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LCZ696/Entresto®

Clinical Trial Protocol CLCZ696D2302

A 24-week, randomized, double-blind, multi-center, parallel group, active controlled study to evaluate the effect of LCZ696 on NT-proBNP, exercise capacity, symptoms and safety compared to individualized medical management of comorbidities in patients with heart failure and preserved ejection fraction

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List of abbreviations

6MWD	six-minute walk distance
6MWT	six-minute walk test
ACE	angiotensin converting enzyme
ACEi	angiotensin converting enzyme inhibitor
ACR	Albumin-creatinine ratio
AE	adverse event
AF	atrial fibrillation and atrial flutter
ALB	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANP	atrial natriuretic peptide
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
AST	aspartate aminotransferase
AT_1	angiotensin type 1
AUC	area under curve
B6MWD	baseline six-minute walk distance
BCSS	baseline clinical summary score
bid	twice a day
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
bpm	beats per minute
BMSS	baseline SF-36 mental component summary score
BPSS	baseline SF-36 physical component summary score
BSBP	baseline systolic blood pressure
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCB	calcium channel blocker
CFR	US Code of Federal Regulations
cGMP	cyclic guanosine monophosphate
CNP	C-type natriuretic peptide
CNS	central nervous system
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

CSS	clinical summary score
CV	cardiovascular
DBP	diastolic blood pressure
DM	diabetes mellitus
DMC	data monitoring committee
DS&E	drug safety & epidemiology
EC	ethics committee
ECG	electrocardiogram
echo	echocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EF	ejection fraction
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	end of study
ER	emergency room
ESC	European Society of Cardiology
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HA	Health Authority
hCG	human chorionic gonadotropin
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HfrEF	heart failure with reduced ejection fraction
Hgb	hemoglobin
HTN	hypertension
IA	interim analysis
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IN	investigator notification
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine system
iv	intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	left atrial
LAE	left atrial enlargement

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LFT	liver function test
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MAR	missing at random
MCHC	mean corpuscular hemoglobin concentration
MCS	mental component summary
MCV	mean corpuscular volume
MDRD	Modification in Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMRM	mixed model for repeated measures
MRA	mineralocorticoid antagonist
NEP	neprilysin
NEPi	neprilysin inhibitor
NP	natriuretic peptide
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PCR	protein-creatinine ratio
PCS	physical component summary
PDE-5	phosphodiesterase-5
PPS	per protocol set
PSD	premature study discontinuation
QoL	quality of life
RAS	renin angiotensin system
RASi	renin angiotensin system inhibitors
RBC	red blood cell
RDW	red blood cell distribution width
RoW	Rest of the World
SAE	serious adverse event
SAF	safety
SBP	systolic blood pressure
SF-36	The Short Form (36) Health Survey
SUSAR	suspected unexpected serious adverse reactions
TBL	total bilirubin
ULN	upper limit of normal
US	United States
WHO	World Health Organization
WoC	withdrawal of consent

Glossary of terms

Cohort	A specific group of patients/subjects fulfilling certain criteria
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug(s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

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Withdrawal of informed consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

Protocol summary

Protocol number	CLCZ696D2302
Full title	A 24-week, randomized, double-blind, multi-center, parallel group, active controlled study to evaluate the effect of LCZ696 on NT-proBNP, exercise capacity, symptoms and safety compared to individualized medical management of comorbidities in patients with heart failure and preserved ejection fraction
Brief title	A randomized, double-blind controlled study to evaluate the effect of LCZ696 compared to individualized medical therapy for comorbidities in HFpEF patients
Sponsor and clinical phase	Novartis, Phase 3
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to demonstrate superiority of LCZ696 over individualized medical therapy for comorbidities in reducing N-terminal pro-brain natriuretic peptide (NT-proBNP) and improving exercise capacity and symptoms and QOL in patients with heart failure with preserved ejection fraction (HFpEF).
Primary objective(s)	The primary objectives of this study are • To demonstrate that LCZ696 is superior to individualized medical therapy for comorbidities in reducing NT-proBNP from baseline after 12 weeks of treatment • To demonstrate that LCZ696 is superior to individualized medical therapy for comorbidities in improving exercise capacity as assessed by the six-minute walk test (6MWT) at Week 24 in a subset of patients
Secondary objectives	To compare LCZ696 to individualized medical therapy for comorbidities on: • Mean change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score (CSS) at Week 24 • Proportion of patients with ≥ 5-points change in KCCQ clinical summary score at Week 24 (separate analyses for ≥ 5-points improvement and ≥ 5-points deterioration) • Improvement in New York Heart Association (NYHA) functional class at Week 24 • Improvement in symptoms as assessed by The Short Form (36) Health Survey (SF-36) physical component summary (PCS) score at Week 24
Study design	This study is a 24-week, randomized, double-blind, multi-center, parallel group, active controlled study to evaluate LCZ696 compared to individualized medical therapy on NT-proBNP, exercise capacity, and symptoms in patients with HF and preserved left ventricular ejection fraction (LVEF >40%)

Population	Approximately 2500 patients ≥ 45 years with symptomatic HF (NYHA class II-IV), preserved ejection fraction (LVEF>40%), documented structural heart disease and KCCQ CSS < 75 will be randomized.
Key inclusion criteria	1. Written informed consent must be obtained before any assessment is performed 2. ≥ 45 years of age, male, or female 3. LVEF >40% by echocardiography performed within 6 months prior to Visit 1 or during the screening epoch 4. Symptom(s) of HF requiring treatment with diuretic(s) (including loop or thiazide diuretics, or mineralocorticoid antagonist (MRAs) 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 demonstrated by echocardiographic evidence of left atrial enlargement (LAE) or left ventricular hypertrophy (LVH) as defined below (any local measurement made during the screening epoch or within the 6 months prior to Visit 1): a. LAE 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. LVH defined by septal thickness or posterior wall thickness ≥1.1 cm 7. Receiving evidence based therapy for relevant comorbidities as determined by the individual clinical profile of the patient (eg age and number and type of comorbidities) with stable doses for the previous four weeks prior to randomization 8. NT-proBNP > 220 pg/mL for patients with no atrial fibrillation/atrial flutter (AF) or > 600 pg/mL for patients with AF on the Visit 1 electrocardiogram (ECG) 9. KCCQ CSS < 75 at Visit 1 10. Patients on angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) therapy must have a history of HTN
Key exclusion criteria	1. Any prior echocardiographic measurement of LVEF ≤ 40%, under stable conditions 2. Acute coronary syndrome (including myocardial infarction [MI]), cardiac surgery, other major cardiovascular (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 (eg MI, coronary artery bypass graft [CABG]), unless an echo measurement was performed after the event confirming the LVEF to be > 40% 4. Current (within 30 days from visit 1) acute decompensated HF requiring augmented therapy with diuretics, vasodilators and/or inotropic drugs 5. Current (within 30 days from visit 1) use of renin inhibitor(s), dual RAS blockade or LCZ696 6. History of hypersensitivity to LCZ696 or its components

	7. Patients with a known history of angioedema 8. Walk distance primarily limited by non-cardiac comorbid conditions at Visit 1 9. Probable alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms (ie 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) (ie 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 males and < 9.5 g/dL females **or** c. body mass index (BMI) > 40 kg/m^2 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, MRA, ACEi, ARB, beta blocker and calcium channel blocker (CCB), **or** c. SBP < 110 mmHg or symptomatic hypotension at Visit 1 11. Patients with HbA1c > 7.5% not treated for diabetes 12. Patients with history of any dilated cardiomyopathy, including peripartum cardiomyopathy, chemotherapy induced cardiomyopathy, or viral myocarditis 13. Evidence of right sided HF in the absence of left-sided structural heart disease 14. Known pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy 15. Clinically significant congenital heart disease that could be the cause of the patient's symptoms and signs of HF 16. Presence of hemodynamically significant valvular heart disease in the opinion of the investigator 17. Stroke, transient ischemic attack, carotid surgery or carotid angioplasty within the 3 months prior to Visit 1 18. Coronary or carotid artery disease or valvular heart disease likely to require surgical or percutaneous intervention during the trial 19. Life-threatening or uncontrolled arrhythmia, including symptomatic or sustained ventricular tachycardia and atrial fibrillation or flutter with a resting ventricular rate > 110 beats per minute (bpm) 20. Patients with a cardiac resynchronization therapy (CRT) device 21. Patients with prior major organ transplant or intent to transplant (ie on transplant list) 22. 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 23. Evidence of hepatic disease as determined by any one of the following: SGOT (AST) or SGPT (ALT) values exceeding 3 × the upper limit of normal (ULN), bilirubin > 1.5 mg/dl at Visit 1 24. Patients with eGFR < 30 mL/min/1.73 m^2 as calculated by the Modification in Diet in Renal Disease (MDRD) formula at Visit 1 25. Patients with serum potassium > 5.2 mmol/L (or equivalent plasma potassium value) (mEq/L) at Visit 1 26. History or presence of any other disease with a life expectancy of < 3 years 27. 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 1 year, regardless of whether there is evidence of local recurrence or metastases; as well as, patients with any planned treatment for malignancy 28. 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
Study treatment	LCZ696 50 mg bid (dose level 1), 100 mg bid (dose level 2), 200 mg bid (dose level 3) Enalapril 2.5 mg bid (dose level 1), 5 mg bid (dose level 2), 10 mg bid (dose level 3) Valsartan 40 mg bid (dose level 1), 80 mg bid (dose level 2), 160 mg bid (dose level 3)
Efficacy assessments	• NT-proBNP • 6MWT • KCCQ • NYHA functional classification • SF-36
Key safety assessments	• Adverse event monitoring • Physical examinations • Laboratory values (including monitoring for hyperkalemia, renal dysfunction) • ECG changes • Angioedema surveillance
Data analysis	The following primary null hypotheses will be included in the testing strategy. • H_1: LCZ696 is no better than the comparator in change from baseline in log(NT-proBNP) at Week 12 in the overall study population • H_2: LCZ696 is no better than the comparator in change from baseline in 6MWD at Week 24 in patients with baseline six-minute walk distance (B6MWD) ranging from 100 meters to 450 meters.

[redacted]

	The following secondary null hypotheses will be included in the testing strategy. • H_3: LCZ696 is no better than the comparator in change from baseline in KCCQ clinical summary score (CSS) at Week 24 in the overall study population. • H_4: LCZ696 is no better than the comparator in NYHA change from baseline at Week 24 in the overall study population. Each null hypothesis is tested against the one-sided alternative that LCZ696 is better than the comparator in the corresponding variable. In order to control the family-wise type-I error rate at the one-sided 0.025 significance level, a sequentially rejective multiple testing procedure based on the graphical presentation (Bretz et al 2009) will be employed, whereby the testing procedure is graphically illustrated in Figure 9-1. Based on the above testing procedure, if applicable, H_1, H_2 and H_3 will be tested based on the corresponding MMRM models (Section 9.4.2, Section 9.5.1.1), and H_4 will be tested based on the longitudinal proportional cumulative odds model (Section 9.5.1.3). If statistical significance had been established in the mean difference in change from baseline to Week 24 for KCCQ CSS, the following responders will be analyzed accordingly, based on the longitudinal binary logistic regression models (Section 9.5.1.1), to further illustrate the clinical relevance of the observed differences in terms of proportion of responders. • KCCQ CSS improvement (defined by at least 5 points improvement); • KCCQ CSS deterioration (defined by at least 5 points deterioration); No multiplicity adjustment will be done for these supportive responder analyses (i.e., the tests for the responder analyses will be performed at nominal level of one-sided 0.025).
Key words	Heart failure with preserved ejection fraction, exercise capacity, symptoms, NT-proBNP, 6MWD, 6MWT, KCCQ, NYHA, SF-36

[redacted]

Amendment 2

Amendment rationale

The completed study CLCZ696B2314 (PARADIGM-HF) targeted patients with HF and reduced ejection fraction (EF ≤ 40%). Two ongoing studies (PARAGON and PARALLAX), and one completed phase 2 study (PARAMOUNT) in patients with HF and preserved ejection fraction include patients with EF ≥ 45%. Therefore, this amendment will expand the EF inclusion criteria from current ≥45% to >40% in order to ensure that the LCZ696 clinical development program will cover the full EF spectrum.

Due to the increasing importance of generating exercise capacity data in the HFpEF population, this amendment elevates change in six-minute walk distance (6MWD) to a primary endpoint. The primary analysis was selected to be performed in a sub-set of patients with baseline six-minute walk distance (B6MWD) ranging from 100 meters to 450 meters. Similar criteria was used in other HF studies (Abraham et al 2002, Abraham et al 2015, Redfield et al 2015 and Palau et al 2016).

The amendment also includes a strategy for the multiplicity testing of the primary and secondary efficacy endpoints, as agreed with major Health Authorities.

An additional 300 patients will be enrolled to ensure that patients with LVEF >40% are represented in CLCZ696D2302 study population without jeopardizing or compromising any key study objective or assessment, which have previously been agreed upon with key external stakeholders.

Changes to the protocol

The main changes in this amendment are:

1. To expand the EF inclusion criteria from the current ≥ 45% to > 40%
2. To increase sample size from current 2,200 to 2,500 patients.
3. To elevate change in 6MWD as a primary endpoint in a subset of patients and remove it as a secondary endpoint
4. To include a testing strategy of the primary and secondary efficacy variables in the multiple testing procedure to control the family-wise Type-I error rate.
5. To provide clarifications, both on the patient profile and the study design; as well as, making editorial changes.

   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. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval of a revised Informed Consent that takes into account the changes described in this amended protocol.

[redacted]

Amendment 1

Amendment rationale

The purpose of this amendment is to correct a typographic error in the original protocol (version 00). In the original protocol, the eGFR exclusion criteria appeared as eGFR < 15 ml/min/1.73m^2. The correct eGFR exclusion criteria for the study is eGFR < 30 ml/min/1.73m^2. This has been corrected in this version of the protocol. In addition, minor clarifications have been added to List of abbreviations, Figure 3-1, Table 3-3 and the footnotes of Table 6-1.

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.

This version of the protocol will be used for submission to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

[redacted]

1 Introduction

1.1 Background

Heart failure (HF) is a major public health problem associated with a high mortality rate, frequent hospitalizations, and poor quality of life (QoL). Despite existing treatment options, HF remains a progressive syndrome with a high mortality rate, and an illness with an unmet need for new therapies to improve health outcomes (McMurray et al 2012).

Heart failure has been shown to occur with either reduced systolic function or preserved systolic function. HF with normal ejection fraction (EF) has been designated HF with preserved ejection fraction (HFpEF). HFpEF accounts for approximately half of HF cases, and is associated with substantial morbidity, mortality and deteriorated QoL (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 (CAD) (Lenzen et al 2004).

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 (Tan et al 2009, Tartière-Kesri et al 2012). 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).

Unlike HFrEF, there is no proven pharmacologic therapy for patients with HFpEF (McMurray et al 2012). All four major outcomes trials (PEP-CHF, perindopril; CHARM-Preserved, candesartan; I-PRESERVE, irbesartan; TOPCAT, spironolactone) have failed to convincingly show a clinical benefit in HFpEF (Yusuf et al 2003, Cleland et al 2006, Massie et al 2008, Pitt et al 2014). Since no treatment has yet been shown convincingly to reduce morbidity or mortality in patients with HFpEF, the current focus is to alleviate symptoms and improve well-being. This has been reiterated in the latest European Society of Cardiology (ESC) guidelines (Ponikowski et al 2016). Consequently, guidelines focus on treating symptoms with diuretics and treating comorbid conditions, such as diabetes mellitus (DM), HTN, renal insufficiency, AF and CAD, which are common in HFpEF patients (Hunt et al 2005, McMurray et al 2012).

LCZ696 is a first-in-class, angiotensin receptor neprilysin inhibitor (ARNI). Neprilysin (NEP) degrades biologically active natriuretic peptides (NPs), including atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). LCZ696, through its dual mode of action potentiates natriuretic peptides (NPs) via NEP inhibition while inhibiting the renin angiotensin system (RAS) via angiotensin type 1 (AT_1) receptor blockade; both mechanisms are considered to act in a complementary and additive manner to improve survival in patients with chronic heart failure. Consistent with the theorized mechanism of action, LCZ696 was shown to be superior to enalapril in reducing cardiovascular deaths and hospitalization in patients with chronic heart failure with reduced ejection fraction in the completed PARADIGM-HF trial. In addition, as compared with enalapril, LCZ696 significantly decreased the symptoms and physical limitations of heart failure assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score (CSS), and

reduced total HF hospitalization, all cause hospitalization and emergency room (ER) visit. LCZ696 is approved globally including the United States (US) and European Union (EU) for the treatment of HFrEF with the trade name ENTRESTO.

The mechanism of action of LCZ696 also suggests that LCZ696 may impact the suspected pathophysiology of HFpEF, in which it is believed that excessive fibrosis and myocyte hypertrophy lead to abnormal left ventricular diastolic filling, impaired diastolic distensibility and/or increased vascular stiffness, with consequent elevated cardiac filling pressures (Krum and Abraham 2009). It was recently reported that patients with HFpEF have lower levels of myocardial cyclic guanosine monophosphate (cGMP) concentration (and lower protein kinase G activity) compared with patients with HFrEF or patients with aortic stenosis (van Heerebeek et al 2012). Therefore, enhancing NP action seems a reasonable potential therapeutic option. By augmenting the active NPs, neprilysin 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-HF (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 demonstrated a 23% greater reduction in NT-proBNP ($p = 0.005$) at 12 weeks (primary endpoint) for LCZ696 compared with valsartan. In addition, the study showed significant improvements in New York Heart Association (NYHA) classification along with greater reductions in all echocardiographic measures of left atrial (LA) size in the LCZ696 group compared with the valsartan group at 36 weeks. LCZ696 is currently being investigated in a phase III clinical outcomes study (PARAGON-HF) to confirm its efficacy in HF patients with preserved EF (left ventricular ejection fraction [LVEF] $\geq 45\%$). No therapy to date has convincingly been shown to reduce morbidity and mortality (Yusuf et al 2003, Cleland et al 2006, Massie et al 2008).

Since HFpEF patients are often elderly and highly symptomatic, and have a poor quality of life, a key goal of therapy is to alleviate symptoms (Ponikowski et al 2016). No therapy other than diuretics has been shown to improve symptoms in this population. This study will evaluate the effect of LCZ696 on NT-proBNP, exercise capacity and symptoms in a large population of HFpEF patients. LCZ696 will be compared to physician individualized therapy for comorbidities and allow patients in the comparator arm to continue on an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB), based upon their prior renin angiotensin system inhibitors (RASi) therapy. This study in approximately 2500 patients will complement the PARAGON-HF outcomes study and represent the largest HF symptoms and exercise data set in HFpEF patients with EF > 40% and help further our understanding of what limits patients with this disease.

1.2 Purpose

The purpose of this study is to demonstrate superiority of LCZ696 over individualized medical therapy for comorbidities in reducing NT-proBNP and improving exercise capacity, symptoms and QoL in patients with HFpEF.

[redacted]

2 Study objectives and endpoints

2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s) • To demonstrate that LCZ696 is superior to individualized medical therapy for comorbidities in reducing NT-proBNP from baseline after 12 weeks of treatment • To demonstrate that LCZ696 is superior to individualized medical therapy for comorbidities in improving exercise capacity as assessed by the six-minute walk test (6MWT) at Week 24 in a subset of patients	**Endpoint(s) for primary objective(s)** • Change from baseline in NT-proBNP (in log scale) at Week 12 • Change from baseline in six-minute walk distance (6MWD) at Week 24
Secondary Objective(s) • To compare LCZ696 to individualized medical therapy for comorbidities on mean change of KCCQ clinical summary score (CSS) at Week 24 • To compare LCZ696 to individualized medical therapy for comorbidities on proportion of patients with ≥ 5-points change in KCCQ CSS at Week 24 (separate analyses for ≥ 5-points improvement and ≥ 5-points deterioration) • To compare LCZ696 to individualized medical therapy for comorbidities in improving NYHA functional class at Week 24 • To compare LCZ696 to individualized medical therapy for comorbidities in improving symptoms as assessed by The Short Form (36) Health Survey (SF-36) physical component summary (PCS) score at Week 24	**Endpoint(s) for secondary objective(s)** • Mean change from baseline in KCCQ CSS at Week 24 • Proportion of patients with ≥ 5-points deterioration in KCCQ CSS at Week 24 • Proportion of patients with ≥ 5-points improvement in KCCQ CSS at Week 24 • Change from baseline in NYHA functional class at Week 24 • Change from baseline in SF-36 PCS score at Week 24
Exploratory Objective(s) • To compare LCZ696 to individualized medical therapy for comorbidities in reducing NT-proBNP at Week 24	**Endpoint(s) for exploratory objective(s)** • Change from baseline in NT-proBNP (in log scale) at Week 24

Objective(s)	Endpoint(s)
• To explore the relative effect of LCZ696 vs individualized medical therapy for comorbidities on renal function as assessed by eGFR at Week 24 • To compare LCZ696 to individualized medical therapy for comorbidities on mean change of KCCQ overall summary score (OSS) at Week 24 • To compare LCZ696 to individualized medical therapy for comorbidities on proportion of patients with ≥ 5 points change in KCCQ OSS at Week 24 (separate analyses for ≥ 5-points improvement and ≥ 5-points deterioration) • To evaluate safety of LCZ696 vs individualized medical therapy for comorbidities	• Rate of change (slope) in eGFR from baseline • Mean change from baseline in KCCQ OSS at Week 24 • Proportion of patients with ≥ 5-points deterioration in KCCQ OSS at Week 24 • Proportion of patients with ≥ 5-points improvement in KCCQ OSS at Week 24 • Frequency of adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities

3 Investigational plan

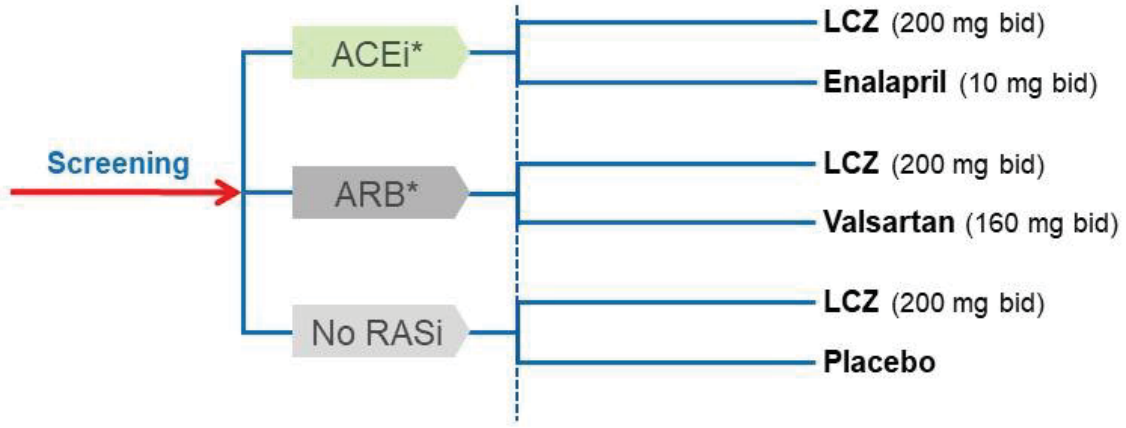
3.1 Study design

This study is a 24-week, randomized, double-blind, multi-center, parallel group, active controlled study to evaluate LCZ696 compared to individualized medical therapy on NT-proBNP, exercise capacity, symptoms and QoL in patients with HF and preserved left ventricular ejection fraction (LVEF > 40%) (Figure 3-1). Patients will be initially stratified into one of three strata according to prior treatment for comorbidities: ACEi, ARB or no RASi. Patients will then be randomized 1:1 to receive either LCZ or comparator. Patients in the ACEi strata will be randomized to receive either LCZ696 or enalapril. Patients in the ARB strata will be randomized to receive either LCZ696 or valsartan, and patients in the no RASi strata will be randomized to receive either LCZ696 or placebo. Patients in the ACEi and ARB strata must have a history of HTN. There will be no designated proportion of patients in each strata, the strata will populate based upon the patient's prior treatment regimen.

A screening epoch of up to 2 weeks will be used to assess eligibility. Patients on appropriate therapy for comorbidities will be eligible for the study. Patients will be required to have been on stable doses of baseline medications for at least four weeks prior to randomization. After randomization, patients will begin a 1 to 4 week study drug up-titration epoch followed by a 20 to 23 week maintenance epoch (Figure 3-1). Visits to assess safety and efficacy are scheduled at 4 to 6 week intervals during the maintenance epoch. The assessment to address the primary objective of reduction in NT-proBNP will be performed using data up to Week 12, and the primary objective of change in 6MWD and all secondary objectives will be performed using data up to Week 24. No interim analysis (IA) is planned.

[redacted]

Figure 3-1 Study design



Screening	Stratified Randomization	Double-Blind Treatment	
Up to 2 weeks	Visit 101	24 weeks	
		Titration	*Maintainance*
		1-4 weeks	20-23 weeks

ACEi = angiotensin converting enzyme inhibitor
ARB = angiotensin receptor blocker
RASi = renin angiotensin system inhibitors
* Patients in the ACEi and ARB strata must have a history of HTN

Screening epoch

At screening (Visit 1), patients will sign the informed consent and be assessed for eligibility for study participation through review of study inclusion/exclusion criteria. Patients enrolled in the study will continue their baseline medication regimen and enter a screening epoch of up to 2 weeks in order to allow adequate time for the completion of all qualifying screening and eligibility evaluations.

Screening NT-proBNP, complete lab evaluations, and pregnancy testing will be assessed by sending samples to the central lab. 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.

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 study drug is dispensed to the patient. No imaging method other than echocardiography will be accepted for inclusion into the study.

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KCCQ questionnaire will be administered at screening to determine eligibility for study (CSS < 75). A 6MWT will be performed at screening in all patients to familiarize patients with the assessment.

A patient who enters screening but is determined not to be eligible 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 once. A minimum of 2 weeks must elapse between screen failure and re-screening.

Randomized treatment epoch

At the randomization visit (Visit 101), all patients who fulfill the inclusion/exclusion criteria will be stratified based upon prior therapy as described above. Subsequent to stratification, patients will be randomized into either the LCZ696 or the comparator treatment group at a 1:1 ratio. Table 3-1 categorizes low and high total daily doses for commonly used ACEis and ARBs. Study drug dose levels are outlined in Table 3-2 and study drug up-titration outlined in Figure 3-2. The goal of treatment is to ensure that each patient receives the maximal tolerated dose of study medication.

ACEis are required to be discontinued 36 hours prior to the randomization visit (Visit 101) to minimize potential risk of angioedema, and ARBs are required to be discontinued at the randomization visit. With the exception of ACEi, ARB or renin inhibitor, patients will continue on their prior medication for the treatment of comorbidities. All patients must be on stable doses of appropriate therapy for comorbidities for at least 4 weeks prior to enrollment.

For patients who are not currently treated with ACEi/ARB, the starting dose should be dose level 1 for LCZ696. Those patients previously treated with low dose of ACEi/ARB (Table 3-1) should be initiated at dose level 1 for LCZ696, enalapril and valsartan. For patients previously treated with high dose RASi, the starting dose is dose level 2 for LCZ696, enalapril and valsartan. The target dose for LCZ696 is 200 mg bid, for enalapril is 10 mg bid and for valsartan 160 mg bid (dose level 3). However, maximal doses for study medication will be determined by the investigator based upon the patient's clinical status. It is recommended that patients remain at each dose level during up-titration for 1 to 2 weeks such that patients initiated at dose level 1 reach target dose in 2 to 4 weeks and those patients initiated at dose level 2 reach target dose in 1 to 2 weeks. In certain circumstances, longer up-titration periods may be required as deemed necessary by the investigator. Patients must meet the safety criteria (Table 3-3) before initiation of study drug and prior to any up-titration.

Patients will remain at the target dose (dose level 3) for the remainder of the study. If patients cannot tolerate the target dose of study medication (dose level 3), down titration to a lower dose is allowed (see Section 5.5.5). Patients should be re-challenged to the target dose of study medication when their condition permits up-titration based on their systolic blood pressure (SBP), eGFR, potassium values, and at the investigator's discretion. However, patients can remain at low doses (level 1 or 2), based on their tolerability and clinical judgment of the investigator.

The duration of the double-blind treatment period is 24 weeks.

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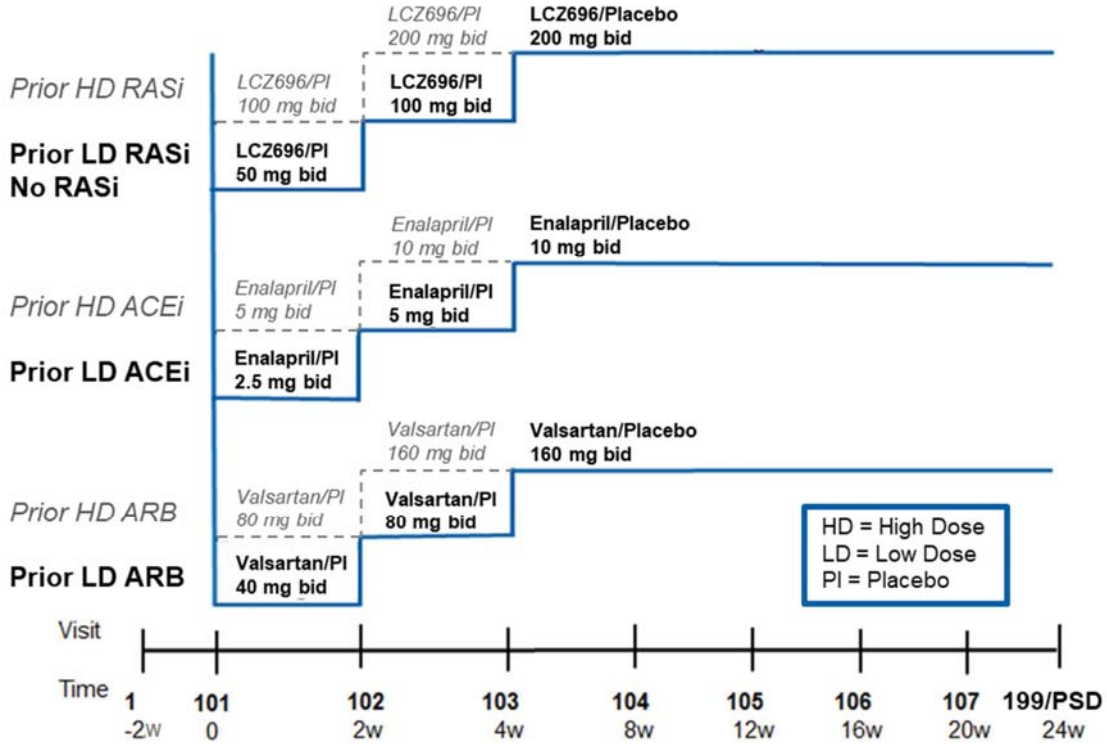
Figure 3-2 Study drug up-titration



ACEi = angiotensin converting enzyme inhibitor
ARB = angiotensin receptor blocker
RASi = renin angiotensin system inhibitors
TD = study treatment discontinuation
PSD = premature study discontinuation

Table 3-1 Definition of low and high total daily doses for commonly used ACEis and ARBs

Study medication	Low RASi stratum	High RASi stratum
ACEis		
Enalapril	≤ 10 mg	> 10 mg
Benazepril	≤ 20 mg	> 20 mg
Captopril	≤ 100 mg	> 100 mg
Cilazapril	≤ 2.5 mg	> 2.5 mg
Delapril	≤ 30 mg	> 30 mg
Fosinopril	≤ 20 mg	> 20 mg
Imidapril	≤ 10 mg	> 10 mg
Lisinopril	≤ 10 mg	> 10 mg
Moexipril	≤ 7.5 mg	> 7.5 mg
Perindopril	≤ 4 mg	> 4 mg

Study medication	Low RASi stratum	High RASi stratum
Quinapril	≤ 20 mg	> 20 mg
Ramipril	≤ 5 mg	> 5 mg
Spirapril	≤ 6 mg	> 6 mg
Temocapril	≤ 2 mg	> 2 mg
Trandolapril	≤ 2 mg	> 2 mg
Zofenopril	≤ 30 mg	> 30 mg
ARBs		
Azilsartan	≤ 80 mg	> 80 mg
Candesartan	≤ 16 mg	> 16 mg
Eprosartan	≤ 400 mg	> 400 mg
Irbesartan	≤ 150 mg	> 150 mg
Losartan	≤ 50 mg	> 50 mg
Olmesartan	≤ 10 mg	> 10 mg
Telmisartan	≤ 40 mg	> 40 mg
Valsartan	≤ 160 mg	> 160 mg

Table 3-2 Study drug dose levels during double-blind treatment epoch

Dose level	LCZ696	Enalapril	Valsartan
1	50 mg bid	2.5 mg bid	40 mg bid
2	100 mg bid	5 mg bid	80 mg bid
3	200 mg bid	10 mg bid	160 mg bid

Table 3-3 Safety monitoring criteria requirements prior to study drug initiation and during up-titration

Parameter	Study drug initiation (Visit 101)	Study drug up-titration (Any visit with up-titration or re-initiation)
Serum potassium (or equivalent plasma potassium value)	*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 101
Blood pressure	SBP ≥ 110 mmHg	No symptomatic hypotension as determined by the investigator and SBP ≥ 100 mmHg

Parameter	Study drug initiation (Visit 101)	Study drug up-titration (Any visit with up-titration or re-initiation)
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

*Laboratory values from the screening visit (Visit 1) may be used for study drug initiation

3.2 Rationale for study design

3.2.1 Rationale for target study population

The study population will consist of patients ≥ 45 years of age with a LVEF > 40% and evidence of structural heart disease (left atrial enlargement [LAE] and/or left ventricular hypertrophy [LVH]), current symptoms of HF (NYHA class II-IV), use of diuretics within the prior 30 days, NT-proBNP > 220 pg/mL for patients with no atrial fibrillation/atrial flutter (AF) or > 600 pg/mL for patients with AF, and KCCQ CSS < 75. Eligible patients will be on appropriate medical therapy for comorbidities in the opinion of the investigator.

Structural heart disease (LAE and LVH) is a key diagnostic criterion for HFpEF in the most recent guidelines (Ponikowski et al 2016). 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 echocardiographic evidence of structural heart disease consistent with HFpEF will help facilitate homogeneity of the study population. Both TOPCAT (Pitt et al 2014) and I-Preserve (Massie et al 2008) used an EF lower boundary threshold of 45%. This is also the threshold used in PARAGON-HF, an ongoing large outcomes study (4600 patients) comparing valsartan 160 mg bid to LCZ696 200 mg bid in HFpEF. Elevated NT-proBNP levels aid in the diagnosis of HFpEF. Current guidelines include NT-proBNP > 125 pg/mL as one of the criteria to be used for the diagnosis of HFpEF (Ponikowski et al 2016). In this symptoms study, we have chosen a threshold for NT-proBNP of 220 pg/mL which is consistent with prior guidelines (Paulus et al 2007) to increase the likelihood that patients' symptoms at baseline are related to HF rather than their comorbid conditions. NT-proBNP was the strongest independent predictor of mortality and subsequent HF hospitalizations in the I-PRESERVE study (Solomon et al 2007, Komajda et al 2011) and was used as an inclusion criterion in TOPCAT. 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 patients with EF < 45% will be targeted to approximately 300 patients and the number of AF patients will be limited to approximately one-third in the current study (based on the Visit 1 electrocardiogram [ECG]) so that the proportion of patients with EF < 45% and AF in the study will be representative of the HFpEF population (Massie et al 2008, Steinberg et al 2012, West et al 2011, Tsuji et al 2017, Lund et al 2018).

3.2.2 Rationale for the primary endpoints

The study has two primary endpoints: NT-proBNP and 6MWD.

NT-proBNP: One of the primary endpoints of this study is the change from baseline in NT-proBNP (in log scale) at Week 12. In a prior study in over 300 HFpEF patients, LCZ696 showed

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a significantly greater reduction in NT-proBNP at Week 12 as compared to valsartan (Solomon et al 2012). Aggregate clinical data have demonstrated that NT-proBNP not only provides value for the diagnosis, and helps the management of patients with HF, but also predicts clinical outcome (mortality and morbidity). Studies suggest that NT-proBNP levels strongly correlate with adverse clinical outcomes in HF patients including death and hospital admission for chronic HF (Hartmann et al 2004, Hunt et al 2005, Masson et al 2008, McMurray et al 2014).

Across all stages of HF, elevated BNP/NT-proBNP concentration are the most robust prognostic predictor of mortality and cardiovascular events compared to other traditional outcome predictors (peak oxygen consumption, blood urea nitrogen (BUN), SBP and pulmonary capillary wedge pressure) with increasing BNP/NT-proBNP concentration predicting worse prognosis in a linear fashion (Sachdeva et al 2010).

In this short term study in patients with HF, change of NT-proBNP is considered an appropriate surrogate endpoint for clinical outcomes of HF. We will use this data to determine the treatment effect of LCZ696 compared to individualized medical therapy for comorbidities on the risk and clinical status of the population. In addition, the NT-proBNP data from this study can be used as a bridge to the PARAGON-HF study where NT-proBNP is also measured.

Six-minute walk distance (6MWD): The other primary endpoint is change from baseline in 6MWD which is derived from a simple, inexpensive, and reproducible test (6MWT) for the assessment of exercise capacity. It evaluates the global and integrated responses of all the systems involved during exercise including the pulmonary and cardiovascular systems. The 6MWD correlates well with results using formal treadmill exercise testing and has been shown to predict outcomes in patients with HF, particularly, in patients with more advanced HF (Pollentier et al 2010).

Many different studies have investigated whether the distance walked during the walking test is a prognostic indicator in heart failure patients. The 6MWD correlates with changes in symptoms after HF therapy, suggesting that it may be useful as a measure of symptom benefit (Olsson et al 2005). Lower levels of exercise capacity (a distance < 300 meters during 6MWT) have proven to be predictive of mortality (total or cardiovascular) and morbidity (hospitalization for worsening HF) both in patients with mild to moderate (Bittner et al 1993, Roul et al 1998, Zugck et al 2000) and advanced HF (Cahalin et al 1996, Shah et al 2001). In the SOLVD study, a 6MWD ≥ 450 meters indicated low mortality risk (Bittner et al 1993). Furthermore, it has been demonstrated that a 6MWD < 450 m constitutes impaired exercise capacity (Abraham et al 2015). More recently, 6MWT has been used in prior studies to assess the effect of therapeutic interventions in HFpEF patients (Kamp et al 2009, Kitzman et al 2010, Redfield et al 2015).

The primary analysis was selected to be performed in a sub-set of patients with baseline six-minute walk distance (B6MWD) ranging from 100 meters to 450 meters. The selected cut-off was chosen a) by expert opinion b) since < 450 meters indicates exercise impairment and c) because previous studies have used similar cutoffs (Abraham et al 2002, Abraham et al 2015, Redfield et al 2015 and Palau et al 2016).

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3.2.3 Rationale for the secondary endpoints selection

KCCQ: KCCQ is a valid, reliable and responsive health status measure for patients with heart failure and may serve as a clinically meaningful outcome in cardiovascular research, patient management and quality assessment (Green et al 2000). The KCCQ instrument includes a clinical summary score (CSS) that encompasses the physical limitation score and the total symptom score. The CSS is a combined score based upon the clinical symptoms and physical function domains of the questionnaire. CSS specifically, has been shown both to be predictive of outcomes and has been used to measure response to therapy in patients with HFrEF (Ekman et al 2011). Further, KCCQ has been shown to be a valid and reliable tool to measure health status and predict outcomes in patients with HFpEF (Joseph et al 2013).

Data from HF-ACTION suggest that a 5-points change in the KCCQ overall score corresponds to clinically significant changes in measures of exercise capacity (peak oxygen consumption and 6MWT) (Flynn et al 2012). Importantly, analysis of KCCQ scores in 1, 358 patients enrolled in the EPHESUS study showed a linear correlation with both all-cause mortality and the combined endpoint of cardiovascular mortality and hospitalizations, for each 5-points decrease in KCCQ CSS (Kosiborod et al 2007). The proposed study will evaluate not only mean change from the baseline but also proportion of patients with ≥ 5-points change including both improvement and deterioration at the end of the study.

NYHA: NYHA classification is an assessment of a patient's functional capacity and symptomatic status of HF; it is a well-established and internationally recognized prognostic indicator of outcomes. NYHA classification reflects the limitations that the patient with HF has to cope with on a daily basis because of his/her symptoms. Further, NYHA is used in daily clinical practice and clinical studies to record the patient's current functional status and provide important information on disease progression in HF patients. In the recently issued draft guideline on drug development for the treatment of HF, the European Medicines Agency (EMA) recognized the importance of the NYHA classification in the assessment of symptoms in patients with HF, and emphasized that NYHA class as an established standard that should be included to allow comparisons across trials (European Medicines Agency, 2016).

SF-36: SF-36 is a generic health-related quality of life (HRQOL) instrument which comprises of 36 questions across 8 domains: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); 8) general health perceptions (Ware and Sherbourne 1992). The SF-36 is considered to be a valid, reliable, concise generic measure of state of health and has demonstrated to detect clinical treatment benefits across medical conditions including chronic disorders such as HF (Ware and Gandek 1998, Frendl and Ware 2014, Nolte et al 2015, Karlström 2016).

[redacted]

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

LCZ696 200 mg twice daily is the dose that has been used across all HF studies in the LCZ696 program. Biomarker analysis and modeling indicate that this dose of LCZ696 delivers approximately 90% of its maximal NEP inhibition. In addition, LCZ696 200 mg delivers similar valsartan exposure (assessed by area under curve [AUC]) as Diovan® (valsartan) 160 mg twice daily. 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. The primary endpoint of change in NT-proBNP (in log scale) will be assessed at Week 12, consistent with the effect of LCZ696 seen in HFpEF in the PARAMOUNT-HF study (Solomon et al 2012). The primary endpoint of change in 6MWD and all secondary endpoints (including symptoms, and QoL) will be evaluated at Week 24, which has been shown to be sufficient time to demonstrate changes in HF status using these measures (Green et al 2000).

3.4 Rationale for choice of comparator

Presently, there is no evidence-based, guideline-recommended, pharmacologic therapy for HFpEF patients. However, there are guideline recommendations for the treatment of the comorbidities that are prevalent in HFpEF, such as HTN, DM, and CAD (Ponikowski et al 2016). ACEi and ARB are commonly used for treatment of comorbidities. Patients will be stratified into three strata based upon their prior RASi use (ACEi, ARB or no RASi) and then randomized to active therapy with LCZ696 or comparator. In the comparator arm, patients previously treated with an ACEi will receive enalapril. Patients previously treated with an ARB will receive valsartan. Patients not previously treated with RASi will not receive RASi. Only patients with a history of HTN will be included in the ACEi and ARB strata. Background therapy for comorbidities (eg beta blockers, calcium channel blockers) will be optimized in all patients throughout the study; diuretics will be adjusted to manage the symptoms of heart failure as needed during the study.

Enalapril is chosen as the angiotensin converting enzyme (ACE) comparator as it is a commonly prescribed ACEi in patients with HFpEF for treating prevalent comorbidities. The enalapril dose of 10 mg bid (total daily dose of 20 mg) is selected as the comparator target dose for this study because it is the recommended maintenance dose for hypertension (Enalapril SmPC 2003). Data from the EU HF registry indicates that the median dose of enalapril for HF in real world practice is about 10 mg/day with approximately only 46% of the patients achieving the target dose of 20 mg/day (Maggioni et al 2010).

Valsartan is chosen as the ARB comparator as it is the ARB component of LCZ696. Valsartan is an orally active, potent and specific competitive type 1 angiotensin II receptor **(**AT_1) receptor antagonist. The exposure delivered by LCZ696 200 mg bid is similar to valsartan 160 mg bid (320 mg total daily dose), which is the Food and Drug Administration (FDA) and EMEA approved maximal and guideline recommended dose strength for the treatment of HTN. Thus, the target dose of valsartan chosen for the comparator arm is 160 mg bid. The same dosing regimen of valsartan is also used in the PARAGON-HF study.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

Patients will be instructed not to take any other RAS blockade medications (ACEi, ARB or renin inhibitor) except study drug (LCZ696, enalapril, or valsartan) to avoid excess RAS blockade and minimize potential risk of angioedema. Washout of prior RAS agents is ensured by the discontinuation of prior ACEis at least 36 hours prior to randomization and discontinuation of prior ARBs on the day of randomization. If the patient is to be started on open-label ACEi during the study, study drug will be stopped ≥ 36 hours prior to initiating ACEi treatment. All patients will continue other individualized medical therapy for comorbidities as directed by the investigator. The risk to patients in this trial will be minimized by compliance with the eligibility criteria, study procedures, and close clinical monitoring (eg hypotension).

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 after stopping of 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 ≥ 45 years of age and therefore the risk of pregnancy during the trial is minimal.

Clinical trial data in adults demonstrate that LCZ696 has an overall safety profile generally comparable to other RASi agents. For patients participating in this study: the risks common to LCZ696, enalapril and valsartan include hypotension, hyperkalemia, worsening renal function and angioedema. Potential risks of LCZ696 also include hepatotoxicity, effects on bone growth and mineralization, and changes in amyloid beta in the central nervous system (CNS).

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 patients ≥ 45 years of age with a LVEF > 40% and evidence of structural heart disease (LAE and/or LVH), current symptoms of HF (NYHA class II-IV), use of diuretics within the prior 30 days, NT-proBNP > 220 pg/mL for patients with no AF or > 600 pg/mL for patients with AF, and KCCQ CSS < 75. Eligible patients will be on appropriate medical therapy for comorbidities in the opinion of the investigator.

4.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed.
2. ≥ 45 years of age, male, or female
3. LVEF > 40% by echocardiography performed within 6 months prior to Visit 1 or during the screening epoch

4. Symptom(s) of HF requiring treatment with diuretics (including loop, or thiazide diuretics, or mineralocorticoid antagonist [MRAs]) 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 demonstrated by echocardiographic evidence of left atrial enlargement (LAE) **or** left ventricular hypertrophy (LVH) as defined below (any local measurement made during the screening epoch or within the 6 months prior to Visit 1):
   a. left atrial 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 defined by septal thickness or posterior wall thickness ≥ 1.1 cm
7. Receiving evidence based therapy for relevant comorbidities as determined by the individual clinical profile of the patient (eg age and number and type of comorbidities) with stable doses for the previous four weeks prior to randomization
8. NT-proBNP > 220 pg/mL for patients with no atrial fibrillation/atrial flutter (AF) or > 600 pg/mL for patients with AF on the Visit 1 ECG
9. KCCQ clinical summary score < 75 at Visit 1
10. Patients on ACEi or ARB therapy must have a history of HTN

4.2 Exclusion criteria

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

1. Any prior echocardiographic measurement of LVEF ≤ 40%, under stable conditions
2. Acute coronary syndrome (including myocardial infarction [MI]), cardiac surgery, other major cardiovascular (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 (eg MI, coronary artery bypass graft [CABG]), unless an echo measurement was performed after the event confirming the LVEF to be > 40%
4. Current (within 30 days from Visit 1) acute decompensated HF requiring augmented therapy with diuretics, vasodilators and/or inotropic drugs
5. Current (within 30 days from Visit 1) use of renin inhibitor(s), dual RAS blockade or LCZ696
6. History of hypersensitivity to LCZ696 or its components
7. Patients with a known history of angioedema
8. Walk distance primarily limited by non-cardiac comorbid conditions at Visit 1
9. Probable alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms (ie dyspnea, fatigue) such as significant pulmonary disease (including primary pulmonary HTN), anemia or obesity. Specifically, patients with the following are excluded:

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a. severe pulmonary disease including chronic obstructive pulmonary disease (COPD) (ie 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 males and < 9.5 g/dL females **or**
c. body mass index (BMI) > 40 kg/m^2

10. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer
11. 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, MRA, ACEi, ARB, beta blocker and calcium channel blocker (CCB), **or**
    c. SBP < 110 mmHg or symptomatic hypotension at Visit 1
12. Patients with HbA1c > 7.5% not treated for diabetes
13. Patients with history of any dilated cardiomyopathy, including peripartum cardiomyopathy, chemotherapy induced cardiomyopathy, or viral myocarditis
14. Evidence of right sided HF in the absence of left-sided structural heart disease
15. Known pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy
16. Clinically significant congenital heart disease that could be the cause of the patient's symptoms and signs of HF
17. Presence of hemodynamically significant valvular heart disease in the opinion of the investigator
18. Stroke, transient ischemic attack, carotid surgery or carotid angioplasty within the 3 months prior to Visit 1
19. Coronary or carotid artery disease or valvular heart disease likely to require surgical or percutaneous intervention during the trial
20. Life-threatening or uncontrolled arrhythmia, including symptomatic or sustained ventricular tachycardia and atrial fibrillation or flutter with a resting ventricular rate > 110 beats per minute (bpm)
21. Patients with a cardiac resynchronization therapy (CRT) device
22. Patients with prior major organ transplant or intent to transplant (ie on transplant list)
23. 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
24. 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

[redacted]

25. Evidence of hepatic disease as determined by any one of the following: SGOT (AST) or SGPT (ALT) values exceeding 3 × the upper limit of normal (ULN), bilirubin > 1.5 mg/dl at Visit 1
26. Patients with eGFR < 30 mL/min/1.73m^2 as calculated by the Modification in Diet in Renal Disease (MDRD) formula at Visit 1
27. Presence of known functionally significant bilateral renal artery stenosis
28. Patients with serum potassium > 5.2 mmol/L (or equivalent plasma potassium value) (mEq/L) at Visit 1
29. History or presence of any other disease with a life expectancy of < 3 years
30. History of non-compliance to medical regimens and patients who are considered potentially unreliable
31. History or evidence of drug or alcohol abuse within the last 12 months
32. Persons directly involved in the execution of this protocol
33. 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 1 year, regardless of whether there is evidence of local recurrence or metastases; as well as, patients with any planned treatment for malignancy
34. Patients taking medications prohibited by the protocol (see Section 5.5.8)
35. 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
36. 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 after stopping of study medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (eg 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) total hysterectomy or tubal ligation at least six weeks before taking investigational drug. 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 screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception
    - In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug
    - In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the informed consent form (ICF)

[redacted]

- 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 (eg age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

The sponsor will provide the following study drugs:

Randomized treatment period

LCZ696 is available as 24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg sacubitril/valsartan, and will be subsequently referred to as LCZ696 50 mg, 100 mg, and 200 mg in this study protocol for simplicity.

At the randomization visit (Visit 101), all patients who fulfill the inclusion/exclusion criteria will be stratified based upon prior therapy as described above. Subsequent to stratification, patients will be randomized into either the LCZ696 or the comparator treatment group at a 1:1 ratio. Table 3-1 categorizes low and high total daily doses for commonly used ACEis and ARBs. Study drug initiation is dependent on prior RASi dose. Study drug dose levels during up-titration are outlined in Table 3-2. The goal of treatment is to ensure that each patient receives the maximal tolerated dose of study medication up to the target dose of LCZ69 200 mg bid, enalapril 10 mg bid and valsartan 160 mg bid (dose level 3). Background therapy for comorbidities will be optimized in all patients throughout the study; diuretics will be adjusted to manage the symptoms of heart failure as needed during the study.

Patients in the ACEi and ARB strata will receive two study medications and patients in the no RASi strata will receive one study medication. 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
- Enalapril 2.5 mg, 5 mg and 10 mg tablets
- Placebo to match enalapril 2.5 mg, 5 mg, and 10 mg tablets
- Valsartan 40 mg, 80mg, 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

[redacted]

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 treatment

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

5.2 Treatment arms

At the randomization visit (Visit 101), all patients who fulfill the inclusion/exclusion criteria will be stratified based upon prior therapy (Figure 3-1). Subsequent to stratification, patients will be randomized within one of the three strata to either the LCZ696 or the comparator group at a 1:1 ratio.

- LCZ696
- Comparator
  - Enalapril
  - Valsartan
  - No RASi

5.3 Treatment assignment and randomization

At Visit 101, all eligible patients will be stratified via Interactive Response Technology (IRT) into one of three strata based upon prior RASi use and subsequently randomized to either LCZ696 or comparator (Figure 3-1). In addition, randomization will be stratified by region. 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 Randomization Office.

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:

[redacted]

- 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:
  - The independent unblinded statistician, programmer and data personnel who are involved in preparing safety reports for the Data Monitoring Committee (DMC). These personnel will not be involved in any other trial conduct related activities
  - The program level DMC members who will review safety data in an unblinded manner
- 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 for the two RASi strata because the identity of the investigational treatment cannot be disguised due to their different forms. A single dummy will be used for the no RASi strata.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.9) and at the conclusion of the study.

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 Treating the patient

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

5.5.1 Patient numbering

Each patient is uniquely identified 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 informed consent form, 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 must select the CRF book with a matching Subject Number from the electronic data capture (EDC) system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the Screening epoch Study Disposition eCRF.

5.5.2 Dispensing the study drug

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

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the 2 treatment arms (LCZ696 vs comparator) and a dose level. Investigator staff will identify the study drug package(s) to dispense to the

[redacted]

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 and additional treatment

5.5.3.1 Handling of study treatment

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

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

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

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

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

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 in the ACEi and ARB strata will be required to take a total of two tablets: one tablet from the LCZ696/matching placebo pack and one tablet from the enalapril/matching placebo or valsartan/matching placebo pack, twice a day for the duration of the study. Patients in the no RASi strata will be required to take one tablet from the LCZ696/matching placebo pack twice a day for the duration of the study. There will be three dose levels for LCZ696, enalapril and valsartan; and three dose levels for each corresponding matching placebo.

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). 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 eCRF. All kits of study treatment assigned by the IRT will be recorded/databased in the IRT.

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

5.5.5 Permitted dose adjustments and interruptions of study treatment

For patients who are unable to tolerate the protocol-specified dosing scheme, dose level adjustments and 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 comorbid conditions to rectify the situation, before considering to down-titrate to the next lower study drug dose level.

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 study drug dose level. As outlined previously, patients in the ACEi and ARB strata take two study medications while patients in the non RASi strata take one study medication. In the ACEi and ARB strata, both study medications must be adjusted simultaneously.

During the randomized treatment epoch, down titration of 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. If down-titration occurs due to an (S)AE (Section 7.1 and 7.2), then the appropriate reporting guidelines must be followed (Section 7.2.2). 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 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. The maximal dose for study medication will be determined by the investigator based upon the patient's individual clinical status.

[redacted]

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. 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 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 prohibited while the patient is taking study drug. Should the patient receive open-label RASi or renin inhibitor during the study, study drug must be withdrawn and the patient continued to be followed within the study. Patients must wait 36 hours after last study drug administration prior to initiating open label ACEi. Whenever possible, as dictated by clinical status, patients should resume study drug. Study drug re-initiation should be at the dose level deemed appropriate by the investigator and up-titration to target dose undertaken as described above. Patients who received open label ACEi should wait 36 hours before resuming study medication. These changes must be recorded on the Dosage Administration Record eCRF.

In case of pregnancy discovered during the screening epoch, the patient will be excluded from the study. In case of pregnancy discovered during the randomization epoch, the patient should be instructed to immediately discontinue study drug and encouraged to continue to attend scheduled study visits.

See Section 7.6 for further details on pregnancies and reporting guidelines.

[redacted]

5.5.6 Rescue medication

Guidance on handling renal dysfunction, hyperkalemia, and hypotension are provided to investigators in Appendix 3, Appendix 4, and Appendix 5, respectively.

Use of rescue medication must be recorded on the Concomitant Medications eCRF.

5.5.7 Concomitant medication

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

Diuretics will be adjusted in all patients to manage the symptoms of heart failure as needed during the study. Changes in diuretic dose must be recorded in the Concomitant Medications eCRF.

Management of comorbidities

The patient should be receiving evidence based medical therapy for relevant comorbidities such as but not limited to HTN, DM, AF, dyslipidemia, COPD and CAD (including diuretics, beta blockers, calcium channel blockers as appropriate). Medical management of comorbidities should be individualized based upon the clinical profile of the patient, taking into consideration age and the number and type of comorbidities.

During the course of the study, investigators should continue to optimize background medications for comorbidities based upon the patient's clinical situation. Elevations in BP during the study should be treated by initiation or adjustment of non RASi therapies. Should the investigator feel that addition of open label RASi or renin inhibitor is required, study drug must be discontinued as outlined above in section 5.5.5 (initiation of open label ACEi should be deferred for 36 hours after discontinuation of study drug). Patients who have discontinued study medication for this reason will continue to be followed within the study and study drug reinitiated as deemed appropriate by the investigator. HbA1c and lipid profile will be performed pre-randomization and during the course of the study; diabetes and lipid management should be optimized during the course of the study as appropriate. All changes in medical therapy for the treatment of comorbidities during the study will be recorded in the eCRF. Additional information will be collected from the investigator for those patients with poorly controlled blood pressure, diabetes and lipids, as to whether medications were adjusted and if not, the reason why no changes in medical therapy were made.

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

[redacted]

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

The concomitant administration of LCZ696 with neseritide has not been studied. In the event a study patient requires the concomitant administration of neseritide 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 (eg simvastatin, pravastatin) that are substrates of OATP1B1 and OATP1B3 because of the potential to raise plasma statin levels.

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-1 is **NOT** allowed after the start of study drug due to safety reasons, unless the actions specified are taken.

Table 5-1 Prohibited treatment

Medication	Action to be taken
Any ACEI	Temporarily discontinue study drug while on ACEi. The open label ACEi treatment must be stopped for ≥ 36 hours prior to re-initiation of study drug.
Any ARB	Temporarily discontinue study drug while on ARB. The open label ARB treatment must be stopped prior to re-initiation of study drug.
Any renin inhibitor	Temporarily discontinue study drug while on renin inhibitor. 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. Should an investigator wish to give open label RASi during the study, study drug will be withdrawn and the patient will continue to be followed within the study. If the patient is to be started on open-label ACEi, study drug must be stopped ≥ 36 hours prior to initiating ACEi treatment. Study drug may be resumed after discontinuation of open label ACEis, ARBs or a renin inhibitor as described above.

5.5.9 Emergency breaking of assigned treatment code

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

[redacted]

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 unblinding can be performed at any time.

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

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol. The study will be completed when the last patient enrolled has completed their last visit (24 weeks after randomization). Patients will continue to be followed in the study regardless of study drug discontinuation.

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 available through the sponsor dependent on the results of the PARAGON-HF study.

5.6.2 Discontinuation of study treatment

Patients may voluntarily discontinue study treatment for any reason at any time. However, study treatment discontinuation does not constitute withdrawal from the study, does not constitute withdrawal of consent and should not lead to the patient being withdrawn from the study. Patients who have discontinued study drug 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. The investigator must also contact the IRT to register the patient's interruption from study treatment and record it on the Dosage Administration Record.

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 pre-specified in the protocol have

[redacted]

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 (Section 6.5.7). A patient with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator
- Pregnancy and post-pregnancy during lactation period (Section 6.5.6 and Section 7.6)

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

- Use of an open label ACE inhibitor, ARB, or renin inhibitor (Section 5.5.8)
- Any laboratory abnormalities that in the judgment of the investigator warrant discontinuation of study drug after taking into consideration the patient's overall status (Section 6.5.4)

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

- Any severe suspected drug-related AE (Section 7.1)
- 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.

5.6.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator must make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

[redacted]

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and Rest of the World (RoW): All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

5.6.4 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study (EOS) visit has passed.

5.6.5 Early study termination by the sponsor

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

6 Visit schedule and assessments

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

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

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

[redacted]

Table 6-1 Assessment schedule

Epoch	**Screen**	**Double-blind treatment**							
Visit	1	101	102	103	104	105	106	107	199 and/or PSD
Week(w)	-2	0	2	4	8	12	16	20	24
Day	-14	1	14	28	56	84	112	140	168
Obtain informed consent*	X								
Inclusion/exclusion criteria	X	S							
Medical history/demography	X								
Heart failure and diabetes history	X								
Cardiovascular medical history	X								
Concomitant medications	X	X	X	X	X	X	X	X	X
Alcohol & smoking history	X								
Complete physical exam	S								S
Short physical exam		S	S	S	S	S	S	S	
Vital signs (BP and pulse)	X	X	X	X	X	X	X	X	X
Height	X								
Weight	X	X	X	X	X	X	X	X	X
Waist/hip circumference	X					X			X
12-lead ECG assessment	X					X			X
Echocardiography[1]	X								
NYHA classification (HF signs/symptoms)	X	X	X	X	X	X	X	X	X
KCCQ questionnaire	X	X		X		X	X		X
Six-minute walk test	X	X					X		X
SF-36		X					X		X

[redacted]

Epoch	**Screen**	**Double-blind treatment**							
Visit	1	101	102	103	104	105	106	107	199 and/or PSD
Week(w)	-2	0	2	4	8	12	16	20	24
Management of comorbidities (Blood Pressure)	x	x	x	x	x	x	x	x	x
Management of comorbidities (Diabetes, Lipids)	x	x				x			x
Management of comorbidities (Arrhythmias)	x					x			x
Complete laboratory evaluations[2]	X	X				X			X
Abbreviated laboratory evaluations[3]			X	X	X		X	X	
FSH[4]	X								
Serum/urine pregnancy test[5]	X	X	X	X	X	X	X	X	X
Plasma NT-proBNP[6]	X	X		X		X			X
AEs/SAEs		X	X	X	X	X	X	X	X
Contact IRT	X	X	X	X	X	X	X	X	X
Dispense study medication		X	X	X	X	X	X	X	
Screening disposition	X								
Treatment compliance			X	X	X	X	X	X	X
Treatment disposition									X
Study completion form									X

PSD = Premature Subject Discontinuation
X = assessment to be recorded on clinical data base
S = assessment to be recorded on source documentation only
*IC obtained prior to all study specific screening procedures

[redacted]

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

[2] Complete laboratory evaluations including urinalysis will be sent to the central lab at all specified visits.

[3] Abbreviated laboratory evaluations will be sent to the central lab and include: BUN, creatinine, potassium, and eGFR, and may additionally be performed in the local lab as needed and include: creatinine, potassium, and eGFR. Lab results must be available and assessed before any study drug up-titration (see table 3-3)

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

[5] Not required for males or post-menopausal women. Serum pregnancy test performed at Visit 1 and 199/PSD. Urine pregnancy test performed at all other study visits.

[6] Only the Visit 1 NT-proBNP results will be reported to the investigator and the sponsor. Local measurements of BNP or NT-proBNP during the course of the study is strongly discouraged.

6.1 Information to be collected on screening failures

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

Re-screening

A patient who enters screening but is determined not to be eligible 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 once. A minimum of 2 weeks must elapse between screen failure and re-screening. The patient must provide new written informed consent before they are re-screened.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: year 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.

Investigators will have the discretion to record abnormal test findings on the medical history eCRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.3 Treatment exposure and compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient or care giver. This information should be captured in the Study Treatment Compliance eCRF 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. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

The duration of randomized treatment exposure will be calculated based upon the start and stop dates recorded in the Dosage Administration Record eCRFs.

6.4 Efficacy

6.4.1 Primary efficacy assessment

The primary efficacy variables are change from baseline in NT-proBNP (in log scale) at Week 12 and change from baseline in six-minute walk distance (6MWD) at Week 24.

[redacted]

6.4.2 Secondary efficacy assessment

The secondary efficacy variables include:

- KCCQ CSS at Week 24
- NYHA functional classification at Week 24
- SF-36 PCS score at Week 24

6.4.3 Appropriateness of efficacy assessments

Rationale for the choice of endpoints for the study has been outlined previously (Section 3.2.2 and 3.2.3). The primary efficacy assessments, NT-proBNP and 6MWT, are key clinical measures in this patient population for response to therapy, exercise capacity improvement and assessment of overall risk. The secondary efficacy assessments (KCCQ, SF-36 and NYHA) are validated measures of symptoms and quality of life in patients with HFpEF.

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. Complete physical examination will be performed at Visit 1 and 199/PSD.

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 101 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 eCRF. Significant findings made after signing the informed consent which meet the definition of an AE must be recorded on the AE section of the eCRF.

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 (eg OMRON) or a standard sphygmomanometer with an appropriately sized cuff on the non-dominant arm. Vital signs will be performed at each study visit.

[redacted]

6.5.3 Height, weight and waist/hip circumference

Height in centimeters (cm) will be measured at Visit 1. Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at each study visit.

Waist/hip circumference (to the nearest centimeter [cm] in indoor clothing) will be measured at Visit 1, 105, and 199/PSD.

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 such as hematology and blood chemistry (Table 6-2) for the assessment of safety in this study will be performed at Visits 1, 101, 105 and 199/PSD.

Abbreviated laboratory evaluations will be performed as indicated in Table 6-1. Abbreviated central laboratory includes: BUN, creatinine, potassium, and eGFR.

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

Laboratory values that exceed the boundaries of a notable laboratory abnormality (Appendix 1) must be commented on by the investigator in the patient's eCRF 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 eCRF. If the laboratory abnormality is the primary reason for an unforeseen hospitalization or otherwise fulfills the seriousness category of an AE, then the procedure for rapid notification of SAEs must be followed. If the laboratory abnormality leads to study drug discontinuation (temporarily or permanently), the patient must be followed until the abnormality resolves or until it is judged to be permanent. The investigation may include continued monitoring by repeat laboratory testing or by performing additional laboratory tests as deemed necessary by the investigator or the Novartis medical monitor.

All central laboratory results will be communicated to the investigators and the sponsor, with the exception of NT-proBNP of which only the Visit 1 NT-proBNP will be reported (Section 6.6.1.4).

[redacted]

Table 6-2 Complete laboratory evaluations

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)	eGFR*	
	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 > 2 x 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 (TBL), fractioned bilirubin (if total bilirubin > 2 x ULN), AST, ALT, alkaline phosphatase, sodium, glucose (plasma), hemoglobin A1C, lipid profile, potassium, phosphate, chloride, calcium, total protein, albumin, and uric acid will be measured. Potassium, BUN, creatinine, and eGFR will be obtained at study visits where abbreviated central laboratory evaluations are scheduled.

[redacted]

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

6.5.4.4 Urinalysis

Urinalysis with dipstick measurements for specific gravity, pH, total protein, bilirubin, ketones, leukocytes and blood will be performed by central lab. 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 locally at Visit 1, 105 and Visit 199/PSD. Interpretation of the tracing must be made by a qualified health care provider and documented on the ECG section of the eCRF. 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 eCRF page.

6.5.6 Pregnancy and assessments of fertility

Serum FSH will be performed at Visit 1 in post-menopausal women.

All pre-menopausal women who are not surgically sterile will have a serum pregnancy test at Visit 1 and Visit 199/PSD. Additional pregnancy testing might be performed if requested by local requirements. 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. A positive urine test needs to be confirmed with serum pregnancy test. If positive, the patient must discontinue study drug.

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. In addition, all appropriate angioedema eCRFs should be completed.

For suspected and confirmed angioedema, the study medication should be discontinued.

[redacted]

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" (eg 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 Clinical outcome assessments

6.6.1.1 Clinician reported outcomes (ClinRO)

NYHA classification is a subjective assessment of patient's functional capacity and symptomatic status and can change frequently over time. It is a well-established prognostic indicator of outcomes. Further, NYHA is used in daily clinical practice and research to record the patient's current functional status and provide important information on disease progression in HF patients. NYHA assessment will be performed by a delegated and trained health care professional at every study visit.

6.6.1.2 Patient Reported Outcomes (PRO)

The Kansas City Cardiomyopathy Questionnaire (KCCQ)

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

The CSS is a combined score based upon the clinical symptoms and physical function domains of the questionnaire. The CSS specifically, has been shown both to be predictive of outcomes and has been used to measure response to therapy in patients with HF (Ekman et al 2011). In addition, the overall summary score (OSS) is derived from the physical function, symptom (frequency and severity), social function and quality of life domains (Green et al 2000). Scores are transformed to a range of 0 - 100, in which higher scores reflect better health status.

A 5-points change in the KCCQ corresponds to clinically significant changes in measures of exercise capacity (Flynn et al 2012). Further, KCCQ scores show a linear correlation with all-cause mortality for each 5-points decrease in KCCQ CSS (Kosiborod et al 2007). The proposed study will evaluate not only mean change from the baseline but also the proportion of patients with ≥ 5-points change including both improvement and deterioration at the end of the study.

[redacted]

KCCQ will be performed at Visit 1 as part of study screening. Patients with CSS < 75 will be included in the study. In addition, KCCQ will be performed during the study at Visit 101, 103, 105, 106, 199/PSD.

SF-36 Version 2

The Short Form Health Survey (SF-36) is a widely used and extensively studied instrument to measure health-related quality of life among healthy patients and patients with acute and chronic conditions. It consists of eight subscales that can be scored individually: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health (Ware et al 1993). Two overall summary scores, the physical component summary (PCS) and the mental component summary (MCS) also can be computed (Ware et al 1994). The SF-36 has proven useful in monitoring general and specific populations, comparing the relative burden of different disease, differentiating the health benefits produced by different treatments, and in screening individual patients. In this study the four week recall questionnaire will be used.

Patients will require approximately 5 to 10 minutes to complete this form.

SF-36 will be completed at Visit 101, 106 and 199/PSD.

Completion of Questionnaires

All questionnaires will be completed in the language most familiar to the respondent, at the scheduled study visit prior to the patient seeing the investigator for any clinical assessment or evaluation.

The patient should be given sufficient instruction, space, time and privacy to complete the questionnaire. The study coordinator should check the responses to the questionnaire for completeness and encourage the patient to complete any missing responses.

Under special circumstances, such as but not limited to illiteracy and poor vision, the completion of the questionnaires can be done with assistance, by a caregiver or a study coordinator not directly involved in the care of the patient, if a patient is unable to complete it on their own. This situation should be clearly noted both in source documents and as an investigator notification in the eCRF

All patients will complete the PRO questions via an electronic tablet. If patients experience any difficulties with submission after they complete the Patient Reported Outcome (PROs), the study staff should assist them with submitting their responses. Attempts should be made to collect responses to all PROs for all patients, including from those who prematurely discontinue prior to the study evaluation completion visit; however, if patients refuse to complete PROs, (after screening visit), this should be documented in study source records. Patient's refusal to complete study PROs are not protocol deviations and do not require the patient be discontinued from the trial.

Completed questionnaires will be reviewed and examined by the investigator for responses that may indicate potential AEs or SAEs. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol.

[redacted]

6.6.1.3 Performance Outcomes

Six-minute walk test (6MWT)

The 6MWT is a simple, inexpensive, and reproducible method for the assessment of exercise capacity. The 6MWT has good reliability and a significant ability to predict functional capacity in patients with HF (Pollentier et al 2010). Scoring is based on the total distance walked. Lower levels of exercise capacity (a distance < 300 m during 6MWT) have proven to be predictive of mortality and morbidity in HF (Bittner et al 1993, Roul et al 1998, Zugck et al 2000). The 6MWT also correlates with changes in symptoms after HF therapy, suggesting that it may be useful as a measure of symptom benefit (Olsson et al 2005).

The 6MWT will be performed in accordance with the guidelines of the American Thoracic Society 2002 (American Thoracic Society, 2002). A detailed description of the 6MWT is provided in Appendix 6.

Patients will perform 6MWT at Visit 1, 101, 106 and 199/PSD.

6.6.1.4 Other Clinical Outcome Assessments

NT-proBNP

Change from baseline in NT-proBNP (in log scale) at Week 12 is one of the two primary endpoints for this study. NT-proBNP provides value for the diagnosis, and helps in the management of patients with heart failure and predicts clinical outcome (mortality and morbidity).

NT-proBNP measurements will be performed by the central lab in all patients at Visits 1, 101, 103, 105, and 199/PSD. 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. Any, local measurements of BNP or NT-proBNP during the course of the study is strongly discouraged.

7 Safety monitoring

7.1 Adverse events

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

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

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

[redacted]

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

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

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

Adverse events must be recorded in the Adverse Events eCRF 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

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

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

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

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

[redacted]

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

7.2 Serious adverse events

7.2.1 Definition of SAE

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

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

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

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

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

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

[redacted]

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent until either screen failure or until 30 days after the last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment.

At a minimum, randomized 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.

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

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

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

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

7.2.2.1 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 these will not be unblinded and will not be reported as SUSARs to regulatory agencies, ECs, or investigators during the study. These events will be unblinded and presented in the

[redacted]

clinical study report (CSR) after unblinding at the end of the study, and any SUSARs will be reported also at the end of the study.

If specifically requested by a local Health Authority (HA), 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 HA 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 HA will be expedited to the HA 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 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.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver eCRF pages

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

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

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation.

[redacted]

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

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

For the liver events:

- 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 must be recorded on appropriate eCRF pages, including the liver event overview eCRF pages.

7.4 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum event:
  - Serum events are outlined in detail in Appendix 3; surveillance situation (decrease in eGFR ≥ 25% from randomization) and action situation (decrease in eGFR ≥ 40% from randomization) are described
- Urine event
  - new onset (≥ 1 +) proteinuria; confirmed by doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable)
  - new onset (≥ 1 +), hematuria or glycosuria

Every renal laboratory trigger or renal event as defined in Table 15-1 in Appendix 3 should be followed up by the investigator or designated personnel at the trial site.

7.5 Reporting of study treatment errors including misuse/abuse

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

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

[redacted]

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

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

Table 7-2 Guidance for capturing the study treatment errors including misuse/abuse

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

7.6 Pregnancy reporting

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

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

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

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 data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, 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. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics

organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain 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 eCRFs 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 data capture and/or data entry. 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

The trial will be conducted in a fully validated Data Capture system which conforms to US CRF 21 Part 11 requirements. Investigator site staff will not be given access to the system until they have been trained. Designated investigator staff will enter the data required by the protocol into the Data Capture system. Automatic validation programs within the system check for data discrepancies in the eCRFs and by generating appropriate error messages, allow the data to be confirmed or corrected by the investigator staff. The investigator staff must certify that the data entered 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 eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

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

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

[redacted]

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

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

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

8.4 Data monitoring committee

An established program level Data Monitoring Committee (DMC) independent of Novartis that reviews safety data from LCZ696 studies will be used for this study. The DMC will review SAEs in an unblinded manner on a regular basis and determine if it is safe to continue the study. Any major recommendation from the DMC will be communicated to the Executive Committee and must be reviewed and ratified by the Executive Committee in consultation with Novartis prior to its enactment.

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

8.5 Adjudication committee

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. The project-level angioedema adjudication committee will be used for this trial.

[redacted]

9 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

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, and the exception of those patients who have been inadvertently randomized within a wrong stratum (ACEi, ARB, No RASi) and have not received study drug. 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 set.

The safety (SAF) set 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 SAF 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 set 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.

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, BNP, and vital signs. BMI will be calculated as weight (kg) / height^2 (m^2) from the collected height and weight at Visit 1 (screening). Continuous variables will be summarized using n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequencies and percentages.

The FAS will be used 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.

[redacted]

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 SAF.

The number and percentage of patients on different CV background medications (eg 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 variables

The primary objectives are to demonstrate that LCZ696 is superior to individualized medical therapy for comorbidities in reducing NT-proBNP from baseline after 12 weeks of treatment, and/or in improving exercise capacity as assessed by the 6MWT at Week 24 in a subset of patients with B6MWD ranging from 100 meters to 450 meters.

9.4.1 Primary variables

The primary efficacy variables are the change from baseline in log(NT-proBNP) at Week 12, and the change from baseline in six-minute walk distance (6MWD) at Week 24.

For patients who have died, the 6MWD after the death will be defined as zero.

For patients who permanently discontinue from study treatment, assessment values collected after permanent discontinuation will generally be included in the analysis.

9.4.2 Statistical model, hypothesis, and method of analysis

Testing strategy

The following primary null hypotheses will be included in the testing strategy.

- H_1: LCZ696 is no better than the comparator in change from baseline in log(NT-proBNP) at Week 12 in the overall study population
- H_2: LCZ696 is no better than the comparator in change from baseline in 6MWD at Week 24 in patients with B6MWD ranging from 100 meters to 450 meters.

The following secondary null hypotheses will be included in the testing strategy.

- H_3: LCZ696 is no better than the comparator in change from baseline in KCCQ CSS at Week 24 in the overall study population.
- H_4: LCZ696 is no better than the comparator in NYHA change from baseline at Week 24 in the overall study population.

Each null hypothesis is tested against the one-sided alternative that LCZ696 is better than the comparator in the corresponding variable.

In order to control the family-wise type-I error rate at the one-sided 0.025 significance level, a sequentially rejective multiple testing procedure based on the graphical presentation (Bretz et al 2009) will be employed, whereby H_1 and H_2 will be tested first at initially assigned level of one-sided $(9/10) \times \alpha = 0.0225$ and one-sided $(1/10) \times \alpha = 0.0025$, accordingly. If H_1 and/or H_2 are rejected, the alpha for the rejected null hypotheses will be propagated to H_3, such that, H_3

[redacted]

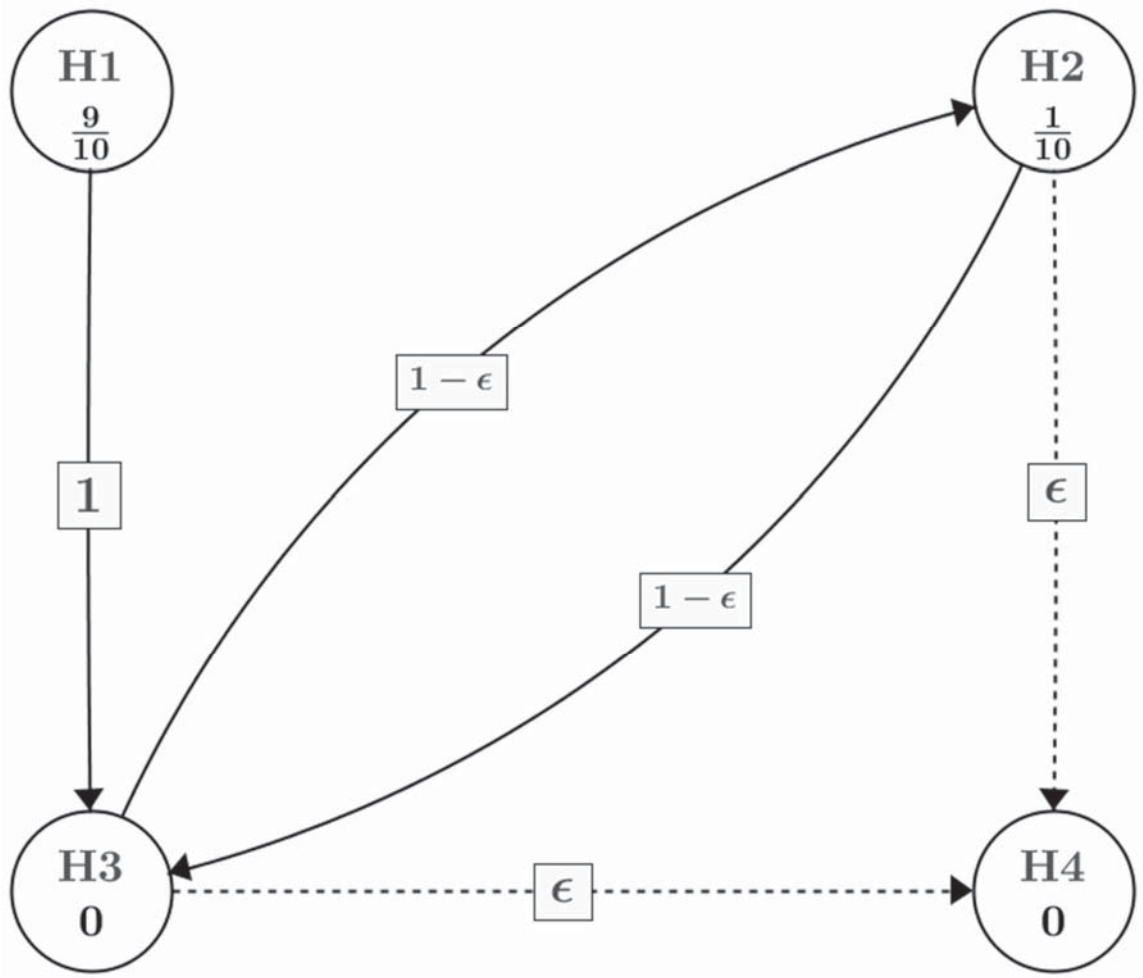
will be tested at the updated alpha level (one-sided 0.025 if both H_1 and H_2 are rejected; one-sided 0.0225 if H_1 is rejected but H_2 is not rejected; one-sided 0.0025 if H_2 is rejected but H_1 is not rejected); if H_3 is rejected, the alpha will be propagated to H_2 or H_4 based on the initial step rejection status.

- With H_1 rejected but H_2 not rejected at the initial step, if H_3 is rejected at one-sided 0.0225, the alpha will be propagated to H_2, such that, H_2 will be tested again at one-sided 0.025; if H_2 is rejected at one-sided 0.025, the alpha will be further propagated to H_4. Otherwise, the testing procedure will stop.
- With H_2 rejected but H_1 not rejected at the initial step, if H_3 is rejected at one-sided 0.0025, the alpha will be propagated to H_4, such that, H_4 will be tested at one-sided 0.0025. Otherwise, the testing procedure will stop.
- With both H_1 and H_2 rejected at the initial step, if H_3 is rejected at one-sided 0.025, the alpha will be propagated to H_4, such that, H_4 will be tested at full alpha (one-sided 0.025). Otherwise, the testing procedure will stop.

Figure 9-1 provides graphical illustration of the sequentially rejective testing procedure.

[redacted]

Figure 9-1 Graphical illustration of the sequentially rejective testing procedure



Based on the above testing procedure, if applicable, H_1, H_2 and H_3 will be tested based on the corresponding MMRM models (Section 9.4.2, Section 9.5.1.1), H_4 will be tested based on the longitudinal proportional cumulative odds model (Section 9.5.1.3)

If statistical significance had been established in the mean difference in change from baseline to Week 24 for KCCQ CSS, the following responders will be analyzed accordingly, based on the longitudinal binary logistic regression models (Section 9.5.1.1), to further illustrate the clinical relevance of the observed differences in terms of proportion of responders.

- KCCQ CSS improvement (defined by at least 5 points improvement);
- KCCQ CSS deterioration (defined by at least 5 points deterioration);

No multiplicity adjustment will be done for these supportive responder analyses (i.e., the tests for the responder analyses will be performed at nominal level of one-sided 0.025).

NT-proBNP analyses

The changes from baseline in log(NT-proBNP) will be analyzed using a mixed model for repeated measures (MMRM), in which, the response variable will be the changes from baseline in log(NT-proBNP); stratum (defined by prior ACEi/ARB medication usage [ACEi, ARB, None]), region, treatment (LCZ696, individualized medical therapy), visit and treatment-by-visit interaction will be included as fixed-effect factors; baseline log(NT-proBNP), stratum-by-baseline and visit-by-baseline interactions will be included as covariates; the within-patient covariance will be modeled using an unstructured covariance matrix (a common matrix for the two treatment groups). The analysis will include all post-baseline scheduled visits up to Week 12 (Week 4, Week 12) and will be performed based on the likelihood method with an assumption of missing at random (MAR) for missing data (Siddiqui et al 2009, National Research Council 2010).

Based on the MMRM model, the primary null hypothesis, H_1, will be tested based on the testing strategy, the estimates and the two-sided 95% confidence intervals will be provided for the adjusted geometric means for the ratio to baseline in NT-proBNP at Week 12 in each of the two treatment groups (LCZ696 and individualized medical therapy), and for the ratio of the adjusted geometric means (LCZ696 over individualized medical therapy).

The FAS will be used for the above primary analyses.

As a supportive analysis, the same approach will also be performed on the PPS.

6MWD analyses

The changes from baseline in 6MWD will be analyzed using a MMRM model, in which, the response variable will be the changes from baseline in six-minute walk distance; stratum (defined by prior ACEi/ARB medication usage [ACEi, ARB, None]), region, treatment (LCZ696, individualized medical therapy), visit and treatment-by-visit interaction will be included as fixed-effect factors; baseline six-minute walk distance (B6MWD), baseline systolic blood pressure (BSBP), stratum-by-B6MWD, stratum-by-BSBP and visit-by-B6MWD interactions will be included as covariates; the within-patient covariance will be modeled using an unstructured covariance matrix (a common matrix for the two treatment groups). The analysis will include all patients with B6MWD ranging from 100 meters to 450 meters, and all post-baseline scheduled visits up to Week 24 (Week 16 and Week 24), and will be performed based on the likelihood method with an assumption of MAR for missing data (other than due to death).

Based on the MMRM model, the primary null hypothesis, H_2, will be tested based on the testing strategy, the estimates and the two-sided 95% confidence intervals will be provided for the adjusted means for the change from baseline in 6MWD at Week 24 in each of the two treatment groups (LCZ696 and individualized medical therapy), and for the adjusted mean difference (LCZ696 minus individualized medical therapy) at Week 24.

All patients in the FAS with B6MWD ranging from 100 meters to 450 meters will be used for the above primary analysis.

As a supportive analysis, the same approach will also be performed on the FAS with all patients included, regardless of B6MWD values, and on the PPS.

[redacted]

9.4.3 Handling of missing values/censoring/discontinuations

Missing data will be handled with the likelihood method with the assumption that they are MAR in the primary analyses.

9.4.4 Sensitivity analyses

In order to explore the robustness of the MAR assumption on the primary analysis, a sensitivity analysis will be carried out which assesses the situation where the data are missing not at random (MNAR); In particular, the sensitivity analysis will assume that LCZ696 patients who discontinue due to adverse events, death or lack of efficacy will not have adhered to therapy if they had stayed in the study.

A controlled multiple imputation approach based on pattern mixture models will be applied (Carpenter and Kenward 2013), whereby all missing data of patients in the LCZ696 group who permanently discontinue study treatment due to: adverse events, death or lack of efficacy, will be assumed to behave like patients in the control group (individualized medical therapy) after permanent discontinuation and will be imputed based on the data from patients in the control group (individualized medical therapy) according to the stratum (defined by prior ACEi/ARB medication usage [ACEi, ARB, None]).

All other missing data will be considered as MAR within each arm and will be imputed using a multiple imputation approach (Carpenter and Kenward 2013) based on observed data within each arm according to the stratum. Of note, patients who permanently discontinue study treatment, are not considered discontinued from the study. It is planned to continue to collect and use data at scheduled visits even after permanent discontinuation of study treatment.

Furthermore, the missing data patterns in the change from baseline in log(NT-proBNP) and the change from baseline in 6MWD will be explored via by-treatment-group box plots for patients who permanently discontinue from study treatment due to adverse events, death or lack of efficacy, for patients who permanently discontinue from study treatment due to any other reasons, for patients who did not permanently discontinue from study treatment, and for patients who take open label LCZ696 after permanent discontinuation from study treatment.

As additional supportive analyses, the primary analyses for the primary variables (the change from baseline in log[NT-proBNP] at Week 12, and the change from baseline in 6MWD at Week 24) described in Section 9.4.1 will be performed for the following data as applicable:

- Data where the 6MWD after the death were set to missing for patients who died.
- Data where the last observation carry forward (LOCF) approach was performed for missing data.
- Data where the responses after the first dose of open-label RASi or open-label LCZ696 after permanent discontinuation of the study treatment will be set to missing and considered MAR. (This is called on-treatment analysis.)

The FAS will be used for the above analyses.

[redacted]

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

All secondary efficacy variables will be analyzed using the FAS, unless otherwise specified.

9.5.1.1 KCCQ clinical summary score change from baseline

For patients who have died, the KCCQ CSS after the death will be imputed as zero. For patients who permanently discontinue study treatment, values collected after permanent discontinuation will generally be included in the analysis.

The changes from baseline in KCCQ CSS will be analyzed using a MMRM model, in which, the response variable will be the changes from baseline in KCCQ clinical summary score; stratum (defined by prior ACEi/ARB medication usage [ACEi, ARB, None]), region, treatment (LCZ696, individualized medical therapy), visit and treatment-by-visit interaction will be included as fixed-effect factors; baseline KCCQ clinical summary score (BCSS), baseline systolic blood pressure (BSBP), stratum-by-BCSS, stratum-by-BSBP, and visit-by-BCSS interactions will be included as covariates; the within-patient covariance will be modeled using an unstructured covariance matrix (a common matrix for the two treatment groups). If the model fitting procedure does not converge, the AR(1) covariance structure will be used. The analysis will include all post-baseline scheduled visits up to Week 24 (Week 4, Week 12, Week 16 and Week 24) and will be performed based on the likelihood method with an assumption of MAR for missing data (other than due to death).

Based on the MMRM model, the secondary null hypothesis, H_3, will be tested (if applicable) based on the testing strategy, the estimates and the two-sided 95% confidence intervals will be provided for the adjusted means for the change from baseline in KCCQ CSS at Week 24 in each of the two treatment groups (LCZ696 and individualized medical therapy), and for the adjusted mean difference (LCZ696 minus individualized medical therapy) at Week 24.

In addition, the improvement and the deterioration in KCCQ CSS will be analyzed separately using longitudinal binary logistic regression models, in which, the response variables will be, accordingly, the KCCQ CSS improvement (event defined by at least 5-points improvement in KCCQ CSS) and the KCCQ CSS deterioration (event defined by at least 5-points deterioration in KCCQ clinical summary score); stratum (defined by prior ACEi/ARB medication usage [ACEi, ARB, None]), region, treatment (LCZ696, individualized medical therapy), visit and treatment-by-visit interaction will be included as fixed-effect factors; BCSS, BSBP, stratum-by-BCSS, stratum-by-BSBP and visit-by-BCSS interactions will be included as covariates; patient-specific intercepts will be included as random effects. The analysis will include all post-baseline scheduled visits up to Week 24 (Week 4, Week 12, Week 16 and Week 24) and will be performed based on the likelihood method with an assumption of MAR for missing data (other than due to death).

Based on the longitudinal binary logistic regression models, the estimates and the two-sided 95% confidence intervals will be provided for the adjusted odds ratios (LCZ696 over individualized medical therapy) at Week 24.

Besides, the KCCQ clinical summary score and the change from baseline in KCCQ CSS summary score will be summarized by visit and treatment group using n, mean, standard

[redacted]

deviation, min, Q1, median, Q3 max; the improvement and the deterioration in KCCQ CSS of at least 5-points will be summarized by visit and treatment group using frequencies and percentages.

The FAS will be used for the above analyses.

9.5.1.2 KCCQ overall summary score change from baseline

As an exploratory analysis, the same analyses as KCCQ CSS will also be performed for KCCQ OSS, except that the baseline KCCQ CSS in the models will be replaced by baseline KCCQ OSS.

The FAS will be used for the above analyses.

9.5.1.3 NYHA class change

The NYHA class change is a three-category ordinal variable with levels: "improved", "unchanged", and "worsened", defined by at least one class improvement, no change, at least one class worsening, in NYHA class, respectively. For patients who died, the NYHA class change after the death will be categorized into "worsened". For patients who permanently discontinue study treatment, values collected after permanent discontinuation will generally be included in the analysis.

The NYHA class change will be analyzed using a longitudinal proportional cumulative odds model, in which, the response variable will be the NYHA class change (order defined by "improved" < "unchanged" < "worsened"); stratum (defined by prior ACEi/ARB medication usage [ACEi, ARB, None]), region, treatment (LCZ696, individualized medical therapy), visit, treatment-by-visit interaction, baseline NYHA class, stratum-by-baseline and visit-by-baseline interactions will be included as fixed-effect factors; BSBP and stratum-by-BSBP interaction will be included as covariates; patient-specific intercepts will be included as random effects. The analysis will include all post-baseline scheduled visits up to Week 24 (Week 2, Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24) and will be performed based on the likelihood method with an assumption of MAR for missing data (other than due to death).

Based on the longitudinal proportional cumulative odds model, the secondary null hypothesis, H_4, will be tested (if applicable) based on the testing strategy, the estimate and the two-sided 95% confidence interval will be provided for the adjusted odds ratio (LCZ696 over individualized medical therapy) at Week 24.

In addition, the improvement and deterioration in NYHA class will be analyzed separately using longitudinal binary logistic regression models, in which, the response variables will be, accordingly, the NYHA class improvement (event defined by NYHA class change of level "improved") and the NYHA class deterioration (event defined by NYHA class change of level "worsened"); stratum (defined by prior ACEi/ARB medication usage [ACEi, ARB, None]), region, treatment (LCZ696, individualized medical therapy), visit, treatment-by-visit interaction, baseline NYHA class, stratum-by-baseline and visit-by-baseline interactions will be included as fixed-effect factors; BSBP and stratum-by-BSBP interaction will be included as covariates; patient-specific intercepts will be included as random effects. The analysis will include all post-baseline scheduled visits up to Week 24 (Week 2, Week 4, Week 8, Week 12,

Week 16, Week 20 and Week 24) and will be performed based on the likelihood method with an assumption of MAR for missing data (other than due to death).

Based on the longitudinal binary logistic regression models, the estimates and the two-sided 95% confidence intervals will be provided for the adjusted odds ratios (LCZ696 over individualized medical therapy) at Week 24.

Besides, the NYHA class and the NYHA class change will be summarized by visit and treatment group using frequencies and percentages.

The FAS will be used for the above analyses.

9.5.1.4 SF-36 physical component summary score

For patients who have died, the SF-36 PCS score after the death will be imputed as zero. For patients who permanently discontinue from study treatment, values collected after permanent discontinuation will generally be included in the analysis.

The changes from baseline in SF-36 PCS score will be analyzed using a MMRM model, in which, the response variable will be the changes from baseline in SF-36 physical component summary score; stratum (defined by prior ACEi/ARB medication usage [ACEi, ARB, None]), region, treatment (LCZ696, individualized medical therapy), visit and treatment-by-visit interaction will be included as fixed-effect factors; baseline SF-36 physical component summary score (BPSS), BSBP, stratum-by-BPSS, stratum-by-BSBP and visit-by-BPSS interactions will be included as covariates; the within-patient covariance will be modeled using an unstructured covariance matrix (a common matrix for the two treatment groups). The analysis will include all post-baseline scheduled visits up to Week 24 (Week 16 and Week 24) and will be performed based on the likelihood method with an assumption of MAR for missing data (other than due to death).

Based on the MMRM model, the estimates and the two-sided 95% confidence intervals will be provided for the adjusted means for the change from baseline in SF-36 PCS score at Week 24 in each of the two treatment groups (LCZ696 and individualized medical therapy), and for the adjusted mean difference (LCZ696 minus individualized medical therapy) at Week 24.

In addition, the SF-36 PCS score will be summarized by visit and treatment group using n, mean, standard deviation, min, Q1, median, Q3 max.

The FAS will be used for the above analyses.

9.5.1.5 SF-36 mental component summary score

The same analyses as SF-36 PCS score will also be performed for SF-36 MCS score, except that the BPSS in the models will be replaced by baseline SF-36 MCS score (BMSS), stratum-by-BPSS and visit-by-BPSS interactions in the analysis models will be replaced by stratum-by-BMSS and visit-by-BMSS interactions.

The FAS will be used for the above analyses.

[redacted]

9.5.1.6 Missing data handling in the secondary endpoint analyses

In the analyses described in Sections 9.5.1.1 to 9.5.1.5, death is considered the worst possible outcome and hence scheduled visits after death will be imputed accordingly. Other missing data is assumed to be MAR.

As a sensitivity analysis, the controlled multiple imputation approach based on pattern mixture models will be applied (Carpenter and Kenward 2013), whereby all missing data of patients in the LCZ696 group who permanently discontinue study treatment due to: adverse events or lack of efficacy, will be assumed to behave like patients in the control group (individualized medical therapy) after permanent discontinuation and will be imputed based on the data from patients in the control group (individualized medical therapy) according to the stratum (defined by prior ACEi/ARB medication usage [ACEi, ARB, None]).

All other missing data will be considered as MAR within each arm and will be imputed using a multiple imputation approach (Carpenter and Kenward 2013) based on observed data within each arm according to the stratum. Of note, patients who permanently discontinue study treatment, are not considered discontinued from the study. It is planned to continue to collect and use data at scheduled visits even after permanent discontinuation of study treatment.

Furthermore, the missing data patterns in the secondary endpoint variables will be explored via by-treatment-group box plots or bar plots as appropriate for patients who permanently discontinue from study treatment due to adverse events or lack of efficacy, for patients who permanently discontinue study treatment due to any other reasons, for patients who did not permanently discontinue study treatment and for patients who take open label LCZ696 after permanent discontinuation from study treatment.

As additional supportive analyses, the main analyses for the secondary endpoints described in Sections 9.5.1.1 to 9.5.1.5 will be performed for the following data.

- Data where the responses after the death were set to missing for patients who died.
- Data where the LOCF approach was performed for missing data.
- Data where the responses after the first dose of open-label RASi or open-label LCZ696 after permanent discontinuation of study treatment will be set to missing and considered MAR. (This is called on-treatment analysis.)

9.5.1.7 Subgroup analyses

Subgroup analyses will be performed utilizing the corresponding analysis model used for primary and secondary endpoints, after adding the factors of subgroup and subgroup-treatment interaction to the model, to assess the consistency of the treatment effects across key clinically relevant subgroups listed below. The estimated treatment effect, two-sided 95% confidence interval, and the interaction p-value will be provided for each of the subgroups.

- Stratum (defined by prior ACEI/ARB medication usage [ACEi, ARB, None])
- Age group (< 65 years, ≥ 65 years; < 75 years, ≥ 75 years)
- Sex
- Region
- Baseline NYHA (Class I-II, Class III-IV)

[redacted]

- Diabetes (Yes [history of diabetes mellitus or HbA1c at screening ≥ 6.5%], No[no history of diabetes mellitus and HbA1c at screening < 6.5%])

9.5.2 Safety variables

The safety and tolerability assessments are listed below:

- Identified and potential risks (including angioedema, hyperkalemia, hypotension, renal dysfunction, liver)
- 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 frequencies 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 (eg 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 SAF. There will be no formal statistical inference analysis.

9.6 Analysis of exploratory variables

9.6.1 NT-proBNP up to Week 24

The changes from baseline in log(NT-proBNP) will be analyzed using a MMRM model, in which, the response variable will be the changes from baseline in log-transformed NT-proBNP; stratum (defined by prior ACEi/ARB medication usage [ACEi, ARB, None]), region, treatment (LCZ696, individualized medical therapy), visit and treatment-by-visit interaction will be

[redacted]

included as fixed-effect factors; baseline log-transformed NT-proBNP, stratum-by-baseline and visit-by-baseline interactions will be included as covariates; the within-patient covariance will be modeled using an unstructured covariance matrix (a common matrix for the two treatment groups). If the model fitting procedure does not converge, the AR(1) covariance structure will be used. The analysis will include all post-baseline scheduled visits up to Week 24 (Week 4, Week 12 and Week 24) and will be performed based on the likelihood method with an assumption of MAR for missing data.

Based on the MMRM model, the estimates and the two-sided 95% confidence intervals will be provided for the adjusted geometric means for the ratio of NT-proBNP over baseline NT-proBNP in each of the two treatment groups (LCZ696 and individualized medical therapy) at Week 24; and for the adjusted geometric mean ratio (LCZ696 over individualized medical therapy) at Week 24.

The FAS will be used for the above analyses

9.6.2 Estimated glomerular filtration rate (eGFR)

For the rate change in eGFR, the eGFR slope will be estimated from a mixed model, in which, the response variable will be the eGFR; stratum (defined by prior ACEi/ARB medication usage [ACEi, ARB, None]), region, and treatment (LCZ696, individualized medical therapy) will be included as fixed-effect factors; time (in month) and treatment-by-time interaction will be included as covariates; a patient level random intercept and a patient level random slope (time) will be included as random effects with a unstructured covariance matrix (a common matrix for the two treatment groups). Here, the time is computed as (date of assessment – date of randomization + 1)/30.4375. The analysis will include all assessments from central lab at all visits up to Week 24 (Baseline to Week 24, scheduled or unscheduled) and will be performed based on the likelihood method with an assumption of MAR for missing data.

Based on the mixed model, the estimates and the two-sided 95% confidence intervals will be provided for the adjusted mean slope in each of the two treatment groups (LCZ696 and individualized medical therapy), and for the adjusted mean difference (LCZ696 minus individualized medical therapy).

In addition, the eGFR and the change from baseline in eGFR will be summarized by visit and treatment group.

The FAS will be used for the above analyses.

9.7 Interim analyses

No efficacy interim analysis is planned.

9.8 Sample size calculation

The sample size (2500 randomized patients) has been chosen in order to provide adequate power to evaluate both primary and secondary endpoints.

With an alpha of one-sided 0.0225, the power for the NT-proBNP will range from 92% to more than 99%, to detect a relative reduction ranging from 11% to 24% in change from baseline to Week 12 in NT-proBNP, assuming a standard deviation of 0.81 for change from baseline in the

log-transformed NT-proBNP (based on PARAMOUNT-HF data of patients with baseline KCCQ CSS < 75) and an overall drop-out rate of 10%.

With an alpha of one-sided 0.0025, the power for the 6MWD will range from 90% to 99%, to detect a mean difference ranging from 22 meters to 30 meters in change from baseline to Week 24 in 6MWD, assuming a standard deviation of 120 meters (Ingle et al 2005), an overall drop-out rate of 10%, and an overall proportion of 88% for patients with B6MWD ranging from 100 meters to 450 meters.

With an alpha of one-sided 0.0225, the power for the KCCQ CSS will range from 87% to 99%, to detect a mean difference ranging from 2 points to 3 points in change from baseline to Week 24 in KCCQ CSS, assuming a standard deviation of 15.52 points for change from baseline in the KCCQ CSS (based on PARAMOUNT-HF data of patients with baseline KCCQ CSS < 75) and an overall drop-out rate of 5%.

All alpha levels in the following sample size calculations will be one-sided 0.025.

This sample size of 2500 randomized patients aims to provide a power of approximately 90%, with the one-sided alpha level of 0.025, to demonstrate a 5% responder advantage in at least 5-point deterioration for patients who are treated with LCZ696 over individualized medical therapy when assuming the proportion of patients with at least 5-point deterioration from baseline to Week 24 in the individualized medical therapy group is 20% (based on PARAMOUNT-HF data of patients with baseline KCCQ CSS < 75) and an overall 5% dropouts.

With the same assumption of the dropout rate, this sample size will also provide a power of 69% to detect a 5% responder advantage in at least 5-points improvement in the KCCQ clinical summary score for patients who are treated with LCZ696 over individualized medical therapy when assuming the proportion of patients with at least 5-points improvement from baseline to Week 24 in the individualized medical therapy group is 55% (based on PARAMOUNT-HF data of patients with baseline KCCQ CSS < 75).

The sensitivity of power for at least 5-points deterioration in the KCCQ clinical summary score to changes in assumptions is outlined in Table 9-1.

Table 9-1 Sensitivity of power for at least 5-points deterioration in KCCQ clinical summary score to changes in assumptions for N = 2500

Assumed probability of at least 5-points deterioration			Power for at least 5-points deterioration (one-sided alpha = 0.025)			
Individualized medical therapy	LCZ696	Difference	With 5% drop-out rate	With 10% drop-out rate	With 15% drop-out rate	With 20% drop-out rate
20%	15%	-5%	90%	88%	86%	84%
35%	30%	-5%	74%	72%	69%	67%

The sensitivity of power for at least 5-points improvement in the KCCQ CSS to changes is outlined in Table 9-2.

Table 9-2 Sensitivity of power for at least 5-points improvement in KCCQ clinical summary score to changes in assumptions for N = 2500

Assumed probability of at least 5-points improvement			Power for at least 5-points improvement (one-sided alpha = 0.025)			
Individualized medical therapy	LCZ696	Difference	With 5% drop-out rate	With 10% drop-out rate	With 15% drop-out rate	With 20% drop-out rate
55%	60%	5%	69%	67%	65%	62%
41%	46%	5%	69%	67%	64%	62%

The assumed dropout rates (Table 9-1 and Table 9-2) are for the purpose of power sensitivity analysis. During the conduct of the study, all efforts will be made to reduce missing data.

For other secondary endpoints, this sample size will provide adequate powers for reasonable effect size assumptions: power of 90% for NYHA class change, assuming 14% of the patients in the comparator and 19% of the patients in the LCZ696 group are improved in NYHA class change, 6% of the patients in the comparator and 5% of the patients in the LCZ696 group are worsened in NYHA class change (based on Week 24 PARAMOUNT-HF data of patients with baseline KCCQ CSS < 75); and power of approximately 90% to detect a between treatment group mean difference of 1.4 points or more in change from baseline in SF-36 physical component summary score, assuming a standard deviation of 10-points (Edelmann et al 2013).

East 6.3 was used for the sample size calculations.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

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

*[*] For **Germany only**, the first paragraph will read as follows:*
Eligible patients may only be included in the study after providing written (witnessed, where

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

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

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

10.3 Responsibilities of the investigator and IRB/IEC

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

10.4 Publication of study protocol and results

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

10.5 Quality Control and Quality Assurance

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

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

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

11 Protocol adherence

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

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

11.1 Protocol amendments

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

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13 Appendix 1: Clinically notable laboratory values and vital signs

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

Hematology

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

Blood Chemistry

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

[redacted]

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

Table 14-1 Liver event and laboratory trigger definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

Table 14-2 Follow-up requirements for liver events and laboratory triggers

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

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

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

[redacted]

15 Appendix 3: Specific Renal Alert Criteria and Actions

Table 15-1 Specific renal alert criteria and actions

Serum Event	
See detailed guidance below	
Urine Event	
New dipstick proteinuria ≥1+ Albumin- or Protein-creatinine ratio increase ≥ 2-fold	Confirm value after 24 to 48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick glycosuria ≥1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: sCr level with ± 10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ± 50% variability over last 6 months.	

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 randomization (Visit 101) (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

[redacted]

Action situation

If a patient's eGFR decreases by ≥ 40% from randomization (Visit 101) (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 drugs. If the investigator judges that study drugs have 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.

[redacted]

16 Appendix 4 – Treatment guidelines for hyperkalemia (serum potassium* greater than 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)

1. Confirm potassium concentration in a non-hemolyzed sample
2. Reinforce low potassium diet and restriction of food/drinks with high potassium content (eg orange juice, melon, bananas, tomatoes, dried fruits, potatoes, low-salt substitutes, tomatoes, coffee, etc.)
3. Correct metabolic acidosis if necessary.
4. 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 (eg amiloride and triamterene) including in combination products with thiazide or loop diuretics
    - Potassium supplements, eg potassium chloride
    - Salt substitutes
    - Non-steroidal anti-inflammatory drugs (NSAIDs)
    - Cyclo-oxygenase-2 (COX-2) inhibitors
    - Trimethoprim and trimethoprim-containing combination products, such as Bactrim® and Septra® (trimethoprim/sulfamethoxazole fixed combination)
    - Herbal Supplements:
        - For example, Noni juice, alfalfa (*Medicago sativa*), dandelion (*Taraxacum officinale*), horsetail (*Equisetum arvense*), nettle (*Urtica dioica*), milkweed, lily of the valley, Siberian ginseng, hawthorn berries

[redacted]

5. 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.
6. 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 drugs, 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 drugs 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 drugs 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 drugs
- 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 drugs without individualized case discussion with and permission from Novartis medical monitor or his/her designee.

* or equivalent plasma potassium value

[redacted]

17 Appendix 5 – Guidelines for the management of hypotension

Guidelines

1. Investigator should monitor BP closely
2. If symptomatic hypotension occurs:
   a. Correct any treatable cause, eg 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 drugs are 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 drugs should be down-titrated or even temporarily withdrawn. The dose re-challenge and medications adjust guidelines described in Section 5.5.5 should be adhered to as much as possible.

[redacted]

18 Appendix 6 – Six-minute walk test

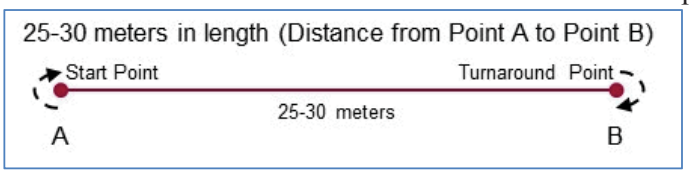
A standardized 6MWT will be performed in accordance with the guidelines of the American Thoracic Society 2002. All patients will undergo the 6MWT at Visit 1 (screening), 101, 106 & 199.

The 6MWT is preferably performed indoors along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course must be 25-30 meters in length; therefore, a corridor of at least 30 meters is required for the test. The beginning and end of the course should be marked with a cone. The patient will be asked to walk as far as possible for 6 minutes timed on a stop watch. The number of complete course lengths walked will be recorded as well as any partial length walked. If the patient discontinues the test prematurely, the time, distance and reason for discontinuation will be recorded in the eCRFs. During the study, the 6MWT should be performed about the same time of day on each occasion.

Prior to the test, the patient should sit at rest in a chair, located near the starting position for at least 10 minutes and resting baseline heart rate and blood pressure measured. Then, have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale. Heart rate, blood pressure, dyspnea and overall fatigue using the Borg scale should be repeated immediately after completion of the test.

REQUIRED EQUIPMENT

1. Countdown timer (or stopwatch)
2. Two small cones or similar item to mark the turnaround points



3. A chair that can be easily moved along the walking course
4. Sphygmomanometer
5. Automated electronic defibrillator
6. Source Document Worksheet

PATIENT PREPARATION

1. At screening visit assess eligibility as per Exclusion Criterion #8 and refer to the provided eligibility check list.
2. Comfortable clothing should be worn
3. Appropriate shoes for walking should be worn
4. Patients should use their usual walking aids during the test (cane, walker, etc.)
5. The patient's usual medical regimen should be continued
6. A light meal is acceptable before early morning or early afternoon tests
7. Patients should not have exercised vigorously within 2 hours of beginning the test

[redacted]

MEASUREMENTS

1. Testing should be performed about the same time of day to minimize intraday variability
2. A "warm-up" period before the test should not be performed
3. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, and make sure that clothing and shoes are appropriate.
4. Measure and record baseline heart rate and blood pressure with the patient resting on a chair for at least 10 minutes
5. Have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale
6. Move to the starting point
   Instruct the patient as follows:

"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

Demonstrate by walking one length yourself. Walk and pivot around a cone briskly.

"Are you ready to do that?
Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

Start now, or whenever you are ready."

7. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.
8. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the lengths. Each time the participant reaches a turnaround point, mark the completed length on the source document worksheet.

After the first minute, tell the patient the following (in even tones):
"You are doing well. You have 5 minutes to go."

When the timer shows 4 minutes remaining, tell the patient the following:
"Keep up the good work. You have 4 minutes to go."

[redacted]

When the timer shows 3 minutes remaining, tell the patient the following:
"You are doing well. You are halfway done."

When the timer shows 2 minutes remaining, tell the patient the following:
"Keep up the good work. You have only 2 minutes left."

When the timer shows only 1 minute remaining, tell the patient:
"You are doing well. You have only 1 minute to go."

Do not use other words of encouragement (or body language to speed up).

If the patient stops walking during the test and needs a rest, say this:
"You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the patient sits down, the test is over or if the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, say this:
"In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

When the timer rings (or buzzes), say: ***"Stop!"*** Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

9. Post-test: Immediately after completion of the test, record the post walk Borg dyspnea and fatigue levels and ask:
   "What if anything, kept you from walking farther (faster)?"
10. Measure and record heart rate and blood pressure while the patient is sitting
11. Record the number of lengths walked
12. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
13. Congratulate the patient on good effort and offer a drink of water.

Reference: American Thoracic Society, 2002

[redacted]