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LCZ696

Clinical Trial Protocol CLCZ696I12201 / NCT04164732

A multi-center, randomized, placebo-controlled patient and investigator-blinded study to explore the efficacy of oral sacubitril/valsartan in adult patients with non-obstructive hypertrophic cardiomyopathy (nHCM)

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study procedures. Note: The SOM will not be a part of the Clinical Study Report.

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List of abbreviations

ACEI	Angiotensin-converting-enzyme inhibitor (ACE inhibitor)
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANP	Atrial natriuretic peptide
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
AST	aspartate aminotransferase
AT1	Angiotensin II type 1
b.i.d.	twice a day
BMI	Body Mass Index
BNP	Brain-type natriuretic peptide
BP	Blood pressure
BUN	blood urea nitrogen
cGMP	cyclic guanosine monophosphate
CMO&PS	Chief Medical Office & Patient Safety
CNP	C-type natriuretic peptide
CPET	Cardiopulmonary exercise testing
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
ELISA	Enzyme-linked immunosorbent assay
EOS	End of study
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	human Chorionic Gonadotropin
HCM	Hypertrophic cardiomyopathy
HCV	Hepatitis C virus
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HIV	human immunodeficiency virus
i.v.	intravenous
IB	Investigator's 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
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
[redacted]	[redacted]
LFT	Liver function test
LLOQ	lower limit of quantification
LV	Left ventricle (heart)
[redacted]	[redacted]
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MRA	Mineralocorticoid receptor antagonist
NEPi	Neprilysin inhibitor
nHCM	non-obstructive hypertrophic cardiomyopathy
NPR	Natriuretic peptide receptor
NYHA	New York Heart Association
p.o.	oral
PD	pharmacodynamic(s)
PDE-5	Phosphodiesterase-5
[redacted]	[redacted]
PPS	Per protocol set
[redacted]	[redacted]
PT	prothrombin time
[redacted]	[redacted]
QTcF	QT interval corrected by Fridericia's formula
RAS	Randomized analysis set
RBC	red blood cell(s)
SAE	serious adverse event
SBP	Systolic Blood Pressure
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
sMDRD	simplified Modification of Diet in Renal Disease
SMQ	Standardized MedDRA Query
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
ULN	upper limit of normal

VO2	Volume of Oxygen
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study patient
Dosage	Dose of the study treatment given to the subject 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.
Investigational drug/treatment	The drug whose properties are being tested in the study
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Run in Failure	A patient who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to patient's medications or other intervention)
Screen Failure	A patient who is screened but is not treated or randomized
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 treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 2 (April 2022)

Amendment rationale

[redacted]

In addition, text has been added to existing sections of the protocol for 1) clarification on the Informed Consent process prior to all assessments performed as well as 2) the investigator SAE reporting timelines.

Changes to the protocol

[redacted]

- **Section 5.1 Inclusion criteria**
  - Added additional text to emphasize to sites that Informed Consent must be signed *prior* to discontinuation of ACE-I/ARB during the >36 hour washout period, if applicable.

[redacted]

- **Section 10.1.3 SAE reporting**
  Added additional text for clarification on investigator reporting timelines for SAEs

Amendment 1 (February 2020)

Amendment rationale

The purpose of this amendment is to address concerns raised by several Health Authorities and Ethics Committees during their review of the protocol. First, the Health Authorities requested greater clarification on the use of a 250 pg/ml cutoff of NT-proBNP as a criterion for screening asymptomatic patients. A justification for this value has now been added into Section 4.2 of the protocol. Second, clarification of the risk of fetal harm was requested in Section 4.7 of the protocol. Third, further clarification of the scope of the interim analysis was also requested and has now been added to Section 12.7. Finally, a number of typographical errors in the inclusion and exclusion criteria listed in the Protocol Summary were corrected to be consistent with the inclusion and exclusion criteria listed in Section 5. Additional minor clarifications and typographical errors throughout the protocol have also been corrected.

Changes to the protocol

- **Protocol summary**
  - Key inclusion and exclusion criteria were corrected to reflect the criteria listed in Section 5 of the protocol.
- **Section 3 Study design**
  - Clarified the use of safety criteria to assess tolerability of study medication.
- **Section 4.2 Rationale for selection of patient population**
  - Added rationale for the NT-proBNP cutoff required to screen asymptomatic patients.
- **Section 4.7 Risks and benefits**
  - Clarified risk of fetal harm by study medication if women of childbearing potential become pregnant while on study medication.
- **Section 5.1 Inclusion criteria**
  - Inclusion criteria 4 has been updated to allow asymptomatic/NYHA Class I patients with peak VO_2 of 80% to enroll in the study to harmonize with exclusion criteria 4.
- **Section 5.2 Exclusion criteria**
  - Exclusion criteria 3 was clarified to exclude only those patients with a history of atrial fibrillation within 6 months of the screening/baseline visit.
- **Section 8 Visit schedule and assessments**
  - Corrected a typographical error to make clear the requirement for recording adverse events during the screening/baseline period.
- **Section 8.4.4 Laboratory evaluations**
  - Added clarification that plasma samples instead of serum samples can be collected for local laboratory analysis as per local practice.
- **Section 10.2.1 Liver safety monitoring**
  - Correction made to indicate that results of local liver chemistry tests associated with a liver event should be recorded in source documents rather than in the CRF.

- **Section 12.7 Interim Analysis**
  - Added clarification that the planned interim analysis will also include review of safety data.

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

IRBs/IECs

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

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

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

Protocol summary

Protocol number	CLCZ696I12201
Full Title	A multi-center, randomized, placebo-controlled patient and investigator-blinded study to explore the efficacy of oral sacubitril/valsartan in adult patients with non-obstructive hypertrophic cardiomyopathy (nHCM)
Brief title	Study of efficacy of oral sacubitril/valsartan in adult patients with non-obstructive hypertrophic cardiomyopathy
Sponsor and Clinical Phase	Novartis - Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine if LCZ696 is safe, tolerable and can improve exercise capacity (via improved peak VO_2) in non-obstructive HCM patient population over the course of 50 weeks of treatment. [redacted]
Primary Objective(s)	The primary objective of this study is to evaluate the efficacy of LCZ696 on cardiopulmonary exercise test (CPET) parameters in patients with non-obstructive HCM, based on Peak VO_2 , after 50 weeks of treatment
Secondary Objectives	To evaluate the safety and tolerability of LCZ696 in patients with non-obstructive HCM, based on standard safety assessments (AE, vital signs, ECGs, physical examinations and safety labs)
Study design	This multi-center study includes a single-blind (i.e., patient-blinded) treatment run-in period aimed to ensure as large a proportion as possible of patients tolerate LCZ696 throughout the study, followed by a randomized, placebo-controlled, parallel-group, patient and investigator-blinded study in patients with non-obstructive HCM, over a total of 50 week treatment period. The maximum study duration, from initial screening to end of study (EOS) for each patient is approximately 58 weeks.
Population	Approximately 44 male and female adult (≥ 18 years of age) non-obstructive HCM patients will be randomized into the study with the intention of 40 completing the 50 week treatment period.

Key Inclusion criteria	• Diagnosed with Hypertrophic Cardiomyopathy (hypertrophied and non-dilated left ventricle in the absence of any systemic cause) with a left ventricular wall thickness ≥ 13mm by the echocardiogram obtained during the screening/baseline period, based on local evaluation of echocardiographic images.
	• LVEF ≥ 50% by echocardiogram obtained during the screening/baseline period, based on local evaluation of echocardiographic images.
	• Symptoms consistent with New York Heart Association (NYHA) Class II-III heart failure by physician assessment, or asymptomatic/NYHA Class I patients with:
	  • NT-proBNP above 250 pg/ml and
	  • peak VO_2 of ≤80% of predicted based on age and gender.

Key Exclusion criteria	• Patients with a resting or provokable left ventricular outflow tract gradient of ≥30mm Hg, based on local evaluation of echocardiographic images obtained during the screening/baseline period. • Septal reduction procedure within 3 months of the screening/baseline visit. • Patients with a peak VO_2 on the screening/baseline cardiopulmonary exercise test of > 80% of predicted based on age and gender. • Patients who require treatment with ACE inhibitors, angiotensin receptor blockers (ARBs), or renin inhibitors. Patients who can discontinue ACE inhibitors, angiotensin receptor blockers, or renin inhibitors can participate if they are off these medicines for at least 36 hours prior to the screening/baseline assessments. • Known infiltrative or storage disorder causing cardiac hypertrophy that mimics hypertrophic cardiomyopathy, such as Fabry disease, or amyloidosis. • Systolic blood pressure of <100 mmHg or symptomatic hypotension during the screening/baseline period or treatment run-in period. • Contraindication to ARB administration, including hyperkalemia (serum K>5.2 mmol/L) or prior history of angioedema.
Study treatment	• LCZ696 at doses of 50 mg, 100 mg and 200 mg b.i.d. • Placebo to LCZ696
Efficacy assessments	Cardiopulmonary exercise testing (CPET)
[redacted]	
Key safety assessments	• Adverse event monitoring • Vital signs • Physical examinations • Monitoring of laboratory markers in blood • ECGs
[redacted]	
Data analysis	The primary analysis will assess the effect of LCZ696 on the change from baseline in peak VO_2 at week 50 compared to placebo. A longitudinal mixed effects model for the change from baseline will be used. The least-squares (LS) mean and associated 90% confidence interval (CI) for the change from baseline in peak VO_2 for each treatment, and the estimated mean treatment difference, the p-value, and the corresponding 2-sided 80% CI will be extracted from the model at each time point.
Key words	non-obstructive, hypertrophic cardiomyopathy, genetic cardiomyopathy

1 Introduction

1.1 Background

Hypertrophic Cardiomyopathy (HCM)

Hypertrophic cardiomyopathy (HCM) is a genetic, primary disorder of cardiac myocytes characterized by cardiac hypertrophy, unexplained by secondary causes, and a non-dilated left ventricle with preserved or increased ejection fraction (Marian and Braunwald 2017).

Prevalence of HCM has been estimated at 0.16% to 0.29% (≈ 1:625–1:344 individuals) in the general adult population, without a distinct geographic, ethnic, or sex pattern of distribution (Maron et al 1995).

Recent genetic discoveries have identified several mutations in genes encoding sarcomere-associated proteins causing HCM. MYH7 and MYBPC3, encoding β-myosin heavy chain and myosin-binding protein C, respectively, are the two most common genes involved, together accounting for ~50% of the HCM families (Richard et al 2003). The penetrance and phenotypic expression of the sarcomere mutations are highly variable; therefore, genetic testing, although supporting the diagnosis of HCM, is not predictive of severity or prognosis of this disease. In addition, in ~ 40% of HCM patients, the causal genes still remain to be identified.

The clinical diagnosis of HCM is based on detection of cardiac hypertrophy by imaging techniques, such as echocardiography or cardiac magnetic resonance imaging. HCM is defined by an end-diastolic ventricular septal thickness in adults ≥13 mm, occurring in the absence of abnormal loading conditions or other secondary causes, such as hypertension, aortic stenosis, the physiological hypertrophy of athletes, or other conditions that mimic the HCM phenotype (i.e. Fabry disease, glycogen and lysosomal storage diseases and others). The hypertrophy is frequently asymmetrical, and predominantly involves the basal interventricular septum. The left ventricle in HCM usually has a normal end-diastolic volume, a high-normal (65% to 70%) or elevated (>70%) ejection fraction, and a reduced end-systolic volume. Obstruction of the left ventricular outflow tract is present at rest (defined as echocardiographic pressure gradient ≥30 mmHg due to mitral-septal contact during systole) in about one third of HCM patients and can be provoked in another third of patients, while the remaining third have left ventricular hypertrophy without obstruction at rest or with provocation. The histopathology features of HCM include myocyte disarray and interstitial fibrosis, observed in cardiac tissue samples from HCM patients (either from autopsy or biopsy samples).

The clinical manifestations and related prognosis of HCM are highly variable and mainly dependent on the grade of diastolic ventricular dysfunction and left ventricular outflow obstruction, imbalance between myocardial oxygen supply and demand (ischemic chest pain) and the presence of cardiac arrhythmias (palpitations, presyncope, syncope, sudden cardiac death). Therefore, evaluation and monitoring of patients with HCM commonly include a complete clinical history, physical examination, cardiac imaging, electrocardiography and cardiopulmonary exercise testing (CPET). In non-obstructive, asymptomatic HCM patients, CPET is especially useful as a tool for the evaluation of undiagnosed exercise intolerance and for the objective determination of functional capacity and impairment (Coats et al 2015).

Pharmacological treatments of patients with HCM are currently limited to β-Adrenergic receptor blockers, L-type calcium channel blockers, and disopyramide, intended to improve cardiac perfusion and symptoms. Septal reduction therapy, either by surgical septal myectomy or alcoholic septal ablation, is an invasive treatment in HCM patients with left ventricular outflow tract obstruction (systolic pressure gradient ≥30 mm Hg at rest or with provocation) who are symptomatic and not responding to pharmacological treatment. Advanced stages of heart failure with preserved or reduced ejection fraction who have failed pharmacotherapy and, when indicated, septal reduction therapy, may require implantation of a left ventricular device or cardiac transplantation. Therefore, there is still an unmet medical need for new therapies for HCM.

Recently more pharmacological agents have been tested in HCM patients targeting different aspects in the pathogenesis of this disease. However, several drugs, such as spironolactone as a potential antifibrotic agent (Maron et al 2018), perhexiline as a metabolic modulator (Abozguiaet al 2010), ranolazine and eleclazine as late sodium current blockers (Olivotto et al 2018), did not show clear clinical benefits. Mavacamten, a selective allosteric modulator of cardiac myosin ATPase, and valsartan, an angiotensin receptor blocker, are currently being evaluated in clinical studies in HCM patients.

LCZ696 Clinical Profile and Development in HCM

LCZ696, also known as Entresto® (sacubitril/valsartan), is a first in class angiotensin receptor neprilysin inhibitor (ARNI), currently approved in over 100 countries including the United States and European Union for the treatment of chronic heart failure with reduced ejection fraction.

Upon oral administration, LCZ696 delivers systemic exposure of valsartan, an angiotensin receptor blocker (ARB), and sacubitril (AHU377), a neprilysin inhibitor (NEPi) prodrug

Angiotensin receptor blockade by valsartan is selective and competitive at the AT1 receptor, which mediates the deleterious effects of angiotensin II on the cardiovascular system, including pro-fibrotic/pro-hypertrophic mechanisms.

The NEPi component of LCZ696, sacubitril, is a prodrug that is further metabolized via esterases to the active NEPi, sacubitrilat (LBQ657), which inhibits the degradation of natriuretic peptides and therefore enhances the effects of their biological activity.

These effects are mediated by the natriuretic peptide receptor-A (NPR-A or NPR-1), a guanylyl cyclase-linked receptor whose activation generates the second messenger cyclic guanosine monophosphate (cGMP). This intracellular signal elicits the well-characterized blood pressure lowering, diuretic and natriuretic effects of these peptides (Espiner et al 1995).

There is also evidence for a direct role of the natriuretic peptides in suppressing cardiac remodeling, supported by both *in vitro* and *in vivo* data. Hypertrophy of cardiac myocytes in culture is inhibited by ANP (Horio et al 2000) and all the three members of the natriuretic peptide family, ANP, BNP and C-type natriuretic peptide (CNP), inhibit fibroblast proliferation (Cao and Gardner 1995). *In vivo*, the lack of ANP and BNP bioactivities in NPR-1 gene knockout (NPR-$1^{-/-}$) mice leads to both cardiac hypertrophy and fibrosis (Oliver et al 1997). Gene delivery of ANP is reported to attenuate hypertension and cardiac hypertrophy in a salt-

sensitive rat model (Lin et al 1998). Data from patients with hypertension demonstrated a greater reduction in left ventricular mass following both 12 and 52 weeks of treatment with LCZ696 compared to olmesartan (Schmieder et al 2017).

Clinically, several LCZ696 pharmacology studies have been completed to date, showing clear benefits to patients with cardiovascular disease, including heart failure and hypertension, in which vasoconstriction, volume expansion, and target organ damage (i.e., fibrosis, hypertrophy, myocardial/vascular stiffness) play a key role in their pathophysiology.

The PARAMOUNT-HF clinical trial in patients with heart failure and preserved left ejection fraction (HFpEF) demonstrated a statistically significantly greater reduction in NT pro-BNP from baseline to Week 12 for LCZ696 200 mg twice per day (b.i.d.) compared to valsartan 160 mg b.i.d., with a difference between groups of 23% (p=0.005) This study was also able to demonstrate a reduction in the size of the left atrium and improvement in NYHA functional class scores with LCZ696 compared to valsartan (Solomon et al 2012).

A larger Phase III clinical trial, PARAGON-HF, evaluating the effect of LCZ696 compared to valsartan in the reduction of cardiovascular death and rate of HF hospitalizations in patients with HFpEF is currently on going (NCT01920711). Of note, patients with a clinical diagnosis of HCM were excluded from both the PARAMOUNT and PARAGON clinical studies and, thus, a clinical study to directly evaluate the effects of LCZ696 in HCM patients has not been conducted to date.

1.2 Purpose

The purpose of this study is to determine if LCZ696 can improve functional capacity ($VO_{2\ max}$) in patients with non-obstructive hypertrophic cardiomyopathy over the course of 50 weeks of treatment.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the effect of LCZ696 on cardiopulmonary exercise test (CPET) parameters in patients with non-obstructive HCM	• Peak VO_2 after 50 weeks of treatment
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the safety and tolerability of LCZ696 in patients with non-obstructive HCM	• Adverse events (AEs), vital signs, ECGs, physical examinations and safety labs

Objective(s)	Endpoint(s)
[redacted]	

3 Study design

This multi-center study of non-obstructive HCM patients includes a single-blind (i.e., patient-blinded) treatment run-in period aimed to ensure as large a proportion as possible of patients (1) have stable symptoms and can comply with study visits during the placebo run-in period, and (2) can tolerate at least low dose LCZ696. The treatment run-in period is followed by a randomized, placebo-controlled, parallel-group, patient and investigator-blinded treatment period. It is estimated that 44 patients will be randomized into the double-blind placebo-controlled part of the study in order to have approximately 40 patients complete the week 50 CPET assessment.

The study will be comprised of a ≤ 35 day screening/baseline period, a 4-week single-blind treatment run-in period, followed by a 46 week double-blind placebo-controlled treatment period (total treatment period of 50 weeks), and a follow-up period approximately 30 days after the last dose. The maximum study duration, from initial screening to end of study (EOS) for each patient is approximately 58 weeks. More details are provided in the Site Operations Manual.

Screening/baseline period

Patients who sign informed consent and pass the initial screening/baseline evaluations will then have CPET and echocardiogram testing conducted. The 35 day screening/baseline period is designed to allow for scheduling and availability of results in order to establish patient's study

eligibility and baseline status. All screening/baseline safety evaluation results must be available prior to dosing. Patients who enter screening/baseline but are determined not to be eligible to enter the treatment run-in period will be considered as screen failures. See protocol Section 8.1 for permitted re-screening criteria.

Treatment run-in period

Patients who qualify for study eligibility will then enter a single-blind treatment run-in period, during which all patients will receive oral (p.o.) placebo b.i.d. for 2 weeks followed by 50 mg p.o. b.i.d. of active LCZ696 for 2 weeks. Patients who are unable to tolerate either placebo or the 50 mg p.o. b.i.d. dose level, (i.e. do not meet safety criteria as specified in Table 3-1), will be considered treatment run-in failures and will not be randomized into the double-blind, placebo-controlled study, nor included in the efficacy analysis. At the end of the 4-week treatment run-in period, patients who meet the safety criteria (Table 3-1) will be eligible for randomization.

Randomized treatment period

At randomization (week 4 visit), eligible patients will be randomized into the study to receive oral (p.o.) doses of LCZ696 or placebo in a 1:1 ratio in a double-blind, placebo-controlled treatment period. All randomized patients will be titrated up to the 100 mg p.o. b.i.d. dose.

All patients will return to the study center approximately 14 days later for assessment of tolerability of the 100 mg p.o. b.i.d. dose (i.e. must meet safety criteria as specified in Table 3-1). Patients whose assessments demonstrate that they tolerate the 100 mg p.o. b.i.d. dose will be up-titrated to 200 mg p.o. b.i.d. dose, whereas those who do not meet the safety criteria (Table 3-1) will be titrated back down to the 50 mg b.i.d. dose. Tolerance to the current dose (50 mg b.i.d. or 200 mg b.i.d.) will be again assessed ~14 days later, and those patients who demonstrate tolerance will remain on this dose throughout the remaining treatment period, unless a change in tolerance is noted as defined by the criteria in Section 16.3 - Section 16.5. Those patients who do not tolerate the 200 mg p.o. b.i.d. dose will be titrated down to 100 mg p.o. b.i.d. as outlined in Section 6.5.

Tolerability can be assessed at scheduled visits or at any time during an unscheduled visit throughout the study as deemed appropriate by the investigator. Investigators are encouraged to have patients who report intolerance to study medication shortly after dose titration to return to the clinic as soon as possible for re-assessment and dose modification via an unscheduled visit. Those patients who do not tolerate higher doses will be adjusted down to the previous dose as outlined in Section 6.5. Patients who no longer tolerate the 50 mg p.o. b.i.d. dose will be discontinued from study treatment.

Table 3-1 Safety monitoring criteria that must be met for initial treatment and throughout all treatment periods

Parameter	Screening/baseline Period	Safety Monitoring during treatment run-in and randomized treatment periods
Potassium	≤ 5.2 mmol/L (mEg/L)	≤ 5.4 mmol/L (mEg/L)
eGFR	≥ 30 mL/min/1.73m^2	≥ 25 mL/min/1.73m^2
Blood Pressure	SBP ≥ 100 mmHg	No symptomatic hypotension as determined by the investigator and SBP ≥ 100 mmHg
AEs / Med History	No conditions that preclude continuation according to the eligibility criteria	No AEs that preclude continuation according to the investigator's judgment

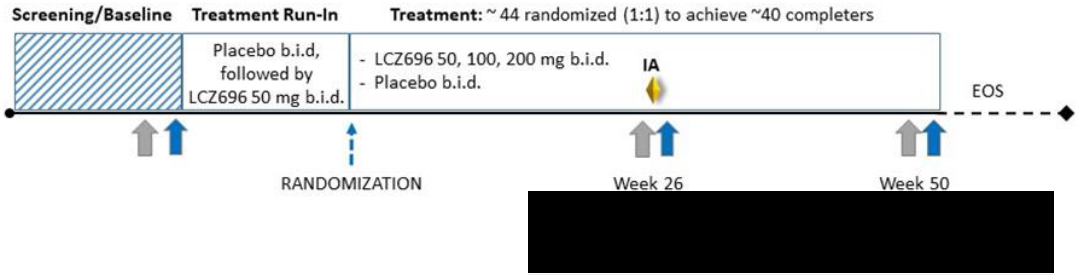
Note that for abnormalities in potassium and eGFR, laboratory values should be repeated to confirm abnormality as outlined in Section 16.3 and Section 16.4. For out-of-range blood pressure readings, measurement may be repeated up to two times as detailed in the Site Operations Manual and Section 16.5.

Note that for Screening/baseline Period and the Treatment Run-in Period exclusion criteria (Section 5.2) also reflect these safety monitoring criteria.

Patients will receive study treatment for ~50 weeks, which includes the 4-week treatment run-in period, with dose tolerability being assessed at each visit as well as at unscheduled visits (as necessary) and through feedback that patients may provide between visits. Safety and tolerability assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology and blood chemistry), AE and SAE monitoring. At week [redacted] week 50, patients will have follow-up CPET [redacted]. No further treatment will be provided after the week 50 visit, and patients will return to the study center ~30 days later for final safety and EOS evaluations.

Refer to the Assessment Schedule (Table 8-1) for full visit schedule.

Figure 3-1 Study Design



4 Rationale

4.1 Rationale for study design

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Overall	This study has a parallel arm design to reduce treatment assignment bias and allow an assessment of placebo and treatment in the same setting with a similar patient population. The 4-week treatment run-in period prior to randomization is utilized to ensure that only patients who have stable symptoms and can tolerate the active treatment will be randomized into the double-blind portion of the study.
Randomization	This study has a 1:1 randomization scheme with no pre-specified strata. The 1:1 randomization ratio was chosen to maximize study power to detect differences in the primary endpoint, given the sample size.
Blinding	This is a patient- and investigator-blinded study. Blinding is used to reduce investigator and patient bias in reporting safety and efficacy outcomes.
Duration of study periods	A screening/baseline period of 35 days was chosen to provide trial sites with flexibility in the scheduling of the CPET and echocardiography assessments prior to the start of treatment. The treatment period of 50 weeks was chosen to allow sufficient time for cardiac remodeling based on the observations from the PARAMOUNT trial, in which left atrial volume was significantly reduced only after 36 weeks of treatment with LCZ696 in patients with HFpEF (Solomon et al 2012). A follow up period of 30 days was designed to allow for a final safety after complete washout of LCZ696.

4.2 Rationale for selection of patient population

This study will enroll only patients with non-obstructive hypertrophic cardiomyopathy (nHCM) who have a reduced exercise capacity as determined by their screening VO_{2max} measurement. These patients can include both those who are symptomatic, as well as those who may be asymptomatic. The nHCM asymptomatic patients with reduced VO_{2max} may not report symptoms despite impaired exercise tolerance because they limit daily their physical activity to avoid the onset of symptoms.

As indicated in Appendix 6 of the protocol, local laboratory assessment of NT-proBNP is required for subjects who are asymptomatic (NYHA Class I) in order to assess their eligibility for subsequent CPET evaluation to determine their % predicted VO_{2max}. Only asymptomatic patients with an NT-proBNP level >250 pg/ml are required to be screened for reduced VO_{2max} levels. Previous work in the field has shown that NT-proBNP levels correlate with VO_{2max} measurements in patients with hypertrophic cardiomyopathy and further, a NT-proBNP cutoff level of 316 pg/ml had a 78% sensitivity to detect HCM patients with a VO_{2max} of <80% of predicted (Thaman et al 2006). The cutoff of 250 pg/ml of NT-proBNP was chosen to improve the sensitivity to detect patients with a peak VO_{2max} of <80% predicted without dramatically increasing the screen failure rate.

The patient population is selected based on the effects seen with LCZ696 in the Phase II study PARAMOUNT-HF, where patients with heart failure and preserved left ejection fraction (HFpEF) demonstrated a reduction in the size of the left atrium and resulting improvement in NYHA functional class with LCZ696 compared to valsartan alone (Solomon et al 2012). In both the PARAMOUNT-HF study and the ongoing Phase III study of LCZ696 in HFpEF patients (PARAGON-HF), HCM patients were excluded.

This study will determine whether the improvement in structural as well as symptomatic effects of LCZ696 as seen in PARAMOUNT-HF could translate to the HCM population.

4.3 Rationale for dose/regimen and duration of treatment

The 4-week treatment run-in period, prior to randomization, is utilized to help ensure that only patients who can tolerate the active treatment will be randomized into the double-blind portion of the study.

The starting dose for LCZ696 for patients entering into the treatment run-in period of this trial is set at 50 mg p.o. administered twice daily (b.i.d.). After 2 weeks of treatment, the dose of LCZ696 will be increased to 100 mg p.o. b.i.d. For those patients who tolerate the 100 mg p.o. b.i.d. dose, a final dose titration to 200 mg p.o. b.i.d. will be done after another 2 weeks of treatment. The 200 mg p.o. b.i.d. dose will be continued for the remainder of the trial as tolerated, or titrated back down if not tolerated. The selection of the starting dose, dose titration, and maximum dose is based on the approved package insert for sacubitril/valsartan for the treatment of patients with reduced ejection fraction heart failure.

See Section 3 and Section 6.5 for further details regarding dose modification and tolerability.

4.4 Rationale for choice of control drugs (placebo)

LCZ696 will be administered in addition to standard of care for nHCM patients, with placebo control used in addition to standard of care for nHCM patients to enable an unbiased comparison of safety and pharmacodynamic effects in active-treated patients when compared to placebo-treated patients.

4.5 Rationale for choice of background therapy

The trial will be done on top of standard of care for non-obstructive hypertrophic cardiomyopathy (e.g., β-blockers, verapamil, and/or disopyramide) as per study investigator. If necessary during the course of the trial, standard of care therapy may be down-titrated as described in Section 6.5.

4.6 Purpose and timing of interim analyses/design adaptations

An interim analysis is planned after approximately 20 patients complete their Week 26 visit. [redacted] No other changes to the design of the study are anticipated as a result of the analysis. Additional information is presented in Section 12.7.

4.7 Risks and benefits

The benefit for patients participating in this study is unknown, as LCZ696 has never been studied in patients with nHCM.

In patients treated with LCZ696, there is an increased risk of hyperkalemia, especially in cases of severe renal impairment, diabetes mellitus, hypoaldosteronism or high potassium diet. Medications known to raise potassium levels (e.g. potassium-sparing diuretics, potassium supplements) should be used with caution. In case of hyperkalemia, adequate measures should be considered e.g. reduce dietary potassium, adjust the dose of concomitant medications as discussed in Section 16.4 (Appendix 4).

In HFrEF patients treated with LCZ696, symptomatic hypotension, dizziness, and syncope have been reported and thus are risks in this trial. Correctable causes of hypotension (e.g. hypovolemia) should be treated and drugs known to affect blood pressure such as diuretics, calcium channel antagonists should be down-titrated or discontinued as described in Section 16.5 (Appendix 5). If required, immediate treatment for symptomatic hypotension may include volume replacement.

LCZ696 is teratogenic in rabbits, and is associated with increased embryo-fetal toxicity, including embryo-fetal lethality in rats and rabbits. Both sacubitril and valsartan have been associated with fetal-toxicity and embryo-fetal lethality in rabbits. Pre- and post-natal development studies in rats with valsartan, but not sacubitril, indicate reductions in pup development and survival.

Sacubitril/valsartan can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Therefore, women of child bearing potential must be informed that taking the study treatment can cause harm to the fetus if pregnancy were to occur during the study and must agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

The risk to patients in this trial may be minimized by compliance with the eligibility criteria and study procedures and close clinical monitoring, including monitoring for low blood pressure and changes in potassium or serum creatinine to down titrate dose or withdrawal patient from treatment.

4.7.1 Potential risks of cardiopulmonary exercise testing

CPET is routinely performed in patients with cardiovascular disease. Overall, the incidence of adverse events (AEs) secondary to this test is very low when performed under appropriately supervised conditions. The major, but rare, complications include myocardial infarction, cardiac arrhythmia, syncope, and orthopedic injury. Adherence to the exercise test protocol with continuous ECG and hemodynamic monitoring will help to minimize the risk of such complications.

[redacted]

4.7.3 Blood sample volume

Risks associated with blood collection include pain, swelling and/or bruising at the insertion site of the needle. Although rare, localized clot formation, infections and nerve damage may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

A volume smaller than a typical blood donation is planned to be collected over a period of approximately 12 months from each patient as part of the study. Additional samples may be required for safety monitoring. The timing of blood sample collections is outlined in the Assessment Schedule (Table 8-1).

5 Population

Approximately 44 patients, male and females age 18 and over, with non-obstructive HCM will be enrolled into this study and treated with study drug for 50 weeks.

The Investigator must ensure that all patients being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible patients.

Patient selection is to be established by checking through all eligibility criteria during the screening/baseline period.

Eligibility should be re-discussed with potential study patients, in case of changes to their health, at the time of their Day 1 visit prior to the administration of the first dose of study medication. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from any entry criterion excludes a patient from enrollment into the study.

5.1 Inclusion criteria

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

1. Male or female, ≥ 18 years of age at the time of consent
2. Diagnosed with Hypertrophic Cardiomyopathy (hypertrophied and non-dilated left ventricle in the absence of any systemic cause) with a left ventricular wall thickness ≥13mm by the echocardiogram obtained during the screening/baseline period, based on local evaluation of echocardiographic images.

3. LVEF ≥50% by echocardiogram obtained during the screening/baseline period, based on local evaluation of echocardiographic images.
4. At the screening/baseline visit symptoms consistent with New York Heart Association (NYHA) Class II-III heart failure by physician assessment, or asymptomatic/NYHA Class I patients with:
   - NT-proBNP above 250 pg/ml and
   - peak VO_2 of ≤80% of predicted based on age and gender.

   Refer to Section 16.6 for further details on screening patients who are asymptomatic/NYHA Class I.
5. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
6. Written informed consent must be obtained before any assessment is performed (including discontinuation of prior ACE-I/ARB as part of >36 hour washout period, where applicable)

5.2 Exclusion criteria

Patients meeting any of the following criteria during the screening/baseline period are not eligible for inclusion in this study.

1. Patients with a resting or provokable (i.e., exercise or valsalva-induced) left ventricular outflow tract gradient of ≥30mm Hg, based on local evaluation of echocardiographic images obtained during the screening/baseline period.
2. Septal reduction procedure within 3 months of the screening/baseline visit.
3. History of atrial fibrillation within 6 months of the screening/baseline visit, or secondary prevention implantable cardioverter-defibrillator device (ICD; primary prevention ICDs without a history of appropriate therapy, including shock or anti-tachycardia pacing, are allowable), or patients who are pacemaker dependent.
4. Patients with a peak VO_2 on the screening/baseline cardiopulmonary exercise test of > 80% of predicted based on age and gender.
5. Patients who require treatment with ACE inhibitors, angiotensin receptor blockers (ARBs), or renin inhibitors. Patients who can discontinue ACE inhibitors, angiotensin receptor blockers, or renin inhibitors can participate if they are off these medicines for at least 36 hours prior to the screening/baseline assessments and are expected to be able to remain off these medicines for the duration of the study treatment period.
6. Treatment with sacubitril/valsartan within three months prior to screening.
7. Known infiltrative or storage disorder causing cardiac hypertrophy that mimics hypertrophic cardiomyopathy, such as Fabry disease, or amyloidosis.
8. Acute decompensated heart failure requiring augmented therapy with diuretics within 30 days of the screening/baseline visit.
9. Known or suspected symptomatic coronary artery disease or evidence of prior myocardial infarction based on symptoms or cardiac imaging history.
10. More than moderate valvular heart disease or clinically significant congenital heart disease. Allowable conditions include systolic anterior motion of the mitral valve (SAM), bicuspid aortic valve without clinically significant stenosis or regurgitation; spontaneously

closed ventricular septal defects; patent foramen ovale, small (≤ 2 mm) restrictive ventricular septal defects with normal ventricular size, and other minor defects following consultation with the sponsor's medical lead.

11. Systolic blood pressure of <100 mmHg or symptomatic hypotension during the screening/baseline period or treatment run-in period.
12. Persistent uncontrolled hypertension, defined as a systolic blood pressure (SBP) ≥150 mmHg, during the screening/baseline period, or a history of uncontrolled hypertension that could have led to cardiac hypertrophy.
13. Presence of known, functionally significant, bilateral renal artery stenosis.
14. Contraindication to ARB administration, including hyperkalemia (serum potassium >5.2 mmol/L during screening/baseline period) or prior history of angioedema.
15. Concomitant medical conditions that would preclude performance of exercise testing (e.g., lung disease, orthopedic/rheumatologic conditions,).
16. Impaired renal function, defined as an estimated glomerular filtration rate (eGFR), during the screening/baseline period and prior to entering treatment at day 1, < 30 mL/min/1.73 m^2, calculated using the simplified Modification of Diet in Renal Disease (sMDRD) equation.
17. Evidence of hepatic disease as determined by any one of the following: SGOT (AST) or SGPT (ALT) values exceeding 3x the upper limit of normal (ULN), bilirubin >1.5 mg/dl during the screening/baseline period.
18. 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 5 years of the screening/baseline visit, regardless of whether there is evidence of local recurrence or metastases.
19. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
20. History of hypersensitivity to any constituent of the study drugs or to drugs of similar chemical classes.
21. Patients with prior major organ transplant or intent to transplant (i.e. on transplant list).
22. Use of other investigational drugs during the screening/baseline period, or within 30 days or 5 half- lives of entering the screening/baseline period, whichever is longer.
23. History of non-compliance to medical regimens and patients who are considered potentially unreliable.
24. History of drug abuse or unhealthy alcohol use within the 12 months prior to dosing, where unhealthy alcohol use is defined as (1) Five or more drinks for men or 4 or more drinks for women on the same occasion on each of 5 or more days in the past 30 days or (2) an average of > 14 drinks per week for men or > 7 drinks per week for women.
25. Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test, or if standard local practice, a positive HBV core antigen test, excludes a patient. Patients with a positive HCV antibody test should have HCV RNA levels measured. Patients with positive (detectable) HCV RNA should be excluded.
26. 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 serum

human chorionic gonadotropin (hCG) laboratory test at screening/baseline or a positive urine pregnancy test (to be confirmed by serum hCG testing) at the day 1 visit.

27. 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 study drug. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up follicle stimulating hormone (FSH) level assessment.
    - Sterilization of the sole male partner of a female study participant (at least 6 months prior to completing the screening/baseline period).
    - Combination of any two of the following (a+b or a+c, or b+c), according to country approvals and availability:
        a. use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
        b. placement of an intrauterine device (IUD) or intrauterine system (IUS)
        c. barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.
    - In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
    - Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of reported post-menopausal status or oophorectomy alone (e.g. without hysterectomy), only when the reproductive status of the woman has been confirmed by follow up FSH hormone level assessment is she considered not of child bearing potential.
28. 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.

6 Treatment

Patients will be instructed to take their study medication in accordance to the guidance outlined in the Site Operations Manual.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosing Log CRF. All kits of investigational treatment assigned by the IRT will be recorded/databased in the IRT.

The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

6.1 Study treatment

The study treatment is LCZ696 and placebo to LCZ696 in dosages of 50 mg, 100 mg, and 200 mg administered as an oral tablet (p.o.), twice per day (b.i.d.). All study drug will be dispensed through IRT as double-blind labeled supply.

Details on the requirements for storage and management of study treatment, and instructions to be followed for patient numbering, prescribing/dispensing, and taking study treatment are outlined in the Site Operations Manual.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
LCZ696 50 mg or matching placebo	Tablet	Oral use	Double Blind supply	Sponsor (global)
LCZ696 100 mg or matching placebo	Tablet	Oral use	Double Blind supply	Sponsor (global)
LCZ696 200 mg or matching placebo	Tablet	Oral use	Double Blind supply	Sponsor (global)

6.1.2 Additional study treatments

No other treatment beyond investigational drug and placebo are included in this trial.

6.1.3 Treatment arms/group

Treatment run-in period

During the treatment run-in period, all patients will be assigned to receive placebo and 50 mg doses of LCZ696 in a single-blind manner, although the study medication will be packed and labeled according to double-blind requirements.

Randomized treatment period

During the double-blind, placebo-controlled randomized treatment period, patients will be assigned at the day 29 visit to one of the following 2 treatment arms in a ratio of 1:1:

- LCZ696
- Placebo to LCZ696

Patients will be randomized to one of the 2 treatment arms, but the dose in each treatment arm (50 mg, 100 mg or 200 mg) will depend on individual tolerability. See Section 3 and Section 6.5 for further details regarding dose modification and tolerability.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

In general, the use of any concomitant medication/therapy deemed necessary for the care of the patient is permitted except when specifically prohibited (see Section 6.2.2). 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 on the appropriate CRFs.

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. If the patient is already enrolled, contact Novartis to determine if the patient should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Medications known to raise potassium levels

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

Phosphodiesterase-5 (PDE-5) inhibitors

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

Neseritide and intravenous (i.v.) nitrates

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

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

In elderly patients, volume depleted patients (including those on diuretic therapy), or patients with compromised renal function, concomitant use of LCZ696 and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is

recommended when initiating or modifying treatment in patients on LCZ696 who are taking NSAIDs concomitantly.

Lithium

Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Monitor serum lithium levels during concomitant use with LCZ696.

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are NOT allowed after the start of study drug due to safety reasons, unless the actions specified are taken.

Table 6-2 Prohibited medication

Medication	Prohibition period	Action taken
Any ACE Inhibitor	Treatment period	Discontinue study treatment. The ACEI must be stopped for ≥36 hours prior to re-initiation of study drug.
Any Angiotensin Receptor Blocker (ARB)	Treatment period	Discontinue study treatment. The ARB must be stopped prior to re-initiation of study drug.
Any renin inhibitor	Treatment period	Discontinue study treatment. The renin inhibitor must be stopped prior to re-initiation of study drug

ACEIs, ARBs and renin inhibitors

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

6.2.3 Rescue medication

Guidance on handling renal dysfunction, hyperkalemia and hypotension are provided to investigators in Section 16.3 (Appendix 3), Section 16.4 (Appendix 4) and Section 16.5 (Appendix 5), respectively. Patients may receive ACEIs, ARBs or a renin inhibitor during the study ONLY if the study drug has been temporarily or permanently discontinued (Table 6-2). Use of rescue medication must be recorded on the Concomitant medications/Significant nondrug therapies CRF.

6.2.4 Restriction for study subjects

6.2.4.1 Dietary restrictions and smoking

There are no specific dietary or smoking restrictions for the duration of this study.

6.2.4.2 Other restrictions

There are no specific restrictions for the duration of this study.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

The "subject number" assigned to a patient at screening/baseline remains the unique identifier for the patient throughout the study. For information on subject numbering, please see ‘Subject numbering’ section in the Site Operations Manual.

6.3.2 Treatment assignment, randomization

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 "subject 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 Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

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

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of patients.

6.4 Treatment blinding

Prior to randomization, this study will include a single-blinded treatment run-in period, where the investigator will be aware that all patients who sign informed consent and pass the screening/baseline period will be treated with placebo p.o. b.i.d. for 2 weeks, followed by treatment with 50 mg p.o. b.i.d. of active LCZ696. Investigative staff will be aware of the order of study drug administration during the treatment run-in period. Investigative staff will not inform patients of the order of the treatments in the run-in period to minimize risk of patient bias. After randomization the study will be conducted as a patient and investigator-blinded study. Patients and investigators will remain blinded to study treatment throughout the rest of the study, except where indicated below. The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, appearance, and schedule of administration.

Site staff

All site staff (including study investigator and study nurse) will be blinded to study treatment throughout the double-blind, placebo-controlled portion of the study. Unblinding a single

patient at site for safety reasons (necessary for patient management) will occur via the IRT system.

Sponsor staff

[redacted]

The study statistician, programmers, and other personnel involved in data analyses [redacted] will be able to access treatment assignment information at any time throughout the study. For interim analyses, they will be allowed to share unblinded information (unblinded individual data and/or unblinded summaries) with the rest of the clinical trial team for internal decision making purposes. The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g., decision boards) as required for internal decision making on the study or the project at the time of interim analyses while the study is ongoing.

Following final database lock all roles may be considered unblinded.

Refer to Table 6-3 for detailed blinding rules for this patient and investigator-blinded study.

Table 6-3 Blinding levels

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis & dose escalation
Subjects/Patients	B	B	B	B
Site staff	B	B	UI	B
Drug Supply and Randomization Office	UI	UI	UI	UI
Statistician/statistical programmer/data analysts	UI	UI	UI	UI
All other sponsor staff not identified above	B	B	UI	UI

B Remains blinded

UI Allowed to be unblinded on individual patient level

6.5 Dose escalation and dose modification

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 (200 mg b.i.d.) throughout the trial. If the patient does not tolerate the target study drug dose level, the investigator can adjust or stop concomitant background medications for co-morbid conditions to rectify the situation, before considering to down titrate to the next lower study drug dose level. For hypotension or dizziness, consideration should be given to reduce the dose or to stop

concomitant antihypertensive agents and non-antihypertensive agents that lower BP, or the dose of diuretic can be reduced.

Adjustment of study drug dose level

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

During the treatment period, down titration of the study drug at any time based on the judgment of the investigator will be allowed according to the safety and tolerability criteria defined in Section 16.3 (Appendix 3), Section 16.4 (Appendix 4) and Section 16.5 (Appendix 5). If down titration is necessary, the patient should be down titrated to the next lower study drug dose level (Table 6-1). The patient may continue receiving the lower dose level for a recommended period of 1 to 2 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 (200 mg b.i.d.), should receive the study drug at 100 mg b.i.d. for 1 to 2 weeks at the discretion of the investigator. Then, he/she should be re-challenged with up-titration back to 200 mg b.i.d. of study drug.

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 2 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 2 weeks in an attempt to bring back the patient gradually to the target study drug dose level (200 mg b.i.d.). The investigator may choose the next dose level for down- or up-titration according to his or her judgment (Table 6-1).

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 (50 mg b.i.d.) or 2 (100 mg b.i.d.) 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 (200 mg b.i.d.). In this case, it would be acceptable to maintain the patient at dose level 1 or level 2, whichever is the higher and tolerated dose level by the patient.

Study drug restart after temporary treatment interruption

Study drug should be reintroduced in those patients who temporarily discontinue it as soon as medically justified in the opinion of the investigator. Once the investigator considers the patient's condition appropriate for receiving the study drug, the investigator should re-start the patient on the study drug at the most appropriate and allowable dose level (Table 6-1) per his/her medical judgment. If tolerated, the patient should be up-titrated a dose level every 2 weeks to the target dose (200 mg b.i.d.), 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 ACEI, ARB or a renin inhibitor is prohibited while the patient is taking study drug. However, if for any reason a patient off study drug has started treatment with an ACEI it must be discontinued ≥36 hours prior to restarting study drug. For patients off study drug treated with an ARB or a renin inhibitor it must be discontinued prior to re-initiation of study drug (Table 6-2).

These changes must be recorded on the Dosing Log CRF.

More dosing guidance can be found in the Site Operations Manual.

In case of pregnancy, the patient will be discontinued from study treatment immediately, and encouraged to return for safety follow-up/EoS visit assessments approximately 30 days after the last dose of study medication. See Section 10.1.4 for further details on pregnancies and reporting guidelines.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

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. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts (if applicable) and information provided by the patient. This information should be captured in the source document at each visit.

The investigator and/or study personnel should counsel the patient if compliance is below 80% at any time during the study. Study drug accountability will be determined by the site monitor while performing routine site visits and at the completion of the study.

All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.6.2 Recommended treatment of adverse events

Treatment guidelines for renal dysfunction, hyperkalemia, and management of blood pressure are provided in Section 16.3 (Appendix 3), Section 16.4 (Appendix 4) and Section 16.5 (Appendix 5), respectively.

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.6.3 Emergency breaking of assigned treatment code

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

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

- protocol number
- name
- subject number

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

Patients for whom an emergency unblinding occurs will be discontinued from further study treatment.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under the investigational and control drugs section.

LCZ696 or placebo will be self-administered by the patient on an outpatient basis twice daily via oral route of administration.

See the Site Operations Manual for further details.

7 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the patient's representative(s) gives consent (if allowed according to local requirements), 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 agreement by personally signing and dating the written informed consent document.

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.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's 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 investigational drug 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 then must be discussed with the patient.

Women of child bearing potential must be informed that taking the study treatment involves 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 requirements.

[redacted]

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

Refer to the Site Operations Manual for a complete list of informed consent forms (ICFs) included in this study.

8 Visit schedule and assessments

The Assessment schedule (Table 8-1) lists all of the assessments in this study and when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Visit windows are outlined in the Site Operations Manual.

Patients who prematurely discontinue the study for any reason, including during the treatment run-in period, should be scheduled for an EOS visit approximately 30 days after their last dose of study drug, at which time all of the assessments listed for the final EOS visit, as well as safety labs if labs were not collected at the time of discontinuation, will be performed. At the EOS visit, all dispensed investigational product should be reconciled, and any adverse event(s) and concomitant medication(s) recorded in the CRF.

Table 8-1 Assessment Schedule

Period	Screening	Treatment run-in[1]		Randomized Treatment								Safety F/U
Visit Name	**Screening/Baseline**	**Week 0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 14 - Phone Call**	**Week 26**	**Week 38 - Phone Call**	**Week 50**	**UNSCH[2]**	**EOS Visit[3]**
Days	**-35 to -1**	**1**	**15**	**29**	**43**	**57**	**99**	**183**	**267**	**351**		**381**
Informed consent	X											
[redacted]												
Inclusion / Exclusion criteria	X	X	X	X								
Medical history/current medical conditions	X											
Demography	X											
Physical Examination	S	S	S[4]	S[4]	S[4]	S[4]		S		S	S[4]	S
[redacted]												
Body Height	X											
Body Weight	X	X				X		X		X	X	X

Period	Screening	Treatment run-in[1]		Randomized Treatment								Safety F/U
Visit Name	Screening/Baseline	Week 0	Week 2	Week 4	Week 6	Week 8	Week 14 - Phone Call	Week 26	Week 38 - Phone Call	Week 50	UNSCH[2]	EOS Visit[3]
Days	-35 to -1	1	15	29	43	57	99	183	267	351		381
Vital Signs	X	X	X	X	X	X		X		X	X	X
Electrocardiogram (ECG)	X	X				X		X		X	X	
Hepatitis and HIV screen	S											
Follicle stimulating hormone (FSH)[5]	X											
Serum Pregnancy Test[6]	X											X
Urine Pregnancy Test[6]		S		S		S	Monthly home testing				S	
Hematology	X	X				X		X		X	X	
Clinical Chemistry	X	X				X		X		X	X	
Local Potassium and Serum Creatinine		X	X	X	X	X					X	
[redacted]												
Cardiopulmonary Exercise Test (CPET)	X[9]							X		X		
[redacted]												
Randomization				X								
[redacted]												

Period	Screening	Treatment run-in[1]		Randomized Treatment								Safety F/U
Visit Name	Screening/Baseline	Week 0	Week 2	Week 4	Week 6	Week 8	Week 14 - Phone Call	Week 26	Week 38 - Phone Call	Week 50	UNSCH[2]	EOS Visit[3]
Days	-35 to -1	1	15	29	43	57	99	183	267	351		381
Drug dispensation		X	X	X	X	X		X			X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications and Therapies	X	X	X	X	X	X	X	X	X	X	X	X
Study completion information												X

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] All assessments should be completed prior to dispensing study medication to establish pre-dose baseline.
[2] These Unscheduled Visit assessments are optional procedures that may be performed at investigator's discretion.
[3] Patients who prematurely discontinue from the study, but do not withdraw consent will be asked to return to the clinic approximately 30 days after their last dose of study drug for an end of study visit. All scheduled EOS assessments should be collected at this visit. In addition, if no safety labs were collected at the date of study drug discontinuation, safety labs should also be collected at the EOS visit.
[4] Abbreviated physical exam; Details of physical exams are provided in the Site Operations Manual.
[5] Only from women who have had oophorectomy without hysterectomy, and from women who are reported to be post-menopausal.
[6] All female patients will have serum pregnancy test at screening/baseline. Women whose FSH results demonstrate that they are not capable of becoming pregnant will not have further pregnancy assessments. Women who are still considered to be of child-bearing potential will have a urine pregnancy test on a monthly basis throughout the study as per the assessment table and an EOS serum test. The results of the urine test must be available prior to dispensing any/additional study medication.

[redacted]

8.1 Screening

It is permissible to re-screen a patient if s/he fails the initial screening/baseline, based on visit windows or eligibility criteria; however, each case must be discussed and agreed with the sponsor on a case-by-case basis.

In the case where a safety laboratory assessment at screening/baseline is more than 10% outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the patient must be excluded from the study.

Information on what data must be collected for screening failures and further information on re-screening is outlined in the Site Operations Manual.

8.1.1 Eligibility screening

All patients will be screened for HIV and Hepatitis B and C. See Site Operations Manual for details.

8.1.2 Information to be collected on screening failures

Information on what data must be collected for screening failures and further information on re-screening is outlined in the Site Operations Manual.

8.2 Subject demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with the CRF. Patient demographic and baseline characteristic data to be collected on all patients which will include (at least): year of birth, age, sex, race, ethnicity, a detailed medical history (including cardiac and other conditions relevant to the study population to be enrolled) and current medical conditions present before the signing of informed consent.

Investigators will have the discretion to record abnormal test findings on the appropriate CRF whenever, in their judgment, the test abnormality occurred prior to the informed consent signature. Details are outlined in the Site Operations Manual.

8.3 Efficacy

Pharmacodynamic measurements will be assessed at the timepoints defined in the Assessment Schedule (Table 8-1). Detailed instructions on these assessments are outlined in the Site Operations Manual.

Pharmacodynamic (PD) assessments will be conducted in all patients at all dose levels, including the placebo group.

8.3.1 Cardiopulmonary Exercise Test (CPET)

Cardiopulmonary exercise testing (CPET) is a non-invasive method used to assess the performance of the heart and lungs at rest and during exercise. The primary efficacy endpoint in this study is peak VO_2, as determined by CPET.

CPET assessments will take place at visits specified in the Assessment Schedule (Table 8-1). Please refer to the Site Operations Manual for more details on the procedure.

8.3.2 Echocardiography

[redacted]

The screening/baseline echocardiographic assessment will include evaluation of any resting left ventricular outflow tract (LVOT) gradient as well as any exercise-induced LVOT gradient. Qualified investigator staff will review the screening/baseline echocardiography results as they relate to study eligibility. Additionally, echocardiographic images will be evaluated by a central reader for all randomized patients as detailed in the Imaging Charter.

[redacted]

Refer to the Site Operations Manual and Imaging Charter for more details on the methods for assessment and recording.

8.3.3 Appropriateness of efficacy assessments

Cardiopulmonary exercise testing is a well-established assessment technique that combines standard exercise testing and measurement of ventilator gas exchanges for an objective determination of functional capacity and impairment in patients with hypertrophic cardiomyopathy.

Echocardiography is a commonly used technique to measure cardiac structure and functional parameters.

8.4 Safety and Tolerability

Safety and tolerability assessments are specified below with the Assessment Schedule (Table 8-1) detailing when each assessment is to be performed. The methods, assessment, specification, and data recording for each assessment will be detailed in the Site Operations Manual.

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. For details on AE collection and reporting, refer to AE section.

8.4.1 Physical Examination

Qualified site staff will conduct complete or abbreviated physical examinations at times indicated in the Assessment Schedule (Table 8-1). Details of system classes examined during the complete and the abbreviated physical examinations are provided in the Site Operations Manual.

Information about all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to informed consent are included in the appropriate page of the CRF. Significant findings observed after informed consent signature which meet the definition of an AE must be appropriately recorded on the Adverse Event CRF.

8.4.2 Vital signs

Vital signs will be collected at visits outlined in the Assessment Schedule (Table 8-1) and will include measurements of oral body temperature, blood pressure and pulse rate. Refer to the Site Operations Manual for details.

8.4.3 Height and weight

Height and weight will be collected at visits outlined in the Assessment Schedule (Table 8-1). Body Mass Index (BMI) will be calculated. Refer to the Site Operations Manual for details.

8.4.4 Laboratory evaluations

A central laboratory will be used for analysis or specimen management of most specimens collected. Details on the collection, shipment of samples, and reporting of results by the central laboratory are provided to investigators in the laboratory manual. The list of safety related laboratory tests that will be analyzed in this study are specified in the Site Operations Manual.

At visits specified in the Assessment Schedule (Table 8-1), sites will collect a sample for local analysis of serum potassium and serum creatinine levels. There are countries where plasma potassium and creatinine are used instead of serum potassium for routine clinical care. Plasma samples can be used instead of serum samples in this study. Serum potassium thresholds in the study protocol, including those values cited in Appendix 4, can be converted to plasma potassium thresholds for the study by subtracting 0.4 mmol/L from the serum potassium threshold (Hartland and Neary 1999). No conversion is required for plasma creatinine.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions, or as AEs as appropriate.

All abnormal lab results must be evaluated for criteria defining an AE and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

8.4.5 Electrocardiogram (ECG)

Electrocardiogram (ECG) assessments will be conducted at visits specified in the Assessment Schedule (Table 8-1). Full details of all procedures relating to the ECG collection and reporting are contained in the Site Operations Manual.

Sites will record in the CRF the following parameters: PR interval, QRS duration, heart rate, RR interval, QT interval, and Fridericia QT correction (QTcF). As applicable, QTcF may be calculated in-house unless auto-calculated by the ECG machine.

Clinically significant abnormalities must be reported as adverse events.

8.4.6 Pregnancy and assessments of fertility

All women will have serum pregnancy testing at screening/baseline. Those women who are noted to have history of oophorectomy without hysterectomy, and those who are reported to be post-menopausal - based on reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile - will have hormone levels (FSH) assessed at screening/baseline.

After the screening/baseline period, all women of child bearing potential will continue to have urine and serum pregnancy testing throughout the study as per the Assessment Schedule (Table 8-1). Additional pregnancy testing may be performed as per local requirements. The results of the local urine pregnancy testing must be available prior to dispensing any/additional study medication. A positive pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative.

Medical documentation of oophorectomy, hysterectomy or tubal ligation must be retained as source documents and documented as medical history in the CRF.

8.4.7 Appropriateness of safety measurements

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

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the patient or the investigator. The investigator must discontinue study treatment for a given patient if, he/she believes that continuation would negatively impact the patient's well-being.

Study treatment must be discontinued under the following circumstances:

- Patient/guardian decision
- An episode of sustained ventricular tachycardia
- New onset of persistent atrial fibrillation
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the patient
- Following emergency unblinding
- Suspected occurrence of angioedema. A patient with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator

- Any adverse events or laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study
- If a liver, renal, hyperkalemic, or hypotensive event occurs, follow guidelines outlined in Section 16.2 , Section 16.3, Section 16.4 or Section 16.5 regarding discontinuation of study treatment.

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the patient's premature discontinuation of study treatment and record this information.

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' section). Where possible, they should return for the EOS assessments indicated in the Assessment Schedule (Table 8-1) approximately 30 days after their last dose of study medication. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the patient/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If any patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, if a patient cannot or is unwilling to come to the clinic for the EOS visit, at a minimum, the following data should be collected via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

9.1.2 Withdrawal of informed consent

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

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

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient'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 patient are not allowed unless safety findings require communicating or follow-up.

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

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a patient's samples until the 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 World": 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.

9.1.3 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered as lost to follow-up until due diligence has been completed or until the patient's scheduled EOS visit would have occurred.

9.1.4 Study stopping rules

Enrollment in the study will be placed on hold if any of the following occurs:

- After any patient experiences sudden cardiac death
- The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold.
- The Sponsor unilaterally requests it.

The study may resume following the safety review, if the Lead Investigator(s) and Sponsor agree it is safe to proceed.

9.1.5 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 (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible, study medication should be discontinued, and patients treated as a prematurely discontinued 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 or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last patient finishes their EOS/Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

The investigator has the responsibility for managing the safety of individual patient and identifying AEs.

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

The occurrence of AEs 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.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade
    1. mild: usually transient in nature and generally not interfering with normal activities
    2. moderate: sufficiently discomforting to interfere with normal activities
    3. severe: prevents normal activities
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be ‘Not suspected.’ The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient.
3. Its duration (start and end dates). If the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes a SAE (see Section 10.1.2for definition of SAE) and which seriousness criteria have been met

5. Action taken regarding with study treatment. All AEs must be treated appropriately. Treatment may include one or more of the following:
    1. Dose not changed
    2. Dose Reduced/increased
    3. Drug interrupted/discontinued
6. Its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Conditions that were already present at the time of informed consent should be recorded in medical history of the patient.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

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

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

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

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 patients with the underlying disease. Clinically notable lab ranges are included in Section 16.1 (Appendix 1).

Follow the instructions found in the Site Operations Manual for data capture methodology regarding AE collection for screening failures.

10.1.2 Serious adverse events

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:

- fatal
- life-threatening

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 the ICH-E2D Guidelines).

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

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. Such events should be considered as "medically significant." 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 the ICH-E2D Guidelines).

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

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions

regarding the submission process and requirements are to be found in the investigator folder provided to each site.

The following timelines should be noted for SAE reporting period:

1. Screen failures (e.g. a patient who is screened but does not enter the treatment run-in period/never receives study treatment): SAEs occurring after the patient has provided informed consent until the time the patient is deemed a Screen Failure must be reported to Novartis.
2. Treatment run-in failures (e.g. a patient who is screened and treated in the treatment run-in period but not randomized): SAEs collected between time patient signs ICF until 30 days after the patient has discontinued or stopped study treatment.
3. Randomized patients (e.g. a patient who completes the treatment run-in period and is randomized into the double-blind, placebo-controlled portion of the study): SAEs collected between time patient signs ICF until 30 days after the patient has discontinued or stopped 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 immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). 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.

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 CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day reporting period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 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 at the time of birth.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same

form and should include an assessment of the possible relationship to the study treatment for any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF 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 within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (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

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 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 AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

Please refer to Table 16-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the patient. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded in source documents.
- If the initial elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the patient if appropriate
- Causality assessment of the liver event
    - Other investigations can include, based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

Refer to Appendix 2 (Section 16.2) and the SOM for additional details.

10.2.2 Renal safety monitoring

The serum creatinine will be used to monitor for renal injury. A serum creatinine increase ≥ 25% compared to baseline during normal hydration status is considered a renal event and should be followed up by the investigator or designated personnel at the trial site as summarized in Section 16.3 (Appendix 3). Abnormal renal event findings must be confirmed ≥ 24 hours but ≤ 5 days after first assessment.

Refer to Section 16.3 (Appendix 3) and the Site Operations Manual for additional details.

11 Data Collection and Database management

11.1 Data collection

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs

check for data discrepancies in the eCRFs and allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

After final database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior 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. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

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

For echocardiograms, a dedicated imaging CRO will collect all randomized patient echo data from sites and provide analysis by a central reader. The analysis results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study treatment (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 data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

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.

Once all the necessary 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 to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative or designated CRO will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and 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 or designated CRO staff. 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 CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the 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.

12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

For all analysis sets, patients will be analyzed according to the study treatment(s) received. The safety analysis set will include all patients that received any study drug. The randomized analysis set (RAS) will consist of all randomized patients. The per-protocol set (PPS) will be a subset of the RAS that will consist of all randomized patients who have no major protocol deviations with relevant impact on PD/efficacy data and whom are at least 80% compliant with study drug administration. PD/efficacy variables will be analyzed based on the PPS.

12.2 Subject demographics and other baseline characteristics

Baseline will be defined as the last non-missing assessment prior to the first dose of study drug, unless specified otherwise.

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the RAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. Relevant medical histories and current medical

conditions at baseline will be summarized by system organ class and preferred term, by treatment group.

12.3 Treatments

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system by treatment for the RAS.

12.4 Analysis of the primary endpoint(s)

12.4.1 Definition of primary endpoint(s)

The primary endpoint will be the change from baseline in peak VO_2 (ml/kg/min) at week 50, where baseline peak VO_2 will come from the screening/baseline CPET.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis will assess the effect of LCZ696 on the change from baseline in peak VO_2 at week 50 compared to placebo. A longitudinal mixed effects model for the change from baseline will be used. The model will include treatment, time (as a categorical variable), and the treatment-by-time interaction as fixed effects, patient as a random effect, and baseline peak VO_2 as a covariate. The least-squares (LS) mean and associated 90% confidence interval (CI) for the change from baseline in peak VO_2 for each treatment, and the estimated mean treatment difference, the p-value, and the corresponding 2-sided 80% CI will be extracted from the model at each time point.

12.4.3 Handling of missing values/censoring/discontinuations

There will be no imputation of missing data. The primary model implicitly imputes missing measurements under a missing at random assumption.

12.4.4 Sensitivity and Supportive analyses

Three supportive analyses will be performed to further assess the effect of LCZ696 on changes in peak VO_2:

(1) An analysis of the change from baseline in % of predicted peak VO_2. The same model as described for the primary endpoint will be used.
(2) An analysis of the ratio to baseline in peak VO_2. A similar model as described for the primary analysis will be used, but with ratio to baseline as the response, and all peak VO_2 measurements will be log transformed prior to analysis.
(3) The primary analysis performed on the RAS.

12.5 Analysis of secondary endpoints

12.5.1 Safety endpoints

All safety analyses will be presented separately for the run-in period and the double-blind period using the safety set. All listings and tables will be presented by treatment.

Adverse events

All information obtained on AEs will be displayed by treatment and patient. The number (and percentage) of patients with treatment emergent AEs (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class, and preferred term.
- by treatment, primary system organ class, preferred term, and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ), and preferred term.

A patient with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment, patient, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

12-lead ECG

All ECG data will be listed by treatment, patient, and visit/time, and abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Shift tables using the low/normal/high classification will be used to compare baseline to the worst on-treatment value.

[redacted]

[redacted]

[redacted]

12.7 Interim analyses

An interim analysis for safety and efficacy will be performed when approximately 20 patients have completed the Week 26 CPET assessment. The same analysis described for the primary analysis will be performed using all the available CPET data at the time of the interim database freeze. Unblinded results will be reviewed by the clinical team. The clinical team may communicate the results (e.g., evaluation of PoC criteria or information needed for planning/modifying another study) to relevant Novartis teams for information, consulting, and/or decision purposes. Additional interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general, or in case of any safety concerns.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Approximately forty-four (44) patients will be enrolled in the study with the anticipation that at least 40 patients complete the study. With 40 completers, there will be 80% power to achieve

an efficacy criteria of at least 50% confidence that LCZ696 increases peak VO_2 by at least 3 ml/kg/min over placebo, provided that the true effect of LCZ696 is at least a 4.15 ml/kg/min increase over placebo and the standard deviation of the change from baseline is 4.25 ml/kg/min (Olivotto et al 2018). If LCZ696 is not different from placebo, there will be a 1.5% chance of achieving the efficacy criteria (i.e., the false positive rate will be 1.5%). For the interim analysis, with week 26 data from at least 20 patients, there will be 70% power to meet the efficacy criteria under the same assumptions, and a 6% false positive rate if there is no increase over placebo.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, 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.

14 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 including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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.

14.1 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 required for patient safety 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, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values

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

Hematology

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

Blood Chemistry

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

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

Table 16-1 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 16-2 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 • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT 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 • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT 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 • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT 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 • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate 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 • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT 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

Criteria	Actions required	Follow-up monitoring
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT 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 • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate 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.
*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

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.3 Appendix 3: Guidelines for the management of renal dysfunction

General principles:

Glomerular filtration rate in HF patients depends on intrinsic renal function and on a balance between afferent and efferent glomerular arterial tonicity. This tonicity is partly regulated by a stimulation of angiotensin II and could be affected by 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 start of study treatment, eGFR decreases by ≥25% from the screening/baseline visit (or if serum creatinine concentration increase to 2.5 mg/dL [221 µmol/L]), the investigator will repeat the laboratory evaluation. If the eGFR on repeat evaluation is still decreased by ≥25%, the investigator will check for potentially reversible causes of renal dysfunction such as:

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

Action situation

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

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

16.4 Appendix 4: Treatment guidelines for hyperkalemia (serum potassium greater than or equal to 5.3 mmol/L [mEq/L]

General principles

Elevation of serum (or equivalent plasma) 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 initiation of study treatment requires the Investigator to confirm the potassium concentration in a non-hemolyzed sample via an immediate repeat lab sample to both the clinic local lab and the study central lab.

Regular, repeated checks of potassium concentration (beyond that prescribed in the protocol) should continue until it is clear that the potassium concentration is stable and not rising into the range of concern (≥ 5.5 and < 6.0 mmol/L [mEq/L]) or potential danger (≥ 6.0 mmol/L [mEq/L]).

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

Corrective action for management of hyperkalemia

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

- Confirm potassium concentration in a non-hemolyzed sample.
- Reinforce low potassium diet and restriction of food/drinks with high potassium content (e.g. orange juice, melon, bananas, tomatoes, dried fruits, potatoes, low-salt substitutes, coffee, etc.).
- Correct metabolic acidosis if necessary.
- Review medical regimen (including dietary supplements and over-the-counter medications) for agents known to cause hyperkalemia. Consider reduction in dose or discontinuation of these agents:
    - MRAs (if they are believed to be the most likely cause of hyperkalemia)
    - Potassium-sparing diuretics (e.g. amiloride and triamterene) including in combination products with thiazide or loop diuretics
    - Potassium supplements, e.g., potassium chloride
    - Salt substitute
    - Non-steroidal anti-inflammatory drugs (NSAIDs)
    - Cyclo-oxygenase-2 (COX-2) inhibitors
    - Trimethoprim and trimethoprim-containing combination products, such as Bactrim® and Septra® (trimethoprim/sulfamethoxazole fixed combination)
    - Herbal Supplements:
        - For example, Noni juice, alfalfa (Medicago sativa), dandelion (Taraxacum officinale), horsetail (Equisetum arvense), nettle (Urtica dioica), milkweed, lily of the valley, Siberian ginseng, hawthorn berries.

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

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

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

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

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

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

16.5 Appendix 5: Guidelines for the management of blood pressure

Guidelines

1. Investigator should monitor BP closely
2. If symptomatic hypotension occurs:
   a. Correct any treatable cause, e.g. hypovolemia.
   b. If hypotension persists, any antihypertensive drug such as diuretics, calcium channel blockers (CCBs), nitrates, beta blockers, aldosterone antagonists and α-blockers, should be down-titrated or stopped first before down-titration of the study drug is considered. Any non-antihypertensive drug (such as nitrates) should be considered for down-titration prior to study drug as determined by the best judgment of the investigator.
   c. If hypotension persists, the study drug should be down-titrated or even temporarily discontinued. The dose re-challenge and medications adjust guidelines described in Section 6.5 should be adhered to as much as possible.

16.6 Appendix 6: Screening flow chart for asymptomatic patients

Figure 16-1 Screening flow chart for asymptomatic patients