NOVARTIS

Clinical Development

LCZ696

CLCZ696G2301 / NCT02924727

A multi-center, randomized, double-blind, active-controlled, parallel group Phase 3 study to evaluate the efficacy and safety of LCZ696 compared to ramipril on morbidity and mortality in high risk patients following an acute myocardial infarction

Statistical Analysis Plan (SAP)

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
bid	bis in diem/twice a day
CSR	Clinical Study report
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
o.d.	Once Daily
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
[redacted]	[redacted]
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The statistical analysis plan (SAP) describes the detailed methodology and implementation of the planned statistical analyses outlined in the study protocol for CLCZ696G2301. The analyses following the SAP below will be used for clinical study reporting purposes while the same analysis plan will also be used for the planned interim efficacy analysis unless otherwise specified.

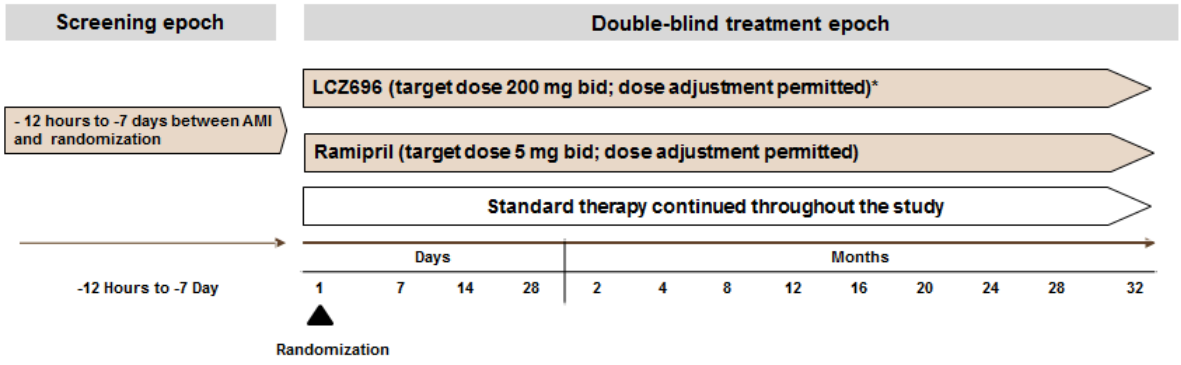
It is important to note that this version of statistical analysis plan details the statistical methodology for the analyses planned and agreed to at the time of finalization of the CLCZ696G2301 protocol (Version 00 – original protocol). Any statistical analysis planned thereafter will be prospectively furnished with relevant details in subsequent versions as amendments and will be finalized before database lock (DBL) prior to the final analysis.

1.1 Study design

This is a multicenter, randomized, double-blind, active controlled, event-driven phase III clinical trial designed to evaluate the efficacy and safety of LCZ696 compared to ramipril when added to standard therapy in post-AMI patients with LV systolic dysfunction and/or pulmonary congestion.

The study population consists of high risk patients who have sustained a spontaneous acute myocardial infarction (ST segment elevation MI (STEMI) or non-ST segment elevation MI (NSTEMI) within the last 12 hours to 7 days prior to randomization) with evidence of LV systolic dysfunction and/or pulmonary congestion associated with index MI. In addition, patients need to have at least one predefined risk factor and without known prior history of chronic HF.

Figure 1-1 Study Design



*Treatment with two doses of valsartan 40 mg or 80 mg (bid) required before starting study medication for patients who are randomized to LCZ696 and previously treated with ACE inhibitors

As per the study design (Figure 1-1), a screening epoch of no more than 7 days after index MI presentation will be used to determine if patients qualify to enter the double-blind treatment phase of the study with respect to protocol specified inclusion/ exclusion criteria.

Eligible patients, stratified by type of MI (STEMI/ NSTEMI) and region, will be randomized 1:1 to receive LCZ696 titrated to a target dose of 200 mg twice daily or ramipril titrated to a target dose of 5 mg twice daily. Patients may be randomized on the same day that they are consented and screened. To reduce the potential risk of angioedema, patients on ACEI during the last 36 hours prior to randomization will undergo a valsartan bridging treatment for 1 day in a blinded manner.

Three dose levels of study medication will be administered in a stepwise titration (Table 1-1). Randomized patients are planned to start at dose level 1 while those who were on prior ARB/ACEI may start at dose level 2 at investigator's discretion.

Table 1-1 Study drug dose levels during treatment epoch

Dose Level	LCZ696 Treatment Arm*	Ramipril Treatment Arm
1	50 mg b.i.d.†	1.25 mg b.i.d.
2	100 mg b.i.d.†	2.5 mg b.i.d.
3	200 mg b.i.d.	5 mg b.i.d.
* LCZ696 dosing is based on the total amount of both components of sacubitril/valsartan; dose levels 1, 2 and 3 are equivalent to sacubitril/valsartan 24/26 mg, 49/51 mg and 97/103 mg, respectively. † Patients who are randomized to LCZ696 and received ACE inhibitors in the 36 hours prior to randomization will be given a bridging valsartan dose in a blinded manner for one day (two doses at either dose level V1 or V2: 40 or 80 mg b.i.d.) prior to beginning double-blind LCZ696 treatment.		

Patients can be up-titrated to the next dose level subject to satisfying pre-defined safety / tolerability criteria (SBP $\geq$ 100 mmHg, eGFR $\geq$ 30 mL/min/1.73m^2 or serum creatinine increase < 0.5 mg/dl from baseline, serum potassium < 5.5 mmol/L (mEq/L)). The titration scheme aims to achieve the target dose within 2 weeks of randomization.

The study is event-driven and will continue until both a total of 800 confirmed primary triple composite endpoint events **and** 633 confirmed double composite events of CV death or HF hospitalization (i.e., first secondary endpoint) have been achieved. Approximately 4,650 randomized post-AMI patients are estimated to provide the necessary number of confirmed endpoints over a total study duration of 32 months with a projected patient recruitment period of 24 months. The overall estimated mean follow-up time will be 20 months for the study.

1.2 Study objectives and endpoints

Table 1-2 Objectives and related endpoints

Objective	Related endpoint and Definition	Analysis method
Primary objective		
To demonstrate that LCZ696 is superior to ramipril in delaying the time-to-first occurrence of the composite endpoint of CV death, HF hospitalization or outpatient HF in patients with LV systolic dysfunction and/or pulmonary	The primary efficacy endpoint is defined as the time to the first confirmed occurrence of CV death, heart failure hospitalization* or outpatient heart failure**. ** Heart failure hospitalization also includes the development of new symptomatic heart failure*	Section 2.5

Objective	Related endpoint and Definition	Analysis method
congestion following an AMI	*during an ongoing hospitalization including the index AMI hospitalization.* *** Outpatient heart failure is defined as:* • *An urgent/unscheduled visit to an ED, acute/urgent care facility or outpatient clinic or a non-urgent office/practice or study visit for a primary diagnosis of HF that does not require an overnight hospital stay.* • *Patients must exhibit at least one documented new HF symptom with objective evidence of clinical HF consisting of at least 2 physical examination findings or one physical examination findings and at least one laboratory criterion.* • *The event requires initiation or intensification of treatment specifically for HF. Such treatment can include administration of intravenous agent (e.g., diuretic, vasodilator, vasopressor, or inotrope) or mechanical or circulatory intervention for HF, OR initiation of oral loop diuretic treatment, or intensification of oral maintenance loop diuretics for the diagnosis of HF, over a sustained period (i.e., initiation or doubling of total daily dose through a period of ≥ 4 weeks), which is confirmed at a subsequent outpatient visit*	
Secondary objective		
To demonstrate the superiority of LCZ696, compared to ramipril, in delaying the time-to-first occurrence of CV death or HF hospitalization	Time-to-first occurrence of CV death or HF hospitalization (days).	Section 2.6
To demonstrate the superiority of LCZ696, compared to ramipril, in delaying the time to new onset of symptomatic HF defined as time-to-first occurrence of HF hospitalization or outpatient HF	Time-to-first occurrence of HF hospitalization or outpatient HF (days)	Section 2.6
To demonstrate the superiority of LCZ696 compared to ramipril, in delaying the time-to-first occurrence of CV death, non-fatal spontaneous MI[1] or non-fatal stroke	Time-to-first occurrence of CV death, non-fatal spontaneous MI[1] or non-fatal stroke (days).	Section 2.6
To demonstrate the superiority of LCZ696, compared to ramipril, in reducing the rate of the composite endpoint of CV death and total (first and recurrent) hospitalizations due to HF, non-fatal spontaneous MI[1] or non-fatal stroke	Cumulative number of composite endpoint of CV death and total (first and recurrent) hospitalizations due to HF, non-fatal spontaneous MI[1] or non-fatal stroke (count).	Section 2.6

Objective	Related endpoint and Definition	Analysis method
To demonstrate the superiority of LCZ696, compared to ramipril, in delaying the time to all-cause mortality	Time to all-cause mortality (days).	Section 2.6
To evaluate the safety and tolerability of LCZ696 compared to ramipril	• Number and percentage of adverse events, serious adverse events, drug-related discontinuations, etc. • Change from baseline in laboratory assessments and vital signs measurements	Section 2.7
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Objective	Related endpoint and Definition	Analysis method
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

2 Statistical methods

The following section contains important information on detailed statistical methodology used for analysis and reporting purposes.

2.1 Data analysis general information

Data will be analyzed by Novartis Biostatistics and Statistical Reporting department according to the statistical analysis section 9.1 of the study protocol using SAS 9.4, unless otherwise specified. Further details on planned statistical analyses and data-driven regression diagnostics will be presented in the following section and in CSR Appendix 16.1.9. The same analysis plan will also be used for planned interim efficacy analysis, as applicable.

In general, the continuous variables will be summarized descriptively by presenting n, mean, SD, median, quartiles, minimum and maximum while categorical variables will be summarized by presenting count and percentage of patients in each category. Graphical presentation of summary data will also be provided as applicable.

The randomization in this study will be stratified by region and type of MI (STEMI or NSTEMI). The stratification factors will be appropriately accounted for in the planned statistical analyses.

For planned interim efficacy, the analysis cutoff date will be determined as date when 2/3rd of target primary composite outcome i.e. approximately 540 primary composite outcomes will be reported and adjudication-confirmed. If the assumptions of the study design regarding event rate, accrual rate and drop-out rate remain valid, the final analysis cut-off date will be a predicted date when either a total of 800 confirmed primary triple composite and 633 confirmed double composite events have been achieved, or study termination has been decided based on other study termination criteria.

2.1.1 General definitions

Study treatment or drug

In future sections through this document, ‘study treatment’ or ‘study drug’ will be used to refer to investigational therapy assigned to a patient. Specifically, for the double-blind treatment phase, study treatment refers to LCZ696 or ramipril as assigned to a patient at randomization.

Screening epoch

Screening epoch is defined as the period starting from date of signed of informed consent until date of randomization or decision on randomization.

Randomized treatment phase

The randomized treatment phase begins at the time of randomization and ends with the last study drug intake or the death of the patient, whichever comes earlier. During the randomized treatment phase, patients will return for scheduled clinic visits. For all related safety analyses randomized treatment starts with the first intake of randomized, double-blind study drug. Temporary interruption of the study drug will not be counted as randomized treatment phase discontinuation.

Post-treatment follow-up phase

The post-treatment follow-up phase (usually after premature permanent study drug discontinuation) begins after last study drug intake + 1 day and ends on the date last seen (or vital status confirmed by indirect contact).

Double-blind treatment phase

The double-blind treatment phase is the combination of the randomized treatment phase and the post-treatment follow-up phase.

Baseline and study day

For analysis purpose, baseline value for all variables is defined to be the last results obtained at or prior to randomization (or prior to 1st study drug intake for safety assessments). Most of variables will have their baseline at visit 101, unless otherwise specified. For assessments not performed at visit 101, the assessment at screening visit or most recent assessment prior to randomization will be used as baseline. [redacted]

Study day of any assessment refers to the number of days to the assessment relative to randomization (day 1), or relative to the 1st study drug intake for safety assessments.

On-treatment data for an efficacy endpoint

The on-treatment data refers to any observation occurring while the patient is on-study medication or within 28 days inclusive of permanent treatment discontinuation excluding any observation occurring thereafter.

2.2 Analysis sets

The following analysis populations will be defined for statistical analysis:

- **Screened (SCR) set –** All patients who have signed informed consent. The screened set includes only unique screened patients, i.e., in the case of re-screened patients only the chronologically last screening data is counted.
- **Randomized (RAN) set** – All patients who received a randomization number, regardless of receiving trial medication.
- **Safety set (SAF) -** All randomized patients who received at least one dose of study drug. Patients in the SAF will be analyzed according to treatment received.
- **Full analysis set (FAS)** – All patients in the RAN population who were not mis-randomized patients*. Following the intent-to-treat (ITT) principle, patients in the FAS are analyzed according to the treatment they have been assigned to at the randomization.
- **Per-protocol set (PPS)** will be a subset of the FAS which will consist of the patients who do not have major deviations. Major protocol deviations will be pre-specified prior to unblinding.

* Mis-randomized patients are those who were not qualified for randomization and who did not take study drug, but have been inadvertently randomized into the study.

A sample of rules leading to exclusion from specific analysis sets of patients violating protocol specified inclusion/ exclusion criteria and any other protocol deviations developed during the study has been provided in Appendix 5-5. The final list may be different from this which will be finalized and signed off before DBL.

2.2.1 Subgroups of interest

Subgroups will be formed to explore the consistency of treatment effects and safety pro filing on selected parameters between the subgroups and the overall population. In general, subgroups will be defined based on baseline information as defined in section 2.1.

In Table 2-1, we have listed all subgroups defined for this study and the ways to derive them. Subsets of these subgroups will be used depending on the parameter under consideration. Also note that only important parameters or variables in these analyses will have subgroup analyses. The details about the parameters having subgroup analyses will be presented in the corresponding sections as appropriate. Also, additional subgroups may be formed later for regional or country-wise analyses as applicable.

Table 2-1 Specification of subgroups

Subgroup	Method of derivation	Disposition/ Background & Demographics / Exposure	Efficacy	Safety
Age groups: (<65 vs. ≥65 years, <75 vs. ≥75 years)	Screening (derived)	X	X	X
Gender (male/ female)	Screening	X	X	X
Race	Screening	X	X	X
Region*	Derived (pooled countries or country), using Screening	X	X	X
Baseline LVEF (by quartiles)	Screening		X	
Baseline LVEF ≤40% vs. > 40%	Screening		X	
Worst Killip class (I vs. ≥ II)	Randomization		X	
Type of MI (STEMI vs. NSTEMI)	Randomization	X	X	X
Infarct location (anterior, inferior, and other)			X	
PCI use at baseline (PCI use versus medical management after index MI up to randomization)		X	X	

Subgroup	Method of derivation	Disposition/ Background & Demographics / Exposure	Efficacy	Safety
Time from the index MI presentation to randomization (< median, ≥median)			X	
Baseline SBP (three groups: ≤110 mmHg; >110 mmHg and ≤140 mmHg; >140 mmHg)	Randomization		X	
Baseline eGFR (<60 vs ≥ 60 mL/min/1.73 m2)	Randomization		X	
History of diabetes (yes/no)			X	
Atrial Fibrillation associated with index MI at baseline (yes/no)			X	
Prior history of MI			X	
History of hypertension (yes/no)	Screening		X	
Prior ACEi or ARB use (yes/no)	Randomization		X	
Use of β-blocker at baseline (yes/no)			X	
Use of mineralocorticoid antagonists at baseline (yes/no)			X	
Use of oral loop diuretics at baseline (yes/no)			X	

* ***North America:*** *Canada, USA*

Latin America (including Central America): *Argentina, Peru, Brazil, Colombia, Mexico*

Western Europe: *Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom*

Central Europe: *Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Russia, Slovakia, Turkey*

Asia Pacific & Others: *Australia, South Africa, Israel, China, India, Korea, Philippines, Singapore, Taiwan, Thailand*

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Based on all patients in the screened set, number and percentage of patients screened successfully will be provided. In addition, screen failure patients will be summarized by primary reason for screen failure.

The number and percentage of randomized patients included in different analysis sets (Section 2.2) will be summarized based on the randomized patients. Patients with premature study discontinuation during the double-blind treatment epoch will be summarized by the primary reason of discontinuation for each randomized treatment group and overall based on all patients in randomized set (RAN).

In addition, the number and percentage of patients with protocol deviations as well as the criteria leading to exclusion from analysis sets will be provided for the patients in randomized set (RAN). All the disposition data will also be listed at a patient level separately for screening phase disposition and double-blind treatment phase disposition.

2.3.2 Demographics and baseline characteristics

Following demographic and baseline characteristics will be summarized by randomized treatment group for all patients in full analysis set (FAS):

- **Continuous variables**
  Age (in years), height (in meters), weight (in Kg.), body mass index (BMI) in Kg/m^2, SBP (in mmHg), DBP (in mmHg), heart rate (in bpm), eGFR (in $ml/min/1.73m^2$), time from index MI presentation to randomization
- **Categorical variables**
  Age group (<65 years vs. ≥65 years; <75 years vs. ≥75 years), sex, race, ethnicity, region

2.3.2.1 Characteristics and therapies associated with qualifying MI

Qualifying MI related characteristics, cardiovascular (CV) risk factors associated with qualifying MI and therapies used to manage qualifying MI will be summarized separately for all patients in the Full Analysis set (FAS) which includes:

- **Disease characteristics**
  Location of infraction (anterior / inferior), type of MI (STEMI/ NSTEMI), number of diseased vessels, ejection fraction (EF) (in %), Killip class
- **CV risk factors/co-morbidity/past history at baseline**
  Age (<70, ≥70 years), screening eGFR (<60, ≥60 $ml/min/1.73m^2$), diabetes (yes/no), history of prior MI (yes/ no), atrial fibrillation associated with qualifying MI (yes/ no), categories of EF (<30%, >=30%), worst Killip class (<III, ≥III), STEMI without reperfusion therapy within the first 24 hours after presentation (yes/no)
- **Therapies used to manage qualifying MI –**
  Use of reperfusion therapies (yes / no) –

- use of PCI (yes/ no) (including procedures performed for qualifying MI both prior to and after randomization but before discharge)
- type of stenting if PCI performed (bare metal/drug eluting stent)
- use of antithrombotic therapy (yes/no) which includes aspirin, P2Y12 inhibitor, antithrombin agents, glycoprotein (GP) IIb/IIIa inhibitors
- use of oral CV medications including (but not limited to) ARB/ACE inhibitors, beta blockers, mineralocorticoid receptor antagonists (MRA), statins, oral anticoagulants, non-loop diuretics, loop diuretics, digitalis glycosides, oral nitrates and calcium channel blockers..
- use of IV diuretics (yes/no), IV vasodilator (yes/no), IV vasopressors (yes/no), IV inotropes (yes/no)

In general, all continuous variables will be summarized by presenting descriptive statistics (n, mean, SD, Q1, Q3, median, minimum, maximum) and all categorical variables will be summarized by number and percentage of patients in each category. The summaries will be provided by randomized treatment group for all patients in Full Analysis set (FAS).

2.3.3 Medical history

Any condition entered on the relevant medical history / current medical conditions CRF will be coded using the most updated version of MedDRA dictionary. Medical history includes heart failure history and cardiovascular disease history, and other medical history in this study, which are collected at Visit 1 (Screening visit). The number and percentage of subjects with each medical condition will be provided by treatment group and system of organ class for the Full Analysis Set (FAS).

Patient disposition, demographic/ baseline and other disease characteristics will also be summarized similarly for the following subgroups:

- Age group (<65 vs. ≥65 years), age group (<75 vs. ≥75 years)
- Gender (male/female)
- Region
- Race
- Type of MI (STEMI vs. NSTEMI)
- PCI use at baseline (Yes vs. No)

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

2.4.1 Study treatment / compliance

Overall treatment exposure

The duration of overall treatment exposure (in days) will be calculated as –

Last known date when the patient took study medication – Date of 1st intake of randomized study medication during double-blind treatment epoch + 1

This includes days patient is off-treatment due to temporary treatment interruption.

The overall treatment exposure duration (in days) will be summarized by randomized treatment group using mean, standard deviation, median, minimum and maximum. Additionally, the treatment exposure duration will also be summarized categorically by presenting number and percentage of patients with exposure

- <2 weeks
- 2 to < 4weeks
- 4weeks to < 6months
- 6months to < 1 year
- 1 year to < 2 years
- >= 2 years

Mean daily dose and mean dose level for each patient will be summarized by treatment group. Mean daily dose and mean daily dose level for each patient will be calculated as –

$$\frac{\sum_{i=0}^{3}(\text{Number of days spent on Dose}_i)X(\text{Dose}_i)}{\sum_{i=0}^{3}(\text{Number of days spent on Dose}_i)}$$

For mean daily dose calculation 'Dose_i' represents actual dose (in mg) administered at dose level 'i' according to Table 1-1, whereas for mean daily dose calculation 'Dose_i' represents the categorical dose level (0, 1, 2 or 3) administered at dose level 'i'. Further, dose level '0' refers to zero dose signifying treatment interruption. Mean daily dose and mean daily dose level calculated as above will be summarized by treatment groups for overall study duration. Mean doses and mean dose levels of study drug at each visit will also be summarized by treatment group and visit. Last dose and last dose level when patients are alive will also be summarized by treatment group.

Descriptive summary of number of days spent at each dose level as mentioned in Table 1-1 will be provided by treatment group. Also, number and percentage of randomized patients at each dose level will be summarized by visit and treatment group. Time to first reach the dose at each dose level and time to first reach the target dose will be summarized for each treatment group during the double-blind treatment epoch. In addition, reasons for down-titrating treatment will be summarized by each treatment group for each dose level.

Time to permanent discontinuation of study medication will be summarized according to the Kaplan-Meier analysis. A summary table by treatment group will be provided to display the number and percentage of patients who discontinued study medication by the primary reason for discontinuing and the number and percentage of patients who subsequently received the following medications during the study: ACE inhibitors, ARB, and Entresto™, (sacubitril/valsartan). Exposure durations, dosages and dose levels will be summarized by treatment group for these medications. The last doses and dose levels of study drugs for these switchers will also be summarized by treatment group.

Overall study drug exposure

Duration of overall study drug exposure is defined as the duration of treatment exposure (in days) excluding days of treatment interruption and is calculated as –

(Last known date when the patient took study medication – Date of 1st intake of randomized study medication during double-blind treatment epoch + 1) – number of days of treatment interruption

The duration of study drug exposure (in days) will be summarized by randomized treatment group using mean, standard deviation, median, minimum and maximum. Additionally, the treatment exposure duration will also be summarized categorically by presenting number and percentage of patients with exposure

- <2 weeks
- 2weeks to < 4weeks
- 4weeks to < 6months
- 6months to < 1 year
- 1 year to < 2 year
- >=2 years

Treatment and study drug exposure in subgroups

Both overall treatment exposure and overall study drug exposure will be summarized by the following subgroups -

- Age group (< 65 vs ≥ 65 years; < 75 vs ≥ 75 years)
- Gender
- Race
- Region
- Type of MI (STEMI vs. NSTEMI)

Overall study exposure (Follow-up duration)

Following the definition of double blind phase in section 2.1.1, for each patient duration of study exposure (in days) during double blind phase is calculated as total duration of on-treatment randomized phase and post-randomized treatment phase where –

Duration of on-randomized treatment phase (in days) is calculated as –

Date of last study drug intake – randomization date + 1.

Duration of post-randomized treatment phase or off-treatment phase (in days) is calculated as –

min(Last date patient is known to be alive, Last visit date before analysis cutoff date) – Last known date patient took randomized study medication + 1

Hence, overall study exposure duration (follow-up duration) = Duration of on-randomized treatment phase + Duration of post-randomized treatment phase – 1.

Of note, for randomized patients not receiving double-blind randomized study medication, overall study exposure duration is calculated as –

min(Last date patient is known to be alive, Last visit date before analysis cu toff date) – randomization date + 1

The duration of overall study exposure, on-treatment randomized phase and post-randomized treatment phase are summarized by randomized treatment group for all patients in FAS by providing descriptive statistics (n, mean, SD, Q1, Q3, median, minimum, maximum).

2.4.2 Prior, concomitant therapies

'Prior medications' are defined as drugs taken prior to first dose of double-blind study medication. Any medication which has been started during the double-blind treatment epoch including medications started prior to randomization but continued in the double-blind treatment epoch are identified as **'Concomitant medications'**.

Prior and Concomitant medications and significant non-drug therapies will be summarized separately by therapeutic class (by ATC code), preferred term, and treatment group for the safety set. The number and percentage of patients on following CV background medications during double-blind treatment epoch will be tabulated by randomized treatment group –

- Aspirin
- P2Y12 inhibitors
- Antithrombin agents
- Glycoprotein (GP) IIb/IIIa inhibitor
- ARBs
- ACE inhibitors
- Beta Blockers
- Mineralocorticoid Receptor Antagonists
- Statins
- Diuretics (Loop/non-loop diuretics, summarized by IV/ oral diuretics)
- Cardiac glycosides (Digoxin/digitalis glycoside)
- Calcium channel blockers
- Other vasodilators
- Oral anticoagulants
- Antiarrhythmic agents
- Nitrates
- Other lipid lowering agents

Apart from the CV medications listed above, reperfusion therapies used during post-randomized treatment phase for managing index MI and any other post-randomization MI will be summarized separately in a similar way as in section 2.3.2.1. The summaries of background medications and non-drug therapies will be provided for Safety set (SAF) and Full Analysis Set (FAS).

Analysis of dose intensity of RAS blockade during double-blind period

Dose intensity of RAS blockades during post-randomization phase will be captured in terms of mean total daily dose levels of blinded study drug and open label ARB/ACEIs used after study drug discontinuation. Mean total daily dose for each study medication is defined by average of different doses for the medications (including no or zero dose) weighted by

number of days patient is on that dose during the specified analysis period. The total daily dose of RAS blockades (high/low) are categorized based on the table 2-2 below.

Table 2-2 Definition of high and low RAAS blockade group based on total daily dose of commonly used ARB/ACEIs

ARBs	Low RAAS blockade group	High RAAS blockade group	ACEIs	Low RAAS blockade group	High RAAS blockade group
Azilsartan	<80 mg	≥ 80 mg	Enalapril	<10 mg	≥ 10 mg
Candesartan	<16 mg	≥ 16 mg	Benazepril	<20 mg	≥ 20 mg
Eprosartan	<400 mg	≥ 400 mg	Captopril	<100 mg	≥ 100 mg
Irbesartan	<150 mg	≥ 150 mg	Cilazapril	<2.5 mg	≥ 2.5 mg
Losartan	<50 mg	≥ 50 mg	Delapril	<30 mg	≥ 30 mg
Olmesartan	<10 mg	≥ 10 mg	Fosinopril	<20 mg	≥ 20 mg
Telmisartan	<40 mg	≥ 40 mg	Imidapril	<10 mg	≥ 10 mg
Valsartan	<160 mg	≥ 160 mg	Lisinopril	<10 mg	≥ 10 mg
			Moexipril	<7.5 mg	≥ 7.5 mg
			Perindopril	<4 mg	≥ 4 mg
			Quinapril	<20 mg	≥ 20 mg
			Ramipril	<5 mg	≥ 5 mg
			Spirapril	<6 mg	≥ 6 mg
			Temocapril	<2 mg	≥ 2 mg
			Trandolapril	<2 mg	≥ 2 mg
			Zofenopril	<30 mg	≥ 30 mg

For patients randomized to taking blinded LCZ696 (sacubitril/ valsartan) or patients taking open-label Entresto after permanent discontinuation of study drug, total mean daily dose is categorized into high/low dose level according to the dose of valsartan component. LCZ696 dose levels 50mg bid (low), 100 mg bid (high), 200 mg bid (high) are equivalent to sacubitril/ valsartan 24/26 mg bid, 49/51 mg bid, 97/103 mg bid. Combined RAS blockade based on blinded study medication dose level and open label ARB/ACEI dose level will be considered to determine whether a patient is on high or low dose level of RAS blockade.

Overall mean total daily dose levels combining RAS blockades through study medication and open label ARB/ACEIs will be summarized for each treatment group by providing number and percentage of patients on high and low dose level during the first 12 months from randomization for the following patient populations -

- FAS
- FAS patients who discontinue study treatment during the first 12 months after randomization.

2.5 Analysis of the primary objective

All patients in the Full Analysis Set (FAS) will be included in the primary analysis.

2.5.1 Primary endpoint

The primary efficacy variable is time to first occurrence of a confirmed composite endpoint of cardiovascular death, HF hospitalization or outpatient HF. The confirmation of the primary composite events will be based on an adjudication process by an independent CEC.

Note that deaths which cannot be classified by the adjudication committee as CV or non-CV death (for example due to lack of information), will be counted as a CV death for the purpose of the primary endpoint.

Time-to-event is computed as the number of days from randomization to the date of the primary endpoint event (first occurrence). A patient without an event will be censored at the last date the endpoint status was completely known* or at the time of death from non-CV causes (i.e. any death which is confirmed to be a non-CV death by the CEC).

* This date could include the date of withdrawal of informed consent, date of the patient's last visit prior to the cut-off date of the analysis (whichever occurred first).

2.5.2 Statistical hypothesis, model, and method of analysis

The following null hypothesis versus the alternative will be tested at the 1-sided 2.5% type I error rate.

$H_0 : \lambda_2/\lambda_1 \geq 1$ (i.e., the hazard rate of the first confirmed primary event in the LCZ696 group (λ_2) is greater than or equal to the hazard rate in the ramipril group (λ_1)) *versus*

$H_1 : \lambda_2/\lambda_1 < 1$ (i.e. the hazard rate of the first confirmed primary event in the LCZ696 group (λ_2) is less than the hazard rate in the ramipril group (λ_1))

λ_2/λ_1 is called the hazard ratio of LCZ696 relative to ramipril.

The time-to-first confirmed primary endpoint will be analyzed using a Cox proportional hazards model stratified by STEMI/NSTEMI, with treatment, PCI use at baseline and region included as factors in the model. This model allows the hazard rates to vary with time while the hazard ratio is assumed to be constant, i.e., independent of time, within each stratum. The hazard ratio for LCZ696 vs. ramipril, the associated 2-sided 95% confidence interval and the 1-sided and 2-sided p-values will be presented from the analysis.

The Kaplan-Meier estimates of the cumulative event rate (1-survival function) for each treatment (and strata) will be tabulated and will also be presented graphically.

2.5.3 Handling of missing values/censoring/discontinuations

For patients without a primary event prior to the analysis time point, the censoring date is defined as one of the following (whichever occurred first):

- Date when the patient withdrew informed consent
- Date of the patient's last visit before analysis cut-off date (including telephone visit)
- Date of death from non-CV causes (i.e. date of death which is confirmed as a non- CV death by the adjudication committee).

Note that every effort will be made to follow all patients until the end of the study, regardless of adherence to study treatment. The analysis methods specified is valid under the assumption

that the censoring mechanism is independent of the event generating process (non-informative censoring).

2.5.4 Supportive analyses

The composition of the first confirmed composite primary efficacy endpoint will be summarized by treatment group descriptively. The time to reach the first of each individual component will be analysed using the same methodology as the described for the primary endpoint. Note that for the components CV death and HF hospitalization, all events observed will be included in the individual component analyses and not just those which were counted as a 'first event' in the primary composite endpoint. In addition to the standard censoring mechanism described in Section 2.5.3, for the analysis of time to outpatient HF, patients will be censored at the time of HF hospitalization or CV death. For the analysis of time to first HF hospitalization, patients will be censored at the time of CV death.

An 'on-treatment' analysis (Section 2.1.1) will also be performed for the primary endpoint whereby events that occurred more than 28 days after permanent study treatment discontinuation will be excluded from the analysis. For patients without events before or at 28 days after treatment withdrawal, the censoring date will be the minimum of the date of permanent study treatment discontinuation + 28 days and the date of standard censoring for the endpoint.

The primary analysis will also be repeated for per-protocol set (PPS) for assessing robustness of results to significant protocol deviations leading to exclusion from FAS.

Sensitivity analysis

As a sensitivity analysis to the above proportional hazards analysis, treatment groups will be compared for the primary efficacy variable using a stratified log-rank test with STEMI/NSTEMI as a stratification factor.

2.5.5 Subgroup analysis

For primary endpoint and its components, subgroup analyses will be performed based on the pre-defined subgroups in section 2.2.1 for patients in FAS only.

Displays of treatment effects by subgroup categories (defined as marginal groupings) will be provided for descriptive purposes.

The estimated hazard ratio, and 2-sided 95% confidence interval, will be provided for each individual subgroup using a Cox's proportional hazards model stratified by STEMI/NSTEMI with treatment, region and PCI use at baseline as fixed effects factor in the model, with the exception for type of MI (STEMI/ NSTEMI) subgroup for which the analysis will not be stratified by STEMI/ NSTEMI.

For subgroups other than type of MI (STEMI vs. NSTEMI), the p-value associated with the test of treatment-by-subgroup interaction effect will be calculated from a Cox's proportional hazards model, stratified by STEMI/NSTEMI, including treatment, PCI use at baseline, region, subgroup, and treatment-by-subgroup as fixed-effect factors. For STEMI vs. NSTEMI,

p-value for interaction term will be provided from a similar model but STEMI/NSTEMI only included as a fixed effect factor and not a stratifying factor.

Since no adjustment for multiple comparisons will be made, findings should be interpreted with caution. Additionally, the frequency and percentage of patients reaching primary composite endpoint will be presented by treatment group for each of the subgroups listed in Section 2.2.1.

2.6 Analysis of secondary efficacy objective(s)

The Full Analysis Set (FAS) will be used for all secondary analyses.

2.6.1 Secondary endpoints

The secondary variables are as follows-

1. Time from randomization to first occurrence of a confirmed composite of CV death or HF hospitalization
2. Time from randomization to first occurrence of a confirmed composite of HF hospitalization or outpatient HF
3. Time from randomization to first occurrence of a confirmed composite of CV death, non-fatal spontaneous MI or non-fatal stroke
    - *Non-fatal spontaneous MI is defined as either Type 1 or Type 2 MI confirmed by the independent Clinical Event Committee*
4. The cumulative number of composite events, including hospitalizations due to HF, hospitalizations due to non-fatal spontaneous MI, hospitalizations due to non-fatal stroke and CV death.
5. Time from randomization to all-cause mortality

Censoring of secondary endpoints

The event generating process for the secondary endpoints will be censored following the mechanism below-

- Endpoints (1) and (3) will be censored following a similar censoring mechanism followed for primary endpoint (Section 2.5.3). Event generating process for endpoint (4) will also be censored following the same mechanism as the follow up time is censored at last date the status of the patient was known (which could be the date of withdrawal from the study, the last visit prior to analysis cut off or the date of death).
- Endpoint (2) will be censored following the same mechanism with the exception that occurrence of death regardless of reason (CV / non-CV) constitutes a censoring for the endpoint.
- Endpoint (5) will be censored at the earlier of
    - date of withdrawal from the study or
    - the last date till when patient was known to be alive (which may be obtained via telephone contact or the last visit prior to analysis cut off).

2.6.2 Statistical hypothesis, model, and method of analysis

The secondary endpoints will be analyzed in order to compare LCZ696 vs ramipril using the ITT approach (i.e. estimation of the treatment effect under the 'treatment policy').

Analysis of time to event variables

The time to event endpoints (1), (2), (3), (5) will be analyzed using the same statistical analysis methods as specified for the primary analysis. Treatment groups will be descriptively compared by presenting number and percentage of patients with events while inferential comparisons between treatment groups will be provided based on estimated hazard ratio and 95% CI. Both 1-sided and 2-sided p-values will be reported for treatment group comparison (LCZ696 vs. ramipril). Kaplan-Meier estimates of event rates will be tabulated for specific time points and will also be presented graphically.

Analysis of count variable

Secondary endpoint (4) will be analyzed using a negative binomial regression model with a Weibull baseline intensity function to allow flexibility if the baseline intensity is non-constant (Lawless, 1987). The regression model will consider the number of composite events as dependent variable with randomized treatment, STEMI/NSTEMI, PCI use at baseline and region as factors having fixed effects. Every event jump time, including the terminal event time, will be used to estimate the parameters specified in this model. For treatment group comparison LCZ696 vs ramipril, the relative rate ratio will be presented together with 2-sided 95% confidence interval and 1-sided and 2-sided p-values from the fitted model.

For descriptive summary, unadjusted annualized incidence rate will be provided along with the model-based estimates and their 95% confidence intervals will be presented by treatment groups. Also, adjusted event rate functions over time will be graphically presented from the estimated Weibull intensity .

2.6.3 Control of familywise type I error rate

The primary endpoint and the first four secondary efficacy endpoints will be included in a statistical testing strategy to control the familywise type I error rate at the 1-sided 2.5% level (in the strong sense). A hierarchical testing procedure will be employed whereby the primary hypothesis will be tested first, if rejected then the hypothesis associated with the first secondary endpoint will be tested and so on. The order of testing of the composite endpoints will be as follows:

1. Primary endpoint
2. Time to first CV death or HF hospitalization
3. Time to first HF hospitalization or outpatient HF
4. Time to first CV death, non-fatal spontaneous MI or non-fatal stroke
5. The total number of composite events (hospitalizations (including CV death) due to HF, non-fatal spontaneous MI or non-fatal stroke and CV death).

2.6.4 Handling of missing values/censoring/discontinuations

For each patient, the information on secondary endpoints censoring will be censored as defined earlier. The primary analysis methods are valid under the assumption that the censoring mechanism is independent of the event generating process (non-informaitve censoring).

Sensitivity analyses have been proposed to assess robustness of the results to the potential violation of this assumption, wherever applicable.

2.6.5 Supportive analysis

It is recognized that at the time of the first onset of symptomatic HF event some patients may discontinue randomized treatment and may be prescribed an alternative treatment for HF which could be locally available Entresto™ (sacubitril/valsartan, LCZ696). For the pre-specified secondary endpoints (1), (3), (4) and (5), the analysis described in Section 2.7.2 will estimate the treatment effect of LCZ696 vs ramipril including any effect of prescribed Entresto™ for ramipril patients who discontinued study drug and took Entresto™ as an alternative treatment. Hence, the following supportive analyses aim to estimate the pure treatment effect as though in a situation whereby Entresto™ was not an available treatment option for HFrEF. In this regard, as a sensitivity analysis, inverse probability of censoring weighted (IPCW) Cox proportional hazards model (Robins and Finkelstein 2000) will be performed on the secondary endpoints (1), (3) and (5).

Inverse probability of censoring weighted (IPCW) Cox proportional hazards model

In the IPCW analysis, the following censoring mechanism will be used for the event generating process for secondary endpoints:

- For patients randomized to LCZ696 and patients randomized to ramipril but did not take open label Entresto upon diagnosis of HFrEF event will be censored according to the mechanism described for the secondary endpoints.
- For patients randomized to ramipril who subsequently start taking open label Entresto, (defined as treatment switch), censoring will occur at the minimum of the last date the endpoint status was known, the time of death from non-CV causes, 28 days after study treatment discontinuation or start of open-label Entresto.

To adjust for the potential informative censoring, patients in the ramipril arm with event times censored due to treatment switch will be dynamically replaced in the patient risk-set by remaining uncensored patients in the ramipril arm with a matching prognostic profile by up-weighting such patients in the analysis set. At a specific time, patients in the ramipril arm who have not switched to taking open label Entresto will be assigned a weight inversely proportional to the probability of not switching till that time (i.e., patients who do not switch, but have covariates implying a high probability of switching, get a larger weight in the analysis).

Estimating IPC weights

In order to predict these patient specific time-varying probabilities, the time scale is split into small intervals based on the visit schedules. In each interval the conditional probability of being switched given patient has not switched at any earlier interval is modelled using a logistic regression model with the following covariates–

- **Time independent (baseline) covariates:**
  Age (in years), baseline LVEF, baseline eGFR (ml/min/1.73m^2), history of prior MI (yes/ no), history of diabetes (yes/ no), Atrial Fibrillation associated with qualifying MI (yes/ no), baseline Killip class, use of PCI for qualifying MI (yes/ no), use of ACEI/ARB in last 24 hours prior to randomization (yes/ no),), use of IV treatment for qualifying MI (yes/ no)
- **Time dependent covariates:**
  Systolic BP (mmHg), Heart rate (bpm), eGFR (ml/min/1.73m^2), *use of PCI or CABG (yes/ no), *use of ICD/CRT (yes / no)
  (**procedures related to any post-randomization MI event)*

Predicted probability of switching at a specific time for a patient will be obtained by multiplying individual conditional probabilities of switching in intervals prior to that time point. To minimize impact of extreme weights (e.g. patients not switched though having very high estimated probability to switch), the stabilized version of weights will be used which is defined as the ratio of predicted probabilities of not being switched by time t –

- from the logistic regression with only baseline covariates
- from the logistic regression with both baseline and post-baseline covariates

It is conceivable that the above logistic regression procedure of estimating weights may not converge due to reasons including (but not limited to) sparseness of switchers in the subpopulations implied by the selected covariates resulting into an infinite likelihood due to complete or quasi-complete separation or numerical difficulties in evaluating an overly complex likelihood function. Should such problems arise, the logistic regression model used to determine the IPC weights will be simplified by pooling pre-specified time intervals (thereby extending the time windows in which time-dependent covariates are assessed). If that still does not solve convergence problems, the model will be simplified by removing covariates.

All patients randomized to LCZ696 will be assigned a weight of 1 for all time intervals.

Estimation of treatment effect

Following the estimation of weights, a weighted Cox proportional hazard model will be fitted to the time to event endpoints (1), (3) and (5). The model will be stratified by STEMI/NSTEMI while treatment, region, PCI use at baseline will be included as fixed effects factors. The hazard ratio for LCZ696 vs. ramipril, the associated 2-sided 95% confidence interval and the 1-sided and 2-sided p-values will be presented from the analysis.

On-treatment analysis

Endpoint (4), the total number of confirmed hospitalizations for HF, MI and stroke (including CV death) will be redefined for the patients who are prescribed open label Entresto™ as the total number of composite endpoints from randomization up to 28 days after the time of study treatment discontinuation. The analysis methods will remain the same as specified above.

2.6.6 Subgroup analysis

Subgroup analysis for the secondary endpoints (1), (2), (3) and (5) will also be performed similarly as described in Section 2.5.5 for the primary endpoint based on pre-defined subgroups (Section 2.2.1).

For secondary endpoint (4), subgroup analysis will be performed following a similar modeling as used for primary analysis of this endpoint (Section 2.6.2). Specifically, a negative binomial regression with Weibull baseline intensity function will be fitted within each subgroup with randomized treatment, STEMI/NSTEMI, PCI use at baseline and region as factors having fixed effects. P-value for treatment-subgroup interaction will be reported based on the same model but including factors for subgroup and treatment-subgroup interaction fitted to the overall population. Additionally, for descriptive purposes, exposure adjusted incidence rate and 95% CI for the secondary events will be reported by treatment group for each subgroup.

All the subgroup analyses for secondary endpoints will be performed for patients in FAS only.

2.7 Safety analyses

All safety analyses will be carried out for the Safety set (SAF).

2.7.1 Adverse events (AEs)

In this study, all adverse events and all serious adverse events occurring through the first two weeks post-randomization will be collected and reported. After the first two weeks post-randomization, the following targeted safety data will be collected and reported in this study:

- all serious adverse events,
- adverse events of special interest (angioedema, hyperkalemia, hypotension, renal impairment, cognitive impairment, hepatotoxicity, hypersensitivity, malignancy, pregnancy and exposure during breast feeding)
- adverse events leading to a change in dose (down titration) or discontinuation of study drugs, and
- all suspected non-serious adverse events

Any AE defined by the study protocol occurred during the study period will be included in AE summary tables by the specific treatment phase as described in Table 2-3, i.e., AEs/ SAEs occurred during screening and double blind period. Specifically, adverse events occurring during the randomized treatment phase will be summarized both as overall and also by following periods

- AEs/ SAEs from randomization up to 2 weeks
- AEs/ SAEs from 2 weeks to permanent study drug discontinuation
- AEs/ SAEs from permanent study drug discontinuation until end of study.

Table 2-3 Allocation of AEs

Screening epoch (V1-V101)	Double-blind treatment epoch		Phase AE to be reported in
	Randomization - EOT (V101-EOT)	EOT – EOS (EOT- V199)	
X			Reported by site from informed consent
	X		Report AE in double-blind period
X	X2		Report as two separate AEs: One with onset date X (X) during screening epoch and one with onset date X2 for DB
	X, X2		Report as one AE: One with onset date X during DB
		X	Report AE in post-EOT phase
		X, X2	Report as one AE: One with onset date X after EOT
	X	X2	Report as one AE in summaries for double-blind treatment epoch. For other summaries, report as two separate AEs; One with onset date X before EOT and one with onset date X2 during post-EOT
X indicates onset date of an AE. X2 stands for the same AE but with increased severity			

The number (and proportion) of patients with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary System Organ Class (SOC) and Preferred Term (PT).
- by treatment, primary System Organ Class (SOC), Preferred Term (PT) and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and Preferred Term (PT)

according to the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA version used for reporting will be described in the footnote

Within each reporting phase (Table 2-3), the following rules are applicable.

- If a subject reported more than one adverse event with the same preferred term, the adverse event with the maximum 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 maximum severity at the system organ class level, where applicable.
- Statistical analyses performed for the randomized treatment phase will include all post-randomization AEs up to and including the analysis cut-off irrespective of whether patient was on or off study drug.

- Separate summary of AEs will also be provided for double-blind treatment epoch in which separate incidence of same AE (or same episode with increased severity) during before and after end of treatment will be considered as separate AEs.

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, for each reporting phase (Table 2-3), will be provided for study medication related adverse events, death, serious adverse event, other significant adverse events leading to study discontinuation and adverse events leading to dose adjustment / interruption.

For each reporting phase, incidence of AEs will also be listed at a patient level by randomized treatment group including outcome, severity and action taken with the AE.

2.7.1.1 Adverse events of special interest / grouping of AEs

Specific AEs of interest will be summarized separately in addition to the above analysis. These specific AEs of interest are: angioedema, hyperkalemia, hypotension, renal impairment, cognitive impairment, hepatotoxicity, hypersensitivity, malignancy, pregnancy and exposure during breast feeding. Besides providing the crude percentages, annualized exposure adjusted incidence rates will also be provided by treatment group.

The search paths for the related preferred terms (PTs), high level group term (HLGT), high level term (HLT), in Standard Medical Queries (SMQs), or NMQ in MedDRA for these risks are stored (or alternatively "summarized") in the latest version of LCZ696 Case Retrieval Strategy.

In addition to above standard analyses, for double blind phase, analysis for time-to-first selected AEs by treatment group will be performed using Kaplan-Meier estimate. The annualized exposure duration adjusted event rates will also be provided.

2.7.2 Deaths

Patients experiencing deaths during the study period will be reported separately for screening epoch and double-blind treatment epoch. Deaths occurring during double-blind treatment epoch will be summarized by actually received treatment group to present number and percentage of patients died by overall and adjudicated reason categories (CV/ non-CV). Separate listings will be provided for patients died during the study period with primary reason of death as confirmed by adjudication committee.

2.7.3 Laboratory data

Each laboratory parameter, evaluations will be summarized by visit and actually received treatment group by presenting summaries (n, mean, standard deviation, median, minimum and maximum) for actual and change from baseline values. The summary will be provided separately for biochemistry and hematology laboratory parameters.

Shift tables based on the standard ranges for each laboratory parameters will be provided by treatment group at each visit to present incidence of transitions from a baseline high, normal or low laboratory value to a post-baseline high, normal or low value.

The number and percentage of patients with clinically notable laboratory results after baseline will be presented in accordance with Table 2-4.

Table 2-4 Clinically notable laboratory values and vital signs

Hematology	
Hematocrit	>50% increase, >20% decrease
Hemoglobin	>50% increase, >20% decrease
Platelet count	>75% increase, >50% decrease
RBC Count	>50% increase, >20% decrease
WBC count	>50% increase, >50% decrease
Hematocrit	>50% increase, >20% decrease
Hemoglobin	>50% increase, >20% decrease
Blood chemistry	
Alkaline phosphatase	>100% increase
ALT (SGPT)	>150% increase
AST (SGOT)	>150% increase
BUN	>50% increase
Calcium	>10% increase, >10% decrease
Chloride	>10% increase, >10% decrease
Creatinine	>50% increase
Potassium	>20% increase, >20% decrease
Total bilirubin	>100% increase
Uric acid	>50% increase

Patients with liver enzymes (ALT/AST and CPK) falling within predefined categories of elevations and persistent elevations will be summarized by treatment group in accordance with the Table 2-5 for the following treatment phases –

- Overall randomized treatment phase
- from randomization up to first 2 weeks
- from week 3 until end of study.

Descriptive summaries will be provided by presenting count and percentage of patients with each type of Liver event in addition to graphical summaries, as applicable.

Table 2-5 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and

	TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*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 neoplasms
TBL: total bilirubin; ULN: upper limit of normal

2.7.4 Other safety data

2.7.4.1 Vital signs

Sitting systolic blood pressure (SBP), sitting diastolic blood pressure (DBP) and Sitting pulse pressure (PP) will be descriptively summarized by presenting summaries (n, mean, standard deviation, median, minimum, maximum) of actual value and change from baseline values for each scheduled assessment visit and treatment group.

2.8 Pharmacokinetic endpoints

Not applicable

2.9 PD and PK/PD analyses

Not applicable

[redacted]

[redacted]

[redacted]

[redacted]

2.13 Interim analysis

One interim analysis for efficacy is planned. The cut-off time for this interim analysis will be when about two-thirds of the target number of primary events have been reported and adjudication-confirmed, approximately 540 of adjudication-confirmed CV deaths, HF hospitalizations and outpatient HF events. In the interim analysis, the analysis dataset will comprise of all patients who were randomized before the cutoff date. Haybittle-Peto boundaries will be adopted for the interim statistical comparisons between treatments. An alpha of 0.1% (1-sided alpha) will be spent for the comparison of primary endpoint at the interim analysis and the rest of alpha (1-sided 2.49% for the current specified boundary, based on East version 6.3) will be utilized at the final analysis. In the interim analysis, the study may be stopped for superior efficacy only when both the primary endpoint and CV death are significant at level of 0.1% (1-sided).

If the study is stopped early for superior efficacy at the interim analysis, the secondary endpoints will be tested using the same hierarchical testing procedure as described in Section 2.6.3 for the same level of alpha (i.e. 1-sided alpha 0.1%). If the study continues, then secondary endpoints will be tested at the final analysis using 1-sided alpha of 2.49%.

Interim analyses are also planned for the monitoring of safety data, and will be performed approximately every 6 months during the course of the study. Such safety analyses do not

inflate the type I error for the primary efficacy hypothesis testing and thus no adjustment for multiplicity is required.

Interim analyses will be performed by an independent statistician (at a CRO or academic institution) who will not be involved in the trial conduct. The results will be reviewed by an independent DMC. The trial investigators, Novartis employees and other personnel who are involved in the conduct of the trial and in the analysis of the final trial results, or who have contact with study centers, will remain blinded to the treatment codes and interim analysis results until all monitoring decisions have been made and the database has been locked for final analysis. Full details of the interim analysis plan will be described in the DMC charter.

3 Sample size calculation

A sample size of 4,650 patients, randomized to LCZ696:ramipril using a 1:1 allocation ratio, has been chosen with the aim to obtain at least 800 first primary events and at least 633 CV death or HF hospitalization events in this event-driven study. Eight hundred primary events provide at least 80% power assuming a true Relative Risk Reduction (RRR) of 18% (i.e. a hazard ratio of 0.82) for LCZ696 vs ramipril with statistical testing at the overall 2.5% 1-sided type I error rate (with strong control of the FWER). Six hundred and thirty three CV death or first HF hospitalization events will provide at least 80% nominal power assuming a true RRR of 20% (for the intent-to-treat analysis) for the secondary endpoint for the same type I error rate.

Additional assumptions are described below.

- 0.5% per year lost to follow-up rate
- Recruitment duration of 24 months, with approximately 8 months follow-up anticipated for last randomized patient (i.e. 32 months total study duration) and constant recruitment rate
- One interim analysis is planned to allow for stopping for efficacy, using a Haybittle-Peto boundary, thus 2.49% 1-sided alpha will be available for the final analysis (Section 2.13).
- Cumulative event rates of CV death or HF hospitalization were estimated from selected patients from the VALIANT database (Pfeffer et al, 2003) who were considered to be representative of the target patient population of this study. In the calculation, adjustments were made for expected differences between the sample of patients from VALIANT and the patients likely to be recruited in PARADISE-MI. In particular PCI use is expected to increase (2/3 PCI use vs. 1/3 in VALIANT), and a larger number of NSTEMI patients are expected (60% NSTEMI patients vs. approximately 30% in VALIANT). Following these adjustments, a further 10% reduction in hazard rate for other changes in standard of care was also included. The cumulative event rates for the primary endpoint were based on a further 15% increase in hazard rate in order to account for the third component of outpatient HF (refer to Table 3-1 for the cumulative event rates assumed for the sample size calculation.

Table 3-1 Cumulative event rates assumed for the sample size calculation

Time period following randomization	CV death or HF hospitalization	CV death, HF hospitalization or outpatient HF (assuming 15% increase in hazard rate compared to CV death or HF hospitalization)

Time period following randomization	CV death or HF hospitalization	CV death, HF hospitalization or outpatient HF (assuming 15% increase in hazard rate compared to CV death or HF hospitalization)
0-3 months	9.9%	11.3%
3-6 months	12.3%	14.0%
6-12 months	14.8%	16.8%
12-32 months	19.4%	21.9%

The sample size calculations were carried out using PASS 2008, citation software and applying the Lakatos method (Lakatos,1988) and confirmed using East version 6.3.

Sample size sensitivity

This is an event driven study and the assumption about the event rates for the primary endpoint is a key driver for the sample size calculation. In this regard there are two main areas of uncertainty:

- The hazard rates calculated from the post-hoc analysis of VALIANT data as described above are thought to reflect the contemporary setting, however, there may have been other changes over time which are difficult to quantify and may decrease the event rates, hence for the final sample size calculation an additional 10% discount of the hazard rate was assumed.
- The hazard rates for the primary endpoint were calculated as 1.15 x the hazard rate for the secondary endpoint of CV death or HF hospitalization (i.e. assuming a 15% increase in hazard will be observed when adjudicated outpatient HF is included in the composite endpoint together with CV death and HF hospitalization). However, there is no adequate information available about the expected event rates of the primary triple composite endpoint.

In order to understand the impact of the uncertainties described above, Table 3-2 provides the sample sizes estimated to achieve at least 800 primary events with different underlying assumptions.

Table 3-2 Total sample size required to achieve 800 primary events for different event rate assumptions

Increase in hazard rate when outpatient HF is included in primary composite endpoint	Discount of event rates for change in SoC		
	0% ↓	**10% ↓ ***	**20% ↓**
20% ↑	4066	4468	4968
15% ↑ *	4224	**4643**	5167
10% ↑	4395	4834	5382

* Assumptions used for protocol specified study design
Number of randomized patients required calculated using East version 6.3

Power for secondary endpoints

Table 3-3 summarizes the nominal power for secondary endpoints which will be included in the statistical testing strategy. A 1-sided alpha of 2.5% has been used for the calculations. All assumptions are based on exploratory analyses performed using VALIANT data (data on file).

Table 3-3 Summary of power to reject secondary hypotheses

Endpoint	Assumption about true treatment effect for LCZ696 vs ramipril for ITT analysis	Assumptions	Nominal power
(1) Time to first CV death or HF hospitalization	20% RRR	Expect 698 events[1]	84%
(2) Time to first HF hospitalization or outpatient HF	17% RRR	Expect 536 events[2]	58%
(3) Time to first composite of CV death, non-fatal MI or non-fatal stroke	15% RRR	Expect 680 events[3]	56%
(4) Total number of hospitalizations for HF, MI and stroke related reasons including CV death	17% reduction in rate ratio	Over-dispersion=9; Rate of events on ramipril per year = 0.236[4]	46%

[1]Event rates as per Table 3-1

[2] Cumulative event rates for HF hospitalization of 6.5%, 8.2%, 9.9% and 12.8% were assumed for 0-3m, 3-6m, 6-12m and 12-32m periods respectively. Then event rates were increased by a further 15% to account for outpatient HF.

[3] Cumulative event rates of 8.5%, 10.9%, 14.0% and 18.6% were assumed

[4] For the power calculation the rate was assumed to be constant over time

The number of events were calculated for a sample size of 4,650 patients; 24 months recruitment and 8 months minimum follow-up.

HF = Heart Failure; RRR = Relative Risk Reduction

The power calculations were carried out using East Version 6.3.

Blinded sample size re-estimation

When approximately 1/2 of patients have been randomized and have reached the 3 month time point, the piecewise hazard rates for the primary endpoint and the double composite endpoint (CV death or HF hospitalization) will be estimated based on blinded data.

The piecewise hazard rates estimated from the observed data will be compared to the original assumptions. If there is reason to believe that the original assumptions about event rates may not hold, the sample size will be re-estimated taking into consideration the new information. The duration of the trial and minimum follow-up will also be reconsidered as part of the calculation. This approach will allow flexibility to achieve the required number of events in an acceptable time frame.

4 Change to protocol specified analyses

Not applicable

5 Appendix

5.1 Imputation rules

The missing or partially missing AE start/end date and concomitant medication start/end date will be imputed using the Novartis ADaM Governance Board (AGB) global standard approach. Details will be provided in the study Programming Datasets Specifications.

5.2 Statistical models

5.2.1 Primary analysis

See Section 2.5.2.

5.2.2 Key secondary analysis

Not applicable.

5.3 Rule of exclusion criteria of analysis sets

Following tables present a sample of the rules for subject classification in the analysis sets based on protocol deviation specifications (Table 5-1) and non-protocol deviation classification criteria (Table 5-2). The PDs leading to exclusion of patients from analysis sets may be updated prospectively and will be finalized before DB lock.

Table 5-1 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses
INCL04	Spontaneous MI event secondary to other medical conditions such as anemia, hypotension, or an arrhythmia OR thought to be caused by coronary vasospasm with documented normal coronary arteries	Excluded from PP analysis
INCL05	Non-spontaneous MI	Excluded from PP analysis
INCL06	LVEF >40% after index MI presentation or prior to randomization without symptoms of pulmonary congestion	Excluded from PP analysis
INCL07	Subject with no risk factors	Excluded from PP analysis
INCL11	Time from presentation to randomization < 12 hours or > 7 days	Excluded from PP analysis
EXCL01	Known history of chronic HF at randomization	Excluded from PP analysis
EXCL03	Persistent clinical HF at the time of randomization	Excluded from PP analysis
EXCL05	Clinically significant right ventricular MI as index MI	Excluded from PP analysis
EXCL15	Previous use of LCZ696 or Entresto™	Excluded from PP analysis
TRT03	Patients were misrandomized	Excluded from primary and PP analysis
OTH01	Treatment accidentally unblinded at site.	Excluded from primary and PP analysis
OTH03	Major GCP violation at site.	Excluded from primary and PP analysis

Table 5-2 Subject classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
SCR	NA	NA
RAN	NA	Not randomized
FAS	TRT03, OTH01, OTH03	Not in RAN;
PPS	INCL04, INCL05, INCL06, INCL07, INCL11, EXCL01, EXCL03, EXCL05, EXCL15, TRT03, OTH01, OTH03	Not in FAS;
SAF	NA	No double-blind study drug taken

6 Reference

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NOVARTIS

Clinical Development

LCZ696

CLCZ696G2301

A multi-center, randomized, double-blind, active-controlled, parallel group Phase 3 study to evaluate the efficacy and safety of LCZ696 compared to ramipril on morbidity and mortality in high risk patients following an acute myocardial infarction

Statistical Analysis Plan (SAP) Amendment 2

Author:	Trial Statistician, [redacted]

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Document History – Changes compared to previous final version of SAP

SAP version	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
Amendment 1	Prior to DB lock	Update introduction for this SAP amendment 1	Section 1 Introduction first and second paragraphs have been updated.	Section 1
		Change in study design as per study protocol up to v04	Updated text about the study duration, sample size (including sample size re-estimation in protocol v03), and interim analyses change as per study protocol v04	Section 1.1, 2.1, 2.14, 3
		[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	Section 1.2, 2.13.1
		Clarification for the definitions of non-fatal spontaneous MI and non-fatal stroke	Added clarification for non-fatal spontaneous MI/stroke definition in the Table 1-2 footnote	Section 1.2
		[redacted]	[redacted]	[redacted]
		Clarification for the grouping of	Added text for clarification of the grouping of “NSTEMI” type of MI	Section 2.1

SAP version	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		stratification factor type of MI		
		Additional analyses due to mis-stratification	Added analyses for mis-stratification by type of MI/region	Section 2.1
		Clarification for censoring methods for time-to-event variables	Added/modified censoring methods for time-to-event endpoints with a structure for more clarity	Section 2.1, 2.5.3, 2.6.1
		Changes as per study protocol v04 for COVID-19 impact	Added additional analyses for potential COVID-19 impact	Section 2.1, 2.3.1, 2.5, 2.5.4, 2.6, 2.6.5, 2.10, 2.11, 2.13
		Clarification of baseline definition	Updated baseline definition	Section 2.1.1
		Adding rules for unscheduled visit	Added rules for use of unscheduled visit	Section 2.1.1
		Change as per study protocol v02	Text added about the exclusion of subjects without a valid informed consent from all analyses sets	Section 2.2
		Update of the derivation of subgroups due to refinement / feasibility / scientific reasons	Updated Table 2-1 definition and derivation of subgroups; Updated Table 2-1 footnote for region classification to align with the LCZ project standard; Added subgroup of number of CV risk factors in Table 2-1	Section 2.2.1
		Update of CV medication classification	Updated the classification of CV medications	Section 2.4.2

SAP version	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Clarification for hierarchical testing procedure	Clarified that the components of the primary endpoint are not part of the testing procedure	Section 2.6.3
		Adding an endpoint in the IPCW analysis	Added an endpoint ((2) time-to-first event of CV death or HF hospitalization) in the IPCW analysis	Section 2.6.5
		Update AE summaries	Summaries of AEs have been updated	Section 2.7.1
		Update AEs of special interest terms	Updated AEs of special interest terms	Section 2.7.1
		Update RAAS blockade summaries	Summaries of RAAS blockade and open-label Entresto have been updated	Section 2.4.2
		Clarification of central lab data use	Clarified that central lab data will be used for the summary of lab results	Section 2.7.3
		Adding abnormal criteria for vital signs	Added abnormal criteria for vital signs	Section 2.7.4
		Update renal injury endpoint as per study protocol v03	Clarified the definition of renal injury endpoints as measured by serum creatinine change from baseline	Section 2.13.1
		Adding imputation rules for dates	Updated imputation rules for various types of missing or partially missing dates	Section 2.1, 5.1
		Update of PD or non-PD criteria for exclusion from analysis sets	Updated the text and code for the PDs leading to exclusion from analysis sets in Table 5-1; Updated the text for non-PDs in Table 5-2	Section 5.3

SAP version	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
Amendment 2	Prior to DBL	Adding definition for initiation or intensification of antihyperglycemic medications per protocol requirement before DBL	Added the definition of initiation or intensification of antihyperglycemic medications	Sections 1.2, 2.13.1
		Removing alternative definition of renal composite endpoint (not specified in protocol)	Deleted the alternative definition of renal composite endpoint	Sections 1.2, 2.13.1
		[redacted]	[redacted]	[redacted]
		Adding number of CV risk factors summary	Added number of CV risk factors to the summary of CV risk factors	Section 2.3.2.1
		Clarification of definition for time to treatment discontinuation analysis	Update the text for "time to permanent discontinuation of study medication not due to death"	Section 2.4.1
		Update of study exposure summary	Updated study exposure summary	Section 2.4.1
		Clarification of definition of CV death endpoint	Added text for the CV death endpoint definition	Section 2.5.1
		Adding analysis cut-off date	Analysis cut-off date	Sections 2.1,

SAP version	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				2.5.3, 2.6, 2.13
		Adding supportive analyses for primary endpoint	Added alternative definitions for primary endpoint as supportive analyses	Section 2.5.4
		Adding a sensitivity analysis for primary endpoint	Added a Bayesian sensitivity analysis with robust prior to combine potentially COVID-19 affected results with pre-COVID-19 results	Sections 2.5.4, 5.4, 6
		Removing an endpoint from the IPCW analysis to align with protocol	Removed the composite endpoint of HF hospitalization or outpatient HF from the IPCW analysis	Section 2.6.5
		Update of AE summaries for clarity	Updated text for AE summaries	Section 2.7.1
		Update of AEs of special interest risk names	Updated the risk names of AEs of special interest	Section 2.7.1, 2.7.1.1
		[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]

SAP version	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Added missing date handling for endpoint event with completely missing date	Added the data handling method for event with completely missing event date	Section 5.1.3

Table of contents

List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
bid	bis in diem/twice a day
CRF	Case Report Form
CV	Cardiovascular
CSR	Clinical Study report
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
HF	Heart failure
IRT	Interactive Response Technology
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
o.d.	Once Daily
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
[redacted]	[redacted]
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The statistical analysis plan (SAP) describes the detailed methodology and implementation of the planned statistical analyses outlined in the study protocol for CLCZ696G2301 (up to version 04 – protocol amendment 4). The analyses following the SAP below will be used for clinical study reporting purposes while the same analysis plan will also be used for the planned interim efficacy analyses unless otherwise specified.

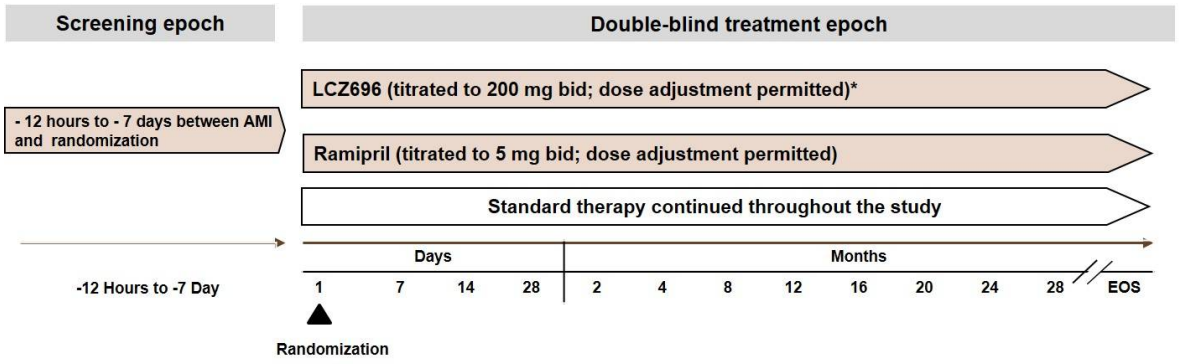
Any future change in statistical analysis will be prospectively furnished with relevant details in subsequent versions as amendments and will be finalized before database lock (DBL) prior to the final analysis.

1.1 Study design

This is a multicenter, randomized, double-blind, active controlled, event-driven phase III clinical trial designed to evaluate the efficacy and safety of LCZ696 compared to ramipril when added to standard therapy in post-AMI patients with LV systolic dysfunction and/or pulmonary congestion.

The study population consists of high risk patients who have sustained a spontaneous acute myocardial infarction (ST segment elevation MI (STEMI) or non-ST segment elevation MI (NSTEMI) within the last 12 hours to 7 days prior to randomization) with evidence of LV systolic dysfunction and/or pulmonary congestion associated with index MI. In addition, patients need to have at least one predefined risk factor and without known prior history of chronic HF.

Figure 1-1 Study Design



*Treatment with two doses of valsartan 40 mg or 80 mg (bid) required before starting study medication for patients who are randomized to LCZ696 and previously treated with ACE inhibitors

As per the study design (Figure 1-1), a screening epoch of no more than 7 days after index MI presentation will be used to determine if patients qualify to enter the double-blind treatment phase of the study with respect to protocol specified inclusion/ exclusion criteria.

Eligible patients, stratified by type of MI (STEMI/ NSTEMI) and region, will be randomized 1:1 to receive LCZ696 titrated to a target dose of 200 mg twice daily or ramipril titrated to a target dose of 5 mg twice daily. Patients may be randomized on the same day that they are

consented and screened. To reduce the potential risk of angioedema, patients on ACEI during the last 36 hours prior to randomization will undergo a valsartan bridging treatment for 1 day in a blinded manner.

Three dose levels of study medication will be administered in a stepwise titration (Table 1-1). Randomized patients are planned to start at dose level 1 while those who were on prior ARB/ACEI may start at dose level 2 at investigator's discretion.

Table 1-1 Study drug dose levels during treatment epoch

Dose Level	LCZ696 Treatment Arm*	Ramipril Treatment Arm
1	50 mg b.i.d.†	1.25 mg b.i.d.
2	100 mg b.i.d.†	2.5 mg b.i.d.
3	200 mg b.i.d.	5 mg b.i.d.
* LCZ696 dosing is based on the total amount of both components of sacubitril/valsartan; dose levels 1, 2 and 3 are equivalent to sacubitril/valsartan 24/26 mg, 49/51 mg and 97/103 mg, respectively. † Patients who are randomized to LCZ696 and received ACE inhibitors in the 36 hours prior to randomization will be given a bridging valsartan dose in a blinded manner for one day (two doses at either dose level V1 or V2: 40 or 80 mg b.i.d.) prior to beginning double-blind LCZ696 treatment.		

Patients can be up-titrated to the next dose level subject to satisfying pre-defined safety / tolerability criteria (SBP $\geq$ 100 mmHg, eGFR $\geq$ 30 mL/min/1.73m^2 or serum creatinine increase $<$ 0.5 mg/dl from baseline, serum potassium $<$ 5.5 mmol/L (mEq/L)). The titration scheme aims to achieve the target dose within 2 weeks of randomization.

The study is event-driven and will continue until both a total of 708 confirmed primary triple composite endpoint events **and** 592 confirmed double composite events of CV death or HF hospitalization (i.e., first secondary endpoint) have been achieved. Note that the actual number of CEC-confirmed primary events at the end of the study may differ (slightly) from the target number of 708 since the close-out timeline is predicted based on observed data while the study is still ongoing and it is subject to reporting and adjudication gaps. Approximately 5,650 randomized post-AMI patients are estimated to provide the necessary number of confirmed endpoints over a total study duration of 43 months with a projected patient recruitment period of 37 months. The overall estimated mean follow-up time will be 19 months for the study.

1.2 Study objectives and endpoints

Table 1-2 Objectives and related endpoints

Objective	Related endpoint and Definition	Analysis method
Primary objective		

Objective	Related endpoint and Definition	Analysis method
To demonstrate that LCZ696 is superior to ramipril in delaying the time-to-first occurrence of the composite endpoint of CV death, HF hospitalization or outpatient HF in patients with LV systolic dysfunction and/or pulmonary congestion following an AMI	The primary efficacy endpoint is defined as the time to the first confirmed occurrence of CV death, heart failure hospitalization* or outpatient heart failure**. ** Heart failure hospitalization also includes the development of new symptomatic heart failure during an ongoing hospitalization including the index AMI hospitalization.* *** Outpatient heart failure is defined as:* • *An urgent/unscheduled visit to an ED, acute/urgent care facility or outpatient clinic or a non-urgent office/practice or study visit for a primary diagnosis of HF that does not require an overnight hospital stay.* • *Patients must exhibit at least one documented new HF symptom with objective evidence of clinical HF consisting of at least 2 physical examination findings or one physical examination findings and at least one laboratory criterion.* • *The event requires initiation or intensification of treatment specifically for HF. Such treatment can include administration of intravenous agent (e.g., diuretic, vasodilator, vasopressor, or inotrope) or mechanical or circulatory intervention for HF, OR initiation of oral loop diuretic treatment, or intensification of oral maintenance loop diuretics for the diagnosis of HF, over a sustained period (i.e., initiation or doubling of total daily dose through a period of ≥ 4 weeks), which is confirmed at a subsequent outpatient visit*	Section 2.5
Secondary objective		
To demonstrate the superiority of LCZ696, compared to ramipril, in delaying the time-to-first occurrence of CV death or HF hospitalization	Time-to-first occurrence of CV death or HF hospitalization (days).	Section 2.6
To demonstrate the superiority of LCZ696, compared to ramipril, in delaying the time to new onset of symptomatic HF defined as time-to-first occurrence of HF hospitalization or outpatient HF	Time-to-first occurrence of HF hospitalization or outpatient HF (days)	Section 2.6
To demonstrate the superiority of LCZ696 compared to ramipril, in delaying the time-to-first occurrence of CV death, non-fatal spontaneous MI[1,3] or non-fatal stroke[4]	Time-to-first occurrence of CV death, non-fatal spontaneous MI[1,3] or non-fatal stroke[4] (days).	Section 2.6

Objective	Related endpoint and Definition	Analysis method
To demonstrate the superiority of LCZ696, compared to ramipril, in reducing the rate of the composite endpoint of CV death and total (first and recurrent) hospitalizations due to HF, non-fatal spontaneous MI[1,3] or non-fatal stroke[4]	Cumulative number of composite endpoint of CV death and total (first and recurrent) hospitalizations due to HF, non-fatal spontaneous MI[1,3] or non-fatal stroke[4] (count).	Section 2.6
To demonstrate the superiority of LCZ696, compared to ramipril, in delaying the time to all-cause mortality	Time to all-cause mortality (days).	Section 2.6
To evaluate the safety and tolerability of LCZ696 compared to ramipril	• Number and percentage of adverse events, serious adverse events, drug-related discontinuations, etc. • Change from baseline in laboratory assessments and vital signs measurements	Section 2.7
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Objective	Related endpoint and Definition	Analysis method
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Objective	Related endpoint and Definition	Analysis method
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Section 2.13.1

Objective	Related endpoint and Definition	Analysis method
[redacted]	[redacted]	[redacted]

1. The protocol-defined spontaneous MI is comprised of CEC adjudicated Type 1 and Type 2 MI.
2. Refers to any hospitalization after discharge from hospitalization due to qualifying MI
3. Non-fatal spontaneous MI is CEC-confirmed Type 1 or Type 2 MI that occurred at least 14 days prior to death.
4. Non-fatal stroke is comprised of all CEC-confirmed stroke.

2 Statistical methods

The following section contains important information on detailed statistical methodology used for analysis and reporting purposes.

2.1 Data analysis general information

Data will be analyzed by Novartis Biostatistics and Statistical Reporting department according to the statistical analysis section 9.1 of the study protocol using SAS 9.4, unless otherwise specified. Further details on planned statistical analyses and data-driven regression diagnostics will be presented in the following section and in CSR Appendix 16.1.9. The same analysis plan will also be used for planned interim efficacy analyses, as applicable.

In general, the continuous variables will be summarized descriptively by presenting n, mean, SD, median, quartiles, minimum and maximum while categorical variables will be summarized by presenting count and percentage of patients in each category. Graphical presentation of summary data will also be provided as applicable.

For time-to-event variables, the general censoring methods are specified in Section 2.5.3 for fatal or non-fatal time-to-first event endpoints, and in Section 2.6.1 for time-to-recurrent event endpoints.

Some missing or partially missing dates in the analyses require imputation. The handling of missing or partially missing dates has been detailed in Section 5.1.

The randomization in this study will be stratified by region and type of MI (STEMI or NSTEMI). "Other" type of MI has been grouped together with "NSTEMI" as "NSTEMI/Other" type of MI for stratification at randomization. In this document, "NSTEMI" refers to the grouping of "NSTEMI/Other" for type of MI. The stratification factors will be appropriately accounted for in the planned statistical analyses. At Visit 101 all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The stratification factors of region and type of MI entered and used by IRT at randomization sometimes can be different from the data collected on the Case Report Form (CRF), which is called mis-stratification. In this study, there have been some cases of mis-stratification by type of MI and one case of mis-stratification by region. Analyses using region and/or type of MI will consider the following rules:

- In general, unless otherwise specified, statistical models for all efficacy endpoints will use region and type of MI based on information from IRT where applicable.
- In addition, the primary/main analysis model for each of the primary and secondary efficacy endpoints (Section 2.5 and 2.6) will be repeated using CRF based region and type of MI.
- Subgroup analyses corresponding to the primary/main analysis models for the primary and secondary efficacy endpoints (Section 2.5 and 2.6) will be repeated using both IRT and CRF based region and type of MI where applicable.
- For patient disposition, demographic and background characteristics data analyses: the subgroup definition of type of MI (Table 2-1) will use both IRT and CRF based information; the subgroup definition of region (Table 2-1) will use CRF based information.
- For exposure and safety data analyses, the subgroup definitions of type of MI and region (Table 2-1) will be based on data collected from CRF.

Two interim analyses (IAs) are planned to assess efficacy. The analysis cutoff date for the first IA will be determined as date when 2/3rd of target primary composite outcome i.e. approximately 472 primary composite outcomes will be reported and adjudication-confirmed. The analysis cut-off time for the second IA (IA2) is planned to be 01-Mar-2020 (estimated start of COVID-19 impact globally). All primary events that occurred prior to 01-Mar-2020, will be included in the second IA. Analyses using pre-Covid data (prior to 1-Mar-2020) will include patients randomized before 1-Mar-2020. It is estimated that the second IA will include approximately 80% of the target number of 708 Clinical Event Committee (CEC)-confirmed primary events. If the assumptions of the study design regarding event rate, accrual rate and drop-out rate remain valid, the final analysis cut-off date will be a predicted date when a total of 708 confirmed primary triple composite and 592 confirmed double composite events have been achieved, or study termination has been decided based on other study termination criteria. The final analysis cut-off date for this study is 31-Dec-2020.

Additional efficacy analyses (for primary, secondary, [redacted] efficacy endpoints) will be considered to assess the potential impact of COVID-19 on study outcomes. See the following table for an overview of these analyses under different trial conduct scenarios:

Scenario	**Primary/main analysis**	**Sensitivity/supplementary analysis**
Early termination (without IA2)	Pre-specified primary/main analysis model, using pre-Covid data (prior to 1-Mar-2020)	Pre-specified primary/main analysis model, using all data accrued up to the end-of-study analysis cut-off
With IA2, early stop	Pre-specified primary/main analysis model, using pre-Covid data (prior to 1-Mar-2020)	Pre-specified primary/main analysis model, using all data accrued up to the end-of-study analysis cut-off
With IA2, no early stop	Pre-specified primary/main analysis model, using all data accrued up to the end-of-study analysis cut-off (31-Dec-2020[redacted])	Pre-specified primary/main analysis model, using pre-Covid data (prior to 1-Mar-2020);

		For primary endpoint, additional sensitivity and supplementary analyses will be performed as specified in Section 2.5.4
Note: Analyses using pre-Covid data (prior to 1-Mar-2020) will include patients randomized before 1-Mar-2020. [redacted]		

2.1.1 General definitions

Study treatment or drug

In future sections through this document, 'study treatment' or 'study drug' will be used to refer to investigational therapy assigned to a patient. Specifically, for the double-blind treatment phase, study treatment refers to LCZ696 or ramipril as assigned to a patient at randomization.

Screening epoch or screening period

Screening epoch or screening period is defined as the period starting from date of signed of informed consent until date of randomization or decision on randomization.

Randomized treatment phase

The randomized treatment phase begins at the time of randomization and ends with the last study drug intake or the death of the patient, whichever comes earlier. During the randomized treatment phase, patients will return for scheduled clinic visits. For all related safety analyses randomized treatment starts with the first intake of randomized, double-blind study drug. Temporary interruption of the study drug will not be counted as randomized treatment phase discontinuation.

Post-treatment follow-up phase

The post-treatment follow-up phase (usually after premature permanent study drug discontinuation) begins after last study drug intake + 1 day and ends on the date last seen (or vital status confirmed by indirect contact).

Double-blind period or double-blind treatment epoch

The double-blind period, also called the double-blind treatment epoch, is the combination of the randomized treatment phase and the post-treatment follow-up phase.

Baseline and study day

For analysis purpose, baseline value for all variables is defined to be the last results obtained at or prior to randomization date (or prior to 1st study drug intake for safety assessments). Most of variables will have their baseline at visit 101, unless otherwise specified. [redacted]

Study day of any assessment refers to the number of days to the assessment relative to randomization (day 1), or relative to the 1st study drug intake for safety assessments.

Unscheduled visit

Only for the analysis of safety laboratory evaluation will unscheduled measurements be taken into account. For efficacy evaluations, measurements from unscheduled visits will generally not be used, unless specifically specified.

On-treatment data for an efficacy endpoint

The on-treatment data refers to any observation occurring while the patient is on-study medication or within 28 days inclusive of permanent treatment discontinuation excluding any observation occurring thereafter.

2.2 Analysis sets

The following analysis populations will be defined for statistical analysis:

- **Screened (SCR) set –** All patients who have signed informed consent. The screened set includes only unique screened patients, i.e., in the case of re-screened patients only the chronologically last screening data is counted.
- **Randomized (RAN) set** – All patients who received a randomization number, regardless of receiving trial medication.
- **Safety set (SAF) -** All randomized patients who received at least one dose of study drug. Patients in the SAF will be analyzed according to treatment received.
- **Full analysis set (FAS)** – All patients in the RAN population who were not mis-randomized patients*. Following the intent-to-treat (ITT) principle, patients in the FAS are analyzed according to the treatment they have been assigned to at the randomization.
- **Per-protocol set (PPS)** will be a subset of the FAS which will consist of the patients who do not have major deviations. Major protocol deviations will be pre-specified prior to unblinding.

* Mis-randomized patients are those who were not qualified for randomization and who did not take study drug, but have been inadvertently randomized into the study.

Subjects without valid written informed consent will be excluded from all analysis sets.

A sample of rules leading to exclusion from specific analysis sets of patients violating protocol specified inclusion/ exclusion criteria and any other protocol deviations developed during the study has been provided in Appendix 5. The final list may be different from this which will be finalized and signed off before DBL.

2.2.1 Subgroups of interest

Subgroups will be formed to explore the consistency of treatment effects and safety profiling on selected parameters between the subgroups and the overall population. In general, subgroups will be defined based on baseline information as defined in section 2.1.

In Table 2-1, we have listed all subgroups defined for this study and the ways to derive them. Subsets of these subgroups will be used depending on the parameter under consideration. Also note that only important parameters or variables in these analyses will have subgroup analyses. The details about the parameters having subgroup analyses will be presented in the corresponding sections as appropriate. Also, additional subgroups may be formed later for regional or country-wise analyses as applicable.

Table 2-1 Specification of subgroups

Subgroup	Method of derivation	Disposition/ Background & Demographics / Exposure	Efficacy	Safety
Number of cardiovascular (CV) risk factors (1 CV risk factor vs. > 1 CV risk factor)[1]	Screening		X	
Age groups: (<65 vs. ≥65 years, <75 vs. ≥75 years)	Screening (derived)	X	X	X
Gender (male/ female)	Screening	X	X	X
Race	Screening	X	X	X
Region*	Derived (pooled countries or country), using Screening	X	X	X
Baseline LVEF (by quartiles)	Screening		X	
Baseline LVEF ≤40% vs. > 40%	Screening		X	
Worst Killip class (I vs. ≥ II)	Randomization		X	
Type of MI (STEMI vs. NSTEMI)	Randomization	X	X	X
Infarct location (anterior, inferior, and other)			X	
PCI use at baseline (PCI use versus medical management after index MI)		X	X	

Subgroup	Method of derivation	Disposition/ Background & Demographics / Exposure	Efficacy	Safety
Time from the index MI presentation to randomization (< median, ≥median)			X	
Baseline SBP (three groups: ≤110 mmHg; >110 mmHg and ≤140 mmHg; >140 mmHg)	Randomization		X	
Screening eGFR (<60 vs ≥ 60 mL/min/1.73 m2)	Screening		X	
History of diabetes (yes/no)			X	
Atrial Fibrillation associated with index MI at baseline (yes/no)			X	
Prior history of MI			X	
History of hypertension (yes/no)	Screening		X	
Prior ACEi or ARB use (yes/no)	Randomization		X	
Use of β-blocker at baseline (yes/no)			X	
Use of mineralocorticoid antagonists at baseline (yes/no)			X	
Use of loop diuretics at baseline (yes/no)			X	

* ***North America:*** *Canada, USA*

[1] *Patients with no CV risk factor are categorized in the "1 CV risk factor" group.*

Latin America (including Central America): *Argentina, Peru, Brazil, Colombia, Mexico*

Western Europe: *Austria, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom*

Central Europe: *Bulgaria, Croatia, Czech Republic, Greece, Hungary, Poland, Romania, Russia, Slovakia, Turkey*

Asia Pacific & Others: *Australia, South Africa, Israel, China, India, Korea, Philippines, Singapore, Taiwan, Thailand*

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Based on all patients in the screened set, number and percentage of patients screened successfully will be provided. In addition, screen failure patients will be summarized by primary reason for screen failure.

The number and percentage of randomized patients included in different analysis sets (Section 2.2) will be summarized based on the randomized patients. Patients with premature study discontinuation during the double-blind treatment epoch will be summarized by the primary reason of discontinuation for each randomized treatment group and overall based on all patients in randomized set (RAN).

In addition, the number and percentage of patients with protocol deviations as well as the criteria leading to exclusion from analysis sets will be provided for the patients in randomized set (RAN). All the disposition data will also be listed at a patient level for double-blind period disposition.

The number and percentage of patients with any and each of the following COVID-19 impacted criteria will be provided for all randomized patients, patients randomized prior to 1-Mar-2020, and patients randomized on or after 1-Mar-2020: (1) cancelled/rescheduled doctor's appointment due to COVID-19; (2) cancelled/rescheduled procedure due to COVID-19; (3) missed study visit due to COVID-19; (4) study visit performed outside the study site due to COVID-19; (5) study assessment or visit procedures changed due to COVID-19; (6) method of dispensing the study drug to the subject changed due to COVID-19; (7) study drug interruption due to COVID-19; (8) study drug discontinuation due to COVID-19; (9) endpoint(s) impacted by COVID-19; (10) had symptom(s) for which the patient felt the need to go to an outpatient clinic, urgent care, emergency department, or hospital but chose not to due to COVID-19.

2.3.2 Demographics and baseline characteristics

Following demographic and baseline characteristics will be summarized by randomized treatment group for all patients in full analysis set (FAS):

- **Continuous variables**
  Age (in years), height (in centimeters), weight (in Kg.), body mass index (BMI) in Kg/m^2, SBP (in mmHg), DBP (in mmHg), heart rate (in bpm), eGFR (in $ml/min/1.73m^2$),
  Categorical variables
  - Age group (<65 years vs. ≥65 years; <75 years vs. ≥75 years)
  - Sex
  - Race
  - Ethnicity
  - Region

2.3.2.1 Characteristics and therapies associated with qualifying MI

Qualifying MI related characteristics, cardiovascular (CV) risk factors associated with qualifying MI and therapies used to manage qualifying MI will be summarized separately for all patients in the Full Analysis set (FAS) which includes:

- **Disease characteristics**
  Time from index MI presentation to randomization,
  Location of infraction (anterior / inferior), type of MI (STEMI/ NSTEMI), number of diseased vessels, ejection fraction (EF) (in %), Killip class
- **CV risk factors/co-morbidity/past history at baseline**
  Age (<70, ≥70 years), screening eGFR (<60, ≥60 ml/min/1.73m^2), diabetes (yes/no), history of prior MI (yes/ no), atrial fibrillation associated with qualifying MI (yes/ no), categories of EF (<30%, >=30%), worst Killip class (<III, ≥III), STEMI without reperfusion therapy within the first 24 hours after presentation (yes/no).
  Number of CV risk factors will be summarized descriptively.
- **Therapies used to manage qualifying MI –**
  Use of reperfusion therapies (yes / no) –
  - use of PCI (yes/ no) (including procedures performed for qualifying MI both prior to and after randomization but before discharge)
  - type of stenting if PCI performed (bare metal/drug eluting stent)
  - use of antithrombotic therapy (yes/no) which includes aspirin, P2Y12 inhibitor, antithrombin agents, glycoprotein (GP) IIb/IIIa inhibitors
  - use of oral CV medications including (but not limited to) ARB/ACE inhibitors, beta blockers, mineralocorticoid receptor antagonists (MRA), statins, oral anticoagulants, non-loop diuretics, loop diuretics, digitalis glycosides, oral nitrates and calcium channel blockers..
  - use of IV diuretics (yes/no), IV vasodilator (yes/no), IV vasopressors (yes/no), IV inotropes (yes/no)

In general, all continuous variables will be summarized by presenting descriptive statistics (n, mean, SD, Q1, Q3, median, minimum, maximum) and all categorical variables will be summarized by number and percentage of patients in each category. The summaries will be provided by randomized treatment group for all patients in Full Analysis set (FAS).

2.3.3 Medical history

Any condition entered on the relevant medical history / current medical conditions CRF will be coded using the most updated version of MedDRA dictionary. Medical history includes cardiovascular disease history and other medical history in this study, which are collected at Visit 1 (Screening visit). The number and percentage of subjects with each medical condition will be provided by treatment group and system of organ class and preferred term for the Full Analysis Set (FAS).

Patient disposition, demographic/ baseline and other disease characteristics will also be summarized similarly for the following subgroups:

- Age group (<65 vs. ≥65 years), age group (<75 vs. ≥75 years)

- Gender (male/female)
- Region
- Race
- Type of MI (STEMI vs. NSTEMI)
- PCI use at baseline (Yes vs. No)

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

2.4.1 Study treatment / compliance

Overall treatment exposure

The duration of overall treatment exposure (in days) will be calculated as –

Last known date when the patient took study medication – Date of 1st intake of randomized study medication during double-blind treatment epoch + 1

This includes days patient is off-treatment due to temporary treatment interruption.

The overall treatment exposure duration (in days) will be summarized by randomized treatment group using mean, standard deviation, median, minimum and maximum. Additionally, the treatment exposure duration will also be summarized categorically by presenting number and percentage of patients with exposure

- <2 weeks
- 2 to < 4weeks
- 4weeks to < 6months
- 6months to < 1 year
- 1 year to < 2 years
- >= 2 years

Mean daily dose and mean dose level for each patient will be summarized by treatment group. Mean daily dose and mean daily dose level for each patient will be calculated as –

$$\frac{\sum_{i=0}^{3}(\text{Number of days spent on Dose}_i)\text{X}(\text{Dose}_i)}{\sum_{i=0}^{3}(\text{Number of days spent on Dose}_i)}$$

For mean daily dose calculation 'Dose_i' represents actual dose (in mg) administered at dose level 'i' according to Table 1-1, whereas for mean daily dose calculation 'Dose_i' represents the categorical dose level (0, 1, 2 or 3) administered at dose level 'i'. Further, dose level '0' refers to zero dose signifying treatment interruption. Mean daily dose and mean daily dose level calculated as above will be summarized by treatment groups for overall study duration. Mean doses and mean dose levels of study drug at each visit will also be summarized by treatment group and visit. Last dose and last dose level when patients are alive will also be summarized by treatment group.

Descriptive summary of number of days spent at each dose level as mentioned in Table 1-1 will be provided by treatment group. Also, number and percentage of randomized patients at each

dose level will be summarized by visit and treatment group. Time to first reach the dose at each dose level and time to first reach the target dose will be summarized for each treatment group during the double-blind treatment epoch. In addition, reasons for down-titrating treatment will be summarized by each treatment group for each dose level.

Time to permanent discontinuation of study medication not due to death will be summarized according to the Kaplan-Meier analysis. A summary table by treatment group will be provided to display the number and percentage of patients who discontinued study medication by the primary reason for discontinuing and the number and percentage of patients who subsequently received the following medications during the study: ACE inhibitors, ARB, and Entresto™ (sacubitril/valsartan). Exposure durations will be summarized by treatment group for these medications. The last doses and dose levels of study drugs for these switchers will also be summarized by treatment group.

Overall study drug exposure

Duration of overall study drug exposure is defined as the duration of treatment exposure (in days) excluding days of treatment interruption and is calculated as –

(Last known date when the patient took study medication – Date of 1st intake of randomized study medication during double-blind treatment epoch + 1) – number of days of treatment interruption

The duration of study drug exposure (in days) will be summarized by randomized treatment group using mean, standard deviation, median, minimum and maximum. Additionally, the treatment exposure duration will also be summarized categorically by presenting number and percentage of patients with exposure

- <2 weeks
- 2weeks to < 4weeks
- 4weeks to < 6months
- 6months to < 1 year
- 1 year to < 2 year
- >=2 years

Treatment and study drug exposure in subgroups

Both overall treatment exposure and overall study drug exposure will be summarized by the following subgroups -

- Age group (< 65 vs ≥ 65 years; < 75 vs ≥ 75 years)
- Gender
- Race
- Region
- Type of MI (STEMI vs. NSTEMI)

Overall study exposure (Follow-up duration)

Following the definition of double blind phase in section 2.1.1, for each patient duration of study exposure (in days) during double blind phase is calculated as total duration of on-treatment randomized phase and post-randomized treatment phase where –

Duration of on-randomized treatment phase (in days) is calculated as –

Date of last study drug intake – randomization date + 1.

Duration of post-randomized treatment phase or off-treatment phase (in days) is calculated as –

min(Last date patient is known to be alive, Last visit date before analysis cutoff date) – Last known date patient took randomized study medication + 1

Hence, overall study exposure duration (follow-up duration) = Duration of on-randomized treatment phase + Duration of post-randomized treatment phase – 1.

Of note, for randomized patients not receiving double-blind randomized study medication, overall study exposure duration is calculated as –

min(Last date patient is known to be alive, Last visit date before analysis cutoff date) – randomization date + 1

The duration of overall study exposure and on-treatment randomized phase are summarized by randomized treatment group for all patients in FAS by providing descriptive statistics (n, mean, SD, Q1, Q3, median, minimum, maximum).

2.4.2 Prior, concomitant therapies

'Prior medications' are defined as drugs taken prior to first dose of double-blind study medication. Any medication which has been started during the double-blind treatment epoch including medications started prior to randomization but continued in the double-blind treatment epoch are identified as **'Concomitant medications'**.

Prior and Concomitant medications will be summarized separately by therapeutic class (by ATC code), preferred term, and treatment group for the safety set. Prior and Concomitant non-drug therapies will be summarized separately by SOC, preferred term, and treatment group for the safety set. The number and percentage of patients on following CV background medications during double-blind treatment epoch will be tabulated by randomized treatment group –

- Aspirin
- Antiplatelet agents (excl. Aspirin)
  - P2Y12 inhibitors
  - Glycoprotein (GP) IIb/IIIa inhibitors
  - Other
- ARBs
- ACE inhibitors
- Beta Blockers

- Mineralocorticoid Receptor Antagonists
- Statins
- Diuretics (Loop/non-loop diuretics, summarized by IV/ oral diuretics)
- Cardiac glycosides (Digoxin/digitalis glycoside)
- Calcium channel blockers
- Anticoagulants
- Antiarrhythmic agents
- Nitrates
- Other lipid lowering agents
- Anti-diabetic drugs
  - Insulins
  - Oral anti-diabetic drugs
- Other

Apart from the CV medications listed above, reperfusion therapies used during post-randomized treatment phase for managing index MI and any other post-randomization MI will be summarized separately in a similar way as in section 2.3.2.1. The summaries of background medications and non-drug therapies will be provided for Safety set (SAF) unless otherwise specified.

Analysis of dose intensity of RAS blockade during double-blind period

Dose intensity of RAS blockades during double-blind period will be captured in terms of mean total daily dose levels of open label ARB/ACEIs/Entresto used after study drug discontinuation. Mean total daily dose for each study medication is defined by average of different doses for the medications (including no or zero dose) weighted by number of days patient is on that dose during the specified analysis period. The total daily dose of RAS blockades (high/low) are categorized based on the table 2-2 below.

Table 2-2 Definition of high and low RAAS blockade group based on total daily dose of commonly used ARB/ACEIs

ARBs	Low RAAS blockade group	High RAAS blockade group	ACEIs	Low RAAS blockade group	High RAAS blockade group
Azilsartan	<80 mg	≥ 80 mg	Enalapril	<10 mg	≥ 10 mg
Candesartan	<16 mg	≥ 16 mg	Benazepril	<20 mg	≥ 20 mg
Eprosartan	<400 mg	≥ 400 mg	Captopril	<100 mg	≥ 100 mg
Irbesartan	<150 mg	≥ 150 mg	Cilazapril	<2.5 mg	≥ 2.5 mg
Losartan	<50 mg	≥ 50 mg	Delapril	<30 mg	≥ 30 mg
Olmesartan	<10 mg	≥ 10 mg	Fosinopril	<20 mg	≥ 20 mg
Telmisartan	<40 mg	≥ 40 mg	Imidapril	<10 mg	≥ 10 mg
Valsartan	<160 mg	≥ 160 mg	Lisinopril	<10 mg	≥ 10 mg
			Moexipril	<7.5 mg	≥ 7.5 mg
			Perindopril	<4 mg	≥ 4 mg
			Quinapril	<20 mg	≥ 20 mg

ARBs	Low RAAS blockade group	High RAAS blockade group	ACEIs	Low RAAS blockade group	High RAAS blockade group
			Ramipril	<5 mg	≥ 5 mg
			Spirapril	<6 mg	≥ 6 mg
			Temocapril	<2 mg	≥ 2 mg
			Trandolapril	<2 mg	≥ 2 mg
			Zofenopril	<30 mg	≥ 30 mg

For patients taking open-label Entresto, total mean daily dose is categorized into high/low dose level according to LCZ696 dose levels 50mg bid (low), 100 mg bid (high), 200 mg bid (high). The open label ARB/ACEI and open-label Entresto/LCZ696 dose level will be considered to determine whether a patient is on high or low dose level of RAS blockade.

Overall mean total daily dose levels of open label ARB/ACEIs/Entresto will be summarized for the double-blind period for each treatment group by providing number and percentage of patients on high and low dose level during the first 12 months from randomization for the following patient populations -

- FAS
- FAS patients who discontinue study treatment during the first 12 months after randomization.

2.5 Analysis of the primary objective

All patients in the Full Analysis Set (FAS) will be included in the primary analysis.

In the event that the study is stopped early for efficacy at the second interim analysis, or the study is terminated early by the sponsor due to prolonged COVID-19 impact, the main, supportive and subgroup analyses for the primary endpoint described in this section will be performed using the same analysis cut-off date as the second interim analysis to include data prior to 01-Mar-2020.

If the study is not stopped at the second interim analysis and continues to the end, the main, supportive and subgroup analyses for the primary endpoint described in this section will be performed as planned using all data accrued up to the end-of-study analysis cut-off (31-Dec-2020).

See Section 2.5.4 for sensitivity and supplementary analyses for the primary endpoint, including those added for the COVID-19 impact.

2.5.1 Primary endpoint

The primary efficacy variable is time to first occurrence of a confirmed composite endpoint of cardiovascular death, HF hospitalization or outpatient HF. The confirmation of the primary composite events will be based on an adjudication process by an independent CEC.

Note that deaths which cannot be classified by the adjudication committee as CV or non-CV death (for example due to lack of information), will be counted as a CV death for the purpose

of the primary endpoint. Unless otherwise specified, this is applicable to all efficacy endpoints with a CV death component.

Time-to-event is computed as the number of days from randomization to the date of the primary endpoint event (first occurrence). A patient without an event will be censored at the last date the endpoint status was completely known* or at the time of death from non-CV causes (i.e. any death which is confirmed to be a non-CV death by the CEC).

* This date could include the date of withdrawal of informed consent, date of the patient's last visit prior to the cut-off date of the analysis (whichever occurred first).

2.5.2 Statistical hypothesis, model, and method of analysis

The following null hypothesis versus the alternative will be tested at the 1-sided 2.5% type I error rate.

$H_0 : \lambda_2/\lambda_1 \geq 1$ (i.e., the hazard rate of the first confirmed primary event in the LCZ696 group (λ_2) is greater than or equal to the hazard rate in the ramipril group (λ_1)) *versus*

$H_1 : \lambda_2/\lambda_1 < 1$ (i.e. the hazard rate of the first confirmed primary event in the LCZ696 group (λ_2) is less than the hazard rate in the ramipril group (λ_1))

λ_2/λ_1 is called the hazard ratio of LCZ696 relative to ramipril.

The time-to-first confirmed primary endpoint will be analyzed using a Cox proportional hazards model stratified by STEMI/NSTEMI, with treatment, PCI use at baseline and region included as factors in the model. This model allows the hazard rates to vary with time while the hazard ratio is assumed to be constant, i.e., independent of time, within each stratum. The hazard ratio for LCZ696 vs. ramipril, the associated 2-sided 95% confidence interval and the 1-sided and 2-sided p-values will be presented from the analysis.

The Kaplan-Meier estimates of the cumulative event rate (1-survival function) for each treatment (and strata) will be tabulated and will also be presented graphically.

2.5.3 Handling of missing values/censoring/discontinuations

In general, for a time-to-first event endpoint, the censoring date for a non-fatal endpoint or an endpoint with non-fatal event as a component (even if fatal event is also another component) is defined as one of the following (whichever occurred first):

- Date when the patient withdrew informed consent
- Date of the patient's last visit (including telephone visit)
- Date of death
- Analysis cut-off date[1]

The censoring date for a fatal endpoint (time-to-first event) is defined as one of the following (whichever occurred first):

- Date when the patient withdrew informed consent
- Patient's last known alive date
- Date of death
- Analysis cut-off date[1]

[1] Analysis cut-off date will be 31-Dec-2020 for the primary/main analyses, and 29-Feb-2020 for analyses using pre-COVID impact data prior to 1-Mar-2020.

Note that every effort will be made to follow all patients until the end of the study, regardless of adherence to study treatment. The analysis methods specified are valid under the assumption that the censoring mechanism is independent of the event generating process (non-informative censoring).

Missing or partially missing event dates will be imputed according to the rules specified in Section 5.1.3.

The censoring date for the primary endpoint will be derived using the non-fatal endpoint censoring method as described above in this section, with the censoring component date of death being that of non-CV death.

The censoring date for the components of the primary endpoint will be derived using the same principle for fatal/non-fatal endpoint as described above in this section:

- Time-to-first event of HF hospitalization (using censoring method for non-fatal endpoint)
- Time-to-first event of outpatient HF (using censoring method for non-fatal endpoint)
- Time to CV death (using censoring method for fatal endpoint)

2.5.4 Supportive analysis and sensitivity/supplementary analysis

Supportive analysis

The composition of the first confirmed composite primary efficacy endpoint will be summarized by treatment group descriptively. The time to reach the first of each individual component will be analyzed using the same methodology as the described for the primary endpoint. Note that for the components CV death and HF hospitalization, all events observed will be included in the individual component analyses and not just those which were counted as a 'first event' in the primary composite endpoint. In addition to the standard censoring mechanism described in Section 2.5.3, for the analysis of time to outpatient HF, patients will be censored at the time of HF hospitalization or CV death. For the analysis of time to first HF hospitalization, patients will be censored at the time of CV death.

As supportive analyses, the following alternative definitions of the primary endpoint will be used with the primary analysis model described in Section 2.5.2:

(a) Time to first occurrence of an investigator-reported composite endpoint of CV death, HF hospitalization or outpatient HF (with and without the analysis cut-off date of 31-Dec-2020);
(b) Time to first occurrence of a confirmed composite endpoint of all-cause death, HF hospitalization or outpatient HF;

(c) Time to first occurrence of a confirmed composite endpoint of CV death (including only deaths from CV causes, unknown or missing cause of deaths are not included as events), HF hospitalization or outpatient HF.

Above (a) is the investigator-reported version of the primary endpoint. (b) is the alternative definition of the primary endpoint by replacing the CV death component with all-cause death.

(c) differs from the primary endpoint in that the CV death is defined as death from CV causes only, while the primary endpoint includes CV death from unknown causes. For (c), the component analysis of CV death will also include deaths from CV causes only, and unknown or missing cause of deaths will not be considered as events.

An 'on-treatment' analysis (Section 2.1.1) will also be performed for the primary endpoint whereby events that occurred more than 28 days after permanent study treatment discontinuation will be excluded from the analysis. For patients without events before or at 28 days after treatment withdrawal, the censoring date will be the minimum of the date of permanent study treatment discontinuation + 28 days and the date of standard censoring for the endpoint.

The primary analysis will also be repeated for per-protocol set (PPS) for assessing robustness of results to significant protocol deviations leading to exclusion from FAS.

Sensitivity and supplementary analyses

1. If the study is stopped early for efficacy at the second interim analysis, or the study is terminated early by the sponsor due to prolonged COVID-19 impact, the following sensitivity and supplementary analyses will be performed:

   (1) As a sensitivity analysis to the above proportional hazards analysis, treatment groups will be compared for the primary efficacy variable using a stratified log-rank test with STEMI/NSTEMI as a stratification factor, including CEC-confirmed primary endpoint events that occurred prior to 01-Mar-2020 (estimated start of COVID-19 impact globally).

   (2) Analysis with adjustment of country instead of region in the primary analysis model as specified in Section 2.5.2, using CEC-confirmed primary endpoint events that occurred prior to 01-Mar-2020.

   (3) A supplementary analysis using the primary analysis model as specified in Section 2.5.2, including all CEC-confirmed primary endpoint data accrued up to the end-of-study analysis cut-off.

2. If the study is not stopped at the second interim analysis and continues to the end, the following sensitivity and supplementary analyses will be performed:

   (1) As a sensitivity analysis to the above proportional hazards analysis, treatment groups will be compared for the primary efficacy variable using a stratified log-rank test with STEMI/NSTEMI as a stratification factor, including all CEC-confirmed primary endpoint data accrued up to the end-of-study analysis cut-off.

   (2) Hypothetical estimand approach (see Table 2-4 for the definition of the hypothetical estimand in a world without the COVID-19):

   The estimand targeted in the original study protocol is defined in Table 2-3. In comparison, in a hypothetical world without COVID-19, the new intercurrent event due to COVID-19 is the onset of COVID-19 pandemic impact on study (see Table 2-4), which can be derived by a fixed global COVID-19 impact start date (01-Mar-

2020) or subject-specific impact start date based on information from the COVID CRF pages. A hypothetical strategy (see below methods i and ii) will be used for this new intercurrent event.

The analyses targeting this estimand will be performed with the following censoring methods:

i. Endpoint data will be censored on 29-Feb-2020 if the patient has not experienced the endpoint by this time

   This analysis will be performed using the primary analysis model as specified in Section 2.5.2.

ii. Endpoint data will be censored at the time of subject-specific COVID-19 impact start date, derived as the earliest date of the following for each patient based on the COVID-19 eCRF: (a1) study treatment discontinuation due to COVID-19; (a2) start of treatment interruption for > 3 months due to COVID-19; (b) first missed visit due to COVID-19; (c) first endpoint event impacted by COVID-19; (d) symptom onset of the first occurrence of a condition for which the patient felt the need to go to an outpatient clinic, urgent care, emergency department, or hospital but chose not to due to COVID-19.

   This analysis will be performed using inverse probability of censoring weighted (IPCW) Cox proportional hazards model (Robins and Finkelstein 2000) as described in Section 2.6.5. IPCW is used to account for potential informative censoring using the subject-specific censoring method.

Table 2-3 Estimand in the original protocol :

Intercurrent event	**Strategy**
Permanent treatment discontinuation	Treatment policy strategy
Non-CV death	Hypothetical strategy
Primary scientific question of interest / Estimand: What would be the relative risk reduction (HR) for Entresto vs Ramipril (regardless of treatment discontinuation) in patients with LV systolic dysfunction and/or pulmonary congestion following an AMI, in the composite primary endpoint, as measured by the time to first composite of CV death, HFH and outpatient HF, in the absence of death from non-CV related causes?	

Table 2-4 Estimand in a world without the COVID-19 pandemic:

Intercurrent event	**Strategy**
Permanent treatment discontinuation	Treatment policy strategy

Non-CV death	Hypothetical strategy
Onset of COVID-19 pandemic impact on study	Hypothetical strategy
Primary scientific question of interest / Estimand: What would be the relative risk reduction (HR) for Entresto vs Ramipril (regardless of treatment discontinuation) in patients with LV systolic dysfunction and/or pulmonary congestion following an AMI, in the composite primary endpoint, as measured by the time to first composite of CV death, HFH and outpatient HF, in the absence of COVID-19 pandemic and death from non-CV related causes?	

Since the study was designed without a COVID-19 pandemic in mind, both the analysis targeting the estimand "in a world without COVID-19 pandemic" and the primary analysis based on all data up to the end-of-study analysis cut-off may be interpreted as addressing the estimand in the original study protocol, acknowledging that the treatment effect estimate based on the latter might be affected by the pandemic.

(3) Bayesian analysis with robust prior

Let us denote by $y_{pre} = \log(\widehat{HR}_{pre})$ the observed log(hazard ratio) based on data obtained **before** the global outbreak of COVID-19, and by $y_{post} = \log(\widehat{HR}_{post})$ the observed log(hazard ratio) based on data obtained **after** the outbreak. The true underlying log(hazard ratio) is denoted by θ. We use the normal approximation for the log(hazard ratio), and thus, when denoting the number of events by n_{pre}, n_{post}, we obtain for the likelihood

$$y_{pre}|\,\theta \sim N\left(\theta, \frac{4}{n_{pre}}\right)$$

$$y_{post}|\theta \sim \left(\theta, \frac{4}{n_{post}}\right)$$

Our goal is to leverage the information obtained after the outbreak to inform the hazard ratio from the data obtained before the outbreak. However, since the impact of COVID-19 on the endpoint is unclear, we aim doing so in a robust way. Therefore, we build a prior for θ that fulfills the following two requirements:

- In case of similarity of y_{pre} and y_{post}, the information obtained after the outbreak is, to a substantial extent, taken into account
- In case of a conflict between y_{pre} and y_{post}, the information obtained after the outbreak is down-weighted in a dynamic way

These requirements can be addressed using a robust mixture prior (see e.g. Schmidli et al, 2014) consisting of two components:

Component 1: Informative prior distribution $p_{inf}(\theta) = N(y_{post}, \frac{4}{n_{post}})$, which is the posterior distribution of θ given y_{post}, when starting with an improper prior for θ

Component 2: Vague prior distribution $p_{vague}(\theta) = N(y_{post}, 2^2)$, which is a vague (unit-information) prior distribution for θ

The robust mixture prior is obtained by mixing these distributions with weights w and $1 - w$, respectively:

$$p(\theta) = w * p_{inf}(\theta) + (1 - w) * p_{vague}(\theta)$$

Finally, we obtain the posterior distribution $p(\theta|y_{pre})$ through standard Bayesian updating. As a fact of mixture calculus, the posterior is a mixture of the component-wise posteriors, but with updated weights:

$$p(\theta|y_{pre}) = \tilde{w} \times p_{inf}(\theta|y_{pre}) + (1 - \tilde{w}) \times p_{vague}(\theta|y_{pre})$$

where $p_x(\theta|y_{pre})$ is the posterior distribution of θ given data y_{pre} and prior $x \in \{inf, vague\}$.

The weights are updated according to the following rule:

$$\tilde{w} = \frac{w * m}{w * m + (1 - w) * m'}$$
$$m = \int p(y_{pre}|\theta) p_{inf}(\theta) d\theta$$
$$m' = \int p(y_{pre}|\theta) p_{vague}(\theta) d\theta$$

Finally, the weights chosen for the analysis are $w = 1 - w = 0.5$, i.e. we a priori assume there is an equal chance of similarity and conflict between y_{pre} and y_{post}. This choice is common practice in applications (Dominguez et al, 2017). The point estimate and 95% probability interval will be obtained from this posterior distribution as the median and 2.5th and 97.5th percentile, respectively. Furthermore, the posterior probability that the hazard ratio is favoring LCZ696 (i.e., HR < 1), will be provided.

SAS code for this analysis can be found in Appendix 5.4.

(4) Analysis of all CEC-confirmed primary endpoint data accrued up to the end-of-study analysis cut-off, using a Cox model with a "during-COVID" indicator and its interaction with treatment as time-varying covariates.

Consider the following model:

$h(t) = h_0(t)\exp(\beta_1 \times trt + \beta_2 \times \mathbb{I}\{C(t)\} + \beta_3 \times \mathbb{I}\{C(t)\} \times trt)$,

where $\mathbb{I}\{C(t)\}$ is an indicator of "during-COVID" at patient-time t. $\mathbb{I}\{C(t)\}$ is equal to 1 if the patient-time t falls in the COVID-19 impacted period (on or after 1-Mar-2020), and is equal to 0 otherwise.

This analysis model will allow the assessment of the treatment effect in non-COVID impacted periods (before and after the COVID-impacted period, estimated by β_1). It will also allow to quantify the change in event rate during the COVID-impacted period (β_2) and the change of the treatment effect during the COVID-impacted period (β_3), however the number of events and hence precision may be low. In addition to including treatment, "during-COVID" indicator, treatment by "during-COVID" indicator interaction as covariates, this model will also adjust for region and PCI use at baseline, and be stratified by type of MI (STEMI/NSTEMI).

(5) Weibull regression model stratified by type of MI (STEMI/NSTEMI), with treatment, PCI use at baseline and region included as factors in the model, including all CEC-confirmed primary endpoint events that occurred prior to 01-Mar-2020. Parametric model may be more powerful than the semiparametric primary model.

(6) Analysis with adjustment of country instead of region in the primary analysis model as specified in Section 2.5.2, both using all CEC-confirmed primary endpoint data accrued up to the end-of-study analysis cut-off and event data with onset date prior to 01-Mar-2020. This may recover some of the lost power by accounting for the heterogeneity of the COVID-19 impact and also the standard of care among countries within regions)

2.5.5 Subgroup analysis

For primary endpoint and its components, subgroup analyses will be performed based on the pre-defined subgroups in section 2.2.1 for patients in FAS only.

Displays of treatment effects by subgroup categories (defined as marginal groupings) will be provided for descriptive purposes.

The estimated hazard ratio, and 2-sided 95% confidence interval, will be provided for each individual subgroup using a Cox's proportional hazards model stratified by STEMI/NSTEMI with treatment, region and PCI use at baseline as fixed effects factor in the model, with the exception for type of MI (STEMI/ NSTEMI) subgroup for which the analysis will not be stratified by STEMI/ NSTEMI.

For subgroups other than type of MI (STEMI vs. NSTEMI), the p-value associated with the test of treatment-by-subgroup interaction effect will be calculated from a Cox's proportional hazards model, stratified by STEMI/NSTEMI, including treatment, PCI use at baseline, region, subgroup, and treatment-by-subgroup as fixed-effect factors. For STEMI vs. NSTEMI, p-value for interaction term will be provided from a similar model but STEMI/NSTEMI only included as a fixed effect factor and not a stratifying factor.

Since no adjustment for multiple comparisons will be made, findings should be interpreted with caution. Additionally, the frequency and percentage of patients reaching primary composite endpoint will be presented by treatment group for each of the subgroups listed in Section 2.2.1.

2.6 Analysis of secondary efficacy objective(s)

The Full Analysis Set (FAS) will be used for all secondary analyses.

The general strategies for the main, sensitivity, and subgroup analyses of the secondary efficacy endpoints will be similar to those of the primary efficacy endpoint (see Section 2.5).

In the event that the study is stopped early for efficacy at the second interim analysis, or the study is terminated early by the sponsor due to prolonged COVID-19 impact, the main and subgroup analyses for the secondary endpoints described below (Section 2.6.2 and 2.6.6) will be performed using the same analysis cut-off date as the second interim analysis to include data prior to 01-Mar-2020.

If the study is not stopped at the second interim analysis and continues to the end, the main and subgroup analyses for the secondary endpoints described in this section will be performed as planned using all data accrued up to the end-of-study analysis cut-off (31-Dec-2020).

See Section 2.6.5 for sensitivity analyses added for the COVID-19 impact.

2.6.1 Secondary endpoints

The secondary variables are as follows-

(1) Time from randomization to first occurrence of a confirmed composite of CV death or HF hospitalization

(2) Time from randomization to first occurrence of a confirmed composite of HF hospitalization or outpatient HF

(3) Time from randomization to first occurrence of a confirmed composite of CV death, non-fatal spontaneous MI or non-fatal stroke

- *Non-fatal spontaneous MI is defined as either Type 1 or Type 2 MI confirmed by the independent Clinical Event Committee*

(4) The cumulative number of composite events, including hospitalizations due to HF, hospitalizations due to non-fatal spontaneous MI, hospitalizations due to non-fatal stroke and CV death.

(5) Time from randomization to all-cause mortality

Censoring of secondary endpoints

For time-to-first event endpoints, the general rules of the censoring methods in Section 2.5.3 will be followed.

For a time-to-recurrent event endpoint, the censoring date is defined as one of the following (whichever occurred first):

- Date when the patient withdrew informed consent
- Date of the patient's last visit (including telephone visit)
- Date of death
- Analysis cut-off date[1]

[1] Analysis cut-off date will be 29-Feb-2020 for analyses using pre-COVID impact data prior to 1-Mar-2020.

The event generating process for the secondary endpoints will be censored following the mechanism below-

- Endpoints (1), (2) and (3) will be censored following a similar censoring mechanism followed for a non-fatal endpoint (Section 2.5.3).
- Event generating process for endpoint (4) will be censored following the censoring mechanism for a recurrent time-to-event endpoint as summarized above in this section.
- Endpoint (5) will be censored following the fatal endpoint censoring method (Section 2.5.3). For all-cause death, this means censoring at the earlier of
  - date when the patient withdrew informed consent
  - Patient's last known alive date

- Analysis cut-off date[1]

2.6.2 Statistical hypothesis, model, and method of analysis

The secondary endpoints will be analyzed in order to compare LCZ696 vs ramipril using the ITT approach (i.e. estimation of the treatment effect under the 'treatment policy').

Analysis of time to event variables

The time to event endpoints (1), (2), (3), (5) will be analyzed using the same statistical analysis methods as specified for the primary analysis. Treatment groups will be descriptively compared by presenting number and percentage of patients with events while inferential comparisons between treatment groups will be provided based on estimated hazard ratio and 95% CI. Both 1-sided and 2-sided p-values will be reported for treatment group comparison (LCZ696 vs. ramipril). Kaplan-Meier estimates of event rates will be tabulated for specific time points and will also be presented graphically.

Analysis of count variable

Secondary endpoint (4) will be analyzed using a negative binomial regression model with a Weibull baseline intensity function to allow flexibility if the baseline intensity is non-constant (Lawless, 1987). The regression model will consider the number of composite events as dependent variable with randomized treatment, STEMI/NSTEMI, PCI use at baseline and region as factors having fixed effects. Every event jump time, including the terminal event time, will be used to estimate the parameters specified in this model. For treatment group comparison LCZ696 vs ramipril, the relative rate ratio will be presented together with 2-sided 95% confidence interval and 1-sided and 2-sided p-values from the fitted model.

For descriptive summary, unadjusted annualized incidence rate will be provided along with the model-based estimates and their 95% confidence intervals will be presented by treatment groups. Also, adjusted event rate functions over time will be graphically presented from the estimated Weibull intensity.

2.6.3 Control of familywise type I error rate

The primary endpoint and the first four secondary efficacy endpoints will be included in a statistical testing strategy to control the familywise type I error rate at the 1-sided 2.5% level (in the strong sense). A hierarchical testing procedure will be employed whereby the primary hypothesis will be tested first, if rejected then the hypothesis associated with the first secondary endpoint will be tested and so on. The order of testing of the composite endpoints will be as follows:

1. Primary endpoint
2. Time to first CV death or HF hospitalization
3. Time to first HF hospitalization or outpatient HF
4. Time to first CV death, non-fatal spontaneous MI or non-fatal stroke
5. The total number of composite events (hospitalizations (including CV death) due to HF, non-fatal spontaneous MI or non-fatal stroke and CV death).

Note: Time to CV death, time to first HF hospitalization, and time to first outpatient HF (as components of the primary composite endpoint) will not be part of the above-mentioned hierarchical testing procedure.

2.6.4 Handling of missing values/censoring/discontinuations

For each patient, the information on secondary endpoints censoring will be censored as defined earlier. The primary analysis methods are valid under the assumption that the censoring mechanism is independent of the event generating process (non-informative censoring).

Sensitivity analyses have been proposed to assess robustness of the results to the potential violation of this assumption, wherever applicable.

2.6.5 Supportive analysis and sensitivity analysis

Supportive analysis

It is recognized that at the time of the first onset of symptomatic HF event some patients may discontinue randomized treatment and may be prescribed an alternative treatment for HF which could be locally available Entresto™ (sacubitril/valsartan, LCZ696). For the pre-specified secondary endpoints (1), (3) and (5) (numbering refers to Section 2.6.1), the analysis described in Section 2.6.2 will estimate the treatment effect of LCZ696 vs ramipril including any effect of prescribed Entresto™ for ramipril patients who discontinued study drug and took Entresto™ as an alternative treatment. Hence, the following supportive analyses aim to estimate the pure treatment effect as though in a situation whereby Entresto™ was not an available treatment option for HFrEF. In this regard, as a sensitivity analysis, inverse probability of censoring weighted (IPCW) Cox proportional hazards model (Robins and Finkelstein 2000) will be performed on the secondary endpoints (1), (3) and (5).

Inverse probability of censoring weighted (IPCW) Cox proportional hazards model

In the IPCW analysis, the following censoring mechanism will be used for the event generating process for secondary endpoints:

- For patients randomized to LCZ696 and patients randomized to ramipril but did not take open label Entresto upon diagnosis of HFrEF event will be censored according to the mechanism described for the secondary endpoints.
- For patients randomized to ramipril who subsequently start taking open label Entresto, (defined as treatment switch), censoring will occur at the minimum of the last date the endpoint status was known, the time of death from non-CV causes, 28 days after study treatment discontinuation or start of open-label Entresto.

To adjust for the potential informative censoring, patients in the ramipril arm with event times censored due to treatment switch will be dynamically replaced in the patient risk-set by remaining uncensored patients in the ramipril arm with a matching prognostic profile by up-weighting such patients in the analysis set. At a specific time, patients in the ramipril arm who have not switched to taking open label Entresto will be assigned a weight inversely proportional to the probability of not switching till that time (i.e., patients who do not switch, but have covariates implying a high probability of switching, get a larger weight in the analysis).

Estimating IPC weights

In order to predict these patient specific time-varying probabilities, the time scale is split into small intervals based on the visit schedules. In each interval the conditional probability of being switched given patient has not switched at any earlier interval is modelled using a logistic regression model with the following covariates–

- **Time independent (baseline) covariates:**
  Age (in years), baseline LVEF, baseline eGFR (ml/min/1.73m^2), history of prior MI (yes/ no), history of diabetes (yes/ no), Atrial Fibrillation associated with qualifying MI (yes/ no), baseline Killip class, use of PCI for qualifying MI (yes/ no), use of ACEI/ARB in last 24 hours prior to randomization (yes/ no), use of IV treatment for qualifying MI (yes/ no)
- **Time dependent covariates:**
  Systolic BP (mmHg), Heart rate (bpm), eGFR (ml/min/1.73m^2), *use of PCI or CABG (yes/ no), *use of ICD/CRT (yes / no)
  (**procedures related to any post-randomization MI event)*

Predicted probability of switching at a specific time for a patient will be obtained by multiplying individual conditional probabilities of switching in intervals prior to that time point. To minimize impact of extreme weights (e.g. patients not switched though having very high estimated probability to switch), the stabilized version of weights will be used which is defined as the ratio of predicted probabilities of not being switched by time t –

- from the logistic regression with only baseline covariates
- from the logistic regression with both baseline and post-baseline covariates

It is conceivable that the above logistic regression procedure of estimating weights may not converge due to reasons including (but not limited to) sparseness of switchers in the subpopulations implied by the selected covariates resulting into an infinite likelihood due to complete or quasi-complete separation or numerical difficulties in evaluating an overly complex likelihood function. Should such problems arise, the logistic regression model used to determine the IPC weights will be simplified by pooling pre-specified time intervals (thereby extending the time windows in which time-dependent covariates are assessed). If that still does not solve convergence problems, the model will be simplified by removing covariates.

All patients randomized to LCZ696 will be assigned a weight of 1 for all time intervals.

Estimation of treatment effect

Following the estimation of weights, a weighted Cox proportional hazard model will be fitted to the time to event endpoints (1), (3) and (5). The model will be stratified by STEMI/NSTEMI while treatment, region, PCI use at baseline will be included as fixed effects factors. The hazard ratio for LCZ696 vs. ramipril, the associated 2-sided 95% confidence interval and the 1-sided and 2-sided p-values will be presented from the analysis.

On-treatment analysis

Endpoint (4), the total number of confirmed hospitalizations for HF, MI and stroke (including CV death) will be redefined for the patients who are prescribed open label Entresto™ as the

total number of composite endpoints from randomization up to 28 days after the time of study treatment discontinuation. The analysis methods will remain the same as specified above.

Sensitivity analysis

If the study is stopped early for efficacy at the second interim analysis, or the study is terminated early by the sponsor due to prolonged COVID-19 impact, a sensitivity analysis using the primary/main analysis model as specified in Section 2.6.2 will be performed for each secondary endpoint, including all data accrued up to the end-of-study analysis cut-off.

If the study is not stopped at the second interim analysis and continues to the end, a sensitivity analysis using the primary/main analysis model as specified in Section 2.6.2 will be performed for each secondary endpoint, including data accrued prior to 01-Mar-2020.

2.6.6 Subgroup analysis

Subgroup analysis for the secondary endpoints (1), (2), (3) and (5) will also be performed similarly as described in Section 2.5.5 for the primary endpoint based on pre-defined subgroups (Section 2.2.1).

For secondary endpoint (4), subgroup analysis will be performed following a similar modeling as used for primary analysis of this endpoint (Section 2.6.2). Specifically, a negative binomial regression with Weibull baseline intensity function will be fitted within each subgroup with randomized treatment, STEMI/NSTEMI, PCI use at baseline and region as factors having fixed effects. P-value for treatment-subgroup interaction will be reported based on the same model but including factors for subgroup and treatment-subgroup interaction fitted to the overall population. Additionally, for descriptive purposes, exposure adjusted incidence rate and 95% CI for the secondary events will be reported by treatment group for each subgroup.

All the subgroup analyses for secondary endpoints will be performed for patients in FAS only.

2.7 Safety analyses

All safety analyses will be carried out for the Safety set (SAF).

2.7.1 Adverse events (AEs)

The following safety data will be collected and reported in this study for the double-blind period:

- all adverse events,
- all serious adverse events,
- adverse events of special interest (angioedema, hyperkalemia, hypotension, renal impairment, cognitive impairment, hepatotoxicity, statin drug-drug interaction , hypersensitivity, anaphylaxis, malignancy, embryo-fetal toxicity/lethality and neonatal/infantile toxicity through exposure from breast milk)
- adverse events leading to a change in dose (down titration), interruption or discontinuation of study drugs
- AEs occurred in the specific treatment phases are described in Table 2-5. AEs/ SAEs occurred during screening and double blind period will be summarized.

Table 2-5 Allocation of AEs

Screening epoch (V1-V101)	Double-blind treatment epoch		Phase AE to be reported in
	Randomization - EOT (V101-EOT)	EOT – EOS (EOT-V199)	
X			Reported by site from informed consent
	X		Report AE in double-blind period
X	X2		Report as two separate AEs: One with onset date X (X) during screening epoch and one with onset date X2 for DB
	X, X2		Report as one AE: One with onset date X during DB
		X	Report AE in post-EOT phase
		X, X2	Report as one AE: One with onset date X after EOT
	X	X2	Report as one AE in summaries for double-blind treatment epoch. For other summaries, report as two separate AEs; One with onset date X before EOT and one with onset date X2 during post-EOT
X indicates onset date of an AE. X2 stands for the same AE but with increased severity			

The number (and proportion) of patients with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary System Organ Class (SOC) and Preferred Term (PT).
- by treatment, primary System Organ Class (SOC), Preferred Term (PT) and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and Preferred Term (PT)

AEs will be summarized according to the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA version used for reporting will be described in the footnote.

Within each reporting phase (Table 2-5), the following rules are applicable.

- If a subject reported more than one adverse event with the same preferred term, the adverse event with the maximum 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 maximum severity at the system organ class level, where applicable.

- Statistical analyses performed for the double-blind period will include all post-randomization AEs up to the end of double-blind period irrespective of whether patient was on or off study drug.

The most common adverse events reported (≥ 2 % 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. Summaries for the double-blind period will be provided for study medication related adverse events, death, serious adverse event, other significant adverse events leading to study discontinuation and adverse events leading to dose adjustment / interruption.

COVID-19 infections will be collected as AEs.

For each reporting period, incidence of AEs will also be listed at a patient level by randomized treatment group including outcome, severity and action taken with the AE.

2.7.1.1 Adverse events of special interest / grouping of AEs

Specific AEs of interest will be summarized separately in addition to the above analysis. These specific AEs of interest are: angioedema (AAC adjudicated), hyperkalemia, hypotension, renal impairment, cognitive impairment, hepatotoxicity, statin drug-drug interaction, anaphylaxis, hypersensitivity, malignancy, embryo-fetal toxicity/lethality and neonatal/infantile toxicity through exposure from breast milk. Besides providing the crude percentages, annualized exposure adjusted incidence rates will also be provided by treatment group.

The search paths for the related preferred terms (PTs), high level group term (HLGT), high level term (HLT), in Standard Medical Queries (SMQs), or NMQ in MedDRA for these risks are stored (or alternatively "summarized") in the latest version of LCZ696 Case Retrieval Strategy.

In addition to above standard analyses, for double blind phase, analysis for time-to-first selected AEs by treatment group will be performed using Kaplan-Meier estimate. The annualized exposure duration adjusted event rates will also be provided.

2.7.2 Deaths

Patients experiencing deaths during the study period will be reported separately for screening epoch and double-blind treatment epoch. Deaths occurring during double-blind treatment epoch will be summarized by actually received treatment group to present number and percentage of patients died by overall and adjudicated reason categories (CV/ non-CV). Separate listings will be provided for patients died during the study period with primary reason of death as confirmed by adjudication committee.

2.7.3 Laboratory data

Each laboratory parameter, evaluations will be summarized by visit and actually received treatment group by presenting summaries (n, mean, standard deviation, median, minimum and maximum) for actual and change from baseline values. The summary will be provided separately for biochemistry and hematology laboratory parameters. Central laboratory data will be used for the summaries.

Shift tables based on the standard ranges for each laboratory parameters will be provided by treatment group at each visit to present incidence of transitions from a baseline high, normal or low laboratory value to a post-baseline high, normal or low value.

The number and percentage of patients with clinically notable laboratory results after baseline will be presented in accordance with Table 2-6.

Table 2-6 Clinically notable laboratory values and vital signs

Hematology	
Hematocrit	>50% increase, >20% decrease
Hemoglobin	>50% increase, >20% decrease
Platelet count	>75% increase, >50% decrease
RBC Count	>50% increase, >20% decrease
WBC count	>50% increase, >50% decrease
Blood chemistry	
Alkaline phosphatase	>100% increase
ALT (SGPT)	>150% increase
AST (SGOT)	>150% increase
BUN	>50% increase
Calcium	>10% increase, >10% decrease
Chloride	>10% increase, >10% decrease
Creatinine	>50% increase
Potassium	>20% increase, >20% decrease
Total bilirubin	>100% increase
Uric acid	>50% increase

Patients with liver enzymes (ALT/AST and CPK) falling within predefined categories of elevations and persistent elevations will be summarized by treatment group in accordance with the Table 2-7 for the double-blind period.

Descriptive summaries will be provided by presenting count and percentage of patients with each type of Liver event in addition to graphical summaries, as applicable.

Table 2-7 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5

	• Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*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 neoplasms
TBL: total bilirubin; ULN: upper limit of normal

2.7.4 Other safety data

2.7.4.1 Vital signs

Sitting systolic blood pressure (SBP), sitting diastolic blood pressure (DBP) and Sitting pulse pressure (PP) will be descriptively summarized by presenting summaries (n, mean, standard deviation, median, minimum, maximum) of actual value and change from baseline values for each scheduled assessment visit and treatment group.

The number and percentage of patients with clinically notable vital signs changes from baseline will be presented. Clinically notable vital sign results are provided in Table 2-8 below.

Table 2-8 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 >=20
	>=180 and increase from baseline >=20
Sitting diastolic blood pressure (mmHg)	<=50 and decrease from baseline >=15
	>=105 and increase from baseline >=15
Pulse (bpm)	<=50 and decrease from baseline >=15
	>=120 and increase from baseline >=15

2.8 Pharmacokinetic endpoints

Not applicable

2.9 PD and PK/PD analyses

Not applicable

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.14 Interim analysis

One interim analysis for efficacy was initially planned. The cut-off time for the first interim analysis was planned to be when about two-thirds of the target number of 708 primary events were reported and adjudication-confirmed. Approximately 472 of adjudication-confirmed primary events (i.e., first CV deaths, HF hospitalizations, or outpatient HF events) were planned; 464 adjudication-confirmed primary events were included. In the first interim analysis, the analysis dataset was comprised of all patients who were randomized before the cutoff date.

A second interim analysis for efficacy will be added in response to the potential impact from the COVID-19 pandemic, allowing the study to stop for overwhelming efficacy for the primary endpoint at one-sided alpha of 0.005. The second efficacy interim analysis will include all patients randomized prior to 01-Mar-2020 and all primary endpoint events that occurred prior to 01-Mar-2020, approximately 80% of the target 708 total primary endpoint events in the PARADISE-MI study. The data collected prior to 01-Mar-2020 are generally considered not impacted by the COVID-19 pandemic at the global level. Accordingly, patients who do not have a primary endpoint event prior to 01-Mar-2020 will be included in the second IA as censored.

Generalized Haybittle-Peto boundaries will be adopted for the interim statistical comparisons between treatments. An alpha of 0.001 (1-sided) was spent at the first interim analysis, and an alpha corresponding to the nominal level of 0.005 (1-sided) will be spent at the second interim analysis for the comparison of the primary endpoint. The rest of alpha (resulting in a nominal 1-sided 0.0244, with the currently specified target number of primary events of 708 and the planned addition of a second interim analysis to include 80% of the target 708 primary events, based on East version 6.4) will be utilized at the final analysis. The alpha to be spent for the final analysis will be updated according to the actual number of primary events included in the second IA and final analysis in case of deviation from the current specification. In the first interim analysis, as designed, the study could be stopped for superior efficacy only when both the primary endpoint and CV death were significant at an alpha level of 0.001 (1-sided). In the second interim analysis, the study may be stopped for superior efficacy when the primary endpoint is significant at the alpha level of 0.005 (1-sided).

If the study is stopped early for superior efficacy at the interim analysis, the secondary endpoints will be tested using the same hierarchical testing procedure as described in Section 2.6.3 for the same level of alpha (i.e. 1-sided alpha of 0.001 if stopped at the first interim analysis, or of 0.005 if stopped at the second interim analysis). If the study continues, then secondary endpoints will be tested at the final analysis using the same 1-sided alpha as the primary endpoint (i.e., 1-sided alpha of 0.0244, which may be updated according to the actual number of primary events included in the second IA and final analysis in case of deviation from the current specification).

In the event that the COVID-19 pandemic continues over a prolonged period of time, the sponsor may consider terminating the study early without performing the second interim analysis. In this case, the final analysis will include all primary endpoint events with onset date prior to 01-Mar-2020. The remaining alpha to be spent at the final analysis will be calculated based on the number of primary events included in the final analysis using the generalized Haybittle-Peto boundaries, and will be specified in the SAP prior to database lock.

Interim analyses are also planned for the monitoring of safety data, and will be performed approximately every 6 months during the course of the study. Such safety analyses do not inflate the type I error for the primary efficacy hypothesis testing and thus no adjustment for multiplicity is required.

Interim analyses will be performed by an independent statistician (at a CRO or academic institution) who will not be involved in the trial conduct. The results will be reviewed by an independent DMC. The trial investigators, Novartis employees and other personnel who are involved in the conduct of the trial and in the analysis of the final trial results, or who have contact with study centers, will remain blinded to the treatment codes and interim analysis results until all monitoring decisions have been made and the database has been locked for final analysis. Full details of the interim analysis plan will be described in the DMC charter.

3 Sample size calculation

The sample size and power calculations described in the entire Section 3 are based on the study design prior to the protocol amendment 4 when only one efficacy interim analysis had been planned. With the planned addition of a second efficacy interim analysis to include 80% of the target 708 primary events (see Section 2.14), there will be a small impact on power for the primary endpoint (approximately 0.1% power loss for the primary endpoint with a second interim analysis, compared to 80% power with only one planned interim analysis).

The study was initially planned to randomize 4,650 patients to LCZ696:ramipril with a 1:1 allocation ratio, with the aim to obtain at least 800 primary endpoint events and at least 633 first CV death or HF hospitalization events. See details in Section 3.1.

Following the planned sample size re-estimation using blinded data, the study has been re-designed to randomize 5,650 patient to LCZ696:ramipril with a 1:1 allocation ratio. This aims to obtain at least 708 confirmed first primary endpoint events and at least 592 first confirmed CV death or HF hospitalization events in this event-driven study. Seven hundred eight primary endpoint events will provide 80% power assuming a true Relative Risk Reduction (RRR) of 19% (i.e. a hazard ratio of 0.81) for LCZ696 vs ramipril with statistical testing at the overall 2.5% 1-sided type I error rate (with strong control of the Family Wise error rate (FWER)). Five hundred

ninety two first CV death or HF hospitalization events will provide 77.5% nominal power assuming a true RRR of 20% (for the ITT analysis) for this double composite endpoint for the same type I error rate. See details in Section 3.2.

3.1 Original sample size planning

A sample size of 4,650 patients, randomized to LCZ696:ramipril using a 1:1 allocation ratio, has been chosen with the aim to obtain at least 800 first primary events and at least 633 CV death or HF hospitalization events in this event-driven study. Eight hundred primary events provide at least 80% power assuming a true Relative Risk Reduction (RRR) of 18% (i.e. a hazard ratio of 0.82) for LCZ696 vs ramipril with statistical testing at the overall 2.5% 1-sided type I error rate (with strong control of the FWER). Six hundred and thirty three CV death or first HF hospitalization events will provide at least 80% nominal power assuming a true RRR of 20% (for the intent-to-treat analysis) for the secondary endpoint for the same type I error rate.

Additional assumptions are described below.

- 0.5% per year lost to follow-up rate
- Recruitment duration of 24 months, with approximately 8 months follow-up anticipated for last randomized patient (i.e. 32 months total study duration) and constant recruitment rate
- One interim analysis is planned to allow for stopping for efficacy, using a Haybittle-Peto boundary, thus 2.49% 1-sided alpha will be available for the final analysis (Section 2.14).
- Cumulative event rates of CV death or HF hospitalization were estimated from selected patients from the VALIANT database (Pfeffer et al, 2003) who were considered to be representative of the target patient population of this study. In the calculation, adjustments were made for expected differences between the sample of patients from VALIANT and the patients likely to be recruited in PARADISE-MI. In particular PCI use is expected to increase (2/3 PCI use vs. 1/3 in VALIANT), and a larger number of NSTEMI patients are expected (60% NSTEMI patients vs. approximately 30% in VALIANT). Following these adjustments, a further 10% reduction in hazard rate for other changes in standard of care was also included. The cumulative event rates for the primary endpoint were based on a further 15% increase in hazard rate in order to account for the third component of outpatient HF (refer to Table 3-1 for the cumulative event rates assumed for the sample size calculation.

Table 3-1 Cumulative event rates assumed for the sample size calculation

Time period following randomization	CV death or HF hospitalization	CV death, HF hospitalization or outpatient HF (assuming 15% increase in hazard rate compared to CV death or HF hospitalization)
0-3 months	9.9%	11.3%
3-6 months	12.3%	14.0%
6-12 months	14.8%	16.8%
12-32 months	19.4%	21.9%

The sample size calculations were carried out using PASS 2008, citation software and applying the Lakatos method (Lakatos, 1988) and confirmed using East version 6.3.

Sample size sensitivity

This is an event driven study and the assumption about the event rates for the primary endpoint is a key driver for the sample size calculation. In this regard there are two main areas of uncertainty:

- The hazard rates calculated from the post-hoc analysis of VALIANT data as described above are thought to reflect the contemporary setting, however, there may have been other changes over time which are difficult to quantify and may decrease the event rates, hence for the final sample size calculation an additional 10% discount of the hazard rate was assumed.
- The hazard rates for the primary endpoint were calculated as 1.15 x the hazard rate for the secondary endpoint of CV death or HF hospitalization (i.e. assuming a 15% increase in hazard will be observed when adjudicated outpatient HF is included in the composite endpoint together with CV death and HF hospitalization). However, there is no adequate information available about the expected event rates of the primary triple composite endpoint.

In order to understand the impact of the uncertainties described above, Table 3-2 provides the sample sizes estimated to achieve at least 800 primary events with different underlying assumptions.

Table 3-2 Total sample size required to achieve 800 primary events for different event rate assumptions

Increase in hazard rate when outpatient HF is included in primary composite endpoint	Discount of event rates for change in SoC		
	0% ↓	**10% ↓ ***	**20% ↓**
20% ↑	4066	4468	4968
15% ↑ *	4224	**4643**	5167
10% ↑	4395	4834	5382

* Assumptions used for protocol specified study design
Number of randomized patients required calculated using East version 6.3

Power for secondary endpoints

Table 3-3 summarizes the nominal power for secondary endpoints which will be included in the statistical testing strategy. A 1-sided alpha of 2.5% has been used for the calculations. All assumptions are based on exploratory analyses performed using VALIANT data (data on file).

Table 3-3 Summary of power to reject secondary hypotheses

Endpoint	Assumption about true treatment effect for LCZ696 vs ramipril for ITT analysis	Assumptions	Nominal power
(1) Time to first CV death or HF hospitalization	20% RRR	Expect 698 events[1]	84%

Endpoint	Assumption about true treatment effect for LCZ696 vs ramipril for ITT analysis	Assumptions	Nominal power
(2) Time to first HF hospitalization or outpatient HF	17% RRR	Expect 536 events[2]	58%
(3) Time to first composite of CV death, non-fatal MI or non-fatal stroke	15% RRR	Expect 680 events[3]	56%
(4) Total number of hospitalizations for HF, MI and stroke related reasons including CV death	17% reduction in rate ratio	Over-dispersion=9; Rate of events on ramipril per year = 0.236[4]	46%

[1]Event rates as per Table 3-1

[2] Cumulative event rates for HF hospitalization of 6.5%, 8.2%, 9.9% and 12.8% were assumed for 0-3m, 3-6m, 6-12m and 12-32m periods respectively. Then event rates were increased by a further 15% to account for outpatient HF.

[3] Cumulative event rates of 8.5%, 10.9%, 14.0% and 18.6% were assumed

[4] For the power calculation the rate was assumed to be constant over time

The number of events were calculated for a sample size of 4,650 patients; 24 months recruitment and 8 months minimum follow-up.

HF = Heart Failure; RRR = Relative Risk Reduction

The power calculations were carried out using East Version 6.3.

Blinded sample size re-estimation

When approximately 1/2 of patients have been randomized and have reached the 3 month time point, the piecewise hazard rates for the primary endpoint and the double composite endpoint (CV death or HF hospitalization) will be estimated based on blinded data.

The piecewise hazard rates estimated from the observed data will be compared to the original assumptions. If there is reason to believe that the original assumptions about event rates may not hold, the sample size will be re-estimated taking into consideration the new information. The duration of the trial and minimum follow-up will also be reconsidered as part of the calculation. This approach will allow flexibility to achieve the required number of events in an acceptable time frame.

3.2 Blinded sample size re-estimation

Sample size re-estimation was planned and performed when approximately 1/2 of patients had been randomized and had reached the 3 month time point. The cumulative event rates and the corresponding piecewise hazard rates for the primary endpoint (first CV death, HF hospitalization or outpatient HF event) and the double composite endpoint (first CV death or HF hospitalization event) were estimated based on blinded data according to the plan. The estimated cumulative event rates based on the available blinded data were sizably lower than the originally assumed event rates for both the primary endpoint and the double composite endpoint (see Table 3-4 and Table 3-5 for the comparisons), which indicates that the original assumptions about the event rates may not hold. Therefore, in order to limit the impact in terms

of a considerable increase in overall trial duration, sample size re-estimation was performed, taking into consideration the new information. The minimum follow-up was also reconsidered in the calculation.

There are two points to be considered in the sample size re-estimation: the estimated lower event rates and a potentially higher hazard reduction in the primary endpoint. As shown in Table 3-4 and Table 3-5, the estimated event rates using blinded data are lower than the originally assumed event rates, for both the primary endpoint (see Table 3-4) and the double composite endpoint (see Table 3-5). An RRR of 19% is assumed for the primary endpoint in place of the original RRR of 18%. This change is based on the newly available efficacy data from the PIONEER-HF (CLCZ696BUS01) study in hospitalized patients with stabilized acute decompensated heart failure, which showed a 46% relative risk reduction (HR 0.54, 95% CI 0.37, 0.79) in patients treated with sacubitril/valsartan for 8 weeks compared to enalapril for an exploratory composite of serious clinical endpoint of death, rehospitalization for heart failure, implantation of a left ventricular assist device, and inclusion on the list of patients eligible for heart transplantation (Velazquez, et al. 2019). The observed risk reduction on the composite endpoint from the PIONEER-HF study was primarily driven by rehospitalization. Given a similar underlined pathophysiological mechanism between HFrEF and post-AMI with left ventricular dysfunction, and also acute setting for both PIONEER-HF and PARADISE-MI studies, this new data indicated that the effect size may have previously been underestimated.

Following the blinded sample size re-estimation, a sample size of 5,650 patients, randomized to LCZ696:ramipril using a 1:1 allocation ratio, has been chosen with the aim to obtain at least 708 first primary endpoint events and at least 592 first CV death or HF hospitalization events in this event-driven study. Seven hundred eight primary endpoint events will provide 80% power assuming a true Relative Risk Reduction (RRR) of 19% (i.e. a hazard ratio of 0.81) for LCZ696 vs ramipril with statistical testing at the overall 2.5% 1-sided type I error rate (with strong control of the FWER). Five hundred ninety two first CV death or HF hospitalization events will provide 77.5% nominal power assuming a true RRR of 20% (for the ITT analysis) for this double composite endpoint for the same type I error rate.

Additional assumptions are described below.

- 0.5% per year lost to follow-up rate (same as the original protocol assumption)
- Recruitment duration of 37 months, and approximately 4 months follow-up for the last randomized patient are assumed (i.e., approximately 41 months for endpoint accrual). Constant recruitment rates are assumed in each of the following time period based on the observed PARADISE-MI study data and projection: (1) 0 to 10 months, with a total of 463 patients randomized by month 10; (2) 10 to 24 months, with approximately a total of 2400 patients randomized by month 24; (3) 24 to 37 months, with 250 patients randomized each month.
- One interim analysis is planned to allow for stopping for efficacy, using a Haybittle-Peto boundary, thus 2.49% 1-sided alpha will be available for the final analysis, see Section 2.14.
- Cumulative event rates for the primary composite endpoint at 3, 6, 12, and 18 months were derived based on Kaplan-Meier estimates using blinded data from all randomized patients in the PARADISE-MI study at the time of sample size re-estimation. Constant

piecewise hazard rates were then derived accordingly for the following time periods: 0 to 3 months, 3 to 6 months, 6 to 12 months, and 12 to 41 months. The hazard rate for the time period of 12 to 41 months was derived through extrapolation of the 18 months cumulative event rate assuming a constant hazard rate during this time period. See Table 3-4 for the cumulative event rates (pooled) based on the originally assumed event rates from Table 3-1, as well as the estimated event rates from the blinded sample size re-estimation.

Table 3-4 Cumulative event rates (pooled) for the primary endpoint (first CV death, HF hospitalization or outpatient HF event)

Time from randomization	Cumulative event rate (original assumption)[2]	Cumulative event rate (estimated using blinded data)
3 months	10.3%	7.2%
6 months	12.8%	8.6%
12 months	15.4%	11.0%
32 months[1]	20.1%	17.5%

[1] 32 months event rates were derived through extrapolation of the 18 months cumulative event rates, assuming constant monthly hazard rates from 12 to 32 months. The 18 months cumulative event rate was estimated to be 13.0% for the primary endpoint (first CV death, HF hospitalization or outpatient HF event).

[2] Cumulative event rates (pooled) were derived according to the original assumption of the control group rates in Table 3-1.

Table 3-5 Cumulative event rates (pooled) for the double composite endpoint (first CV death or HF hospitalization event)

Time from randomization	Cumulative event rate (original assumption)[2]	Cumulative event rate (estimated using blinded data)
3 months	9.0%	6.0%
6 months	11.1%	7.5%
12 months	13.4%	9.6%
32 months[1]	17.6%	13.9%

[1] 32 months event rates were derived through extrapolation of the 18 months cumulative event rates, assuming constant monthly hazard rates from 12 to 32 months. The 18 months cumulative event rate was estimated to be 10.9% for the double composite endpoint (first CV death or HF hospitalization event).

[2] Cumulative event rates (pooled) were derived according to the original assumption of the control group rates from Table 3-1.

The sample size calculations were carried out using East version 6.4.

Power for secondary endpoints

Table 3-6 summarizes the nominal power for secondary endpoints which will be included in the statistical testing strategy. A 1-sided alpha of 2.5% has been used for the calculations. All assumptions are based on the sample size re-estimation using blinded data.

Table 3-6 Summary of power to reject secondary endpoints' null hypotheses

Endpoint	Assumption about true treatment effect for LCZ696 vs ramipril for ITT analysis	Assumptions	Nominal power
(1) Time to first CV death or HF hospitalization	20% RRR	Expect 592 events[1]	77.5%
(2) Time to first HF hospitalization or outpatient HF	17% RRR	Expect 566 events[2]	60.1%
(3) Time to first composite of CV death, non-fatal MI or non-fatal stroke	15% RRR	Expect 594 events[3]	50.8%
(4) Total number of hospitalizations for HF, MI and stroke related reasons including CV death	17% reduction in rate ratio	Over-dispersion=6; Rate of events per year (pooled) = 0.192[4]	55.1%

[1] Event rates as per Table 3-5, estimated using blinded data

[2] Cumulative event rates (pooled) for the composite endpoint (first HF hospitalization or outpatient HF event) at 3, 6, 12, and 18 months were estimated to be 5.4%, 6.6%, 8.3% and 10.3%, respectively. Constant piecewise hazard rates were derived accordingly for the following time periods: 0 to 3 months, 3 to 6 months, 6 to 12 months, and 12 to 41 months. The hazard rate for the time period of 12 to 41 months was derived through extrapolation of the 18 months cumulative event rate.

[3] Cumulative event rates (pooled) for the composite endpoint (first CV death, non-fatal MI or non-fatal stroke event) at 3, 6, 12, and 18 months were estimated to be 4.6%, 6.0%, 8.7% and 11.0%, respectively. Constant piecewise hazard rates were derived accordingly for the following time periods: 0 to 3 months, 3 to 6 months, 6 to 12 months, and 12 to 41 months. The hazard rate for the time period of 12 to 41 months was derived through extrapolation of the 18 months cumulative event rate.

[4] For the power calculation the rate was assumed to be constant over time

The number of events were calculated for a sample size of 5,650 patients; 37 months recruitment and approximately 4 months minimum follow-up.

HF = Heart Failure; RRR = Relative Risk Reduction

The power calculations were carried out using East Version 6.4.

4 Change to protocol specified analyses

Not applicable

5 Appendix

5.1 Imputation rules

5.1.1 Missing or partially missing AE or concomitant medication start/end date

The partially missing AE start/end date and concomitant medication start/end date will be imputed using the Novartis ADaM Governance Board (AGB) global standard approach. Details will be provided in the study Programming Datasets Specifications.

5.1.2 Missing visit date

In any analysis or evaluation, if the visit date(s) is used but is missing, then the date(s) calculated based on the planned date(s) in the schedule specified in the protocol should be used to impute the missing date(s).

5.1.3 Missing or partially missing event date

If the date of an event is not known or is incomplete, the imputation rules are:
1) If the day of the event is unknown, then the 15th day of this month will be imputed for a missing day;
2) If only the month is unknown, then July will be used for imputation of the missing;
3) If only the year of the event is known, then the 1st of July will be imputed for a missing day and month;
4) If the event date is completely missing, the last visit date (for non-fatal endpoint, an endpoint with non-fatal event as a component, or recurrent endpoints) or the last known alive date (for fatal endpoint) will be used to impute the event date;
5) 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.

5.1.4 Missing medication stop date

If medication stop date is unknown or is incomplete, the imputation rules are:
1) If only the day field of the drug stop is missing, then the missing date is imputed by using the 15th of the month;
2) If year and month are missing, then use the next scheduled visit date (using the protocol specified visit schedule) from the previous last non-missing visit date to replace the missing drug stop date;
3) If the drug stop date is completely missing, then:
   a. If patient had fatal AEs (identified as either start or end date is equal to the date of death and the AE is flagged as an SAE), handling rules are (in the specified order):
      i. AE end date is not missing: use the AE end date to replace the missing drug stop date;
      ii. AE end date is completely missing but AE onset date not missing: use the AE onset date to replace the missing drug stop date;
      iii. AE end date is partially missing (only day field is missing): use Novartis

standard procedure to impute the AE end date, and then use the imputed AE end date to replace the missing drug stop date;
iv. AE end date is completely missing and AE onset date is partial missing (missing the date field only): impute the AE onset date using Novartis standard procedure, and then use the imputed AE onset date to replace the missing drug stop date;
v. If both AE onset and end dates are completely missing, then use the last previous non-missing visit date plus 35 days to replace the missing drug stop date.

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

5.2 Statistical models

5.2.1 Primary analysis

See Section 2.5.2.

5.2.2 Key secondary analysis

Not applicable.

5.3 Rule of exclusion criteria of analysis sets

Following tables present a sample of the rules for subject classification in the analysis sets based on protocol deviation specifications (Table 5-1) and non-protocol deviation classification criteria (Table 5-2). The PDs leading to exclusion of patients from analysis sets may be updated prospectively and will be finalized before DB lock.

Table 5-1 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses
INCL04	Index MI event secondary to other medical conditions such as anemia, hypotension, or an arrhythmia OR thought to be caused by coronary vasospasm with documented normal coronary arteries	Excluded from PP analysis
INCL05	Index MI is non-spontaneous MI	Excluded from PP analysis
INCL06	LVEF >40% after index MI presentation or prior to randomization without symptoms of pulmonary congestion	Excluded from PP analysis
INCL07	Subject with no risk factors	Excluded from PP analysis
INCL08	SBP less than 100 mmHg at randomization for patients who received ACE inhibitor/ARB during the 24 hours prior to randomization.	Excluded from PP analysis
INCL09	SBP less than 110 mmHg at randomization for patients who did not receive ACE inhibitor/ARB during the 24 hours prior to randomization.	Excluded from PP analysis

Deviation ID	Description of Deviation	Exclusion in Analyses
INCL10	Use of intravenous treatment with diuretics, vasodilators, vasopressors and/or inotropes during the 24 hours prior to randomization.	Excluded from PP analysis
INCL11	Time from presentation to randomization < 12 hours or > 7 days	Excluded from PP analysis
EXCL01	Known history of chronic HF at randomization	Excluded from PP analysis
EXCL03	Persistent clinical HF at the time of randomization	Excluded from PP analysis
EXCL05	Clinically significant right ventricular MI as index MI	Excluded from PP analysis
EXCL15	Previous use of LCZ696 or Entresto™	Excluded from PP analysis
OTH04	Patients were misrandomized	Excluded from primary and PP analysis
OTH01	Blinding broken locally	Excluded from PP analysis
OTH02	Subject was classified into incorrect stratum	Excluded from PP analysis
OTH03	Major GCP violation at site.	Excluded from primary and PP analysis

Table 5-2 Subject classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
SCR	NA	No written informed consent
RAN	NA	Not in SCR; Not randomized
FAS	OTH03, OTH04	Not in RAN;
PPS	INCL04, INCL05, INCL06, INCL07, INCL08, INCL09, INCL10, INCL11, EXCL01, EXCL03, EXCL05, EXCL15, OTH01, OTH02, OTH03, OTH04	Not in FAS;
SAF	NA	No double-blind study drug taken

5.4 SAS code for Bayesian sensitivity analysis

```
/* define input data:
log(HR_pre), HR_pre assumed 0.81;
sepre2 = 4/540
post-COVID, HR_post assumed 1.00;
sepost2 = 4/184
i.e. total number of events assumed to be 724, pre-Covid number of events
assumed to be 540 */
data dat;
input y se2; datalines;
-0.210721 0.007407407
;
```

```
* call proc MCMC with pre-defined mixture prior;
proc mcmc data=dat outpost=postout seed=23 nmc=5000000 ntu=10000 thin = 10
nbi=100000 statistics=(summary interval) diagnostics=none;
ods exclude nobs parameters;
array p[2] (0.5 0.5);
array m[2] (0 0);
array sd[2] (0.147442 2);
parm z loghr;
prior z ~ table(p);
prior loghr ~ normal(m[z], sd=sd[z]);
model y ~ n(loghr, var=se2);
run;

* obtain summary of hazard ratio (posterior);
* including mean, median, 95% interval;
data postout;
  set postout;
  hr = exp(loghr);
run;

proc means data=postout n mean std median;
run;

proc stdize data=postout pctlmtd=ord_stat outstat=pctls
           pctlpts=2.5,97.5;
var hr loghr;
run;

* obtain summary of posterior weights;
proc freq data=postout;
tables z / out=FreqCount;
title 'Posterior mixture weights';
run;

* obtain probability that loghr < 0 (i.e. HR < 1);
data postout2;
set postout;
suc = loghr < 0;
run;
proc means data=postout2 n mean;
run;
```

6 Reference

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Summary of all amendments to the SAP:

Date	Amendment	Summary
19-OCT-2020	Amendment 1 prior to database lock (DBL)	Update introduction for this SAP: Section 1 - Introduction first and second paragraphs have been updated. Change in study design as per study protocol up to v04: Section 1.1, 2.1, 2.14, 3 - Updated text about the study duration, sample size (including sample size re-estimation in protocol v03), and interim analyses change as per study protocol v04 [redacted] [redacted] Clarification for the definitions of non-fatal spontaneous MI and non-fatal stroke: Section 1.2 - Added clarification for non-fatal spontaneous MI/stroke definition in the Table 1-2 footnote [redacted] Clarification for the grouping of stratification factor type of MI: Section 2.1 - Added text for clarification of the grouping of “NSTEMI” type of MI Additional analyses due to mis-stratification: Section 2.1 - Added analyses for mis-stratification by type of MI/region Clarification for censoring methods for time-to-event variables: Section 2.1, 2.5.3, 2.6.1 - Added/modified censoring methods for time-to-event endpoints with a structure for more clarity Changes as per study protocol v04 for COVID-19 impact: Section 2.1, 2.3.1, 2.5, 2.5.4, 2.6, 2.6.5, 2.10, 2.11, 2.13 - Added additional analyses for potential COVID-19 impact Clarification of baseline definition: Section 2.1.1 - Updated baseline definition Adding rules for unscheduled visit: Section 2.1.1 - Added rules for use of unscheduled visit Change as per study protocol v02: Section 2.2 - Text added about the exclusion of subjects without a valid informed consent from all analyses sets

		Update of the derivation of subgroups due to refinement / feasibility / scientific reasons: Section 2.2.1 - Updated Table 2-1 definition and derivation of subgroups; Updated Table 2-1 footnote for region classification to align with the LCZ project standard; Added subgroup of number of CV risk factors in Table 2-1 Update of CV medication classification: Section 2.4.2 - Updated the classification of CV medications Clarification for hierarchical testing procedure: Section 2.6.3 - Clarified that the components of the primary endpoint are not part of the testing procedure Adding an endpoint in the IPCW analysis: Section 2.6.5 - Added an endpoint ((2) time-to-first event of CV death or HF hospitalization) in the IPCW analysis Update AE summaries: Section 2.7.1 - Summaries of AEs have been updated Update AEs of special interest terms: Section 2.7.1 - Updated AEs of special interest terms Update RAAS blockade summaries: Section 2.4.2 - Summaries of RAAS blockade and open-label Entresto have been updated Clarification of central lab data use: Section 2.7.3 - Clarified that central lab data will be used for the summary of lab results Adding abnormal criteria for vital signs: Section 2.7.4 - Added abnormal criteria for vital signs Update renal injury endpoint as per study protocol v03: Section 2.13.1 - Clarified the definition of renal injury endpoints as measured by serum creatinine change from baseline Adding imputation rules for dates: Section 2.1, 5.1 - Updated imputation rules for various types of missing or partially missing dates Update of PD or non-PD criteria for exclusion from analysis sets: Section 5.3 - Updated the text and code for the PDs leading to exclusion from analysis sets in Table 5-1; Updated the text for non-PDs in Table 5-2
18 March 2021	Amendment 2 prior to database lock (DBL)	Adding definition for initiation or intensification of antihyperglycemic medications per protocol requirement before DBL: Sections 1.2, 2.13.1 - Added the definition of initiation or intensification of antihyperglycemic medications Removing alternative definition of renal composite endpoint (not specified in protocol): Sections 1.2, 2.13.1 - Deleted the alternative definition of renal composite endpoint [redacted]

		endpoints days alive out of HF hospitalization through month 6, month 12 and through end of study (EOS) Adding number of CV risk factors Summary: Section 2.3.2.1 - Added number of CV risk factors to the summary of CV risk factors Clarification of definition for time to treatment discontinuation analysis: Section 2.4.1 - Update the text for “time to permanent discontinuation of study medication not due to death” Update of study exposure summary: Section 2.4.1 - Updated study exposure summary Clarification of definition of CV death endpoint: Section 2.5.1 - Added text for the CV death endpoint definition Analysis cut-off date: Sections 2.1, 2.5.3, 2.6, 2.13 Adding supportive analyses for primary endpoint: Section 2.5.4 - Added alternative definitions for primary endpoint as supportive Analyses Adding a sensitivity analysis for primary endpoint: Sections 2.5.4, 5.4, 6 - Added a Bayesian sensitivity analysis with robust prior to combine potentially COVID-19 affected results with pre- COVID-19 results Removing an endpoint from the IPCW analysis to align with protocol: Section 2.6.5 - Removed the composite endpoint of HF hospitalization or outpatient HF from the IPCW analysis Update of AE summaries for clarity: Updated text for AE summaries Section 2.7.1 Update of AEs of special interest risk names: Section 2.7.1, 2.7.1.1 - Updated the risk names of AEs of special interest [redacted] [redacted] [redacted] Added missing date handling for endpoint event with completely missing date: Section 5.1.3 - Added the data handling method for event with completely missing event date