NOVARTIS

Clinical Development

LCZ696B

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A randomized, double-blind, active-controlled study to assess the effect of LCZ696 compared with enalapril to improve exercise capacity, daily physical activity and quality of life in patients with heart failure with reduced ejection fraction (HFrEF)

Statistical Analysis Plan (SAP)

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List of abbreviations

ACE	angiotensin converting enzyme
ACEI(s)	angiotensin converting enzyme inhibitor(s)
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ANCOVA	analysis of covariance model
ARB(s)	angiotensin receptor blocker(s)
AST	aspartate aminotransferase
bid	twice a day
BP	blood pressure
CCB	Calcium channel blockers
CHF	chronic heart failure
CPET	cardiopulmonary exercise testing
CRF	Case Report/Record Form
CSR	Clinical Study Report
CV	Cardiovascular
DBP	diastolic blood pressure
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOS	end of study
[redacted]	[redacted]
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
[redacted]	[redacted]
IA	interim analysis(es)
ICD	implanatable cardioverter defibrillator
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
i.v.	intravenous(ly)
[redacted]	[redacted]
LCZ696	Novartis compound code
LFT	Liver function test
LVEF	left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease
MET	metabolic equivalent of task
mg	Milligram
MI	myocardial infarction
mmHg	millimeter mercury
mph	mile per hour
MRI	magnetic resonance imaging
NYHA	New York Heart Association

PK	pharmacokinetic(s)
PCI	percutaneous coronary intervention
RER	respiratory exchange ratio
SAE(s)	serious adverse event(s)
SBP	systolic blood pressure
[redacted]	[redacted]
ULN	upper limit of normal
VAT	Ventilatory anaerobic threshold
VO_2	respiratory oxygen uptake
VO_{2max}	respiratory oxygen uptake (max.)
VO_{2peak}	respiratory oxygen uptake (peak)
WBC	White blood cell

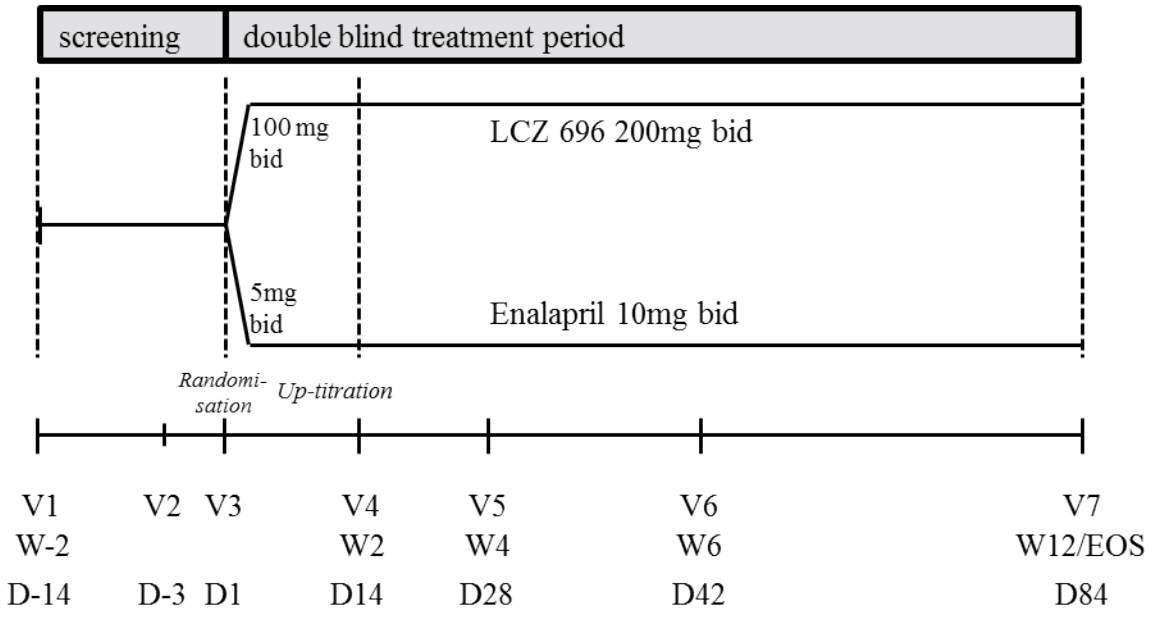
1 Introduction

The purpose of this document is to provide summary of the statistical methodology that will be used for this clinical 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 Statistical Analysis Plan (SAP) module describes the statistical analysis according to Section 9 of the study protocol along with any additional analyses, 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 (Analysis of secondary efficacy), 2.8 (Safety evaluation), 2.14 (Interim analysis) and 3 (Sample size calculation).

1.1 Study design



This study is a randomized, double-blind, double-dummy, parallel-group, active-controlled, two-arm, long-term trial to compare LCZ696 200 mg bid to enalapril 10 mg bid in improving exercise capacity, daily physical activity and quality of life in patients with stable CHF (NYHA III) and reduced ejection fraction (LVEF ≤ 40%).

Eligible patients at stable dose of at least enalapril 10 mg/d or equivalent for at least 4 weeks before Visit 1 and LVEF ≤ 40% can be randomized at Visit 3.

VO_{2peak} inclusion criterion will only be checked after assessment of patients' eligibility according to all other inclusion and exclusion criteria. Thus, ergospirometry will be performed on Visit 2 to get a complete assessment of CPET (for screening), [redacted]

Once patients' eligibility has been ascertained, they will attend Visit 3 for randomization approximately two weeks after Visit 1 to start enalapril 5 mg bid versus LCZ 100 mg bid for 2 weeks.

At baseline, all eligible patients will be randomized to receive either LCZ696 or enalapril in a 1:1 allocation during the double-blind period.

1.2 Study objectives and endpoints

1.2.1 Primary objectives

The primary objective of this study is to demonstrate the superiority of LCZ696 200 mg bid compared to enalapril 10 mg bid in improving exercise tolerance (VO_{2peak}, adjusted to body weight) as assessed by cardiopulmonary exercise testing (CPET) in patients with stable chronic heart failure (NYHA class III) and reduced ejection fraction (LVEF ≤ 40%) after 3 months treatment.

1.2.2 Secondary objectives

Secondary objectives are:

- To demonstrate the superiority LCZ696 versus enalapril regarding improvement of exercise tolerance (VO_{2peak}, adjusted to body weight) as assessed by cardiopulmonary exercise testing (CPET) in patients with chronic heart failure after 6 weeks treatment.
- To compare LCZ696 versus enalapril on the following CPET parameters:
    - Change of VE/VCO_2 slope after 6 weeks and 3 months
    - Change in exercise capacity (Watt) at ventilatory anaerobic threshold (VAT) after 6 weeks and 3 months
    - Change in rate of perceived exertion during exercise (Borg Scale) after 3 month
    - To assess the safety and tolerability of LCZ696 in patients with stable chronic heart failure with NYHA class III and reduced ejection fraction (LVEF ≤ 40%)

[redacted]

2 Statistical methods

Descriptive statistics will be provided for all study variables. The descriptive statistics will include mean, median, SD, minimum, maximum, and 95% confidence interval of the mean, as needed for continuous scale variables and frequency distributions for categorical variables.

For categorical data, percentages will be rounded up to 1 decimal place. For continuous data, mean, and median 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.

2.1.1 General definitions

Patients who are eligible for randomization at Visit 3 will be assigned to one of the following two treatment arms in a 1:1 ratio.

- LCZ696 bid and placebo to match enalapril bid
- Enalapril bid and placebo to match LCZ696 bid

All randomized patients will receive either LCZ696 100mg or enalapril 5mg in a 1:1 allocation during the double-blind period at visit 3. Dose will be up-titrated after 2 weeks (Visit 4) to the final dose of enalapril 10mg bid or LCZ696 200mg bid. For allowed investigational treatment dose adjustments during double-blind period refer to Section 5.5.5 in the protocol.

Baseline: Baseline value is defined as the last non-missing assessment prior to the first dose of randomized study medication unless specified otherwise.

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

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.

2.2 Analysis sets

The following analysis sets will be defined for statistical analysis:

- Screened set (SCR) – All patients who signed the informed consent. The screened set includes patients based on their patient IDs assigned at each screening visit.
- Randomized set (RAN) - All patients who received a randomization number, regardless of receiving trial medication.
- Full analysis set (FAS) - The full analysis set (FAS) will consist of all randomized patients who have received at least one dose of study drug. Efficacy variables will be analyzed based on the FAS as the primary population.
- Safety set (SAF) - The Safety Set (SAF) will consist of all randomized patients who received at least one dose of study drug. The safety Set will be used for the analyses of safety variables.

2.2.1 Subgroup of interest

Not applicable.

2.3 Patient disposition, demographics and other baseline characteristics

Patient demographic and baseline characteristic data will be summarized based on FAS. Patient demographic and baseline characteristics include age, sex, and race. Relevant medical history/current medical condition, includes data until the start of study drug will be summarized. HF medications and other CV medications will be summarized separately from other medications. Likewise, detailed HF history and other relevant CV medical history will be summarized separately from other medical history.

2.3.1 Patient disposition

The number and percentage of patients enrolled, completed, and discontinued in the study and reason for the discontinuation will be summarized by treatment group. The reasons for screen failure will also be provided. All data will be listed. The analysis set will be 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 for the FAS.

2.3.2 Demographic characteristics

Summary statistics will be provided based on FAS by treatment group for demographics and baseline characteristics, including age, age group (<65 years, >= 65 and < 85 Years, and ≥85 years), sex, race, weight, height, body mass index (BMI), category of prior CHF medication, prior HF hospitalization, NYHA class, and vital signs. BMI will be calculated as weight (kg) / (height (m))^2 collected at Visit 1 (Screening Visit).

Continuous variables will be summarized using n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency and percentage.

The following demographic variables will be analyzed:

- Age (years)
- Age group (<65 years, >= 65 and < 85 Years, and ≥85)
- Gender (Male, Female)
- Race (Caucasian, Black, Asian, Other)

The following baseline characteristic variables will be analyzed:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- NYHA Class
- LVEF (%)
- Smoking History (Yes / No)
- Alcohol History (Yes / No)
- SBP
- DBP
- eGFR
- Prior CHF medication

2.3.3 Medical History

Any condition entered on the relevant medical history / current medical conditions CRF will be coded using the MedDRA dictionary. HF history and other CV medical history will be summarized.

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

The above medical conditions will also be listed.

Medical history possibly contributing to liver dysfunction and medical history possible related to statin will be summarized and listed seperatly based on FAS.

- **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)
    - Vitium (Yes/No)
      - If Yes, hemodynamically significant? (Yes/No)
- Prior heart failure hospitalization(yes/no)
- Number of hospitalization in the last 12 months
- Ejection Fraction (%) in last 6 months

The heart failure history will also be listed for FAS.

- **Cardiovascular Medical history**

Cardiovascular history will be summarized by number and percent for following categories:

- Prior myocardial infection (Yes/No)
- Prior angina pectoris (Yes/No)

- If Yes, precise Angina Class (Class I, Class II, Class III, Class IV)

- Did the subject have any prior PCIs? (Yes/No)
- Did the subject have any prior CABGs (Yes/No)
- Does the subject have a pacemaker? (Yes/No)
- Does the subject have an ICD (Yes/No)

The cardiovascular history will also be listed for FAS.

Smoking history and alcohol history will be summarized in the separate tables based on FAS and will also be listed.

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

2.4.1 Study treatment / compliance

The overall duration on the double-blind study drug will be summarized by treatment group using n, mean, standard deviation, median, minimum, and maximum. Additionally, the number and percentage of patients will be summarized by treatment group for duration category. The analysis will be based on the SAF.

Dose levels

Exposition to the different dose levels will be analyzed as patient numbers on the specified dose levels on visit 4, visit 6 and visit 7.

Doses and dose levels in the double blind phase as defined in the clinical study protocol are:

LCZ696: dose level 1 = 50 mg bid, **dose level 2** = 100 mg bid, **dose level 2a** = 100 mg bid and **dose level 3** = 200 mg bid.
Enalapril: dose level 1 = 2.5 mg bid, **dose level 2** = 5 mg bid, **dose level 2a** = 10 mg bid, and **dose level 3** = 10 mg bid.
Duration of double-blind study drug exposure will be calculated based upon the start and stop dates recorded in the eCRF.

- Last date of study drug – start date of study drug+ 1

2.4.2 Prior, concomitant and post therapies

Medications will be identified using Novartis Drug and Therapy Dictionary, NovDTD which is a modified Novartis internal version of Q3 2004 WHO Drug Reference List (DRL) including Anatomical Therapeutic Chemical (ATC) code.

The concomitant medication information for the double blind phase will be summarized based on the SAF.

Concomitant medications, significant non-drug therapies and surgical and medical procedures, prior to and after the randomization date respectively, will be summarized by treatment group based on the latest version of dictionary. Medications will be presented in alphabetical order, by ATC codes and grouped by anatomical main group (the 1st level of the ATC codes). Table

will also show the overall number and percentage of subjects receiving at least one drug of particular ATC code and at least one drug in a particular anatomical main group.

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.

Concomitant heart failure and CV medications administered during double blind period will be summarized separately, in the same way. More specifically, the following classes of medication will be summarized separately.

- Aldosterone antagonists
- β- blockers
- Ivabradine
- Diuretics
- Digoxin
- Other
- Statin
- ACEI
- ARBs

Below ATCs will be used to present ATC specific table for during and/or prior to study period:

ATC codes	Sub group	Sub sub group	Period
C CARDIOVASCULAR SYSTEM	C01 CARDIAC THERAPY	C01A CARDIAC GLYCOSIDES	Prior, During
		C01B ANTIARRHYTHMICS, CLASS I AND III	Prior, During
		C01C CARDIAC STIMULANTS EXCL. CARDIAC GLYCOSIDES	Prior, During
		C01D VASODILATORS USED IN CARDIAC DISEASES	Prior, During
		C01E OTHER CARDIAC PREPARATIONS	Prior, During
	C02 ANTIHYPERTENSIVES	C02A ANTIADRENERGIC AGENTS, CENTRALLY ACTING	Prior, During
		C02B ANTIADRENERGIC AGENTS, GANGLION-BLOCKING	Prior, During
		C02C ANTIADRENERGIC AGENTS, PERIPHERALLY ACTING	Prior, During
		C02D ARTERIOLAR SMOOTH MUSCLE, AGENTS ACTING ON	Prior, During
		C02K OTHER ANTIHYPERTENSIVES	Prior, During
		C02L ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION	Prior, During
		C02N COMBINATIONS OF ANTIHYPERTENSIVES IN ATC-GR. C02	Prior, During
	C03 DIURETICS	C03A LOW-CEILING DIURETICS, THIAZIDES	Prior, During
		C03B LOW-CEILING DIURETICS, EXCL. THIAZIDES	Prior, During
		C03C HIGH-CEILING DIURETICS	Prior, During

		C03D POTASSIUM-SPARING AGENTS	Prior, During
		C03E DIURETICS AND POTASSIUM-SPARING AGENTS IN COMBINATION	Prior, During
		C03X OTHER DIURETICS	Prior, During
	C04 PERIPHERAL VASODILATORS		Prior, During
	C05 VASOPROTECTIVES		Prior, During
	C07 BETA BLOCKING AGENTS	C07A BETA BLOCKING AGENTS	Prior, During
		C07B BETA BLOCKING AGENTS AND THIAZIDES	Prior, During
		C07C BETA BLOCKING AGENTS AND OTHER DIURETICS	Prior, During
		C07D BETA BLOCKING AGENTS, THIAZIDES AND OTHER DIURETICS	Prior, During
		C07E BETA BLOCKING AGENTS AND VASODILATORS	Prior, During
		C07F BETA BLOCKING AGENTS, OTHER COMBINATIONS	Prior, During
	C08 CALCIUM CHANNEL BLOCKERS	C08C SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS	Prior, During
		C08D SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CARDIAC EFFECTS	Prior, During
		C08E NON-SELECTIVE CALCIUM CHANNEL BLOCKERS	Prior, During
		C08G CALCIUM CHANNEL BLOCKERS AND DIURETICS	Prior, During
	C10 LIPID MODIFYING AGENTS	C10A LIPID MODIFYING AGENTS, PLAIN	Prior, During
		C10B LIPID MODIFYING AGENTS, COMBINATIONS	Prior, During
	C09 AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	C09A ACE INHIBITORS, PLAIN	Prior
		C09B ACE INHIBITORS, COMBINATIONS	Prior
		C09C ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs), PLAIN	Prior
		C09D ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs), COMBINATIONS	Prior
		C09X OTHER AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	Prior

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary endpoint is change of VO_{2peak} compared to baseline measurements (adjusted to body weight) after 3 months of treatment.

As per the protocol amendement, the primary variable changed from "VO_{2peak} adjusted to lean body weight" to "VO_{2peak} adjusted to body weight". Furthermore, VO_{2peak} adjusted will be derived programatically as follows for the analysis:

$$VO_{2peak}\text{ (adjusted)} = \frac{VO_{2peak}\text{ (unadjusted)}}{\text{Body weight}}$$

VO_{2peak} (adjusted) will be calculated at visit 2, 6 and 7 based on the every visit's VO_{2peak} (unadjusted) and weight data.

Efficacy analysis will be summarized based on FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary analysis will be performed using analysis of covariance (ANCOVA) model with treatment and center as factors and baseline VO_{2peak} as a covariate. The raw as well as the adjusted (LS) group means will be presented. Additionally, a 95% confidence interval and p-value will be presented for the treatment contrast.

Listing will be based on dervied VO_{2peak} data.

2.5.3 Handling of missing values/censoring/discontinuations

Missing values of VO_{2peak} will be replaced with the last observed value (LOCF). Since the trial aims to estimate which improvements are achievable under the respective treatment regiments, LOCF seems to provide meaningful estimates for this purpose.

2.5.4 Supportive analyses

In case of deviations from the normality assumptions, treatments may additionally be compared by a non-parametric test (Mann-Whitney-U-test). In case of a substantial rate of missing data (>15%) or strong imbalances between treatment groups, Multiple Imputation (MI) may be considered as a sensitivity analysis.

2.6 Analysis of the key secondary objective

2.6.1 Key secondary endpoint

The key secondary endpoint is change of VO_{2peak} compared to baseline measurements (adjusted to body weight) at week 6. Efficacy analysis will be summarized based on FAS.

2.6.2 Statistical hypothesis, model, and method of analysis

The key secondary endpoint, the change from baseline in VO_{2peak} (adjusted to body weight) at week 6 will be analyzed similarly to the primary endpoint. The significance level will not be adjusted for multiplicity, the result of the test for week 6 will be regarded as providing confirmatory evidence, only if the test of the primary hypothesis (month 3) is also significant (a-priori ordered hypotheses).

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

The following secondary endpoints will be analyzed:

- Change from in VE/VCO_2 slope after 6 weeks and 3 months
- Change in exercise capacity (Watt) at VAT after 6 weeks and 3 months
- Change in rate of perceived exertion (Borg Scale) during exercise after 6 weeks and 3 months

2.7.2 Statistical hypothesis, model, and method of analysis

Secondary efficacy variables will be analyzed using ANCOVA models analogous to the analyses of the primary endpoint.

2.7.3 Handling of missing values/censoring/discontinuations

Missing values will not be imputed and will be considered missing at that particular visit.

2.8 Safety analyses

Safety assessments will be based mainly on the frequency of adverse events. Adverse events will be coded by primary system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). An adverse event related to study drug is defined as one considered by the investigator to have a suspected relationship with the study drug. The adverse events will be summarized by the number and percentage of patients in each primary system organ class and preferred term. For summaries by severity of event, the most severe occurrence for a particular preferred term will be used for a given patient. Summary tables of adverse events by treatment and severity will be provided.

Multiple occurrences of the same AE or SAE in the same patient will be counted only once, using the worst severity and drug relationship.

In the data listings of adverse events, the severity of an AE, whether or not an AE is study drug related, and whether or not it is a serious AE, will be indicated.

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy.

Laboratory data will be summarized by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges) and by presenting number and percentage of patients with notable laboratory abnormalities according to Appendix 1.

Data from other tests (vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

All safety analysis will be based on SAF.

2.8.1 Adverse events (AEs)

Any AE occurred during the study period will be included in AE summary tables, i.e. AEs occurred in screening phase and double blind period and SAE up to 30 days after the study completion.

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

Within each reporting phase, the following rules are applicable. 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. Statistical analyses, which will only be performed for the double blind or later phase, will include all post-baseline AEs up to and including the analysis cut-off (AEs up to the final visit and SAEs up to 30 days after the final visit for each patient) irrespective of how long after the last day of study treatment they occurred.

The number and percentage of subjects reporting any adverse event during reporting will be summarized by primary system organ class, preferred term and treatment. The most common adverse events reported (≥ 1 % in any group for each preferred term in the SOC-PT table) will be presented in descending frequency according to its incidence in the LCZ696 group starting from the most common event.

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

The following summaries will be generated for AEs during the double blind period:

- 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

AEs of special interest will be summarized separately in addition to the above analysis. The following are the AEs of special interest: angioedema events and angioedema-like events, dementia-related events, hepatotoxicity (drug related hepatic disorders) and statin-related events (only rhabdomyolysis, acute pancreatitis, myalgia and muscle spasm). The information will also be listed. Analysis will be based on SAF.

2.8.2 Deaths

Death will be summarized by number and percentage of patients in each primary system organ class and preferred term based on SAF.

2.8.3 Laboratory data

Laboratory data will be summarized for double blind period based on the SAF and also be listed.

Laboratory data for hematology (including hemoglobin, hematocrit, red blood cell count(RBC), white blood cell count with differential (WBC), and platelet count), and blood chemistry (including Blood urea nitrogen (BUN), glucose, creatinine, total bilirubin, AST (SGOT), ALT

(SGPT), alkaline phosphatase, sodium, potassium, chloride, calcium, HbA_1C, total protein, albumin, uric acid, and lipid profile, estimated glomerular filtration rate (eGFR)) will be summarized by treatment.

The eGFR is calculated according to the formula:

$$eGFR\ (mL/min/1.73\ m^2) = 175 \times (Serum\ creatinine/88.4)^{-1.154} \times (Age)^{-0.203} \times (0.742\ if\ female) \times (1.212\ if\ black),$$

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

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 and treatment group. 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 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 appendix 1 below. For the calculation the denominator are based on the evaluable post-baseline subjects who did not have the notable abnormality at baseline from the central laboratory.

2.8.3.1 Hematology

Hematology tests performed may include the following:

- Hemoglobin
- Hematocrit
- RBC
- WBC count with differential
- Platelet

The above tests will be analysed at visit 1 and 7.

2.8.3.2 Clinical chemistry

Blood Chemistry tests performed may include the following:

- Blood urea nitrogen (BUN)
- Creatine kinase (CK)
- Glucose
- Creatinine
- Total bilirubin (TBL)
- AST (SGOT)
- ALT (SGPT)

- Alkaline phosphatase (ALP)
- Sodium
- Potassium
- Potassium
- Calcium
- Hemoglobin A1C
- Total protein
- Albumin
- Uric acid
- Lipid profile

The above tests will be analysed at visit 1 and 7.

- Thyroid-stimulating hormone (TSH) will be assessed at Visit 1 only.

BUN, serum potassium, and serum creatinine value for eGFR calculation will be obtained from patients at every visit when a complete laboratory test is not done (i.e., Visits 3-5).

2.8.3.3 Liver event

Liver event data of sign and symptoms will be summarized and listed based on data collected on eCRF. Analysis will be based on SAF.

Liver events –imaging will be listed based on SAF.

2.8.3.4 Specific laboratory data

Liver function test (LFT) data will be analyzed according to what specified in hepatotoxicity in appendix 2 in section 5.

Laboratory data related to renal dysfunction (serum creatinine, eGFR) will be analyzed according to what specified in renal dysfunction in appendix 3 in section 5.

Laboratory data related to hyperkalemia (serum potassium greater than or equal to 5.3 mmol/L) will be analyzed according what specified in appendix 4 in section 5.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Not applicable.

2.8.4.2 Vital signs

Sitting systolic blood pressure (SSBP), sitting diastolic blood pressure (SDBP), sitting pulse rate and body weight will be summarized by treatment group and visit, including changes from

baseline. Summary statistics will be based on SAF. Where the baseline is defined as visit 2 and double blind period is from visit 3 to visit 7.

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.

2.8.4.3 Height and Weight and waist hip circumference

Height (cm), Body weight (kg), Waist/hip circumference (cm) will be summarized by treatment group and visit, including changes from baseline using SAF.

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.

2.8.4.4 NYHA Class assessment

Patients' NYHA class will be assessed at baseline and post-baseline. At baseline, only patients with heart failure NYHA class III can be enrolled in the study. The total number and percentage of patient with each NYHA class will be provided by treatment group and visits based on SAF. The change in NYHA class at every post-baseline visit compared to baseline will be summarized by frequency distribution.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Ergospirometry analysis

Ergospirometry data will be summarized for visit 2 (baseline), visit 6 and visit 7.

The data will be collected for the below parameters:

- $VO_{2peak\ adjusted}$
- [redacted]
- VE/VCO_2
- Exercise capacity (Watt) at VAT
- [redacted]
- [redacted]
- [redacted]

Descriptive summary statistics (mean, median, standard deviation, min and max) for baseline (visit 2) and change from the baseline to visit 6 and visit 7 will be presented. The descriptive summaries will be presented by ergospirometry parameters and treatment group based on FAS. 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.

Reason for termination will also be summarized seperatly based on FAS.

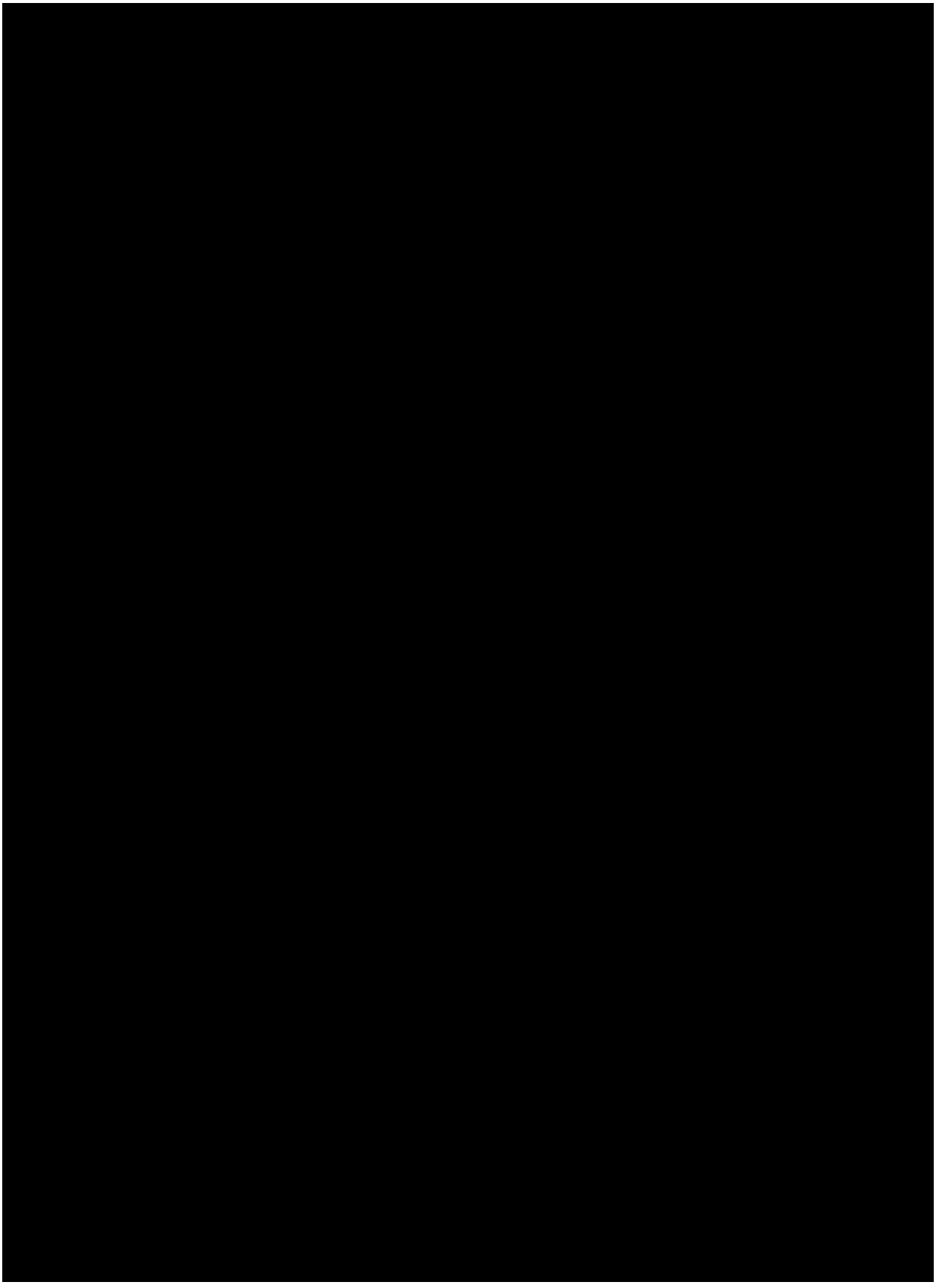
[redacted]

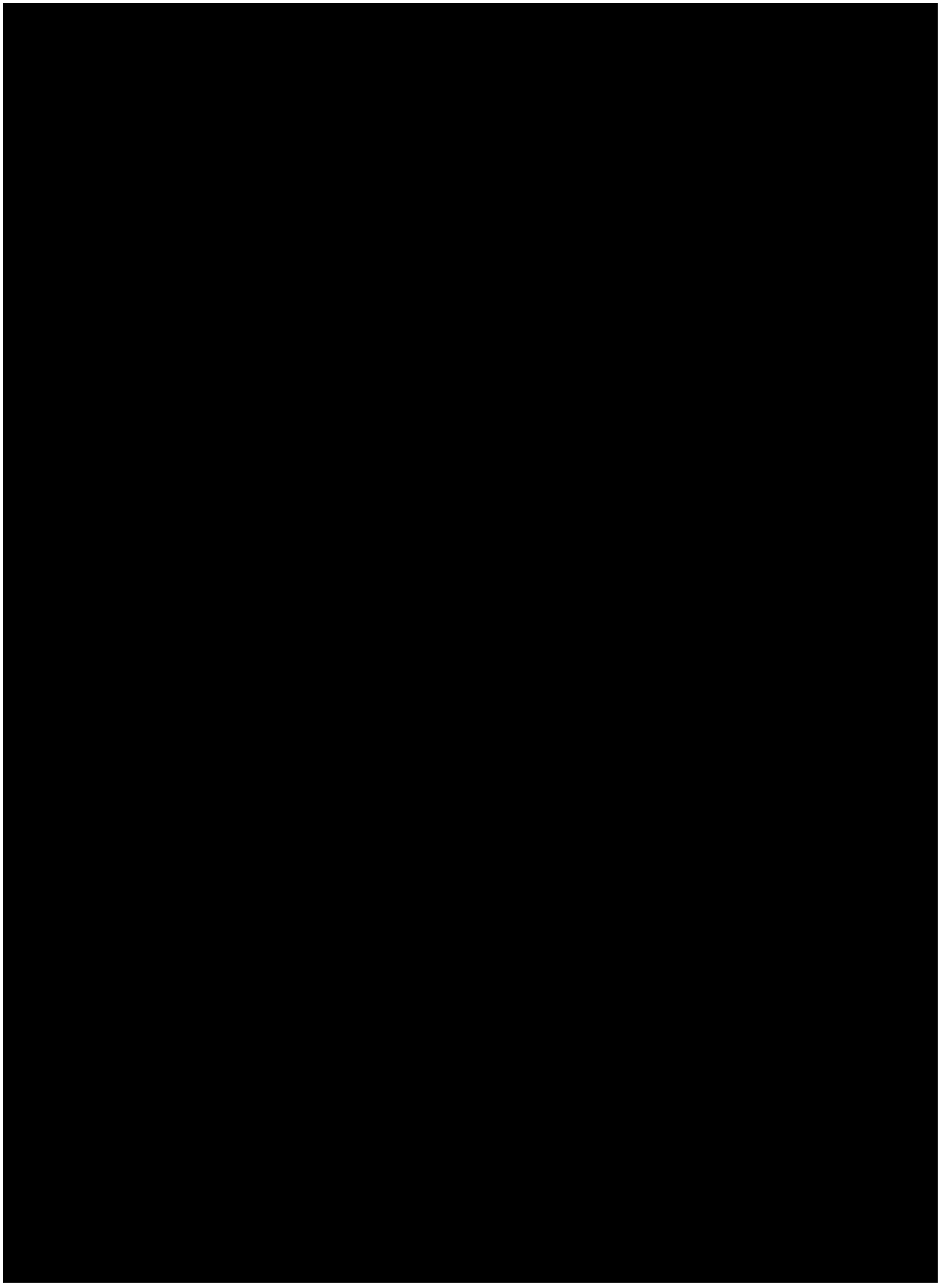
2.13 Borg scale analysis

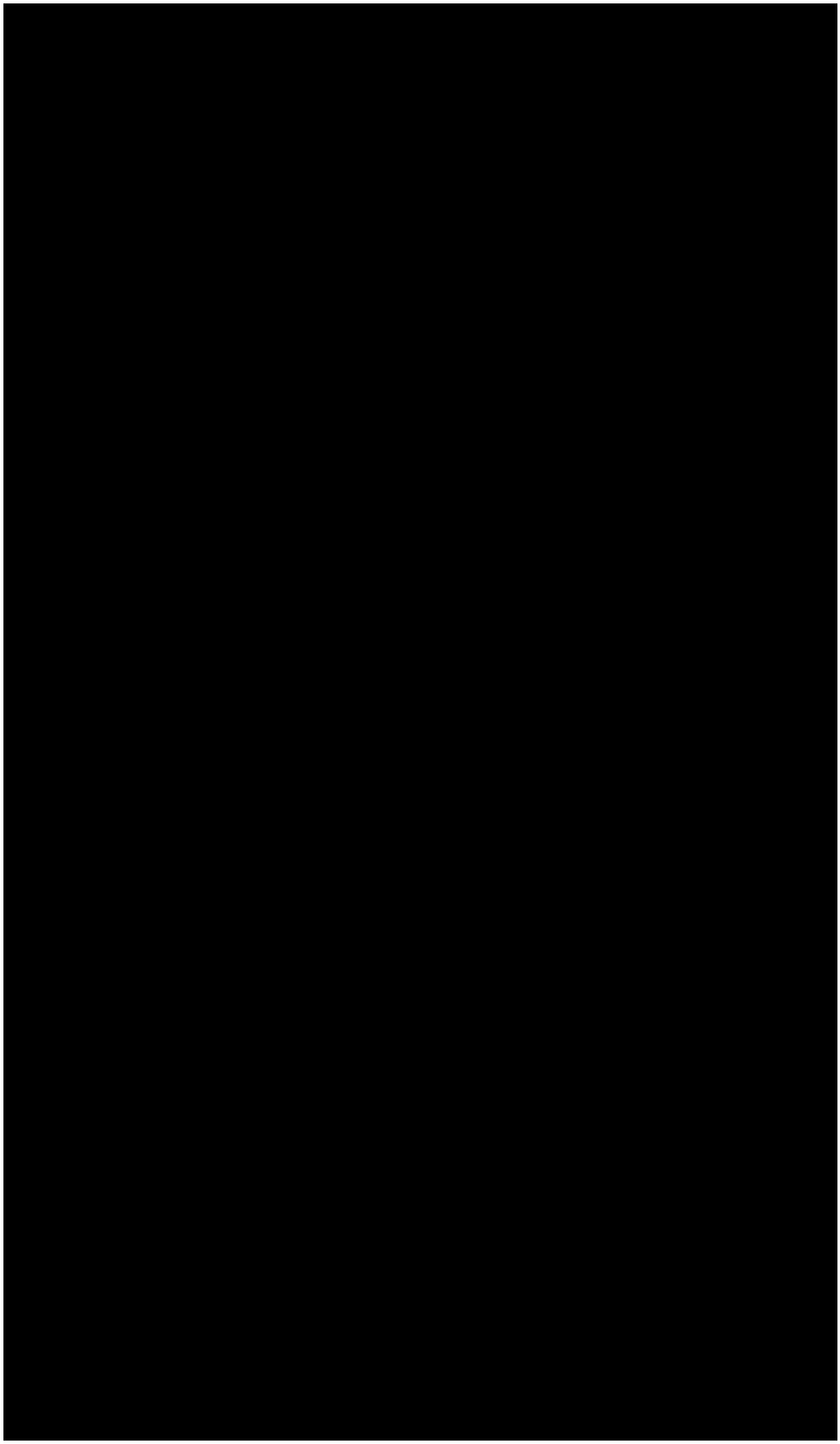
Borg scale data will be summarized for visit 2 (baseline), visit 6 and visit 7.

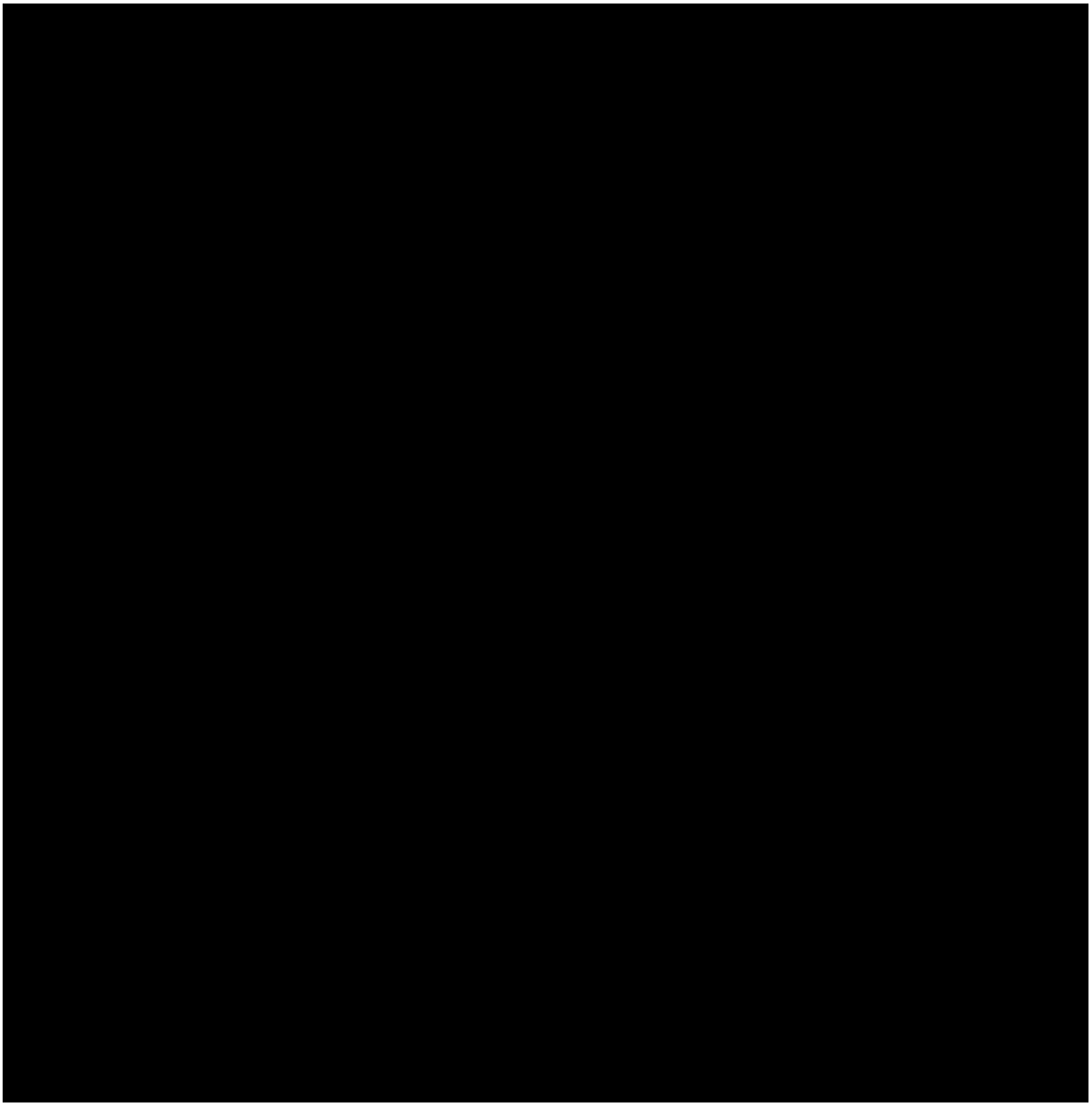
Descriptive summary statistics (mean, median, standard deviation, min and max) for the baseline and change from the baseline to visit 6 and visit 7 will be presented. The descriptive summaries will be presented by treatment group. Change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as defined in section 2.1.1. Maximum value among the timepoints at every visit will be used for the analysis. In case of multiple maximum values at the same visit, the most recent timepoint will be considered in the analysis. Listings will be provided with all the timepoint values at all visits.

[redacted]









2.19 Biomarkers

Not applicable.

2.21 Interim analysis

Not applicable.

3 Sample size calculation

Existing data suggest that the difference between LCZ696 and enalapril in VO_{2peak} at month 3 may be about 1.5 mL kg^{-1} min^{-1} with a (common) SD of 3 (Guazzi et al. 1999; Lewis et al. 2007). Under these assumptions, 86 patients per treatment arm would be required to achieve 90% power on a 2-sided, 5% significance level. To compensate for some drop-out and other protocol deviation 100 patients per treatment group (200 in total) will need to be enrolled into this trial. The above mentioned literature suggests that the treatment effect for the key secondary endpoint, VO_{2peak} after 6 weeks, might be of a similar magnitude, therefore, the sample size calculation above applies also for the key secondary endpoint.

4 Change to protocol specified analyses

VO_{2peak} adjusted to body weight will be calculated as follows for the analysis:

$$VO_{2peak}\text{ (adjusted)} = \frac{VO_{2peak}\text{ (unadjusted)}}{\text{Body weight}}$$

VO_{2peak} (adjusted) will be calculated at visit 2, 6 and 7 based on the visit's VO_{2peak} (unadjusted) and body weight data.

Note1: The collected data of VO_{2peak} adjusted will remain as it is in source data.

Note2: Patient [redacted] was unblinded at site on [redacted] for safety purpose. However, as confirmed by CTT, the patient would not be excluded from the analyses.

5 Appendix

Appendix 1: 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

Appendix 2: Liver event definitions and follow-up requirements

Table 19-1 Liver event definitions

	Definition/
Adverse event of special interest	
Laboratory values	ALT or AST > 3 x ULN ALP TBL >

Medically significant event (SAE)	
Laboratory values	ALT or AST > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction])
	ALP > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction])
	TBL
	Potential Hy's Law cases (defined as ALT/AST > 3 x ULN and TBL > 2 x ULN [mainly conjugated fraction] without notable
Adverse events	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
	Any event that links to a preferred term (PT) in the MedDRA dictionary falling under the SMQ sub-module "Drug-related hepatic disorders – severe events only"* or

* These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver

Table 19-2 Liver event follow up requirements

Criteria	**Event**	**Actions required**	**Follow-up monitoring**
Potential Hy's Law case[a]	Medically significant	Discontinue the study drug immediately Hospitalize, if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST			
> 8 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists for *more than 2 weeks*, discontinue the study drug Report to Novartis as an	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 x ULN accompanied by symptoms[b]	Medically significant	Discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)

> 3 to ≤ 5 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Investigator & Novartis Repeat LFT once or twice in the week If elevation persists,	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 3 x ULN (patient is asymptoma	N/A	Repeat LFT at next visit	
ALP (isolated)			
> 5 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, report to Novartis as an SAE	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
> 2 to ≤5 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Investigator & Novartis Repeat LFT once or twice in the week. If elevation	Investigator discretion Monitor LFT within 1 to 4 Weeks or at next visit
≤ 2 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
TBL (isolated)			
> 3 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolutionc (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 3 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Novartis Repeat LFT once or twice in the week If elevation persists, establish causality	investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 1.5 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
Preferred terms			

Jaundice	Medically significant	Discontinue the study drug immediately Hospitalize the patient Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
"Drug-related hepatic disorders - severe events only" SMQ AE	Medically significant	Discontinue the study drug hospitalization if clinically appropriate Report to Novartis as an SAE Establish causality	Investigator discretion

[a] Elevated ALT/AST > 3 x ULN and TBL > 2 x ULN but with no notable increase in ALP to > 2 x ULN

[b] General malaise, fatigue, abdominal pain, nausea, or vomiting, rash with eosinophilia

[c] Resolution is defined as an outcome of one of the following: return to baseline values, stable values at three subsequent monitoring visits at least 2 weeks apart, remain at elevated level after a maximum of 6 months, liver transplantation, and death.

Appendix 3: Guidelines for the management of renal dysfunction

General principles:

Glomerular filtration rate in HF patients depends on intrinsic renal function and on a balance between afferent and efferent glomerular arterial tonicity. This tonicity is partly regulated by a stimulation of angiotensin II and could be affected by either study medication. Moreover, renal dysfunction may develop or may deteriorate in some patients after study drug administration. These recommendations have been developed to guide the investigators in managing patients with renal dysfunction after randomization.

Two types of response to serum creatinine increase are described:

Surveillance situation

If, at any time after randomization, eGFR decreases by ≥ 25% from baseline (Visit 2) (or if serum creatinine concentration increase to 2.5 mg/dL [221 µmol/L]), the investigator will check for potentially reversible causes of renal dysfunction such as:

- Non-steroidal anti-inflammatory drug intake, antibiotics, or other treatments known to affect creatininemia
- Volume decrease, including that resulting from excessive dosing of diuretics
- Urinary infection
- Urinary tract obstruction
- Study medication

Action situation

If a patient eGFR decreases by ≥ 40% from baseline (Visit 2) (or if serum creatinine concentration rises above 3 mg/dL (265 µmol/L)), the investigator will check for potentially reversible causes of renal dysfunction (see above).

If the investigator judges that study medication has to be stopped, he/she will have to contact the Novartis medical monitor or his/her designee. Thereafter, serum creatinine assessments will have to be repeated at least each week until levels return to acceptable values. If study medication was stopped, every effort will be done to restart it again, according to clinical conditions.

Appendix 4: Treatment guidelines for hyperkalemia (serum potassium greater than or equal to 5.3 mmol/L)

General principles

Elevation of potassium levels above the predefined values should be repeated and confirmed before any action is taken.

Any patient with a serum potassium ≥ 5.3 mmol/L after enrollment into the study requires regular, repeated checks of potassium concentration (beyond that prescribed in the protocol) until it is clear that the potassium concentration is stable and not rising into the range of concern (≥ 5.5 and < 6.0 mmol/L) or potential danger (≥ 6.0 mmol/L).

Patients with elevated potassium value will be managed according to the corrective actions outlined below. Hyperkalemia should be followed until resolution.

Corrective action for management of hyperkalemia

Serum potassium ≥ 5.3 and less than or equal to 5.5 mmol/L

- Confirm potassium concentration in a non-hemolyzed sample
- Reinforce low potassium diet and restriction of food/drinks with high potassium content (e.g. orange juice, melon, bananas, low-salt substitutes etc.)
- Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia. Consider reduction in dose or discontinuation of these agents:
    - Aldosterone antagonists (if they are believed to be the most likely cause of hyperkalemia)
    - Potassium-sparing diuretics (e.g. amiloride and triamterene) including in combination products with thiazide or loop diuretics
    - Potassium supplements, e.g., potassium chloride
    - Salt substitutes
    - Non-steroidal anti-inflammatory drugs (NSAIDs)
    - Cyclo-oxygenase-2 (COX-2) inhibitors
    - Trimethoprim and trimethoprim-containing combination products, such as trimethoprim/sulfamethoxazole fixed combinations
    - Herbal Supplements:

- For example, Noni juice, alfalfa (Medicago sativa), dandelion (Taraxacum officinale), horsetail (Equisetum arvense), nettle (Urtica dioica), milkweed, lily of the valley, Siberian ginseng, hawthorn berries

- Repeat serum potassium measurement within 3 to 5 days
- If serum potassium remains ≥ 5.3 and ≤ 5.5 mmol/L, regularly monitor serum potassium levels to ensure stability (suggested once monthly)
- Consider down-titration of study medication, according to investigator's medical judgment.

Serum potassium > 5.5 and < 6.0 mmol/L

- Confirm potassium concentration in a non-hemolyzed sample
- Consider down-titration or temporarily discontinue study drug according to investigator medical judgment.
- Apply all measures outlined for serum potassium ≥ 5.3 and ≤ 5.5 mmol/L
- Repeat serum potassium measurement after 2-3 days
- If serum potassium < 5.5 mmol/L, consider resumption of study drug at lower dose with repeat potassium within 5 days

Serum potassium greater than or equal to 6.0 mmol/L

- Immediately discontinue study drug
- Confirm potassium concentration in a non-hemolyzed sample
- Urgently evaluate patient and treat hyperkalemia as clinically indicated
- Apply all measures outlined for serum potassium ≥ 5.3 and < 6.0 mmol/L

No resumption of study drug without individualized case discussion with and permission from Novartis medical monitor or his/her designee.

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

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

AE Start Date Imputation (#IMPUTAEV)

This algorithm is expressed in the Variable Source Derivation column as **#IMPUTAEV (*event*)** where *event* is the partial date of the adverse event.

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

	Day	**Month**	**Year**
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date(TRTSTD)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON<TRTM	MON=TRTM	MON>TRTM
YYYY MISSING	**NC** Uncertain	**NC** Uncertain	**NC** Uncertain	**NC** Uncertain
YYYY<TRTM	**(D)** Before Treatment Start	**(C)** Before Treatment Start	**(C)** Before Treatment Start	**(C)** Before Treatment Start
YYYY=TRTM	**(B)** Uncertain	**(C)** Before Treatment Start	**(A)** Uncertain	**(A)** After Treatment Start
YYYY>TRTM	**(E)** After Treatment Start	**(A)** After Treatment Start	**(A)** After Treatment Start	**(A)** After Treatment Start

The following table is the legend to the logic matrix.

If AE end date is complete and AE end date < Treatment start date or AE end date is partial and AE imputed end date < Treatment start date, then AE start reference = min (informed consent date, earliest visit date from SV)

Else if AE end date is partial, AE end date ≥ Treatment start date or AE is ongoing , then AE start reference = treatment start date.

Relationship		
Before AE Start reference	Partial date indicates AE start date **prior** to AE start reference	
After AE Start reference	Partial date indicates AE start date **after** AE start reference	
Uncertain	Partial date **insufficient to determine** relationship of AE start date to AE start reference	
Imputation Calculation		
NC/Blank	No convention	

(A)	MAX(01MONYYYY, AE start reference+1 day)	
(B)	AE start reference+1	
(C)	15MONYYYY	
(D)	01JULYYYY	
(E)	01JANYYYY	

Complete date	No date imputation	If time is captured for the study:
		Case 1. if AE start date is not
		equal to AE start reference
		then do the following:
		if minutes missing then
		AESTMF = M and time is
		imputed to hh:00
		if time missing then
		AESTMF = H and time is
		imputed to 00:00
		Case 2: if AE start date = AE
		start reference then AESTMF =
		H and time is imputed to
		treatment start time + 1 hour

Adverse Event End Date Imputation

Imputed date = date part of original date, if complete date

Imputed date = min (visit 299 date, DEC 31, date of death), if month is missing,

Imputed date = min (visit 299 date, last day of the Month, date of death), if day is missing.

Adverse Event End Time Imputation

If the AE end date is complete and time is captured in the study then:

Case 1. if AE end date is not equal to Treatment end date, then do the following:

if minutes missing then time is imputed to hh:00

if time missing then time is imputed to 00:00

Case 2: if AE end date = treatment end date then time is imputed to treatment end time

If the AE end date is partial then end time is imputed to 00:00.

Imputed Date Flag

If year of the imputed date is not equal to YYYY then date flag = Y

else if month of the imputed date is not equal to MON then date flag = M

else if day of the imputed date is not equal to day of original date then date_flag = D

else date flag = null

Imputed Time Flag

If hours of the imputed time is not equal to hours of original time then time flag = H

else if minutes of the imputed time is not equal to minutes of original time then time flag = M

else time flag = null

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 -

Imputed date = date part of CMENDTC, if complete date

Imputed date = min(visit 299 date, DEC 31) , if month is missing, (C2, D, E)

Imputed date = min(visit 299 date, last day of the Month) , if day is missing. (A, B, C1)

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

Not applicable.

5.1.3.2 Post therapies date imputation

Not applicable.

5.1.3.3 Other imputations

5.2 AEs coding/grading

Not applicable.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

5.4.1 Primary analysis

For ANCOVA model

```
proc mixed data = a;
  class TRTN CENTRE;
  model Estimate = TRTN CENTRE BSL_VO2peak;
  lsmeans TRTN/om;
  estimate 'LCZ696 - Enalapril' trtn 1 -1 /cl;
run;
```

For Mann-Whitney-U-test

In case of deviations from the normality assumptions, treatments will additionally be compared by a non-parametric test (Mann-Whitney-U-test).

```
proc NPAR1WAY data=a wilcoxon;
  class TRTN CENTRE;
  var VO2peak;
  exact wilcoxon;
run;
```

here VO2peak variable contains change from baseline to Week X.

5.4.2 Key secondary analysis

Key secondary endpoint will be analyzed similarly to the primary endpoint.

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:

Category	**Description of Protocol Deviation**	**Inclusion / Exclusion in analyses**	**Severity code**
Study treatment	Patient was misrandomized (patient randomized in error and no DB study medication taken).	Excluded from FAS, SAF	3
Inclusion criteria	Informed consent missing	Excluded from FAS, SAF	3
General	All other PDs	Include in FAS, SAF	0

6 Reference

Same as protocol.

Benjamin Waschki, Anne Kirsten, Olaf Holz, Kai-Christian Müller, Thorsten Meyer, Henrik Watz and Helgo Magnussen

Chest; Prepublished online January 27, 2011; OI 10.1378

http://chestjournal.chestpubs.org/content/early/2011/01/18/chest.10-2521