
- The total number and percentage of patients who experience an AE overall,
- The number and percent of patients who experience an AE within each system organ class (SOC) and preferred terms (PTs) within individual SOCs.

Analysis of the number of patients who experience each AE will be performed in the following manner: patients experiencing the same AE multiple times will only be counted once for the corresponding PT; similarly, if a patient experiences multiple AEs within the same SOC, that patient will be counted only once for that SOC.

Number and percent of patients who experience an SAE within each system organ class (SOC) and preferred terms (PTs) within individual SOCs will also be summarized.

AEs and SAEs with related to the study treatment (definitely related, probably related, possibly related) will be summarized.

Summary of the total number of AEs by seriousness (serious, non-serious), severity (mild, moderate, severe), relationship to study medication (definitely related, probably related, possibly related, unlikely related, definitely not related), action taken and outcome will also be provided.

Any AE/SAE occurred during the study will be included in AE/SAE summary tables, i.e. AEs/SAEs occurred on or after study day 1 and up to 30 days after the discontinuation of the study drug.

The following summaries will be generated for AEs:

- All adverse events
- Serious adverse events
- Adverse event by severity grade
- Adverse events causing study drug discontinuation
- Adverse events requiring dose adjustment or study-drug interruption
- Investigator reported causes of deaths by primary system organ class and preferred Term

The above information also be listed. Analysis will be based on SAF.

2.8.1.1 Adverse events of special interest / grouping of AEs

Liver events of special interest (AESI) which consist of LFTs elevations will be presented. Adverse event (liver events) of special events defiend as:

- Any clinical event of jaundice (or equivalent term)
- ALT or AST > 3 x ULN (accompanied by general malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia)
- Any event with a preferred term (PT) in the MedDRA dictionary falling under the SMQ sub-module “Drug-related”
    - hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions;
    - non-infectious hepatitis;
    - benign, malignant and unspecified liver neoplasms
    - Hy’s law case (PT)

2.8.2 Deaths

Primary cause of death will be summarized by system organ class (SOC) and preferred term (PT) by providing number and percent. Death information will be summarized on SAF.

2.8.3 Laboratory data

The Laboratory Analysis will be carried out on SAF.

Clinically notable laboratory findings are defined as in section 5.3.

The summary of laboratory evaluations will be presented for laboratory tests: hematology which include hemoglobin, hematocrit, RBC count, WBC count, platelet count, and blood chemistry which includes blood urea nitrogen (BUN), creatinine, AST (SGOT), ALT (SGPT), alkaline phosphatase, potassium, eGFR, chloride, and uric acid as conduct per routine care.

Descriptive summary statistics (mean, median, standard deviation, min and max) for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test. Change from baseline will only be summarized for subjects with

both baseline and post baseline values and will be calculated as defined in section 2.1.1 i.e. General defanations.

In addition, shift tables will be provided for all parameters to compare a subject's baseline laboratory evaluation relative to the visit's observed 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 baseline value was normal, low, or high. These summaries will be presented by laboratory test.

The number and percentage of subjects with clinically notable laboratory results after baseline will be presented. Clinically notable laboratory results, for those parameters where ranges are available, are given in Table 1 below. For the calculation the denominator are based on the evaluable post-baseline subjects who did not have the notable abnormality at baseline.

For all laboratory evaluation scheduled and unscheduled laboratory measurements will be taken into account.

As confirmed from the sites about erroneous lab unit entry of the parameters creatinine and uric acid, the appropriate conversion of these units will be handled programmatically.

The parameters that will be considered for unit conversion are Creatinine and Uric acid.

Parameter	Original unit	Standard unit	Conversion factor
Creatinine	mmol/l	umol/L	1000
Creatinine	Mg/dL	umol/L	88.40
Urate	mmol/L	umol/L	1000

Table 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
Blood Chemistry	
ALT (SGOT)	>150% increase
AST (SGPT)	>150% increase
BUN	>50% increase
	>14.28 mmol/L
Creatinine	>50% increase
	>136.8 µmol/L
CPK	>300% increase
Alkaline phosphatase	>100% increase
Potassium	>20% increase, >20% decrease
	≥6.0 mmol/L
	>5.0 mmol/L
	<3.5 mmol/L
Chloride	>10% increase, >10% decrease

Uric acid	>50% increase

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

2.8.3.1 Urinalysis

Not Applicable.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Electrocardiograms will be conducted as per routine care and documented in the site's source documents. No analysis will be performed.

2.8.4.2 Vital signs

Vital signs tests performed includes the following:

- Sitting systolic blood pressure(SSBP) (mmHg)
- Sitting diastolic blood pressure(SDBP) (mmHg)
- Pulse rate (beats/min)
- Body weight (kg)

These parameters will be summarized by visit with standard summary statistics (mean, median, standard deviation, min, max), including changes from baseline. Change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as defined in section 2.1.1 i.e. General definations.

The number and percentage of subjects with clinically notable vital signs changes from baseline will also be presented. Clinically notable vital sign results are provided in Table 2 below.

Table 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

2.8.4.3 NYHA Class assessment

Patients NYHA class will be assessed at Baseline, at month 3, at month 6 and at month 12. At baseline, only patients with heart failure NYHA class II or III can be enrolled in the study. The total number and percentage of patient with each NYHA class will be provided by visits based

FAS. The change in NYHA class at month 3, 6 and 12 each compared to baseline (Day 1) will be summarized by frequesncy distribution.

2.9 Pharmacokinetic endpoints

Not applicable

2.10 PD and PK/PD analyses

Not applicable

2.11 6 MWT analysis

6 MWT data will be summarized for visit 1 (baseline), visit 5 (month 6) and visit 6 (month 12). Descriptive summary statistics (mean, median, standard deviation, min and max) for the baseline and change from baseline to visit 5 and visit 6 will be presented based on the total distance each patient walks in six minutes. The descriptive summaries will be presented by visit. Change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as defined in section 2.1.1.

The 6 MWT analysis will be summarized based on the FAS. For the patients with two six minute walk test, best of the results based on longest distance covered will be considered for analysis.

The observations with total distance walked > 1000m will be excluded from the analysis as confirmed by the sites and CTT due to erroneous data entry.

2.13 Biomarkers

Not applicable

2.15 Interim analysis

An interim analysis may be performed after 50 patients have reached 12 weeks of treatment, [redacted] and at any time during the study as long as it does not impact the study completion.

3 Sample size calculation

The primary outcome measure for the current study will be the proportion of patients on 97 mg sacubitril / 103 mg valsartan bid of LCZ696 at 6 months of treatment. The data from clinical trials have shown that at 12 weeks (3 months) approximately 80% of patients have achieved this dose. In this current real – life study of 6 months (primary endpoint) a reasonable estimate of patients achieving this dose would be 70%.

Given that this is a single cohort, prospective study in which all patients are receiving the same treatment and the objective is to describe the proportion of patients reaching 97 mg sacubitril / 103 mg valsartan bid LCZ696, sample size requirements are based on the precision of the estimate. This is assessed with the 95% confidence interval. A reasonable level of precision is one with a 95% confidence interval width (ω) that is between 5 and 15% of the point estimate. With 300 patients enrolled in the study, the 95% Confidence Interval width will be ± 5.2% which is equivalent to 7.4% of the point estimate of 70%, with upper and lower limits of 64.8% – 75.2% respectively. This is within the limits of reasonable precision.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

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.

5.1.2 AE date imputation

AE date imputation is based only on a comparison of the partial AE start date to the treatment start date as mentioned in the Table 1-2 below.

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

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

Table 1-2 AE date imputation

	MON **MISSING**	**MON < CFM**	**MON = CFM**	**MON > CFM**
YYYY MISSING	NULL	NULL	NULL	NULL
	Uncertain	Uncertain	Uncertain	Uncertain
YYYY < CFY	(D) = 01JULYYYY	(C)= 15MONYYYY	(C)= 15MONYYYY	(C)= 15MONYYYY
	Before Treatment Start	Before Treatment Start	Before Treatment Start	Before Treatment Start
YYYY = CFY	(B)= TRTSTD+1	(C)= 15MONYYYY	(A)= TRTSTD+1	(A)= 01MONYYYY
	Uncertain	Before Treatment Start	Uncertain	After Treatment Start
YYYY > CFY	(E)= 01JANYYYY	(A)= 01MONYYYY	(A)= 01MONYYYY	(A)= 01MONYYYY
	After Treatment Start	After Treatment Start	After Treatment Start	After Treatment Start

Before Treatment Start	Partial indicates date prior to Treatment Start Date
After Treatment Start	Partial indicates date after Treatment Start Date
Uncertain	Partial insufficient to determine relationship to Treatment Start Date
LEGEND:	
(A)	MAX(01MONYYYY,TRTSTD+1)
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

5.1.3 Concomitant medication date imputation

Date imputation for concomitant medications will be imputed according to Novartis conventions described in [RAP Module 8].

Concomitant medication(CMD) start date imputation (#IMPUTMED)

Rules for imputing the CMD start date:

This algorithm is used when event is the partial start date of the concomitant medication, non-drug therapy/procedure, or prior anti-neoplastic therapy.

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

	Day	Month	Year
Partial CM Start Date	Not used	MON	YYYY

Treatment Start Date(TRTSDT)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON<TRTM	MON=TRTM	MON>TRTM
YYYY MISSING	(C2) Uncertain	(C1) Uncertain	(C1) Uncertain	(C1) Uncertain
YYYY<TRTY	(D) Before Treatment Start	(A) Before Treatment Start	(A) Before Treatment Start	(A) Before Treatment Start
YYYY=TRTY	(C2) Uncertain	(A) Before Treatment Start	(C1) Uncertain	(B) After Treatment Start
YYYY>TRTY	(E) After Treatment Start	(B) After Treatment Start	(B) After Treatment Start	(B) After Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Treatment Start	Partial date indicates CMD start date **prior** to Treatment Start Date
After Treatment Start	Partial date indicates CMD start date **after** Treatment Start Date
Uncertain	Partial date **insufficient to determine** relationship of CMD start date relative to Treatment Start Date
Imputation Calculation	
(A)	15MONYYYY
(B)	01MONYYYY
(C1 or C2)	IF relative reference start = before treatment start THEN TRTSDT-1 ELSE IF relative reference start = ‘ ’ THEN TRTSDT+1
(D)	01JULYYYY

(E)	01JANYYYY

Concomitant medication end date imputation

If not ongoing then -

If the CM end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the CM end year value is missing or ongoing, the imputed CM end date is set to NULL.

Else, if the CM end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death).

If the CM end date day is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, last day of the month, date of death).

If the imputed CM end date is less than the existing CM start date, use the CM start date as the imputed CM end date

Concomitant medication date flag

If not a complete date then

Y - If year of the imputed date is not equal to YYYY else

M – If month of the imputed date is not equal to MON else

D

5.1.3.1 Prior therapies date imputation

As explained above in the section 5.1.3.

5.1.3.2 Post therapies date imputation

As explained above in the section 5.1.3.

5.2 AEs coding/grading

NA

5.3 Laboratory parameters derivations

Clinically notable laboratory values

Clinically notable laboratory abnormalities for selected tests based on a percent change from baseline:

Hematology

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

Blood Chemistry

ALT (SGPT)	>150% increase
AST (SGOT)	>150% increase
BUN	>50% increase
Creatinine	>50% increase
Total bilirubin	>100% increase
CPK	>300% increase
Alkaline phosphatase	>100% increase
Potassium	>20% increase, >20% decrease
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease
Uric acid	>50% increase

5.4 Statistical models

5.4.1 Primary anlysis

For the proportion and percentage along with 95% confidence limits estimated using normal approximation (binomial proportion) , statistical programmer may use the following code:

```
<Sample code>
proc freq data= <xxx>;
tables <xxx> / binomial;
run;
```

5.4.2 Secondary anlysis

For Incidence density rate for the number of dose reduction, following code may be used:

```
<Sample code>
proc genmod data=mydata;
model ndt =/dist=poisson link=log obstats; /* where ndt is the number of down
                                        titrations for each of the patients.*/
run;
```

For Kaplan-Meier estimates of the probability of reaching LCZ 200 mg, following code may be used:

```
ods listing close;
proc lifetest data = <xxx> outsurv = <xxx> ;
      time TIME*censor(0);
      ods output productlimitestimates = res;
      ods output HomTests=pvalue;
      ods output Quartiles=med;
run;
ods listing;
```

5.5 Rule of exclusion criteria of analysis sets

The following protocol deviations will be considered as major and will lead to exclusion of subjects from the respective analysis set:

Protocol Deviation ID (DVSPID)	Decription used to Report PDs to HA/IRBs (DVTERM)	Population	Severity code
INCL01	Written informed consent is not obtained before assessment is performed	Excluded from PPS	4
INCL02	Age less than 18 years and greater than 80 years.	-Excluded from PPS if Age < 18 years -Included in both FAS & PPS if Age > 80 years	4 0
INCL04	Not diagnosed with Heart Failure NYHA class II or III	Excluded from PPS	4
INCL05	Not diagnosis of Heart Failure with reduced Ejection Fraction (LVEF lessthan 40%) and NYHA class II or III	Excluded from PPS	4
INCL06	Unstable to any dose of ACEI or ARB prior to enrolment in the study	Excluded from PPS only if patient is NOT on any dose of ACEI or ARB	4
INCL07	Unstable to any dose of a beta-blocker prior to enrolment in the study	Excluded from PPS only if patient is	4

		NOT on any dose of Beta-Blocker	
INCL08	Not Eligible for treatment with LCZ696 (ENTRESTOTM) as per Canadian product monograph	Excluded from PPS	4
INCL09	Not Treated as an outpatient	Excluded from PPS	4
INCL10	Informed consent is not signed on agreeing to participate in the study	Excluded from, PPS, SAF and FAS	4, 3
EXCL01A	Symptomatic hypotension at Baseline	Excluded from PPS	4
EXCL01B	SBP less than 100 mmHg at baseline visit	Excluded from PPS	4
EXCL02	Estimated GFR lessthan 30 mL/min/1.73m2 as measured by the simplified Modification of Diet in Renal Disease (MDRD) formula at baseline visit.	Excluded from PPS	4
EXCL03	Known history of angioedema related to previous ACEI or ARBs therapy, or history of hereditary or idiopathic angioedema.	Excluded from PPS	4
EXCL04	Requirement of concomitant treatment with both ACEIs and ARBs	Excluded from PPS	4
EXCL05	Concurrent participation in other clinical trials or receiving other investigational drugs within 30 days of enrollment.	Excluded from PPS	4
EXCL06	Hypersensitivity to the active substances, sacubitril or valsartan, or to any of the excipients.	Excluded from PPS	4
EXCL07	Concomitant use of aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR lessthan 60ml/min/1.73m2).	Excluded from PPS	4
EXCL08	History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.	Excluded from PPS	4
EXCL09	History of malignancy of organ system (other than local basal cell carcinoma of skin), treated or untreated, within the past 5 years, regardless there is evidence	Excluded from PPS	4
EXCL10	Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.	Excluded from PPS	4

EXCL11	Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment	Excluded from PPS	4
WITH01	Patient become pregnant, while taking study medication.	Excluded from PPS	0
WITH02	Due to the potential risk of angioedema when used concomitantly with an ACEI, LCZ696 is started within 36 hours without discontinuation of ACEI therapy.	Excluded from PPS	4
OTH01	Pregnancy test not performed as required per protocol	Excluded from PPS	0
OTH02	Pregnancy not reported within 24 hrs to Novartis while patient is on study treatment	Excluded from PPS	4
OTH03	Approved ICF update available but patient has not signed this version		
TRT01	Treatment with ARBs is not discontinued prior to intiation of study treatment	Excluded from PPS	4

5.6 Adverse event of special interest

For reporting of AESIs, document “AEs of special interest preferred terms” will be used.

Document received for Medical Lead will be placed in CREDI as it is.

5.7 Target dose of cardiovascular medication

For reporting of targed dose of beta blockers and MRAs, document “Canadian drugs for HFrEF” will be used. Document received for Medical Lead will be placed in CREDI as it is.

6 Reference

Protocol has been used as a reference.