NOVARTIS

Clinical Development

LCZ696

Clinical Trial Protocol CLCZ696D2301 / NCT01920711

A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to valsartan, on morbidity and mortality in heart failure patients (NYHA Class II-IV) with preserved ejection fraction

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Document type:	Amended Protocol Version
EUDRACT number:	2013-001747-31
Version number:	v04 Clean
Development phase:	III
Release date:	09-Dec-2015

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List of abbreviations

AAC	Angioedema Adjudication Committee
ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
AE	adverse event
AESI	adverse event of special interest
AF	atrial fibrillation and atrial flutter
ALB	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANP	atrial natriuretic peptide
APP	aminopeptidase P
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
AST	aspartate aminotransferase
AT_1	angiotensin type 1
AUC	area under the curve
b.i.d.	twice a day
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CCB	calcium channel blocker
CEC	Clinical Endpoint Committee
cGMP	cyclic guanosine monophosphate
CHF	chronic heart failure
CNP	C-type natriuretic peptide
COPD	chronic obstructive pulmonary disease
COX-2	cyclo-oxygenase-2
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRT	cardiac resynchronization therapy
CSR	clinical study report
CV	cardiovascular
DBP	diastolic blood pressure

DM	diabetes mellitus
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
echo	echocardiogram
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
FMV	first morning void
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
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
i.v. (IV)	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
IVRS	Interactive Voice Response System
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	left atrial
LAE	left atrial enlargement
LFT	liver function test
LV	left ventricular

LVEDP	left ventricular end diastolic pressure
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDRD	Modification in Diet in Renal Disease
MI	myocardial infarction
MMSE	Mini-Mental State Examination
MRA	mineralocorticoid antagonist
NEP	neprilysin
NEPi	neprilysin inhibitor
NOAF	new onset atrial fibrillation
NODM	new onset diabetes mellitus
NP	natriuretic peptide
NSAID	non-steroidal anti-inflammatory drug
NTG	nitroglycerin
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
o.d.	once a day
PCI	percutaneous coronary intervention
PDE-5	phosphodiesterase-5
PK	pharmacokinetics
PT	preferred term
p.o.	oral
PP	per protocol
QoL	quality of life
RAS	renin angiotensin system
RBC	red blood cell
RDW	red blood cell distribution width
RR	rate ratio
RU	resource utilization
SAE	serious adverse event
SAF	safety
SBP	systolic blood pressure
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SUSAR	suspected unexpected serious adverse reactions
TBL	total bilirubin
T1/2	half life

UACR	urine albumin creatinine ratio
ULN	upper limit of normal
US	United States
WBC	white blood cell
γGT	gamma-glutamyltransferase

Glossary of terms

Assessment	A procedure used to generate data required by the study
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
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	The planned stage of the subjects' participation in the study. Each epoch serves a purpose in the study as a whole. Typical epochs are: determination of subject eligibility, wash-out of previous treatments, exposure of subject to treatment or to follow-up on subjects after treatment has ended.
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."
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Subject Number	A number assigned to each patient who enrolls into the study
Part	A subdivision of a single protocol into major design components. These parts often are independent of each other and have different populations or objectives. For example, a single dose design, a multiple dose design that are combined into one protocol, or the same design with different patient populations in each part.
Period	A subdivision of a cross-over study
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all investigational/study treatment administration and all assessments (including follow-up)
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study/investigational treatment was discontinued whichever is later
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), treatment drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

Protocol synopsis

Protocol number	CLCZ696D2301
Title	A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to valsartan, on morbidity and mortality in heart failure patients (NYHA Class II-IV) with preserved ejection fraction
Brief title	Study of efficacy and safety of LCZ696 in heart failure (HF) patients (New York Heart Association [NYHA] Class II-IV) with preserved ejection fraction (EF)
Sponsor and Clinical Phase	Novartis, Phase 3
Investigation type	Drug
Study type	Interventional
Purpose	The purpose of this study is to evaluate the effect of LCZ696 compared to valsartan in the reduction of cardiovascular (CV) death and HF hospitalizations in patients with HF with preserved EF (HFpEF).
Primary Objective	The primary objective of this study is to compare LCZ696 to valsartan in reducing the rate of the composite endpoint of CV death and total (first and recurrent) HF hospitalizations in HF patients (NYHA Class II - IV) with preserved EF (left ventricular EF [LVEF] ≥45%).
Secondary Objectives	• To compare LCZ696 to valsartan on changes in the clinical summary score for HF symptoms and physical limitations as assessed by Kansas City Cardiomyopathy Questionnaire [KCCQ]) at 8 months. • To compare LCZ696 to valsartan in improving NYHA functional classification at 8 months. • To compare LCZ696 to valsartan in delaying the time to first occurrence of a composite renal endpoint, defined as: o renal death, **or** o reaching end stage renal disease (ESRD), **or** o ≥ 50% decline in estimated glomerular filtration rate (eGFR) relative to baseline • To compare LCZ696 to valsartan in delaying the time to all-cause mortality. Note: randomized treatment epoch baseline is used in the secondary objectives efficacy analysis
Study design	This study is a multi-center, randomized, double-blind, parallel group, active comparator, morbidity and mortality trial designed to evaluate the efficacy and safety of LCZ696 compared to valsartan in HFpEF patients (NYHA class II-IV).
Population	Approximately 4,600 male and female patients ≥ 50 years of age with a prior history of HF and current symptoms of HF (NYHA class II-IV), a LVEF ≥45%, and documented structural heart disease will be randomized.
Inclusion criteria	1. Written informed consent must be obtained before any assessment is performed.

	2. ≥ 50 years of age, male or female 3. LVEF ≥45% by echocardiogram (echo) during the screening epoch, or within 6 months prior to Visit 1(any local LVEF measurement made using echo only) 4. Symptom(s) of HF requiring treatment with diuretic(s) for at least 30 days prior to Visit 1 5. Current symptom(s) of HF (NYHA Class II-IV) at Visit 1 6. Structural heart disease evidenced by at least one of the following echo findings (any local measurement made during the screening epoch or within the 6 months prior to Visit 1): a. left atrial (LA) enlargement defined by at least one of the following: LA width (diameter) ≥3.8 cm or LA length ≥5.0 cm or LA area ≥20 cm^2 or LA volume ≥55 mL or LA volume index ≥29 mL/m^2 b. left ventricular hypertrophy (LVH) defined by septal thickness or posterior wall thickness ≥1.1 cm 7. Patients with at least one of the following: a. a HF hospitalization (defined as HF as the major reason for hospitalization) within 9 months prior to Visit 1 and NT-proBNP >200 pg/ml for patients not in atrial fibrillation/flutter (AF) or >600 pg/ml for patients in AF on Visit 1 ECG, OR b. NT-proBNP >300 pg/ml for patients not in AF or >900 pg/ml for patients in AF on the Visit 1 ECG.
Key Exclusion criteria	1. Any prior echocardiographic measurement of LVEF <40%. 2. Acute coronary syndrome (including MI), cardiac surgery, other major CV surgery, or urgent percutaneous coronary intervention (PCI) within the 3 months prior to Visit 1 or an elective PCI within 30 days prior to Visit 1. 3. Any clinical event within the 6 months prior to Visit 1 that could have reduced the LVEF (e.g., MI, coronary artery bypass graft [CABG]), unless an echo measurement was performed after the event confirming the LVEF to be ≥45%. 4. Current acute decompensated HF requiring augmented therapy with diuretics, vasodilators and/or inotropic drugs. 5. Patients who require treatment with 2 or more of the following: an angiotensin converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB) or a renin inhibitor. 6. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes. 7. Patients with a known history of angioedema. 8. Probable alternative diagnoses that in the opinion of the investigator could account for patient's HF symptoms (i.e., dyspnea, fatigue) such as significant pulmonary disease (including primary pulmonary hypertension), anemia or obesity. Specifically, patients with the below are excluded: a. severe chronic obstructive pulmonary disease (COPD) (i.e., requiring home oxygen, chronic nebulizer therapy, chronic oral steroid therapy or hospitalized for pulmonary decompensation within 12 months) **or** b. hemoglobin (Hgb) <10 g/dl, **or** c. body mass index (BMI) > 40 kg/m^2 9. Patients with any of the following:

	a. systolic blood pressure (SBP) ≥ 180 mmHg at Visit 1, **or** b. SBP >150 mmHg and <180 mmHg at Visit 1 unless the patient is receiving 3 or more antihypertensive drugs. Antihypertensive drugs include, but are not limited to, a thiazide or other diuretic, mineralocorticoid antagonist (MRA), ACEI, or ARB, beta blocker and calcium channel blocker (CCB), **or** c. SBP <110 mmHg at Visit 1, **or** d. SBP < 100 mmHg or symptomatic hypotension as determined by the investigator at Visit 103 or Visit 199/201. 10. Patients with history of any dilated cardiomyopathy, including peripartum cardiomyopathy, chemotherapy induced cardiomyopathy, or viral myocarditis. 11. Evidence of right sided HF in the absence of left-sided structural heart disease. 12. Known pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy. 13. Clinically significant congenital heart disease that could be the cause of the patient's symptoms and signs of heart failure. 14. Presence of hemodynamically significant valvular heart disease in the opinion of the investigator. 15. Stroke, transient ischemic attack, carotid surgery or carotid angioplasty within the 3 months prior to Visit 1. 16. Coronary or carotid artery disease or valvular heart disease likely to require surgical or percutaneous intervention during the trial. 17. Life-threatening or uncontrolled dysrhythmia, including symptomatic or sustained ventricular tachycardia and atrial fibrillation or flutter with a resting ventricular rate >110 beats per minute (bpm). 18. Patients with a cardiac resynchronization therapy (CRT) device. 19. Patients with prior major organ transplant or intent to transplant (i.e. on transplant list). 20. Any surgical or medical condition, which in the opinion of the Investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study. 21. Evidence of hepatic disease as determined by any one of the following: SGOT (AST) or SGPT (ALT) values exceeding 3x ULN, bilirubin >1.5 mg/dl at Visit 1. 22. Patients with one of the following: a. eGFR <30 mL/min/1.73m^2 as calculated by the Modification in Diet in Renal Disease (MDRD) formula at Visit 1, **or** b. eGFR <25 mL/min/1.73m^2 at Visit 103 or Visit 199/201, **or** c. eGFR reduction ≥35% (compared to Visit 1) at Visit 103 or Visit 199/201. 23. Patients with one of the following: a. serum potassium >5.2 mmol/L (mEq/L) at Visit 1, **or** b. serum potassium >5.4 mmol/L (mEq/L) at Visit 103 or Visit 199/201. 24. Pregnant or nursing (lactating) women. 25. Women of child-bearing potential unless they are using highly effective methods of contraception.

Investigational and reference therapy	LCZ696 50 mg (dose level 1), 100 mg (dose level 2), 200 mg (dose level 3) Valsartan 40 mg (dose level 1), 80 mg (dose level 2), 160 mg (dose level 3)
Efficacy assessments	• CV death • Total HF hospitalizations • KCCQ clinical summary score for HF symptoms and physical limitations scores at 8 months • NYHA functional classification at 8 months • Composite renal endpoint • All-cause mortality
Safety assessments	• AEs and SAEs • Sitting systolic BP, sitting diastolic BP, and heart rate • Laboratory values (including monitoring for hyperkalemia, renal dysfunction) • ECG changes • Angioedema surveillance
Other assessments	• Total non-fatal MIs • Total non-fatal strokes • Resource utilization • Health-related Quality of Life o KCCQ overall summary score and subdomain scores; KCCQ clinical summary score relative to the beginning of run-in epoch (in the subset of patients in whom KCCQ assessment was collected at that point) and relative to randomization o Clinical composite assessment o EuroQol (EQ-5D) • New onset of atrial fibrillation (NOAF) • Echocardiography parameters • Pharmacokinetics • Pharmacogenetics/Pharmacogenomics • Biomarkers • Mini-Mental State Examination score
Data analysis	The primary efficacy variable is the cumulative number of primary composite endpoint events for a given patient, over time during the double blind period of the study. The secondary efficacy variables are: • Change in KCCQ clinical summary score from baseline to Month 8 • Change in NYHA class from baseline to Month 8 • Time to composite renal endpoint • Time to all-cause mortality Note: randomized treatment epoch baseline is used in the secondary efficacy analysis The primary efficacy analysis will be using a proportional conditional rates model based on cumulative, recurrent events approach analyzing CV

	death and HF hospitalizations. The primary hypothesis will be tested at a one-sided significance level of 0.024 adjusted for interim analysis (IA). One efficacy interim analysis is planned when approximately two-thirds of the target number of adjudicated primary events is obtained.
Key words	heart failure with preserved ejection fraction, cardiovascular death, heart failure hospitalization, atrial fibrillation, echocardiography, NYHA, Clinical Composite Assessment, Kansas City Cardiomyopathy Questionnaire, EQ-5D

Amendment 4

Amendment rationale

Recruitment in Study CLCZ696D2301, also known as PARAGON-HF, began on 15-Jul-2014. As of 07-Dec-2015, 1,514 patients have been randomized into the study.

This is the fourth amendment to the current protocol. The purpose of the current amendment is to include changes required by the Japanese Health Authority (PMDA) and the Indian Health Authority. The following changes have been made and will only be applicable to Japan and India, as indicated:

Japan:

1. All patients must enter the treatment run-in epoch at Visit 101.
2. Patients who have not received an ACEI or an ARB during the 30 days prior to the screening visit will be required to attend an additional clinic visit (Visit 101J) approximately one week after Visit 101 and will have the same procedures as Visit 102. Visit 102 will occur approximately one week after Visit 101J in these patients.
3. Central safety laboratory assessments will be required at Visit 101J and Visit 102.
4. All patients will be required to attend three additional clinic visits at approximately 1 week (Visit 201J1), 8 weeks (Visit 202J8), and 12 weeks (Visit 202J12) following randomization.
5. Visits 206, 208, 210, 212, 214, 216, 218 and 220 will be conducted as clinic visits, not phone visits, with the same procedures as Visit 202. Study medication dispensing, drug accountability and serum/urine pregnancy tests are not required at any of the additional double-blind treatment epoch visits implemented for Japan.

India:

1. All patients will be required to attend an additional clinic visit (Visit 201I1) approximately 1 week following randomization (i.e. start of double-blind study medication dose level 3) where a potassium assessment will be performed.
2. For inclusion in the study, the ejection fraction must be measured using 2D volumetric methods.

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 are also reflected in the Informed Consent.

Summary of previous amendments

The first amendment of protocol CLCZ696D2301 (v01 of the protocol) was dated 10-Jun-2014. The main purpose of this amendment was to increase the contraception period for women of child-bearing potential after being taken off study medication from 4 days to 7 days

in the exclusion criteria. Also, information on the results of the TOPCAT and PARADIGM-HF studies were included.

The second amendment of protocol CLCZ696D2301 (v02 of the protocol) was dated 06-May-2015. The main purposes of this amendment were (1) to promote two exploratory endpoints (KCCQ clinical summary score at 8 months and the composite renal endpoint) to key secondary endpoints; (2) to demote the extended composite endpoint (i.e., the composite of cardiovascular [CV] death, total HF hospitalizations, total non-fatal strokes, and total non-fatal myocardial infarctions [MIs]) and the new onset atrial fibrillation (NOAF) endpoint to exploratory endpoint status; (3) to eliminate the ambulatory cardiac monitoring substudy and the associated exploratory objectives; (4) to include cognitive function assessments using the Mini-Mental State Examination (MMSE) instrument at baseline and annually thereafter; (5) to modify several entry criteria; (6) to move the interim efficacy analysis to occur after approximately two-thirds of the target number of primary composite events (i.e., ~1148 primary composite events) rather than half as previously defined; and (7) to eliminate the futility analysis.

The third amendment of protocol CLCZ696D2301 (v03 of the protocol) was dated 04-Dec-2015. The main purpose of this amendment was (1) to add the KCCQ assessment at V101/102 (whichever occurs first); (2) to include a mechanism for central source data verification of medical history; (3) to adjust the sample size from 4300 to 4600; (4) to modify the stopping rules for interim analysis; and (5) clarify responsibilities of the investigator with regards to emergency unblinding.

1 Introduction

1.1 Background

Heart failure with preserved ejection fraction (HFpEF)

Cardiovascular (CV) disease is the leading cause of death in the western world. Heart failure (HF) incidence approaches 10 per 1000 population after 65 years of age in the United States (US) (Roger et al 2012) with HF prevalence between 2 and 3% in Europe and between 10 and 20% in European elderly (McMurray et al 2012). It affects nearly 6.6 million people over the age of 18 in the US with an additional 3 million new cases expected by 2030; a 25% increase from 2010 (Roger et al 2012).

In recent years, HF has been shown to occur with normal systolic function. HF with normal or "near-normal" ejection fraction (EF) has been designated HF with preserved ejection fraction (HFpEF). Studies have typically defined preserved EF with a cut-off of 40-50%, with 45% being the most common EF cut-off utilized in clinical trials. HFpEF accounts for approximately half of HF cases, and is associated with substantial morbidity and mortality (Lam et al 2011). Moreover, the prevalence of HFpEF, as well as its relative prevalence compared with HF with reduced ejection fraction (HFrEF), has been increasing in recent years (Owan et al 2006, Borlaug and Paulus 2011). Compared with HFrEF, patients with HFpEF are older, predominantly female, more likely to have hypertension (HTN) and atrial fibrillation (AF), and less likely to have coronary artery disease (Lenzen et al 2004, MAGGIC 2012). Mechanisms implicated in HFpEF include abnormal diastolic function with resultant increase in ventricular filling pressures, increased vascular stiffness, and abnormal systolic function despite preserved EF (Tartière-Kesri et al 2012, Tan et al 2009). Recently, these individuals have also been shown to have an impaired natriuretic and renal endocrine response to acute volume expansion early in the development of this syndrome (McKie et al 2011).

HF hospitalization is the single most common cause of admission in patients with HFpEF, representing an important marker of disease progression and, thus, an important indicator of poor subsequent outcomes, including death. Hospitalization for HF also adversely affects quality of life (QoL) and, in addition, because these events are frequently recurrent, HF hospitalization places a huge economic burden on health-care systems. This problem is a growing one in patients with HFpEF, as HF hospitalization is becoming relatively more common in patients with HFpEF compared to those with HFrEF (Lewis et al 2007, Hoekstra et al 2011). Recurrent HF hospitalizations are frequent in HFpEF with rates similar to HFrEF (Lenzen et al 2004, Fonarow et al 2007, Ahmed et al 2008, Solomon et al 2007, Steinberg et al 2012).

Unlike HFrEF, no pharmacologic therapies have shown benefit in HFpEF. Current guidelines focus on treating co-morbid conditions, such as diabetes mellitus (DM), HTN, renal insufficiency, AF and coronary artery disease, which are common in HFpEF patients (Hunt et al 2005, McMurray et al 2012). Thus, there is no evidence-based therapy specific for HFpEF and a substantial need exists for clinical trials investigating therapeutic options for patients

with HFpEF. Three recent outcomes trials (PEP-CHF, perindopril; CHARM-Preserved, candesartan; I-PRESERVE, irbesartan) have failed to show a clinical benefit in HFpEF (Cleland et al 2006, Yusuf et al 2003, Massie et al 2008, Pitt et al 2014). In TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist), a recent outcomes study in HFpEF, spironolactone did not significantly reduce the incidence of the primary composite outcome of death from CV causes, aborted cardiac arrest, or hospitalization for the management of HF (Pitt et al 2014).

LCZ696 Clinical Profile and Development in HFpEF

Natriuretic peptides (NPs), acting through the second messenger cyclic guanosine monophosphate (cGMP), have potent natriuretic and vasodilator properties, inhibit the activity of the renin angiotensin system (RAS), lower sympathetic drive and have antifibrotic and antihypertrophic effects (Levin et al 1998, Gardner et al 2007, Pandey 2008). Neprilysin degrades biologically active NPs, including atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) but not the biologically inert N-terminal pro-brain natriuretic peptide (NT-proBNP) which is not a substrate for this enzyme (Martinez-Rumayor et al 2008).

LCZ696 is a first-in-class, angiotensin receptor neprilysin inhibitor (ARNI). Following ingestion, LCZ696 provides systemic exposure to AHU377, a neprilysin (neutral endopeptidase 24.11, NEP) inhibitor (NEPi) and valsartan, an angiotensin receptor blocker (ARB). AHU377 is further metabolized via esterases to the active NEPi, LBQ657. Exposures to AHU377, LBQ657, and valsartan increased dose linearly in the 80-600 mg dose range. With a 2-fold increase in LCZ696 dose, the exposure of AHU377 and LBQ657 increases by 1.8- and 1.9-fold, and valsartan exposure increases by 1.46-fold. Minimal accumulation of the analytes occurs after multiple dosing. The mean elimination half-life (T1/2) is approximately 1, 12 and 14 hours for AHU377, LBQ657 and valsartan, respectively. Following multiple dose administration of LCZ696, steady-state is achieved within 3-4 days. In patients with HFrEF, administration of LCZ696 100 mg and 200 mg doses (CLCZ696A2117) resulted in half-life estimates for LBQ657 (active NEPi) and valsartan that were comparable to those in healthy subjects. At corresponding doses (LCZ696 100, 200 and 400 mg vs. Diovan® 80, 160 and 320 mg, respectively), LCZ696 or Diovan® administration results in comparable valsartan exposure (AUC) in healthy volunteers and in patients with HFrEF.

LCZ696, through its dual mode of action, potentiates NPs via NEP inhibition while inhibiting the RAS via angiotensin type 1 (AT_1) receptor blockade; mechanisms which are considered to act in a complementary and at least additive manner. Prior research had suggested that the potential clinical benefits from NEP inhibition can only be leveraged if the RAS system is inhibited concomitantly (Campbell 2003, Mangiafico et al 2012). Enhancement of the NP system through NEP inhibition alone has not been successful in trials, likely due to its effects of increasing angiotensin II levels, which, would be expected to counteract the beneficial vasodilatory, antifibrotic, and antihypertrophic effects of NPs. By contrast, when the RAS system is inhibited concurrently, there is a potential synergy of enhanced beneficial and inhibited negative effects.

Previous attempts to simultaneously augment the NP system while blocking the RAS, using ACE-NEP (“vasopeptidase”) inhibitors, were complicated by safety issues. Omapatrilat,

which was the most extensively evaluated vasopeptidase inhibitor, simultaneously inhibited NEP and angiotensin converting enzyme (ACE) but was associated with an increased incidence of angioedema. (Kostis et al 2004). It was hypothesized that omapatrilat's concomitant inhibition of three pathways (ACE, aminopeptidase P [APP], and NEP) involved in bradykinin breakdown (the putative mediator of ACE inhibitor [ACEI]-induced angioedema) was the most likely explanation for this finding (Fryer et al 2008). Different from omapatrilat, the risk of angioedema associated with LCZ696 is considered low, as LCZ696 inhibits NEP and is a poor inhibitor of ACE and APP, the two major enzymes responsible for bradykinin breakdown. To date, the angioedema rate with LCZ696 has been low and similar to comparator agents.

It is anticipated that LCZ696, an inhibitor of NEP and a blocker of the AT_1 receptor, may deliver clinical benefits to patients with CV disease, including HF and HTN, in which vasoconstriction, volume expansion, and target organ damage (i.e., fibrosis, hypertrophy, myocardial/vascular stiffness) play a key role in pathophysiology.

In a dose-ranging study (n=1328), a total of 497 hypertensive patients received LCZ696 (100 mg, 200 mg and 400 mg). This study showed that LCZ696 (400 mg/d and 200 mg/d) lowered blood pressure (BP) to a greater extent than corresponding doses of valsartan 320 mg/d and 160 mg/d. Discontinuation rate due to adverse events (AEs) was similar to placebo. No dose related trends were observed for any specific AEs. The most frequent AE was headache, which was more frequent in the placebo group compared to any other group.

There is an ongoing Phase III outcomes study (PARADIGM-HF, CLCZ696B2314, n=8442) in patients with HFrEF comparing LCZ696 and enalapril for the reduction of CV death and HF hospitalization. Patient enrollment has completed. The study design incorporates a single-blind, treatment run-in epoch aimed to ensure as large a proportion as possible of patients remain on high dose study drug during the long term follow up. On 28 March 2014, the Data Monitoring Committee (DMC) unanimously recommended stopping of the PARADIGM-HF study ahead of schedule because patients treated with LCZ696 were less likely than those treated with enalapril to die from CV causes or be admitted to the hospital with worsening HF (McMurray et al 2014).

The mechanisms of action of LCZ696 suggests that it may impact the suspected pathophysiology of HFpEF, in which it is believed that excessive fibrosis and myocyte hypertrophy lead to abnormal left ventricular relaxation filling, impaired diastolic distensibility and/or increased vascular stiffness, with consequent elevated cardiac filling pressures (Krum and Abraham 2009). Of interest, it was recently reported that patients with HFpEF have lower levels of myocardial cGMP concentration (and lower protein kinase G activity) compared with patients with HFrEF or patients with aortic stenosis (van Heerebeek et al 2012). Enhancing NP action therefore seems a reasonable potential therapeutic option. By augmenting the active NPs, NEP inhibition increases the generation of cGMP, thereby, potentially, enhancing myocardial relaxation and reducing hypertrophy. Natriuretic peptides also stimulate natriuresis, and vasodilation, and may have additional antifibrotic and antisympathetic effects (Potter et al 2006, Gardner et al 2007).

PARAMOUNT (CLCZ696B2214) was a recently completed, Phase II proof of concept (therapeutic validation) trial in HFpEF comparing LCZ696 with valsartan. It consisted, of a

12 week core study period and a 24 week extension period (Solomon et al 2012). The study met its primary endpoint, demonstrating a 23% greater reduction in NT-proBNP (p=0.005) at 12 weeks for LCZ696 compared with valsartan. At 36 weeks, NT-proBNP remained reduced from baseline in the LCZ696 group, but the treatment difference was not statistically significant (p=0.20). At 36 weeks, however, there were greater reductions in all echocardiographic measures of left atrial size (left atrial volume, p = 0.003; left atrial dimension, p = 0.03), along with improvements in New York Heart Association (NYHA) classification (p=0.05), in the LCZ696 group compared with the valsartan group. No differences were observed for quality of life measures. LCZ696 was well tolerated. Three deaths were reported, one occurring in the LCZ696 arm and two occurring in the valsartan arm. None were suspected to be related to study drug by the investigator. Serious adverse events (SAEs) were reported by 22 (14.8%) and 30 (19.7%) patients in the LCZ696 and valsartan groups, respectively. While hyperkalemia >5.5 mmol was more frequent in the LCZ696 group than in the valsartan group (16.2% vs. 11.2%, p=0.21), hyperkalemia >6.0 mmol was reported in 5 vs. 6 patients in the two groups, respectively.

NT-proBNP is a marker of left ventricular wall stress. Elevated NP levels are associated with adverse outcomes and reductions in NT-proBNP levels have been associated with better outcomes in patients with HF (Masson et al 2008, Komajda et al 2011). An enlarged left atrium is a characteristic finding in HFpEF and is reflective of sustained elevations in left ventricular filling pressures; reductions in left atrial size have also been associated with better in CV outcomes (Brenyo et al 2011, Gerdts et al 2007, Meris et al 2009).

While the positive results in PARAMOUNT were based on a biomarker (NT-proBNP) and surrogate endpoints (left atrial size) these data provide strong support for a Phase III outcomes trial in HFpEF patients.

Please refer to the LCZ696 Investigator Brochure (IB) for further details on the clinical profile of LCZ696.

1.2 Purpose

The purpose of this study is to evaluate the effect of LCZ696 compared to valsartan in the reduction of CV death and rate of HF hospitalizations in patients with HFpEF. This study will serve as a registration trial for LCZ696 as a treatment for patients with HFpEF.

2 Study objectives

2.1 Primary objective

The primary objective of this study is to compare LCZ696 to valsartan in reducing the rate of the composite endpoint of CV death and total (first and recurrent) HF hospitalizations, in HF patients (NYHA Class II-IV) with preserved EF (LVEF ≥45%).

2.2 Secondary objectives

- To compare LCZ696 to valsartan on changes in the clinical summary score for HF symptoms and physical limitations, as assessed by the Kansas City Cardiomyopathy Questionnaire [KCCQ]) at 8 months.

- To compare LCZ696 to valsartan in improving NYHA functional classification at 8 months.
- To compare LCZ696 to valsartan in delaying the time to first occurrence of a composite renal endpoint, defined as:
  1. renal death, **or**
  2. reaching end stage renal disease (ESRD), **or**
  3. ≥ 50% decline in estimated glomerular filtration rate (eGFR) relative to baseline
- To compare LCZ696 to valsartan in delaying the time to all-cause mortality.

2.3 Exploratory objectives

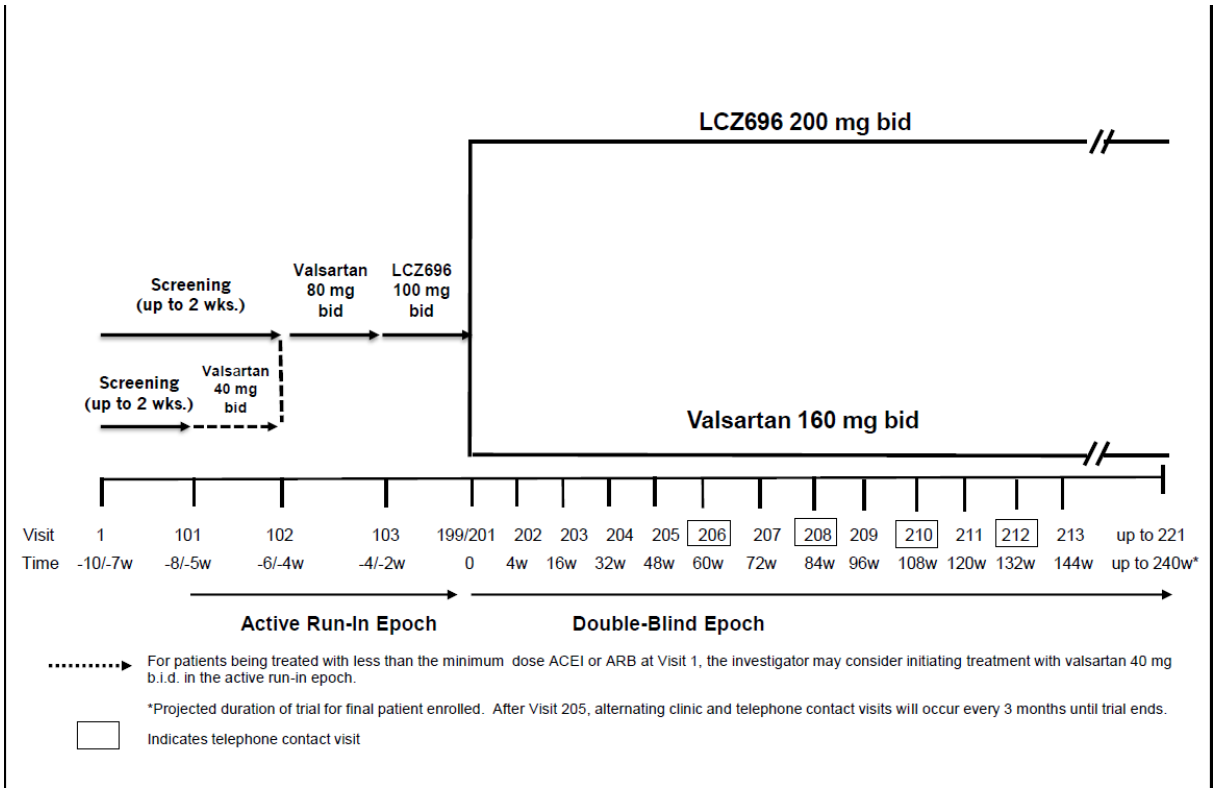
- To compare LCZ696 to valsartan in reducing the rate of the composite endpoint of CV death, total HF hospitalizations, total non-fatal strokes, and total non-fatal myocardial infarctions (MIs). Total is defined as the first and all recurrent events.
- To compare LCZ696 to valsartan on changes in clinical composite assessment (assessed by NYHA, global patient assessment, and major adverse clinical events as defined by CV death and hospitalization for HF) at 8 months.
- To compare LCZ696 to valsartan on patient global assessment at 8 months.
- To compare LCZ696 to valsartan in reducing the rate of the composite endpoint of CV death, total non-fatal HF hospitalizations, total non-fatal strokes, and total non-fatal myocardial infarctions (MIs). Total is defined as the first and all recurrent events.
- To compare LCZ696 to valsartan in delaying the time to new onset AF (NOAF).
- To compare LCZ696 to valsartan on changes in the health related quality of life (assessed by overall summary score, clinical summary score and individual scores of the sub-domains from the KCCQ [relative to treatment run-in epoch baseline scores and relative to randomized treatment epoch baseline scores] and total score of the EQ-5D for health status).
- To compare LCZ696 to valsartan in reducing CV deaths and total worsening HF events. A subject will be defined as having a CV death or worsening HF event when the subject has:
  1. CV death **or**
  2. a hospitalization for HF **or**
  3. received intravenous (IV) decongestive therapy (IV diuretics, IV neseritide or other natriuretic peptide, IV inotropes, and IV nitroglycerin [NTG]), and does not result in formal inpatient hospital admission, regardless of the setting (i.e. in an emergency room (ER) setting, in the physician's office, an outpatient treatment facility, etc.).
- To compare LCZ696 to valsartan on hospitalizations (all cause and cause specific).
- To compare LCZ696 to valsartan on the number of days alive and out of hospital at 12 months.
- To compare LCZ696 to valsartan in slowing the rate of decline in eGFR.
- To compare LCZ696 to valsartan on delaying time to new onset diabetes mellitus (NODM).

- To compare LCZ696 to valsartan on reducing healthcare resource utilization, e.g., number of days/stays in intensive care unit (ICU), number of re-hospitalizations, and number of ER visits for HF.
- To compare LCZ696 to valsartan on 30 day HF hospital readmissions and readmission rate after a prior HF hospitalization.
- To compare LCZ696 to valsartan on the time between HF hospital readmissions.
- To compare LCZ696 to valsartan on the profile of pre-specified biomarkers (e.g., cardiac, vascular, renal, collagen, metabolism, inflammatory, and/or other relevant biomarkers) from baseline to predefined time points in a subset of patients.
- To characterize LCZ696 and valsartan pharmacokinetics (PK) at steady-state using population modeling and/or non-compartmental based methods in a subset of patients.
- To compare LCZ696 to valsartan on the primary composite and secondary endpoints, and key exploratory endpoints in ACEI-intolerant patients.
- To compare LCZ696 to valsartan in evaluating the changes in cognitive function (assessed by the Mini-Mental State Examination [MMSE]) at 2 years.

3 Investigational plan

3.1 Study design

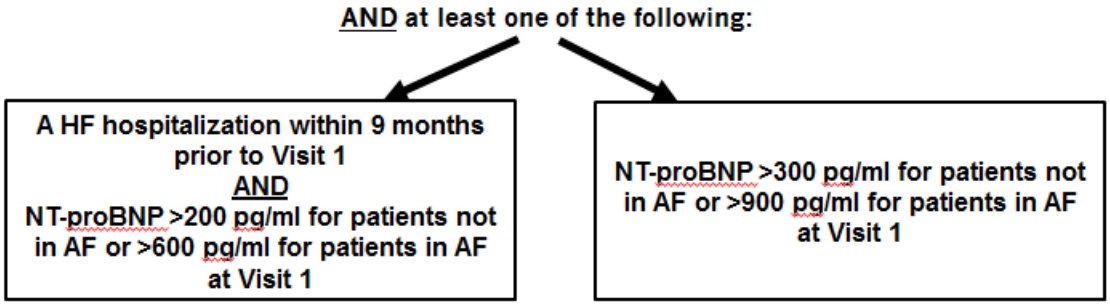
Figure 3-1 Study design



This study is a multi-center, randomized, double-blind, parallel group, active comparator, morbidity and mortality trial designed to evaluate the efficacy and safety of LCZ696 compared to valsartan in HF patients (NYHA class II-IV) with preserved EF (Figure 3-1). The study population will consist of patients ≥ 50 years of age with a LVEF ≥45% and evidence of structural heart disease (left atrial enlargement [LAE] or left ventricular hypertrophy [LVH]) within 6 months prior to enrollment, current symptomatic HF (NYHA class II-IV) and symptoms of HF requiring treatment with diuretic therapy for at least 30 days prior to Visit 1. In addition, patients will have at least one of the following: (1) a hospitalization for HF within 9 months prior to enrollment and NT-proBNP >200 pg/ml for patients not in AF or >600 pg/ml for patients in AF at Visit 1, **OR** (2) NT-proBNP >300 pg/ml for patients not in AF or >900 pg/ml for patients in AF at Visit 1 (Figure 3-2).

Figure 3-2 Abbreviated inclusion criteria

1. **≥50 years of age and LVEF ≥45%**
2. **Symptom(s) of HF requiring treatment with diuretic(s) for at least 30 prior to Visit 1**
3. **Current symptomatic HF (NYHA class II-IV)**
4. **Structural heart disease (LAE or LVH)**



LVEF = left ventricular ejection fraction; HF = heart failure; NYHA = New York Heart Association; LAE = left atrial enlargement; LVH = left ventricular hypertrophy; AF = atrial fibrillation/flutter

Complete inclusion criteria, including diagnostic criteria, are available in Section 4.1.

Patients with documented AF on the Visit 1 ECG will be limited to approximately 33% of the overall study population.

Patients should be on an optimal medical regimen of diuretics and background medications to effectively treat co-morbidities such as HTN, DM, AF and coronary artery disease. Investigators should make every effort to control a patient's BP in accordance with local treatment guidelines and investigator judgment (see Section 5.5.7)

Screening epoch

A screening period, or epoch, of approximately 2 weeks will be used to determine if patients qualify to enter the treatment run-in epoch. Qualifying echocardiogram (echo) measurements will be based on locally obtained echoes performed within 6 months of Visit 1. If a qualifying echo within 6 months of Visit 1 is not available, the patient must enter the study based on a qualifying echo performed during the screening epoch before any treatment run-in study drug is dispensed to the patient. No imaging method other than echocardiography will be accepted for inclusion into the study.

Screening NT-proBNP, potassium, eGFR, and liver function tests will be assessed by sending blood samples to the central lab. Since it may take up to 72 hours to obtain the results of the clinical laboratory assessments to evaluate the patient's eligibility for the study, it is recommended that at Visit 1 the site schedule the patient's next visit approximately one week after Visit 1.

A patient who enters screening but is determined not to be eligible to enter the treatment run-in epoch will be considered a screen failure. The investigator may consider re-screening the patient at a later time if he/she believes that the patient's condition has changed and they may potentially be eligible. A patient may be re-screened up to two times. A minimum of 2 weeks must elapse between re-screenings.

Treatment run-in epoch

The screening epoch will be followed by a single-blind, treatment run-in epoch, or period, ranging from 3 to 8 weeks (Figure 3-3). The concomitant use of open label ACEI, ARB or renin inhibitor in addition to study drug during the treatment run-in epoch is strictly prohibited. Patients will enter the treatment run-in period based on their use of RAS blockade medications at the time of enrollment (Figure 3-3 and Table 3-1).

Figure 3-3 Treatment run-in epoch overview

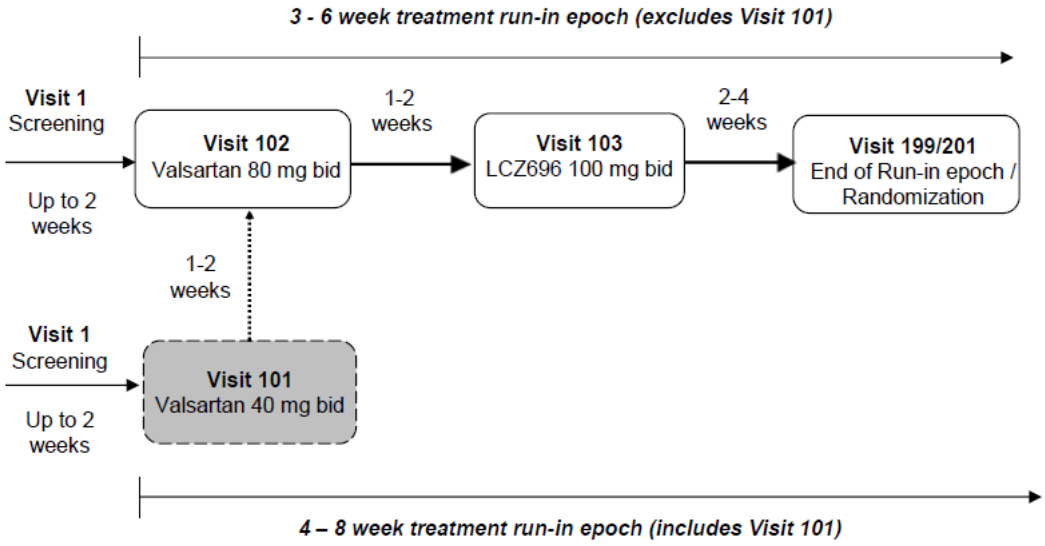


Table 3-1 Minimum pre-study total daily doses of commonly used ACEIs and ARBs allowing patients to begin the treatment run-in epoch at Visit 102

ACEI	Dose	ARB	Dose
Benazepril	20 mg	Azilsartan	40 mg
Captopril	100 mg	Candesartan	16 mg
Cilazapril	2.5 mg	Eprosartan	400 mg

ACEI	Dose	ARB	Dose
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		

Patients should enter the treatment run-in epoch at Visit 101 if they have been on an ACEI or ARB medication at doses considered to be less than the total daily dose defined in Table 3-1. Study drug should not be dispensed unless the patient meets all inclusion criteria and none of the exclusion criteria at Visit 1. These patients will begin treatment with valsartan 40 mg b.i.d. for 1 to 2 weeks. At Visit 102, patients can be up-titrated to valsartan 80 mg b.i.d. for 1 to 2 weeks. Patients who meet the safety monitoring criteria (Table 3-2) at Visit 103 will be switched to treatment with LCZ696 100 mg b.i.d. for 2 to 4 weeks.

Patients should enter the treatment run-in epoch at Visit 102 if they have been on an ACEI or ARB medication at doses considered to be at least the total daily dose (Table 3-1). At the investigator's discretion, these patients can also enter the treatment run-in epoch at Visit 101. Study drug should not be dispensed unless the patient meets all inclusion criteria and none of the exclusion criteria at Visit 1. These patients will begin treatment with valsartan 80 mg b.i.d. for 1 to 2 weeks. Patients who meet the safety monitoring criteria (Table 3-2) at Visit 103 can begin treatment with LCZ696 100 mg b.i.d. for 2-4 weeks.

To assess the patient's eligibility to continue in the study, either local or central laboratory should be used for the assessment of potassium and eGFR at Visits 103 and 199 (end of treatment run-in visit). If central laboratory is used, since it may take up to 72 hours to obtain the results, it is recommended that the site take this into consideration when scheduling subsequent study visits, while keeping the patient on the study medication. If a local laboratory is selected, the same samples should also be sent to the central laboratory, while the evaluation should be solely based on the local laboratory results. Patients should NOT enter Visits 103 or 199 without evaluating the safety monitoring criteria (Table 3-2).

Down-titration or interruption of study drug is not allowed during the treatment run-in period. Patients who are not able to tolerate study drug at the doses prescribed during the treatment run-in epoch will be discontinued.

Investigators may consider adjusting (dose reduced or discontinued) background medications (e.g., diuretic(s), antihypertensive agents nitrates) if the study drug is not tolerated (e.g., occurrence of AEs such as hyperkalemia, hypotension, and renal dysfunction) to ensure patients meet the safety criteria in Table 3-2 during the treatment run-in epoch. Patients may be seen at any time for unscheduled visits during the treatment run-in epoch for re-evaluation of safety criteria parameters.

Patients who experience angioedema at any time during the treatment run-in epoch must be discontinued from the study.

Patients who are discontinued from the treatment run-in epoch due to intolerance to the study drug dosages during the period, angioedema or for failure to meet the specified safety criteria will be considered treatment run-in failures and are not eligible to be re-screened for study entry (Section 6.1).

Table 3-2 Safety monitoring criteria that must be met at Visit 1 (screening), Visit 103 and Visit 199/201

Parameter	Visit 1 (screening)	Visits 103 (treatment run-in) and Visit 199/201 (end of treatment run-in/randomization)
Potassium level	K ≤5.2 mmol/L (mEq/L)	K ≤5.4 mmol/L (mEq/L)
Kidney function	eGFR ≥30 mL/min/1.73m^2	eGFR ≥25 mL/min/1.73m^2
		eGFR reduction <35% compared to Visit 1
Blood pressure	SBP ≥110 mmHg	No symptomatic hypotension as determined by the investigator and SBP ≥100 mmHg.
AEs or conditions	No conditions that preclude continuation according to the investigator's judgment	No postural symptoms or any AEs that preclude continuation according to the investigator's judgment

At the end of the treatment run-in epoch (Visit 199/201), patients who meet the safety criteria (Table 3-2) and tolerate LCZ696 100 mg b.i.d. for at least 2 weeks are eligible for randomization at Visit 201. For these patients, Visit 199 and 201 should be combined into one clinic visit (Visit 199/201), and occur on the same day. Patients should be instructed not to take their morning (AM) dose of treatment run-in study drug on the day they start randomized study drug.

Randomized treatment epoch

At randomization (Visit 199/201), eligible patients will be randomized to 1 of 2 treatment arms, LCZ696 200 mg b.i.d. or valsartan 160 mg b.i.d (Table 3-3).

Every attempt should be made to maintain patients on the target study drug dose (dose level 3) (Table 3-3) throughout the trial. If the patient does not tolerate the target study drug dose level the investigator should consider if appropriate, adjusting background medications to rectify the situation before considering to down-titrate to the next lower study drug dose level (see Section 5.5).

Table 3-3 Study drug dose levels during randomized treatment epoch

Dose level	LCZ696 Treatment Arm	Valsartan Treatment Arm
3	200 mg b.i.d.	160 mg b.i.d.
2	100 mg b.i.d.	80 mg b.i.d.
1	50 mg b.i.d.	40 mg b.i.d.

At each dose level the patient will also take matching placebo for the other treatment arm study drug.

Study drug dose level adjustments should be based on overall safety and tolerability with special focus on a) hyperkalemia, b) symptomatic hypotension, and c) clinically significant decrease in eGFR/increase in serum creatinine. Treatment guidelines for hyperkalemia, management of BP, and renal dysfunction are provided in Appendix 3, Appendix 4, and Appendix 5, respectively.

The trial will be event driven with a target total of 1847 primary endpoint events to be accrued. It is anticipated that the total trial duration will be approximately 4.75 years, with a projected recruitment period of 2.75 years, followed by approximately 2 years of follow-up after the last patient is enrolled.

3.2 Rationale of study design

3.2.1 Target study population and rationale

The study population will consist of patients ≥50 years of age with a LVEF ≥45% and evidence of structural heart disease (LAE or LVH), current symptoms of HF (NYHA class II-IV) and prior symptoms of HF requiring treatment with diuretic therapy. In addition, patients will have at least one of the following: (1) a hospitalization for HF within 9 months prior to enrollment and NT-proBNP >200 pg/ml for patients without AF or >600 pg/ml for patients with AF on Visit 1 ECG; **OR**, (2) NT-proBNP >300 pg/ml for patients not in AF or >900 pg/ml for patients in AF on Visit 1 ECG. These criteria should identify the target HFpEF population at risk for major CV events.

Structural heart disease (LAE and LVH) is a key diagnostic criterion for HFpEF in the most recent guidelines (McMurray et al 2012). Left atrial (LA) size (an integrative measure of left ventricular diastolic pressure) is independently associated with an increased risk of morbidity and mortality (Zile et al 2011). Including either LAE or LVH will help ensure a diagnosis of HFpEF. The EF lower boundary at 45% was selected to include a wide spectrum of patients for whom no proven therapy is currently available. Prior HF hospitalization and elevated NT-proBNP were the strongest independent predictors of mortality and subsequent HF hospitalization in the I-PRESERVE study (Solomon et al 2007, Komajada et al, 2011). Patients with baseline AF are required to have higher NT-proBNP levels, as AF is strongly associated with higher levels of NT-proBNP (McKelvie et al 2010). The number of AF patients will be limited to approximately one third in the current study (based on the Visit 1 ECG) so that the proportion of patients with AF in the study will be representative of the HFpEF population (Massie et al 2008, Steinberg et al 2012, West et al 2011).

3.2.2 Rationale for primary endpoint

The primary endpoint is the composite of CV death and total HF hospitalizations. There is general agreement that the major goal of treating HFpEF is to reduce the major fatal and non-fatal consequences of this illness; CV death and hospitalization for worsening HF. Hospitalization for worsening HF is the single most common cause of hospitalization in these patients. It is an important clinically relevant problem for HF patients and represents a key component of the patient's clinical course. Importantly, HF hospitalization reflects progression of the HF syndrome and portends high subsequent risk, both of readmission and death (Ahmed et al 2008, Solomon et al 2007).

Traditionally, outcomes studies have assessed composite endpoints using a time-to-first-event-analysis. Limitations of this approach have been increasingly recognized (Cohn et al 2009, Neaton et al 2005, Pocock et al 2012). Time-to-first event only focuses on the first occurring event and does not consider subsequent events, leading to a substantial loss of information. This is particularly relevant to HFpEF, which is characterized by a high frequency of recurrent HF hospitalizations. A review of recent HF studies found that approximately 40% of all CV deaths and HF hospitalizations are "ignored" in a time-to-first event analysis (Anker and McMurray 2012). A total events approach as applied to a progressive disorder such as HF has the benefit of more accurately capturing the patient's clinical course and better reflects the true burden of the illness on the patient and the healthcare system. This understanding of HF and its treatment has led to the choice of a disease-specific composite outcome of CV death and total HF hospitalization as the primary endpoint in this study.

3.2.3 Rationale for secondary endpoints

There are four secondary endpoints: (1) KCCQ clinical summary score, (2) change in NYHA functional classification, (3) the time to first occurrence of a composite renal endpoint, defined as renal death, reaching ESRD, or ≥ 50% decline in eGFR relative to baseline (whichever occurs first), and (4) all-cause mortality. These endpoints are clinically relevant and particularly appropriate as secondary endpoints in this population.

The KCCQ is a validated instrument for assessing quality of life and health status on HF patients. The clinical summary score, which is derived from the physical limitations and HF symptoms domains of the KCCQ is a valid measure for assessing the patient's health aspects that may be influenced by CV medications. Given the symptomatic burden of HF and its associated physical limitations, this endpoint is of particular relevance to patients and is an important goal of HF treatment. The KCCQ clinical summary score has been used frequently as an endpoint in other trials, and is appropriate for use in the current trial.

NYHA classification is an accepted measure of functional status and will provide important information on disease progression. NYHA classification will be analyzed at month 8 to minimize the number of missing data points.

The composite renal endpoint of renal death, reaching ESRD, or ≥ 50% decline in eGFR relative to baseline is frequently used in clinical trial of medications that may influence renal function, such as the medications used in the current trial. This endpoint is of significance because renal dysfunction is common in HF patients, is associated with poorer clinical outcomes, and complicates clinical management. Also, outcome modifying agents, such as ACEIs and ARBs, are often sub-optimally prescribed due to concerns of further worsening renal dysfunction. Thus, prevention of renal dysfunction is of considerable clinical importance and deserves further investigation in the HFpEF population.

All-cause mortality is a standard endpoint that is routinely assessed in morbidity and mortality trials, such as the current one.

3.2.4 Rationale for treatment run-in epoch

The single-blind treatment run-in epoch most closely mimics clinical practice (where patients are only continued on treatments if they are tolerated). The goal of the single-blind treatment run-in epoch is to (1) optimize safety in an older vulnerable population (exclude patients developing renal dysfunction, hypotension and hyperkalemia), (2) maximize adherence, both to the treatment and the protocol, and consequently, (3) minimize the loss to follow-up. As a result, the trial should provide the most robust test of its hypothesis.

The current abbreviated treatment run-in design will assess the safety and tolerability of patients to drug dose level 2. Drug dose level 3 is not included in the run-in design, because (a) BP effect is largely attained by LCZ696 100 mg b.i.d. with small incremental BP effect at 200 mg b.i.d., and (b) the great majority of patients who tolerated LCZ696 100 mg b.i.d. were able to tolerate 200 mg b.i.d. in the run-in period of the PARADIGM-HF trial.

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

An LCZ696 dose of 200 mg twice daily was chosen as the target dose because it delivers similar valsartan exposure (assessed by AUC) as Diovan® (valsartan) 160 mg twice daily, which is the evidence based dose of valsartan and the one thought to be equivalent to the dose of ACE inhibitors. Biomarker analysis and modeling indicate that this dose of LCZ696 delivers approximately 90% of its maximal NEP inhibition. Twice daily dosing schedule is considered necessary for sustained NEP inhibition over a 24-hour period and it is anticipated to reduce the incidence of hypotension in HF patients, particularly in elderly patients.

3.4 Rationale for choice of comparator

The active comparator valsartan (a RAS blocker) is not being used to treat HFpEF, as no therapy to date has convincingly been shown to reduce morbidity and mortality (Cleland et al 2006, Yusuf et al 2003, Massie et al 2008). Valsartan is being given to treat the comorbidities that are prevalent in HFpEF, such as HTN, DM, and coronary artery disease where there is an indication for RAS blocking therapy (McMurray et al 2012). For the same reason, background ACEIs or ARBs were permitted in other outcomes studies in HFpEF for treating co-morbidities, including the most recently completed TOPCAT study where a RAS blocker was used in 85% of patients at baseline (Desai et al 2011).

Valsartan was chosen as the RAS blocker comparator because it is a commonly prescribed ARB, and the target dose of LCZ696 delivers systemic exposure similar to the target dose of valsartan. Furthermore, a placebo comparator is not considered appropriate in this long term trial, as the comorbidities commonly present in HFpEF patients require RAS inhibition (i.e., ACEI or ARB). RAS inhibition should not be used concomitantly with LCZ696 due to the potential increased risk of angioedema (ACEI), and because LCZ696 already provides AT1 blockade (ARB).

3.5 Purpose and timing of interim analyses

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 events adjudicated (i.e. approximately a total of 1231 events of either HF hospitalizations or CV deaths).

3.6 Risks and benefits

Patients will be instructed not to take any RAS blockade medications (ACEI or ARB) on the day they start treatment run-in study drug to avoid excess RAS blockade. The risk of discontinuation of concomitant ACEIs or ARBs will be minimal as it will be reflective of the typical dosing schedule of most ACEIs and ARBs. All patients will be allowed to continue receiving the rest of their background CV medications. The risk to patients in this trial will be minimized by compliance with the eligibility criteria and close clinical monitoring. 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 and for 7 days off study medication. If there is any question that the patient will not reliably comply, they should not be entered in the study. All patients in this study will be ≥50 years of age and therefore the risk of pregnancy during the trial is minimal.

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 50 years or older with current symptomatic HF (NYHA class II-IV) and symptoms of HF requiring treatment with diuretic therapy for HF for at least 30 days prior to Visit 1, an LVEF ≥45% and documented structural heart disease. It is aimed to randomize approximately 4,600 patients in approximately 800 centers worldwide. With an expected screening and run-in failure rate of approximately 50%, it is estimated that approximately 9,200 patients will have to be screened.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. ≥ 50 years of age, male or female.
3. LVEF ≥45% by echo during the screening epoch, or within 6 months prior to Visit 1 (any local LVEF measurement made using echo only).
4. Symptom(s) of HF requiring treatment with diuretic(s) for at least 30 days prior to Visit 1.
5. Current symptom(s) of HF (NYHA class II-IV) at Visit 1.
6. Structural heart disease evidenced by at least one of the following echo findings (any local measurement made during the screening epoch or within the 6 months prior to Visit 1):

a. left atrial (LA) enlargement defined by at least one of the following: LA width (diameter) ≥3.8 cm **or** LA length ≥5.0 cm **or** LA area ≥20 cm^2 or LA volume ≥55 mL **or** LA volume index ≥29 mL/m^2
b. left ventricular hypertrophy (LVH) defined by septal thickness or posterior wall thickness ≥1.1 cm

7. Patients with at least one of the following:
   a. a HF hospitalization (defined as HF as the major reason for hospitalization) within 9 months prior to Visit 1 **and** NT-proBNP >200 pg/ml for patients not in AF or >600 pg/ml for patients in AF on Visit 1 ECG, **OR**
   b. NT-proBNP >300 pg/ml for patients not in AF or >900 pg/ml for patients in AF on the Visit 1 ECG.

4.2 Exclusion criteria

Patients fulfilling **any** of the following criteria during the screening period, unless otherwise specified, 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. Any prior echocardiographic measurement of LVEF <40 %.
2. Acute coronary syndrome (including MI), cardiac surgery, other major CV surgery, or urgent percutaneous coronary intervention (PCI) within the 3 months prior to Visit 1 **or** an elective PCI within 30 days prior to Visit 1.
3. Any clinical event within the 6 months prior to Visit 1 that could have reduced the LVEF (e.g., MI, coronary artery bypass graft [CABG]), unless an echo measurement was performed after the event confirming the LVEF to be ≥45%.
4. Current acute decompensated HF requiring augmented therapy with diuretics, vasodilators and/or inotropic drugs.
5. Patients who require treatment with 2 or more of the following: an ACEI, an ARB or a renin inhibitor.
6. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
7. Patients with a known history of angioedema.
8. Probable alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms (i.e., dyspnea, fatigue) such as significant pulmonary disease (including primary pulmonary HTN), anemia or obesity. Specifically, patients with the following are excluded:
   a. severe pulmonary disease including chronic obstructive pulmonary disease (COPD) (i.e., requiring home oxygen, chronic nebulizer therapy, chronic oral steroid therapy or hospitalized for pulmonary decompensation within 12 months) or
   b. hemoglobin (Hgb) <10 g/dl, **or**
   c. body mass index (BMI) >40 kg/m^2
9. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer.
10. Patients with any of the following:

a. systolic blood pressure (SBP) ≥180 mmHg at Visit 1, **or**
b. SBP >150 mmHg and < 180 mmHg at Visit 1 unless the patient is receiving 3 or more antihypertensive drugs. Antihypertensive drugs include, but are not limited to, a thiazide or other diuretic, mineralocorticoid (MRA), ACEI, ARB, beta blocker and calcium channel blocker (CCB), **or**
c. SBP <110 mmHg at Visit 1, **or**
d. SBP <100 mmHg or symptomatic hypotension as determined by the investigator at Visit 103 or Visit 199/201

11. Patients with history of any dilated cardiomyopathy, including peripartum cardiomyopathy, chemotherapy induced cardiomyopathy, or viral myocarditis.
12. Evidence of right sided HF in the absence of left-sided structural heart disease.
13. Known pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy.
14. Clinically significant congenital heart disease that could be the cause of the patient's symptoms and signs of HF.
15. Presence of hemodynamically significant valvular heart disease in the opinion of the investigator.
16. Stroke, transient ischemic attack, carotid surgery or carotid angioplasty within the 3 months prior to Visit 1.
17. Coronary or carotid artery disease or valvular heart disease likely to require surgical or percutaneous intervention during the trial.
18. Life-threatening or uncontrolled dysrhythmia, including symptomatic or sustained ventricular tachycardia and atrial fibrillation or flutter with a resting ventricular rate >110 beats per minute (bpm).
19. Patients with a cardiac resynchronization therapy (CRT) device.
20. Patients with prior major organ transplant or intent to transplant (i.e. on transplant list).
21. Any surgical or medical condition, which in the opinion of the investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study.
22. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs, including but not limited to any of the following:
    - any history of pancreatic injury, pancreatitis or evidence of impaired pancreatic function/injury within the last 5 years
23. Evidence of hepatic disease as determined by any one of the following: SGOT (AST) or SGPT (ALT) values exceeding 3x the upper limit of normal (ULN), bilirubin >1.5 mg/dl at Visit 1.
24. Patients with one of the following:
    a. eGFR <30 mL/min/1.73m^2 as calculated by the Modification in Diet in Renal Disease (MDRD) formula at Visit 1, **or**
    b. eGFR <25 mL/min/1.73m^2 at Visit 103 or Visit 199/201, **or**
    c. eGFR reduction >35% (compared to Visit 1) at Visit 103 or Visit 199/201

25. Presence of known functionally significant bilateral renal artery stenosis
26. Patients with either of the following:
    a. serum potassium >5.2 mmol/L (mEq/L) at Visit 1
    b. serum potassium >5.4 mmol/L (mEq/L) at Visit 103 or Visit 199/201
27. History or presence of any other disease with a life expectancy of <3 years
28. History of non-compliance to medical regimens and patients who are considered potentially unreliable
29. History or evidence of drug or alcohol abuse within the last 12 months
30. Persons directly involved in the execution of this protocol
31. History of malignancy of any organ system (other than localized basal or squamous cell carcinoma of the skin or localized prostate cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
32. 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.
33. 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 and for 7 days off study drug. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. 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 subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Combination of any two of the following (a+b or a+c, or b+c), according to country approvals and availability:
        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 Protocol requested treatment

5.1.1 Investigational treatment

The sponsor will provide the following study drugs:

Treatment run-in period

All eligible patients will enter a treatment run-in epoch where they will receive valsartan followed by LCZ696.

The following study drugs will be provided:

- Valsartan 40 mg and 80 mg
- Placebo to match valsartan 80 mg
- LCZ696 100 mg
- Placebo to match LCZ696 50 mg and 100 mg tablets

The use of an ACEI, ARB or renin inhibitor in addition to study drug during the treatment run-in epoch is strictly prohibited.

Randomized treatment period

All eligible patients will be randomized to either LCZ696 200 mg b.i.d. (dose level 3) or valsartan 160 mg b.i.d. (dose level 3). In addition, patients will continue to take optimal background therapy to treat co-morbid conditions, as considered appropriate by the investigator and in accordance with standard therapy guidelines, with the exception of an ACEI or ARB as this will be replaced by study drug. The use of an open label ACEI 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
- Placebo to match LCZ696 50 mg, 100 mg, and 200 mg tablets
- Valsartan 40 mg, 80 mg and 160 mg tablets
- Placebo to match valsartan 40 mg, 80 mg, 160 mg tablets

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.

5.1.2 Additional study treatment

No additional treatment beyond investigational treatment is requested for 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 199/201.

- LCZ696 200 mg b.i.d.
- Valsartan 160 mg b.i.d.

5.3 Treatment assignment, randomization

At Visit 199/201, 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 and none of the 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 investigational treatment 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).

The randomization scheme for patients will be reviewed and approved by a member of the IIS 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. The DMC members, due to their review of pooled data from other LCZ696 studies by the program level DMC.

3. The PK analysts, randomization codes associated with patients from whom pharmacokinetics (PK) samples are taken will be disclosed to PK analysts who will keep the PK results confidential until database lock.

- 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 investigational treatment cannot be disguised due to their different forms.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.12), 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 discontinue the study treatment.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the study informed consent, the patient is assigned the next sequential number by the investigator. 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. The site should select the case report form (CRF) book with a matching Subject Number from the Electronic Data Capture (EDC) system to enter data.

If the patient fails to be treated during the treatment run-in epoch for any reason, the IRT must be notified within 2 days of when the investigator or his/her staff are informed that the patient was not treated. The reason for not being treated with treatment run-in study drug will be entered on the Screening Epoch Study Disposition CRF. Patients that take treatment run-in study drug and are not randomized are considered run-in failures. The reason for not being treated with randomized study drug will be entered on the appropriate Treatment Run-in epoch CRF.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with the investigational treatment in packaging of identical appearance.

The investigational treatment pack has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the 2 treatment arms and a dose level. Investigator staff will identify the investigational treatment 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.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

Investigational 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 investigational treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the investigational 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 investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial. Patients will be asked to return all unused investigational treatment and packaging at the end of the study or at the time of discontinuation of investigational treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational 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 other study 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 tablets (one tablet from the LCZ696/LCZ696 matching placebo pack and one tablet from the valsartan/valsartan matching placebo pack) twice a day for the duration of the study. Table 5-1 summarizes the study drug that will be taken during the run-in epoch and Table 5-2 summarizes the study drug that will be taken during the randomized treatment epoch.

Table 5-1 Study drug dispensed for the treatment run-in epoch by study visit

Study visit	Dose level	LCZ696	Valsartan
101[a]	1	50 mg matching placebo b.i.d.	40 mg b.i.d.
102	2	100 mg matching placebo b.i.d.	80 mg b.i.d.
103	2	100 mg b.i.d.	80 mg matching placebo b.i.d.

a. Investigators may consider initiating treatment on dose level 2 (valsartan 80 mg b.i.d. and 100 mg matching placebo b.i.d.) at Visit 102 (see Figure 3-3) in those patients being treated with at least the minimum dose of ACEI or ARB at Visit 1 (see Table 3-1)

Table 5-2 Study drug dispensed during the randomized treatment epoch by study visit

Study visit	Dose level	LCZ696	Valsartan
201	3[a]	200 mg or matching placebo b.i.d.	160 mg or matching placebo b.i.d.
Available for any visit after Visit 201	2[b]	100 mg or matching placebo b.i.d.	80 mg or matching placebo b.i.d.
Available for any visit after Visit 201	1[c]	50 mg or matching placebo b.i.d.	40 mg or matching placebo b.i.d.

a. This dose level must be maintained for as long a duration as possible. If down-titration is necessary due to side effects, the patient should be re-challenged as soon as medically possible per the investigator's judgment.

b. Only if dose level 3 is not tolerated despite modification of other concomitant medications.

c. Only if dose levels 2 or 3 are not tolerated despite modification of other concomitant medications.

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 19:00 (7 PM). Patients participating in the PK substudy will be required not to take their study drug on the morning of the PK substudy visits where blood samples are taken. 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 CRF. All kits of investigational treatment assigned by the IRT will be recorded/databased in the IRT.

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

5.5.5 Permitted dose adjustments and interruptions of treatment

For patients who are unable to tolerate the protocol-specified dosing scheme, dose level adjustments and 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 adjust or stop concomitant background medications for co-morbid conditions to rectify the situation, before considering to down titrate to the next lower study drug dose level. For hypotension or dizziness, consideration should be given to reduce the dose or to stop concomitant antihypertensive agents and non-antihypertensive agents that lower BP, or the dose of diuretic can be reduced.

Adjustment of study drug dose level

If despite adjustment of concomitant medications per the guidance provided the situation is not rectified, the investigator may consider down titrating the study drug dose level according to the following instructions:

During the randomized treatment epoch, down titration of the study drug at any time based on the judgment of the investigator will be allowed according to the safety and tolerability criteria defined in Appendix 3, Appendix 4, and Appendix 5. If down titration is necessary, the patient should be down titrated to the next lower study drug dose level (Table 5-2). 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 (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 (dose level 3). The investigator may choose the next dose level for down- or up-titration according to his or her judgment (Table 5-2). As discussed in Section 5.5.4, 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 (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.

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 (Table 5-2) per his/her medical judgment. If tolerated, the patient should be up-titrated a 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 ACEI, ARB or a renin inhibitor is strongly discouraged while patient is taking study drug. However, if for any reason a patient off study drug has started open-label

treatment with an ACEI it must be discontinued ≥36 hours prior to restarting study drug. For patients off study drug treated with an ARB or a renin inhibitor it must be discontinued prior to re-initiation of study drug (Table 5-3).

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

In case of pregnancy discovered during the screening or run-in epochs, the patient will be withdrawn from the study immediately. In case of pregnancy discovered during the double blind 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 7.5 for further details on pregnancies and reporting guidelines.

5.5.6 Rescue medication

Guidance on handling hyperkalemia, hypotension, and renal dysfunction are provided to investigators in Appendix 3, Appendix 4, and Appendix 5, respectively. Patients may receive open-label ACEIs, ARBs or a renin inhibitor during the study ONLY if the study drug has been temporarily or permanently discontinued (Table 5-3).

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

5.5.7 Concomitant treatment

The investigator should 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.

CV medications

The patient should be on an optimal medical regimen of diuretics and background medications to effectively treat comorbidities, such as HTN, DM, AF and coronary artery disease. 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 in accordance with international and local treatment guidelines (Mancia et al 2013), as well as other evidence-based medicine.

Medications known to raise potassium levels

Potassium-sparing diuretics, potassium supplements, MRAs 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.

Neseritide and intravenous (IV) nitrates

The concomitant administration of LCZ696 with neseritide and IV nitrates has not been studied. In the event a study patient requires the concomitant administration of neseritide and/or IV nitrates with the study medications, the investigator should consider starting them at a lower dose or a slower infusion rate while monitoring the patient's BP carefully.

HMG-CoA reductase inhibitors

Caution is recommended when co-administering LCZ696 with atorvastatin or other statins (e.g. simvastatin, pravastatin) that are substrates of OATP1B1 and OATP1B3 because of the potential to raise plasma statin levels.

5.5.8 Prohibited Treatment

Use of the treatments displayed in Table 5-3 is **NOT** allowed after the start of study drug due to safety reasons, unless the actions specified are taken.

Table 5-3 Prohibited treatment

Medication	Action to be taken
Any ACEI	Discontinue study drug. The open label ACEI 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 renin inhibitor	Discontinue study drug. The open label renin inhibitor must be stopped prior to re-initiation of study drug

ACEIs, ARBs and renin inhibitors

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

5.5.9 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 discontinued study drug are expected, and should be

encouraged to, attend all the protocol specified study visits and perform all measurements 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 as specified in Section 5.5.11. The investigator must also contact the IRT to register the patient's interruption from study treatment and record it on the drug administration form CRF.

If the patient does not attend the study visits, follow-up should continue according to the specified schedule by telephone to determine if any AEs/endpoints pre-specified in the protocol have occurred, except in the case that the patient **specifically** refuses such follow-up and withdraws his/her consent.

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

- Withdrawal of informed consent
- Investigator thinks that continuation would be detrimental to the patient's well-being
- Suspected occurrence of 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 ACEI, ARB or renin inhibitor
- Pregnancy and post-pregnancy during lactation period (Section 7.5)

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

The appropriate personnel from the site and Novartis will assess whether study drug should be permanently discontinued for any patient whose treatment code has been broken inadvertently for any reason.

5.5.10 Withdrawal of 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.

5.5.11 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to 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 source documents steps taken to contact the patient (e.g., dates of telephone calls, registered letters, etc.). A patient should not be considered lost to follow-up until his/her scheduled end of study visit would have occurred.

5.5.12 Emergency breaking of treatment assignment

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study drug 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 Lead or designee 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 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 subject 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.

5.5.13 Study completion and post-study treatment

The study will be completed when either: the target total of endpoints are 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 299) 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 be initiated to allow for study medication to be made available to qualified patients, upon formal request, if the study is terminated prematurely due to overwhelmingly efficacy of LCZ696 over valsartan by the DMC.

5.5.14 Early study termination

The study can be terminated at any time for any reason by Novartis. The patient should 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 IRBs and/or ECs 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. A Visit 199 (end of treatment run-in visit) will be completed for all patients who enter the treatment run-in epoch. For patients who discontinue during the treatment run-in epoch Visit 199 will be their discontinuation visit. For patients that are randomized, Visit 199 will be their end of treatment run-in disposition visit and will be performed on the same day as Visit 199/201. Safety monitoring criteria, vital signs and laboratory evaluations for randomization (Visit 201) are reflected at Visit 199/201 in Table 6-1.

Patients will have regular clinic visits performed for the first year (up to and including Week 48 [Visit 205]). Thereafter, patients will have clinic visits alternating with telephone contact visits every 12 weeks.

After randomization, study drug discontinuation (permanent or temporary) for any reason does not constitute withdrawal from the study and should not lead to the patient being withdrawn from the study. Patients who discontinue study drug should be requested to return for all of the assessments outlined in Table 6-1 as scheduled. If any patient refuses to return for these assessments or is unable to do so, every effort should be made to contact him/her or knowledgeable informant by telephone to ask if any of the study endpoint events have occurred at the foreseen visit dates for the remaining duration of the study. Documentation of attempts to contact the patient should be recorded in the patient's record.

Visit 201 will be considered the reference visit for all study visits during the randomized treatment epoch. Regardless of the occurrence of any unscheduled visits, scheduled visits should be performed within the specified timeframe in relation to Visit 201 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.

Additional Procedures to be implemented in Japan only

In Japan, all patients must enter the treatment run-in epoch at Visit 101, i.e. start the valsartan run-in on 40 mg b.i.d. For patients who have not received an ACEI or an ARB during the 30 days prior to the screening visit, an additional clinic visit (Visit 101J), which will be conducted approximately one week after Visit 101 and followed by V102 approximately 1 week later. V101J will have the same procedures as Visit 102 (Table 6-1) with the exception that for both V101J and V102 central abbreviated safety laboratory evaluations are mandatory. Also, all patients enrolled in Japan will be required to attend three additional clinic visits at approximately 1 week (201J1), 8 weeks (202J8) and 12 weeks (V202J12) after randomization (V201). In Japan, Visits 206, 208, 210, 212, 214, 216, 218 and 220 will be conducted as clinic visits, rather than phone visits. All additional clinical visits in the double-blind period will be

conducted with the same procedures as Visit 202 (Table 6-1) with the exception that study medication dispensing, drug accountability and serum/urine pregnancy tests are not required.

Additional procedures to be implemented in India only

In India, all patients will be required to attend an additional clinic visit (Visit 201I1) approximately 1 week following randomization where serum potassium will be assessed.

Table 6-1 Assessment schedule

Epoch		**Screen**	**Treatment Run-in**			**Randomized Treatment**																
Visit	**DS /S**	**1**	**101†**	**102**	**103**	**199/ 201††**	**202**	**203**	**204**	**205**	**206°**	**207**	**208°**	**209**	**210°**	**211**	**212°**	**213**	**214° 216° 218° 220°**	**215 217 219 221***	**UNS**	**299††† EOS**
Day		**-70/-49**	**-56/ -35**	**-42/ -28**	**-28/ -14**	**1**	**28**	**112**	**224**	**336**	**420**	**504**	**588**	**672**	**756**	**840**	**924**	**1008**	**1092 1260 1428 1596**	**1176 1344 1512 1680**		
Week(w)		**-10/-7**	**-8/-5**	**-6/-4**	**-4/-2**	**0**	**4**	**16**	**32**	**48**	**60**	**72**	**84**	**96**	**108**	**120**	**132**	**144**	**156 180 204 228**	**168 192 216 240**		
Obtain informed consent	S	x																				
Inclusion/Exclusion criteria	DS	x																				
Safety monitoring criteria	DS			(x)[15]	x	x§																
Relevant Medical History/Current Medical Conditions /Demography	DS	x																				
Medical History Possibly Contributing to Liver Dysfunction	DS	x																				
HF and Diabetes History/Smoking History/Alcohol History	DS	x																				
Concomitant Medications	DS	x	x	x	x	x§	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Visit Contact Information	DS		x	x	x	x§	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
NYHA Classification (HF Signs/Symptoms)	DS	x		x	x	x§	x	x	x	x		x		x		x		x		x	x	x
Physical Exam[1]	S	x		x	x	x	x	x	x	x		x		x		x		x		x	x	x
Vital signs (BP and pulse)	DS	x	x	x	x	x§	x	x	x	x		x		x		x		x		x	x	x

Epoch		**Screen**	**Treatment Run-in**			**Randomized Treatment**																
Visit	**DS /S**	**1**	**101†**	**102**	**103**	**199/ 201††**	**202**	**203**	**204**	**205**	**206°**	**207**	**208°**	**209**	**210°**	**211**	**212°**	**213**	**214° 216° 218° 220°**	**215 217 219 221***	**UNS**	**299††† EOS**
Day		**-70/-49**	**-56/ -35**	**-42/ -28**	**-28/ -14**	**1**	**28**	**112**	**224**	**336**	**420**	**504**	**588**	**672**	**756**	**840**	**924**	**1008**	**1092 1260 1428 1596**	**1176 1344 1512 1680**		
Week(w)		**-10/-7**	**-8/-5**	**-6/-4**	**-4/-2**	**0**	**4**	**16**	**32**	**48**	**60**	**72**	**84**	**96**	**108**	**120**	**132**	**144**	**156 180 204 228**	**168 192 216 240**		
Height	DS	x																				
Weight	DS	x				x§	x	x	x	x		x		x		x		x		x	x	x
Waist/hip circumference	DS					x§																x
ECG[2]	DS	x				x				x				x				x		X[2]	(x)	x
Echocardiography[3]	DS	x																				
QOL Questionnaire (KCCQ)[4]	DS		x			x		x	x	x				x				x		X		x
Patient Global Assessment[4]	DS					x		x	x	x				x				x		X		x
EuroQol (EQ-5D)[4]	DS					x		x	x	x				x				x		X		x
Mini-Mental State Examination (MMSE)[16]	DS					x				x				x				x		X		x
Complete Laboratory Evaluations[5]	DS	x			x	x§		x		x				x				x		x[13]		x
Abbreviated Laboratory Evaluations[6]	DS			(x)			x		x			x				x				x[13]	(x)	
Local Laboratory[15] Evaluation				(x)	(x)	(x§)															(x)	
Urinalysis	DS	x				x		x		x				x				x			(x)	x

Epoch		**Screen**	**Treatment Run-in**			**Randomized Treatment**																
Visit	**DS /S**	**1**	**101†**	**102**	**103**	**199/ 201††**	**202**	**203**	**204**	**205**	**206°**	**207**	**208°**	**209**	**210°**	**211**	**212°**	**213**	**214° 216° 218° 220°**	**215 217 219 221***	**UNS**	**299††† EOS**
Day		**-70/-49**	**-56/ -35**	**-42/ -28**	**-28/ -14**	**1**	**28**	**112**	**224**	**336**	**420**	**504**	**588**	**672**	**756**	**840**	**924**	**1008**	**1092 1260 1428 1596**	**1176 1344 1512 1680**		
Week(w)		**-10/-7**	**-8/-5**	**-6/-4**	**-4/-2**	**0**	**4**	**16**	**32**	**48**	**60**	**72**	**84**	**96**	**108**	**120**	**132**	**144**	**156 180 204 228**	**168 192 216 240**		
FSH[7]	DS	x																				
Plasma NT-proBNP[8]	DS	x	x		x	x		x		x												
Biomarkers/Biobanking[9]	DS		x		x	x		x		x												
1st morning void (urine)[9]	DS		x		x	x		x		x												
Pharmacogenomics[14]	DS				x			x		x												
Pharmacogenetics[10]	DS				x																	
Pharmacokinetic Sampling[11]	DS					x		x		x												
Serum/Urine Pregnancy Test[12]	DS	x	x	x	x	x§	x	x	x	x		x		x		x		x		x	(x)	x
AEs/SAEs	DS		x	x	x	x§	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Drug Accountability	DS			x	x	x§	x	x	x	x		x		x		x		x		x	(x)	x
Contact IVRS/IWRS	S	x	x	x	x	x§	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dispense Study Medication	S		x	x	x	x	x	x	x	x		x		x		x		x		x	(x)	
Screening Disposition	DS	x																				
Endpoint Information	DS		x	x	x	x§	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Run-in Disposition	DS					x§																
Treatment Disposition	DS																					x

UNS = Unscheduled visit

EOS = End of Study

DS = assessment to be recorded in clinical database

S = assessment to be recorded on source document

(x) = optional assessment

† = Visit to be performed only for patients that enter the treatment run-in epoch due to having been on an ACEI or ARB medication at doses lower than the total daily dose listed in Table 3-1 or per the investigator's discretion based on the patient's clinical status. Patients enrolled in Japan must enter the treatment run-in epoch at Visit 101. Patients who have not been on an ACEI or an ARB during the 30 days prior to the screening visit will have an additional clinic visit (V101J), approximately one week after Visit 101 and followed by V102 approximately one week later. V101J will have the same procedures similar to V102 (Table 6-1) with the exception that for both V101J and V102 central abbreviated safety laboratory evaluations and safety monitoring criteria are mandatory rather than optional.

†† = Visit 199/201 will be completed for all patients who enter the treatment run-in epoch. For patients that are randomized, Visit 199/201 should be combined into one clinic visit. For patients who discontinue during the treatment run-in epoch, only procedures with "§" will be performed. Patients enrolled in Japan will be required to attend three additional clinic visits at approximately 1 week (201J1), 8 weeks (202J8), and 12 weeks (V202J12) after randomization (Visit 201); with procedures similar to Visit 202 with the exception of study medication dispensing, drug accountability and serum/urine pregnancy tests. Patients enrolled in India will be required to attend an additional clinic visit (V201I1) approximately 1 week following randomization and start of the double-blind study medication where serum potassium will be assessed by the central laboratory; a local laboratory assessment can be performed at the investigators discretion.

††† = Visit 299 (end of randomized treatment visit) will be completed for all patients that enter the randomized treatment epoch

º Indicates study visits to be conducted as a telephone contact visit, except for patients enrolled in Japan where these visits will be conducted as clinic visits with procedures similar to Visit 202 with the exception that study medication dispensing, drug accountability and serum/urine pregnancy tests are not required.

§ At Visit 199/201, only procedures marked with "§" will be performed for patients who discontinue during the run-in epoch.

[1] Complete physical examination required at Visit 1 and 201 and annually thereafter (Visit 205, 209, 213, 217, 221) up until Visit 299 (EOS). Short physical exam required at all interim visits.

[2] ECG is performed at Visits 1, 201, and annually thereafter.

[3] Qualifying LVEF measurements/documentation of structural heart disease will be based on locally obtained echocardiograms (echo) performed ≤ 6 months prior to Visit 1. If an echo performed ≤ 6 months prior to Visit 1 is not available, an echo must be performed during the screening epoch.

[4] Patient Global Assessment is not evaluated at Visit 201; patients should be asked to remember how he/she feels at Visit 201, throughout the study the patient will be asked to rate how he/she feels compared to at the randomization visit (Visit 201). KCCQ value will be assessed at the beginning of run-in, i.e. Visit 101 or 102 (whichever occurs first), If the study is extended beyond Visit 221, KCCQ, Patient Global Assessment, and EuroQOL will be conducted annually.

[5] 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 221 a complete laboratory evaluation will be performed annually. Complete blood chemistry laboratory will be evaluated at Visit 103.

[6] Abbreviated laboratory includes: blood urea nitrogen (BUN), creatinine, potassium and eGFR. If the study is extended beyond Visit 221 an abbreviated laboratory evaluation will be performed at all interval visits except annual visits.

[7] Not required for males or pre-menopausal women.

[8] Visits 1, 101/102 (whichever is first), 103, 199/201, 203 and 205 (central lab) for all patients. Only the Visit 1 NT-proBNP results will be reported to the investigator and the sponsor.

[9] For patients participating in the biomarker substudy. If patient has biomarker sampled at Visit 101 there is no need for biomarker sample at Visit 102

[10] If the pharmacogenetics substudy sample is not obtained at Visit 103, it can be obtained at any time during the study.

[11] Patients participating in the PK substudy will also participate in the biomarker substudy; however patients may participate in the biomarker substudy without having to participate in the PK substudy. PK substudy samples will be collected pre-dose (trough) prior to the start of double-blind study drug (Visit 199/201). Samples will also be collected pre-dose (trough) prior to administration of study drug and at 0.5 to 2 hours and 3 to 5 hours post dose at Visit 203. If the samples are not collected at Visit 203 they will be obtained at Visit 205.

[12] Serum pregnancy test (not required for post-menopausal women) at Visit 1. Urine pregnancy tests at all other visits (not required for post-menopausal women). A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative. If positive during the screening or treatment run-in period the patient must be discontinued from the trial. After randomization (Visit 201) a positive pregnancy test requires immediate interruption of study drug.

[13] A complete laboratory evaluation will be done at the annual visits (Visits 217 and 221), an abbreviated laboratory will be done at Visit 215, 219.

[14] If the pharmacogenomics sample is not obtained at Visit 203, it will be obtained at Visit 205.

[15] Serum potassium and eGFR to be performed at Visit 102 only if patient enters the run in epoch at Visit 101.

[16] MMSE is performed at Visit 201 and yearly (Visit 205, 209, 213, 217, 221) thereafter up until Visit 299 (EOS).

*If the trial is extended, Visit 222, 223 and so forth to be performed as follows: alternating a telephone contact visit (same evaluations as Visit 212) with a clinic visit (same evaluations as Visit 213) every 12 weeks.

6.1 Information to be collected on screening and run-in failures

All patients who have signed informed consent but are not entered into the treatment run-in period will have the disposition page for the screening epoch, demographics, inclusion/exclusion, and SAE data collected. Adverse events that are not considered SAEs will be followed by the investigator and collected only in the source data. These patients are considered screening failures.

All patients that sign informed consent and take treatment run-in study drug will have the visit specific CRFs and Run-in disposition (Visit 199) collected. The reason for patient discontinuation during the treatment run-in period must be carefully documented in the appropriate CRF. These patients are considered treatment run-in failures.

For all patients who have signed informed consent and receive study treatment all AEs **occurring after informed consent is signed will be** recorded on the Adverse Event CRF.

Re-screening

A patient who enters screening but is determined not to be eligible to enter the treatment run-in epoch will be considered a screen failure. The investigator may consider re-screening the patient at a later time if he/she believes that the patient's condition has changed and they may potentially be eligible. In this case, a new patient number will be allocated to the subject and he/she will need to re-perform all Visit 1 procedures.

A patient may be re-screened up to two times. A minimum of 2 weeks must elapse between re-screenings. The patient must provide new written informed consent before each time they are re-screened.

No re-screening of patients that are discontinued from the treatment run-in period will be allowed.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race, ethnicity and source of patient referral. A detailed medical history (including HF, CV and other conditions relevant to the study population to be enrolled) and current medical conditions present before the signing of the informed consent will be collected.

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 care giver. This information should be captured in the 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. Study drug accountability will be determined by the site monitor while performing routine site visits and at the completion of the study.

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

6.4 Efficacy

The primary composite endpoint consists of the following components:

- CV death
- HF hospitalization (including first and recurrent hospitalizations)

The secondary endpoints are:

- KCCQ clinical summary score at 8 months
- NYHA functional classification at 8 months
- composite renal endpoint, defined as:
  1. renal death **or**
  2. reaching end stage renal disease (ESRD) **or**
  3. ≥ 50% decline in estimated glomerular filtration rate (eGFR) relative to baseline
- All-cause mortality

A 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 were met for 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.

6.4.1 Appropriateness of efficacy assessments

These measurements are standard and have been used in previous HF trials. The definition of CV endpoints is consistent with the FDA CV endpoints draft guidelines (Hicks et al 2012).

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 DBP] and pulse). A short physical exam will be conducted at all visits starting from Visit 102 except where a complete physical examination is required (see Table 6-1).

Information from all physical examinations must be included in the 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.

Waist/hip circumference (to the nearest centimeter [cm] in indoor clothing) will be measured at Visit 199/201 and the final study visit (Visit 299).

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all 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 laboratory evaluations (hematology, blood chemistry, and urine) for the assessment of safety in this study will be performed at Visit 1, 199/201, 203, 205 and then at yearly intervals (Visits 209, 213, 217 and 221) until the end of the study. Complete blood chemistry measurement will be performed at Visit 103. Abbreviated laboratory evaluations will be performed as indicated in Table 6-1. In Japan, patients will have abbreviated central laboratory evaluations at V201J1, V202J8, V202J12, V206, V208, V210, V212, V214, V216, V218 and V220 (Table 6-1). In India, the serum potassium for all patients will be assessed at V201I1 using the central laboratory; a local laboratory assessment may be performed at the discretion of the investigator.

In addition to the required central laboratory assessments, a local laboratory may be used for the assessment of potassium and eGFR during the treatment run-in period as indicated in Table 6-1. The results from the local laboratory during the treatment run-in period and at Visit 199/201 will be allowed to be used for decision making regarding the eligibility of the patient to continue on in the study and will be recorded on the appropriate CRF. In addition, local laboratory assessments may be performed on an as-needed basis to monitor tolerability to study drug at unscheduled visits during the randomized treatment period.

All central laboratory results will be communicated to the investigators and the sponsor, with the exception of biomarkers, of which only the Visit 1 NT-proBNP will be reported (Section 6.6.3).

Laboratory values that exceed the boundaries of a notable laboratory abnormality must be commented on by the investigator in the patient's CRF and additional laboratory evaluations should be performed, as judged appropriate by the investigator. If the laboratory abnormality

induces clinical signs or symptoms, 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 (Section 7.2). 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	Urine measurements
Hematocrit	Alanine aminotransferase (ALT)	Urinalysis
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 for the abbreviated laboratory evaluation at visits where the complete laboratory evaluation is not performed.

6.5.4.1 Hematology

Hemoglobin, hematocrit, RBC, RDW, MCHC, MCV, 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 ULN), AST, 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 laboratory evaluations are scheduled.

6.5.4.3 eGFR

Estimated eGFR 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 S_{Cr} in mg/dL)$^{-1.154}$ × (age in years)$^{-0.203}$ × (0.742 if female) × (1.212 if black), where S_{Cr} is the standardized serum creatinine value.

6.5.4.4 Urine assessments

Urinalysis with dipstick measurements for specific gravity, pH, total protein, bilirubin, ketones, leukocytes and blood will be performed. If a dipstick is positive, a qualitative microscopic determination, of WBC and RBC sediments will also be measured.

6.5.5 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed at Visit 1, Visit 199/201, annual visits, and Visit 299. Interpretation of the tracing must be made by a qualified physician and documented on the ECG section of the CRF. Each ECG tracing should be labeled with the study and subject number, date, and kept in the source documents at the study site. Clinically significant abnormalities should also be recorded on the Medical History/AE CRF page.

6.5.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum pregnancy test at Visit 1. A urine dip-stick pregnancy test will be performed locally at all other visits. The urine dip-stick pregnancy test is not required for post-menopausal women. A positive urine pregnancy test requires immediate interruption of study drug. If positive, 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.

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 assessment.

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.

6.6 Other assessments

6.6.1 Resource utilization

Analyses will be undertaken, as appropriate, to assess the effects of treatment on Healthcare Resource Utilization (RU) parameters.

These measures may include hospitalization (e.g. number of hospital days), physician visits, other drugs used, and laboratory tests and procedures performed.

At Visit 202 and each subsequent scheduled visit, the level of health care resource utilization will be assessed through procedures during hospital stays. The frequency and duration of any inpatient hospitalization will be recorded along with the primary reason for the hospital admission and discharge. All attempts will be made to collect RU variables in all patients throughout the duration of the study to avoid selection bias. There may also be circumstances when the collection of such data after completion of the study may be warranted.

6.6.2 Health-related Quality of Life

HF symptoms reduction and reduction in physical limitation

The KCCQ is a self-administered questionnaire that requires 4-6 minutes to complete. It contains 23 items, covering physical function, clinical symptoms, social function, self-efficacy and knowledge, and Quality of Life (QoL).

The HF symptoms and physical limitation domains scores show the best correlation for improvements following a chronic heart failure (CHF) exacerbation (Green et al 2000). Thus, one of the secondary endpoints is a clinical summary score based on the HF symptoms and physical limitation domains scores of the KCCQ at 8 months. All other domains will be analyzed as exploratory endpoints.

The KCCQ is available in a number of validated translations. Patients in whose language a validated translation of the KCCQ is not available will be exempt from completing this instrument.

Clinical composite assessment

The clinical composite assessment is one of the exploratory endpoints of this study. It is derived from the patient global assessment and the NYHA class, combined with the occurrence of major adverse clinical events as defined by CV death and hospitalization for HF.

The patient global assessment is a seven-point patient self-evaluation scale. At Visit 201, the investigator should call the patient's attention to how he/she feels about his/her condition at that time and explain that periodically throughout the study the patient will be asked to rate how he/she feels compared to at the randomization visit (Visit 201). This evaluation is combined with the NYHA class, a reliable instrument for rating HF patients' functionality, and with major adverse clinical events as defined by CV death and hospitalization for HF to arrive at an overall evaluation of whether a patient is considered to have improved, worsened, or remain unchanged after a pre-specified period of time (Packer 2001).

Assessment of HF signs and symptoms/NYHA class will be conducted at all visits.

EuroQol (EQ-5D)

The EuroQol (EQ-5D) instrument assesses the current health status of patients. It consists of five domains and one visual analogue scale. This instrument assesses morbidity, self-care, usual activity, pain, and anxiety and depression of patients.

The EQ-5D is available in a number of validated translations. However, patients in whose language a validated translation of the EQ-5D is not available will be exempt from completing this questionnaire.

6.6.3 NT-proBNP

NT-proBNP measurements will be performed by the central lab in all patients at Visits 1, 101/102 (whichever occurs first), 103, 199/201, 203 and 205. Only the Visit 1 NT-proBNP results will be reported to the investigator and the sponsor. All other measurements will be blinded to the site and the Novartis clinical study team.

6.6.4 Echocardiography

All patients must have a qualifying echo for study entry defined as either a locally obtained echo performed within 6 months prior to Visit 1 **or** if a qualifying echo within 6 months of Visit 1 is not available; the patient must enter the study based on a qualifying echo performed during the screening epoch. For patients enrolled in India, all ejection fractions must be performed using 2D volumetric methods.

For a subset of approximately 1200 patients at selected centers, the qualifying echoes will be sent to a core laboratory for assessment. The details of the echo procedures will be outlined in the manual provided to all participating sites.

6.6.5 Atrial fibrillation

The exploratory endpoint of new onset atrial fibrillation will be assessed in patients with no history of AF at baseline. This will be assessed at study visits by the investigator submitting

ECG tracings demonstrating the occurrence of atrial fibrillation to the clinical endpoint committee for adjudication (see Section 6.5.5 and Section 8.5).

Atrial fibrillation is common in HF and can contribute to the symptomatic and hemodynamic decline of the patient (Agostoni et al 2008, Clark et al 1997). Activation of the RAS system may contribute to the development of atrial fibrillation by promoting atrial fibrosis and detrimental hemodynamics (Healey et al 2005). Prior clinical studies have yielded conflicting results on the benefit of RAS inhibition for primary prevention of AF (Khatib et al 2013). In PARAMOUNT (CLCZ696B2214), there was a greater reduction in left atrial size in the LCZ696 group compared to the valsartan group (Solomon et al 2012). This atrial reverse remodeling may be a result of the beneficial effects of RAS inhibition and increased NPs and its second messenger cGMP resulting from neprilysin inhibition in the presence of RAS blockade.

6.6.6 Cognitive function assessment

Cognitive impairment is common in patients with heart failure (HF) (Hajduk et al 2013). Available literature suggests that treatment of hypertension and improved cardiac function and cerebral blood flow in HF patients might improve cognitive function (Almeida & Tamai 2001; Birns et al 2006; Zuccala et al 2005; Jesus et al 2006). On the other hand, NEP inhibition may inhibit the breakdown of amyloid β (Aβ), a peptide linked to cognitive impairment (Hersh & Rodgers 2008). In a two week cynomolgus monkey CSF study, short term LCZ696 treatment resulted in increases in CSF Aβ1-40, 1-42, and 1-38 levels. No increase in Aβ levels in brain was observed. In a chronic toxicology study, young (2-4 year old) cynomolgus monkeys treated for 39-weeks with LCZ696 at 300 mg/kg/day had no compound-related microscopic brain changes or increases in brain or cerebral vascular Aβ content or plaque formation. A two week clinical study in healthy human subjects did not find increases in Aβ1-40 and Aβ1-42 (although an increase in Aβ1-38 was observed), despite relevant concentrations of the NEPi, LBQ657, in the CSF. These findings suggest that degradation and transport mechanisms other than neprilysin, including enzymes such as angiotensin-converting enzyme (ACE), endothelin-converting enzyme (ECE) and insulin-degrading enzyme (IDE), may play a compensatory role in the clearance of CSF Aβ fragments in humans.

In the recently completed PARADIGM-HF (Study LCZ696B2314), in which 8442 patients were randomized to LCZ696 or enalapril for a median follow-up of 27 months, there were no differences between the two treatments in cognitive impairment or dementia-related adverse events. However cognitive function was not assessed in this trial. Therefore, global cognitive function will be assessed as an exploratory endpoint in the current protocol to evaluate the effect of LCZ696 compared to valsartan on cognition.

In the current study the effects of RAAS inhibition alone with valsartan is compared to the effects of combined RAAS and NEP inhibition with LCZ696 on cognitive function using the Mini-Mental State Examination (MMSE) instrument. The MMSE is the most commonly used instrument for assessing cognitive function in adults. It is a comprehensive screening tool that can be administered by non-specialist staff. It is a 30-point questionnaire that tests various aspects of a patient's cognition, including orientation to time and place, recall, attention, and

repetition. The instrument will be administered at randomization, annually thereafter, and at end of study visit (V299).

The MMSE is available in a number of validated translations. Patients in whose language a validated translation of the MMSE is not available will be exempt from completing this instrument.

6.6.7 Biomarker substudy

Biomarkers related to cardiac and renal function/injury and associated comorbidities and their consequences in the HFpEF population will be obtained from blood and first morning void (FMV) urine in a subset of approximately 1500 - 2000 patients as indicated in Table 6-1 as part of a substudy. Biomarkers will be used to elucidate the effect of study drugs as well as to explore risk. Blood biomarkers of potential interest may include, but are not limited to: NT-proBNP, BNP, ST2, high-sensitivity troponin, Galectin 3, Cystatin C and/or other relevant markers. FMV urine biomarkers may include markers such as cGMP and creatinine. The list of blood and urine biomarkers may change during the course of the study as new or more relevant biomarkers are determined. Biomarker analysis may also occur retrospectively after study close with biomarker decisions dependent on study outcome and/or new biomarkers relevant to the HFpEF patient population or drug mechanism.

The results of the biomarkers analyzed during the conduct of the study will be blinded to the site and the Novartis clinical study team with the exception of the Visit 1 NT-proBNP.

6.6.8 Pharmacokinetics substudy

Approximately 400 of the patients participating in the biomarker substudy (Section 6.6.7) will also participate in the PK substudy during the randomized treatment period at selected study sites. Plasma levels of valsartan, AHU377, and LBQ657 will be determined from these patients.

On the morning of Visit 199/201 (end of treatment run-in/randomization) prior to starting the double blind study drug, participating patients will have a trough (C_{min}) PK sample taken. Patients should be instructed to take their last dose of treatment run-in study drug at approximately at 19:00 (7 PM) on the night prior to the visit that the trough PK sample will be obtained.

On the morning of Visit 203 a total of 3 samples will be collected. Patients should be instructed not to take their morning dose of study drug prior to the clinic visit. The samples will be collected at the following intervals (Appendix 6):

- Sample #1: pre-dose trough (immediately before the administration of study drug)
- Sample #2: 0.5 to 2 hours post-dose
- Sample #3: 3 to 5 hours post-dose

If the PK samples are not taken at Visit 203, they will be taken at Visit 205. The site should make every effort to collect sample as close to the interval periods as possible. The exact time of the treatment administration, dose level of study medication, sample number, and time of sample collection will be recorded for each sample collected on the Pharmacokinetic Sample CRF.

Patients participating in the PK substudy are not required to provide all three required blood samples during the same study visit. Samples should always be taken when the patient is expected to be at steady state, i.e., has been receiving the study drug regularly on the same dose level as prescribed for at least 1 week.

Special instructions on preparation, labeling, storage, and shipment of PK samples will be provided to the sites in a separate document.

6.6.9 Pharmacogenetics/Pharmacogenomics

Pharmacogenetics/pharmacogenomic substudies will be conducted in countries where approval is granted.

6.6.9.1 Pharmacogenetics

The study includes an optional pharmacogenetic component to be conducted at all participating sites and requires a separate signed informed consent if the patient agrees to participate. The Investigator where this component of the study is conducted will offer this option to the patient.

This study will identify inherited genetic factors which may (1) be related to the causes and consequences of CHF, its' pathophysiology and associated comorbidities, (2) predict response to treatment with LCZ696, (3) predict genetic predisposition to side effects. The goal is to develop a better understanding of CHF and how subjects respond to LCZ696. The genetic markers (or polymorphisms) that may be studied relate to the etiology of or modifiers of CHF include ACE I/D, which was reported to be associated with event-free survival in patients with HF. The specific genetic markers to be assessed may evolve during the course of the study as new or more relevant markers are determined relating to, for instance, ventricular structure or prediction of mortality or as new markers relevant to the HFpEF patient population develop. Additional polymorphisms may be considered at any time within the restricted scope of these studies as described. Analyses may occur retrospectively after study close.

The ApoE4 gene has been identified as a genetic marker that predicts predisposition to cognitive decline and Alzheimer's disease (Corder et al 1993). To control for this predisposing factor, patients will be asked to provide blood samples for genotyping which will include assessment of their ApoE4 genotype so that genetic predisposition is taken into account when assessing the cognitive function of the study participants.

Recent advances in genotyping technologies have made genome-wide approaches possible. Genome wide studies may also be undertaken to identify genes that may be associated with HF or response to therapy as described above.

Sample collection: One blood sample will be collected from participating patients at Visit 103, or at any visit thereafter when consent is obtained. The protocol for the preparation of the samples for pharmacogenetics will be detailed in the study lab manual. The samples will be shipped to the central lab for DNA extraction. The extracted DNA will then be transferred to Novartis Pharmaceuticals Corporation for pharmacogenetic analysis and storage.

Any DNA derived from the sample that remains after analysis will be double-coded (see Section 8.3) and may be stored for up to 15 years to address scientific questions related to LCZ696, CHF or HFpEF.

6.6.9.2 Pharmacogenomics

This study includes an optional pharmacogenomics component to be conducted at all participating sites and requires a separate signed informed consent if the patient agrees to participate. The investigator where this component of the study is conducted will offer this option to the patient.

The pharmacogenomic samples will be obtained with the intention of assessing the effects of LCZ696 and valsartan on peripheral cellular and circulating plasma mRNAs, miRNAs and other oligonucleotides. Having access to these data could in turn assist: i) pre-treatment molecular stratification of disease, ii) evaluation of longitudinal treatment-induced molecular effects, and iii) the enrichment of responders to treatment at baseline.

Sample collection: One blood sample will be collected at two timepoints/visits: i.e. prior to treatment with single-blind run-in study drug at Visit 103 and at Visit 203 (or Visit 205) during the double blind treatment epoch. RNA will be obtained from cellular components and from plasma. The protocol for the preparation of the samples for pharmacogenomics testing will be detailed in the study lab manual.

Any RNA or other oligonucleotides derived from the sample that remains after analysis will be double-coded and may be stored for up to 15 years to address scientific questions related to LCZ696, CHF or HFpEF.

7 Safety monitoring

7.1 Adverse events

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

An untoward medical occurrence may be a study endpoint as well as meeting the definition for an AE. Specific guidance on the appropriate recording and reporting of events that meet the criteria for both a study endpoint and an AE are provided in Section 7.3.

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

Abnormal laboratory values or test results constitute AEs 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 should 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 AEs. Alert ranges for labs and other test abnormalities are included in Appendix 1.

AEs should be recorded in the AE 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 (no/yes)
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes an SAE
- action taken regarding study treatment
- whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

An SAE is any AE (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, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

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

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug(s) permanently discontinued; concomitant medication given; non-drug therapy given. The action taken to treat the AE should be recorded on the AE CRF.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should 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.

Novartis may request additional information on specific AEs 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.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

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

7.2 Serious adverse event reporting

To ensure patient safety all SAEs, 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.

At a minimum, patients will be contacted for safety evaluations during the 30 days following the last study visit or following the last administration of study drug, including a final contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the source documentation. Furthermore, under this category, SAEs experienced after the 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be

submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure (new occurrence) and is thought to be related to the investigational treatment, a Novartis Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. If the SAE is considered Suspected Unexpected Serious Adverse Reactions (SUSARs), Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. All SUSARs will be collected and reported to the competent authorities and relevant ethics committees (ECs) in accordance with Directive 2001/20/EC 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 (European Commission ENTR/CT12 Guideline 2006; 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 (atrial fibrillation, CV death, heart failure hospitalization, myocardial infarction and 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 will not issue an 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 (Table 7-1) but they will not be unblinded and will not be reported as SUSARs to regulatory agencies, ECs, or investigators during the study. These events will be presented in the clinical study report (CSR) at the end of the study.

If specifically requested by a local Health Authority, pre-specified AEs commonly observed in the study population (Table 7-1) 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.

Table 7-1 Adverse events commonly seen in study population

Cardiovascular events		Non-cardiovascular events	
Unstable angina	Generalized edema	Arthralgia/Arthritis	COPD (including bronchitis and emphysema)
Arrhythmia (excluding AF)	Hypertension	Constipation	Cough
Transient ischemic attack	Hypotension	Diarrhea	Fatigue
Renal impairment	Peripheral edema	Headache	Sepsis
Chest pain	Syncope	Nausea	Nasopharyngitis
Dizziness/vertigo	Angina pectoris	Anemia	Pneumonia
Cerebrovascular accident	Dyspnea	Upper respiratory infection/insufficiency	

7.3.3 Exploratory endpoints and other SAEs that meet the definition of SUSARs

Exploratory endpoints that meet SUSAR criteria, and all other SAEs that do not meet the criteria in Section 7.3.1 and Section 7.3.2 but do meet SUSAR criteria will be unblinded and reported to regulatory agencies, ECs, or investigators during the study.

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 data throughout the trial in a semi-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.

7.4 Liver safety monitoring

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 are divided into two categories:

- Liver events of special interest (AESI) which consist of LFT elevations
- Medically significant liver events which are considered as SAEs and which consist of marked elevations of LFTs and / or pre-specified AEs.

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

Any liver event which meets the criteria for "**medically significant**" event as outlined in Table 14-1 of Appendix 2 should follow the **standard procedures for SAE reporting** as described in Section 7.2.

Every liver event as defined in Table 14-1 of Appendix 2 should be followed up by the investigator or designated personnel at the trial site as summarized below. Detailed information is outlined in Table 14-2 in Appendix 2.

- 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.

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.

7.5 Pregnancy reporting

To ensure patient safety, each pregnancy occurring while the patient is on study treatment 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 should be recorded on a Clinical Trial 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 pregnancy must be reported on the SAE Report Form.

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, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good

Clinical Practice, 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.

The investigator must maintain 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 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 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 source data with the CRFs are performed according to the study-specific monitoring plan. No information in 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 EDC 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 Contract 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. A 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 WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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.

Pharmacogenetic/pharmacogenomic samples

To maximize confidentiality, all samples are coded with a unique number and no personal identifiers are on the sample tubes. DNA samples are double-coded to ensure added confidentiality. The process of double-coding allows Novartis to go back and destroy the sample at the patient's request. All information relating to the samples is stored in a secured database under the control of Novartis. In addition, the results obtained from these exploratory samples will be stored in a secured database that is separate from and not linked to the sample database.

The use of pharmacogenetics/pharmacogenomics to search for biomarkers of disease and drug action is exploratory. Any results from this pharmacogenetic study will not be placed in the patient's medical records.

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 efficacy and safety on a regular basis and determine if it is safe to continue the study according to the protocol. 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 Committees

Clinical Endpoint Committee

All events, which could potentially fulfill the criteria for the primary, secondary, or other endpoints will be assessed during the study and reported to the Clinical Endpoint Committee (CEC) for adjudication.

The CEC will be responsible for classifying all death events and for determining whether pre-specified endpoint criteria were met for the non-fatal events. Sites are instructed to take a conservative approach when reporting endpoints; if the investigator suspects an endpoint may

have occurred, it should report the event to the CEC for the final determination. The membership and responsibilities of the CEC Committee will be defined in a separate document provided to the sites. This document will include definitions for endpoints and guidelines on the endpoint reporting process.

Angioedema Adjudication Committee

If an angioedema or angioedema-like 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.

8.6 Source documentation verification

Novartis will select patients based on pre-defined criteria (e.g., enrollment based on elevated NT-proBNP alone or based on prior hospitalization for heart failure) for collection of select source documentation of medical history records for full medical review of adherence to the inclusion/exclusion criteria as needed to ensure the intended per protocol target patients are enrolled. Sites will be instructed to remove all personal identifiers linking the source documents to the patients prior to submission to a third party vendor via electronic email or fax. The third party vendor will then ensure anonymity of the documents, compile the medical history packets, translate the documents into English (if applicable), and forward them to Novartis for medical review. Only the patient's study identification number will be used to ensure patient's identity and confidentiality are preserved. The review will be conducted centrally by the global study clinical team and will focus on enrolled patients. The aim of this central medical review is to assess compliance with the protocol and provide additional training to the investigator sites if needed.

9 Data analysis

This section describes a preliminary approach to data analysis.

9.1 Analysis sets

The following analysis sets will be used for the statistical analyses:

The full analysis set (FAS) will consist of all randomized patients with the exception of those patients who have not been qualified for randomization and have not received study drug, but have been inadvertently randomized into the study. Following the intent-to-treat principle, patients will be analyzed according to the treatment to which they were assigned at randomization. Efficacy variables will be analyzed based on the FAS as the primary population.

The Safety (SAF) Population will consist of all randomized patients who received at least one dose of study drug. Patients will be analyzed according to the treatment actually received. The safety population will be used for the analyses of safety variables.

The Per-protocol set (PPS) will be a subset of the FAS which will consist of the patients who do not have major deviations from the protocol procedures in the randomized treatment epoch. Major protocol deviations will be pre-specified prior to unblinding treatment codes for analyses. This supplemental efficacy population will be used to support the primary analysis results.

9.2 Patient demographics and other baseline characteristics

Baseline value is defined as the last non-missing assessment prior to the first dose of randomized study drug unless specified otherwise. This baseline is the randomized treatment epoch baseline.

Summary statistics will be provided by treatment group for demographics and baseline characteristics, including age, age group (<65 years vs. ≥65 years; <75 years vs. ≥75 years), sex, race, ethnicity, weight, height, body mass index (BMI), category of prior CV medication, prior HF hospitalization, NYHA class, NT-proBNP, and vital signs. BMI will be calculated as weight (kg) / height^2 (m^2) from the collected height and weight at Visit 1 (Screening Visit). Continuous variables will be summarized using n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency and percentage.

The difference between treatment groups will be compared using the Chi-square test for categorical variables or using t-test for continuous variables. The p-values will be provided for descriptive purposes and will not be considered to define any formal basis for determining factors to be included in statistical models. If a substantial imbalance of treatment groups with respect to some variables does occur, supplemental analyses with addition of these variables in model may be performed to assess the potential impact on efficacy as appropriate.

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.

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 population.

The number and percentage of patients on different CV background medications (e.g., mineralocorticoid receptor antagonist, β-blockers, diuretics, and digoxin) will be tabulated by treatment at baseline and during the randomized treatment epoch.

The FAS will be used for the above analyses unless otherwise specified.

9.4 Analysis of the primary and secondary variable(s)

9.4.1 Variable(s)

The primary and secondary objectives of this study are presented in Section 2.1 and Section 2.2

The primary efficacy variable is the cumulative number of primary composite events, i.e., the composite events of (total) HF hospitalizations and CV death, for a given subject, over time.

The secondary efficacy variables are:

1. Change from baseline in KCCQ clinical summary score for HF symptoms and physical limitations at Month 8**.**
2. Change from baseline to Month 8 NYHA class.
3. Time to first occurrence of the composite renal endpoint, defined as follows:
   - renal death, or
   - reaching ESRD, or
   - ≥50% decline in eGFR relative to baseline
4. Time to all-cause mortality.

The time point of Month 8 is defined as Week 32 in accordance with the assessment schedule (Table 6-1).

9.4.2 Statistical model, hypothesis, and method of analysis

9.4.2.1 Primary analysis

The primary efficacy endpoint of the study consists of the times to recurrent hospitalization due to heart failure and death time due to CV reasons during the patient's follow-up. The comparisons between two treatment groups will be made using statistical procedures which deal with such multiple event time observations. For example, the semi-parametric proportional rates model (abbreviated as LWYY model) (Lin et al 2000) can be utilized for quantifying the treatment difference.

Specifically, let $\lambda_{ij}(t, x_{ij})$ be the individual rate of primary composite events for subject i in region j, given the patient has not died from a CV reason at time t. It is dependent on time from randomization (t) and treatment group (x_{ij}). Let $x_{ij}=1$ if the subject is in the LCZ696 group and $x_{ij}=0$ if the subject is in the valsartan group.

Under the proportional rates model, the individual rate function for the composite endpoint of CV death and total HF hospitalizations is assumed to be, $\lambda_{ij}(t, x_{ij}) = Y_{ij}(t)\lambda_{0j}(t)\exp(\beta_0 x_{ij})$, where $Y_{ij}(t)=1$ if subject i in region j is at risk for HF hospitalization or CV death at time t and $Y_{ij}(t)=0$ if subject i in region j is censored or died from a CV reason at time t- and $\lambda_{0j}(t)$ is the baseline rate function for the event in region j.

The primary hypothesis to be tested is, H_{10}: $\beta_0 \geq 0$ versus H_{1a}: $\beta_0 < 0$, where $\exp(\beta_0)$ is the relative risk or rate ratio (RR) of total hospitalizations for HF and CV death in the LCZ696 group relative to the valsartan group given the patient has not died from a CV reason at time t, which is assumed to be constant over time and across regions.

The primary hypothesis could be equivalently written as:

H_{10}: Rate ratio LCZ696/valsartan ≥ 1 versus H_{1a}: Rate ratio LCZ696/valsartan < 1,

A rate ratio < 1 indicates an effect in favor of LCZ696.

Note that $\exp(\beta_0)$ can also be considered as a ratio of two mean cumulative frequencies of a subject having hospitalizations for HF and CV death when the rate ratio is constant over time and CV mortality is balanced between treatment groups.

The primary hypothesis will be tested at a one-sided significance level of 0.02499 adjusted for interim analysis. The rate ratio and its 95% confidence interval will be estimated from the above proportional rates model through maximization of a partial likelihood score function. The resulting estimate of $\exp(\beta_0)$ is identical to the one described by Anderson and Gill (Anderson and Gill 1982), but unlike Anderson-Gill, a robust variance estimator (sandwich estimator) is used to account for the dependency of within subject events. Note that having CV death is not considered as a censoring variable, but as a primary endpoint event and a conditional factor in this analysis. Time to non-CV death will be considered as a censoring variable. Any censoring due to non-CV death is assumed to be non-dependent in the analysis.

The above presented analysis method based on LWYY provides a treatment comparison based on primary endpoint rate ratio conditional on not having died from a CV reason. A marginal interpretation of the estimates requires that any censoring of the primary composite events will be non-informative and may be challenging if there is an imbalance in CV mortality.

As a part of the primary analysis, the two components in the composite endpoint (total HF hospitalizations and CV mortality) will be analyzed separately to quantify the respective treatment effects and check the consistency between the composite and the components.

For the analysis of total HF hospitalizations component, occurrence of CV death can be regarded as semi-competing risk (informative censoring) and may introduce a bias in the treatment effect estimate for HF hospitalizations (dilution of effect size if the drug has a positive effect on both components). In order to address this concern and to account for the correlation between the two components, the joint modeling (frailty model) approach (Cowling et al 2006) will be used for the component analyses. The joint model is specified as follows.

$$\lambda_{ij}^{H}(t) = Y_{ij}(t)\lambda_0^{H}\exp(\beta_0 x_{ij})\nu_{ij}$$

$$\lambda_{ij}^{\tau}(t) = Y_{ij}(t)\lambda_0^{\tau}\exp(\gamma_0 x_{ij})\nu_{ij}^{\alpha}$$

$$\nu_{ij} \sim f(.)$$

where $\lambda_{ij}^{H}(t)$ is the rate function of the total hospitalizations for HF for subject *i* in region *j* and λ_0^{H} is its constant baseline and $\lambda_{ij}^{H}(t)$ has a similar format as the model described above for the primary endpoint except for the multiplier ν_{ij} that is a subject-specific random effect factor (frailty); and $\lambda_{ij}^{\tau}(t)$ is the hazard function for the component of CV mortality for

subject *i* in region *j* and $\underline{\lambda_0^T}$ is its constant baseline and $\lambda_{ij}^T(t)$ is a frailty Cox proportional hazards model. The parameter α measures the association between $\lambda_{ij}^H(t)$ and $\lambda_{ij}^T(t)$. The frailty distribution *f(.)* will be pre-specified prior to the unblinding of the treatment codes. The parameters in the joint model, including the unknown power for the frailty, will be estimated through maximization of the corresponding likelihood. The model assumes that the correlation between total HF hospitalizations and CV death for each patient is completely explained by the covariates and the frailty and the two analysis variables corresponding to the two components are independent given the patient's frailty and covariates.

For the analysis of CV death, it will be analyzed using Cox's proportional hazards model with a fixed treatment group factor and stratified by region. The analysis in the joint frailty model for this component will be considered as supportive whenever an inference is needed for it.

In all the proposed analyses, it is acknowledged that the study will not be powered to achieve statistically significant results for the CV death. The inference on the total HF hospitalizations can only be made when both the composite endpoint and the total HF hospitalizations itself showed statistically positive results.

Non-parametric estimates of HF hospitalization rates over time allowing for death as terminal event will be provided as well (Ghosh and Lin 2000).

9.4.2.2 Supportive analyses for primary efficacy

The supportive analyses for the primary analysis results will be performed in two ways:

1. Performing the primary analysis (the LWYY model) and the component analyses (the joint frailty model) on the PPS;
2. Evaluating the impact of the informative censoring of CV death on the estimate of the relative rate reduction through performing additional analyses including:
   a. Checking of existence of any non-negligible imbalance in CV mortality between treatment groups through analysis for CV mortality alone; pooling PARADIGM-HF (CLCZ696B2314) and this study to assess any adverse signal on CV mortality, if it deems necessary;
   b. Providing a series of sensitivity analyses to investigate the robustness and consistency of the primary efficacy results:
      - Analysis using the WLW method (Wei et al 1989, Li and Lagakos 1997) on time to first (the conventional time-to-first event analysis) and time to 2nd, 3rd, 4th, 5th, and 6th composite events; an average effect (stratified by event number) will be provided for each of those analyses. This analysis will partially evaluate the robustness of the overall estimate of effect size against the impact from an (expected) small subgroup of patients with higher number of hospitalizations for HF. If the patient's first event is a CV death, then his 2nd, 3rd,…, Kth event will be counted as CV death as well. This analysis avoids informative censoring by counting CV death repeatedly as event. It is acknowledged that some of the analyses, time-to-1st event, for example, may not be powered;
      - Analysis using a negative binomial regression model (McCullagh and Nelder 1989) on total number of primary composite endpoints with an offset of

logarithm of time from randomization to censoring or death. The common rate ratio of composite events will be provided.

- Analysis using a multi-state model (Castaneda and Gerritse 2010) to assess the hazard ratios of transition intensities between different states defined by hospitalization status and CV death.

9.4.2.3 Secondary analysis

9.4.2.3.1 Analysis methods

The four secondary hypotheses to be tested are:

- Comparison of change from baseline in KCCQ clinical summary score at Month 8 (denoted as H_{210}, the parameter is the mean change from randomized treatment epoch baseline to Month 8 in KCCQ clinical summary score);
- Comparison of change from baseline to Month 8 NYHA class (denoted as H_{220}, the parameter is the category change from baseline to Month 8 in NYHA class);
- Time from randomization to first occurrence of composite renal endpoint of renal death, ESRD, or ≥50% decline in eGFR relative to baseline (denoted as H_{230}, the parameter is the hazard ratio for composite renal endpoints);
- All-cause mortality (denoted as H_{240}, the parameter is the hazard ratio for all-cause death).

Changes from baseline in KCCQ clinical summary score at Month 8 will be analyzed based on a repeated measures ANCOVA model in which treatment, region, visit, and treatment-by-visit interaction will be included as fixed-effect factors and baseline value as a covariate, with a common unstructured covariance matrix among visits for each treatment group. Treatment comparisons and effect size estimates at Month 8 will be provided. The analysis will be performed based on all available data up to Month 8 in the FAS and based on likelihood method with an assumption of missing at random for missing data.

In addition, a responder analysis for KCCQ clinical summary score change from randomized treatment epoch baseline at Month 8 (defined as patients with at least 5 point change (deterioration or improvement) will be performed using a generalized mixed model with treatment, region, visit, and visit-by-treatment as fixed factors and baseline score as covariate, with a common compound symmetry covariance matrix among visits for each treatment group. Treatment comparisons and effect size estimates at Month 8 will be provided. The analysis will be performed based on all available data up to Month 8 in the FAS. The goal of the responder analysis is to assess the clinical relevance of the difference between the two groups in the mean change from randomized treatment epoch baseline.

Change from baseline to Month 8 NYHA class will be analyzed using a repeated measures proportional cumulative odds model. The response variable is the category change from baseline to any given time points up to Month 8 (improved, unchanged, worsened). NYHA class change after patients who have died will be categorized into ‘worsened’. The model will include patient as a random effect and the randomized treatment phase baseline NYHA class, region, treatment, visit and treatment-by-visit interaction as fixed effect factors. This model assumes that the treatment effect sizes across measurement categories are the same. Model fittings will be based on likelihood with all available data up to Month 8. As supportive

analysis, the same model will be performed on data with no imputation for missing data in NYHA class change due to death.

Time-to-first occurrence of composite renal endpoint events will be analyzed using the Cox proportional hazard model with treatment as a fixed effect factor, stratified by region. The estimated hazards ratio and the corresponding two-sided 95% confidence interval will be provided.

All-cause mortality will be analyzed using Cox's proportional hazards model with a fixed treatment group factor and stratified by region.

9.4.2.3.2 Multiplicity adjustment

The secondary hypotheses will be tested and statistical inferences will be made only if the primary hypothesis is rejected. The four secondary efficacy hypotheses will be tested for superiority of LCZ696 to valsartan for the FAS. For each secondary variable, the null hypothesis of no treatment difference between LCZ696 and valsartan will be tested against the alternative hypothesis that LCZ696 is more effective than valsartan.

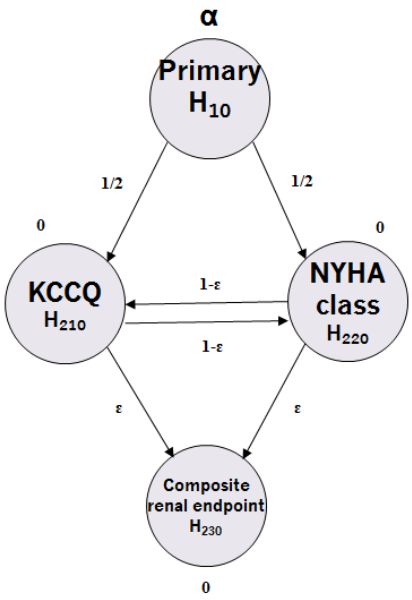
The sequentially rejective multiple test procedures (Bretz et al 2009) will be used for testing the hypotheses of the primary endpoint and the first three secondary endpoints as indicated in Figure 9-1, to control the alpha level. The all-cause mortality (H_{240}) will be tested at a full level of alpha, after the rejection of the primary hypothesis, considering as a hard-endpoint.

In Figure 9-1, the fractions marked in the graph denote the weights or proportions of alpha to be added to the alphas in the next nodes according to where the arrows point once the current node of hypothesis is rejected.

- The initial allocation of (local) significance levels are α, 0, 0, and 0 for the comparisons of the primary endpoint and the first three secondary endpoints, respectively.
- The general algorithm for the testing procedure goes as follows: Test the hypotheses H_{10}, H_{210}, H_{220}, and H_{230} each at its local significance level defined above. If a hypothesis can be rejected, reallocate its level to one of the other hypotheses according to a pre-specified rule represented by the weighted graph in Figure 9-1. Update the reallocation weights in the reduced graph (the rejected hypothesis is removed from the graph) and repeat the testing step for the remaining no-rejected hypotheses with the updated local significance levels. This possibly leads to further rejected null hypotheses with associated reallocation of the local significance levels. The procedure is repeated until no further hypothesis can be rejected. The reallocation of the local alpha levels is fully determined by the initial graph given in Figure 9-1 and the update algorithm for this sequentially rejective multiple test procedure (Bretz et al 2009).
    - In the notation of Bretz et al 2009, a weight of ε for an edge indicates an infinitesimally small weight. If a hypothesis (vertex) with such an outgoing edge is rejected and the vertex removed, no significance level is passed on along such an edge as long as there are other outgoing edges with positive weights. If after removal of another vertex only infinitesimal outgoing edges remain, then the algorithm of Bretz et al 2009 turns them into edges with positive weights that sum to 1. In this specific procedure, this implies that no significance level is passed from the secondary null hypotheses for KCCQ (H_{210}) or NYHA class (H_{220}) to the secondary null hypothesis

for composite renal endpoint (H_{230}) until both KCCQ and NYHA class null hypotheses have been rejected. To ensure the sum of weights on all outgoing edges of a vertex is 1 when such edges are present, some edges are given a weight of 1 – ε.

Figure 9-1 Illustration of weights for alpha relocation in the sequentially rejective multiple test procedure for the secondary hypotheses



The power analyses for each hypothesis in Figure 9-1 are presented in Section 9.7.

For publications the secondary variables may be assessed using a full level of alpha without consideration of multiplicity adjustment.

9.4.2.4 Subgroup analyses for primary and secondary objectives

Subgroup analyses will be performed for the primary and secondary endpoints based on the FAS. To explore beneficial effects in subgroups or homogeneity of beneficial effects among subgroups, the estimated effect sizes, their two-sided 95% confidence intervals, and within subgroup p-value and p-value for the test for the treatment-by-subgroup interaction will be provided for each of the subgroups based on the analysis models. The analysis models will include treatment, subgroup, and treatment-by-subgroup as fixed-effect factors, except for NHYA. No adjustment for multiple comparisons will be made. Therefore, p-values from these subgroup analyses have to be interpreted with caution since there is a non-negligible chance of false-positive findings.

- Age group (<65 vs. ≥65 years; <75 vs. ≥75 years)
- Gender (male/female)
- Race
- Region
- Diabetic at baseline (yes/no)
- Baseline SBP (≤median vs. >median)

- Baseline LVEF (≤median vs. >median)
- Baseline NT-proBNP (≤median vs. > median)
- Baseline eGFR (<60 vs ≥60 mL/min/1.73 m^2)
- AF at baseline (yes/no)
- Use of MRAs at baseline (yes/no)
- ACEI intolerant patients (yes/no)

9.4.3 Handling of missing values/censoring/discontinuations

The primary efficacy variable, the recurrent extended composite events and time to new onset of AF variables are related to the number of events or time to event occurred within a certain time window. The censoring will be the major source of missing data. This type of missing data will be handled by assuming some dependence structures between the censoring mechanism and the event generating mechanism. The dependence structures will be pre-specified in the analysis plan. A variable is considered to be censored at each analysis time point if at least one of the following applies at or prior to the analysis time point:

- Withdrawal of informed consent,
- Lost to follow-up, or
- Death

The censoring date will be defined as the following (whichever occurs first):

- Date when the patient withdrew informed consent
- Date of the patient's last visit before analysis cut-off date
- Date of death

For the analysis of KCCQ clinical summary score, if a patient dies, a worst score (score of 0) will be imputed for the clinical summary score at all subsequent scheduled visits after the date of death where the clinical summary score would have been assessed.

For the analysis of NYHA, the analysis will be based on the likelihood approach. The missing at random (MAR) for missing data is assumed. An unbiased analysis will be produced under MAR.

9.5 Analysis of exploratory variables

Exploratory objectives are defined in Section 2.3.

9.5.1 Exploratory variables

Below are the variables for the exploratory analyses:

1. Time from randomization to occurrences of the composite endpoint events of CV death, total non-fatal HF hospitalizations, total non-fatal strokes, and total non-fatal myocardial infarctions (MIs). Total is defined as the first and all recurrent events;
2. Change in clinical composite assessment (NYHA, global patient assessment, and clinical events defined as CV death and HF hospitalization) at 8 months;
3. Patient global assessment at 8 months;

4. Changes from baseline in health-related QoL (assessed by the overall summary score, clinical summary score, and individual scores of the sub-domains from the KCCQ [relative to the beginning of treatment run-in and randomization epochs] and assessments of the EQ-5D for health status);
5. Number of HF events per-subject;
6. Number of worsening HF events or CV death per-patient;
7. Number of all-cause hospitalizations per-subject and number of cause specific hospitalizations per-subject;
8. Number of days alive and out of hospital at 12 months, and during the study duration;
9. Rate of change in eGFR (eGFR slope);
10. Time from randomization to NODM;
11. Number of days staying in intensive care unit (ICU), number of re-hospitalizations for HF, and number of ER visits for HF;
12. Indicator of 30 day HF rehospitalization (after a prior HF hospitalization);
13. Number of rehospitalizations within 30 days after discharge;
14. Time between HF hospital readmissions;
15. Changes in pre-specified biomarkers (e.g., cardiac, vascular, renal, collagen, metabolism, and/or inflammatory biomarkers) from baseline to predefined time-points (in a subset of patients);
16. Variables to characterize the PK of valsartan, AHU377, and LBQ657 at steady-state in patients receiving LCZ696 using population modeling and/or non-compartmental based methods;
17. Change from baseline in MMSE summary score at year 2 (week 96);
18. Time from baseline to new onset atrial fibrillation;
19. Echocardiographic parameters in a subset of patients

9.5.2 Analysis methods

In general, exploratory variables will be analyzed in the FAS unless specified otherwise. Statistical tests will be performed at the two-sided significance level of 0.05. To better satisfy the normality assumption, the log-transformation will be taken on each biomarker prior to statistical analysis. There will be no multiplicity adjustment for any analysis of exploratory variables.

Analysis of time-to-event data

Time-to-event variables include:

- Time to new onset of DM;
- Time to new onset of AF;

- Time to the composite endpoint events of CV death, total HF hospitalizations, total non-fatal strokes, and total non-fatal myocardial infarctions (MIs).

Time-to-event variables will be analyzed using the Cox proportional hazard model with treatment as a fixed effect factor, stratified by region. The estimated hazards ratio and the corresponding two-sided 95% confidence interval will be provided.

The composite endpoint of CV death, total HF hospitalizations, total strokes, and total MIs will be analyzed using the same proportional rates model used for the primary endpoint. In the component analysis, the four components will be grouped into two components: CV death and the composite of total HF hospitalizations, total strokes, and total MIs.

Analysis of continuous variables

Continuous variables, which are assumed to be normally distributed, are:

- Rate of change (slope) in eGFR from baseline to endpoint;
- Changes in health-related quality of life (assessed by clinical summary score, overall summary score and individual scores of the sub-domains from the KCCQ and scores of the EQ-5D for health status (EQ-5D index derived from EQ-5D descriptive system and EQ-5D VAS) from baseline to pre-defined time-points;
- Changes from baseline to pre-defined time-points in pre-selected biomarkers (e.g., cardiac, vascular, renal, collagen, metabolism, and/or inflammatory biomarkers);
- Days alive out of the hospital during the first 12 months, and during the study duration.
- Change from baseline in MMSE summary score at week 96.

For the rate change in eGFR, the eGFR slope will be estimated from a repeated measures ANCOVA model including treatment, region, time (when the eGFR is assessed in months), and treatment-by-time as fixed effects with random intercept and slope (time) and a common unstructured covariance. The least-squared means of slopes for within and between treatment groups, and the corresponding two-sided 95% confidence intervals will be provided.

Changes from randomized treatment epoch baseline in KCCQ scores, similarly for changes from baseline in EQ-5D VAS and EQ-5D index, will be analyzed based on a repeated measures ANCOVA model in which treatment, region, visit, and treatment-by-visit interaction will be included as fixed-effect factors and baseline value as a covariate, with a common unstructured covariance matrix among visits for each treatment group. Treatment comparisons and effect size estimates at different visits will be provided. The analysis will be performed based on all available data up to 3 years in the FAS and based on likelihood method with an assumption of missing at random for missing data.

KCCQ score obtained at the beginning of treatment run-in epoch is used as the run-in baseline and the analysis of KCCQ changes using a repeated measures ANCOVA model as described above will be repeated again using run-in baseline.

For pre-selected biomarkers, change from baseline to a pre-defined time-point (Week 4 and Month 8) in logarithmic scale will be analyzed using a similar repeated measures ANCOVA model as described above.

For days alive out of the hospital during the first 12 months, it will be treated as a continuous variable. The mean difference between treatment groups will be compared using an ANCOVA model with factors of region and treatment group. Days alive out of the hospital during the study duration will be similarly analyzed as appropriate.

The change from baseline in the summary score of MMSE will be analyzed using a repeated measures ANCOVA model in which treatment, region, baseline hypertension status, baseline diabetes status, visit (Week 48, and Week 96) and treatment-by-visit interaction are included as fixed-effect factors and baseline age, MMSE baseline value and visit by MMSE baseline interaction as covariates, with a treatment-specific unstructured covariance matrix among visits for each treatment group. The adjusted mean changes at week 96 within each treatment, the difference in mean changes at week 96 between two treatments, its 95% confidence interval obtained from the above model will be presented. The analysis will be performed based on all available data up to 96 weeks for patients with both baseline and at least one post-baseline MMSE assessment, and based on likelihood method with an assumption of missing at random (MAR) for missing data. In case that if there is any a problem with model convergence, the factors of baseline hypertension and diabetes status may be dropped from the modeling.

With a total of approximately 2500 patients expected to be eligible for the above analysis, there is more than 90% probability that the lower bound of the 95% confidence interval of the between-treatment difference of mean MMSE summary scores at Week 96 is $\geq$ -0.5 (exclude a between-treatment difference of 0.5 or more reduction), assuming that there is no true between-treatment difference and the common standard deviation is 3. A between-treatment difference of 0.5 or less is not considered clinically meaningful.

To investigate the sensitivity of the analysis results based on the MAR assumption, analyses based on multiple imputations, such as those using a pattern mixture model approach, may be performed, which assumes that missing MMSE scores after death, HF hospitalizations, or stroke were missing not at random (MNAR).

Similar analyses as above will also be performed in the subset of patients who have ApoE4 genotype assessment done.

In addition, changes from baseline in the summary score of MMSE will also be analyzed using a repeated measures ANCOVA model in which treatment, geographic region, baseline hypertension status, baseline diabetes status, visit (Weeks 48, 96, 144, 192, 240), and treatment-by-visit interaction are included as fixed-effect factors, and baseline age, baseline MMSE value and visit by MMSE baseline interaction as covariates, with a common unstructured covariance matrix among visits for each treatment group. Treatment comparisons and effect size estimates and their 95% confidence intervals at different visits (only for visits at Week 48, 96, 144) and averaged over-all-visits will be provided. The analysis will be performed based on likelihood method with an assumption of missing at random for missing data.

Similar repeated measure ANCOVA model will be fitted in the subgroup of patients who have ApoE4 genotype assessment done.

A descriptive summary of MMSE absolute score and change from baseline over time will be tabulated and plotted.

All analyses in MMSE score will be performed in the FAS for patients who have participated in the cognitive function assessment sub-study.

Analyses of categorical and ordinal variables

Binary variables include:

- Indicator of 30 day HF rehospitalization (after a prior in-study HF hospitalization).
- Indicator of KCCQ scores ≥ 5 points change (deterioration or improvement)

Binary variable of 30 day HF rehospitalization will be analyzed using logistic regression with treatment and region as fixed-effect factors. For 30 day hospital readmission, the analysis set will be restricted to patients who had hospitalization for HF at least once during double blind period.

A responder analysis for KCCQ score change from randomized treatment epoch baseline at scheduled visits (defined as patients with at least 5 point change (deterioration or improvement) will be performed using a generalized mixed model with treatment, region, visit, and visit-by-treatment as fixed factors and baseline score as covariate, with a common compound symmetry covariance matrix among visits for each treatment group. Treatment comparisons and effect size estimates at scheduled visits will be provided. The analysis will be performed based on all available data up to Year 3 in the FAS. The goal of the responder analysis is to assess the clinical relevance of the difference between the two groups in the mean change from randomized treatment epoch baseline.

KCCQ score obtained at the beginning of treatment run-in epoch is used as the run-in baseline and the responder analysis of KCCQ as described will be repeated again using run-in baseline.

Ordinal variables include:

- Assessment in the clinical composite assessment (improved, unchanged, and worsened) at post-randomization visits
- Change in NYHA class from randomization
- Changes in HF signs and symptoms from randomization
- Patient global assessment at 8 months

The first three variables will be analyzed, at Month 8, 1 year, 2 years, and 3 years, using a repeated measures proportional cumulative odds model. The model will include patient as a random effect and the randomized treatment phase baseline category (only for NYHA class and HF signs and symptoms), region, treatment, visit (all available post-randomization visits) and treatment-by-visit interaction as fixed effect factors. This model assumes that the treatment effect sizes across measurement categories are the same. The visit-wise effect size estimates and their 95% confidence intervals will also be provided. The analysis will be based on all available data in the FAS and likelihood method with an assumption of missing at random for missing data. The patient global assessment at 8 months will be analyzed similarly but using a non-repeated measures proportional cumulative odds model.

Analysis of count data

Count data include:

- Number of HF events
- Number of worsening HF events or CV deaths
- Number of hospital admissions
- Number of days/stays in ICU
- Number of re-hospitalizations
- Number of ER visits for HF
- Number of 30 day hospital readmissions (after a prior in-study HF hospitalization)

Count variables will be analyzed using a negative binomial model (McCullagh and Nelder 1989) with the count data as the dependent variable and treatment group and region as fixed-effect factors and log(follow-up duration) as the off-set. The model estimated event rates (intensities) and their 95% confidence intervals will be provided by treatment group. The treatment comparison will be performed through the estimated ratio of risk rates. The estimated reduction in event rate (ratio LCZ696/valsartan) and its 95% confidence interval will also be provided. As mentioned before, for 30 day hospital readmission, the analysis set will be restricted to patients who had hospitalization for HF at least once during double blind period. This implies that the baseline treatment group balance obtained from the randomization may be broken.

Subgroup of ACEI intolerant patients

The primary and secondary variables as well as the symptom based variables, such as the NYHA class, clinical composite assessment, and so on, will also be analyzed using methods proposed above for the sub-group of ACEI intolerant patients.

9.5.3 Safety variables

The safety and tolerability assessments are listed below:

- Identified and potential risks
- AEs and SAEs
- Sitting systolic, diastolic BP, and pulse pressure
- Heart rate
- Symptomatic hypotension
- Angioedema
- Hyperkalemia
- Renal dysfunction
- Other relevant laboratory values
- ECG changes

The assessment of safety will be based primarily on the frequency of AEs, SAEs, and laboratory abnormalities. Other safety data will be summarized as appropriate.

The incidence of treatment-emergent AEs (new or worsened) will be summarized by primary system organ class, preferred term, severity, and relationship to study drug. In addition, the

incidence of death, SAEs, and AEs leading to discontinuation will be summarized separately by primary system organ class and preferred term.

The incidence of AEs related to the identified and potential risks will be summarized by SMQ preferred terms.

Laboratory data will be summarized by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (mean, medians, standard deviations, ranges) and by the flagging of notable values in data listings. LFT categorical analysis will also be provided.

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

Safety analyses will be performed based on the safety set. There will be no formal statistical inference analysis.

9.5.4 Resource utilization

Data relating to resource utilization will be used for the purpose of economic evaluation which will be carried out and reported as a separate activity.

9.5.5 Health-related Quality of Life

The reduction in combination of HF symptoms and physical limitation scores assessed by the clinical summary score of the KCCQ and the other KCCQ sub-domains will all be analyzed using a repeated measures ANCOVA model. Within treatment group and between treatment groups comparisons will all be conducted based on this model.

Assessments of EQ-5D VAS and EQ-5D index will also be analyzed similarly.

9.5.6 Pharmacokinetics

Steady-state PK time profile of valsartan, AHU377, and LBQ657 will be analyzed by graphical methods to determine the appropriate structural PK model to fit the data. Following this, a population PK model will be developed using the plasma time profile patient-level data from this study and/or in combination with PK data from other studies with LCZ696 to quantify the PK of valsartan, AHU377, and LBQ657 and test for significant covariates that influence their PK.

9.5.7 Pharmacogenetics

The exploratory pharmacogenetic studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Alternatively, if the number of subjects enrolled in the study is too small to complete proper statistical analyses, these data may be combined, as appropriate, with those from other studies to enlarge the data set for analysis.

9.5.8 Pharmacogenomics

The analysis of pharmacogenomic data (miRNA) will be performed by the Biomarker Development group. Quality control of all individual samples and molecular data will be

conducted. The analysis of genomic data per se will be assisted by the use of "in house' and commercial expert applications and databases. A range of statistics based approaches will be applied to the data.

9.5.9 Biomarkers

NT-proBNP will be collected in all patients at Visits 1, 101/102 (whichever occurs first), 103, 199/201, 203 and 205. Additional biological markers will be collected in a subset of patients. For the FAS, summary statistics by treatment group will be performed for the baseline values, the post-baseline values, and the change from baseline, with biomarker baseline defined as values at Visit 101 or 102, whichever occurs first.

9.6 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 1231 of adjudication-confirmed composite of hospitalizations for HF and CV death. In the interim analysis, the analysis dataset will comprise all patients who were randomized before the cutoff date. Bonferroni multiplicity adjustment will be adopted for the statistical comparisons between treatments. An alpha of 0.001 (one-sided alpha) will be spent for the comparison of primary endpoint at the interim analysis and the rest of alpha (one-sided 0.024 for the current specified boundary) will be utilized for it at the final analysis. In the interim analysis, the study may be stopped for superior efficacy only when the primary endpoint and CV death both are significant at level of 0.001 (one-sided).

If the study is stopped early for claiming superior efficacy at the interim analysis, the secondary endpoints will be tested using the same hierarchical testing procedure as described before with an overall alpha level used for the primary endpoint at the interim analysis (one-sided alpha of 0.001 for the current specified boundary).

Interim safety assessments are planned to be performed every six months. No further alpha adjustment will be made for these interim safety assessments.

Interim analyses will be performed by an independent statistician who will not be involved in the trial conduct. The results will be reviewed by the independent DMC.

9.7 Sample size calculation

9.7.1 Sample size for the primary analysis

Sample size is calculated through simulations for the proportional rates model. The control group rate of total hospitalizations for HF and rate of mortality are estimated in two steps in order to get a reasonable estimate for the selected patient population.

First we estimate the rates from the candesartan group of the CHARM-Preserved study (Yusuf et al 2003) for patients with EF $\geq$45%, using a joint model that joins the Poisson regression model and the exponential regression model together through a shared gamma frailty (Cowling et al 2006). An independent uniform censoring on the events are assumed during the follow-up. With the given frailty between HF hospitalization and CV death, the

estimated baseline intensity in the Poisson model= 0.00032 HF hospitalizations/day per patient and the estimated hazard rate in the exponential model = 0.000136 CV deaths/day per patient. The estimated gamma shape parameter (the frailty parameter that is also assumed to be 1/scale) is 0.193. These specified parameter values produce approximately an annualized rate of 0.083 for time to first primary event and an annualized rate of 0.036 for CV mortality.

Second, we adjust these estimated rates up by 8% (and then increasing the corresponding Poisson intensity rate and hazard rate) based on the results from the recent completed HF studies and publications, which are believed to reflect a higher risk patient population than that in the CHARM-Preserved study. This leads an annualized rate of 0.09 for time to first primary event and an annualized rate of 0.04 for CV mortality for a high risk patient population.

The target reduction in RR for the primary endpoint is chosen to be about 22%, which approximately corresponds to a reduction of 30% for HF hospitalization and a reduction of 10% for CV death, given the gamma frailty defined above between these two components. With the CHARM-Preserved data structure for EF ≥45%, the specified rates will produce an approximately 15% reduction for time-to-first event analysis, see Table 9-1.

The patient enrollment is assumed to be uniform lasting 2 years and 5 months and the minimum follow-up is to be 2 years and 2 months.

In Table 9-1, sample sizes and powers are estimated through simulations for the framework defined above. Three thousand trial replicates are generated for each scenario with different sample sizes in the simulations. Both the power and type I error rate are estimated for the selected proportional rates model (LWYY). For our study, with a one-sided alpha level of 0.025, a total of 4600 patients will provide more than 90% of power for the LWYY method. This will require approximately 1847 primary events (see the row in table below with sample size = 4600 and HR = 0.9 and RR = 0.7). The type I error rates were preserved well in the cases we examined.

Table 9-1 Sample size and power estimations through simulations

Sample size	Simulation specs		Expected no. of composite events	Estimated HR or RR		Power
	HR for death	RR for total hosp for HF		Time to 1st composite event	LWYY	LWYY
4600	0.9	0.7	1847	0.859	0.778	0.95
		0.75	1882	0.881	0.814	0.85
	1.0	0.7	1846	0.876	0.784	0.94
		0.75	1885	0.900	0.822	0.82

3000 simulation runs were performed for each scenario.

9.7.2 Sample size re-estimation

A blinded sample size re-estimation will be considered around the time at the efficacy interim analysis. The pooled intensity/hazard rates for hospitalization for HF and CV death will be

estimated using the same joint shared-gamma-frailty model (with one treatment group) used for the simulations for the sample size calculations in the above sections. The differences between the model parameter estimates used for the sample size calculations and the new ones obtained in the interim analysis will then be evaluated. Sample size simulations based on the new estimates will be performed using the same assumptions used in the initial sample size calculations. The new sample size and/or the duration of follow up will be determined based on the new simulations in order to preserve the target power and to achieve the required number of events in an acceptable timeframe.

9.7.3 Powers for the secondary analyses

9.7.3.1 Power for change in KCCQ clinical summary score at 8 months

For the change from randomized treatment epoch baseline to Month 8 in clinical summary score assessed by KCCQ, the planned sample size will provide 83% power to detect a treatment difference of 2 points at the two-sided significance level of 0.05, assuming a standard deviation of 22 (observed in PARADIGM study). This estimation has taken into consideration that approximately 10% of patients may be excluded from analysis due to no KCCQ assessment done, based on PARADIGM experience.

9.7.3.2 Power for NYHA class

From the PARAMOUNT (CLCZ696B2214) study, which is the phase II pilot study with a similar HFpEF population, after 9 months of treatment with valsartan, the incidence rates in each category distribute as follows in Table 9-2.

Table 9-2 PARAMOUNT NYHA incidence rates

	LCZ696				Valsartan			
	Baseline	Class I	Class II	Class III/IV	Baseline	Class I	Class II	Class III/IV
Class I	1 (0.8)	0 (0.0)	1 (100.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (100)	0 (0.0)
Class II	100 (78.7)	**16 (16.0)**	80 (80.0)	4 (4.0)	102 (81.6)	**9 (8.8)**	89 (87.3)	4 (3.9)
Class III	26 (20.5)	0 (0.0)	**13 (50.0)**	13 (50.0)	22 (17.6)	0 (0.0)	**8 (36.4)**	14 (63.6)

From this table, there are approximately 7% of patients (16/100=16% vs. 9/102=8.8%) within class II and 14% of patients (13/26=50% vs. 8/22=36.4%) in class III improved from baseline to 9 months endpoint in LCZ696 compared with valsartan.

Our power evaluation is based on this data and takes the incidence rates in valsartan group as the rates in the comparator group. A one-sided alpha of 0.025 is used to control the type I error. Table 9-3 shows powers for a sample size of 4600 patients.

Table 9-3 Powers for NYHA class comparisons

	Improved from Baseline to endpoint in Class III			
Improved from baseline to endpoint in Class II	10%	12%	14%	16%
5%	98%	99%	99%	>99%
7%	>99%	>99%	>99%	>99%

	Improved from Baseline to endpoint in Class III			
9%	>99%	>99%	>99%	>99%

The results in this table are based on simulations with 100000 replicates.

9.7.3.3 Power for composite renal endpoint

With an expected hazard reduction of 30% (LCZ696 over valsartan) in composite renal endpoint, an annual first occurrence of renal events rate of 0.63% (or 1%), an average follow-up of 3.375 years, and a two-sided alpha of 0.05, forty-six hundred patients will provide a power of 36% (or 52%). When the hazard reduction is about 35%, forty-six hundred patients will provide a power of 47% (or 66%) when the annual event rate is 0.63% (or 1%). Note that the power provided here is conditional power, when the null hypotheses for the primary endpoint, the secondary endpoints of KCCQ change and NYHA class change at month 8 are all rejected.

The power estimations are mainly based on data observed from recently completed PARADIGM-HF trial. In that trial, the observed annual event rate for composite renal endpoint is 0.63% and the hazard reduction of LCZ696 over enalapril is 37%.

9.7.3.4 Power for all-cause mortality

With a reduction of 20% in mortality, an annual all-cause mortality rate of 5% (25% increase from CV mortality), an average follow-up of 3.375 years, and a two-sided alpha of 0.05, forty-six hundred patients will provide a power of 81%. When the reduction is about 15%, forty-six hundred patients will provide a power of 56%.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 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/Research Ethics Board (IRB/IEC) approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should 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 (i.e., all of the procedures described in the

protocol). The process of obtaining informed consent should be documented in the patient 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 should be informed that taking the study drug 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 should not be entered in the study.

This study includes an optional pharmacogenetic and pharmacogenomic component which requires a separate signature if the patient agrees to participate. It is required as part of this protocol that the Investigator presents this option to the patient at all participating sites where this component of the study is conducted. The process for obtaining informed consent should be exactly the same as described above for the main informed consent.

Declining to participate in pharmacogenetic and/or pharmacogenomic assessments will in no way affect the patient's ability to participate in the main research study.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or ethics committee approval will be obtained.

10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. 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 Clinical 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

Novartis assures that 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.

11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as requests to approve deviations will not be granted.

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

If the 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 it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

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. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. 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, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days or less, if required by local regulations.

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13 Appendix 1: Clinically notable laboratory values

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

14 Appendix 2: Liver event definitions and follow-up requirements

Table 14-1 Liver event definitions

	Definition/ threshold
AE of special interest	
Laboratory values	ALT or AST > 3 x ULN ALP > 2 x ULN TBL > 1.5 x ULN
Medically significant event	

(SAE)	
Laboratory values	ALT or AST > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction])
	ALP > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction])
	TBL > 3 x ULN
	Potential Hy's Law cases (defined as ALT/AST > 3 x ULN and TBL > 2 x ULN [mainly conjugated fraction] without notable increase in ALP to > 2 x ULN)
AEs	Any clinical event of jaundice (or equivalent term)
	ALT or AST > 3 x ULN accompanied by general malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any event that links to a preferred term (PT) in the MedDRA dictionary falling under the SMQ sub-module "Drug-related hepatic disorders – severe events only"* or any "Hy's law case" PT

* 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

Table 14-2 Liver event follow up requirements

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

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

Criteria	Event type	Actions required	Follow-up monitoring
disorders - severe events only" SMQ AE		appropriate Report to Novartis as an SAE Establish causality	

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

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

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

15 Appendix 3: Treatment guidelines for hyperkalemia (serum potassium greater than or equal to 5.3 mmol/L [mEq/L])

General principles

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

Any patient with a serum potassium > 5.3 mmol/L (mEq/L) at any time after randomization requires the Investigator to confirm the 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 potassium concentration (beyond that prescribed in the protocol) should continue until it is clear that the potassium concentration is stable and not rising into the range of concern (≥ 5.5 and < 6.0 mmol/L [mEq/L]) or potential danger (≥ 6.0 mmol/L [mEq/L]).

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

Corrective action for management of hyperkalemia

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

- Confirm potassium concentration in a non-hemolyzed sample
- Reinforce low potassium diet and restriction of food/drinks with high potassium content (e.g. orange juice, melon, bananas, 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:
    - MRAs (if they are believed to be the most likely cause of hyperkalemia)
    - Potassium-sparing diuretics (e.g. amiloride and triamterene) including in combination products with thiazide or loop diuretics
    - Potassium supplements, e.g., potassium chloride
    - Salt substitutes

- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Cyclo-oxygenase-2 (COX-2) inhibitors
- Trimethoprim and trimethoprim-containing combination products, such as 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 potassium concentration in a non-hemolyzed sample
- Consider down-titration or temporarily discontinue study drug according to investigator medical judgment.
- Apply all measures outlined for serum potassium > 5.3 and ≤ 5.5 mmol/L
- Repeat serum potassium measurement after 2-3 days
- If serum potassium < 5.5 mmol/L, consider resumption of study drug at lower dose with repeat potassium within 5 days

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

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

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

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 antihypertensive drug such as diuretics, calcium channel blockers (CCBs), nitrates, beta blockers, aldosterone antagonists and α-blockers, should be down-titrated or stopped first before down-titration of the study drug is considered. Any non-antihypertensive drug (such as nitrates) should be considered for down-titration prior to study drug as determined by the best judgment of the investigator.

c. 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: Guidelines for the management of renal dysfunction

General principles:

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

Two types of response to serum creatinine increase are described:

Surveillance situation

If, at any time after randomization, eGFR decreases by ≥25% from baseline (Visit 1) (or if serum creatinine concentration increase to 2.5 mg/dL [221 µmol/L]), the investigator will check for potentially reversible causes of renal dysfunction such as:

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

Action situation

If a patient's eGFR decreases by ≥40% from baseline (Visit 1) (or if serum creatinine concentration rises above 3 mg/dL (265µmol/L), the investigator will check for potentially reversible causes of renal dysfunction (see above).

The investigator may consider down-titration of study drug. If the investigator judges that study drug has to be stopped, he/she will have to contact the Novartis medical monitor or his/her designee. Thereafter, serum creatinine assessments will have to be repeated at least

each week until levels return to acceptable values. If study drug was stopped, every effort will be done to restart it again, according to clinical conditions.

18 Appendix 6: Blood log for PK sample collection

Visit	Visit name	Timepoint	Volume	Sample Number	Dose reference ID
199	Treatment run in	Predose	2 mL	1	1
203[a]	Week 16	0 hours pre-dose	2 ml	2	2
203[b]	Week 16	0.5 - 2 hours post-dose	2 ml	3	2
203[c]	Week 16	3-5 hours post-dose	2 ml	4	2
205[a]	Week 48	0 hours pre-dose	2 ml	5	3
205[b]	Week 48	0.5 - 2 hours post-dose	2 ml	6	3
205[c]	Week 48	3 - 5 hours post-dose	2 ml	7	3

a, b, c: If the samples are not collected at Visit 203, the samples at the same time points can be collected at Visit 205