NOVARTIS

Global Clinical Development - General Medicine

[LCZ696]

Clinical Trial Protocol LCZ696G2301 / NCT02924727

PARADISE-MI: Prospective ARNI versus ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction

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

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List of abbreviations

ACE	Angiotensin converting enzyme
ACEi	Angiotensin converting enzyme inhibitor
AE	Adverse Event
AESI	Adverse event of special interest
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
AST	Aspartate aminotransferase
AUC	Area under the curve
BB	Beta blocker
bid	twice a day
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CCB	Calcium channel blocker
CCU	Coronary/critical care unit
CEC	Clinical Event Committee
CFR	US Code of Federal Regulations
CDS	Core Data Sheet (for marketed drugs)
CEC	Clinical Event Committee
CHF	Chronic heart failure
COPD	Chronic obstructive pulmonary disease
CPO	Country Pharma Organization
CRF	Case Report/Record Form
eCRF	Electronic Case Report/Record Form
CRT	Cardiac resynchronization therapy
CRO	Contract Research Organization
CSR	Clinical study report
CTC	Common Terminology Criteria
CTRD	Clinical Trial Results Database
CV	Cardiovascular
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DMC	Data Monitoring Committee

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DS&E	Drug Safety & Epidemiology
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EOS	End of study
ER	Emergency room
ESRD	End stage renal disease
FAS	Full analysis set
FDA	Food and Drug Administration
FWER	FamilyWise Error Rate
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
Hgb	Hemoglobin
hsTnT	High-sensitivity troponin T
HTN	Hypertension
IA	Interim analysis
IB	Investigator brochure
ICD	Implantable cardioverter defibrillator
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive care unit
IEC	Independent Ethics Committee
IN	Investigator notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to treat
IUD	Intrauterine device
IUS	Intrauterine system
iv	Intravenous
LFT	Liver function test
LV	Left ventricular
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
MACE	Major Adverse Cardiac Events
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume

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MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
MMRM	Mixed model of repeated measurements
MRA	Mineralocorticoid antagonist
NEP	Neprilysin
NEPi	Neprilysin inhibitor
NSTEMI	Non-ST-elevation myocardial infarction
NT-proBNP	N-terminal pro-brain natriuretic peptide
OC/RDC	Oracle Clinical/Remote Data Capture
od	once a day
PCI	Percutaneous coronary intervention
PDE-5	Phosphodiesterase-5
po	oral(ly)
PRO	Patient reported outcomes
PT	Preferred term
[redacted]	[redacted]
RAS	Renin angiotensin system
RBC	Red blood cell
RDW	Red blood cell distribution width
RRR	Relative risk reduction
[redacted]	[redacted]
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SMQ	Standardized MedDRA Query
STEMI	ST-elevation myocardial infarction
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total bilirubin
TD	Study Treatment Discontinuation
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization
WoC	Withdrawal of Consent

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Glossary of terms

Cohort	A specific group of patients fulfilling certain criteria
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug(s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

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Protocol summary

Protocol number	LCZ696G2301
Title	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
Brief title	PARADISE-MI: Prospective ARNI versus ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction
Sponsor and Clinical Phase	Novartis; Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the efficacy and safety of LCZ696 compared to ramipril, in reducing the occurrence of cardiovascular (CV) death, heart failure (HF) hospitalization and outpatient HF (time-to-first event analysis) in post-AMI patients with evidence of left ventricular (LV) systolic dysfunction and/or pulmonary congestion, without a known prior history of chronic HF. This is an event-driven study which is a well-established study design for long-term cardiovascular outcome trials in post-acute myocardial infarction (AMI) patients. While the composite of CV death or HF hospitalization is a well-established mortality and morbidity endpoint, the addition of the outpatient HF component, which in this study represents the confirmed diagnosis of new onset symptomatic HF, aims to capture the clinically important outpatient event that contributes to the totality of HF morbidity following an AMI presenting as either inpatient (i.e., HF hospitalization) or outpatient (i.e., outpatient HF) events. Ramipril is chosen as an active comparator of the study representing the guideline-recommended standard-of-care angiotensin converting enzyme (ACE) inhibitors shown to improve survival and reduce HF morbidity in high-risk post-AMI patients.
Primary Objective(s)	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 outpatient HF endpoint event is defined as an adjudicated event of clinical development of symptomatic HF (either urgent/unscheduled or non-urgent) in the outpatient setting with symptoms and signs requiring initiation/intensification of intravenous or qualifying oral HF treatment.)
Secondary Objectives	• To demonstrate the superiority of LCZ696, compared to ramipril, in delaying the time-to-first occurrence of CV death or HF hospitalization • To demonstrate the superiority of LCZ696, compared to ramipril, in delaying the new onset of symptomatic HF defined as time-to-first occurrence of HF hospitalization or outpatient HF • To demonstrate the superiority of LCZ696, compared to ramipril, in delaying the time-to-first occurrence of CV death, non-fatal spontaneous MI or non-fatal stroke

	• 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 or non-fatal stroke • To demonstrate the superiority of LCZ696, compared to ramipril, in delaying the time to all-cause mortality • To evaluate the safety and tolerability of LCZ696 compared to ramipril
Study design	This study 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 over a period of approximately 32 months. The study is event-driven and will continue until the requirement of total confirmed endpoint events, i.e., 800 primary composite endpoint events and 633 CV death or HF hospitalization events, has been achieved.
Population	Approximately 4,650 male and female high risk patients ≥ 18 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 have to have at least one predefined risk factor and without known prior history of chronic HF.
Key Inclusion criteria	1. Written informed consent must be obtained before any assessment is performed. 2. Male or female patients ≥ 18 years of age. 3. Diagnosis of spontaneous AMI based on the universal myocardial infarction (MI) definition* with randomization to occur between 12 hours and 7 days after index event presentation**. Spontaneous AMI is defined when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia due to primary coronary event. Under these conditions, the following criteria have to be met for the diagnosis of spontaneous AMI: • Detection of rise and/or fall of cardiac enzymes (cardiac troponin, cTn or the MB fraction of creatinine kinase, CKMB) with at least one value above the 99th percentile of the upper reference limit (URL) or the local laboratory MI diagnosis cut-off value, together with evidence of myocardial ischemia with at least one of the following: • Ischemic discomfort or other ischemia symptom(s) • Electrocardiogram (ECG) characteristics of STEMI or NSTEMI including new or presumably new significant ST-segment-T wave (ST-T) changes • Newly developed pathological Q waves or left bundle branch block (LBBB) in the ECG (*Patients with a spontaneous MI event determined to be secondary to another medical condition such as anemia, hypotension, or an arrhythmia OR thought to be caused by coronary vasospasm with documented normal coronary arteries are not eligible) 4. Evidence of LV systolic dysfunction and/or pulmonary congestion requiring intravenous treatment associated with the index MI event defined as:

	• Left ventricular ejection fraction (LVEF) ≤ 40% assessed locally by echocardiography, magnetic resonance imaging, cardiac CT, radionuclide or contrast ventriculography after index MI presentation** and prior to randomization. (These examinations may be performed as part of patient standard-of-care. In case multiple LVEF measurements have been performed during index event, the last one performed prior to randomization should be considered as the qualifying measurement), and/or • Pulmonary congestion requiring intravenous treatment during the index hospitalization supported by clinical assessment (worst Killip class, II or above) or radiological findings. Radiological evidence of pulmonary congestion is defined as pulmonary venous congestion with interstitial or alveolar edema and must be supported by at least one chest X-ray or CT scan. (***Index MI presentation is the time of patient presentation at either the ER/ED, ICU/CCU or hospital ward etc., at study center, for the treatment of the index MI.)* 5. At least one of the following 8 risk factors: • Age ≥ 70 years • eGFR <60 mL/min/1.73 m^2 based on Modification of Diet in Renal Disease (MDRD) formula at screening visit • Type I or II diabetes mellitus • Documented history of prior MI supported by ECG changes and/or elevation of cardiac enzymes consistent with MI diagnosis. • Atrial fibrillation as noted by ECG, associated with index MI • LVEF < 30% associated with index MI • Worst Killip class III or IV associated with index MI requiring intravenous treatment • STEMI without reperfusion therapy within the first 24 hours after presentation 6. Hemodynamically stable defined as: • Systolic blood pressure (SBP) ≥ 100 mmHg at randomization for patients who received ACE inhibitor/angiotensin receptor blocker (ARB) during the last 24 hours prior to randomization (ACE inhibitor/ARB Yes patients) • SBP ≥ 110 mmHg at randomization for patients who did not receive ACE inhibitor/ARB during the last 24 hours prior to randomization (ACE inhibitor/ARB No patients) • No intravenous treatment with diuretics, vasodilators, vasopressors and/or inotropes during the last 24 hours prior to randomization.
Key Exclusion criteria	1. Known history of chronic HF prior to randomization 2. Cardiogenic shock within the last 24 hours prior to randomization 3. Persistent clinical HF at the time of randomization 4. Coronary artery bypass graft (CABG) performed or planned for index MI 5. Clinically significant right ventricular MI as index MI 6. Symptomatic hypotension at screening or randomization 7. Patients with a known history of angioedema 8. Stroke or transient ischemic attack within one month prior to

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	randomization 9. Known or suspected bilateral renal artery stenosis 10. Clinically significant obstructive cardiomyopathy 11. Open-heart surgery performed within one month prior to randomization or planned cardiac surgery within the 3 months after randomization 12. eGFR < 30 ml/min/1.73 m^2 as measured by the Modification of Diet in Renal Disease (MDRD) formula at screening 13. Serum potassium > 5.2 mmol /L at screening 14. Known hepatic impairment (as evidenced by total bilirubin > 3.0 mg/dL or increased ammonia levels, if performed), or history of cirrhosis with evidence of portal hypertension such as varices 15. Previous use of LCZ696 or Entresto™ 16. Use of other investigational drugs within 30 days prior to screening 17. History of hypersensitivity to the study drugs or drugs of similar chemical classes 18. Known intolerance or contraindications to study drugs or drugs of similar chemical classes including ACE inhibitors, ARB or NEP inhibitors 19. Patients taking medications prohibited by the protocol that cannot be discontinued for the duration of the study 20. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin) within the past 3 years with a life expectancy of less than 1 year 21. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or extraction of study drug at investigators' discretion 22. History or evidence of drug or alcohol abuse within the last 12 months 23. Patients considered unsuitable for the study, including patients with psychiatric, behavioral or cognitive disorders, sufficient to interfere with the patient's ability to understand and comply with the protocol instructions or follow-up procedures 24. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test 25. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of investigational drug
Study treatment	<u>LCZ696*</u> 50 mg (dose level 1), 100 mg (dose level 2) and 200 mg (dose level 3) twice daily (** LCZ696 dose levels 1, 2 and 3 are equivalent to sacubitril/valsartan 24/26 mg, 49/51 mg and 97/103 mg, respectively*) <u>Ramipril</u> 1.25 mg (dose level 1), 2.5 mg (dose level 2), and 5 mg (dose level 3) twice daily <u>Valsartan (VAL489)**</u> 40 mg (dose level V1) and 80 mg (dose level V2) twice daily for one day (*** Patients who are randomized to LCZ696 and received ACE inhibitors in last 36 hours prior to randomization will be given a valsartan bridging in a*

	blinded manner for one day with two doses at dose level V1 or V2: 40 or 80 mg twice daily, prior to beginning the double-blind LCZ696 treatment)
Efficacy assessments	• CV death, • Heart failure hospitalization • Outpatient heart failure • Non-fatal spontaneous MI • Non-fatal stroke • All-cause mortality
Key safety assessments	• All adverse events (AE)s for the first two weeks • All suspected AEs • AEs of special interest (Section 7.1) • AEs leading to a change in dose (down titration) or discontinuation of study medication • All serious adverse events (SAEs) • Sitting systolic blood pressure (SBP), sitting diastolic blood pressure (DBP), and heart rate • Laboratory values (including monitoring for hyperkalemia, renal dysfunction) • Angioedema surveillance
Other assessments	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted]
Data analysis	The primary efficacy variable is time to first occurrence of CV death, HF hospitalization or outpatient HF. The secondary efficacy variables are: • Time to first occurrence of CV death or HF hospitalization • Time to first occurrence of HF hospitalization or outpatient HF (censoring will occur at the time of all-cause death) • Time to first occurrence of CV death, non-fatal spontaneous MI or non-fatal stroke • Cumulative number of events, including HF hospitalization, hospitalization due to non-fatal spontaneous MI, hospitalization due to non-fatal stroke and CV death. • Time to all-cause mortality

[redacted]

	Time-to-event is computed as the number of days from randomization to the start date of the endpoint event (first occurrence). The 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. 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 primary endpoint and the first four secondary endpoints will be included in a hierarchical statistical testing strategy to control the familywise type I error rate at the 1-sided 2.5% level (in the strong sense). One interim analysis for efficacy is planned when approximately two-thirds of the target number of primary adjudicated events has been obtained. 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 this secondary endpoint for the same type I error rate. These calculations assume a 24 month recruitment period and 8 month follow-up of the last randomized patient.
Key words	Spontaneous AMI, HF hospitalization, outpatient HF, LV systolic dysfunction, pulmonary congestion, STEMI, NSTEMI, randomized clinical trial, LCZ696, ramipril

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1 Introduction

1.1 Background

Acute myocardial infarction (AMI) is one of the common reasons for cardiac hospitalization and its annual incidence in US, EU-5, Japan and China is currently estimated at 2.5 million per year. In the US alone, approximately 683,000 patients were discharged from hospitals in 2009 with a diagnosis of acute coronary syndrome (O'Gara, et al 2013). Although the community incidence rates for ST elevation myocardial infarction (STEMI) have declined over the past decade, those for non-ST-elevation myocardial infarction (NSTEMI) have increased. The overall incidence rate of AMI is expected to continuously increase in the next decades due to an ageing population and global rise in diabetes (Mozaffarian, et al 2015).

The in-hospital mortality of post-AMI patients has decreased in several parts of the world as a result of more frequent use of reperfusion strategies. Due to increasing numbers of post-AMI survivors, the prevalence of developing heart failure (HF), a frequent complication following an AMI, has increased worldwide (Jhund and McMurray 2009; Sulo, et al 2016). For example, of 63,853 patients discharged alive from their first AMI without a diagnosis of HF during 2001-2009 in The Cardiovascular Disease in Norway Registry (CVDNOR), 12.6% of patients developed HF during a median follow-up time of 3.2 years and nearly half of these cases occurred within 1 year from the index myocardial infarction (MI) discharge (Sulo, et al 2016). In addition, high-risk patients with left ventricular ejection fraction (LVEF) $\leq$ 40% following an AMI representing approximately 1/4 to 1/3 of the overall post-AMI patient population, are known to have significantly greater risk of HF morbidity and mortality (Miller, et al 2012; van Diepen, et al 2015; Vasaiwala, et al 2012). In the VALIANT study of high-risk post-AMI patients (LVEF $\leq$ 40% and/or transient HF signs with no prior history of chronic HF) who received percutaneous coronary intervention (PCI), approximately 20% of these patients experienced cardiovascular (CV) death or HF hospitalization over the approximate 2-year follow-up period (Pfeffer, et al 2003; Novartis data analyses on file). These real-world registry and controlled clinical trial data underscore the need for additional therapeutic approaches to reduce HF-related morbidity and mortality in post-AMI patients.

There are several mechanisms contributing to an unfavorable long-term prognosis in post-AMI patients. The most notable mechanism underlying the significantly greater risk of HF morbidity events following an AMI is pathological cardiac remodeling resulting from the loss of myocardium and maladaptive changes in the surviving myocardium. This remodeling process with changes in left ventricular (LV) geometry, size, and function is induced by altered myocardial loading conditions and dysregulated neurohumoral system (Pfeffer and Braunwald, et al 1990; Udelson and Konstam, et al 2002; White, et al 1987).

Factors triggering cardiac remodeling are activated within hours after an AMI. As supported by multiple clinical outcome studies conducted in the 1990s, early inhibition of the Renin Angiotensin System (RAS) with angiotensin converting enzyme (ACE) inhibitors has shown to reverse pathological remodeling, improve survival, and reduce HF hospitalization in post-AMI patients with LV systolic dysfunction and/or HF (AIRE Study Investigators, 1993; GISSI-12 Study Investigators, 1994; ISIS-12 Collaborative Group 1995; Kober, et al 1995;

Pfeffer et al 1992). As a consequence, guidelines recommend early initiation of ACE inhibitors after an AMI in patients with LV systolic dysfunction and/or HF for indefinite use (*IA* recommendation) (Anderson, et al 2007; Antman, et al 2008; Roffi, et al 2015; Steg, et al 2012). Despite this progress and a number of other evidence-based pharmacotherapies (β blockers, mineralocorticoid antagonists, etc.), the prognosis of high risk post-AMI patients with LV dysfunction and/or HF remains poor. Novel preventive strategies to reduce the risk for CV mortality and the clinical development of HF are clearly warranted.

Several lines of evidence have suggested that increasing natriuretic peptides in addition to RAS inhibition in post-AMI patients may offer greater benefits over the RAS inhibition alone. The potential mechanisms may include but are not limited to the anti-hypertrophic, anti-fibrotic, anti-ischemic, anti-inflammatory and sympatholytic effects of natriuretic peptides (Braunwald, 2015; D'Souza, et al 2004; Molkentin, 2003). In a small study of 24 anterior wall STEMI patients, the recombinant form of human BNP, nesiritide, given early after index MI presentation for 72 hours was well tolerated and associated with improved LVEF and reduced ventricular remodeling (i.e., smaller LV end-systolic volume) after 1 month (Chen, et al, 2009). A larger clinical study in Japanese STEMI patients (N=569) demonstrated that intravenous administration of atrial natriuretic peptide for 3 days after reperfusion treatment reduced infarct size and improved LVEF at 6-12 months (Kitakaze, et al 2007).

Entresto™ (sacubitril/valsartan, LCZ696) is a combination of neprilysin inhibitor and angiotensin II type 1 receptor blocker, providing concomitant neprilysin inhibition and angiotensin type 1 receptor blockade. Upon oral administration, LCZ696 delivers systemic exposure of sacubitril, a neprilysin inhibitor prodrug, and valsartan, an angiotensin receptor blocker (ARB). Sacubitril is then further metabolized by esterases to the active metabolite, sacubitrilat (LBQ657), which inhibits the degradation of natriuretic peptides and therefore enhances the effects of their biological activity. The efficacy and safety of LCZ696 titrated to a target dose of 200 mg twice daily in chronic HF patients with reduced ejection fraction (HFrEF) (LVEF ≤40%) was evaluated in the PARADIGM-HF study (N=8,442) and demonstrated that LCZ696 significantly reduced the primary composite endpoint of CV death or HF hospitalization by 20%, as compared to enalapril (McMurray, et al 2014).

Given these positive results for the use of LCZ696 in the HFrEF patient population, and the improvement in LVEF, reduction in infarct size and ventricular remodeling observed in the STEMI patient population all of which suggest that increasing natriuretic peptides in addition to RAS inhibition may offer greater benefit in the post-AMI patient population, we hypothesize that early and sustained treatment with LCZ696 in high-risk patients with LV systolic dysfunction and/or pulmonary congestion following an AMI with no known prior history of chronic HF will be superior to the guideline recommended first-line treatment with ACE inhibitor as measured by a reduction in the composite endpoint of CV death, HF hospitalization or outpatient HF.

1.2 Purpose

The purpose of this study is to evaluate the efficacy and safety of LCZ696 titrated to a target dose of 200 mg twice daily, compared to ramipril titrated to a target dose of 5 mg twice daily, in addition to conventional post-AMI treatment, in reducing the occurrence of composite endpoint of CV death, HF hospitalization and outpatient HF (time-to-first event analysis) in

[redacted]

post-AMI patients with evidence of LV systolic dysfunction and/or pulmonary congestion, with no known prior history of chronic HF.

2 Study objectives and endpoints

2.1 Primary objective(s)

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 outpatient HF endpoint event is defined as an adjudicated event of clinical development of symptomatic HF (either urgent/unscheduled or non-urgent) in the outpatient setting with symptoms and signs requiring initiation/intensification of intravenous or qualifying oral HF treatment. See Section 6.4.1 for full definition)

2.2 Secondary objective(s)

- To demonstrate the superiority of LCZ696, compared to ramipril, in delaying the time-to-first occurrence of CV death or HF hospitalization
- 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
- To demonstrate the superiority of LCZ696 compared to ramipril, in delaying the time-to-first occurrence of CV death, non-fatal spontaneous MI or non-fatal stroke
- 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 or non-fatal stroke
- To demonstrate the superiority of LCZ696, compared to ramipril, in delaying the time to all-cause mortality
- To evaluate the safety and tolerability of LCZ696 compared to ramipril

(All secondary efficacy hypotheses except all-cause mortality will be included in a statistical testing strategy to control the familywise type I error rate) (Section 9.5)

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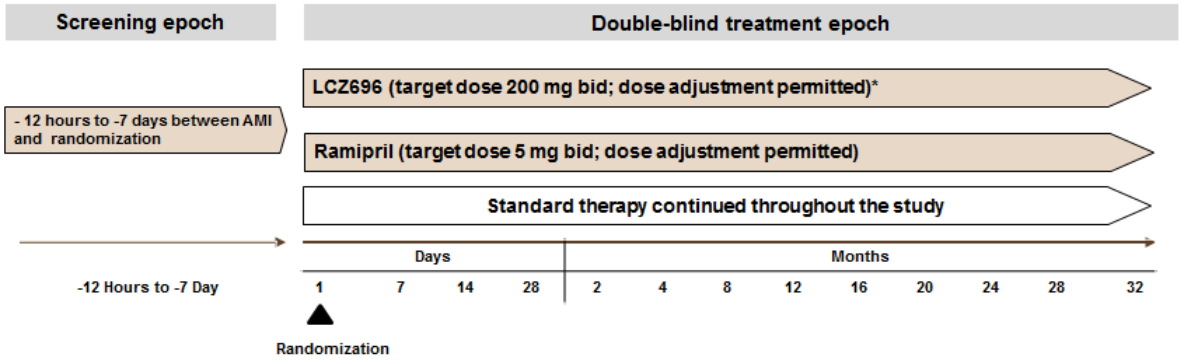
3 Investigational plan

3.1 Study design

Figure 3-1 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

This study 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. Potential study candidates will consist of high-risk patients who have sustained a spontaneous acute myocardial infarction (STEMI or NSTEMI) with evidence of LV systolic dysfunction defined by LVEF $\leq$ 40% and/or pulmonary congestion (worst Killip

[redacted]

class ≥ II or radiological findings requiring intravenous treatment). In addition, patients must have at least one risk factor (age ≥ 70 yrs; diabetes; estimated glomerular filtration rate (eGFR) < 60 ml/min; history of prior MI; occurrence of atrial fibrillation during index hospitalization; LVEF < 30% or Killip class III or IV associated with the index MI, or diagnosis of STEMI without reperfusion therapy within the first 24 hours of the index MI) and should not have known prior history of chronic HF. Study candidates must also be hemodynamically stable defined as systolic blood pressure (SBP) ≥ 100 mmHg if on ACE inhibitors or ARBs or SBP ≥ 110 mmHg if not on ACE inhibitors or ARBs at time of randomization, must not have received intravenous diuretics, vasodilators, vasopressors or inotropes in the last 24 hours prior to randomization, and be considered clinically stable in the opinion of the investigator.

After assessing eligibility during the screening period, consenting patients who meet the study inclusion and exclusion criteria 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 in a double-blind manner for the duration of the study. In addition, in order to minimize the potential risk of angioedema, patients who were previously treated with ACE inhibitors receiving the last dose of that agent during the last 36 hours prior to randomization will receive a valsartan bridge for one day. To achieve this, those who are subsequently randomized to LCZ696 will receive two doses of valsartan in a blinded manner prior to beginning double-blind LCZ696 treatment. Patients randomized to ramipril will immediately start on double-blind ramipril without valsartan bridging. Randomization must occur no earlier than 12 hours and no more than 7 days after index MI presentation.

A screening period, or 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. Patients may be randomized on the same day that they are consented and screened.

Eligible patients 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. Three dose levels of study medication will be administered in a stepwise titration (Table 3-1). The goal of treatment is to ensure that each patient receives the target dose or maximal tolerated dose of study medication (Figure 3-2).

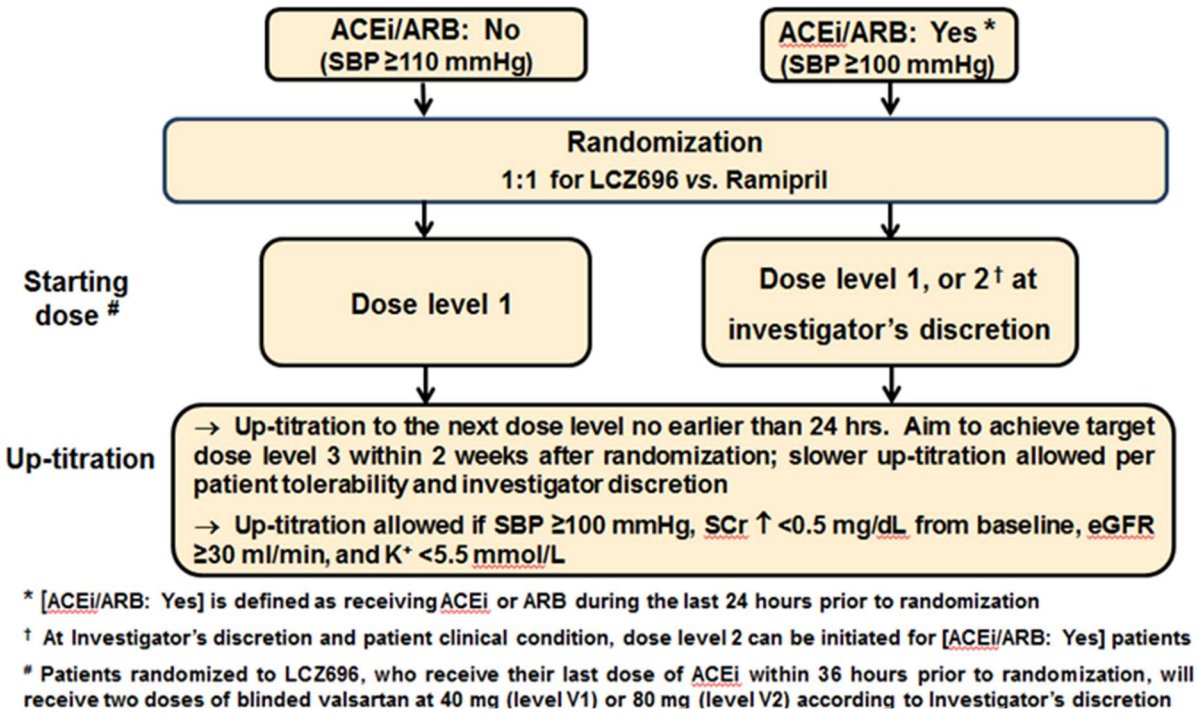
Table 3-1 Study drug dose levels during treatment epoch

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.

Figure 3-2 Study drug initiation and up-titration in PARADISE-MI



The starting dose level of the study drugs will be determined based on the patient's clinical condition and taking into consideration their prior standard background therapy. Patients who did not receive an ACE inhibitor or ARB in the last 24 hours prior to randomization (ACE inhibitor/ARB No patients) will start at dose level 1. Patients who did receive an ACE inhibitor or ARB in the last 24 hours prior to randomization (ACE inhibitor/ARB Yes patients) will start at dose level 1, or at investigator's discretion, dose level 2, after taking into consideration the patients' prior dose level of ACE inhibitor/ARB therapy (Table 3-2) and clinical condition (SBP, renal function, etc.).

Table 3-2 Total daily doses of commonly used ACE inhibitors and ARBs corresponding to dose level 2 of study drug

ACE inhibitor	Dose	ARB	Dose
Benazepril	20 mg	Azilsartan	40 mg
Captopril	100 mg	Candesartan	16 mg
Cilazapril	2.5 mg	Eprosartan	400 mg
Enalapril	10 mg	Irbesartan	150 mg
Fosinopril	20 mg	Losartan	50 mg
Imidapril	10 mg	Olmesartan	10 mg
Lisinopril	10 mg	Telmisartan	40 mg
Moxepril	7.5 mg	Valsartan	160 mg
Perindopril	4 mg		
Quinapril	20 mg		

[redacted]

ACE inhibitor	Dose	ARB	Dose
Ramipril	5 mg		
Trandolapril	2 mg		
Zofenopril	30 mg		

ACE inhibitor/ARB No patients (no treatment with ACE inhibitor/ARB therapy during the 24 hours prior to randomization):

- Start at dose level 1, if SBP is ≥ 110 mmHg

ACE inhibitor/ARB Yes patients (treated with ACE inhibitor/ARB therapy during the 24 hours prior to randomization):

- Start at dose level 1, if SBP is ≥ 100 mmHg OR
- At investigator's discretion, patients may also start at dose level 2, taking into consideration patient's prior dose level of ACE inhibitor/ARB therapy (Table 3-2) and clinical condition (SBP, renal function, etc.).

In order to minimize the potential risk of angioedema, patients who are randomized to LCZ696 but who were previously treated with an ACE inhibitor during the 36 hours prior to randomization will receive valsartan bridging for one day before beginning the double-blind LCZ696 treatment. Two doses of blinded valsartan (dose level V1, valsartan 40 mg or dose level V2 valsartan 80 mg) will be available. As outlined above (Figure 3-2), the dose level of the 1-day valsartan bridging will also be determined based on the patient's prior dose level of ACE inhibitor therapy and clinical condition at the investigator's discretion (Figure 3-2). Patients randomized to ramipril will immediately start on double-blind ramipril without valsartan bridging.

Following initiation of study drug, patients should be uptitrated to the next dose level no earlier than 24 hours after the initial dose of study drug. The aim is to achieve the target dose level 3 within 2 weeks after randomization; however, slower up-titration will be permitted if necessary to manage patient safety and tolerability. Patients that cannot tolerate dose level 3 will be allowed to stay at level 1 or 2 as maintenance dose. Study drug dose level adjustments should be based on overall safety and tolerability with special focus on a) symptomatic hypotension, b) any clinically significant decrease in eGFR/increase in serum creatinine (SCr) and c) hyperkalemia (Table 3-3). Treatment guidelines for blood pressure management and hyperkalemia are provided in Appendix 4 and Appendix 5, respectively. Every attempt should be made to maintain patients on the target study drug dose (dose level 3) or maximally tolerated dose levels throughout the trial. If the patient does not tolerate the target study drug dose level the investigator should consider, if appropriate, adjusting non-disease-modifying background medications (e.g., diuretics, nitrates or calcium channel blockers) to rectify the situation before considering down-titration to the next lower study drug dose level.

Table 3-3 Safety monitoring criteria that must be met for dose uptitration

Parameter	Criteria
Blood pressure	SBP ≥ 100 mmHg
Renal function	eGFR ≥ 30 mL/min/1.73m^2 or serum creatinine

Parameter	Criteria
	increase < 0.5 mg/dl
Serum potassium	K < 5.5 mmol/L (mEq/L)
AEs or conditions	No postural symptoms or any AEs that preclude up-titration according to the investigator's judgment

This is an event-driven trial, the study will continue until 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 will be required to accrue the necessary number of confirmed endpoints. Once randomized, all patients will be followed until the total numbers of required confirmed endpoint events have been achieved and final follow-up has been performed.

It is anticipated that the total trial duration will be approximately 32 months, with a projected recruitment period of 24 months, followed by approximately 8 months of follow-up after the last patient is enrolled. The overall estimated mean follow-up time will be 20 months for the study. Although these are the estimated timelines, they may change according to the rate of randomization and rates of occurrence of the primary and first secondary endpoints.

3.2 Rationale for study design

This phase III outcome study in post-AMI patients is designed as a multicenter, randomized, double-blind, active-controlled, event-driven study in order to assess the efficacy and safety of LCZ696 when added to standard therapy for high-risk post-AMI patients with left ventricular systolic dysfunction and/or pulmonary congestion. Patients entering the study will be randomized to either LCZ696 or ramipril and are required to receive standard-of-care background therapy according to regional or local guidelines / institutional standards throughout the study. Once randomized, all patients will be followed until the total required numbers of confirmed endpoint events have accrued. The study design reflects prior pivotal, long-term, cardiovascular outcome trials in post-AMI patients.

The primary endpoint of this study is a composite of CV death, HF hospitalization or outpatient HF in patients with left ventricular systolic dysfunction and/or pulmonary congestion following an AMI who do not have known prior history of chronic HF. While the composite of CV death or HF hospitalization is a well-established mortality and morbidity endpoint, the addition of the outpatient HF component, which in this study represents the confirmed diagnosis of new onset symptomatic HF, aims to capture the clinically important outpatient event that contributes to the totality of HF morbidity following an AMI presenting as either inpatient (i.e., HF hospitalization) or outpatient (i.e., outpatient HF) events. The diagnostic criteria for adjudication of HF symptoms and signs are identical whether the patient is seen in an inpatient or outpatient setting.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

The selection of LCZ696 200 mg given orally twice daily as the target dose for this study was based primarily on the superior efficacy and safety results of LCZ696 200 mg compared to enalapril 10 mg each given twice daily in the PARADIGM-HF study, in which 60% of the

HFrEF patients enrolled had an ischemic etiology and 43% had prior MI. LCZ696 200 mg twice daily delivers similar valsartan exposure (assessed by AUC) as valsartan 160 mg twice daily, which was demonstrated in the VALIANT study to be as effective as standard-of-care ACE inhibitor in patients with AMI complicated by LV systolic dysfunction and/or HF. Further, biomarker analysis and modeling indicate that this dose of LCZ696 delivers approximately 90% of its maximal neprilysin (NEP) inhibition. The twice daily dosing schedule is considered necessary for sustained NEP inhibition over a 24-hour period and it is also anticipated to reduce the incidence of hypotension, compared to a once daily regimen, particularly in elderly patients.

3.4 Rationale for choice of comparator

Major clinical trials have established ACE inhibitors as the standard-of-care for RAS blockade and ACE inhibitors are recommended by treatment guidelines as the first-line therapy for post-AMI patients with LV systolic dysfunction and/or HF. The primary objective of study LCZ696G2301 is to demonstrate superiority of LCZ696 over an ACE inhibitor in reducing CV mortality and HF morbidity in post-AMI patients with LV systolic dysfunction and/or pulmonary congestion. Ramipril is one of the most commonly used ACE inhibitors in post-AMI patients and is selected as the active comparator of this study. In the AIRE study, ramipril at target dose of 5 mg twice daily compared to placebo demonstrated a significant 27% relative reduction in mortality (p=0.002; principally CV death), also 26% and 23% reductions in the risks of HF hospitalization and progression to severe/resistant HF, respectively (AIRE Investigators 1993). Ramipril in the same daily dose was subsequently shown to reduce cardiovascular mortality in a broader population of patients at cardiovascular risk (The HOPE Investigators, 2000).

3.5 Purpose and timing of interim analyses/design adaptations

One interim analysis (IA) is planned to assess efficacy. The cut-off time for the IA is planned to be when approximately two-thirds of the target number of primary adjudicated events (i.e. approximately 540 of CV death, HF hospitalization or outpatient HF) have occurred.

3.6 Risks and benefits

The risk to patients participating in the study will be minimized by compliance with the inclusion/exclusion criteria and close clinical monitoring. Patients will be instructed not to take any RAS blockade medications (ACE inhibitor or ARB) from the day they start study drug to avoid excess RAS blockade. The risk of discontinuation of concomitant ACE inhibitors or ARBs will be minimal as the study treatment will be reflective of the typical dosing schedule of most ACE inhibitors and ARBs. All patients will be required to continue receiving the rest of their standard of care background CV medications. In addition, for patients randomized to LCZ696 who received ACE inhibitors in the last 36 hours prior to randomization, a one day bridging period with 2 doses of valsartan before starting LCZ696 treatment is instituted to minimize the risk of angioedema (Section 3.1).

In women of child-bearing potential, a possible risk of developmental toxicity cannot be excluded. Women of child-bearing potential should therefore use a highly effective method of

contraception during dosing. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Since this is a long-term outcome study, participating patients will benefit from careful monitoring and follow-up during the entire study duration regardless of whether they are receiving the study medication.

4 Population

The study population will consist of male and female patients age 18 years or older with a diagnosis of acute spontaneous MI and evidence of left ventricular (LV) systolic dysfunction and/or pulmonary congestion associated with the index MI. Patients will be randomized between 12 hours and 7 days following the index acute MI. At the time of randomization, patients should be hemodynamically stable and without persistent clinical HF. The goal is to randomize approximately 4,650 patients in approximately ~650 centers worldwide.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male or female patients ≥ 18 years of age.
3. Diagnosis of spontaneous AMI based on the universal MI definition* with randomization to occur between 12 hours and 7 days after index event presentation**.

   Spontaneous AMI is defined when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia due to primary coronary event. Under these conditions, the following criteria have to be met for the diagnosis of spontaneous AMI:

   - Detection of rise and/or fall of cardiac enzymes (cardiac troponin, cTn or the MB fraction of creatinine kinase, CKMB) with at least one value above the 99th percentile of the upper reference limit (URL) or the local laboratory MI diagnosis cut-off value, together with evidence of myocardial ischemia with at least one of the following:
     - Ischemic discomfort or other ischemia symptom(s)
     - Electrocardiogram (ECG) characteristics of STEMI or NSTEMI including new or presumably new significant ST-segment-T wave (ST-T) changes
     - Newly developed pathological Q waves or left bundle branch block in the ECG

   (* Patients with a spontaneous MI event determined to be secondary to another medical condition such as anemia, hypotension, or an arrhythmia OR thought to be caused by coronary vasospasm with documented normal coronary arteries are not eligible)
4. Evidence of LV systolic dysfunction and/or pulmonary congestion requiring intravenous treatment associated with the index MI event defined as:

   - LVEF ≤40% assessed locally by echocardiography, magnetic resonance imaging, cardiac CT, radionuclide or contrast ventriculography after index MI presentation** and prior to randomization.

     (These examinations may be performed as part of patient standard-of-care. In case multiple LVEF measurements have been performed during index event, the last one

performed prior to randomization should be considered as the qualifying measurement), **and/or**

- Pulmonary congestion requiring intravenous treatment during the index hospitalization supported by clinical assessment (worst Killip class, II or above; see Appendix 3 for Killip class definition) or radiological findings. Radiological evidence of pulmonary congestion is defined as pulmonary venous congestion with interstitial or alveolar edema and must be supported by at least one chest X-ray or CT scan.

(** Index MI presentation is the time of patient presentation at either the emergency room/emergency department (ER/ED), intensive care unit/coronary care unit (ICU/CCU) or hospital ward etc., at study centers, for the treatment of the index MI.)

5. At least one of the following 8 risk factors:
   - Age ≥ 70 years
   - eGFR <60 mL/min/1.73 m^2 based on MDRD formula at screening visit
   - Type I or II diabetes mellitus
   - Documented history of prior MI supported by ECG changes and/or elevation of cardiac enzymes consistent with MI diagnosis.
   - Atrial fibrillation as noted by ECG, associated with index MI
   - LVEF <30% associated with index MI
   - Worst Killip class III or IV associated with index MI requiring intravenous treatment
   - STEMI without reperfusion therapy within the first 24 hours after presentation
6. Hemodynamically stable defined as:
   - SBP ≥ 100 mmHg at randomization for patients who received ACE inhibitor/ARB during the last 24 hours prior to randomization (ACE inhibitor/ARB Yes patients)
   - SBP ≥ 110 mmHg at randomization for patients who did not receive ACE inhibitor/ARB during the last 24 hours prior to randomization (ACE inhibitor/ARB No patients)
   - No intravenous treatment with diuretics, vasodilators, vasopressors and/or inotropes during the last 24 hours prior to randomization.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Known history of chronic HF prior to randomization
2. Cardiogenic shock within the last 24 hours prior to randomization
3. Persistent clinical HF at the time of randomization
4. Coronary artery bypass graft (CABG) performed or planned for index MI
5. Clinically significant right ventricular MI as index MI
6. Symptomatic hypotension at screening or randomization
7. Patients with a known history of angioedema
8. Stroke or transient ischemic attack within one month prior to randomization

[redacted]

9. Known or suspected bilateral renal artery stenosis
10. Clinically significant obstructive cardiomyopathy
11. Open-heart surgery performed within one month prior to randomization or planned cardiac surgery within the 3 months after randomization
12. eGFR < 30 ml/min/1.73 m^2 as measured by the Modification of Diet in Renal Disease (MDRD) formula at screening
13. Serum potassium > 5.2 mmol /L at screening
14. Known hepatic impairment (as evidenced by total bilirubin > 3.0 mg/dL or increased ammonia levels, if performed), or history of cirrhosis with evidence of portal hypertension such as varices
15. Previous use of LCZ696 or Entresto™
16. Use of other investigational drugs within 30 days prior to screening
17. History of hypersensitivity to the study drugs or drugs of similar chemical classes
18. Known intolerance or contraindications to study drugs or drugs of similar chemical classes including ACE inhibitors, ARB or NEP inhibitors
19. Patients taking medications prohibited by the protocol that cannot be discontinued for the duration of the study
20. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin) within the past 3 years with a life expectancy of less than 1year.
21. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or extraction of study drug at investigators' discretion.
22. History or evidence of drug or alcohol abuse within the last 12 months
23. Patients considered unsuitable for the study, including patients with psychiatric, behavioral or cognitive disorders, sufficient to interfere with the patient's ability to understand and comply with the protocol instructions or follow-up procedures
24. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test
25. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of investigational drug. Basic contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
    - Male sterilization (at least 6 months prior to Visit 1). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
    - Combination of any two of the following (a+b or a+c, or b+c), according to country approvals and availability

[redacted]

a. use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
b. placement of an intrauterine device (IUD) or intrauterine system (IUS)
c. barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

All eligible patients will be randomized 1:1 to either LCZ696 titrated to a target dose of 200 mg twice daily or ramipril titrated to a target dose of 5 mg twice daily in a double-blind manner for the duration of the study. In addition, patients will continue to receive optimal standard of care background therapy to treat the index MI event and co-morbid conditions, as considered appropriate by the investigator and in accordance with the local/institutional guidelines, with the exception of an ACE inhibitor or ARB as this will be replaced by study drug. The use of an open label ACE inhibitor or an ARB in addition to randomized study drug is strictly prohibited.

The following study drugs will be provided:

- LCZ696 50 mg, 100 mg and 200 mg tablets, and matching placebo (LCZ696 doses are equivalent to sacubitril/valsartan 24/26 mg, 49/51 mg and 97/103 mg, respectively)
- Ramipril 1.25 mg, 2.5 mg, and 5 mg capsules, and matching placebo
- Valsartan (VAL489) 40 mg and 80 mg tablets, and matching placebo (two doses for 1 day in a subset of randomized patients) (Section 3.1)

All study medications will be supplied in bottles or blister cards. Sufficient medication will be provided for the treatment according to study protocol, including additional medication to allow for delayed visits. Medication labels will be in the local language and comply with the legal requirements of the country. They will include storage conditions for the drug and the medication number, but no information about the patient.

[redacted]

5.1.2 Additional treatment

No additional treatment beyond investigational drug and control drug are included in this trial.

5.2 Treatment arms

Patients will be assigned to one of the following two treatment arms in a ratio of 1:1 at Visit 101.

- LCZ696 at dose levels 1-3 (50, 100 and 200 mg twice daily)
- Ramipril at dose levels 1-3 (1.25, 2.5 and 5 mg twice daily)

5.3 Treatment assignment and randomization

At Visit 101 all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Randomization will be stratified by region and type of index MI (STEMI or NSTEMI).

The randomization scheme for patients will be reviewed and approved by a member of the Novartis Randomization Group.

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods:

- Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone involved in the study with the following exceptions:
    1. The independent and unblinded statistician, programmer and data personnel who are involved in preparing safety and efficacy interim analysis reports for the Data Monitoring Committee (DMC). These personnel will not be involved in any other trial conduct related activities.
    2. DMC members.

[redacted]

- The identity of the treatments will be concealed by the use of investigational treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.
- A double-dummy design is used because the identity of the study drug cannot be disguised, as the drug products are visibly different.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.9), at the time of an interim analysis by the DMC and at the conclusion of the study.

For any patient whose treatment code has been broken the patient must permanently discontinue the study treatment.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Patient numbering,

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigative site.

Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number [redacted], and subsequent patients/subjects are assigned consecutive numbers (e.g. the second patient is assigned patient number [redacted], the third patient is assigned patient number [redacted]). The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. For studies using eCRFs, only the assigned patient number must be entered in the field labeled "Patient ID" on the electronic data capture (EDC) data entry screen (e.g. enter [redacted], etc.). Once assigned to a patient, the patient number will not be reused.

If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Log, and the screening eCRFs should also be completed.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the two treatment arms. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

[redacted]

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis country pharma organization (CPO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused study treatment and packaging at each study visit or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Novartis will supply the investigators with all study medications required for the course of the study. Patients will be provided with medication packs containing study drug corresponding to their assigned treatment arm and dose level, sufficient to last until the next scheduled visit. In order to adequately blind the study, patients will be required to take a total of two pills, (one tablet from the LCZ696/LCZ696 matching placebo pack and one capsule from the ramipril/ramipril matching placebo pack) twice a day for the duration of the study.

For patients randomized to LCZ696 who were previously treated with an ACE inhibitor receiving the last dose of that agent within 36 hours prior to randomization, a valsartan bridge for one day will be administered in a blinded manner prior to initiating the LCZ696 treatment. To achieve this, those who are subsequently randomized to LCZ696 will receive two doses of valsartan in a blinded manner prior to beginning double-blind LCZ696 treatment. Patients randomized to ramipril will immediately start on double-blind ramipril without valsartan bridging.

Table 5-1 summarizes the study drug that will be taken during the treatment epoch.

[redacted]

Table 5-1 Study drug dispensed during the treatment epoch by study visit

Study visit[c]	Dose level	LCZ696	Ramipril	Valsartan[b]
101	1[a]	50 mg or matching placebo b.i.d.	1.25 mg or matching placebo b.i.d.	40 mg or matching placebo b.i.d.
101[a]/102	2	100 mg or matching placebo b.i.d.	2.5 mg or matching placebo b.i.d.	80 mg or matching placebo b.i.d.
103	3	200 mg or matching placebo b.i.d.	5 mg or matching placebo b.i.d.	

[a] At Investigator's discretion, dose level 2 can be administered at Visit 101 for the [ACE inhibitor/ARB: Yes] patients.

[b] For patients who were previously treated with ACE inhibitor receiving the last dose within 36 hours prior to randomization;

If randomized to LCZ696, they will receive a valsartan bridging for one day before beginning the double-blind LCZ696 treatment.

- Two doses of blinded valsartan dose level V1 (valsartan 40 mg) or dose level V2 (valsartan 80 mg) will be available at Visit 101.
- At investigator's discretion dose level V1 or V2 can be administered for one day followed by active LCZ696; these patients will also receive ramipril matching placebo from Visit 101 onwards.

If randomized to ramipril, they will receive active ramipril, and two doses of valsartan matching placebo for one day followed by active ramipril and LCZ696 matching placebo.

[c] If the study drug is up-titrated during the index hospitalization, increase to the next dose level can occur prior to next study visit if tolerable but should be no early than 24 hours; slower up-titration will also be permitted if necessary to manage patient safety and tolerability.

Patients will be instructed to take their morning study drug doses at approximately 08:00 (8 AM) and their evening study drug dose at approximately 20:00 (8 PM). The study drugs should be taken with water, with or without food. If the patient misses taking any study drug dose, he/she should take it as soon as possible, unless it is almost time for the following scheduled dose. In this case, the patient should skip the missed dose and return back to his/her regular study drug administration schedule.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record case report form (CRF). All kits of study treatment assigned by the IRT will be recorded/databased in the IRT.

The investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

5.5.5 Permitted dose adjustments and interruptions of study treatment

For patients who are unable to tolerate the protocol-specified dosing scheme, dose level adjustments and/or temporary interruptions of study treatment are permitted in order to keep the patient on study drug. The following guidelines should be followed:

Every attempt should be made to maintain patients at the target study drug dose level throughout the trial. If the patient does not tolerate the target study drug dose level, the

investigator can, if appropriate, adjust concomitant background medications for co-morbid conditions to rectify the situation, and if necessary down titrate to the next lower study drug dose level. For hypotension or dizziness, consideration should be given to adjusting the dose of diuretic and/or concomitant antihypertensive agents (e.g., calcium channel blockers) and non-antihypertensive agents that lower blood pressure (BP) (e.g., nitrates). It is important to note that dose adjustment of disease-modifying background therapy, e.g., β blockers, or mineralocorticoid (aldosterone) antagonists is discouraged under these circumstances.

Adjustment of study drug dose level

If in the investigator's opinion down titration of study drug to a lower dose level is deemed necessary it should be done in accordance with the following instructions:

During the treatment epoch, down titration of the study drug at any time during the study based on the judgment of the investigator will be allowed according to the safety and tolerability criteria defined in Appendix 4, and Appendix 5. If down titration is necessary, the patient should be down titrated to the next lower study drug dose level in the titration scheme. The patient may continue receiving the lower dose level for a recommended period of 1 to 4 weeks before being re-challenged at the next higher dose level. For example, a patient who encounters tolerability problems at the target study drug dose level (i.e., dose level 3) should receive the study drug at dose level 2 for 1 to 4 weeks at the discretion of the investigator. Then, he/she should be re-challenged with up-titration back to dose level 3.

If the tolerability issues are not alleviated despite down titration by one dose level, the investigator may down titrate further to the next lower study drug dose level for 1 to 4 weeks, up to temporary discontinuation of the study drug. Again, once stable, the patient should be re-challenged with up titration to the next higher dose level every 1 to 4 weeks in an attempt to bring back the patient gradually to the target study drug dose level (i.e., dose level 3). The investigator may choose the next dose level for down- or up-titration according to his or her judgment. The IRT system should be contacted to register any changes in the patient's study drug dose level, including in cases of temporary and permanent discontinuation of the study drug, and to obtain the medication numbers of the study drug supplies required for the new study drug dose level. In some instances, according to the safety and tolerability criteria and the investigator's judgment, dose level 1 or 2 could be maintained if he/she considers that the patient's condition would not allow any further up titration to the target dose level of study drug (i.e., dose level 3). In this case, it would be acceptable to maintain the patient at dose level 1 or level 2, whichever is the higher and tolerated dose level by the patient.

These changes must be recorded on the Dosage Administration Record CRF.

Study drug restart after temporary treatment interruption

Study drug should be reintroduced in those patients who temporarily discontinue it as soon as medically justified in the opinion of the investigator. Once the investigator considers the patient's condition appropriate for receiving the study drug, the investigator should re-start the patient on the study drug at the most appropriate and allowable dose level per his/her medical judgment. If tolerated, the patient should be up-titrated one dose level every 1 to 4 weeks to the target dose level 3, as per the investigator's judgment. Should the patient not tolerate the re-start study drug dose level, he/she may be down titrated again (if appropriate) or

[redacted]

temporarily discontinue the study medication again and a new attempt to up titrate or reintroduce the study drug could be considered by the investigator as soon as medically justified in his/her judgment.

The use of an open-label ACE inhibitor, ARB, commercially available Entresto™ or a direct renin inhibitor is strictly prohibited while patient is taking study drug. However, if for any reason a patient off study drug has started open-label treatment with an ACE inhibitor or Entresto™, it must be discontinued ≥36 hours prior to restarting study drug. For patients off study drug treated with an ARB or a direct renin inhibitor it must be discontinued prior to re-initiation of study drug.

Reinitiation of study medications or any changes in concomitant medications must be recorded on the appropriate eCRFs.

In case of pregnancy discovered during the screening epoch, the patient will be withdrawn from the study immediately. In case of pregnancy discovered during the treatment epoch, the patient should be instructed to temporarily discontinue study drug immediately. Study drug intake should be resumed as soon as possible after the completion of the pregnancy and lactation period. Meanwhile, the patient should continue to attend scheduled study visits.

See Section 7.6 for further details on pregnancies and reporting guidelines

5.5.6 Rescue medication

Guidance on handling hypotension and hyperkalemia are provided to investigators in Appendix 4, and Appendix 5, respectively. Patients may receive open-label ACE inhibitors, ARBs, commercially available Entresto™ or direct renin inhibitors during the study ONLY if the study drug has been temporarily or permanently discontinued (Table 5-1). If the patient is to be started on open-label ACE inhibitor or Entresto™, the study drug must be stopped ≥ 36 hours prior to initiating ACE inhibitor or Entresto™. If reinitiating study drug, the open-label ACE inhibitor or Entresto™ must be stopped ≥ 36 hours prior to resuming study drug. Open-label ARBs or a direct renin inhibitor must also be stopped prior to resuming study drug.

Use of rescue medication must be recorded on the Concomitant medications/Significant nondrug therapies CRF.

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the concomitant medications eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

[redacted]

CV Medications

The patient should be on an optimal medical regimen of background medications to effectively treat the index MI event and comorbidities, such as hypertension, diabetes, dyslipidemia and atrial fibrillation, etc. Investigators should take into consideration the patient's risk factors, such as age and comorbidities, and make every effort to control a patient's BP, lipid and glucose levels in accordance with international and local treatment guidelines.

Medications known to raise potassium levels

Potassium-sparing diuretics, potassium supplements and any other medications known to raise potassium levels should be used with caution while the patient is receiving the study drug due to the increased possibility of occurrence of hyperkalemia. The investigator is encouraged to assess patients' potassium levels regularly, especially in those who are receiving these medications.

Phosphodiesterase-5 (PDE-5) inhibitors

PDE-5 inhibitors should be used with caution while the patient is receiving study medication due to the increased possibility of the occurrence of hypotension.

HMG-CoA reductase inhibitors

Caution is recommended when co-administering LCZ696 with atorvastatin or other statins because of the potential to raise its plasma level.

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-2 is NOT allowed after the start of study drug due to safety reason, unless the actions specified are taken.

Table 5-2 Prohibited medication

Medication	Action taken
Any ACE inhibitor	Discontinue study drug. The open label ACE inhibitor must be stopped for ≥36 hours prior to re-initiation of study drug
Any ARB	Discontinue study drug. The open label ARB must be stopped prior to re-initiation of study drug
Any direct renin inhibitor	Discontinue study drug. The open label direct renin inhibitor must be stopped prior to re-initiation of study drug
Entresto™*	Discontinue study drug. The open label Entresto™ must be stopped for ≥36 hours prior to re-initiation of study drug
*Commercially available sacubitril/valsartan	

The concomitant use of open-label ACE inhibitor, ARBs, commercially available Entresto™ or a direct renin inhibitor is strictly prohibited while the patient is receiving study drug. If the addition of an ACE inhibitor, ARB, Entresto™ or direct renin inhibitor is necessary, then study drug must be temporarily discontinued. If the patient is to be started on open-label ACE inhibitor or Entresto™, the study drug must be stopped ≥36 hours prior to initiating ACE

inhibitor or Entresto™. If study drug is to be re-started, the open-label ACE inhibitor or Entresto™ must also be stopped ≥ 36 hours prior to re-initiating study drug. ARBs or a direct renin inhibitor should be stopped prior to resuming study drug.

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- patient number

In addition, oral and written information to the patient must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and the Medical Lead (or designee) after an emergency treatment code break and the patient must discontinue the study treatment.

5.6 Study Completion and Discontinuation

5.6.1 Study completion and post-study treatment

The study will be completed when either the predefined target total number of adjudicated events has been obtained **or** a recommendation is made by the DMC to prematurely stop the study. At the end of the study, all patients will return for the final end of study (EOS) visit (Visit 199) and be asked to return the remaining study drug.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from study drug, or must refer them for appropriate ongoing care. An open-label extension study may also be initiated to allow for study medication to be made available to qualified patients participating in the trial, upon formal request, if the study is positive and demonstrates the superiority of LCZ696 over ramipril.

[redacted]

5.6.2 Discontinuation of Study Treatment

Patients may voluntarily discontinue study treatment for any reason at any time. However, study treatment discontinuation does not constitute withdrawal from the study, does not constitute withdrawal of consent and should not lead to the patient being withdrawn from the entire study. Patients who have permanently discontinued study drug should be encouraged to attend all the protocol specified study visits and perform, at a minimum, AE/endpoint assessments as stipulated in the visit schedule (Table 6-1) and remain in follow-up for the duration of the trial.

If they fail to return for these assessments for unknown reasons, every effort should be made to contact them. The investigator must also contact the IRT to register the patient's discontinuation from study treatment and record it on the Dosage Administration Record CRF.

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule. After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should to be collected at clinic visits or via telephone visits:

- new / concomitant treatments
- adverse events (AE)/Serious Adverse Events (SAE)

The emergence of the following circumstances will require permanent study drug discontinuation:

- Withdrawal of informed consent
- Investigator thinks that continuation of study drug would be detrimental to the patient's well-being
- Suspected occurrence of clinically significant angioedema. A patient with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator

The emergence of the following circumstances will require temporary or permanent discontinuation (study drug may be restarted once these circumstances no longer exist):

- Use of an open label ACE inhibitor, ARB, Entresto™ (commercially available sacubitril/valsartan) or direct renin inhibitor
- Any laboratory abnormalities that in the judgment of the investigator warrant discontinuation of study drug after taking into consideration the patient's overall status
- Pregnancy and post-pregnancy during lactation period (Section 7.7)

Study drug may be discontinued at the investigator's discretion if any of the following occurs:

- Any severe suspected drug-related AE
- Any other protocol deviation that results in a significant risk to the patient's safety

Study drug should be permanently discontinued for any patient whose treatment code has been broken inadvertently for any reason.

[redacted]

5.6.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. However, withdrawal of consent occurs **only** when a patient does not want to participate in the study anymore **and** does not want any further visits or assessments **and** does not want any further study related contacts **and** does not allow analysis of already obtained biologic material.

If a patient withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up. All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in Table 6-1.

Patients can also refuse to participate in specific aspects of the study and/or take study medication at any time without withdrawing consent and permission should be requested of the patient to conduct follow-up visits or calls. Investigators should make every effort to accommodate the needs of the patients to make it possible for them to continue to participate in the remaining aspects of the study. This includes performing telephone visits to obtain health status and/or mortality and endpoint information for patients who are unable to or refuse to return for clinic visits.

5.6.4 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by contacting the patient, the patient's family, friends and family physician as agreed in the informed consent and by documenting in the eSource/source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until just prior to database lock, after every effort to contact the patient has been exhausted.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed.

[redacted]

Patients should be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

Patients will be contacted for safety evaluations during the 30 days following the last administration of study treatment.

Patients who prematurely discontinue the investigational treatment remain in the study and should undergo all the assessments illustrated in Table 6-1. Patients can also refuse to participate in specific aspects of the study and/or take study medication at any time without withdrawing consent and permission should be requested of the patient to conduct follow-up visits or calls. Investigators should make every effort to accommodate the needs of the patients to make it possible for them to continue to participate in the remaining aspects of the study. This includes performing telephone visits to obtain health status and/or mortality and endpoint information for patients who are unable to or refuse to return for clinic visits.

If a patient withdraws from participation in the study, refuses to return for study assessments or is unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone and/or other measures to determine the patient's survival status during the follow-up period.

Patients eligible to participate in this study must be randomized between 12 hours to 7 days after index AMI event presentation.

Prospective study candidates will be identified either during the hospitalization for the index AMI or post discharge up to 7 days after the index MI presentation. After identifying a potential patient, an informed consent form (ICF) must be signed before performing study-related screening procedures that are not considered standard of care for AMI patients at that site. Procedures that are part of a site's standard of care for an individual with AMI may pre-date the signed ICF. The AE and SAE reporting period will begin at the time the ICF is signed. Screening will continue until the patient has been deemed eligible for randomization into the study up to 7 days after the index MI. Screening and randomization can occur on the same day.

Visit 101 will be considered the reference visit for all study visits during the treatment epoch. Regardless of the occurrence of any unscheduled visits, scheduled visits should be performed within the specified timeframe in relation to Visit 101 as outlined in Table 6-1. If a visit is completed earlier than scheduled or postponed, it should not result in the next visit being brought forward or postponed.

Visits are planned to occur at weeks 1, 2, 4 (month 1), month 2, month 4, and then every 4 months until study end.

[redacted]

Table 6-1 Assessment schedule

Epoch	Screen	Treatment												
Visit	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**199 and PSD**
Day		**1**	**7**	**14**	**28**	**61**	**122**	**243**	**365**	**486**	**608**	**730**	**851**	**973**
Week		**0**	**1**	**2**	**4**	**8**	**17**	**34**	**52**	**69**	**86**	**104**	**121**	**138**
Month					**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**
Obtain informed consent	X													
Inclusion/exclusion criteria	X	X												
Medical History – Protocol Solicited Events	X													
Relevant Medical History/Current Medical Conditions/ Demography	X													
Medical History Possibly Contributing to Liver Dysfunction[1]	X[1]													
History/Smoking History/Alcohol History	X													
12-lead ECG assessment[2]	XS													
Cardiac enzymes[2]	X													
Chest X-ray or CT scan[2, 3]	XS													
Evaluation of left ventricular systolic dysfunction[2]	X													
Record Killip Class[2,3]	S	X												
Risk factor assessment	X	X												
Qualifying AMI Event		X												
Index AMI Hospitalization		X												

[redacted]

Epoch	Screen	Treatment												
Visit	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**199 and PSD**
Day		**1**	**7**	**14**	**28**	**61**	**122**	**243**	**365**	**486**	**608**	**730**	**851**	**973**
Week		**0**	**1**	**2**	**4**	**8**	**17**	**34**	**52**	**69**	**86**	**104**	**121**	**138**
Month					**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**
Summary														
Physical exam[4]	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Height	X													
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (pulse and BP)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAEs[6]		X	X	X	X	X	X	X	X	X	X	X	X	X
Complete laboratory evaluation[7]		X			X		X		X			X		X
Abbreviated laboratory evaluation[8]			X	X		X		X		X	X		X	
Local laboratory evaluation[9]	X	X	X	X										
Endpoint assessment			X	X	X	X	X	X	X	X	X	X	X	X
Angioedema assessment			X	X	X	X	X	X	X	X	X	X	X	X
[redacted]														
Visit Contact Information	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum/urine pregnancy testing[11]	S	S							S			S		S
FSH[12]	S													

[redacted]

Epoch	Screen	Treatment												
Visit	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**199 and PSD**
Day		**1**	**7**	**14**	**28**	**61**	**122**	**243**	**365**	**486**	**608**	**730**	**851**	**973**
Week		**0**	**1**	**2**	**4**	**8**	**17**	**34**	**52**	**69**	**86**	**104**	**121**	**138**
Month					**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**
[redacted]														
Dispense Study Medication		X	X	X	X	X	X	X	X	X	X	X	X	
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Screening disposition	X													
Study Completion form														X

TD = Study treatment discontinuation; PSD = Premature patient discontinuation
X = assessment to be recorded on clinical data base
S = assessment to be recorded on eSource/source documentation only

[1]Collected retrospectively for patients who experience protocol defined liver events (See Appendix 2).

[2]Assessments typically performed as standard of care for index AMI according to local guidelines. Procedures that are part of a site's standard of care for an individual with AMI may pre-date the signed ICF.

[3]Pulmonary congestion is assessed by worst Killip class AND/OR chest x-ray or CT scan findings during index hospitalization.

[4]Complete physical examinations are required at Visit 1 and yearly (Visits 108, 111) thereafter up until Visit 199 (EOS). Short physical examinations are required at all interim visits.

[5] CV medications (e.g., β-blockers, aldosterone antagonists, anti-hypertensives, lipid lowering drugs, antiplatelet agents, etc.) and classes of non-cardiovascular medications will be collected.

[6] All adverse events and all serious adverse events occurring through the first two weeks post-randomization will be collected. After the first two weeks post-randomization, the following safety data will be collected in this study: all serious adverse events, adverse events of special interest (Section 7.1), adverse events leading to a change in dose (down titration) or discontinuation of study medication, and all suspected non-serious adverse events.

[7] Complete laboratory evaluations will be collected and sent to the central lab at all specified visits for all patients. If the study is extended beyond Visit 112 a complete laboratory evaluation will be performed annually.

[8] Abbreviated laboratory evaluations includes: blood urea nitrogen (BUN), serum creatinine, serum potassium and eGFR and will be collected and sent to the central lab at all specified visits for all patients. If the study is extended beyond Visit 112 an abbreviated laboratory evaluation will be

[redacted]

Epoch	Screen	Treatment												
Visit	**1**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**199 and PSD**
Day		**1**	**7**	**14**	**28**	**61**	**122**	**243**	**365**	**486**	**608**	**730**	**851**	**973**
Week		**0**	**1**	**2**	**4**	**8**	**17**	**34**	**52**	**69**	**86**	**104**	**121**	**138**
Month					**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**

performed at all interval visits except annual visits.

[9] Local laboratories for serum potassium, serum creatinine and eGFR are to be performed prior to initial dosing and prior to each dose titration step until target dose is achieved (Visits 1, 101, 102 and 103; additional visits may be added as necessary until target dose level is achieved and/or during dose adjustments throughout the study). If screening (Visit 1) and randomization (Visit 101) occur on the same day, only one local laboratory assessment will be required.

[redacted]

[11] Serum and urine pregnancy tests will be performed locally. Serum pregnancy test (not required for post-menopausal women) to be performed at Visit 1. Urine pregnancy tests at visits 101 and annually (not required for post-menopausal women). If screening (Visit 1) and randomization (Visit 101) occur on the same day, only serum pregnancy test will be required. If serum pregnancy test is positive during the screening and on a confirmatory serum β-hCG test, the patient must not be randomized and must be discontinued from the trial. After randomization (Visit 101) a positive urine pregnancy test requires immediate interruption of study drug and confirmation by serum pregnancy test. If positive upon confirmation test, the patient must discontinue study drug until after the pregnancy and lactation period.

[12] FSH will be performed locally. Not required for males or pre-menopausal women.

[redacted]

[redacted]

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next epoch will have the study completion page for the screening epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the eSource/source data.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients at least include date of birth, age, sex, race, and ethnicity. A detailed medical history (including CV and other conditions relevant to the study population to be enrolled) and current medical conditions present before the signing of informed consent, including the presentation and management of index MI event will also be recorded.

6.3 Treatment exposure and compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient or care giver. This information should be captured in the eSource/source document at each visit. The investigator and/or study personnel should counsel the patient if compliance is below 80% at any time during the study. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

The duration of randomized treatment exposure will be calculated based upon the start and stop dates of study drug recorded in the CRF.

6.4 Efficacy

6.4.1 Efficacy assessment 1

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 criteria.
- 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

6.4.2 Efficacy assessment 2

The secondary endpoints are:

- Time-to-first occurrence of CV death or HF hospitalization (days)
- Time-to-first occurrence of HF hospitalization or outpatient HF (days)
- Time-to-first occurrence of CV death, non-fatal spontaneous MI or nonfatal stroke (days)
- The cumulative number of composite events, including hospitalization due to HF, hospitalization due to non-fatal spontaneous MI, hospitalization due to non-fatal stroke and CV death. This endpoint is based on the total number of recurrent composite endpoints (count) and patient-specific follow-up time from randomization to end of study/death (days).
- Time to all-cause mortality (days)

A blinded central Clinical Endpoint Committee (CEC) will be responsible for adjudicating and classifying all death events (CV vs. non-CV) and for determining whether pre-specified endpoint criteria are met for the primary and secondary non-fatal endpoint events. The CEC will also be responsible for adjudicating and classifying all investigator-reported outpatient HF events as the clinical development of HF under an outpatient setting (urgent/unscheduled or non-urgent) with symptoms and signs requiring initiation/intensification of intravenous or qualifying oral HF treatment. The diagnostic criteria for HF symptoms and signs will be identical whether the patient is seen in an inpatient or outpatient setting. The detailed definitions of the endpoints, required documentation and the adjudication process will be provided to all sites in a separate endpoint manual.

6.4.3 Appropriateness of efficacy assessments

The composite of CV death or HF hospitalization is a well-established mortality and morbidity endpoint. The addition of the outpatient HF component here aims to capture the clinically important outpatient symptomatic HF event that contributes to the totality of HF morbidity following an AMI presenting as either inpatient (i.e., HF hospitalization) or outpatient (i.e., outpatient HF) events. The clinical significance of HF events in the outpatient setting has been increasingly recognized by medical communities and health authorities (Hicks, et al 2014). Outpatient HF events reported in randomized chronic HF trials, of which the definition is analogous to the outpatient HF event proposed for LCZ696G2301 study, have been shown to be associated with significantly increased risks of (CV) mortality. Furthermore, the outpatient HF events are also modifiable events that are equally sensitive to the evidence-based HF therapeutics as are the mortality and composite CV death/HF hospitalization endpoints, which underscores the similar pathology contributing to these events (Skali, et al 2014; Okumura, et al 2016).

[redacted]

6.5 Safety

Novartis may request additional information on specific AEs or laboratory events of interest and may make requests to perform additional diagnostic tests to further assess the safety profile of the study drugs. Such information may include diagnostic procedure reports, discharge summaries, autopsy reports, and other relevant information that may help in assessing the reported AE. All additional information will be de-identified prior to collection by Novartis or its agents.

6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A short physical exam will include the examination of general appearance and vital signs (BP [SBP and diastolic blood pressure (DBP)] and pulse). A short physical exam will be conducted at all visits starting from Visit 101 except where a complete physical examination is required (see Table 6-1).

Information from all physical examinations must be included in the eSource/source documentation at the study site. Significant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after signing the informed consent which meet the definition of an AE must be recorded on the AE section of the CRF.

6.5.2 Vital signs

Vital signs include BP and pulse measurements. BP will be measured in the sitting position after 5 minutes of rest using an automated validated device (e.g., OMRON) or a standard sphygmomanometer with an appropriately sized cuff on the non-dominant arm. Guidelines for the management of BP are provided in Appendix 4.

6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of most specimens collected. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

Complete central laboratory evaluations (hematology and blood chemistry) for the assessment of safety in this study will be performed at Visits 1, 101, 104, 106, 108, 111 and end of study (199). Abbreviated laboratory central evaluations will be performed as indicated in Table 6-1.

[redacted]

In addition to the required central laboratory assessments, a local laboratory may be used for the assessment of serum potassium, serum creatinine and eGFR during the screening period as indicated in Table 6-1. The results from the local laboratory at Visits 101, 102, 103 and 104 will be allowed to make decisions regarding study drug administration and dose titration/dose level adjustments, and will be recorded in the eSource/source documents at the study sites. In addition, local laboratory assessments of serum potassium, serum creatinine and eGFR may be performed on an as-needed basis to monitor tolerability to study drug and dose adjustments at unscheduled visits during the treatment epoch.

Laboratory values that exceed the boundaries of a notable laboratory abnormality should be assessed for AEs and additional evaluations should be performed, as judged appropriate by the investigator. If the laboratory abnormality induces clinical signs or symptoms, results in a dose adjustment of the study medications, is suspected to be study drug-related or requires therapeutic intervention, then the diagnosis or medical condition must be entered on the AE CRF. If the laboratory abnormality is the primary reason for an unforeseen hospitalization or otherwise fulfills the seriousness category of an AE, then the procedure for rapid notification of SAEs must be followed. If the laboratory abnormality leads to study drug discontinuation (temporarily or permanently), the patient must be followed until the abnormality resolves or until it is judged to be permanent. The investigation may include continued monitoring by repeat laboratory testing or by performing additional laboratory tests as deemed necessary by the investigator or the Novartis medical monitor.

Table 6-2 Routine laboratory examinations

Hematology	**Biochemistry**
Hematocrit	Alanine aminotransferase (ALT)
Hemoglobin	Albumin (Alb)
Platelet count	Alkaline phosphatase (ALP)
Red blood cell count (RBC)	Aspartate aminotransferase (AST)
White blood cell count (WBC)	Blood urea nitrogen (BUN)*
WBC differential	Calcium
Red blood cell distribution width (RDW)	Chloride
Mean corpuscular volume (MCV)	Creatinine*
Mean corpuscular hemoglobin concentration (MCHC)	Glucose
	Hemoglobin A1C
	Lipid profile (total cholesterol, LDL, HDL, and triglycerides)
	Phosphate
	Potassium*
	Serum pregnancy test
	Sodium
	Total bilirubin (TBL)
	Fractionated bilirubin (if total bilirubin >2x ULN)
	Total protein

	Uric acid
*Laboratory assessments of BUN, serum creatinine and serum potassium for the abbreviated central laboratory evaluation at visits where the complete laboratory evaluation is not performed; eGFR is derived from serum creatinine values following MDRD formula	

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count (RBC), red blood cell distribution width (RDW), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), white blood count (WBC) with differential, and platelet count will be measured.

6.5.4.2 Clinical chemistry

Blood urea nitrogen (BUN), creatinine, total bilirubin, fractioned bilirubin (if total bilirubin >2x upper limit of normal(ULN)), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), alkaline phosphatase, sodium, glucose (plasma), hemoglobin A1C, lipid profile, potassium, chloride, calcium, total protein, albumin, and uric acid will be measured. Potassium, BUN and creatinine will be obtained at study visits where abbreviated central laboratory evaluations are scheduled.

6.5.4.3 eGFR

Estimated GFR will be calculated by the central or local laboratory using the following MDRD formula (Stevens et al 2006):

Estimated GFR (mL/min/1.73 m^2) = 175 × (standardized SCr in mg/dL)-1.154 × (age in years)-0.203 × (0.742 if female) × (1.212 if black), where SCr is the standardized serum creatinine value.

6.5.4.4 Urinalysis

No urinalysis will be performed.

6.5.5 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed locally in association with the index MI and recorded at Visit 1. Interpretation of the tracing must be made by a qualified physician and the ECG interpretation and the person interpreting the ECG must be recorded in the eSource/source documents at the study sites. The ECG tracing should be labeled with the study and patient number, date, and kept in the eSource/source documents at the study site. Clinically significant abnormalities should also be recorded on the Medical History/AE CRF page as appropriate.

6.5.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum pregnancy test performed locally at Visit 1. A urine dip-stick pregnancy test will be performed locally on an annual basis. The urine dip-stick pregnancy test is not required for post-menopausal women. A positive urine pregnancy test requires immediate interruption of study drug and

confirmation by serum pregnancy test. If positive upon confirmation test, the patient must discontinue study drug until after the pregnancy and lactation period.

6.5.7 Angioedema

Angioedema is a type of abrupt swelling that occurs under the skin and/or mucous membranes and is often localized to the head, neck, throat, and/or tongue, but may occur elsewhere, including the genitalia and intestines. Severe cases may be associated with airway compromise. A patient with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator and study medication must be permanently discontinued.

It is important that the investigator pays special attention to any swelling or edema that may resemble angioedema or angioedema-like events that may be reported by patients. If such an event occurs, the investigator will complete an Adjudication Questionnaire for an Angioedema-like event form (provided by Novartis) to summarize the event, its treatment, and its ultimate outcome. This report along with the requisite medical documentation must be submitted to Novartis as soon as possible. Follow-up reports must be communicated to Novartis as soon as new information regarding the event becomes available. All hospital records related to the event must be communicated to Novartis.

The investigator may be also be contacted by Novartis regarding AEs that may resemble an angioedema-like event. A list of terms that are considered “angioedema-like” (e.g., periorbital swelling) will be provided to sites in a manual. The investigator or his/her delegated staff must complete the required forms and provide the required medical records for all such events, regardless of whether the investigator views the event in question as angioedema or not.

All angioedema reports will be forwarded to an Angioedema Adjudication Committee by Novartis for independent adjudications.

Information regarding this committee is outlined in Section 8.5. Details on the procedures for reporting angioedema events will be provided to investigators in a manual.

6.5.8 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

[redacted]

[redacted]

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient after providing written informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

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

Targeted collection of safety data will permit the further characterization of identified risks, potential risks, and missing information for LCZ696. *Non-suspected, non-serious adverse events that do not result in discontinuation or dose down titration will not be collected after the first two weeks post-randomization*.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

[redacted]

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade:
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment:
  - Yes
  - No

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- treatment dosage increased/reduced
- treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification (IN) or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's eSource/source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

[redacted]

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day

[redacted]

period after the last study visit should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to each specific component of study treatment, (if study treatment consists of several components) complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Protocol specific unblinding rules for SUSARs that are also efficacy endpoints

In studies such as this one, where the efficacy endpoints potentially meet the requirements for SUSAR reporting, the integrity of the study may be compromised if the endpoints are systematically unblinded for expedited reporting to competent authorities/relevant ECs and investigators. In such cases, regulations allow an exemption from SUSAR unblinding and expediting aimed at ensuring the validity of an outcome study (EU Guidance 2011/C 172/01; FDA Guidance 2012). Therefore, the following rules for unblinding SUSARs during the study period will be applied.

7.3.1 Primary and secondary endpoints

The primary and secondary endpoints (CV death, HF hospitalization, outpatient HF, non-fatal spontaneous MI, and non-fatal stroke) will not be unblinded even if they meet the definition of a SUSAR. Novartis will not expedite a report to competent authorities/relevant ECs and

[redacted]

will not issue an investigator notification (IN). However, non-CV death, a secondary endpoint for the study, will be unblinded if it meets the criteria for a SUSAR.

If specifically requested by a local Health Authority, pre-specified endpoints that also meet criteria for SUSARs will be expedited to this Health Authority as blinded reports. Investigator notifications will not be issued for these events.

7.3.2 Adverse events that are commonly seen in the study population

Investigators will report AEs or SAEs that are commonly seen in the study population but they will not be unblinded and will not be reported as SUSARs to regulatory agencies, ECs, or investigators during the study.

In clinical trials evaluating treatments for high morbidity and/or high mortality disease states, SAEs that are known consequences of the underlying disease or condition under investigation, or events common in the study population, are anticipated to occur with some frequency during the course of the trial, regardless of drug exposure. While the investigator must still report all SAEs and all the targeted non-serious AEs during and after the first two weeks after randomization, respectively, as outlined in Section 7.1 SUSARS considered consistent with the following SAE Preferred Terms (PT) will not be unblinded and reported in an expedited timeframe to regulatory agencies, ECs or investigators during the course of the study. These events will be presented in the clinical study report at the end of the study.

abdominal pain, acute coronary syndrome, acute pulmonary oedema, anaemia, angina pectoris *, anxiety, arthralgia, asthenia, azotaemia, back pain, blood creatinine *, blood pressure *, blood urea nitrogen *, bronchitis *, cardiac arrest, cardiac arrhythmias (all Preferred Terms presenting any type of arrhythmia ***excluding*** electrocardiogram QT interval abnormal, electrocardiogram QT prolonged, long QT syndrome, torsade de pointes), cardiac asthma, cardiac catheterization, cardiac failure *, cardiac output *, cardiac pacemaker *, cardiac resynchronization therapy, cardiac surgery (including coronary artery bypass grafting), cardiac tamponade, cardiogenic shock, cardiorenal syndrome, cerebrovascular accident, chest pain, chronic obstructive pulmonary disease, confusional state, constipation, cor pulmonale *, cough *, creatinine renal clearance *, delirium, diarrhea, dizziness, dyspnea *, ejection fraction *, fatigue, generalized oedema, glomerular filtration rate *, gout, headache, heart transplant, hepatic congestion, hyperglycemia, hyperkalemia, hyperlipidemia, hypertension *, hyperuricaemia, hypoglycemia, hypokalemia, hypernatremia, hypotension *, implantable defibrillator *, influenza *, insomnia, intra-aortic balloon pump, loss of consciousness, muscle spasm, musculoskeletal pain, myocardial infarction*, nasopharyngitis, nausea, oedema, oedema due to cardiac disease, oedema peripheral, osteoarthritis, pain in extremity, percutaneous coronary intervention, pericardial effusion, pleural effusion, pneumonia *, presyncope, pulmonary hypertension, pulmonary oedema, renal failure *, renal impairment, respiratory distress *, respiratory failure *, respiratory tract infection *, stroke*, syncope, transient ischemic attack, urinary tract infection, valve insufficiency*, valve stenosis*, ventricular failure *, ventricular assist device, vomiting, weight increased

*More than 1 preferred term can contain this term.

[redacted]

- If specifically requested by a local Health Authority, pre-specified AEs commonly observed in the study population (see above) that also meet the criteria for SUSARs will be expedited to the requesting Health Authority as blinded reports without issuing INs, or
- Pre-specified AEs commonly observed in the study population that occur in patients under the jurisdiction of the requesting Health Authority will be expedited to the Health Authority as unblinded reports; INs will be issued for these events.

[redacted]

7.4 Liver safety monitoring

Liver Function Test (LFT) elevations, including both aspartate transaminase (AST) and alanine transaminase (ALT), are common in patients following an AMI. In a study with a total of 1,783 patients presenting with STEMI, 59.1% patients with Killip class II had AST increase greater than 3x ULN and 5.1% had ALT increase greater than 3x ULN. For patients with liver enzyme increase, AST and ALT levels in majority of them return to baseline within 2 weeks (Lofthus, et al. 2012).

Evaluation of LFT elevations should focus on the potential drug-induced LFT changes. As described by Lofthus et al, any LFT elevations during the first 2 weeks post-AMI are very likely caused by the underlying disease. Therefore, AST and/or ALT elevations within 2 week post-AMI will not be reported as SAEs unless investigators suspect the liver transaminase change is due to the investigational drug. A similar consideration is also applicable to the recurrent MI during the trial.

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Liver events, which cannot be solely explained by apparent AMI (either index or recurrent spontaneous MI event) as the underlying cause, are divided into two categories:

- LFT increases without associated symptoms which will require repeated assessments of the abnormal laboratory parameter
- Liver events (i.e., significant LFT increases or liver-toxicity related symptoms with or without LFT increases), which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Appendix 2 Table 14-1 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger of liver event without apparent AMI (either index or recurrent MI event) as the underlying cause and as defined in Appendix 2 Table 14-1 should be

[redacted]

followed up by the investigator or designated personnel at the trial site as summarized below. Detailed information is outlined in Appendix 2 Table 14-2.

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation.

These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For significant LFT increases or liver-toxicity related symptoms with or without LFT increases:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

It is the investigator's responsibility to investigate the potential occurrence of these events. These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded on appropriate CRF pages, including the liver event overview CRF pages. In addition, independent assessments of the biochemical Hy's law cases (defined as ALT or AST > 3x ULN and total bilirubin > 2x ULN) reported during the study will be performed by an external liver safety expert.

7.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

[redacted]

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes,	Yes, even if not associated with a SAE

7.6 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

7.7 Monitoring of safety data by the Data Monitoring Committee

An external independent Data Monitoring Committee (DMC) (Section 8.4) will be appointed to monitor the safety of study participants and to ensure that the program is being conducted with highest scientific and ethical standards. This DMC will review the endpoint and SAE/AE of special interest data throughout the trial in an unblinded manner. Should the DMC make recommendations on the conduct of the trial that are considered to have significant bearing on the benefit-risk of the trial, these will be communicated by Novartis to HAs, ECs and investigators within an appropriate timeframe and implement any additional actions required.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote

monitoring of each site's data may be performed by a centralized Novartis Clinical Research Associate (CRA) organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain eSource/source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these eSource/source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant eSource/source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the eSource/source data with the CRFs are performed according to the study-specific monitoring plan. No information in eSource/source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Oracle Clinical/Remote Data Capture (OC/RDC) system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff or Clinical Research Organization (CRO) working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

[redacted]

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

An external data monitoring committee (DMC) independent of Novartis will be appointed to monitor the study conduct and to review the results of the interim analyses for safety on a regular basis and determine if it is safe to continue the study according to the protocol. In addition, they will review the results from one interim analysis to allow for early stopping due to overwhelming efficacy. Any major recommendation from the DMC will be communicated to the Executive Committee and must be reviewed and ratified by the Executive Committee in consultation with Novartis prior to its enactment.

The membership of the DMC and the responsibilities of the DMC and Novartis will be defined in a separate document entitled the "Data Monitoring Committee Charter". The DMC Charter will include information about data flow, purpose and timing of DMC meetings, guidance in the decision making process, communication strategy, procedures for ensuring confidentiality, procedures to address conflicts of interest and statistical monitoring guidelines.

8.5 Adjudication Committee

Clinical Endpoint Committee

All clinical events, which could potentially fulfill the criteria for the primary, secondary, or other selected endpoints will be assessed during the study and reported to a blinded central Clinical Endpoint Committee (CEC) for adjudication. The CEC will be responsible for adjudicating and classifying all death events (CV vs. non-CV) and for determining whether pre-specified endpoint criteria are met for selected non-fatal events. The detailed definitions of the endpoints, required documentation and the adjudication process will be provided to all sites in a separate endpoint manual.

Angioedema Adjudication Committee

All angioedema or angioedema-like events will be assessed during the study and reported a blinded angioedema adjudication committee for adjudication. If such an event occurs, the

investigator will complete an Adjudication Questionnaire for an Angioedema-like Event form (provided by Novartis). Details on the process of reporting angioedema and angioedema like events are outlined in a manual provided to investigators.

Submission of an angioedema report is not a substitution for the submission of an SAE report. If an angioedema-like event satisfies the definition of an SAE, the investigator must submit an SAE report in addition to the Adjudication Questionnaire for an Angioedema-like Event.

The membership and responsibilities of the Angioedema Adjudication Committee are defined in a separate document that will be provided to the sites.

9 Data analysis

The analysis will be conducted on all patient data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation. Additional details of the statistical analyses will be documented in a Statistical Analysis Plan (SAP).

9.1 Analysis sets

The following analysis populations will be defined for statistical analysis:

- **Randomized (RAN) set** – All patients who received a randomization number, regardless of receiving trial medication.
- **Safety set (SAF) -** All patients who received at least one dose of study drug. Of note, the statement that a patient had no adverse events also constitutes a safety assessment. Patients 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 are analyzed according to the treatment they have been assigned to at the randomization.
- **The 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.

9.2 Patient demographics and other baseline characteristics

Summary tables will be provided by treatment group for demographic characteristics: including age, age group (<65 years vs. ≥65 years; <75 years vs. ≥75 years), sex, race, ethnicity, weight, height, body mass index (BMI) and baseline characteristics: including but not limited to information about the index MI event, (STEMI/NSTEMI; PCI/medical management; LVEF; Killip class, BP, renal function etc.), medical history and CV risk factors, and category of prior CV medications.

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

[redacted]

The FAS will be the patient population for the above analyses.

9.3 Treatments

The overall duration on the randomized study drug will be summarized by treatment group using mean, standard deviation, median, minimum, and maximum. Additionally, the number and percentage of patients will be summarized by treatment group for duration category. Mean doses and dose levels will be summarized by treatment group and visit. A Kaplan-Meier plot of time to discontinuation of study medication will be provided. A summary table by treatment group will be provided to display the number of patients who discontinued study medication and the number of patients who subsequently received the following medications during the study: ACE inhibitors, ARB, and Entresto™, (sacubitril/valsartan).

The duration of randomized study drug will also be calculated excluding temporary treatment discontinuations.

Concomitant medications and significant non-drug therapies, prior to and after the randomization date respectively, will be summarized by therapeutic class, preferred term, and treatment group for the safety set.

The number and percentage of patients on different CV background medications (e.g., aspirin, P2Y12 inhibitors, β-blockers, ACE inhibitors, ARBs, mineralocorticoid receptor antagonists, statins, and diuretics, etc.) will be tabulated by treatment at baseline and during the treatment epoch.

The SAF will be used for the summaries of exposure data and the FAS will be used for the summaries of concomitant medications.

9.4 Analysis of the primary variable(s)

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

9.4.1 Variable(s)

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 start 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).

[redacted]

9.4.2 Statistical model, hypothesis, 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. 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 plotted.

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 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 9.4.3, 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 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.

Subgroup analysis

Subgroup analyses will be performed for the 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 and including terms for treatment, region and PCI use at baseline in the model. The p-value associated with the interaction term 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. 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 below:

- Age group (< 65 vs ≥ 65 years; < 75 vs ≥ 75 years)
- Gender
- Race
- Region
- STEMI vs. NSTEMI (for this analysis, do not stratify by STEMI/NSTEMI, but include as a factor in the model)
- Baseline LVEF (by quartiles)
- Killip class (I vs. ≥ II)
- Infarct location (anterior, inferior, and other)
- PCI use at baseline (PCI use versus medical management after index MI up to randomization)
- Time from the index MI presentation to randomization (two subgroups cut by the median time)
- Baseline SBP (three groups: ≤110 mmHg; >110 mmHg and ≤140 mmHg; >140 mmHg)
- Baseline eGFR (<60 vs ≥ 60 mL/min/1.73 m^2)
- History of diabetes (yes/no)
- Atrial Fibrillation associated with index MI at baseline (yes/no)
- Prior history of MI
- History of hypertension (yes/no)
- Prior ACEi or ARB use (yes/no)
- Use of β-blocker at baseline (yes/no)
- Use of mineralocorticoid antagonists at baseline (yes/no)
- Use of oral loop diuretics at baseline (yes/no)

9.4.3 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.

[redacted]

9.4.4 Sensitivity analyses

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

9.5 Analysis of secondary variables

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

9.5.1 Efficacy variables

The secondary variables are defined as follows; the censoring mechanism will be the same as defined for the primary endpoint unless indicated otherwise:

(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 (censoring will occur at the time of all-cause death)

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

(4) The cumulative number of composite events, including hospitalization due to HF, hospitalization due to non-fatal spontaneous MI, hospitalization due to non-fatal stroke and CV death. This endpoint is based on the total number of composite endpoints (count) and the patient-specific follow-up time from randomization to the 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).

(5) Time from randomization to all-cause mortality - patients without a death will be censored at the date of withdrawal from the study or the last day known to be alive (which may be established via telephone contact or the last visit prior to analysis cut off).

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'). Endpoints (1), (2), (3), and (5) will be analyzed using the same statistical analysis methods as specified for the primary analysis.

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). Treatment, STEMI/NSTEMI, PCI use at baseline and region will be included in the model as fixed effects. The relative rate ratio will be presented for LCZ696 vs ramipril together with 2-sided 95% confidence interval and 1-sided p-value.

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 endpoints (1), (3), (4) and (5), the secondary analysis described above will estimate the treatment effect of LCZ696 vs ramipril including any effect of prescribed Entresto™ for ramipril patients who

[redacted]

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.

Endpoints (1), (3) and (5) will be analyzed using an inverse probability of censoring weighted (IPCW) Cox proportional hazards model (Robins and Finkelstein 2000)). In this analysis, the censoring mechanism will be the same as described for the primary analysis for patients who are not prescribed Entresto™. For patients who do, censoring will occur at the minimum of the last date the endpoint status was known, the time of death from non-CV causes or 28 days after study treatment discontinuation. To adjust for the potential informative censoring, patients with event times censored due to treatment switch will be dynamically replaced in the patient risk-set to be represented by patients in control arm with a matching prognostic profile by up-weighting such patients in the analysis set. The weights will be calculated using a logistic regression with clinical risk factors determinant of developing the endpoint as covariates in the model (both baseline and post-baseline). A weighted Cox proportional hazard model will be fitted to this modified risk set. The model will be stratified by STEMI/NSTEMI; region, PCI use at baseline will be included as covariates. 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. Further details on appropriate covariate adjustment and associated implementation will be prospectively provided in the statistical analysis plan.

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.

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).

[redacted]

[redacted]

[redacted]

[redacted]

9.7 Interim analyses

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 9.5.1 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

[redacted]

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.

9.8 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, see Section 9.7.
- 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. See Table 9-1 for the cumulative event rates assumed for the sample size calculation.

Table 9-1 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 event rates of the primary triple composite endpoint which would be expected.

In order to understand the impact of the uncertainties described above, Table 9-2 provides the sample sizes estimated to achieve at least 800 primary events with different underlying assumptions.

Table 9-2 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

Number of randomized patients required calculated using East version 6.3

Power for secondary endpoints

Table 9-3 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).

[redacted]

Table 9-3 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 9-1

[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.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Council for Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European

Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient eSource/source documents.*

[*] For Germany only, the first paragraph will read as follows:

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation) IRB/IEC-approved informed consent. He/she should indicate assent by personally signing and dating the written informed consent document. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient eSource/source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the

clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance (CQA), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this

study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

12 References

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[redacted]

13 Appendix 1: Clinically notable laboratory values and vital signs

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

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

[redacted]

14 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 14-1 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

Table 14-2 Follow-up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

[redacted]

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

[redacted]

15 Appendix 3: Killip Classification

Pulmonary congestion following the index MI event will be assessed as the worst Killip class between index MI presentation and randomization using the criteria outlined below:

- Class 1 No rales, no 3rd heart sound
- Class 2 Rales in <½ lung field or presence of a 3rd heart sound
- Class 3 Rales in >½ lung field–pulmonary edema
- Class 4 Cardiogenic shock–determined clinically

16 Appendix 4: Guidelines for the management of blood pressure

Guidelines

1. Investigator should monitor BP closely
2. If symptomatic hypotension occurs:
    a. Correct any treatable cause, e.g. hypovolemia
    b. If hypotension persists, any non-disease modifying background antihypertensive drug such as diuretics, calcium channel blockers (CCBs), nitrates, and/or α-blockers, can be down-titrated or stopped first per investigator's clinical judgement before down-titration of the study drug is considered..
    c. It is important to note that dose adjustment of disease-modifying background therapy, e.g., β blockers, or mineralocorticoid antagonists is discouraged under these circumstances, unless they are believed to be the most likely cause of hypotension.

If hypotension persists, the study drug should be down-titrated or even temporarily withdrawn. The dose re-challenge and medications adjust guidelines described in Section 5.5.5 should be adhered to as much as possible.

17 Appendix 5: Treatment guidelines for hyperkalemia (serum potassium greater than 5.3 mmol/L [mEq/L])

General principles

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

Any patient with a serum potassium > 5.3 mmol/L (mEq/L) at any time after randomization requires the Investigator to confirm the serum potassium concentration in a non-hemolyzed sample via an immediate repeat lab sample to both the clinic local lab and the study central lab. Regular, repeated checks of serum potassium concentration (beyond that prescribed in the protocol) should continue until it is clear that the serum potassium concentration is stable and not rising into the range of concern (≥ 5.5 and < 6.0 mmol/L [mEq/L]) or potential danger (≥ 6.0 mmol/L [mEq/L]).

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

Corrective action for management of hyperkalemia

Serum potassium greater than 5.3 and less than or equal to 5.5 mmol/L (mEq/L)

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

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

- Assess patient for dehydration or any condition that could lead to dehydration (e.g., diarrhea, vomiting) and/or hypovolemia and initiate appropriate corrective measures of rehydration.
- Repeat serum potassium measurement within 3 to 5 days
- If serum potassium remains > 5.3 and ≤ 5.5 mmol/L (mEq/L), regularly monitor serum potassium levels to ensure stability (suggested once monthly)
- Consider down-titration of study drug, according to investigator's medical judgment.

Serum potassium greater than 5.5 and less than 6.0 mmol/L (mEq/L)

- Confirm serum potassium concentration in a non-hemolyzed sample
- Consider down-titration or temporarily discontinue background therapy of mineralocorticoid antagonists (if they are believed to be the most likely cause of hyperkalemia).
- Apply all measures outlined for serum potassium > 5.3 and ≤ 5.5 mmol/L
- Repeat serum potassium measurement after 2-3 days
- If serum potassium < 5.5 mmol/L, consider resumption of study drug at lower dose with repeat serum potassium within 5 days

Serum potassium greater than or equal to 6.0 mmol/L (mEq/L)

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

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

[redacted]

NOVARTIS

Global Clinical Development - General Medicine

[LCZ696]

Clinical Trial Protocol CLCZ696G2301

PARADISE-MI: Prospective ARNI versus ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction

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

Document type:	Amended Clinical Trial Protocol
EUDRACT number:	2016-002154-20
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Clinical trial phase:	III
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Clinical Trial Protocol Template Version 3.1 (February 2016)

[redacted]

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List of abbreviations

ACE	Angiotensin converting enzyme
ACEi	Angiotensin converting enzyme inhibitor
AE	Adverse Event
AESI	Adverse event of special interest
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
AST	Aspartate aminotransferase
AUC	Area under the curve
BB	Beta blocker
bid	twice a day
BMI	Body mass index
BNP	B-type natriuretic peptide
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CCB	Calcium channel blocker
CCU	Coronary/critical care unit
CEC	Clinical Event Committee
CDS	Core Data Sheet (for marketed drugs)
CFR	US Code of Federal Regulations
CHF	Chronic heart failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019 caused by severe acute respiratory syndrome coronavirus 2 (also called SARS-CoV-2)
CPK	Creatine phosphokinase
CPO	Country Pharma Organization
CRF	Case Report/Record Form
eCRF	Electronic Case Report/Record Form
CRT	Cardiac resynchronization therapy
CRO	Contract Research Organization
CSR	Clinical study report
CTC	Common Terminology Criteria
CTRD	Clinical Trial Results Database
CV	Cardiovascular

[redacted]

DBP	Diastolic blood pressure
DM	Diabetes mellitus
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiography
EDC	Electronic Data Capture
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of study
ER	Emergency room
ESRD	End stage renal disease
FAS	Full analysis set
FDA	Food and Drug Administration
FWER	FamilyWise Error Rate
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
Hgb	Hemoglobin
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HR	Hazard ratio
hsTnT	High-sensitivity troponin T
HTN	Hypertension
IA	Interim analysis
IB	Investigator brochure
ICD	Implantable cardioverter defibrillator
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive care unit
IEC	Independent Ethics Committee
IN	Investigator notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to treat
IUD	Intrauterine device
IUS	Intrauterine system
iv	Intravenous
LFT	Liver function test

[redacted]

LV	Left ventricular
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
MACE	Major Adverse Cardiac Events
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
MMRM	Mixed model of repeated measurements
MRA	Mineralocorticoid antagonist
NEP	Neprilysin
NEPi	Neprilysin inhibitor
NSTEMI	Non-ST-elevation myocardial infarction
NT-proBNP	N-terminal pro-brain natriuretic peptide
OC/RDC	Oracle Clinical/Remote Data Capture
od	once a day
PCI	Percutaneous coronary intervention
PDE-5	Phosphodiesterase-5
po	oral(ly)
PRO	Patient reported outcomes
PT	Preferred term
PTA	Post-trial access program
[redacted]	[redacted]
RAS	Renin angiotensin system
RBC	Red blood cell
RDW	Red blood cell distribution width
RRR	Relative risk reduction
RU	Resource utilization
SAE	Serious Adverse Event
SAF	Safety set
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SMQ	Standardized MedDRA Query
STEMI	ST-elevation myocardial infarction
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total bilirubin
TD	Study Treatment Discontinuation
ULN	Upper limit of normal
WBC	White blood cell

[redacted]

[redacted]	[redacted]
WHO	World Health Organization
WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Cohort	A specific group of patients fulfilling certain criteria
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug(s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material, and does not allow any further collection of personal data

[redacted]

Amendment 4 (06-Aug-2020)

Amendment rationale

The purpose of this amendment is to add a second interim analysis in response to the COVID-19 pandemic with the stopping boundary for the primary endpoint at one-sided alpha of 0.005.

A novel coronavirus that had not previously been identified is causing clinical disease in humans (COVID-19). On 11-Mar-2020, the World Health Organization (WHO) characterized COVID-19 as a pandemic. As acknowledged by global Health Authorities in their guidance to the pharmaceutical industry, the COVID-19 pandemic has a global impact on the conduct of clinical trials of medicinal products. Challenges arising include at-risk patient populations, site closures, travel restrictions, shelter-in-place orders, interruptions to the supply chain for the investigational product, and other considerations if trial patients and site personnel become infected with COVID-19.

The significant impact of COVID-19 on the safety of patients and study personnel has greatly impacted study conduct. We have already observed marked increase in missed visits, treatment interruption due to drug supply issues related to the pandemic and substantial reduction of HF hospitalization and outpatient HF events. This observation is consistent with the published data which showed a greater than 50% reduction in the occurrence of HF hospitalization during the COVID-19 pandemic (Hall, et al. 2020), adding to other serious challenges on the conduct of the PARADISE-MI study.

Prior to 01-Mar-2020, timepoint before which clinical trial data has generally not been impacted by the COVID-19 pandemic at the global level, approximately 80% of the 708 target total number of the primary events in the PARADISE-MI study had been accumulated. Considering the advanced state and documented impact of the COVID pandemic on the conduct of the trial, the PARADISE-MI Executive Committee recommended adding a second interim analysis using the primary events accrued prior to 01-Mar-2020 for the primary analysis. In case of early stopping, all additional endpoints occurring on or after 01-Mar-2020 until study close out will be included as a sensitivity analysis. In the event that the data accumulated prior to the adverse influence of the pandemic had already established convincing efficacy, as per the proposed second interim analysis criteria, it would represent the most reliable test of the study hypothesis.

Novartis will continue monitoring the impact of the COVID-19 pandemic, in the event that the COVID-19 pandemic continues over a prolonged period of time hampering the ability to complete the trial in a timely and appropriate fashion, Novartis may consider modifying the proposed interim analysis to be the final analysis and close out the study prematurely.

There is no impact of this amendment on the study population or endpoints. If the trial continues after the interim analysis, the main analysis of the study result will remain as per the original protocol but additional sensitivity analyses will be performed to evaluate the potential impact of COVID-19 on the interpretation of data generated post 01-Mar-2020. The alpha for the final analysis will be adjusted accordingly to control the overall type 1 error (across the 2 interim analyses and the final analysis) at 1-sided alpha of 0.025.

[redacted]

Changes to the protocol

List of abbreviations was updated to include COVID-19.

Previous Amendments were updated to include amendment finalization date as per current Novartis standard.

Protocol Summary Data Analysis section, Section 3.5 Purpose and timing of interim analyses/ design adaptations, and Section 8.4 Data Monitoring Committee were updated to reflect the introduction of a second interim analysis.

Table 6-1 and Section 18 Appendix 6 Investigational Plan [redacted] Table 6-1 has also been updated to indicate echocardiograms performed as standard of care prior to consent are permitted.

Section 9 has been updated to reflect the general data analysis strategies for the added second interim analysis and possible early termination by sponsor if needed due to COVID-19.

Section 9.4.4 has been updated to define the approach for sensitivity analyses related to COVID-19.

Section 9.5 has been updated to describe the general strategies for the main and sensitivity analyses relative to the secondary efficacy endpoints.

[redacted]

Section 9.7 Interim Analysis was updated to describe the plan for the added efficacy interim analysis.

Section 9.8 has been updated to discuss the impact on power for the primary endpoint in adding the second efficacy interim analysis.

Section 12 was updated with the added reference.

Other typographical corrections were also included.

All changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol may require IRB/IEC and Health Authority approval according to local regulations prior to implementation. The changes herein do NOT affect the trial specific model ICF.

[redacted]

Amendment 3 (01-May-2019)

Amendment rationale

The purpose of this amendment is to increase the sample size from 4,650 to 5,650 and adjust the assumption for the primary composite endpoint events of cardiovascular (CV) death, heart failure (HF) hospitalization, or outpatient HF treatment effect from 18% to 19%. These changes were made as an outcome of the per-protocol sample size re-estimation that was conducted when approximately ½ of patients were randomized and reached the 3 month treatment time point as described in Section 9.8. At the time of this protocol amendment release, over 3,500 patients have been randomized.

PARADISE-MI is an event-driven outcomes study. In the per-protocol sample size re-estimation, the estimated cumulative event rates based on the available blinded data were lower than the originally assumed event rates. This indicated that the original assumptions may not hold. Therefore, in order to limit the impact in terms of considerable increase in overall trial duration, sample size re-estimation was performed and sample size increase became necessary. In addition, newly available efficacy data from the PIONEER-HF (CLCZ696BUS01) study showed a 46% relative risk reduction (RRR) (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 underlying pathophysiological mechanism between heart failure with reduced ejection fraction (HFrEF) and post- acute myocardial infarction (AMI) with left ventricular dysfunction, and also the acute setting for both PIONEER-HF and PARADISE-MI studies, this new data indicated that the initial hazard reduction assumption of the primary endpoint in PARADISE-MI may have been an underestimate. The increase in the sample size and the assumption for the treatment effect size maintain the statistical power of 80% for the primary composite endpoint.

Additionally, Section 5.6.1 was updated to replace the described open-label extension study with a post-trial access program (PTA). The purpose of the PTA is to make the investigational drug available to qualified patients participating in the trial after the completion of the trial, in line with local laws and regulations.

Lastly, the assessment schedule has been clarified in regard to additional visits. PARADISE-MI is an event-driven trial and patients will continue to be treated until the required number of endpoints is met and the maximum treatment period is expected to extend beyond month 32. Some minor changes are also made to clarify the entry criteria regarding risk factors, and to correct typographical errors and minor inconsistencies in the protocol. There is no impact of this amendment on the study population or the main analysis of the study results.

[redacted]

Changes to the protocol

The described changes under the amendment rationale regarding the sample size re-estimation are implemented throughout the protocol. In addition, the following updates, clarifications, and omissions are included in this protocol amendment:

Protocol Summary was updated to reflect the extended trial duration, updated sample size and endpoint event assumptions, to add clarity to Inclusion Criteria #5, [redacted]

In Figure 3-1, the duration of double-blind treatment epoch was expanded to reflect treatment until the number of required endpoints is met and patients return for the end of study (EOS) visit.

Table 3-3 The renal function criteria was corrected to estimated globular filtration rate (eGFR) $\geq$ 30 mL/min/1.73m^2 and creatinine increase $<$ 0.5 mg/dl from baseline as noted elsewhere in the protocol.

Section 3.1 The estimated trial duration was updated from 32 months to 43 months and the recruitment period was updated to approximately 37 months.

Section 3.5 Estimated number of endpoints needed at the time of interim analysis was updated.

Section 4 The number of centers with randomized patients was reduced from approximately 650 to approximately 500.

Section 4.1 Inclusion Criteria #5 was updated to clarify that if multiple left ventricular ejection fraction (LVEF) measurements have been performed during index event, the last one performed prior to randomization should be considered as the qualifying measurement.

Section 4.2 Exclusion Criteria #27 was added. [redacted]

Section 5.4, Section 5.5.9, and Section 5.6.2 were aligned to clarify that patients who are intentionally unblinded as per study process must permanently discontinue study treatment; whereas the appropriate personnel from the site and Novartis will assess whether study drug should be discontinued in instances where a patient is inadvertently unblinded for any reason.

Section 5.6.1 Approach for the investigational drug to be made available to qualified patients participating in the trial was refined from an open-label extension study to a post-trial access (PTA) program and added that the mechanism for post-trial access to investigational drug must comply with the local laws and regulations in the participating countries in order to be made available.

Section 5.6.3 Withdrawal of Informed Consent section was updated to align with new laws regarding personal data.

Section 6 Language was added to specify that in addition to vital status, primary endpoint information should be collected for every patient.

[redacted]

Table 6-1 was expanded to reflect patients' continuation in the trial until the number of required events is met and patients are asked to return for the EOS and reflect assessments which are considered standard of care at time of screening and randomization.

Section 6.5.4 Section was updated as per Table 6-1.

Section 6.5.6 Section was updated to reflect that the patient must interrupt, rather than discontinue, study drug in case of pregnancy. Update is also reflected in Table 6-1.

Section 9.3 Section was updated to align with the statistical analysis plan.

Section 9.6.1 Secondary efficacy endpoint regarding changes in serum creatinine was clarified.

Section 9.7 Section was updated to reflect that the interim analysis will be conducted when approximately 472 adjudication-confirmed primary endpoints have been reached.

Section 9.8 Sample Size Calculation was revised following the planned sample size re-estimation using blinded data and the updated sample size calculation is described in Section 9.8.2.

Appendix 5 Pre-defined potassium values for the management of hyperkalemia were updated to correct an inconsistency. Hyperkalemia values that warrant corrective action include serum potassium greater than 5.3 and less than 5.5 mmol/L (mEq/L); serum potassium greater than or equal to 5.5 and less than 6.0 mmol/L (mEq/L).

Appendix 6 Investigational Plan [redacted] nd to reflect the additional exclusion criteria for patients participating in the pulmonary ultrasound assessment.

Other minor updates and corrections were also included.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 2 (25-Apr-2017)

Amendment rationale

[redacted]

The amendment also removes the targeted adverse event data collection, and provides additional guidance for co-administering LCZ696 with atorvastatin or other statins. Further, in order to achieve the target dose in the early phase post AMI, for patients who have not titrated to the target dose level 3 by week 4, an unscheduled dose titration visit on or about week 6 is also recommended. Finally, some minor changes were also made to clarify the valsartan bridging procedure on day 1 post randomization, and to correct typographical errors and inconsistencies in the protocol. There is no impact of this amendment on the study population or the main analysis of the study results.

Changes to the protocol

[redacted]

Section 3 Investigational plan was updated to clarify the one-day valsartan bridging procedure [redacted]

Section 4.1 Inclusion criteria

- Inclusion criteria #3 was updated to clarify that patients with clinical presentation thought to be related to Takotsubo cardiomyopathy are also not eligible.
- Inclusion criteria #4 was updated to add diuretics, vasodilators, vasopressors and/or inotropes as intravenous treatment required for pulmonary congestion. A footnote was also added clarifying the index MI with LV systolic dysfunction **and/or** pulmonary congestion.

Section 4.2 the following exclusion criteria were updated or added

- Exclusion criteria #13 was updated to permit equivalent plasma potassium value.
- Exclusion criteria #25 regarding women of child bearing potential and the use of highly effective contraception was updated to allow local regulations to take precedence when it deviates from the contraception methods listed in the protocol; the local regulations will be described in the ICF.

[redacted]

- [redacted]

Section 5.5.4 Instructions for prescribing and taking study drug was updated to clarify the valsartan bridging procedure.

Section 5.5.7 Concomitant medications was updated to provide additional guidance when co-administering LCZ696 with atorvastatin or other statins.

Table 6-1 Assessment schedule was updated as follows:

- The use of the central laboratory for screening and study drug titration decisions was added if the use of the local laboratory is not possible or will take longer to obtain results than the central laboratory assessments.
- [redacted]
- [redacted]
- The recommended unscheduled dose uptitration visit was added
- More frequent pregnancy testing, if required by local regulatory authorities was added
- [redacted]

Section 6.5.4 Laboratory evaluations was updated to allow equivalent plasma potassium and central laboratory assessments for screening and dose initiation and titration decisions.

Section 6.5.6 Pregnancy and assessments of fertility was updated to allow more frequent pregnancy testing if required by local regulatory authorities.

Sections 6.6.4 [redacted]

Section 7.1 Adverse events were updated to remove the targeted collection of safety data so that all AEs will be collected. Also, statin related adverse events were added to the list of AEs of special interest.

Section 7.4 Liver safety monitoring was updated to include acute heart failure episodes as an underlying cause for events of liver enzyme elevation.

Sections 9.6.6 [redacted].

Section 17, Appendix 5 Treatment guidelines for hyperkalemia was updated to allow serum or equivalent plasma potassium values.

Section 18, Appendix 6 [redacted]

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation. The changes herein do NOT affect the trial specific ICF.

[redacted]

Amendment 1 (29-Jun-2016)

Amendment rationale

The purpose of this amendment is to refine the recommendations for alternative treatment to ensure sufficient RAS blockade in the event a patient needs to discontinue the study drug due to intolerable adverse events. The amendment also clarifies the acceptable methods of contraception for women of child bearing potential. Additional minor changes were also made to correct typographical errors and inconsistencies in the protocol. None of these changes will have an impact on the study population, endpoints, or the analysis of the study results.

Changes to the protocol

Section 5.5.6 Rescue medications was updated to provide guidance on the alternative open-label treatment of RAS blockade in the event a patient needs to discontinue study drug at the investigator's discretion due to intolerable adverse events, despite the dose reduction or temporary interruption/re-challenge of study medication.

Section 4.2 Exclusion criteria #25 was changed to clarify that women physiologically capable of becoming pregnant are excluded unless they are using highly effective methods of contraception not basic methods of contraception. The methods of contraception currently described in the protocol are highly effective, however, the wording was modified to comply with the current Novartis guidelines for the prevention of pregnancy.

Additional minor changes were made to correct inconsistencies and typographical errors in the protocol.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation. The changes herein do NOT affect the trial specific ICF.

[redacted]

Protocol summary

Protocol number	CLCZ696G2301
Title	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
Brief title	PARADISE-MI: Prospective ARNI versus ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction
Sponsor and Clinical Phase	Novartis; Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the efficacy and safety of LCZ696 compared to ramipril, in reducing the occurrence of cardiovascular (CV) death, heart failure (HF) hospitalization and outpatient HF (time-to-first event analysis) in post-AMI patients with evidence of left ventricular (LV) systolic dysfunction and/or pulmonary congestion, without a known prior history of chronic HF. This is an event-driven study which is a well-established study design for long-term cardiovascular outcome trials in post-acute myocardial infarction (AMI) patients. While the composite of CV death or HF hospitalization is a well-established mortality and morbidity endpoint, the addition of the outpatient HF component, which in this study represents the confirmed diagnosis of new onset symptomatic HF, aims to capture the clinically important outpatient event that contributes to the totality of HF morbidity following an AMI presenting as either inpatient (i.e., HF hospitalization) or outpatient (i.e., outpatient HF) events. Ramipril is chosen as an active comparator of the study representing the guideline-recommended standard-of-care angiotensin converting enzyme (ACE) inhibitors shown to improve survival and reduce HF morbidity in high-risk post-AMI patients.
Primary Objective(s)	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 outpatient HF endpoint event is defined as an adjudicated event of clinical development of symptomatic HF (either urgent/unscheduled or non-urgent) in the outpatient setting with symptoms and signs requiring initiation/intensification of intravenous or qualifying oral HF treatment.)
Secondary Objectives	• To demonstrate the superiority of LCZ696, compared to ramipril, in delaying the time-to-first occurrence of CV death or HF hospitalization • To demonstrate the superiority of LCZ696, compared to ramipril, in delaying the new onset of symptomatic HF defined as time-to-first occurrence of HF hospitalization or outpatient HF • To demonstrate the superiority of LCZ696, compared to ramipril, in delaying the time-to-first occurrence of CV death, non-fatal spontaneous MI or non-fatal stroke

[redacted]

	• 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 or non-fatal stroke • To demonstrate the superiority of LCZ696, compared to ramipril, in delaying the time to all-cause mortality • To evaluate the safety and tolerability of LCZ696 compared to ramipril
Study design	This study 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 over a period of approximately 43 months. The study is event-driven and will continue until the requirement of total confirmed endpoint events, i.e., at least 708 first primary composite endpoint events and at least 592 first CV death or HF hospitalization events, has been achieved.
Population	Approximately 5,650 male and female high risk patients ≥ 18 years of age who have sustained a spontaneous acute myocardial infarction (ST segment elevation MI (STEMI) or non-ST segment elevation MI (NSTEMI) between 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 have to have at least one predefined risk factor and without known prior history of chronic HF.
Key Inclusion criteria	1. Written informed consent must be obtained before any assessment is performed. 2. Male or female patients ≥ 18 years of age. 3. Diagnosis of spontaneous AMI based on the universal myocardial infarction (MI) definition* with randomization to occur between 12 hours and 7 days after index event presentation**. Spontaneous AMI is defined when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia due to primary coronary event. Under these conditions, the following criteria have to be met for the diagnosis of spontaneous AMI: • Detection of rise and/or fall of cardiac enzymes (cardiac troponin, cTn or the MB fraction of creatinine kinase, CKMB) with at least one value above the 99th percentile of the upper reference limit (URL) or the local laboratory MI diagnosis cut-off value, together with evidence of myocardial ischemia with at least one of the following: ◦ Ischemic discomfort or other ischemia symptom(s) ◦ Electrocardiogram (ECG) characteristics of STEMI or NSTEMI including new or presumably new significant ST-segment-T wave (ST-T) changes ◦ Newly developed pathological Q waves or left bundle branch block (LBBB) in the ECG (*Patients with a spontaneous MI event determined to be secondary to another medical condition such as anemia, hypotension, or an arrhythmia OR thought to be caused by coronary vasospasm with documented normal coronary arteries are not eligible; patients with clinical presentation thought to be related to Takotsubo cardiomyopathy are also not eligible)

	(**_Index MI presentation is the time of patient presentation at either the ER/ED, ICU/CCU or hospital ward etc., for the treatment of the index MI.)_ 4. Evidence of LV systolic dysfunction and/or‡ pulmonary congestion requiring intravenous treatment associated with the index MI event defined as: • Left ventricular ejection fraction (LVEF) ≤ 40% assessed locally by echocardiography, magnetic resonance imaging, cardiac CT, radionuclide or contrast ventriculography after index MI presentation and prior to randomization. (These examinations may be performed as part of patient standard-of-care. In case multiple LVEF measurements have been performed during index event, the last one performed prior to randomization should be considered as the qualifying measurement), **and/or‡** • Pulmonary congestion requiring intravenous treatment (diuretics, vasodilators, vasopressors and/or inotropes) during the index hospitalization supported by clinical assessment (worst Killip class, II or above) or radiological findings. Radiological evidence of pulmonary congestion is defined as pulmonary venous congestion with interstitial or alveolar edema and must be supported by at least one chest X-ray or CT scan. (‡ denotes that patients with either LVEF ≤40%, or pulmonary congestion requiring IV treatment, or both will qualify for this inclusion criterion) 5. At least one of the following 8 risk factors: • Age ≥ 70 years • eGFR <60 mL/min/1.73 m^2 based on Modification of Diet in Renal Disease (MDRD) formula at screening visit • Type I or II diabetes mellitus • Documented history of prior MI supported by ECG changes and/or elevation of cardiac enzymes consistent with MI diagnosis. • Atrial fibrillation as noted by ECG, associated with index MI • LVEF < 30% associated with index MI (In case multiple LVEF measurements have been performed during index event, the last one performed prior to randomization should be considered as the qualifying measurement.) • Worst Killip class III or IV associated with index MI requiring intravenous treatment • STEMI without reperfusion therapy within the first 24 hours after presentation 6. Hemodynamically stable defined as: • Systolic blood pressure (SBP) ≥ 100 mmHg at randomization for patients who received ACE inhibitor/angiotensin receptor blocker (ARB) during the last 24 hours prior to randomization (ACE inhibitor/ARB Yes patients) • SBP ≥ 110 mmHg at randomization for patients who did not receive ACE inhibitor/ARB during the last 24 hours prior to randomization (ACE inhibitor/ARB No patients) • No intravenous treatment with diuretics, vasodilators, vasopressors and/or inotropes during the last 24 hours prior to randomization.

[redacted]

Key Exclusion criteria	1. Known history of chronic HF prior to randomization 2. Cardiogenic shock within the last 24 hours prior to randomization 3. Persistent clinical HF at the time of randomization 4. Coronary artery bypass graft (CABG) performed or planned for index MI 5. Clinically significant right ventricular MI as index MI 6. Symptomatic hypotension at screening or randomization 7. Patients with a known history of angioedema 8. Stroke or transient ischemic attack within one month prior to randomization 9. Known or suspected bilateral renal artery stenosis 10. Clinically significant obstructive cardiomyopathy 11. Open-heart surgery performed within one month prior to randomization or planned cardiac surgery within the 3 months after randomization 12. eGFR < 30 ml/min/1.73 m^2 as measured by the Modification of Diet in Renal Disease (MDRD) formula at screening 13. Serum potassium > 5.2 mmol /L (or equivalent plasma potassium value) at randomization 14. Known hepatic impairment (as evidenced by total bilirubin > 3.0 mg/dL or increased ammonia levels, if performed), or history of cirrhosis with evidence of portal hypertension such as esophageal varices 15. Previous use of LCZ696 or Entresto™ 16. Use of other investigational drugs within 30 days prior to screening 17. History of hypersensitivity to the study drugs or drugs of similar chemical classes 18. Known intolerance or contraindications to study drugs or drugs of similar chemical classes including ACE inhibitors, ARB or NEP inhibitors 19. Patients taking medications prohibited by the protocol that cannot be discontinued for the duration of the study 20. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin) within the past 3 years with a life expectancy of less than 1 year 21. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or extraction of study drug at investigators' discretion 22. History or evidence of drug or alcohol abuse within the last 12 months 23. Patients considered unsuitable for the study, including patients with psychiatric, behavioral or cognitive disorders, sufficient to interfere with the patient's ability to understand and comply with the protocol instructions or follow-up procedures 24. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test 25. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of investigational drug [redacted]

[redacted]

	27. [redacted]
Study treatment	LCZ696* 50 mg (dose level 1), 100 mg (dose level 2) and 200 mg (dose level 3) twice daily (* *LCZ696 dose levels 1, 2 and 3 are equivalent to sacubitril/valsartan 24/26 mg, 49/51 mg and 97/103 mg, respectively*) Ramipril 1.25 mg (dose level 1), 2.5 mg (dose level 2), and 5 mg (dose level 3) twice daily Valsartan (VAL489)** 40 mg (dose level V1) and 80 mg (dose level V2) twice daily for one day (** *Patients who are randomized to LCZ696 and received ACE inhibitors in last 36 hours prior to randomization will be given a valsartan bridging in a blinded manner for one day with two doses at dose level V1 or V2: 40 or 80 mg twice daily, prior to beginning the double-blind LCZ696 treatment*)
Efficacy assessments	• CV death, • Heart failure hospitalization • Outpatient heart failure • Non-fatal spontaneous MI • Non-fatal stroke • All-cause mortality
Key safety assessments	• All adverse events (AE)s • All serious adverse events (SAEs) • Sitting systolic blood pressure (SBP), sitting diastolic blood pressure (DBP), and heart rate • Laboratory values (including monitoring for hyperkalemia, renal dysfunction) • Angioedema surveillance
Other assessments	• [redacted]

[redacted]

	• [redacted]
Data analysis	The primary efficacy variable is time to first occurrence of CV death, HF hospitalization or outpatient HF. The secondary efficacy variables are: • Time to first occurrence of CV death or HF hospitalization • Time to first occurrence of HF hospitalization or outpatient HF (censoring will occur at the time of all-cause death) • Time to first occurrence of CV death, non-fatal spontaneous MI or non-fatal stroke • Cumulative number of events, including HF hospitalization, hospitalization due to non-fatal spontaneous MI, hospitalization due to non-fatal stroke and CV death. • Time to all-cause mortality Time-to-event is computed as the number of days from randomization to the start date of the endpoint event (first occurrence). The 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. 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 primary endpoint and the first four secondary endpoints will be included in a hierarchical statistical testing strategy to control the familywise type I error rate at the 1-sided 2.5% level (in the strong sense). Two interim analyses are planned to assess efficacy. The first interim analysis for efficacy is planned when approximately two-thirds of the target number of primary adjudicated events has been obtained. The second interim analysis for efficacy is planned to include primary events with onset date prior to 01-Mar-2020 (estimated start of COVID-19 impact globally).Sample size calculation: The sample size and power calculations described below are based on the study design prior to protocol amendment 4 when only one 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 9.7), there will be a small impact on power (approximately 0.1% power loss for the primary endpoint). 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 events and at least 592 first CV death or HF hospitalization events in this event-driven study. Seven hundred eight primary 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 intent-to-treat analysis) for this secondary endpoint for the same type I error rate. These calculations assume a 37 month recruitment period and approximately 4 month follow-up of the last randomized patient for endpoints to accrue in the field. An additional 1-2 months are expected through to the last patient last visit.
Key words	Spontaneous AMI, HF hospitalization, outpatient HF, LV systolic dysfunction, pulmonary congestion, STEMI, NSTEMI, randomized clinical trial, LCZ696, ramipril, echocardiography

[redacted]

1 Introduction

1.1 Background

Acute myocardial infarction (AMI) is one of the common reasons for cardiac hospitalization and its annual incidence in US, EU-5, Japan and China is currently estimated at 2.5 million per year. In the US alone, approximately 683,000 patients were discharged from hospitals in 2009 with a diagnosis of acute coronary syndrome (O'Gara, et al 2013). Although the community incidence rates for ST elevation myocardial infarction (STEMI) have declined over the past decade, those for non-ST-elevation myocardial infarction (NSTEMI) have increased. The overall incidence rate of AMI is expected to continuously increase in the next decades due to an ageing population and global rise in diabetes (Mozaffarian, et al 2015).

The in-hospital mortality of post-AMI patients has decreased in several parts of the world as a result of more frequent use of reperfusion strategies. Due to increasing numbers of post-AMI survivors, the prevalence of developing heart failure (HF), a frequent complication following an AMI, has increased worldwide (Jhund and McMurray 2009; Sulo, et al 2016). For example, of 63,853 patients discharged alive from their first AMI without a diagnosis of HF during 2001-2009 in The Cardiovascular Disease in Norway Registry (CVDNOR), 12.6% of patients developed HF during a median follow-up time of 3.2 years and nearly half of these cases occurred within 1 year from the index myocardial infarction (MI) discharge (Sulo, et al 2016). In addition, high-risk patients with left ventricular ejection fraction (LVEF) $\leq$ 40% following an AMI representing approximately 1/4 to 1/3 of the overall post-AMI patient population, are known to have significantly greater risk of HF morbidity and mortality (Miller, et al 2012; van Diepen, et al 2015; Vasaiwala, et al 2012). In the VALIANT study of high-risk post-AMI patients (LVEF $\leq$ 40% and/or transient HF signs with no prior history of chronic HF) who received percutaneous coronary intervention (PCI), approximately 20% of these patients experienced cardiovascular (CV) death or HF hospitalization over the approximate 2-year follow-up period (Pfeffer, et al 2003; Novartis data analyses on file). These real-world registry and controlled clinical trial data underscore the need for additional therapeutic approaches to reduce HF-related morbidity and mortality in post-AMI patients.

There are several mechanisms contributing to an unfavorable long-term prognosis in post-AMI patients. The most notable mechanism underlying the significantly greater risk of HF morbidity events following an AMI is pathological cardiac remodeling resulting from the loss of myocardium and maladaptive changes in the surviving myocardium. This remodeling process with changes in left ventricular (LV) geometry, size, and function is induced by altered myocardial loading conditions and dysregulated neurohumoral system (Pfeffer and Braunwald, et al 1990; Udelson and Konstam, et al 2002; White, et al 1987).

Factors triggering cardiac remodeling are activated within hours after an AMI. As supported by multiple clinical outcome studies conducted in the 1990s, early inhibition of the Renin Angiotensin System (RAS) with angiotensin converting enzyme (ACE) inhibitors has shown to reverse pathological remodeling, improve survival, and reduce HF hospitalization in post-AMI patients with LV systolic dysfunction and/or HF (AIRE Study Investigators, 1993; GISSI-12 Study Investigators, 1994; ISIS-12 Collaborative Group 1995; Kober, et al 1995;

[redacted]

Pfeffer et al 1992). As a consequence, guidelines recommend early initiation of ACE inhibitors after an AMI in patients with LV systolic dysfunction and/or HF for indefinite use (*IA* recommendation) (Anderson, et al 2007; Antman, et al 2008; Roffi, et al 2015; Steg, et al 2012). Despite this progress and a number of other evidence-based pharmacotherapies (β blockers, mineralocorticoid antagonists, etc.), the prognosis of high risk post-AMI patients with LV dysfunction and/or HF remains poor. Novel preventive strategies to reduce the risk for CV mortality and the clinical development of HF are clearly warranted.

Several lines of evidence have suggested that increasing natriuretic peptides in addition to RAS inhibition in post-AMI patients may offer greater benefits over the RAS inhibition alone. The potential mechanisms may include but are not limited to the anti-hypertrophic, anti-fibrotic, anti-ischemic, anti-inflammatory and sympatholytic effects of natriuretic peptides (Braunwald, 2015; D'Souza, et al 2004; Molkentin, 2003). In a small study of 24 anterior wall STEMI patients, the recombinant form of human BNP, nesiritide, given early after index MI presentation for 72 hours was well tolerated and associated with improved LVEF and reduced ventricular remodeling (i.e., smaller LV end-systolic volume) after 1 month (Chen, et al, 2009). A larger clinical study in Japanese STEMI patients (N=569) demonstrated that intravenous administration of atrial natriuretic peptide for 3 days after reperfusion treatment reduced infarct size and improved LVEF at 6-12 months (Kitakaze, et al 2007).

Entresto™ (sacubitril/valsartan, LCZ696) is a combination of neprilysin inhibitor and angiotensin II type 1 receptor blocker, providing concomitant neprilysin inhibition and angiotensin type 1 receptor blockade. Upon oral administration, LCZ696 delivers systemic exposure of sacubitril, a neprilysin inhibitor prodrug, and valsartan, an angiotensin receptor blocker (ARB). Sacubitril is then further metabolized by esterases to the active metabolite, sacubitrilat (LBQ657), which inhibits the degradation of natriuretic peptides and therefore enhances the effects of their biological activity. The efficacy and safety of LCZ696 titrated to a target dose of 200 mg twice daily in chronic HF patients with reduced ejection fraction (HFrEF) (LVEF ≤40%) was evaluated in the PARADIGM-HF study (N=8,442) and demonstrated that LCZ696 significantly reduced the primary composite endpoint of CV death or HF hospitalization by 20%, as compared to enalapril (McMurray, et al 2014).

Given these positive results for the use of LCZ696 in the HFrEF patient population, and the improvement in LVEF, reduction in infarct size and ventricular remodeling observed in the STEMI patient population all of which suggest that increasing natriuretic peptides in addition to RAS inhibition may offer greater benefit in the post-AMI patient population, we hypothesize that early and sustained treatment with LCZ696 in high-risk patients with LV systolic dysfunction and/or pulmonary congestion following an AMI with no known prior history of chronic HF will be superior to the guideline recommended first-line treatment with ACE inhibitor as measured by a reduction in the composite endpoint of CV death, HF hospitalization or outpatient HF.

1.2 Purpose

The purpose of this study is to evaluate the efficacy and safety of LCZ696 titrated to a target dose of 200 mg twice daily, compared to ramipril titrated to a target dose of 5 mg twice daily, in addition to conventional post-AMI treatment, in reducing the occurrence of composite endpoint of CV death, HF hospitalization and outpatient HF (time-to-first event analysis) in

[redacted]

post-AMI patients with evidence of LV systolic dysfunction and/or pulmonary congestion, with no known prior history of chronic HF.

2 Study objectives and endpoints

2.1 Primary objective(s)

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 outpatient HF endpoint event is defined as an adjudicated event of clinical development of symptomatic HF (either urgent/unscheduled or non-urgent) in the outpatient setting with symptoms and signs requiring initiation/intensification of intravenous or qualifying oral HF treatment. See Section 6.4.1 for full definition)

2.2 Secondary objective(s)

- To demonstrate the superiority of LCZ696, compared to ramipril, in delaying the time-to-first occurrence of CV death or HF hospitalization
- 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
- To demonstrate the superiority of LCZ696 compared to ramipril, in delaying the time-to-first occurrence of CV death, non-fatal spontaneous MI or non-fatal stroke
- 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 or non-fatal stroke
- To demonstrate the superiority of LCZ696, compared to ramipril, in delaying the time to all-cause mortality
- To evaluate the safety and tolerability of LCZ696 compared to ramipril

(All secondary efficacy hypotheses except all-cause mortality will be included in a statistical testing strategy to control the familywise type I error rate) (Section 9.5)

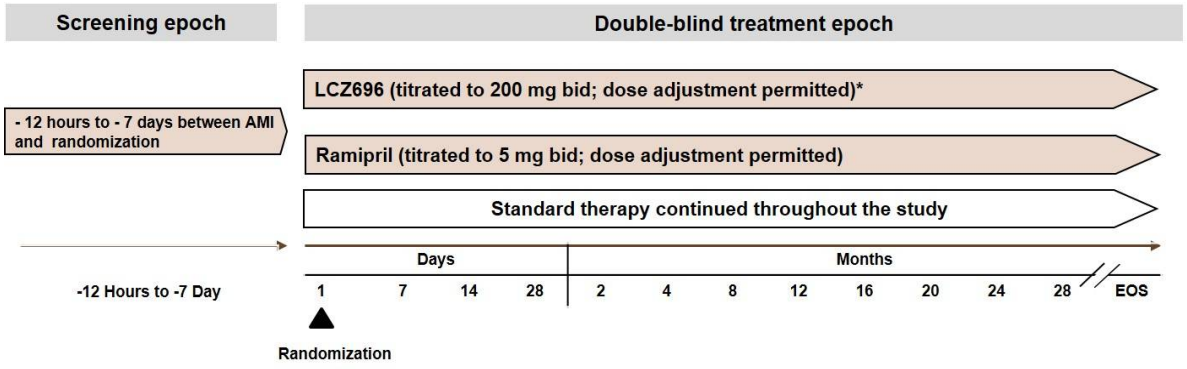
[redacted]

[redacted]

3 Investigational plan

3.1 Study design

Figure 3-1 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

This study 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

[redacted]

when added to standard therapy in post-AMI patients with LV systolic dysfunction and/or pulmonary congestion. Potential study candidates will consist of high-risk patients who have sustained a spontaneous acute myocardial infarction (STEMI or NSTEMI) with evidence of LV systolic dysfunction defined by LVEF ≤ 40% and/or pulmonary congestion (worst Killip class ≥ II or radiological findings requiring intravenous treatment). In addition, patients must have at least one risk factor (age ≥ 70 yrs; diabetes; estimated glomerular filtration rate (eGFR) < 60 ml/min; history of prior MI; occurrence of atrial fibrillation during index hospitalization; LVEF < 30% or Killip class III or IV associated with the index MI, or diagnosis of STEMI without reperfusion therapy within the first 24 hours of the index MI) and should not have known prior history of chronic HF. Study candidates must also be hemodynamically stable defined as systolic blood pressure (SBP) ≥ 100 mmHg if on ACE inhibitors or ARBs or SBP ≥ 110 mmHg if not on ACE inhibitors or ARBs at time of randomization, must not have received intravenous diuretics, vasodilators, vasopressors or inotropes in the last 24 hours prior to randomization, and be considered clinically stable in the opinion of the investigator.

After assessing eligibility during the screening period, consenting patients who meet the study inclusion and exclusion criteria 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 in a double-blind manner for the duration of the study. In addition, in order to minimize the potential risk of angioedema, patients who were previously treated with ACE inhibitors receiving the last dose of that agent during the last 36 hours prior to randomization will receive a valsartan bridging for one day. To achieve this, those who are subsequently randomized to LCZ696 will receive two doses of valsartan in a blinded manner prior to beginning double-blind LCZ696 treatment. Patients randomized to ramipril will receive two doses of ramipril and two doses of valsartan placebo in a blinded manner prior to beginning double-blind ramipril and LCZ696 placebo treatment. Randomization must occur no earlier than 12 hours and no more than 7 days after index MI presentation.

A screening period, or 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. Patients may be randomized on the same day that they are consented and screened.

Eligible patients 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. Three dose levels of study medication will be administered in a stepwise titration (Table 3-1). The goal of treatment is to ensure that each patient receives the target dose or maximal tolerated dose of study medication (Figure 3-2).

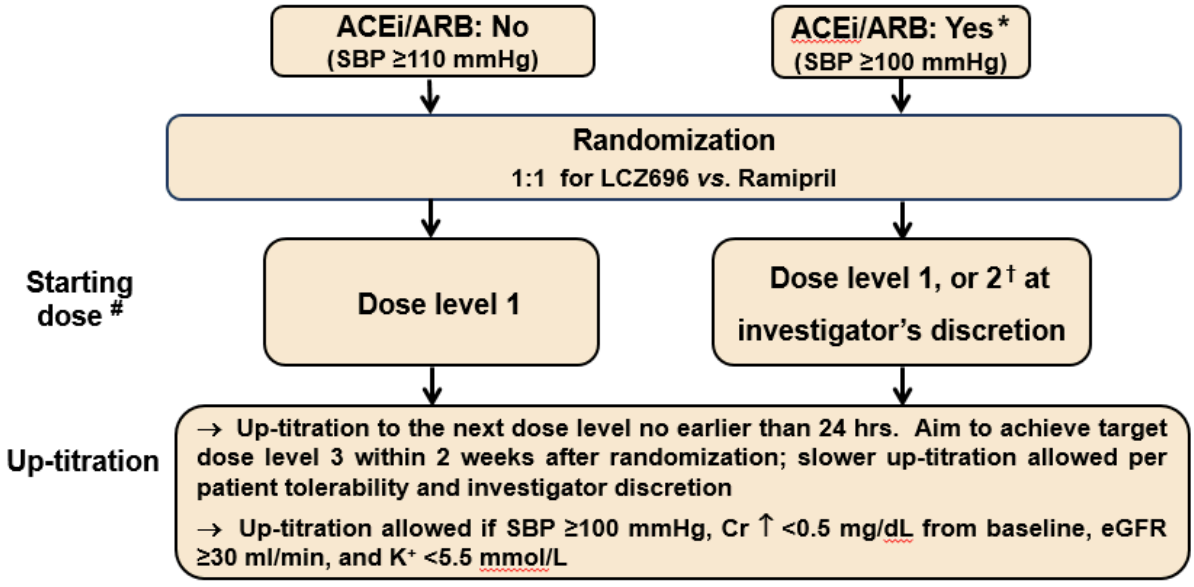
[redacted]

Table 3-1 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.

Figure 3-2 Study drug initiation and up-titration in PARADISE-MI



* [ACEi/ARB: Yes] is defined as receiving ACEi or ARB during the last 24 hours prior to randomization

† At Investigator's discretion and patient clinical condition, dose level 2 can be initiated for [ACEi/ARB: Yes] patients

Patients randomized to LCZ696, who receive their last dose of ACEi within 36 hours prior to randomization, will receive two doses of blinded valsartan at 40 mg (level V1) or 80 mg (level V2) according to Investigator's discretion

The starting dose level of the study drugs will be determined based on the patient's clinical condition and taking into consideration their prior standard background therapy. Patients who did not receive an ACE inhibitor or ARB in the last 24 hours prior to randomization (ACE inhibitor/ARB No patients) will start at dose level 1. Patients who did receive an ACE inhibitor or ARB in the last 24 hours prior to randomization (ACE inhibitor/ARB Yes patients) will start at dose level 1, or at investigator's discretion, dose level 2, after taking into consideration the patients' prior dose level of ACE inhibitor/ARB therapy (Table 3-2) and clinical condition (SBP, renal function, etc.).

[redacted]

Table 3-2 Total daily doses of commonly used ACE inhibitors and ARBs corresponding to dose level 2 of study drug

ACE inhibitor	Dose	ARB	Dose
Benazepril	20 mg	Azilsartan	40 mg
Captopril	100 mg	Candesartan	16 mg
Cilazapril	2.5 mg	Eprosartan	400 mg
Enalapril	10 mg	Irbesartan	150 mg
Fosinopril	20 mg	Losartan	50 mg
Imidapril	10 mg	Olmesartan	10 mg
Lisinopril	10 mg	Telmisartan	40 mg
Moxepril	7.5 mg	Valsartan	160 mg
Perindopril	4 mg		
Quinapril	20 mg		
Ramipril	5 mg		
Trandolapril	2 mg		
Zofenopril	30 mg		

ACE inhibitor/ARB No patients (no treatment with ACE inhibitor/ARB therapy during the 24 hours prior to randomization):

- Start at dose level 1, if SBP is ≥ 110 mmHg

ACE inhibitor/ARB Yes patients (treated with ACE inhibitor/ARB therapy during the 24 hours prior to randomization):

- Start at dose level 1, if SBP is ≥ 100 mmHg OR
- At investigator's discretion, patients may also start at dose level 2, taking into consideration patient's prior dose level of ACE inhibitor/ARB therapy (Table 3-2) and clinical condition (SBP, renal function, etc.).

In order to minimize the potential risk of angioedema, patients who are randomized to LCZ696 but who were previously treated with an ACE inhibitor during the 36 hours prior to randomization will receive valsartan bridging for one day before beginning the double-blind LCZ696 treatment. Two doses of blinded valsartan (dose level V1, valsartan 40 mg or dose level V2 valsartan 80 mg) will be available. As outlined above (Figure 3-2), the dose level of the 1-day valsartan bridging will also be determined based on the patient's prior dose level of ACE inhibitor therapy and clinical condition at the investigator's discretion (Figure 3-2). On day 1, patients randomized to ramipril will receive two doses of ramipril and two doses of valsartan placebo in a blinded manner prior to beginning double-blind ramipril and LCZ696 placebo treatment.

Following initiation of study drug, patients should be uptitrated to the next dose level no earlier than 24 hours after the initial dose of study drug. The aim is to achieve the target dose level 3 within **2 weeks** after randomization; however, slower up-titration will be permitted if necessary to manage patient safety and tolerability. For patients who have not been uptitrated to dose level 3 by week 4, an unscheduled dose titration visit on or about week 6 should be considered to evaluate whether uptitration to the target dose, dose level 3, can be implemented.

[redacted]

In addition, investigators should document the reasons for not achieving target study drug dose level 3 during the Week 2 to Week 8 visits.

Patients that cannot tolerate dose level 3 will be allowed to stay at level 1 or 2 as maintenance dose. Study drug dose level adjustments should be based on overall safety and tolerability with special focus on a) symptomatic hypotension, b) any clinically significant decrease in eGFR/increase in creatinine (Cr) and c) hyperkalemia (Table 3-3). Treatment guidelines for blood pressure management and hyperkalemia are provided in Appendix 4 and Appendix 5, respectively. Every attempt should be made to maintain patients on the target study drug dose (dose level 3) or maximally tolerated dose levels throughout the trial. If the patient does not tolerate the target study drug dose level the investigator should consider, if appropriate, adjusting non-disease-modifying background medications (e.g., diuretics, nitrates or calcium channel blockers) to rectify the situation before considering down-titration to the next lower study drug dose level.

Table 3-3 Safety monitoring criteria that must be met for dose uptitration

Parameter	Criteria
Blood pressure	SBP ≥ 100 mmHg
Renal function	eGFR ≥ 30 mL/min/1.73m^2 and creatinine increase < 0.5 mg/dl from baseline
Serum potassium (or equivalent plasma potassium value)	K < 5.5 mmol/L (mEq/L)
AEs or conditions	No postural symptoms or any AEs that preclude up-titration according to the investigator's judgment

[redacted]

This is an event-driven trial, the study will continue until a total of at least 708 first confirmed primary triple composite endpoint events and at least 592 confirmed double composite events of first CV death or HF hospitalization (i.e., first secondary endpoint) have been achieved. Approximately 5,650 randomized post-AMI patients will be required to accrue the necessary number of confirmed endpoints. Once randomized, all patients will be followed until the total numbers of required confirmed endpoint events have been achieved and final follow-up has been performed.

It is anticipated that the total trial duration will be approximately 43 months, with a projected recruitment period of approximately 37 months, followed by approximately 4 months of follow-up after the last patient is enrolled to accrue the needed number of endpoints, the closeout period is expected to last an additional 1-2 months. The overall estimated mean follow-up time will be approximately 19 months for the study. Although these are the

[redacted]

estimated timelines, they may change according to the rate of randomization and rates of occurrence of the primary and first secondary endpoints.

3.2 Rationale for study design

This phase III outcome study in post-AMI patients is designed as a multicenter, randomized, double-blind, active-controlled, event-driven study in order to assess the efficacy and safety of LCZ696 when added to standard therapy for high-risk post-AMI patients with left ventricular systolic dysfunction and/or pulmonary congestion. Patients entering the study will be randomized to either LCZ696 or ramipril and are required to receive standard-of-care background therapy according to regional or local guidelines / institutional standards throughout the study. Once randomized, all patients will be followed until the total required numbers of confirmed endpoint events have accrued. The study design reflects prior pivotal, long-term, cardiovascular outcome trials in post-AMI patients.

The primary endpoint of this study is a composite of CV death, HF hospitalization or outpatient HF in patients with left ventricular systolic dysfunction and/or pulmonary congestion following an AMI who do not have known prior history of chronic HF. While the composite of CV death or HF hospitalization is a well-established mortality and morbidity endpoint, the addition of the outpatient HF component, which in this study represents the confirmed diagnosis of new onset symptomatic HF, aims to capture the clinically important outpatient event that contributes to the totality of HF morbidity following an AMI presenting as either inpatient (i.e., HF hospitalization) or outpatient (i.e., outpatient HF) events. The diagnostic criteria for adjudication of HF symptoms and signs are identical whether the patient is seen in an inpatient or outpatient setting.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

The selection of LCZ696 200 mg given orally twice daily as the target dose for this study was based primarily on the superior efficacy and safety results of LCZ696 200 mg compared to enalapril 10 mg each given twice daily in the PARADIGM-HF study, in which 60% of the HFrEF patients enrolled had an ischemic etiology and 43% had prior MI. LCZ696 200 mg twice daily delivers similar valsartan exposure (assessed by AUC) as valsartan 160 mg twice daily, which was demonstrated in the VALIANT study to be as effective as standard-of-care ACE inhibitor in patients with AMI complicated by LV systolic dysfunction and/or HF. Further, biomarker analysis and modeling indicate that this dose of LCZ696 delivers approximately 90% of its maximal neprilysin (NEP) inhibition. The twice daily dosing schedule is considered necessary for sustained NEP inhibition over a 24-hour period and it is also anticipated to reduce the incidence of hypotension, compared to a once daily regimen, particularly in elderly patients.

3.4 Rationale for choice of comparator

Major clinical trials have established ACE inhibitors as the standard-of-care for RAS blockade and ACE inhibitors are recommended by treatment guidelines as the first-line therapy for post-AMI patients with LV systolic dysfunction and/or HF. The primary objective of study CLCZ696G2301 is to demonstrate superiority of LCZ696 over an ACE inhibitor in

reducing CV mortality and HF morbidity in post-AMI patients with LV systolic dysfunction and/or pulmonary congestion. Ramipril is one of the most commonly used ACE inhibitors in post-AMI patients and is selected as the active comparator of this study. In the AIRE study, ramipril at target dose of 5 mg twice daily compared to placebo demonstrated a significant 27% relative reduction in mortality (p=0.002; principally CV death), also 26% and 23% reductions in the risks of HF hospitalization and progression to severe/resistant HF, respectively (AIRE Investigators 1993). Ramipril in the same daily dose was subsequently shown to reduce cardiovascular mortality in a broader population of patients at cardiovascular risk (The HOPE Investigators, 2000).

3.5 Purpose and timing of interim analyses/design adaptations

Two interim analyses (IAs) are planned to assess efficacy. The cut-off time for the first IA is planned to be when approximately two-thirds of the target number of primary adjudicated events (i.e. approximately 472 first CV death, HF hospitalization or outpatient HF events) have occurred. The analysis cut-off time for the second IA 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. It is estimated that the second IA will include approximately 80% of the target number of 708 Clinical Event Committee (CEC)-confirmed primary events.

3.6 Risks and benefits

The risk to patients participating in the study will be minimized by compliance with the inclusion/exclusion criteria and close clinical monitoring. Patients will be instructed not to take any RAS blockade medications (ACE inhibitor or ARB) from the day they start study drug to avoid excess RAS blockade. The risk of discontinuation of concomitant ACE inhibitors or ARBs will be minimal as the study treatment will be reflective of the typical dosing schedule of most ACE inhibitors and ARBs. All patients will be required to continue receiving the rest of their standard of care background CV medications. In addition, for patients randomized to LCZ696 who received ACE inhibitors in the last 36 hours prior to randomization, a one day bridging period with 2 doses of valsartan before starting LCZ696 treatment is instituted to minimize the risk of angioedema (Section 3.1).

In women of child-bearing potential, a possible risk of developmental toxicity cannot be excluded. Women of child-bearing potential should therefore use a highly effective method of contraception during dosing. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Since this is a long-term outcome study, participating patients will benefit from careful monitoring and follow-up during the entire study duration regardless of whether they are receiving the study medication.

4 Population

The study population will consist of male and female patients age 18 years or older with a diagnosis of acute spontaneous MI and evidence of left ventricular (LV) systolic dysfunction and/or pulmonary congestion associated with the index MI. Patients will be randomized

between 12 hours and 7 days following the index acute MI. At the time of randomization, patients should be hemodynamically stable and without persistent clinical HF. The goal is to randomize approximately 5,650 patients in approximately 500 centers worldwide.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male or female patients ≥ 18 years of age.
3. Diagnosis of spontaneous AMI based on the universal MI definition* with randomization to occur between 12 hours and 7 days after index event presentation**.

   Spontaneous AMI is defined when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia due to primary coronary event. Under these conditions, the following criteria have to be met for the diagnosis of spontaneous AMI:

   - Detection of rise and/or fall of cardiac enzymes (cardiac troponin, cTn or the MB fraction of creatinine kinase, CKMB) with at least one value above the 99th percentile of the upper reference limit (URL) or the local laboratory MI diagnosis cut-off value, together with evidence of myocardial ischemia with at least one of the following:
     - Ischemic discomfort or other ischemia symptom(s)
     - Electrocardiogram (ECG) characteristics of STEMI or NSTEMI including new or presumably new significant ST-segment-T wave (ST-T) changes
     - Newly developed pathological Q waves or left bundle branch block in the ECG

   (* Patients with a spontaneous MI event determined to be secondary to another medical condition such as anemia, hypotension, or an arrhythmia OR thought to be caused by coronary vasospasm with documented normal coronary arteries are not eligible; patients with clinical presentation thought to be related to Takotsubo cardiomyopathy are also not eligible)

   (** Index MI presentation is the time of patient presentation at either the emergency room/emergency department (ER/ED), intensive care unit/coronary care unit (ICU/CCU) or hospital ward etc., for the treatment of the index MI.)
4. Evidence of LV systolic dysfunction and/or‡ pulmonary congestion requiring intravenous treatment associated with the index MI event defined as:
   - LVEF ≤40% assessed locally by echocardiography, magnetic resonance imaging, cardiac CT, radionuclide or contrast ventriculography after index MI presentation and prior to randomization.

     (These examinations may be performed as part of patient standard-of-care. In case multiple LVEF measurements have been performed during index event, the last one performed prior to randomization should be considered as the qualifying measurement), **and/or** ‡
   - Pulmonary congestion requiring intravenous treatment with diuretics, vasodilators, vasopressors and/or inotropes during the index hospitalization supported by clinical assessment (worst Killip class, II or above; see Appendix 3 for Killip class definition) or radiological findings. Radiological evidence of pulmonary congestion is defined as

[redacted]

pulmonary venous congestion with interstitial or alveolar edema and must be supported by at least one chest X-ray or CT scan.

(ǂ denotes that patients with either LVEF ≤40%, or pulmonary congestion requiring IV treatment, or both will qualify for this inclusion criterion)

5. At least one of the following 8 risk factors:
   - Age ≥ 70 years
   - eGFR <60 mL/min/1.73 m^2 based on MDRD formula at screening visit
   - Type I or II diabetes mellitus
   - Documented history of prior MI supported by ECG changes and/or elevation of cardiac enzymes consistent with MI diagnosis.
   - Atrial fibrillation as noted by ECG, associated with index MI
   - LVEF <30% associated with index MI
     (If multiple LVEF measurements have been performed during index event, the last one performed prior to randomization should be considered as the qualifying measurement.)
   - Worst Killip class III or IV associated with index MI requiring intravenous treatment
   - STEMI without reperfusion therapy within the first 24 hours after presentation
6. Hemodynamically stable defined as:
   - SBP ≥ 100 mmHg at randomization for patients who received ACE inhibitor/ARB during the last 24 hours prior to randomization (ACE inhibitor/ARB Yes patients)
   - SBP ≥ 110 mmHg at randomization for patients who did not receive ACE inhibitor/ARB during the last 24 hours prior to randomization (ACE inhibitor/ARB No patients)
   - No intravenous treatment with diuretics, vasodilators, vasopressors and/or inotropes during the last 24 hours prior to randomization.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Known history of chronic HF prior to randomization
2. Cardiogenic shock within the last 24 hours prior to randomization
3. Persistent clinical HF at the time of randomization
4. Coronary artery bypass graft (CABG) performed or planned for index MI
5. Clinically significant right ventricular MI as index MI
6. Symptomatic hypotension at screening or randomization
7. Patients with a known history of angioedema
8. Stroke or transient ischemic attack within one month prior to randomization
9. Known or suspected bilateral renal artery stenosis
10. Clinically significant obstructive cardiomyopathy

[redacted]

11. Open-heart surgery performed within one month prior to randomization or planned cardiac surgery within the 3 months after randomization
12. eGFR < 30 ml/min/1.73 m^2 as measured by the Modification of Diet in Renal Disease (MDRD) formula at screening
13. Serum potassium > 5.2 mmol /L (or equivalent plasma potassium value) at randomization
14. Known hepatic impairment (as evidenced by total bilirubin > 3.0 mg/dL or increased ammonia levels, if performed), or history of cirrhosis with evidence of portal hypertension such as esophageal varices
15. Previous use of LCZ696 or Entresto™
16. Use of other investigational drugs within 30 days prior to screening
17. History of hypersensitivity to the study drugs or drugs of similar chemical classes
18. Known intolerance or contraindications to study drugs or drugs of similar chemical classes including ACE inhibitors, ARB or NEP inhibitors
19. Patients taking medications prohibited by the protocol that cannot be discontinued for the duration of the study
20. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin) within the past 3 years with a life expectancy of less than 1year.
21. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or extraction of study drug at investigators' discretion.
22. History or evidence of drug or alcohol abuse within the last 12 months
23. Patients considered unsuitable for the study, including patients with psychiatric, behavioral or cognitive disorders, sufficient to interfere with the patient's ability to understand and comply with the protocol instructions or follow-up procedures
24. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test
25. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of investigational drug and for 7 days off of study drug. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
    - Male sterilization (at least 6 months prior to Visit 1). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

[redacted]

- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential

In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the ICF.

26. [redacted]

27. [redacted]

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

All eligible patients will be randomized 1:1 to either LCZ696 titrated to a target dose of 200 mg twice daily or ramipril titrated to a target dose of 5 mg twice daily in a double-blind manner for the duration of the study. In addition, patients will continue to receive optimal standard of care background therapy to treat the index MI event and co-morbid conditions, as considered appropriate by the investigator and in accordance with the local/institutional guidelines, with the exception of an ACE inhibitor or ARB as this will be replaced by study drug. The use of an open label ACE inhibitor or an ARB in addition to randomized study drug is strictly prohibited.

The following study drugs will be provided:

- LCZ696 50 mg, 100 mg and 200 mg tablets, and matching placebo (LCZ696 doses are equivalent to sacubitril/valsartan 24/26 mg, 49/51 mg and 97/103 mg, respectively)
- Ramipril 1.25 mg, 2.5 mg, and 5 mg capsules, and matching placebo
- Valsartan (VAL489) 40 mg and 80 mg tablets, and matching placebo (two doses for 1 day in a subset of randomized patients) (Section 3.1)

All study medications will be supplied in bottles or blister cards. Sufficient medication will be provided for the treatment according to study protocol, including additional medication to allow for delayed visits. Medication labels will be in the local language and comply with the legal requirements of the country. They will include storage conditions for the drug and the medication number, but no information about the patient.

[redacted]

5.1.2 Additional treatment

No additional treatment beyond investigational drug and control drug are included in this trial.

5.2 Treatment arms

Patients will be assigned to one of the following two treatment arms in a ratio of 1:1 at Visit 101.

- LCZ696 at dose levels 1-3 (50, 100 and 200 mg twice daily)
- Ramipril at dose levels 1-3 (1.25, 2.5 and 5 mg twice daily)

5.3 Treatment assignment and randomization

At Visit 101 all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Randomization will be stratified by region and type of index MI (STEMI or NSTEMI).

The randomization scheme for patients will be reviewed and approved by a member of the Novartis Randomization Group.

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods:

- Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone involved in the study with the following exceptions:
    1. The independent and unblinded statistician, programmer and data personnel who are involved in preparing safety and efficacy interim analysis reports for the Data Monitoring Committee (DMC). These personnel will not be involved in any other trial conduct related activities.
    2. DMC members.

[redacted]

- The identity of the treatments will be concealed by the use of investigational treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.
- A double-dummy design is used because the identity of the study drug cannot be disguised, as the drug products are visibly different.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.9), at the time of an interim analysis by the DMC and at the conclusion of the study.

For any patient who was intentionally unblinded by the investigator (treatment code has been broken as per study process) the patient must permanently discontinue the study treatment; whereas the appropriate personnel from the site and Novartis will assess whether study drug should be discontinued in instances where a patient is inadvertently unblinded for any reason.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigative site.

Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number [redacted] and subsequent patients/subjects are assigned consecutive numbers (e.g. the second patient is assigned patient number [redacted] the third patient is assigned patient number [redacted]). The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. For studies using eCRFs, only the assigned patient number must be entered in the field labeled “Patient ID” on the electronic data capture (EDC) data entry screen (e.g. enter [redacted] etc.). Once assigned to a patient, the patient number will not be reused.

If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Log, and the screening eCRFs should also be completed.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the two treatment arms. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient’s unique subject number.

[redacted]

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis country pharma organization (CPO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused study treatment and packaging at each study visit or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Novartis will supply the investigators with all study medications required for the course of the study. Patients will be provided with medication packs containing study drug corresponding to their assigned treatment arm and dose level, sufficient to last until the next scheduled visit. In order to adequately blind the study, patients will be required to take a total of two pills, (one tablet from the LCZ696/LCZ696 matching placebo pack and one capsule from the ramipril/ramipril matching placebo pack) twice a day for the duration of the study.

For patients who were previously treated with an ACE inhibitor receiving the last dose of that agent within 36 hours prior to randomization, a valsartan bridging for one day will be administered in a blinded manner. To achieve this, on day 1, those patients who are subsequently randomized to LCZ696 will receive two doses of ramipril placebo and two doses of valsartan in a blinded manner prior to beginning double-blind LCZ696 plus ramipril placebo treatment. Patients randomized to ramipril on day 1 will receive two doses of ramipril and two doses of valsartan placebo in a blinded manner prior to beginning double-blind ramipril plus LCZ696 placebo treatment.

[redacted]

Patients who were not previously treated with an ACE inhibitor, or who received the last dose of that agent greater than 36 hours prior to randomization, will immediately start on double-blind LCZ696 or ramipril without valsartan bridging.

Table 5-1 summarizes the study drug that will be taken during the treatment epoch.

Table 5-1 Study drug dispensed during the treatment epoch by study visit

Study visit[c]	Dose level	LCZ696	Ramipril	Valsartan[b]
101	1[a]	50 mg or matching placebo b.i.d.	1.25 mg or matching placebo b.i.d.	40 mg or matching placebo b.i.d.
101[a]/102	2	100 mg or matching placebo b.i.d.	2.5 mg or matching placebo b.i.d.	80 mg or matching placebo b.i.d.
103	3	200 mg or matching placebo b.i.d.	5 mg or matching placebo b.i.d.	

[a] At Investigator's discretion, dose level 2 can be administered at Visit 101 for the [ACE inhibitor/ARB: Yes] patients.

[b] For patients who were previously treated with ACE inhibitor receiving the last dose within 36 hours prior to randomization;

If randomized to LCZ696, they will receive a valsartan bridging for one day before beginning the double-blind LCZ696 treatment.

- Two doses of blinded valsartan dose level V1 (valsartan 40 mg) or dose level V2 (valsartan 80 mg) will be available at Visit 101.
- At investigator's discretion dose level V1 or V2 can be administered for one day followed by active LCZ696; these patients will also receive ramipril matching placebo from Visit 101 onwards.

If randomized to ramipril, they will receive active ramipril, and two doses of valsartan matching placebo for one day followed by active ramipril and LCZ696 matching placebo.

[c] If the study drug is up-titrated during the index hospitalization, increase to the next dose level can occur prior to next study visit if tolerable but should be no early than 24 hours; slower up-titration will also be permitted if necessary to manage patient safety and tolerability.

Patients will be instructed to take their morning study drug doses at approximately 08:00 (8 AM) and their evening study drug dose at approximately 20:00 (8 PM). The study drugs should be taken with water, with or without food. If the patient misses taking any study drug dose, he/she should take it as soon as possible, unless it is almost time for the following scheduled dose. In this case, the patient should skip the missed dose and return back to his/her regular study drug administration schedule.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record case report form (CRF). All kits of study treatment assigned by the IRT will be recorded/databased in the IRT.

The investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

[redacted]

5.5.5 Permitted dose adjustments and interruptions of study treatment

For patients who are unable to tolerate the protocol-specified dosing scheme, dose level adjustments and/or temporary interruptions of study treatment are permitted in order to keep the patient on study drug. The following guidelines should be followed:

Every attempt should be made to maintain patients at the target study drug dose level throughout the trial. If the patient does not tolerate the target study drug dose level, the investigator can, if appropriate, adjust concomitant background medications for co-morbid conditions to rectify the situation, and if necessary down titrate to the next lower study drug dose level. For hypotension or dizziness, consideration should be given to adjusting the dose of diuretic and/or concomitant antihypertensive agents (e.g., calcium channel blockers) and non-antihypertensive agents that lower blood pressure (BP) (e.g., nitrates). It is important to note that dose adjustment of disease-modifying background therapy, e.g., β blockers, or mineralocorticoid (aldosterone) antagonists is discouraged under these circumstances.

Adjustment of study drug dose level

If in the investigator's opinion down titration of study drug to a lower dose level is deemed necessary it should be done in accordance with the following instructions:

During the treatment epoch, down titration of the study drug at any time during the study based on the judgment of the investigator will be allowed according to the safety and tolerability criteria defined in Appendix 4, and Appendix 5. If down titration is necessary, the patient should be down titrated to the next lower study drug dose level in the titration scheme. The patient may continue receiving the lower dose level for a recommended period of 1 to 4 weeks before being re-challenged at the next higher dose level. For example, a patient who encounters tolerability problems at the target study drug dose level (i.e., dose level 3) should receive the study drug at dose level 2 for 1 to 4 weeks at the discretion of the investigator. Then, he/she should be re-challenged with up-titration back to dose level 3.

If the tolerability issues are not alleviated despite down titration by one dose level, the investigator may down titrate further to the next lower study drug dose level for 1 to 4 weeks, up to temporary discontinuation of the study drug. Again, once stable, the patient should be re-challenged with up titration to the next higher dose level every 1 to 4 weeks in an attempt to bring back the patient gradually to the target study drug dose level (i.e., dose level 3). The investigator may choose the next dose level for down- or up-titration according to his or her judgment. The IRT system should be contacted to register any changes in the patient's study drug dose level, including in cases of temporary and permanent discontinuation of the study drug, and to obtain the medication numbers of the study drug supplies required for the new study drug dose level. In some instances, according to the safety and tolerability criteria and the investigator's judgment, dose level 1 or 2 could be maintained if he/she considers that the patient's condition would not allow any further up titration to the target dose level of study drug (i.e., dose level 3). In this case, it would be acceptable to maintain the patient at dose level 1 or level 2, whichever is the higher and tolerated dose level by the patient.

These changes must be recorded on the Dosage Administration Record CRF.

[redacted]

Study drug restart after temporary treatment interruption

Study drug should be reintroduced in those patients who temporarily discontinue it as soon as medically justified in the opinion of the investigator. Once the investigator considers the patient's condition appropriate for receiving the study drug, the investigator should re-start the patient on the study drug at the most appropriate and allowable dose level per his/her medical judgment. If tolerated, the patient should be up-titrated one dose level every 1 to 4 weeks to the target dose level 3, as per the investigator's judgment. Should the patient not tolerate the re-start study drug dose level, he/she may be down titrated again (if appropriate) or temporarily discontinue the study medication again and a new attempt to up titrate or reintroduce the study drug could be considered by the investigator as soon as medically justified in his/her judgment.

The use of an open-label ACE inhibitor, ARB, commercially available Entresto™ or a direct renin inhibitor is strictly prohibited while patient is taking study drug. However, if for any reason a patient off study drug has started open-label treatment with an ACE inhibitor or Entresto™, it must be discontinued ≥36 hours prior to restarting study drug. For patients off study drug treated with an ARB or a direct renin inhibitor it must be discontinued prior to re-initiation of study drug.

Reinitiation of study medications or any changes in concomitant medications must be recorded on the appropriate eCRFs.

In case of pregnancy discovered during the screening epoch, the patient will be withdrawn from the study immediately. In case of pregnancy discovered during the treatment epoch, the patient should be instructed to temporarily discontinue study drug immediately. Study drug intake should be resumed as soon as possible after the completion of the pregnancy and lactation period. Meanwhile, the patient should continue to attend scheduled study visits.

See Section 7.6 for further details on pregnancies and reporting guidelines

5.5.6 Rescue medication

The intent in this study is to ensure that, wherever possible, patients are treated with an evidence-based dose (or lower dose if the target dose is not tolerated) of RAS inhibitor. Some patients in the study may experience intolerable adverse effects thought to be due to study drug which could lead to discontinuation of study medication. If study drug discontinuation is considered despite dose reduction and/or temporary interruption as described in Section 5.5.5, substitution of open-label ACE inhibitor or ARB therapy is recommended, according to the following guidance, to ensure patients receive sufficient RAS blockade.

Hypotension, hyperkalemia, renal dysfunction and cough are likely to be common in the patients enrolled in the present study. Guidance on handling hypotension and hyperkalemia by correcting the underlying causes and/or adjusting the non-disease modifying background therapy is provided to investigators in Appendix 4, and Appendix 5, respectively. If these measures do not lead to resolution of the adverse event(s), the dose of study drug should then be down-titrated or temporarily withdrawn if needed, followed by re-challenge, as described in Section 5.5.5. If a patient experiences symptomatic hypotension (despite the above measures) and a study drug discontinuation is required open-label ACE inhibitor or ARB therapy should be administered and titrated to the guideline-recommended target doses if

tolerated. Similar principles (such as emphasizing dose reduction or discontinuation of non-disease modifying drugs of NSAIDs and diuretics, etc., followed by dose adjustment of study drug) should also be exercised when handling the renal dysfunction adverse events.

Cough is also likely to be a common adverse event in the patients enrolled in the present study because of concomitant lung disease and potentially pulmonary congestion. For patients who have to discontinue study drug per investigator's assessment due to persistent and intolerable dry cough despite dose reduction or temporary interruption/re-challenge of study medication, it is recommended that patients are administered open-label valsartan (titrated to the guideline recommended target dose of 160 mg bid) or an alternative ARB if valsartan is not available.

Open-label ACE inhibitors or ARBs during the study can ONLY be given to patients if the study drug has been temporarily or permanently discontinued. If the patient is to be started on open-label ACE inhibitor the study drug must be stopped ≥ 36 hours prior to initiating ACE inhibitor. If reinitiating study drug, the open-label ACE inhibitor must be stopped ≥ 36 hours prior to resuming study drug. Open-label ARBs must also be stopped prior to resuming study drug.

Use of rescue medication must be recorded on the CV Concomitant medications/Significant nondrug therapies CRF.

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the concomitant medications eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

CV Medications

The patient should be on an optimal medical regimen of background medications to effectively treat the index MI event and comorbidities, such as hypertension, diabetes, dyslipidemia and atrial fibrillation, etc. Investigators should take into consideration the patient's risk factors, such as age and comorbidities, and make every effort to control a patient's BP, lipid and glucose levels in accordance with international and local treatment guidelines.

Medications known to raise potassium levels

Potassium-sparing diuretics, potassium supplements and any other medications known to raise potassium levels should be used with caution while the patient is receiving the study drug due to the increased possibility of occurrence of hyperkalemia. The investigator is encouraged to assess patients' potassium levels regularly, especially in those who are receiving these medications.

[redacted]

Phosphodiesterase-5 (PDE-5) inhibitors

PDE-5 inhibitors should be used with caution while the patient is receiving study medication due to the increased possibility of the occurrence of hypotension.

HMG-CoA reductase inhibitors

Caution is recommended when co-administering LCZ696 with atorvastatin or other statins because of the potential to raise its plasma level. No meaningful increase in statin-related AEs was observed when LCZ696 was used concomitantly with statins in the PARADIGM-HF (Streefkerk H, et al. 2017) study. No dose adjustments are currently proposed for atorvastatin or other statins when coadministered with sacubitril/valsartan, Investigators should treat their patients with statins based on their best clinical judgement and local treatment guidelines. Diligent monitoring and reporting of statin-related adverse events should also be performed.

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-2 is NOT allowed after the start of study drug due to safety reasons, unless the actions specified are taken.

Table 5-2 Prohibited medication

Medication	Action taken
Any ACE inhibitor	Discontinue study drug. The open label ACE inhibitor must be stopped for ≥36 hours prior to re-initiation of study drug
Any ARB	Discontinue study drug. The open label ARB must be stopped prior to re-initiation of study drug
Any direct renin inhibitor	Discontinue study drug. The open label direct renin inhibitor must be stopped prior to re-initiation of study drug
Entresto™*	Discontinue study drug. The open label Entresto™ must be stopped for ≥36 hours prior to re-initiation of study drug
*Commercially available sacubitril/valsartan	

The concomitant use of open-label ACE inhibitor, ARBs, commercially available Entresto™ or a direct renin inhibitor is strictly prohibited while the patient is receiving study drug. If the addition of an ACE inhibitor, ARB, Entresto™ or direct renin inhibitor is necessary, then study drug must be temporarily discontinued. If the patient is to be started on open-label ACE inhibitor or Entresto™, the study drug must be stopped ≥36 hours prior to initiating ACE inhibitor or Entresto™. If study drug is to be re-started, the open-label ACE inhibitor or Entresto™ must also be stopped ≥ 36 hours prior to re-initiating study drug. ARBs or a direct renin inhibitor should be stopped prior to resuming study drug.

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide

[redacted]

the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- patient number

In addition, oral and written information to the patient must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and the Medical Lead (or designee) after a patient has been intentionally unblinded and the patient must discontinue the study treatment; whereas the appropriate personnel from the site and Novartis will assess whether study drug should be discontinued in instances where a patient is inadvertently unblinded for any reason.

5.6 Study Completion and Discontinuation

5.6.1 Study completion and post-study treatment

The study will be completed when either the predefined target total number of adjudicated events has been obtained **or** a recommendation is made by the DMC to prematurely stop the study. At the end of the study, all patients will return for the final end of study (EOS) visit (Visit 199) and be asked to return the remaining study drug.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from study drug, or must refer them for appropriate ongoing care. A post trial access (PTA) program may also be initiated to allow for the investigational drug to be made available to qualified patients participating in the trial. The PTA mechanism must comply with the local laws and regulations in the participating countries in order to be made available.

5.6.2 Discontinuation of Study Treatment

Patients may voluntarily discontinue study treatment for any reason at any time. However, study treatment discontinuation does not constitute withdrawal from the study, does not constitute withdrawal of consent and should not lead to the patient being withdrawn from the entire study. Patients who have permanently discontinued study drug should be encouraged to attend all the protocol specified study visits and perform, at a minimum, AE/endpoint assessments as stipulated in the visit schedule (Table 6-1) and remain in follow-up for the duration of the trial.

[redacted]

If they fail to return for these assessments for unknown reasons, every effort should be made to contact them. The investigator must also contact the IRT to register the patient's discontinuation from study treatment and record it on the Dosage Administration Record CRF.

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule. After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should to be collected at clinic visits or via telephone visits:

- new / concomitant treatments
- adverse events (AE)/Serious Adverse Events (SAE)

The emergence of the following circumstances will require permanent study drug discontinuation:

- Withdrawal of informed consent
- Investigator thinks that continuation of study drug would be detrimental to the patient's well-being
- Suspected occurrence of clinically significant angioedema. A patient with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator

The emergence of the following circumstances will require temporary or permanent discontinuation of study drug (study drug may be restarted once these circumstances no longer exist):

- Use of an open label ACE inhibitor, ARB, Entresto™ (commercially available sacubitril/valsartan) or direct renin inhibitor
- Any laboratory abnormalities that in the judgment of the investigator warrant discontinuation of study drug after taking into consideration the patient's overall status
- Pregnancy and post-pregnancy during lactation period (Section 7.7)

Study drug may be discontinued at the investigator's discretion if any of the following occurs:

- Any severe suspected drug-related AE
- Any other protocol deviation that results in a significant risk to the patient's safety

For any patient who was unblinded inadvertently for any reason, the appropriate personnel from the site and Novartis will assess whether study drug should be permanently discontinued.

5.6.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. However, withdrawal of consent occurs **only** when a patient does not want to participate in the study anymore **and** does not want any further visits or assessments **and** does not want any further study related contacts **and** does not allow analysis of already obtained biologic material **and** does not allow further collection of personal data.

If a patient withdraws consent, the investigator must make every reasonable effort (e.g. telephone, email, letter) to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted, and

[redacted]

data that would have been collected at subsequent visits will be considered missing. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up. All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in Table 6-1. Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a patient's samples until their time of withdrawal) according to applicable law.

Patients can also refuse to participate in specific aspects of the study and/or take study medication at any time without withdrawing consent and permission should be requested of the patient to conduct follow-up visits or calls. Investigators should make every effort to accommodate the needs of the patients to make it possible for them to continue to participate in the remaining aspects of the study. This includes performing telephone visits to obtain health status and/or mortality and endpoint information for patients who are unable to or refuse to return for clinic visits.

5.6.4 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by contacting the patient, the patient's family, friends and family physician as agreed in the informed consent and by documenting in the eSource/source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until just prior to database lock, after every effort to contact the patient has been exhausted.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed.

Patients should be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

[redacted]

Patients will be contacted for safety evaluations during the 30 days following the last administration of study treatment.

Patients who prematurely discontinue the investigational treatment remain in the study and should undergo all the assessments illustrated in Table 6-1. Patients can also refuse to participate in specific aspects of the study and/or take study medication at any time without withdrawing consent and permission should be requested of the patient to conduct follow-up visits or calls. Investigators should make every effort to accommodate the needs of the patients to make it possible for them to continue to participate in the remaining aspects of the study. This includes performing telephone visits to obtain health status and/or mortality and endpoint information for patients who are unable to or refuse to return for clinic visits.

If a patient withdraws from participation in the study, refuses to return for study assessments or is unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone and/or other measures to determine the patient's survival status and endpoint information including heart failure hospitalization or outpatient heart failure events during the follow-up period.

Patients eligible to participate in this study must be randomized between 12 hours to 7 days after index AMI event presentation.

Prospective study candidates will be identified either during the hospitalization for the index AMI or post discharge up to 7 days after the index MI presentation. After identifying a potential patient, an informed consent form (ICF) must be signed before performing study-related screening procedures that are not considered standard of care for AMI patients at that site. Procedures that are part of a site's standard of care for an individual with AMI may pre-date the signed ICF. The AE and SAE reporting period will begin at the time the ICF is signed. Screening will continue until the patient has been deemed eligible for randomization into the study up to 7 days after the index MI. Screening and randomization can occur on the same day.

Visit 101 will be considered the reference visit for all study visits during the treatment epoch. Regardless of the occurrence of any unscheduled visits, scheduled visits should be performed within the specified timeframe in relation to Visit 101 as outlined in Table 6-1. If a visit is completed earlier than scheduled or postponed, it should not result in the next visit being brought forward or postponed.

Visits are planned to occur at weeks 1, 2, 4 (month 1), month 2, month 4, and then every 4 months until study end.

[redacted]

Table 6-1 Assessment schedule

Epoch	Screen	Treatment																	
Visit	**1**	**101**	**102**	**103**	**104**[16]	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**113**	**114**	**115**[17]	**116**[17]	**117**[17]	**199 and PSD**
Day		**1**	**7**	**14**	**28**	**61**	**122**	**243**	**365**	**486**	**608**	**730**	**851**	**973**	**1095**	**1216**	**1338**	**1460**	**EOS**
Week		**0**	**1**	**2**	**4**	**8**	**17**	**34**	**52**	**69**	**86**	**104**	**121**	**138**	**156**	**173**	**190**	**208**	**EOS**
Month					**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**EOS**
Obtain informed consent	X																		
Inclusion/exclusion criteria	X	X																	
Medical History – Protocol Solicited Events	X																		
Relevant Medical History/Current Medical Conditions/ Demography	X																		
Medical History Possibly Contributing to Liver Dysfunction[1]	X																		
History/Smoking History/Alcohol History	X																		
12-lead ECG assessment[2]	S																		
Cardiac enzymes[2]	X																		
Chest X-ray or CT scan[2,3]	S																		
Evaluation of left ventricular systolic dysfunction[2]	X																		
Record Killip Class[2,3]	S	X																	

[redacted]

Epoch	**Screen**	**Treatment**																	
Visit	**1**	**101**	**102**	**103**	**104**[16]	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**113**	**114**	**115**[17]	**116**[17]	**117**[17]	**199 and PSD**
Day		**1**	**7**	**14**	**28**	**61**	**122**	**243**	**365**	**486**	**608**	**730**	**851**	**973**	**1095**	**1216**	**1338**	**1460**	**EOS**
Week		**0**	**1**	**2**	**4**	**8**	**17**	**34**	**52**	**69**	**86**	**104**	**121**	**138**	**156**	**173**	**190**	**208**	**EOS**
Month					**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**EOS**
Risk factor assessment	X	X																	
Qualifying AMI Event		X																	
Index AMI Hospitalization Summary		X																	
Physical exam[2,4]	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Height[2]	X																		
Weight[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (pulse and BP)[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAEs[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete laboratory evaluation[7]		X			X		X		X			X			X			X	X
Abbreviated laboratory evaluation[8]			X	X		X		X		X	X		X	X		X	X		
Local laboratory evaluation[2,9]	S	S	S	S	S														
Endpoint assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Angioedema assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																			
Visit Contact Information	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[redacted]

Epoch	Screen	Treatment																	
Visit	**1**	**101**	**102**	**103**	**104**[16]	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**113**	**114**	**115**[17]	**116**[17]	**117**[17]	**199 and PSD**
Day		**1**	**7**	**14**	**28**	**61**	**122**	**243**	**365**	**486**	**608**	**730**	**851**	**973**	**1095**	**1216**	**1338**	**1460**	**EOS**
Week		**0**	**1**	**2**	**4**	**8**	**17**	**34**	**52**	**69**	**86**	**104**	**121**	**138**	**156**	**173**	**190**	**208**	**EOS**
Month					**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**EOS**
Serum/urine pregnancy testing[2,11]	S	S							S			S			S			S	S
[redacted]																			
Dispense Study Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Screening disposition	X																		
Study Completion form																			X

TD = Study treatment discontinuation; PSD = Premature patient discontinuation; EOS = End of study
X = assessment to be recorded on clinical data base
S = assessment to be recorded on eSource/source documentation only

[1]Collected retrospectively for patients who experience protocol defined liver events (See Appendix 2).

[2]Assessments typically performed as standard of care for index AMI according to local guidelines. Procedures that are part of a site's standard of care for an individual with AMI may pre-date the signed ICF. Local laboratory evaluations done as standard of care should not predate randomization by >72 hours. Vitals, weight, and physical exam assessments should be on the same day as visit 1 if they predate the signed ICF.

[3]Pulmonary congestion is assessed by worst Killip class AND/OR chest x-ray or CT scan findings during index hospitalization.

[4]Complete physical examinations are required at Visit 1 and yearly (Visits 108, 111, 114, 117, etc.) thereafter up until Visit 199 (EOS). Short physical examinations are required at all interim visits.

[5] CV medications (e.g., β-blockers, aldosterone antagonists, anti-hypertensives, lipid lowering drugs, antiplatelet agents, etc.) and classes of non-cardiovascular medications will be collected.

[6] All adverse events and all serious adverse events will be collected.

[redacted]

[7] Complete laboratory evaluations will be collected and sent to the central lab at all specified visits for all patients. Complete laboratory evaluation will be performed at visits 101, 104, 106, and annually (Visit 108, 111, 114, 117, etc.).

[8] Abbreviated laboratory evaluations includes: blood urea nitrogen (BUN), serum creatinine, serum potassium and eGFR and will be collected and sent to the central lab at all specified visits for all patients. An abbreviated laboratory evaluation will be performed at all interval visits except annual visits (i.e., visit 108, 111, 114, 117, etc.).

[9] Local laboratories for serum potassium (or equivalent plasma potassium value), creatinine and eGFR are permitted to help guide dosing decisions prior to initial dosing and prior to each dose titration step until target dose is achieved (Visits 1, 101, 102, 103 and potentially 104; additional visits may be added as necessary until target dose level is achieved and/or during dose adjustments throughout the study). If screening (Visit 1) and randomization (Visit 101) occur on the same day, only one laboratory assessment will be required. If local laboratory assessments are not possible or it will take longer to receive results than through the central laboratory assessment, the central laboratory may be used instead.

[11] Serum and urine pregnancy tests will be performed locally. Serum pregnancy test (not required for post-menopausal women) to be performed at Visit 1. Urine pregnancy tests at visits 101 and annual (not required for post-menopausal women) or more frequently if required by local regulatory authorities. If screening (Visit 1) and randomization (Visit 101) occur on the same day, only serum pregnancy test will be required. If serum pregnancy test is positive during the screening and on a confirmatory serum β-hCG test, the patient must not be randomized and must be discontinued from the trial. After randomization (Visit 101) a positive urine pregnancy test requires immediate interruption of study drug and confirmation by serum pregnancy test. If positive upon confirmation test, the patient must interrupt study drug until after the pregnancy and lactation period.

[14] For patient who at the end of the study are completing visit 199 on or before month 8 (visit 107 as per protocol schedule)

[16] For patients who have not been titrated to dose level 3 by week 4, an unscheduled dose titration visit on or about week 6 should be considered to evaluate whether titration to the target dose, dose level 3, can be initiated.

[17] Protocol visits will continue to occur every 4 months until the number of required study endpoints are met for end of study (EOS). If additional visits are required between visit 117/month 48 and EOS visit, patients must continue to complete scheduled visits every 4 months (3 visits per treatment year) increasing the protocol visit number by +1 at each subsequent visit (visit 118, visit 119, etc.). The assessments to be completed at the 3 visits per treatment-year should follow the assessments described in visit 115, 116, and 117 respectively. Example: visit 118 has the same assessments as visit 115, visit 119 has the same assessments as visit 116, and visit 120 has the same assessments as visit 117

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next epoch will have the study completion page for the screening epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the eSource/source data.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients at least include year of birth, age, sex, race, and ethnicity. A detailed medical history (including CV and other conditions relevant to the study population to be enrolled) and current medical conditions present before the signing of informed consent, including the presentation and management of index MI event will also be recorded.

6.3 Treatment exposure and compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient or care giver. This information should be captured in the eSource/source document at each visit. The investigator and/or study personnel should counsel the patient if compliance is below 80% at any time during the study. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

The duration of randomized treatment exposure will be calculated based upon the start and stop dates of study drug recorded in the CRF.

6.4 Efficacy

6.4.1 Efficacy assessment 1

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 criteria.
- 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

[redacted]

total daily dose through a period of ≥ 4 weeks), which is confirmed at a subsequent outpatient visit

6.4.2 Efficacy assessment 2

The secondary endpoints are:

- Time-to-first occurrence of CV death or HF hospitalization (days)
- Time-to-first occurrence of HF hospitalization or outpatient HF (days)
- Time-to-first occurrence of CV death, non-fatal spontaneous MI or nonfatal stroke (days)
- The cumulative number of composite events, including hospitalization due to HF, hospitalization due to non-fatal spontaneous MI, hospitalization due to non-fatal stroke and CV death. This endpoint is based on the total number of recurrent composite endpoints (count) and patient-specific follow-up time from randomization to end of study/death (days).
- Time to all-cause mortality (days)

A blinded central Clinical Endpoint Committee (CEC) will be responsible for adjudicating and classifying all death events (CV vs. non-CV) and for determining whether pre-specified endpoint criteria are met for the primary and secondary non-fatal endpoint events. The CEC will also be responsible for adjudicating and classifying all investigator-reported outpatient HF events as the clinical development of HF under an outpatient setting (urgent/unscheduled or non-urgent) with symptoms and signs requiring initiation/intensification of intravenous or qualifying oral HF treatment. The diagnostic criteria for HF symptoms and signs will be identical whether the patient is seen in an inpatient or outpatient setting. The detailed definitions of the endpoints, required documentation and the adjudication process will be provided to all sites in a separate endpoint manual.

6.4.3 Appropriateness of efficacy assessments

The composite of CV death or HF hospitalization is a well-established mortality and morbidity endpoint. The addition of the outpatient HF component here aims to capture the clinically important outpatient symptomatic HF event that contributes to the totality of HF morbidity following an AMI presenting as either inpatient (i.e., HF hospitalization) or outpatient (i.e., outpatient HF) events. The clinical significance of HF events in the outpatient setting has been increasingly recognized by medical communities and health authorities (Hicks, et al 2014). Outpatient HF events reported in randomized chronic HF trials, of which the definition is analogous to the outpatient HF event proposed for CLCZ696G2301 study, have been shown to be associated with significantly increased risks of (CV) mortality. Furthermore, the outpatient HF events are also modifiable events that are equally sensitive to the evidence-based HF therapeutics as are the mortality and composite CV death/HF hospitalization endpoints, which underscores the similar pathology contributing to these events (Skali, et al 2014; Okumura, et al 2016).

6.5 Safety

Novartis may request additional information on specific AEs or laboratory events of interest and may make requests to perform additional diagnostic tests to further assess the safety

[redacted]

profile of the study drugs. Such information may include diagnostic procedure reports, discharge summaries, autopsy reports, and other relevant information that may help in assessing the reported AE. All additional information will be de-identified prior to collection by Novartis or its agents.

6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A short physical exam will include the examination of general appearance and vital signs (BP [SBP and diastolic blood pressure (DBP)] and pulse). A short physical exam will be conducted at all visits starting from Visit 101 except where a complete physical examination is required (see Table 6-1).

Information from all physical examinations must be included in the eSource/source documentation at the study site. Significant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after signing the informed consent which meet the definition of an AE must be recorded on the AE section of the CRF.

6.5.2 Vital signs

Vital signs include BP and pulse measurements. BP will be measured in the sitting position after 5 minutes of rest using an automated validated device (e.g., OMRON) or a standard sphygmomanometer with an appropriately sized cuff on the non-dominant arm. Guidelines for the management of BP are provided in Appendix 4.

6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] or pound [lb] in indoor clothing, but without shoes) will be measured.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of most specimens collected. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

Complete central laboratory evaluations (hematology and blood chemistry) for the assessment of safety in this study will be performed at Visits 101, 104, 106, 108, 111, 114, 117, annually thereafter, and end of study (199). Abbreviated laboratory central evaluations will be performed at all interim visits as indicated in Table 6-1.

In addition to the required central laboratory assessments, a local laboratory may be used for the assessment of potassium, creatinine and eGFR during the screening period and dose titration period as indicated in Table 6-1. The results from the local laboratory will be allowed

[redacted]

to make decisions regarding randomization, study drug administration and dose titration/dose level adjustments, and will be recorded in the eSource/source documents at the study sites. In addition, local laboratory assessments of potassium, creatinine and eGFR may be performed on an as-needed basis to monitor tolerability to study drug and dose adjustments at scheduled or unscheduled visits during the treatment epoch. If local laboratory assessments are not possible or it will take longer to receive results than through the central laboratory assessment, the central laboratory may be used instead of local labs to make decisions regarding the study drug dosing.

Laboratory values that exceed the boundaries of a notable laboratory abnormality should be assessed for AEs and additional evaluations should be performed, as judged appropriate by the investigator. If the laboratory abnormality induces clinical signs or symptoms, results in a dose adjustment of the study medications, is suspected to be study drug-related or requires therapeutic intervention, then the diagnosis or medical condition must be entered on the AE CRF. If the laboratory abnormality is the primary reason for an unforeseen hospitalization or otherwise fulfills the seriousness category of an AE, then the procedure for rapid notification of SAEs must be followed. If the laboratory abnormality leads to study drug discontinuation (temporarily or permanently), the patient must be followed until the abnormality resolves or until it is judged to be permanent. The investigation may include continued monitoring by repeat laboratory testing or by performing additional laboratory tests as deemed necessary by the investigator or the Novartis medical monitor.

Table 6-2 Routine laboratory examinations

Hematology	**Biochemistry**
Hematocrit	Alanine aminotransferase (ALT)
Hemoglobin	Albumin (Alb)
Platelet count	Alkaline phosphatase (ALP)
Red blood cell count (RBC)	Aspartate aminotransferase (AST)
White blood cell count (WBC)	Blood urea nitrogen (BUN)*
WBC differential	Calcium
Red blood cell distribution width (RDW)	Chloride
Mean corpuscular volume (MCV)	Creatinine*
Mean corpuscular hemoglobin concentration (MCHC)	Glucose
	Hemoglobin A1C
	Lipid profile (total cholesterol, LDL, and HDL)
	Phosphate
	Potassium*
	Sodium
	Total bilirubin (TBL)
	Fractionated bilirubin (if total bilirubin >2x ULN)
	Total protein
	Uric acid
*Laboratory assessments of BUN, serum creatinine and serum potassium for the abbreviated central laboratory evaluation at visits where the complete laboratory evaluation is not performed; eGFR is derived from serum creatinine values following MDRD formula	

[redacted]

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count (RBC), red blood cell distribution width (RDW), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), white blood count (WBC) with differential, and platelet count will be measured.

6.5.4.2 Clinical chemistry

Blood urea nitrogen (BUN), creatinine, total bilirubin, fractioned bilirubin (if total bilirubin >2x upper limit of normal (ULN)), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), alkaline phosphatase, sodium, glucose, hemoglobin A1C, lipid profile, phosphate, potassium, chloride, calcium, total protein, albumin, and uric acid will be measured. Potassium, BUN and creatinine will be obtained at study visits where abbreviated central laboratory evaluations are scheduled.

6.5.4.3 eGFR

Estimated GFR will be calculated by the central or local laboratory using the following MDRD formula (Stevens et al. 2006):

Estimated GFR (mL/min/1.73 m^2) = 175 × (standardized SCr in mg/dL)$^{-1.154}$

× (age in years)$^{-0.203}$ × (0.742 if female) × (1.212 if black), where SCr is the serum creatinine value.

For the calculation of eGFR using local laboratory data, serum creatinine in the above formula will be replaced with plasma creatinine when serum creatinine is not available from local labs.

6.5.4.4 Urinalysis

No urinalysis will be performed.

6.5.5 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed locally in association with the index MI and recorded at Visit 1. Interpretation of the tracing must be made by a qualified physician and the ECG interpretation and the person interpreting the ECG must be recorded in the eSource/source documents at the study sites. The ECG tracing should be labeled with the study and patient number, date, and kept in the eSource/source documents at the study site. Clinically significant abnormalities should also be recorded on the Medical History/AE CRF page as appropriate.

6.5.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum pregnancy test performed locally at Visit 1. A urine dip-stick pregnancy test will be performed locally on an annual basis, or more frequently if required by local regulatory authorities. The urine dip-stick pregnancy test is not required for post-menopausal women. A positive urine pregnancy test requires immediate interruption of study drug and confirmation by serum pregnancy test. If positive upon confirmation test, the patient must interrupt study drug until after the pregnancy and lactation period.

[redacted]

6.5.7 Angioedema

Angioedema is a type of abrupt swelling that occurs under the skin and/or mucous membranes and is often localized to the head, neck, throat, and/or tongue, but may occur elsewhere, including the genitalia and intestines. Severe cases may be associated with airway compromise. A patient with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator and study medication must be permanently discontinued.

It is important that the investigator pays special attention to any swelling or edema that may resemble angioedema or angioedema-like events that may be reported by patients. If such an event occurs, the investigator will complete an Adjudication Questionnaire for an Angioedema-like event form (provided by Novartis) to summarize the event, its treatment, and its ultimate outcome. This report along with the requisite medical documentation must be submitted to Novartis as soon as possible. Follow-up reports must be communicated to Novartis as soon as new information regarding the event becomes available. All hospital records related to the event must be communicated to Novartis.

The investigator may be also be contacted by Novartis regarding AEs that may resemble an angioedema-like event. A list of terms that are considered "angioedema-like" (e.g., periorbital swelling) will be provided to sites in a manual. The investigator or his/her delegated staff must complete the required forms and provide the required medical records for all such events, regardless of whether the investigator views the event in question as angioedema or not.

All angioedema reports will be forwarded to an Angioedema Adjudication Committee by Novartis for independent adjudications.

Information regarding this committee is outlined in Section 8.5. Details on the procedures for reporting angioedema events will be provided to investigators in a manual.

6.5.8 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

[redacted]

[redacted]

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient after providing written informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

Adverse events of special interest (angioedema, hyperkalemia, hypotension, renal impairment, cognitive impairment, hepatotoxicity, hypersensitivity, malignancy, pregnancy and exposure during breast feeding, statin-related adverse events), along with all other AE and SAEs will be summarized and sent to the DMC for periodic safety reviews during the trial. The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

[redacted]

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade:
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment:
  - Yes
  - No

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- treatment dosage increased/reduced
- treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification (IN) or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's eSource/source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

[redacted]

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day

[redacted]

period after the last study visit should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to each specific component of study treatment, (if study treatment consists of several components) complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Protocol specific unblinding rules for SUSARs that are also efficacy endpoints

In studies such as this one, where the efficacy endpoints potentially meet the requirements for SUSAR reporting, the integrity of the study may be compromised if the endpoints are systematically unblinded for expedited reporting to competent authorities/relevant ECs and investigators. In such cases, regulations allow an exemption from SUSAR unblinding and expediting aimed at ensuring the validity of an outcome study (EU Guidance 2011/C 172/01; FDA Guidance 2012). Therefore, the following rules for unblinding SUSARs during the study period will be applied.

7.3.1 Primary and secondary endpoints

The primary and secondary endpoints (CV death, HF hospitalization, outpatient HF, non-fatal spontaneous MI, and non-fatal stroke) will not be unblinded even if they meet the definition of a SUSAR. Novartis will not expedite a report to competent authorities/relevant ECs and

[redacted]

will not issue an investigator notification (IN). However, non-CV death, a secondary endpoint for the study, will be unblinded if it meets the criteria for a SUSAR.

If specifically requested by a local Health Authority, pre-specified endpoints that also meet criteria for SUSARs will be expedited to this Health Authority as blinded reports. Investigator notifications will not be issued for these events.

7.3.2 Adverse events that are commonly seen in the study population

Investigators will report AEs or SAEs that are commonly seen in the study population but they will not be unblinded and will not be reported as SUSARs to regulatory agencies, ECs, or investigators during the study.

In clinical trials evaluating treatments for high morbidity and/or high mortality disease states, SAEs that are known consequences of the underlying disease or condition under investigation, or events common in the study population, are anticipated to occur with some frequency during the course of the trial, regardless of drug exposure. While the investigator must still report all SAEs and all the targeted non-serious AEs during and after the first two weeks after randomization, respectively, as outlined in Section 7.1 SUSARS considered consistent with the following SAE Preferred Terms (PT) will not be unblinded and reported in an expedited timeframe to regulatory agencies, ECs or investigators during the course of the study. These events will be presented in the clinical study report at the end of the study.

abdominal pain, acute coronary syndrome, acute pulmonary oedema, anaemia, angina pectoris *, anxiety, arthralgia, asthenia, azotaemia, back pain, blood creatinine *, blood pressure *, blood urea nitrogen *, bronchitis *, cardiac arrest, cardiac arrhythmias (all Preferred Terms presenting any type of arrhythmia ***excluding*** electrocardiogram QT interval abnormal, electrocardiogram QT prolonged, long QT syndrome, torsade de pointes), cardiac asthma, cardiac catheterization, cardiac failure *, cardiac output *, cardiac pacemaker *, cardiac resynchronization therapy, cardiac surgery (including coronary artery bypass grafting), cardiac tamponade, cardiogenic shock, cardiorenal syndrome, cerebrovascular accident, chest pain, chronic obstructive pulmonary disease, confusional state, constipation, cor pulmonale *, cough *, creatinine renal clearance *, delirium, diarrhea, dizziness, dyspnea *, ejection fraction *, fatigue, generalized oedema, glomerular filtration rate *, gout, headache, heart transplant, hepatic congestion, hyperglycemia, hyperkalemia, hyperlipidemia, hypertension *, hyperuricaemia, hypoglycemia, hypokalemia, hypernatremia, hypotension *, implantable defibrillator *, influenza *, insomnia, intra-aortic balloon pump, loss of consciousness, muscle spasm, musculoskeletal pain, myocardial infarction*, nasopharyngitis, nausea, oedema, oedema due to cardiac disease, oedema peripheral, osteoarthritis, pain in extremity, percutaneous coronary intervention, pericardial effusion, pleural effusion, pneumonia *, presyncope, pulmonary hypertension, pulmonary oedema, renal failure *, renal impairment, respiratory distress *, respiratory failure *, respiratory tract infection *, stroke*, syncope, transient ischemic attack, urinary tract infection, valve insufficiency*, valve stenosis*, ventricular failure *, ventricular assist device, vomiting, weight increased

*More than 1 preferred term can contain this term.

[redacted]

- If specifically requested by a local Health Authority, pre-specified AEs commonly observed in the study population (see above) that also meet the criteria for SUSARs will be expedited to the requesting Health Authority as blinded reports without issuing INs, or
- Pre-specified AEs commonly observed in the study population that occur in patients under the jurisdiction of the requesting Health Authority will be expedited to the Health Authority as unblinded reports; INs will be issued for these events.

[redacted]

7.4 Liver safety monitoring

Liver Function Test (LFT) elevations, including both aspartate transaminase (AST) and alanine transaminase (ALT), are common in patients following an AMI. In a study with a total of 1,783 patients presenting with STEMI, 59.1% patients with Killip class II had AST increase greater than 3x ULN and 5.1% had ALT increase greater than 3x ULN. For patients with liver enzyme increase, AST and ALT levels in majority of them return to baseline within 2 weeks (Lofthus, et al. 2012).

Evaluation of LFT elevations should focus on the potential drug-induced LFT changes. As described by Lofthus et al, any LFT elevations during the first 2 weeks post-AMI are very likely caused by the underlying disease. Therefore, AST and/or ALT elevations within 2 week post-AMI will not be reported as SAEs unless investigators suspect the liver transaminase change is due to the investigational drug. A similar consideration is also applicable to the recurrent MI or acute heart failure events during the trial.

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Liver events, which cannot be solely explained by apparent AMI (either index or recurrent spontaneous MI event) or acute heart failure episodes as the underlying cause, are divided into two categories:

- LFT increases without associated symptoms which will require repeated assessments of the abnormal laboratory parameter
- Liver events (i.e., significant LFT increases or liver-toxicity related symptoms with or without LFT increases), which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Appendix 2 Table 14-1 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger of liver event without apparent AMI (either index or recurrent MI event) as the underlying cause and as defined in Appendix 2 Table 14-1 should be

[redacted]

followed up by the investigator or designated personnel at the trial site as summarized below. Detailed information is outlined in Appendix 2 Table 14-2.

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation.

These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For significant LFT increases or liver-toxicity related symptoms with or without LFT increases:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

It is the investigator's responsibility to investigate the potential occurrence of these events. These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded on appropriate CRF pages, including the liver event overview CRF pages. In addition, independent assessments of the biochemical Hy's law cases (defined as ALT or AST > 3x ULN and total bilirubin > 2x ULN) reported during the study will be performed by an external liver safety expert.

7.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

[redacted]

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes,	Yes, even if not associated with a SAE

7.6 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

7.7 Monitoring of safety data by the Data Monitoring Committee

An external independent Data Monitoring Committee (DMC) (Section 8.4) will be appointed to monitor the safety of study participants and to ensure that the program is being conducted with highest scientific and ethical standards. This DMC will review the endpoint and SAE/AE of special interest data throughout the trial in an unblinded manner. Should the DMC make recommendations on the conduct of the trial that are considered to have significant bearing on the benefit-risk of the trial, these will be communicated by Novartis to HAs, ECs and investigators within an appropriate timeframe and implement any additional actions required.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote

monitoring of each site's data may be performed by a centralized Novartis Clinical Research Associate (CRA) organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain eSource/source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these eSource/source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant eSource/source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the eSource/source data with the CRFs are performed according to the study-specific monitoring plan. No information in eSource/source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Oracle Clinical/Remote Data Capture (OC/RDC) system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff or Clinical Research Organization (CRO) working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

[redacted]

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

An external data monitoring committee (DMC) independent of Novartis will be appointed to monitor the study conduct and to review the results of the interim analyses for safety on a regular basis and determine if it is safe to continue the study according to the protocol. In addition, they will review the results from two interim analyses to allow for early stopping due to overwhelming efficacy. Any major recommendation from the DMC will be communicated to the Executive Committee and must be reviewed and ratified by the Executive Committee in consultation with Novartis prior to its enactment.

The membership of the DMC and the responsibilities of the DMC and Novartis will be defined in a separate document entitled the "Data Monitoring Committee Charter". The DMC Charter will include information about data flow, purpose and timing of DMC meetings, guidance in the decision making process, communication strategy, procedures for ensuring confidentiality, procedures to address conflicts of interest and statistical monitoring guidelines.

8.5 Adjudication Committee

Clinical Endpoint Committee

All clinical events, which could potentially fulfill the criteria for the primary, secondary, or other selected endpoints will be assessed during the study and reported to a blinded central Clinical Endpoint Committee (CEC) for adjudication. The CEC will be responsible for adjudicating and classifying all death events (CV vs. non-CV) and for determining whether pre-specified endpoint criteria are met for selected non-fatal events. The detailed definitions of the endpoints, required documentation and the adjudication process will be provided to all sites in a separate endpoint manual.

Angioedema Adjudication Committee

All angioedema or angioedema-like events will be assessed during the study and reported a blinded angioedema adjudication committee for adjudication. If such an event occurs, the

investigator will complete an Adjudication Questionnaire for an Angioedema-like Event form (provided by Novartis). Details on the process of reporting angioedema and angioedema like events are outlined in a manual provided to investigators.

Submission of an angioedema report is not a substitution for the submission of an SAE report. If an angioedema-like event satisfies the definition of an SAE, the investigator must submit an SAE report in addition to the Adjudication Questionnaire for an Angioedema-like Event.

The membership and responsibilities of the Angioedema Adjudication Committee are defined in a separate document that will be provided to the sites.

9 Data analysis

The analysis will be conducted on all patient data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation. Additional details of the statistical analyses will be documented in a Statistical Analysis Plan (SAP).

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 supportive analyses for efficacy endpoints described in this section will be performed using the same analysis cut-off date as the second interim analysis (i.e., 01-Mar-2020).

Section 9.4.4 provides information about the currently planned sensitivity analyses for the primary endpoint. Additional sensitivity and supportive analyses for the COVID-19 impact will be added if deemed necessary. Details of the additional analyses will be specified in the SAP prior to database lock.

9.1 Analysis sets

The following analysis populations will be defined for statistical analysis:

- **Randomized (RAN) set** – All patients who received a randomization number, regardless of receiving trial medication.
- **Safety set (SAF) -** All patients who received at least one dose of study drug. Of note, the statement that a patient had no adverse events also constitutes a safety assessment. Patients 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 are analyzed according to the treatment they have been assigned to at the randomization.
- **The 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.

[redacted]

9.2 Patient demographics and other baseline characteristics

Summary tables will be provided by treatment group for demographic characteristics: including age, age group (<65 years vs. ≥65 years; <75 years vs. ≥75 years), sex, race, ethnicity, weight, height, body mass index (BMI) and baseline characteristics: including but not limited to information about the index MI event, (STEMI/NSTEMI; PCI/medical management; LVEF; Killip class, BP, renal function etc.), medical history and CV risk factors, and category of prior CV medications.

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

The FAS will be the patient population for the above analyses.

9.3 Treatments

The overall duration on the randomized study drug will be summarized by treatment group using mean, standard deviation, median, minimum, and maximum. Additionally, the number and percentage of patients will be summarized by treatment group for duration category. Mean doses and dose levels will be summarized by treatment group and visit. A Kaplan-Meier plot of time to discontinuation of study medication will be provided. A summary table by treatment group will be provided to display the number of patients who discontinued study medication and the number of patients who subsequently received the following medications during the study: ACE inhibitors, ARB, and Entresto™, (sacubitril/valsartan).

The duration of randomized study drug will also be calculated excluding temporary treatment discontinuations.

Concomitant medications and significant non-drug therapies, prior to and after the randomization date respectively, will be summarized by therapeutic class, preferred term, and treatment group for the safety set.

The number and percentage of patients on different CV background medications (e.g., aspirin, P2Y12 inhibitors, β-blockers, ACE inhibitors, ARBs, mineralocorticoid receptor antagonists, statins, and diuretics, etc.) will be tabulated by treatment at baseline and during the treatment epoch.

The SAF will be used for the summaries of exposure data and the summaries of concomitant medications unless otherwise specified.

9.4 Analysis of the primary variable(s)

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

9.4.1 Variable(s)

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.

[redacted]

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 start 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 or date of the patient's last visit prior to the cut-off date of the analysis (whichever occurred first).

9.4.2 Statistical model, hypothesis, 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. 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 plotted.

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 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 9.4.3, 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 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.

[redacted]

Subgroup analysis

Subgroup analyses will be performed for the 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 and including terms for treatment, region and PCI use at baseline in the model. The p-value associated with the interaction term 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. 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 below:

- Age group (< 65 vs ≥ 65 years; < 75 vs ≥ 75 years)
- Gender
- Race
- Region
- STEMI vs. NSTEMI (for this analysis, do not stratify by STEMI/NSTEMI, but include as a factor in the model)
- Baseline LVEF (by ≤40% and >40%)
- Killip class (I vs. ≥ II)
- Infarct location (anterior, inferior, and other)
- PCI use at baseline (PCI use versus medical management after index MI)
- Time from the index MI presentation to randomization (two subgroups cut by the median time)
- Baseline SBP (three groups: ≤110 mmHg; >110 mmHg and ≤140 mmHg; >140 mmHg)
- Baseline eGFR (<60 vs ≥ 60 mL/min/1.73 m^2)
- History of diabetes (yes/no)
- Atrial Fibrillation associated with index MI at baseline (yes/no)
- Prior history of MI
- History of hypertension (yes/no)
- Prior ACEi or ARB use (yes/no)
- Use of β-blocker at baseline (yes/no)
- Use of mineralocorticoid antagonists at baseline (yes/no)
- Use of oral loop diuretics at baseline (yes/no)

9.4.3 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):

[redacted]

- 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.

9.4.4 Sensitivity analyses

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

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, a sensitivity analysis will be performed using the primary analysis model as specified in Section 9.4.2, including all CEC-confirmed primary endpoint data accrued in the study.

If the study is not stopped at the second interim analysis and continues to the end, a sensitivity analysis will be added using the primary analysis model including CEC-confirmed primary endpoint events that occurred prior to 01-Mar-2020 (estimated start of COVID-19 impact globally). Additional sensitivity analyses to understand and mitigate the potential impact of COVID-19 may be specified in the SAP prior to database lock.

9.5 Analysis of secondary variables

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

The general strategies for the main and sensitivity analyses of the secondary efficacy endpoints will be similar to those of the primary efficacy endpoint (see Section 9 second and third paragraphs for general strategies, and Section 9.4.4 for sensitivity analyses).

9.5.1 Efficacy variables

The secondary variables are defined as follows; the censoring mechanism will be the same as defined for the primary endpoint unless indicated otherwise:

(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 (censoring will occur at the time of all-cause death)

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

(4) The cumulative number of composite events, including hospitalization due to HF, hospitalization due to non-fatal spontaneous MI, hospitalization due to non-fatal stroke and CV death. This endpoint is based on the total number of composite endpoints (count) and the patient-specific follow-up time from randomization to the 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).

[redacted]

(5) Time from randomization to all-cause mortality - patients without a death will be censored at the date of withdrawal from the study or the last day known to be alive (which may be established via telephone contact or the last visit prior to analysis cut off).

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'). Endpoints (1), (2), (3), and (5) will be analyzed using the same statistical analysis methods as specified for the primary analysis.

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). Treatment, STEMI/NSTEMI, PCI use at baseline and region will be included in the model as fixed effects. The relative rate ratio will be presented for LCZ696 vs ramipril together with 2-sided 95% confidence interval and 1-sided p-value.

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 endpoints (1), (3), (4) and (5), the secondary analysis described above 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.

Endpoints (1), (3) and (5) will be analyzed using an inverse probability of censoring weighted (IPCW) Cox proportional hazards model (Robins and Finkelstein 2000)). In this analysis, the censoring mechanism will be the same as described for the primary analysis for patients who are not prescribed Entresto™. For patients who do, censoring will occur at the minimum of the last date the endpoint status was known, the time of death from non-CV causes or 28 days after study treatment discontinuation. To adjust for the potential informative censoring, patients with event times censored due to treatment switch will be dynamically replaced in the patient risk-set to be represented by patients in control arm with a matching prognostic profile by up-weighting such patients in the analysis set. The weights will be calculated using a logistic regression with clinical risk factors determinant of developing the endpoint as covariates in the model (both baseline and post-baseline). A weighted Cox proportional hazard model will be fitted to this modified risk set. The model will be stratified by STEMI/NSTEMI; region, PCI use at baseline will be included as covariates. 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. Further details on appropriate covariate adjustment and associated implementation will be prospectively provided in the statistical analysis plan.

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.

[redacted]

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:

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

[redacted]

[redacted]

[redacted]

[redacted]

9.7 Interim analyses

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 used at the final analysis. The alpha to be spent for the final

[redacted]

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 9.5.1 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.

9.8 Sample size calculation

The sample size and power calculations described in the entire Section 9.8 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 9.7), 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 9.8.1.

[redacted]

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 FamilyWise 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 9.8.2.

9.8.1 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, see Section 9.7.

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. See Table 9-1 for the cumulative event rates assumed for the sample size calculation.

Table 9-1 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 event rates of the primary triple composite endpoint which would be expected.

In order to understand the impact of the uncertainties described above, Table 9-2 provides the sample sizes estimated to achieve at least 800 primary events with different underlying assumptions.

Table 9-2 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

Number of randomized patients required calculated using East version 6.3

[redacted]

Power for secondary endpoints

Table 9-3 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 9-3 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 9-1

[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.

[redacted]

9.8.2 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 9-4 and Table 9-5 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 9-4 and Table 9-5, the estimated event rates using blinded data are lower than the originally assumed event rates, for both the primary endpoint (see Table 9-4) and the double composite endpoint (see Table 9-5). 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).

[redacted]

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 9.7.
- 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 9-4 for the cumulative event rates (pooled) based on the originally assumed event rates from Table 9-1, as well as the estimated event rates from the blinded sample size re-estimation.

Table 9-4 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 9-1.

Table 9-5 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).

[redacted]

Time from randomization	Cumulative event rate (original assumption)[2]	Cumulative event rate (estimated using blinded data)

[2] Cumulative event rates (pooled) were derived according to the original assumption of the control group rates from Table 9-1.

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

Power for secondary endpoints

Table 9-6 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 9-6 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 9-5, 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.

[redacted]

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Council for Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient eSource/source documents.*

[*] For Germany only, the first paragraph will read as follows:

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation) IRB/IEC-approved informed consent. He/she should indicate assent by personally signing and dating the written informed consent document. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient eSource/source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment

[redacted]

procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance (CQA), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to

implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

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13 Appendix 1: Clinically notable laboratory values and vital signs

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

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

[redacted]

14 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 14-1 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

Table 14-2 Follow-up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

[redacted]

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

[redacted]

15 Appendix 3: Killip Classification

Pulmonary congestion following the index MI event will be assessed as the worst Killip class between index MI presentation and randomization using the criteria outlined below:

- Class 1 No rales, no 3rd heart sound
- Class 2 Rales in <½ lung field or presence of a 3rd heart sound
- Class 3 Rales in >½ lung field–pulmonary edema
- Class 4 Cardiogenic shock–determined clinically

16 Appendix 4: Guidelines for the management of blood pressure

Guidelines

1. Investigator should monitor BP closely
2. If symptomatic hypotension occurs:
   a. Correct any treatable cause, e.g. hypovolemia
   b. If hypotension persists, any non-disease modifying background antihypertensive drug such as diuretics, calcium channel blockers (CCBs), nitrates, and/or α-blockers, can be down-titrated or stopped first per investigator's clinical judgement before down-titration of the study drug is considered..
   c. It is important to note that dose adjustment of disease-modifying background therapy, e.g., β blockers, or mineralocorticoid antagonists is discouraged under these circumstances, unless they are believed to be the most likely cause of hypotension.

If hypotension persists, the study drug should be down-titrated or even temporarily withdrawn. The dose re-challenge and medications adjust guidelines described in Section 5.5.5 should be adhered to as much as possible.

[redacted]

17 Appendix 5: Treatment guidelines for hyperkalemia (serum potassium greater than 5.3 mmol/L [mEq/L])

General principles

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

Any patient with a serum* potassium > 5.3 mmol/L (mEq/L) at any time after randomization requires the Investigator to confirm the serum potassium concentration in a non-hemolyzed sample via an immediate repeat lab sample to the clinic local lab, the study central lab or both. Regular, repeated checks of serum potassium concentration (beyond that prescribed in the protocol) should continue until it is clear that the serum potassium concentration is stable and not rising into the range of concern (≥ 5.5 and < 6.0 mmol/L [mEq/L]*) or potential danger (≥ 6.0 mmol/L [mEq/L]*).

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

Corrective action for management of hyperkalemia

Serum potassium greater than 5.3 and less than 5.5 mmol/L (mEq/L)*

- Confirm serum potassium concentration in a non-hemolyzed sample
- Reinforce low potassium diet and restriction of food/drinks with high potassium content (e.g. orange juice, melon, bananas, tomatoes, dried fruits, potatoes, low-salt substitutes, tomatoes, coffee, etc.)
- Correct metabolic acidosis if necessary.
- Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia. Consider reduction in dose or discontinuation of these agents:
    - Potassium-sparing diuretics (e.g. amiloride and triamterene) including in combination products with thiazide or loop diuretics
    - Potassium supplements, e.g., potassium chloride
    - Salt substitutes
    - Non-steroidal anti-inflammatory drugs (NSAIDs)
    - Cyclo-oxygenase-2 (COX-2) inhibitors
    - Trimethoprim and trimethoprim-containing combination products, such as Bactrim® and Septra® (trimethoprim/sulfamethoxazole fixed combination)
    - Herbal Supplements:
        - For example, Noni juice, alfalfa (*Medicago sativa*), dandelion (*Taraxacum officinale*), horsetail (*Equisetum arvense*), nettle (*Urtica dioica*), milkweed, lily of the valley, Siberian ginseng, hawthorn berries

[redacted]

- Assess patient for dehydration or any condition that could lead to dehydration (e.g., diarrhea, vomiting) and/or hypovolemia and initiate appropriate corrective measures of rehydration.
- Repeat serum potassium measurement within 3 to 5 days
- If serum potassium remains > 5.3 and < 5.5 mmol/L (mEq/L)*, regularly monitor serum potassium levels to ensure stability (suggested once monthly)
- Consider down-titration of study drug, according to investigator's medical judgment.

Serum potassium greater than or equal to 5.5 and less than 6.0 mmol/L (mEq/L)*

- Confirm serum potassium concentration in a non-hemolyzed sample
- Consider down-titration or temporarily discontinue background therapy of mineralocorticoid antagonists (if they are believed to be the most likely cause of hyperkalemia).
- Apply all measures outlined for serum potassium > 5.3 and < 5.5 mmol/L*
- Repeat serum potassium measurement after 2-3 days
- If serum potassium < 5.5 mmol/L*, consider resumption of study drug at lower dose with repeat serum potassium within 5 days

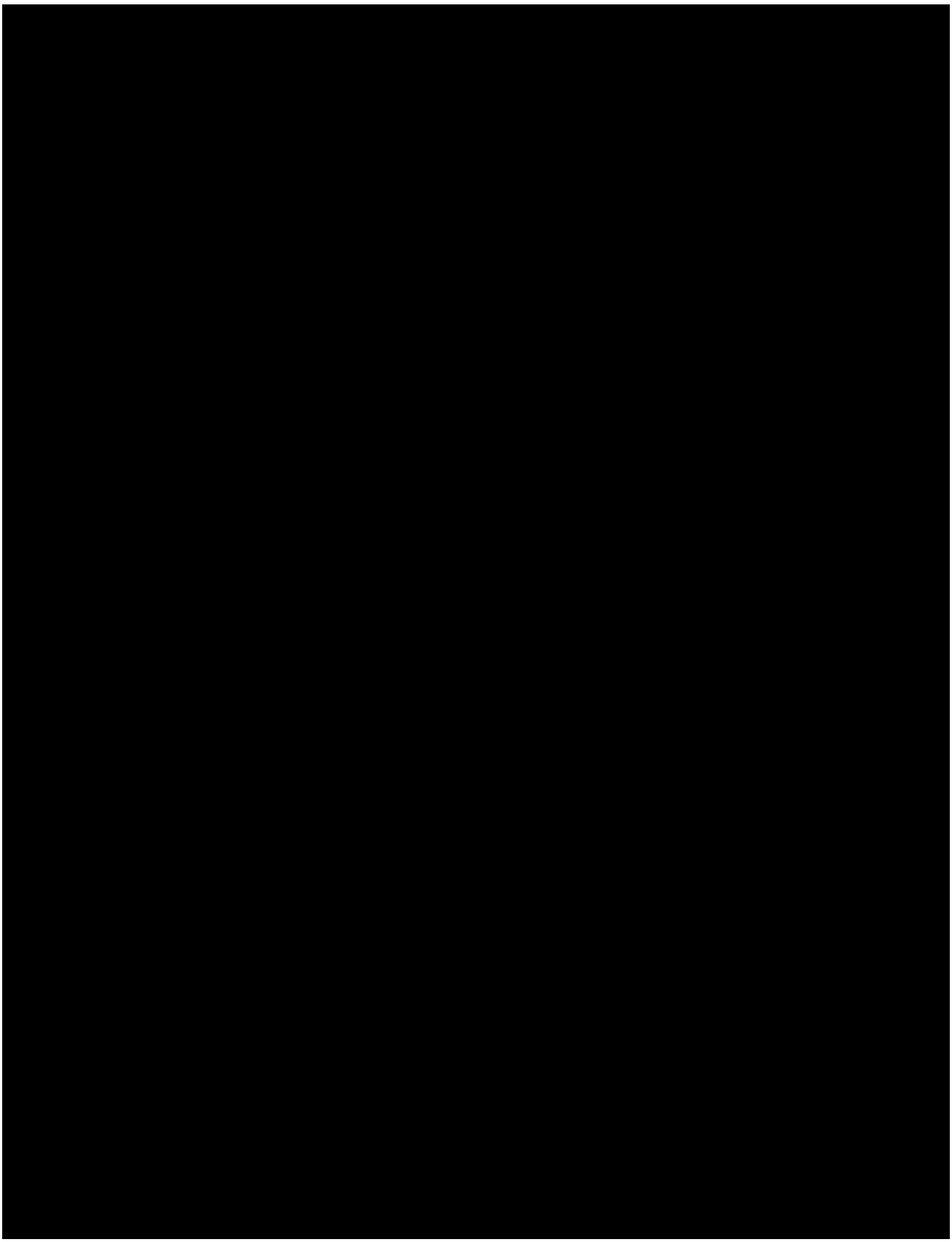
Serum potassium greater than or equal to 6.0 mmol/L (mEq/L)*

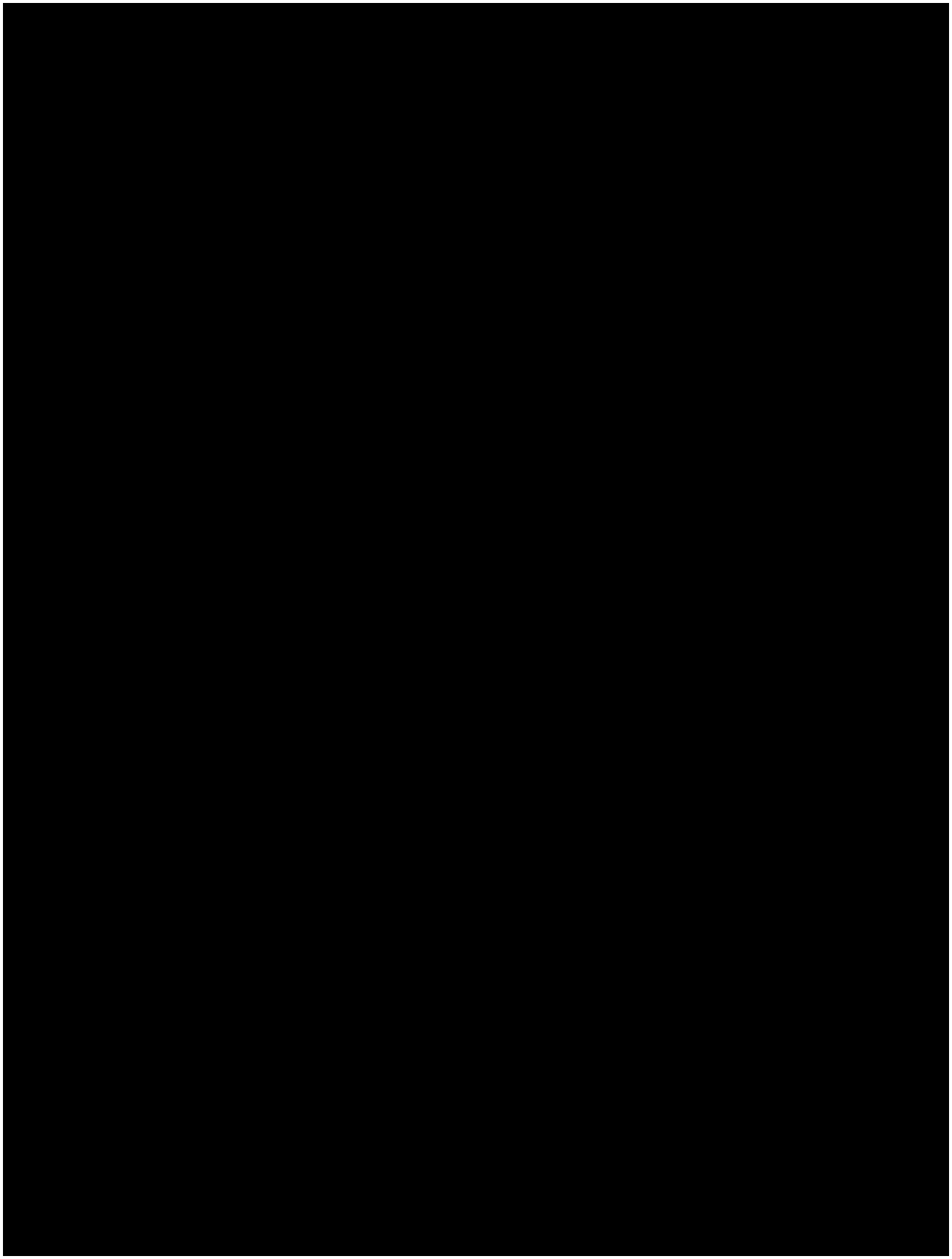
- Immediately discontinue study drug
  - Confirm serum potassium concentration in a non-hemolyzed sample
  - Urgently evaluate patient and treat hyperkalemia as clinically indicated
  - Apply all measures outlined for serum potassium > 5.3 and < 6.0 mmol/L (mEq/L)*

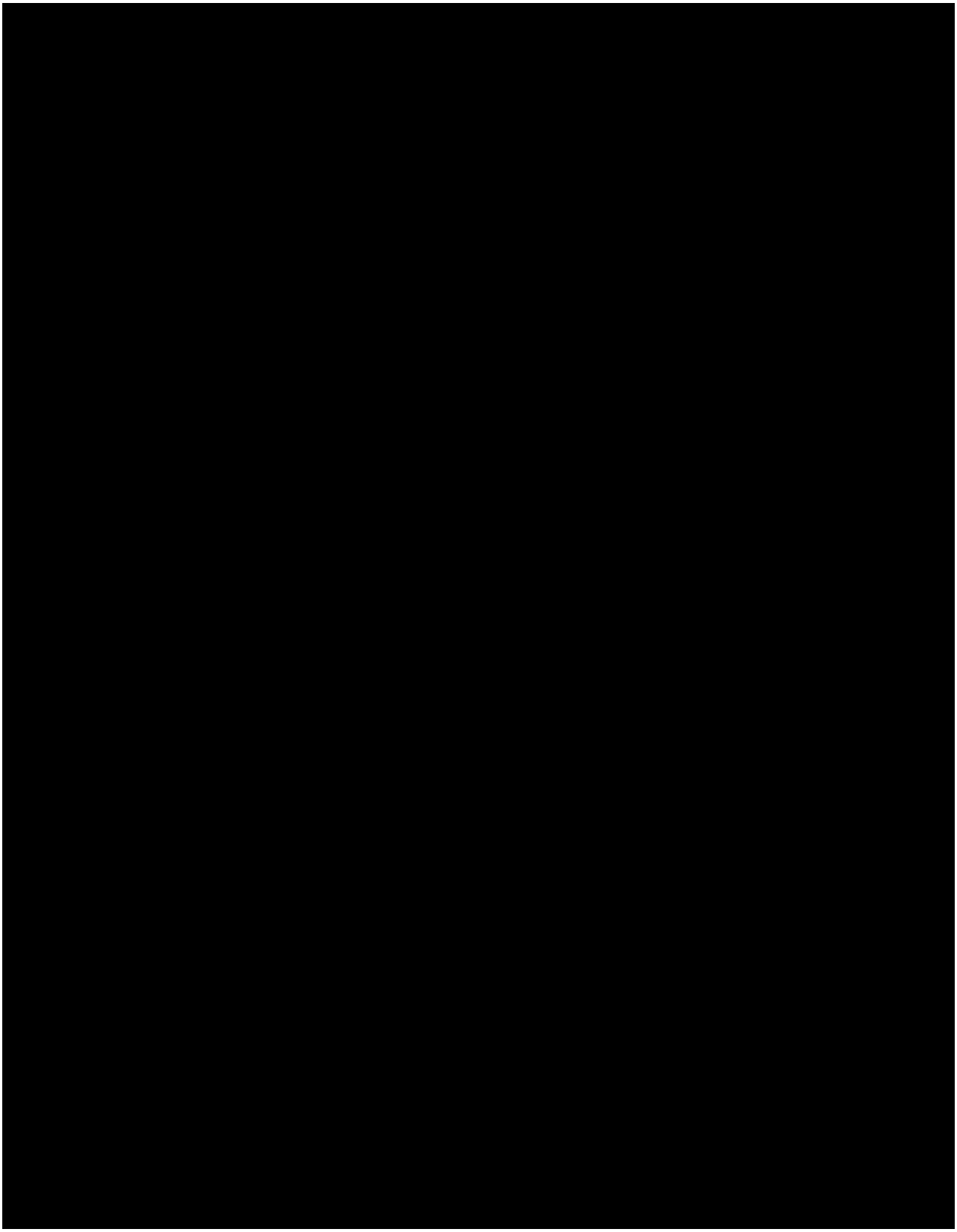
No resumption of study drug without individualized case discussion with and permission from Novartis medical monitor or his/her designee.

*Or equivalent plasma potassium value

[redacted]







Summary of all amendments to the protocol:

Date	Amendment	Summary
29-Jun-2016	Amendment 1	The purpose of this amendment is to refine the recommendations for alternative treatment to ensure sufficient RAS blockade in the event a patient needs to discontinue the study drug due to intolerable adverse events. The amendment also clarifies the acceptable methods of contraception for women of child bearing potential. Additional minor changes were also made to correct typographical errors and inconsistencies in the protocol. None of these changes will have an impact on the study population, endpoints, or the analysis of the study results. The main changes in this amendment are: Section 5.5.6 Rescue medications was updated to provide guidance on the alternative open-label treatment of RAS blockade in the event a patient needs to discontinue study drug at the investigator's discretion due to intolerable adverse events, despite the dose reduction or temporary interruption/re-challenge of study medication. Section 4.2 Exclusion criteria #25 was changed to clarify that women physiologically capable of becoming pregnant are excluded unless they are using highly effective methods of contraception not basic methods of contraception. The methods of contraception currently described in the protocol are highly effective, however, the wording was modified to comply with the current Novartis guidelines for the prevention of pregnancy. Additional minor changes were made to correct inconsistencies and typographical errors in the protocol. Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions. A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation. The changes herein do NOT affect the trial specific ICF.
25-Apr-2017	Amendment 2	[redacted] The amendment also removes the targeted adverse event data collection, and provides additional guidance for co-administering

		LCZ696 with atorvastatin or other statins. Further, in order to achieve the target dose in the early phase post AMI, for patients who have not titrated to the target dose level 3 by week 4, an unscheduled dose titration visit on or about week 6 is also recommended. Finally, some minor changes were also made to clarify the valsartan bridging procedure on day 1 post randomization, and to correct typographical errors and inconsistencies in the protocol. There is no impact of this amendment on the study population or the main analysis of the study results. The main changes in this amendment are: [redacted] [redacted] Section 4.1 Inclusion criteria • Inclusion criteria #3 was updated to clarify that patients with clinical presentation thought to be related to Takotsubo cardiomyopathy are also not eligible. • Inclusion criteria #4 was updated to add diuretics, vasodilators, vasopressors and/or inotropes as intravenous treatment required for pulmonary congestion. A footnote was also added clarifying the index MI with LV systolic dysfunction **and/or** pulmonary congestion. Section 4.2 the following exclusion criteria were updated or added • Exclusion criteria #13 was updated to permit equivalent plasma potassium value. • Exclusion criteria #25 regarding women of child bearing potential and the use of highly effective contraception was updated to allow local regulations to take precedence when it deviates from the contraception methods listed in the protocol; the local regulations will be described in the ICF. • [redacted] Section 5.5.4 Instructions for prescribing and taking study drug was updated to clarify the valsartan bridging procedure. Section 5.5.7 Concomitant medications was updated to provide additional guidance when coadministering LCZ696 with atorvastatin or other statins. Table 6-1 Assessment schedule was updated as follows: • The use of the central laboratory for screening and study drug titration decisions was added if the use of the local laboratory is

		not possible or will take longer to obtain results than the central laboratory assessments. • [redacted] • [redacted] • The recommended unscheduled dose uptitration visit was added • More frequent pregnancy testing, if required by local regulatory authorities was added • [redacted] Section 6.5.4 Laboratory evaluations was updated to allow equivalent plasma potassium and central laboratory assessments for screening and dose initiation and titration decisions. Section 6.5.6 Pregnancy and assessments of fertility was updated to allow more frequent pregnancy testing if required by local regulatory authorities. [redacted] Section 7.1 Adverse events were updated to remove the targeted collection of safety data so that all AEs will be collected. Also, statin related adverse events were added to the list of AEs of special interest. Section 7.4 Liver safety monitoring was updated to include acute heart failure episodes as an underlying cause for events of liver enzyme elevation. Sections [redacted] Section 17, Appendix 5 Treatment guidelines for hyperkalemia was updated to allow serum or equivalent plasma potassium values. [redacted] Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions. A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation. The changes herein do NOT affect the trial specific ICF.
01-May-2019	Amendment 3	The purpose of this amendment is to increase the sample size from 4,650 to 5,650 and adjust the assumption for the primary composite endpoint events of cardiovascular (CV) death, heart failure (HF) hospitalization, or outpatient HF treatment effect from 18% to 19%. These changes were made as an outcome of the per-protocol sample size re-estimation that was conducted when approximately

		½ of patients were randomized and reached the 3 month treatment time point as described in Section 9.8. At the time of this protocol amendment release, over 3,500 patients have been randomized. PARADISE-MI is an event-driven outcomes study. In the per protocol sample size re-estimation, the estimated cumulative event rates based on the available blinded data were lower than the originally assumed event rates. This indicated that the original assumptions may not hold. Therefore, in order to limit the impact in terms of considerable increase in overall trial duration, sample size re-estimation was performed and sample size increase became necessary. In addition, newly available efficacy data from the PIONEER-HF (CLCZ696BUS01) study showed a 46% relative risk reduction (RRR) (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 underlying pathophysiological mechanism between heart failure with reduced ejection fraction (HFrEF) and post- acute myocardial infarction (AMI) with left ventricular dysfunction, and also the acute setting for both PIONEER-HF and PARADISE-MI studies, this new data indicated that the initial hazard reduction assumption of the primary endpoint in PARADISE-MI may have been an underestimate. The increase in the sample size and the assumption for the treatment effect size maintain the statistical power of 80% for the primary composite endpoint. Additionally, Section 5.6.1 was updated to replace the described open-label extension study with a post-trial access program (PTA). The purpose of the PTA is to make the investigational drug available to qualified patients participating in the trial after the completion of the trial, in line with local laws and regulations. Lastly, the assessment schedule has been clarified in regard to additional visits. PARADISE-MI is an event-driven trial and patients will continue to be treated until the required number of endpoints is met and the maximum treatment period is expected to extend beyond month 32. Some minor changes are also made to clarify the entry criteria regarding risk factors, and to correct typographical errors and minor inconsistencies in the protocol. There is no impact of this amendment on the study population or the main analysis of the study results. The main changes in this amendment are: The described changes under the amendment rationale regarding the sample size re-estimation are implemented throughout the protocol. In addition, the following updates, clarifications, and omissions are included in this protocol amendment: Protocol Summary was updated to reflect the extended trial duration, updated sample size and endpoint event assumptions, to

		add clarity to Inclusion Criteria #5, [redacted] In Figure 3-1, the duration of double-blind treatment epoch was expanded to reflect treatment until the number of required endpoints is met and patients return for the end of study (EOS) visit. Table 3-3 The renal function criteria was corrected to estimated globular filtration rate (eGFR)≥ 30 mL/min/1.73m^2 and creatinine increase < 0.5 mg/dl from baseline as noted elsewhere in the protocol. Section 3.1 The estimated trial duration was updated from 32 months to 43 months and the recruitment period was updated to approximately 37 months. Section 3.5 Estimated number of endpoints needed at the time of interim analysis was updated. Section 4 The number of centers with randomized patients was reduced from approximately 650 to approximately 500. Section 4.1 Inclusion Criteria #5 was updated to clarify that if multiple left ventricular ejection fraction (LVEF) measurements have been performed during index event, the last one performed prior to randomization should be considered as the qualifying measurement. Section 4.2 Exclusion Criteria #27 was added. [redacted] Section 5.4, Section 5.5.9, and Section 5.6.2 were aligned to clarify that patients who are intentionally unblinded as per study process must permanently discontinue study treatment; whereas the appropriate personnel from the site and Novartis will assess whether study drug should be discontinued in instances where a patient is inadvertently unblinded for any reason. Section 5.6.1 Approach for the investigational drug to be made available to qualified patients participating in the trial was refined from an open-label extension study to a post-trial access (PTA) program and added that the mechanism for post-trial access to investigational drug must comply with the local laws and regulations in the participating countries in order to be made available. Section 5.6.3 Withdrawal of Informed Consent section was updated to align with new laws regarding personal data. Section 6 Language was added to specify that in addition to vital status, primary endpoint information should be collected for every patient.

		Table 6-1 was expanded to reflect patients' continuation in the trial until the number of required events is met and patients are asked to return for the EOS and reflect assessments which are considered standard of care at time of screening and randomization. Section 6.5.4 Section was updated as per Table 6-1. Section 6.5.6 Section was updated to reflect that the patient must interrupt, rather than discontinue, study drug in case of pregnancy. Update is also reflected in Table 6-1. Section 9.3 Section was updated to align with the statistical analysis plan. Section 9.6.1 Secondary efficacy endpoint regarding changes in serum creatinine was clarified. Section 9.7 Section was updated to reflect that the interim analysis will be conducted when approximately 472 adjudication-confirmed primary endpoints have been reached. Section 9.8 Sample Size Calculation was revised following the planned sample size reestimation using blinded data and the updated sample size calculation is described in Section 9.8.2. Appendix 5 Pre-defined potassium values for the management of hyperkalemia were updated to correct an inconsistency. Hyperkalemia values that warrant corrective action include serum potassium greater than 5.3 and less than 5.5 mmol/L (mEq/L); serum potassium greater than or equal to 5.5 and less than 6.0 mmol/L (mEq/L). [redacted] Other minor updates and corrections were also included. Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions. IRBs/IECs A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation. The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that

		takes into account the changes described in this protocol amendment.
06-Aug-2020	Amendment 4	The purpose of this amendment is to add a second interim analysis in response to the COVID-19 pandemic with the stopping boundary for the primary endpoint at one-sided alpha of 0.005. A novel coronavirus that had not previously been identified is causing clinical disease in humans (COVID-19). On 11-Mar-2020, the World Health Organization (WHO) characterized COVID-19 as a pandemic. As acknowledged by global Health Authorities in their guidance to the pharmaceutical industry, the COVID-19 pandemic has a global impact on the conduct of clinical trials of medicinal products. Challenges arising include at-risk patient populations, site closures, travel restrictions, shelter-in-place orders, interruptions to the supply chain for the investigational product, and other considerations if trial patients and site personnel become infected with COVID-19. The significant impact of COVID-19 on the safety of patients and study personnel has greatly impacted study conduct. We have already observed marked increase in missed visits, treatment interruption due to drug supply issues related to the pandemic and substantial reduction of HF hospitalization and outpatient HF events. This observation is consistent with the published data which showed a greater than 50% reduction in the occurrence of HF hospitalization during the COVID-19 pandemic (Hall, et al. 2020), adding to other serious challenges on the conduct of the PARADISE-MI study. Prior to 01-Mar-2020, timepoint before which clinical trial data has generally not been impacted by the COVID-19 pandemic at the global level, approximately 80% of the 708 target total number of the primary events in the PARADISE-MI study had been accumulated. Considering the advanced state and documented impact of the COVID pandemic on the conduct of the trial, the PARADISE-MI Executive Committee recommended adding a second interim analysis using the primary events accrued prior to 01-Mar-2020 for the primary analysis. In case of early stopping, all additional endpoints occurring on or after 01-Mar-2020 until study close out will be included as a sensitivity analysis. In the event that the data accumulated prior to the adverse influence of the pandemic had already established convincing efficacy, as per the proposed second interim analysis criteria, it would represent the most reliable test of the study hypothesis. Novartis will continue monitoring the impact of the COVID-19 pandemic, in the event that the COVID-19 pandemic continues over a prolonged period of time hampering the ability to complete the trial in a timely and appropriate fashion, Novartis may consider modifying the proposed interim analysis to be the final analysis and close out the study prematurely. There is no impact of this amendment on the study population or endpoints. If the trial continues after the interim analysis, the main analysis of the study result will remain as per the original protocol but additional sensitivity analyses will be performed to evaluate the

		potential impact of COVID-19 on the interpretation of data generated post 01-Mar-2020. The alpha for the final analysis will be adjusted accordingly to control the overall type 1 error (across the 2 interim analyses and the final analysis) at 1-sided alpha of 0.025. The main changes in this amendment are: List of abbreviations was updated to include COVID-19. Previous Amendments were updated to include amendment finalization date as per current Novartis standard. Protocol Summary Data Analysis section, Section 3.5 Purpose and timing of interim analyses/design adaptations, and Section 8.4 Data Monitoring Committee were updated to reflect the introduction of a second interim analysis. Table 6-1 and Section 18 Appendix 6 Investigational Plan [redacted] Table 6-1 has also been updated to indicate echocardiograms performed as standard of care prior to consent are permitted. Section 9 has been updated to reflect the general data analysis strategies for the added second interim analysis and possible early termination by sponsor if needed due to COVID-19. Section 9.4.4 has been updated to define the approach for sensitivity analyses related to COVID-19. Section 9.5 has been updated to describe the general strategies for the main and sensitivity analyses relative to the secondary efficacy endpoints. [redacted] Section 9.7 Interim Analysis was updated to describe the plan for the added efficacy interim analysis. Section 9.8 has been updated to discuss the impact on power for the primary endpoint in adding the second efficacy interim analysis. Section 12 was updated with the added reference. Other typographical corrections were also included. All changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions. IRBs/IECs A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

		The changes described in this amended protocol may require IRB/IEC and Health Authority approval according to local regulations prior to implementation. The changes herein do NOT affect the trial specific model ICF.