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

[redacted]

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

3 Investigational plan

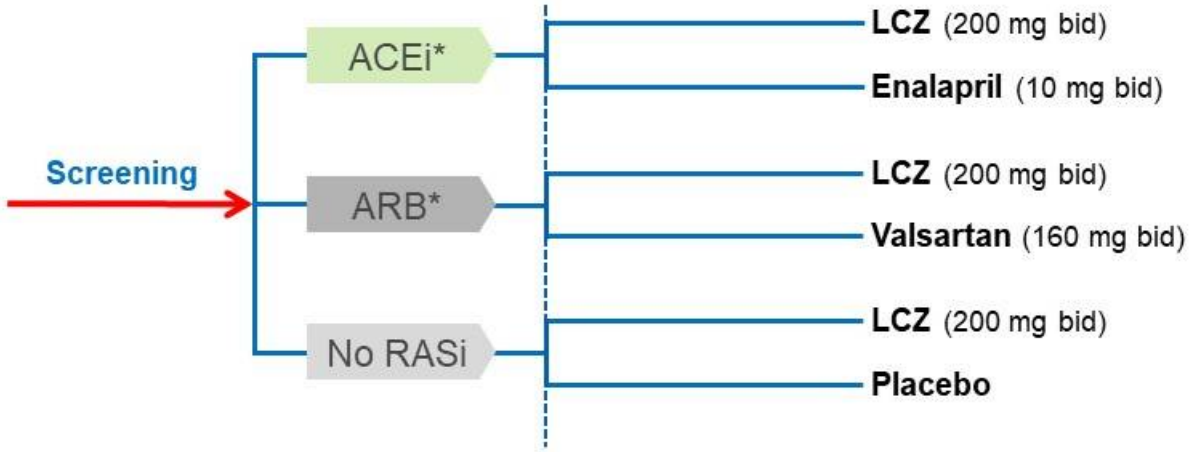
3.1 Study design

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

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

[redacted]

Figure 3-1 Study design



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

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

Screening epoch

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

Screening NT-proBNP, complete lab evaluations, and pregnancy testing will be assessed by sending samples to the central lab. It may take up to 72 hours to obtain the results of the clinical laboratory assessments to evaluate the patient's eligibility for the study.

Qualifying echocardiogram (echo) measurements will be based on locally obtained echoes performed within 6 months of Visit 1. If a qualifying echo within 6 months of Visit 1 is not available, the patient must enter the study based on a qualifying echo performed during the screening epoch before any study drug is dispensed to the patient. No imaging method other than echocardiography will be accepted for inclusion into the study.

[redacted]

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

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

Randomized treatment epoch

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

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

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

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

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

[redacted]

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

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

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

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

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

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

[redacted]

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

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

3.4 Rationale for choice of comparator

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

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

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

[redacted]

4. Symptom(s) of HF requiring treatment with diuretics (including loop, or thiazide diuretics, or mineralocorticoid antagonist [MRAs]) for at least 30 days prior to Visit 1
5. Current symptom(s) of HF (NYHA class II-IV) at Visit 1
6. Structural heart disease demonstrated by echocardiographic evidence of left atrial enlargement (LAE) **or** left ventricular hypertrophy (LVH) as defined below (any local measurement made during the screening epoch or within the 6 months prior to Visit 1):
   a. left atrial enlargement defined by at least one of the following: LA width (diameter) ≥ 3.8 cm **or** LA length ≥ 5.0 cm **or** LA area ≥ 20 cm^2 or LA volume ≥ 55 mL **or** LA volume index ≥ 29 mL/m^2
   b. left ventricular hypertrophy defined by septal thickness or posterior wall thickness ≥ 1.1 cm
7. Receiving evidence based therapy for relevant comorbidities as determined by the individual clinical profile of the patient (eg age and number and type of comorbidities) with stable doses for the previous four weeks prior to randomization
8. NT-proBNP > 220 pg/mL for patients with no atrial fibrillation/atrial flutter (AF) or > 600 pg/mL for patients with AF on the Visit 1 ECG
9. KCCQ clinical summary score < 75 at Visit 1
10. Patients on ACEi or ARB therapy must have a history of HTN

4.2 Exclusion criteria

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

1. Any prior echocardiographic measurement of LVEF ≤ 40%, under stable conditions
2. Acute coronary syndrome (including myocardial infarction [MI]), cardiac surgery, other major cardiovascular (CV) surgery, or urgent percutaneous coronary intervention (PCI) within the 3 months prior to Visit 1 **or** an elective PCI within 30 days prior to Visit 1
3. Any clinical event within the 6 months prior to Visit 1 that could have reduced the LVEF (eg MI, coronary artery bypass graft [CABG]), unless an echo measurement was performed after the event confirming the LVEF to be > 40%
4. Current (within 30 days from Visit 1) acute decompensated HF requiring augmented therapy with diuretics, vasodilators and/or inotropic drugs
5. Current (within 30 days from Visit 1) use of renin inhibitor(s), dual RAS blockade or LCZ696
6. History of hypersensitivity to LCZ696 or its components
7. Patients with a known history of angioedema
8. Walk distance primarily limited by non-cardiac comorbid conditions at Visit 1
9. Probable alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms (ie dyspnea, fatigue) such as significant pulmonary disease (including primary pulmonary HTN), anemia or obesity. Specifically, patients with the following are excluded:

[redacted]

Table 6-1 Assessment schedule

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

[redacted]

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

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

[redacted]

6.5.3 Height, weight and waist/hip circumference

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

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

6.5.4 Laboratory evaluations

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

Clinically notable laboratory findings are defined in Appendix 1.

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

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

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

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

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

[redacted]

Table 6-2 Complete laboratory evaluations

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

*Laboratory assessments for the abbreviated laboratory evaluation at visits where the complete laboratory evaluation is not performed

6.5.4.1 Hematology

Hemoglobin, hematocrit, RBC, RDW, MCHC, MCV, WBC with differential, and platelet count will be measured.

6.5.4.2 Clinical chemistry

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

[redacted]

6.5.4.3 eGFR

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

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

6.5.4.4 Urinalysis

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

6.5.5 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed locally at Visit 1, 105 and Visit 199/PSD. Interpretation of the tracing must be made by a qualified health care provider and documented on the ECG section of the eCRF. Each ECG tracing should be labeled with the study and subject number, date, and kept in the source documents at the study site. Clinically significant abnormalities should also be recorded on the Medical History/AE eCRF page.

6.5.6 Pregnancy and assessments of fertility

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

All pre-menopausal women who are not surgically sterile will have a serum pregnancy test at Visit 1 and Visit 199/PSD. Additional pregnancy testing might be performed if requested by local requirements. A urine dip-stick pregnancy test will be performed locally at all other visits. The urine dip-stick pregnancy test is not required for post-menopausal women. A positive urine pregnancy test requires immediate interruption of study drug. A positive urine test needs to be confirmed with serum pregnancy test. If positive, the patient must discontinue study drug.

6.5.7 Angioedema

Angioedema is a type of abrupt swelling that occurs under the skin and/or mucous membranes and is often localized to the head, neck, throat, and/or tongue, but may occur elsewhere, including the genitalia and intestines. Severe cases may be associated with airway compromise.

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

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

[redacted]

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

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

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

6.5.8 Appropriateness of safety measurements

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

6.6 Other assessments

6.6.1 Clinical outcome assessments

6.6.1.1 Clinician reported outcomes (ClinRO)

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

6.6.1.2 Patient Reported Outcomes (PRO)

The Kansas City Cardiomyopathy Questionnaire (KCCQ)

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

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

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

[redacted]

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

SF-36 Version 2

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

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

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

Completion of Questionnaires

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

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

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

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

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

[redacted]

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

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

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

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

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities

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

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

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

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

[redacted]

7.2.2 SAE reporting

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

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

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

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

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

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

7.2.2.1 Adverse events that are commonly seen in the study population

Investigators will report AEs or SAEs that are commonly seen in the study population (Table 7-1) but these will not be unblinded and will not be reported as SUSARs to regulatory agencies, ECs, or investigators during the study. These events will be unblinded and presented in the

[redacted]

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

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

For the liver events:

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

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed must be recorded on appropriate eCRF pages, including the liver event overview eCRF pages.

7.4 Renal safety monitoring

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

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

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

7.5 Reporting of study treatment errors including misuse/abuse

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

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

[redacted]

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

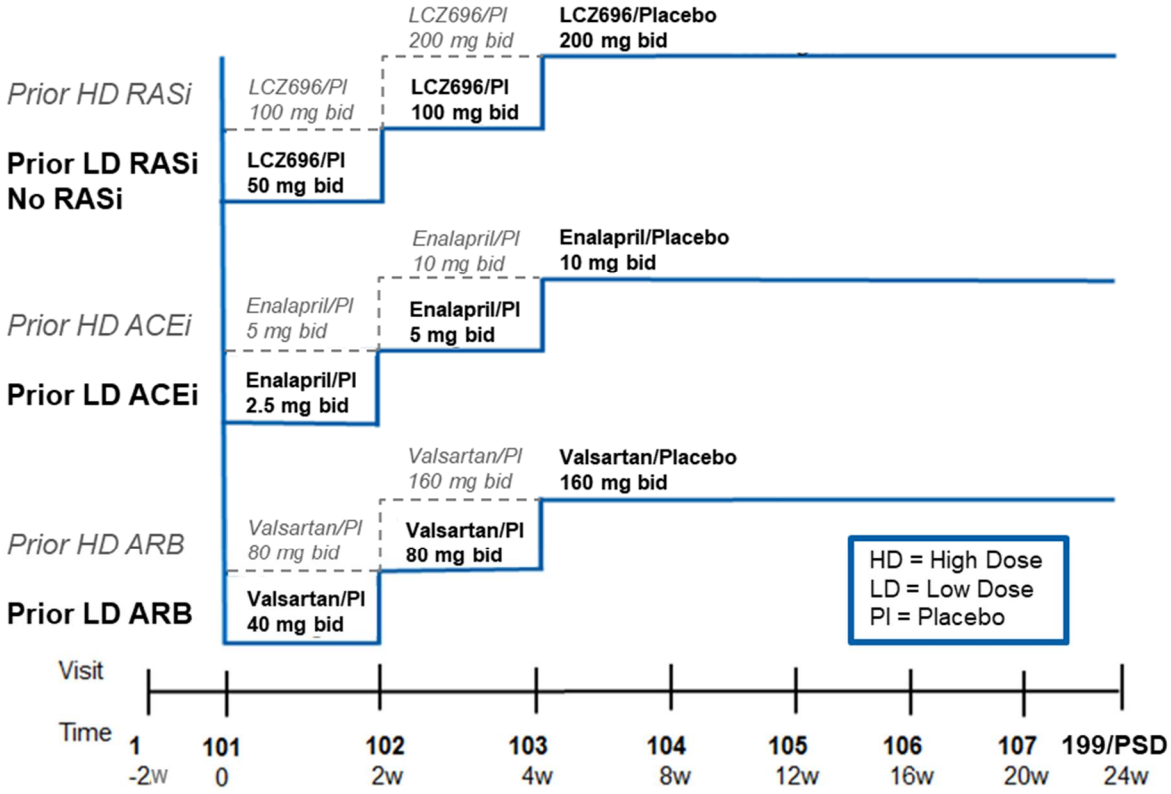
[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values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

[redacted]

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

[redacted]

Figure 3-2 Study drug up-titration



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

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

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

[redacted]

3.2.3 Rationale for the secondary endpoints selection

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

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

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

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

[redacted]

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

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

In women of child-bearing potential, a possible risk of developmental toxicity cannot be excluded. Women of child-bearing potential should therefore, use a highly effective method of contraception during dosing and for 7 days after stopping of study medication. If there is any question that the patient will not reliably comply, they should not be entered in the study. All patients in this study will be ≥ 45 years of age and therefore the risk of pregnancy during the trial is minimal.

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

Participating patients will benefit from careful monitoring and follow-up during the entire study duration regardless of whether they are receiving the study medication.

4 Population

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

4.1 Inclusion criteria

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

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

a. severe pulmonary disease including chronic obstructive pulmonary disease (COPD) (ie requiring home oxygen, chronic nebulizer therapy, chronic oral steroid therapy or hospitalized for pulmonary decompensation within 12 months) or
b. hemoglobin (Hgb) < 10 g/dL males and < 9.5 g/dL females **or**
c. body mass index (BMI) > 40 kg/m^2

10. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer
11. Patients with any of the following:
    a. systolic blood pressure (SBP) ≥ 180 mmHg at Visit 1, **or**
    b. SBP > 150 mmHg and < 180 mmHg at Visit 1 unless the patient is receiving 3 or more antihypertensive drugs. Antihypertensive drugs include, but are not limited to, a thiazide or other diuretic, MRA, ACEi, ARB, beta blocker and calcium channel blocker (CCB), **or**
    c. SBP < 110 mmHg or symptomatic hypotension at Visit 1
12. Patients with HbA1c > 7.5% not treated for diabetes
13. Patients with history of any dilated cardiomyopathy, including peripartum cardiomyopathy, chemotherapy induced cardiomyopathy, or viral myocarditis
14. Evidence of right sided HF in the absence of left-sided structural heart disease
15. Known pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy
16. Clinically significant congenital heart disease that could be the cause of the patient's symptoms and signs of HF
17. Presence of hemodynamically significant valvular heart disease in the opinion of the investigator
18. Stroke, transient ischemic attack, carotid surgery or carotid angioplasty within the 3 months prior to Visit 1
19. Coronary or carotid artery disease or valvular heart disease likely to require surgical or percutaneous intervention during the trial
20. Life-threatening or uncontrolled arrhythmia, including symptomatic or sustained ventricular tachycardia and atrial fibrillation or flutter with a resting ventricular rate > 110 beats per minute (bpm)
21. Patients with a cardiac resynchronization therapy (CRT) device
22. Patients with prior major organ transplant or intent to transplant (ie on transplant list)
23. Any surgical or medical condition, which in the opinion of the investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study
24. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs, including but not limited to any of the following:
    - any history of pancreatic injury, pancreatitis or evidence of impaired pancreatic function/injury within the last 5 years

[redacted]

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

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

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

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

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

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

6.6.1.3 Performance Outcomes

Six-minute walk test (6MWT)

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

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

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

6.6.1.4 Other Clinical Outcome Assessments

NT-proBNP

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

NT-proBNP measurements will be performed by the central lab in all patients at Visits 1, 101, 103, 105, and 199/PSD. Only the Visit 1 NT-proBNP results will be reported to the investigator and the sponsor. All other measurements will be blinded to the site and the Novartis clinical study team. Any, local measurements of BNP or NT-proBNP during the course of the study is strongly discouraged.

7 Safety monitoring

7.1 Adverse events

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

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

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

[redacted]

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

7.2 Serious adverse events

7.2.1 Definition of SAE

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

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

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

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

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

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

[redacted]

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

If specifically requested by a local Health Authority (HA), pre-specified AEs commonly observed in the study population (Table 7-1) that also meet the criteria for SUSARs:

- Will be expedited to the requesting HA as blinded reports without issuing INs, or
- Pre-specified AEs commonly observed in the study population that occur in patients under the jurisdiction of the requesting HA will be expedited to the HA as unblinded reports; INs will be issued for these events.

Table 7-1 Adverse events commonly seen in study population

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

7.3 Liver safety monitoring

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

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

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

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

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

For the liver laboratory trigger:

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

[redacted]

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

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

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

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

7.6 Pregnancy reporting

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

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

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

8 Data review and database management

8.1 Site monitoring

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

15 Appendix 3: Specific Renal Alert Criteria and Actions

Table 15-1 Specific renal alert criteria and actions

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

Guidelines for the Management of Renal Dysfunction

General principles:

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

Two types of response to serum creatinine increase are described:

Surveillance situation

If, at any time after randomization, eGFR decreases by ≥ 25% from randomization (Visit 101) (or if serum creatinine concentration increase to 2.5 mg/dL [221 μmol/L]), the investigator will check for potentially reversible causes of renal dysfunction such as:

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

[redacted]