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LCZ696

Clinical Trial Protocol CLCZ696D1301E1 / NCT03909295

A multicenter, open-label study to evaluate the safety and tolerability of LCZ696 treatment in Japanese heart failure patients (NYHA Class II-IV) with preserved ejection fraction after CLCZ696D2301 (PARAGON-HF)

Document type:	Clinical Trial Protocol
EUDRACT number:	NA
Version number:	00 (Original Protocol)
Clinical Trial Phase:	III
Release date:	17-Dec-2018

Clinical Trial Protocol Template Version 2.0 dated 01-Aug-2018

Table of contents

List of tables

List of figures

List of abbreviations

ACC	American College of Cardiology
ACEI	angiotensin converting enzyme inhibitor
AE	adverse event
AF	atrial fibrillation
AHA	American Heart Association
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
AST	aspartate aminotransferase
AT1	angiotensin type 1
ATC	Anatomical Therapeutic Chemical
b.i.d.	twice a day
BP	blood pressure
BUN	blood urea nitrogen
CAD	coronary artery disease
CCB	calcium channel blocker
CFR	Code of Federal Regulation
CHF	chronic heart failure
CMO&PS	Chief Medical Office and Patient Safety
COX-2	cyclo-oxygenase-2
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CTC	Common Toxicity Criteria
CV	cardiovascular
DBP	diastolic blood pressure
DM	diabetes mellitus
DMC	Data Monitoring Committee
EC	Ethics committee
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
ESC	European Society of Cardiology
EU	European Union
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
hCG	human chorionic gonadotropin
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HTN	hypertension

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
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
JCS	The Japanese Circulation Society
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MoA	mechanism of action
MRA	mineralocorticoid antagonist
NEP	neprilysin
NP	natriuretic peptide
NSAID	non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OATP	organic anion-transporting polypeptide
PDE-5	phosphodiesterase-5
PT/INR	prothrombin time/international normalized ratio
QMS	Quality Management System
RAAS	Renin angiotensin aldosterone system
RAS	renin angiotensin system
RBC	red blood cell(s)
SAE	serious adverse event
SAF	safety set
SBP	systolic blood pressure
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SMQ	Standardized MedDRA query
SOP	standard operational procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
ULN	upper limit of normal
US	United States
WBC	white blood cell(s)
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Screen Failure	A subject who is screened but is not treated or randomized
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
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 subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.

Protocol summary

Protocol number	CLCZ696D1301E1
Full Title	A multicenter, open-label study to evaluate the safety and tolerability of LCZ696 treatment in Japanese heart failure patients (NYHA Class II-IV) with preserved ejection fraction after CLCZ696D2301 (PARAGON-HF)
Brief title	An Open-label extension study evaluating safety and tolerability of LCZ696 in subjects who completed PARAGON-HF in Japan.
Sponsor and Clinical Phase	Novartis, Phase 3
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this open-label study is to evaluate long-term safety and tolerability of LCZ696 in eligible heart failure with preserved ejection fraction (HFpEF) patients who completed PARAGON-HF in Japan.
Primary Objective(s)	The primary objective of this study is to evaluate further the safety and tolerability of long-term treatment with LCZ696 in eligible HFpEF patients who completed PARAGON-HF in Japan.
Secondary Objectives	Not Applicable
Study design	This study is an open-label extension study to the PARAGON-HF to assess the long-term safety and tolerability of LCZ696 treatment.
Population	Approximately 70 Japanese patients with HFpEF who completed PARAGON-HF.
Key Inclusion criteria	1. Signed informed consent must be obtained before any assessment is performed. 2. Patients who have completed PARAGON-HF and are able to be safely enrolled into this study as judged by the investigator.
Key Exclusion criteria	1. Patients who discontinued study drug treatment during PARAGON-HF due to an event or intercurrent illness. Eligibility can be re-considered if the event has resolved and no longer represents a risk to the patient and the patient can safely tolerate the administration of LCZ696 per the investigator's assessment. 2. Any medical condition that in the opinion of the investigator is likely to prevent the patient from safely tolerating LCZ696 or complying with the requirements of the study. 3. Patients who have experience of angioedema event(s) which occurred and reported by the investigator during PARAGON-HF. 4. Pregnant or nursing (lactating) women 5. Women of childbearing potential unless they are using highly effective methods of contraception.
Study treatment	LCZ696 50 mg b.i.d.(dose level 1), 100 mg b.i.d. (dose level 2), 200 mg b.i.d. (dose level 3)
Efficacy assessments	Efficacy is not measured in this study.
Key safety assessments	• Adverse events (AEs) and Serious adverse events (SAEs) • Laboratory values (including monitoring for hyperkalemia and renal dysfunction) • Sitting systolic Blood pressure (BP), sitting diastolic BP and heart rate • Angioedema surveillance
Data analysis	The assessment of safety will be based primarily on the frequency of AEs and SAEs. Other safety data will be summarized as appropriate.
Key words	heart failure with preserved ejection fraction, Japanese patients, extension study, long-term safety and tolerability, open-label

1 Introduction

1.1 Background

Heart failure (HF) is a terminal condition of all heart diseases, characterized by worsening of symptoms such as exertional dyspnea and/or breathlessness requiring repeated hospitalization that lead to premature death, as well as significantly greater risks of sudden death (Ponikowski et al 2016). The mortality within 5 years after diagnosis is approximately 50% in Europe and the United States (US) (Yancy et al 2013); this rate is similar to the 5-year mortality in all patients with cancer. In Japan, a cohort study of chronic heart failure (CHF) Analysis and Registry in the Tohoku District (CHART)-2 (Shiba et al 2011) showed that the total annual mortality was 4.2% and the rate of hospital readmission for HF was 14.3% among Japanese CHF patients classified into Stage C (symptomatic HF) or Stage D (refractory HF) according to the American College of Cardiology (ACC)/American Heart Association (AHA) criteria. These indicated that the prognosis of CHF patients in Japan was as poor as that of CHF patients in Europe and US (Shiba and Shimokawa 2011, Sakata and Shimokawa 2013).

In recent years, the number of patients with HF has rapidly increased due to increased prevalence of ischemic cardiac diseases, outcome improvement of those acute treatment, and population aging, etc., and estimated at approximately 26 million across the world (Ambrosy et al 2014). In Japan, the number of patients with HF is currently approximately 1 million, estimated to reach 1.3 million in 2030 (Okura et al 2008). According to the Japanese Registry of All cardiac and vascular Diseases (JROAD) conducted by the Japanese Circulation Society (JCS), the number of hospitalized patients with HF for FY2017 was 260,157, which have increased yearly (The Japanese Registry Of All cardiac and vascular Diseases (JROAD)). Frequent hospitalization not only adds physical, mental, and economic pressures on the patients and their families, but also imposes an enormous burden on health care financing.

In a part of patients with HF, it has been shown to occur with normal systolic function. HF with normal or “near-normal” ejection fraction (EF) has been designated HF with preserved ejection fraction (HFpEF). HFpEF accounts for approximately half of HF cases, and is associated with substantial morbidity and mortality (Lam et al 2011). Moreover, the prevalence of HFpEF, as well as its relative prevalence compared with HF with reduced ejection fraction (HFrEF), has been increasing in recent years (Owan et al 2006, Shiba and Shimokawa 2011). Increasing prevalence of HFpEF may be a consequence of growing aging population, and increases in hypertension (HTN) and obesity (Blanche et al 2010).

HFpEF is a serious condition associated with substantial morbidity. Hospitalization for worsening HF is common (Lewis et al 2007, Hoekstra et al 2011) and large prospective registries have shown re-hospitalization rates for HFpEF to be high and similar to those of HFrEF (Lenzen et al 2004, Fonarow et al 2007, Tsuchihashi-Makaya et al 2009). The high rate of hospitalization for heart failure associated with HFpEF is a marker of disease progression and poor outcomes (including death) in patients (Solomon et al 2007, Ahmed et al 2008) . Finally, survival rates have not improved over time for HFpEF, unlike for HFrEF (Owan et al 2006).

Unlike HFrEF, no treatment has shown to reduce morbidity or mortality in patients with HFpEF. There is currently no approved therapy for the treatment of HFpEF. Previous therapies tested in patients with HFpEF mainly focused on blocking/inhibiting the detrimental effects of

neurohormonal activation (i.e. angiotensin converting enzyme inhibitor (ACEIs), angiotensin receptor blocker (ARBs), mineralocorticoid antagonist (MRAs)), and largely ignored the physiological compensatory effect of the natriuretic peptide (NP) system. These agents failed to demonstrate outcome benefits in this patient population. The current focus of treatment is to alleviate symptoms and improve well-being. Consequently, the guidelines from the ACC/AHA (Yancy et al 2017) and European Society of Cardiology (ESC) (Ponikowski et al 2016) recommend treating volume overload/symptoms with diuretics and treating comorbid conditions that are common in HFpEF, such as diabetes mellitus (DM), HTN, renal impairment, atrial fibrillation (AF) and coronary artery disease (CAD) as well as Japan (Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure). Addressing this need is of utmost importance given the high morbidity and mortality of patients with HFpEF and the consequent stress on the global health care system (Sharma and Kass 2014).

LCZ696 (sacubitril/valsartan) is a first-in-class, angiotensin receptor neprilysin inhibitor (ARNI), approved in more than 100 countries worldwide for the treatment of adult patients with heart failure and reduced ejection fraction (HFrEF).

LCZ696, through its dual mode of action, potentiates NPs via neprilysin (NEP) inhibition while inhibiting the renin angiotensin system (RAS) via angiotensin type 1 (AT_1) receptor blockade; mechanisms which are considered to act in a complementary and at least additive manner. The mechanism of action (MoA) of LCZ696 suggests that it may impact the suspected pathophysiology of HFpEF, in which it is believed that excessive fibrosis and myocyte hypertrophy lead to abnormal left ventricular diastolic filling, impaired diastolic distensibility and/or increased vascular stiffness, with consequent elevated cardiac filling pressures (Krum and Abraham 2009).

CLCZ696B2214 (PARAMOUNT) was a phase II randomized, double-blind, active-controlled therapeutic validation trial in HFpEF patients (Solomon et al 2012). The study evaluates LCZ696 against the active comparator valsartan. The primary endpoint was change in N- terminal pro-brain natriuretic peptide (NT- proBNP) at 12 weeks. It has been shown that a decrease in NT- proBNP is correlated with reductions in left ventricular wall stress and is correlated with changes in central hemodynamics (Kazanegra et al 2001, Forfia et al 2005, Chow et al 2011, ,).

LCZ696 is the first agent with positive Phase II data in HFpEF, demonstrating significantly reduced NT- proBNP, improvement with left atrial reverse remodeling and improvement in New York Heart Association (NYHA) class. The results of PARAMOUNT in HFpEF emphasize the therapeutic rationale of targeting both neurohormonal systems through simultaneous inhibition of neprilysin and blockade of angiotensin II receptor type 1. Therefore, the phase III outcomes trial PARAGON-HF has started to evaluate the effect of LCZ696 on morbidity and mortality in HFpEF patients.

CLCZ696D2301 (PARAGON-HF) is the largest HFpEF trial ever conducted with 4,822 patients from 43 countries worldwide including 79 patients from Japan. The study is ongoing and evaluates LCZ696 against the active comparator valsartan. The primary endpoint is a composite of cardiovascular (CV) death and total (first and recurrent) HF hospitalizations. Patients will be followed until 1,847 primary composite events have occurred or at least 26 months, whichever occurs last. The study has so far undergone multiple safety reviews by an

independent Data Monitoring Committee (DMC) which has recommended continuing the study without protocol modifications.

LCZ696 is the only product known to be in late stage clinical development that leverages beneficial effects of the endogenous NP system, while simultaneously limiting the detrimental effects of prolonged RAS activation, to provide complimentary dual effects of NEP inhibition and RAS blockade to HFpEF patients.

1.2 Purpose

The purpose of this open-label study is to further evaluate the safety and tolerability of long-term treatment with LCZ696 for the eligible Japanese patients who completed CLCZ696D2301 (PARAGON-HF) until marketed product is available in Japan or 2 years from the date of the first patient enrolled in the open label extension study, whichever occurs first.

2 Objectives and endpoints

The primary objective of this study will be to evaluate further the safety and tolerability of long-term treatment with LCZ696 in eligible HFpEF patients who completed PARAGON-HF in Japan.

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To further evaluate the safety and tolerability of long-term treatment with LCZ696 in eligible HFpEF patients who completed PARAGON-HF in Japan.	• All safety data, including vital signs, adverse events, are considered primary endpoints.

3 Study design

This study is an open-label extension study to the PARAGON-HF. Patients who completed the PARAGON-HF are eligible to participate. During the study, open-label LCZ696 will be taken in addition to background treatments of comorbidities in place of ACEIs, ARBs, and renin inhibitors.

At the first visit of the study (Visit 1), all patients willing to participate will provide informed consent and will provide blood samples for local lab assessment of their health status and their eligibility for the study will be evaluated by the investigator. The patients can be enrolled at the same day as the last visit of PARAGON-HF, or enrolled up to about 6 months after the result of PARAGON-HF is known at the latest. If the first visit of the study (Visit 1) is the same as the last visit of PARAGON-HF, the procedure of blood samples will not be required and the data of the last visit of PARAGON-HF can be used as the data at Visit 1. The study treatment will be dispensed upon confirmation of eligibility.

Patients will start on open-label LCZ696 at a dose that is equivalent to the last dose level (or dose of other renin angiotensin aldosterone syste (RAAS) inhibitors if patient switched) taken at the time of completing PARAGON-HF, but no higher than dose level 2 (Figure 3-1, Table 3-1). The dose and regimen of background treatment medications should be maintained.

Every attempt should be made to up-titrate and maintain the patient at the maximum tolerated LCZ696 dose with a target dose of 200 mg b.i.d. as soon as possible per the investigator's medical judgement taking into account AEs including potassium level, kidney function, blood pressure (referred to Section 16.3 Appendix 3, Section 16.4 Appendix 4, and Section 16.5 Appendix 5).

At Visit 102 (Week 2-4), patients who tolerate open-label LCZ696 should be up-titrated to the next higher dose level by investigator judgement. If in the investigator's judgement, the patient does not tolerate the treatment dose level, then investigator should try to modify background medication in line with Section 6.5.1 in order to re-challenge the patient with a higher dose level at the earliest possible opportunity. Treatment guidelines for hyperkalemia, management of BP and renal dysfunction are provided in Section 16.3 Appendix 3, Section 16.4 Appendix 4, and Section 16.5 Appendix 5.

The patient will continue to receive LCZ696 until it is commercially available, or for a period up to 24 months from the first patient enrolled in this study, whichever comes first. If the primary endpoint of PARAGON-HF is not met, the study will be terminated.

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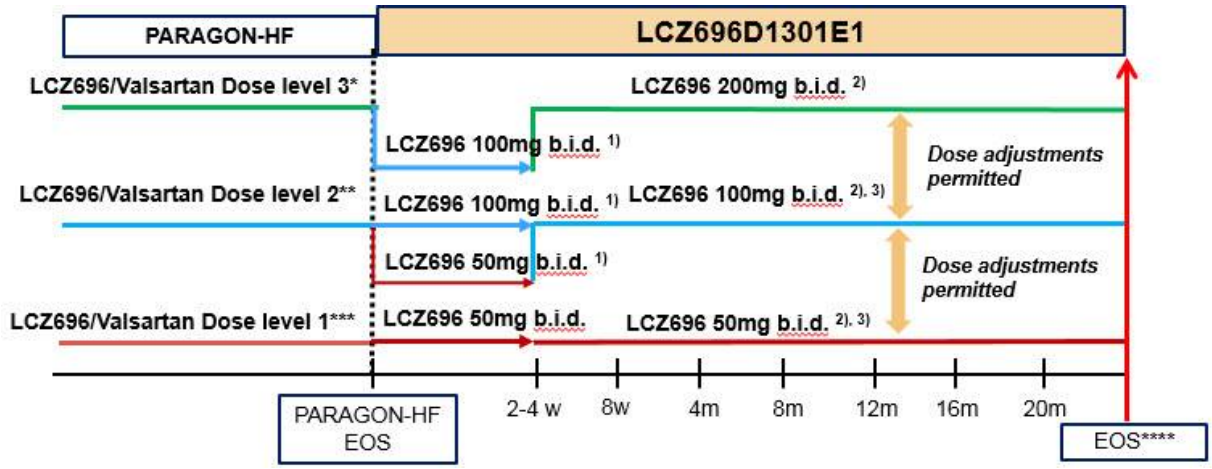
Figure 3-1 Study design



Dose level 3: LCZ696 200 mg b.i.d. or Valsartan 160 mg bid, Dose level 2: LCZ696 100 mg b.i.d. or Valsartan 80 mg b.i.d., Dose level 1: LCZ696 50 mg b.i.d. or Valsartan 40 mg b.i.d..

* patients receiving PARAGON-HF study drug at dose level 3 should start with LCZ696 100 mg (dose level 2) or might start with LCZ696 50 mg bid (dose level 1) at the investigator's discretion taking into account patient condition.

** patients receiving PARAGON-HF study drug at dose level 2 have options to start with either the open-label LCZ696 100 mg b.i.d. (dose level 2) or LCZ696 50 mg b.i.d. (dose level 1) at the investigator's discretion.

*** incudes no treatment case.

**** If the primary endpoint of PARAGON-HF is not met, the study will be terminated.

1) Dosage should be up-titrated at Visit 102 (2-4w) if patient tolerates by investigator's judgement taking into account safety monitoring guidance, and follow the general protocol guidance regarding maintenance dose.

2) Dose adjustment is permitted during the study if the patient does not tolerat the assigned dose following the general protocol guidance regarding maintenance dose.

3) Attempt should be made to up-titrate and maintain the patient at the target LCZ696 200 mg bid for as long as possible.

Table 3-1 Study drug level at the start of the study

Final dose level of study medication of PARAGON-HF	LCZ696
3*	100 mg b.i.d.
2**	50 mg b.i.d. or 100 mg b.i.d.
1	50 mg b.i.d.
No Treatment***	50 mg b.i.d.

* The patient receiving PARAGON-HF study drug at dose level 3 should start with LCZ696 100mg or might start with LCZ696 50 mg b.i.d. at the investigator's discretion taking into account patient condition.
** The patient receiving PARAGON-HF study drug at dose level 2 has options to start with either LCZ696 100 mg b.i.d. or LCZ696 50 mg b.i.d. at the investigator's discretion.
***Patients who finish the PARAGON-HF on no treatment and on an ACEI should observe a 36 hours ACEI-free washout period as per Table 6-1. Patients might start from LCZ696 100mg b.i.d. at the investigator's discretion taking into account patient condition and current treatment (e.g. RAAS inhibitors)

4 Rationale

The purpose of this extension study is to assess the safety and tolerability of long-term treatment with LCZ696 in Japanese HFpEF patients who completed PARAGON-HF trial. This study allows the option of use of LCZ696 in patients benefiting from the study treatment in PARAGON-HF by the investigator judgement.

The mechanism of action of LCZ696 suggests that it may impact the suspected pathophysiology of HFpEF, in which it is believed that excessive fibrosis and myocyte hypertrophy lead to abnormal left ventricular diastolic filling, impaired diastolic distensibility and/or increased vascular stiffness, with consequent elevated cardiac filling pressures. In phase II proof of concept trial in HFpEF (PARAMOUNT), LCZ696 demonstrated greater reductions in NT-proBNP and all echocardiographic measures of left atrial size compared with valsartan. Albeit for HFrEF patients, LCZ696 showed a large benefit in morbidity and mortality compared to enalapril, standard therapy in the guideline in phase III outcome study (PARADIGM-HF).

The rationale for allowing patients the option to receive open-label LCZ696 in this study pending release of the PARAGON-HF study results is twofold. First, if the treatment plan is implemented for a patient by the treating physician, it will minimize treatment disruption in post-PARAGON-HF treatment. PARAGON-HF patients were randomized to either valsartan or LCZ696 (sacubitril/valsartan), which are all components of LCZ696. As of the date of this study, the independent DMC has reviewed the cumulative safety data of the PARAGON-HF study twice annually since its initiation (total of eight safety reviews) and has determined that LCZ696 continues to demonstrate an acceptable safety profile relative to valsartan. Another rationale for allowing PARAGON-HF patients to be offered open-label LCZ696 before release of the PARAGON-HF study results is that there is currently no approved treatment for patients with HFpEF in Japan. Allowing investigators and patients the option to receive open-label LCZ696 in this study will afford them a treatment option that will minimize disruption in their medical regimen. If the results of PARAGON-HF does not show the efficacy, the study will be terminated.

4.1 Rationale for study design

An open-label study design was adopted for this study because it satisfies the main objective of obtaining safety and tolerability data of long-term treatment with LCZ696 in the Japanese HFpEF patients who completed PARAGON-HF. As there is no comparator in this extension study, study blinding is not necessary.

4.2 Rationale for dose/regimen and duration of treatment

The starting dose in this study was set based on the dose level administered in PARAGON-HF. The patients receiving study drug at dose level 3 in PARAGON-HF should start taking a LCZ696 at the next lower dose level to ensure patient's safety. The patients receiving study drug at dose level 2 in PARAGON-HF can start taking a LCZ696 at either the same dose level or the next lower dose level to ensure the patient's safety based on the investigator's clinical judgement.

In case of the patients starting at the next lower dose level from PARAGON-HF, the dosage will be up-titrated to the next higher dose level (original dose level) as soon as possible if tolerated. The patients receiving study drug at dose level 2 in PARAGON-HF can start with either the same dose level or the next lower dose level based on the investigator's clinical judgement. The patients who are not on study medication at screening visit and eligible should start at dose level 1.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.5 Risks and benefits

Patients will be instructed not to take any RAS blockade medications (ACEI or ARB) while they take study drug to avoid excess RAS blockade. All patients will be allowed to continue receiving the rest of their background CV medications. The risk to patients in this study will be minimized by compliance with the eligibility criteria and close clinical monitoring. In women of child-bearing potential, a possible risk of developmental toxicity cannot be excluded. Women of child-bearing potential should therefore use a highly effective method of contraception during dosing and for 7 days off study medication. If there is any question that the patient will not reliably comply, they should not be entered in the study. All patients in this study will be $\geq$ 50 years of age because all patients participated in PARAGON-HF were $\geq$ 50 years of age, and therefore the risk of pregnancy during the trial is minimal.

Since this study is following PARAGON-HF, participating patients to this study will benefit from continuous effect of LCZ696 thorough the continuous access from PARAGON-HF to open-label LCZ696 that avoids the treatment interruption. If the primary endpoint of PARAGON-HF is not met, the study will be terminated as soon as possible.

5 Population

The study population will consist of Japanese patients with HFpEF who completed PARAGON-HF. It is anticipated that approximately 70 Japanese patients will complete the PARAGON-HF, of which approximately 80% are anticipated to enrol into this study.

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained before any assessment is performed.
2. Patients who have completed PARAGON-HF and are able to be safely enrolled into this study as judged by the investigator.

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Patients who discontinued study drug treatment during PARAGON-HF due to an event or intercurrent illness. Eligibility can be re-considered if the event has resolved and no longer represents a risk to the patient and the patient can safely tolerate the administration of LCZ696 per the investigator's assessment.
2. Any medical condition that in the opinion of the investigator is likely to prevent the patient from safely tolerating LCZ696 or complying with the requirements of the study.
3. Patients who have experience of angioedema event(s) which occurred and reported by the investigator during PARAGON-HF.
4. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
5. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and for 7 days of after stopping medication. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception)
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to Visit 1). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
- Combination of any two of the following (a+b, a+c, or b+c), acording to country approvals and availability:
    a. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository

b. Use of oral, (estrogen and progesterone), 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
c. Placement of an intrauterine device (IUD) or intrauterine system (IUS).

- 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), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the Informed Consent Form (ICF).

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

All eligible patients will receive LCZ696 b.i.d. in addition to optimal therapy for HF and other comorbidities, as considered appropriate by the investigator and in accordance with standard therapy guidelines. The use of an ACEI or an ARB, or a renin inhibitor in addition to the study drug is strictly prohibited.

The sponsor will provide the following study medication *in bottles;*

- LCZ696 50 mg film coated tablets (Dose level 1)
- LCZ696 100 mg film coated tablets (Dose level 2)
- LCZ696 200 mg film coated tablets (Dose level 3)

Study medication will be provided for the treatment according to study protocol, including additional medication to allow for delayed visits. Medication labels will be in the local language and comply with the legal requirements of the country. They will include storage conditions for the drug, but no information about the patients.

6.1.2 Additional study treatments

Any background treatment except for ACEI, ARB, and renin inhibitor are allowed to continue in this study.

6.1.3 Treatment arms/group

All patients will be treated with LCZ696.

6.1.4 Treatment duration

This study will continue until marketed product is available in Japan, or approximately for 2 years from the date of the first patient enrolled, whichever comes first. Subjects may be discontinued from treatment earlier due to unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or the subject.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded on the appropriate Case Report Forms (CRF).

CV medications

The patient should be on an optimal medical regimen of diuretics and background medications to effectively treat comorbidities, such as HTN, DM, AF and coronary artery disease. Investigators should take into consideration the patient's risk factors, such as age and comorbidities, and make every effort to control a patient's BP in accordance with international and local treatment guidelines, as well as other evidence-based medicine. The concomitant use of ACEIs, ARBs or renin inhibitor is strictly prohibited while the patient is receiving study drug (Section 6.2.2).

Medications known to raise potassium levels

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

Phosphodiesterase-5 (PDE-5) inhibitors

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

Neseritide and intravenous (IV) nitrates

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

HMG-CoA reductase inhibitors

Caution is recommended when co-administering LCZ696 with atorvastatin or other statins (e.g. simvastatin, pravastatin) that are substrates of organic anion-transporting polypeptide (OATP) 1B1 and OATP1B3 because of the potential to raise plasma statin levels.

6.2.2 Prohibited medication

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

Table 6-1 Prohibited medication

Medication	Action taken
Any ACEI	Discontinue study drug. The ACEI must be stopped for ≥36 hours prior to re-initiation of study drug
Any ARB	Discontinue study drug. The ARB must be stopped prior to re-initiation of study drug
Any renin inhibitor	Discontinue study drug. The renin inhibitor must be stopped prior to re-initiation of study drug

The concomitant use of ACEIs, ARBs or 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 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 hyperkalemia, hypotension, and renal dysfunction are provided to investigators in Section 16.3 Appendix3, Appendix 4 and Appendix 5, respectively. Patients may receive ACEIs, ARBs or a renin inhibitor during the study ONLY if the study drug has been temporarily discontinued.

Use of rescue medication must be recorded on an appropriate CRF.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.) that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.; as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available.

6.3.2 Treatment assignment, randomization

No randomization will be performed in this study. During this study, all patients will be treated with LCZ696 at maximally tolerated dosed with a target dose of 200 mg b.i.d.

6.4 Treatment blinding

Treatment will be open to subjects, investigator staff, persons performing the assessments, and the sponsor.

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are permitted.

6.5.1 Dose escalation guidelines

6.5.1.1 Starting dose

LCZ696 will be dispensed and the patient will be required to take one tablet of the assigned study medication twice a day for the duration of the study. The dose level dispensed at Visit 101 will be either 50 mg b.i.d. (dose level 1) or 100 mg b.i.d. (dose level 2) largely depending on the last dose level taken by the patient at the time of completing PARAGON-HF and patient condition. The dose level should be gradually up-titrated at subsequent visit with the goal of reaching the target dose of 200 mg b.i.d. (dose level 3) as soon as tolerated by the patient (see Figure 3-1 and Table 3-1).

6.5.2 Dose modifications

For subjects who do not tolerate the protocol-specified dosing schedule, dose level adjustments and interruptions of study treatment are permitted in order to allow subjects to continue the study treatment. The following guidelines should be followed:

Every attempt should be made to maintain patients at the target study drug dose level throughout the study. 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 down-titration 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.

These dose changes must be recorded on the appropriate CRF.

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 study, down titration of the study drug at any time based on the judgment of the investigator will be allowed taking into account the safety and tolerability criteria defined in Section 16.3 Appendix3, Appendix 4, and Appendix 5. If down titration is necessary, the patient

should be down titrated to the next lower study drug dose level (Table 6-2). The patient may continue receiving the lower dose level for a recommended period of 1 to 4 weeks before being re-challenged at the next higher dose level. For example, a patient who encounters tolerability problems at the target study drug dose level (dose level 3), should receive the study drug at dose level 2 for 1 to 4 weeks at the discretion of the investigator. Then, he/she should be re-challenged with up-titration back to dose level 3.

If the tolerability issues are not alleviated despite down titration by one dose level, the investigator may down titrate further to the next lower study drug dose level for 1 to 4 weeks, up to temporary discontinuation of the study drug. Again, once stable, the patient should be re-challenged with up titration to the next higher dose level every 1 to 4 weeks in an attempt to bring back the patient gradually to the target study drug dose level (dose level 3). The investigator may choose the next dose level for down- or up-titration according to his or her judgment (Table 6-2).

In some instances, the investigator's judgment, dose level 1 or 2 could be maintained if he/she considers that the patient's condition would not allow any further up titration to the target dose level of study drug (dose level 3). In this case, it would be acceptable to maintain the patient at dose level 1 or level 2, whichever is the higher and tolerated dose level by the patient.

Study drug restart after temporary treatment interruption

Study drug should be reintroduced in those patients who temporarily discontinue it as soon as medically justified in the opinion of the investigator.

Once the investigator considers the patient's condition appropriate for receiving the study drug, the investigator should re-start the patient on the study drug at the most appropriate and allowable dose level (Table 6-2) per his/her medical judgment. If tolerated, the patient should be up-titrated a dose level every 1 to 4 weeks to the target dose level 3, as per the investigator's judgment. Should the patient not tolerate the re-start study drug dose level, he/she may be down titrated again (if appropriate) or temporarily discontinue the study medication again and a new attempt to up titrate or reintroduce the study drug could be considered by the investigator as soon as medically justified in his/her judgment.

The use of an ACEI, ARB or a renin inhibitor is strongly discouraged while patient is taking study drug. However, if for any reason a patient off study drug has started 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 6-1).

These changes must be recorded on an appropriate CRF.

In case of pregnancy discovered during the study, the patient will be withdrawn from the study immediately. See Section 10.1.4 for further details on pregnancies and reporting guidelines.

6.5.3 Follow-up for toxicities

Not applicable.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the appropriate CRF.

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

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient and/or the caregiver. This information should be captured in the source document at each visit. The investigator and/or study personnel should counsel the patient if compliance is below 80% at any time during the study. Study drug accountability will be determined by the site monitor while performing routine site visits and at the completion of the study.

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

6.6.2 Emergency breaking of assigned treatment code

Not applicable.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described for clinical trial use only.

As per the treatment assigned to the subject, investigator staff will select the study treatment to dispense to the subject. The site personnel will record the batch number of study medication dispensed to the subject's source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

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

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

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by

monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

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

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

Novartis will supply the investigators with all medications sufficient for the course of the study. Patients will be provided with study drug corresponding to their assigned dose level, sufficient to last until the next scheduled visit. Patients will be required to take one LCZ696 tablet twice a day for the duration of this study. Table 6-2 summarizes the study drug that will be taken during this study.

Table 6-2 Dose and treatment schedule

Study visit	Dose level	LCZ696
Visit 102 and all subsequent visit	3 [a]	200 mg b.i.d.
Available for any visit after Visit 101	2	100 mg b.i.d.
Available for any visit after Visit 101	1	50 mg b.i.d.
[a] This dose level should be attempted and maintained for as long as possible. If down-titration is necessary due to side effects, the patient should be re-challenged as soon as medically possible per the investigator's judgement.		

Patients will be instructed to take their morning study drug doses at approximately 08:00 (8 AM) and their evening study drug dose at approximately 19:00 (7 PM). The study drugs should be taken with water, with or without food. If vomiting occurs during the course of treatment, subjects should not take LCZ696 again before the next scheduled dose. If the patient misses taking any study drug dose, he/she should take it as soon as possible, unless it is almost time for the following scheduled dose. In this case, the patient should skip the missed dose and return back to his/her regular study drug administration schedule.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the appropriate CRF.

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

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject 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 subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (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 subject informed consent and should be discussed with the subject 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 subject.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

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

8 Visit schedule and assessments

Table 8-1 lists all of the assessments for this study. The table indicates which data are entered into CRF from the source data (X), remain in the source documents only (S). At the study end, all patients will return to the study sites as soon as possible to undergo the End of Study (EOS) visit assessments.

Assessment schedule lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the subject’s source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed

for the final visit will be performed. Permanent discontinuation of study drug constitutes withdrawal from the study. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

At a minimum, patients will be contacted for safety evaluations during the 30 days following the last study visit or following the last administration of study drug (whichever is later), including a final contact at the 30-day point. This follow up may be a phone call. Documentation of attempts to contact the patient should be recorded in the source documentation.

Table 8-1 Assessment Schedule

Period	Screening	Treatment								Treatment	Unplanned
Visit Name	**1**[1]	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**199(EOS)**[2]	**UPV**[3]
Days	**1**	**1**	**14 to 28**	**56**	**122**	**244**	**365**	**487**	**609**	**730**	**-**
Weeks	**1**	**1**	**2 to 4**	**8**	**18**	**35**	**53**	**70**	**87**	**105**	**-**
Informed consent	X										
Inclusion/exclusion/demographics	X	X									
Physical Examination	S	S	S	S	S	S	S	S	S	S	S
Vital Signs		X	X	X	X	X	X	X	X	X	X
Laboratory assessments(locally)[4]	S	S	S	S	S	S	S	S	S	S	(S)
Pregnancy test(locally)[5]	S	S	S	S	S	S	S	S	S	S	(S)
Concomitant medication/Non drug therapies	X	X	X	X	X	X	X	X	X	X	X
AE/SAEs	X	X	X	X	X	X	X	X	X	X	X
Drug accountability			X	X	X	X	X	X	X	X	
Screening phase disposition form	X										
Study completion/ discontinuation form										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] Visit 1 and Visit 101 can be on the same day
[2] End of Study (EOS) visit will be completed at 2 years from the date of the first patient enrolled in the study, or prematurely withdraws from the study, or this study will be terminated by Novartis, or when LCZ696 becomes commercially available and reimbursed for the HFpEF indication in Japan, whichever occurs first.
[3] Unplanned visits (UPV) may occur if a safety issue develops.
[4] serum potassium and creatinine will be performed every visit. Additional laboratory evaluation should be performed by Investigator's judgement.
[5] All pre-menopausal women who are not surgically sterile will have serum pregnancy test locally at Visit 1. A urine dip-stick pregnancy test should be performed locally at other visits by Investigator's judgement.

8.1 Screening

Re-screening will not be allowed in this study.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable Case Report Form. The demographics, inclusion/exclusion, and informed consent pages must also be completed for screening failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a SAE after signing informed consent. A SAE occurred after signing informed consent until confirming screening failure should be reported.

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

8.2 Subject demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: age, sex, race, ethnicity.

8.3 Efficacy

8.3.1 Appropriateness of efficacy assessments

Efficacy is not measured in this study.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed. If the abnormality for each assessment (e.g. laboratory test, vital sign) induces clinical signs or symptoms, or requires therapeutic intervention, then the diagnosis or medical condition must be entered on the AE CRF. For details on AE collection and reporting, refer to AE section.

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

8.4.1 Laboratory evaluations

Laboratory assessments will be analyzed locally during the study. Values outside the normal ranges and notable values should be flagged on the report. It is the responsibility of the investigator to review all laboratory results and make an assessment of whether an abnormal or notable value is clinically significant, whether additional evaluations should be performed as

judged appropriate, and whether the patient may continue in the trial. Sample collection should be conducted according to the standards and requirements of the local laboratory.

Serum potassium and creatinine will be evaluated locally at all visits in Table 8-1. Additional laboratory evaluation should be performed by Investigator's judgement at any visits.

8.4.2 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have serum pregnancy test locally at visit 1. A urine dip-stick pregnancy test should be performed locally at other visits defined in Table 8-1. If positive, the patient must discontinue study drug until after the pregnancy and lactation period.

8.4.3 Appropriateness of safety measurements

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

8.4.4 Physical assessments

A physical exam will include the examination of general appearance and vital signs (BP [systolic blood pressure (SBP) and diastolic blood pressure (DBP)] and pulse). If indicated based on medical history and/or symptoms, other exams will be performed by Investigator's judgement. A physical exam will be conducted at all visits starting from Visit 1(see Table 8-1).

Information from all physical examinations must be included in the source documentation at the study site.Significant findings made after signing the informed consent which meet the definition of an AE must be recorded on the AE section of the CRF.

8.4.5 Vital sign

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

8.4.6 Angioedema

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

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

The investigator may be also be contacted by Novartis regarding AEs that may resemble an angioedema-like event. A list of terms that are considered “angioedema-like” (e.g., periorbital

swelling) will be provided to sites in a manual. The investigator or his/her delegated staff must complete the required forms and provide the required medical records for all such events, regardless of whether the investigator views the event in question as angioedema or not.

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

Information regarding this committee is outlined in Section 10.2.2. Details on the procedures for reporting angioedema events will be provided to investigators in a manual.

8.5 Additional assessments

No additional tests will be performed on subjects entered into this study.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Patients may voluntarily discontinue study treatment for any reason at any time.

Permanent discontinuation of study drug for a subject occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

The investigator must discontinue investigational treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject’s premature discontinuation of study treatment and record this information. Always consider reasons which are related to safety and efficacy first.

Subjects who discontinue investigational treatment permanently 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 Section 9.1.2, withdrawal of informed consent). They will be expected to perform the EOS Visit.

If they fail to return for the EOS visit assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

Subjects who discontinue treatment early will be expected to perform the final visit(EOS). All dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the appropriate CRF.

In case that a patient is to be switched from an LCZ696 to an ACEI, a 36-hour LCZ696-free washout should be implemented prior to the initiation of ACEI intake to minimize the risk of occurrence of angioedema. Similarly, a ACEI-free 36-hour washout should be implemented when switching a patient from an ACEI to an LCZ696. Patient management and safety

monitoring guidelines, including implementation of the appropriate washout periods, should refer to LCZ696D2301 (PARAGON-HF) or approved label whichever is most appropriate.

9.1.2 Withdrawal of informed consent

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

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

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

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

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

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

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

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until the end of the study.

9.1.4 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.

If the primary endpoint of PARAGON-HF is not met, this study will be terminated and the patient must be safely switched from open-label LCZ696 to alternative treatment based on the investigator's clinical judgement as soon as possible.

In taking the decision to terminate the study, Novartis will always consider the subject's welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. 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 subject'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 subject finishes their Study Completion (EOS) 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.

All treated subjects should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the subject should be recorded in the source documentation.

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 subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

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

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject 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 Common Toxicity Criteria (CTC) AE grade (version 5 or higher).
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 subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported

4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment

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

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn
- its outcome (i.e. recovery status or whether it was fatal)

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

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 or end of study visit, whichever is longer.

Once an adverse event 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.

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 subjects with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.1 Appendix1.

For lab values provided without related clinical information, the CTCAE scale must be used to determine the seriousness. Any value of Grade 4 and above on this CTCAE scale must be considered serious.

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 subject 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 subject'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 subject 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 subject 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 and the malignant neoplasm is not a disease progression of the study indication.

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 subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. 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.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

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 the study treatment (if the study treatment consists of several components) complete the SAE Report Form in English and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Consider the following 2 categories (as applicable) to determine SAE reporting timeframes:

1. **Screen Failures (e.g. a subject who is screened but is not treated)**: SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.
2. **Treated Subjects**: SAEs collected between time subject signs ICF until 30 days after the subject 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 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.

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 Chief Medical Office and Patient Safety (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 (EC) in accordance with European Union (EU) Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

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.

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

10.1.4 Pregnancy reporting

To ensure subject 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 should be recorded and reported by the investigator to the Novartis/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 any pregnancy outcome. The follow-up should be for up to 12 months following the birth of the baby. 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, subject or consumer (European Medicines Agency (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 CRF	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 subject 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. alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBL), prothrombin time/international normalized ratio (PT/INR), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT)) to confirm elevation.

- These liver chemistry repeats should be performed using the local laboratory used by the site. Repeated laboratory test results must be reported as appropriate.
- If the initial elevation is confirmed, close observation of the subject 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 subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These 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.

10.2.2 Angioedema Adjudication Committee

If an angioedema or angioedema-like event occurs, the investigator will complete an Adjudication Questionnaire in eCRF. Details on the process of reporting angioedema and angioedema like events are outlined in a manual provided to investigators.

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

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

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 Code of Federal Regulation (CFR) Part 11 requirements, Investigator site staff will not be given access to the Electric Data Capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, 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 subject data for archiving at the investigational site.

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

11.2 Database management and quality control

Novartis personnel (or designated Clinical Research Organization) 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, prior medications and non-drug therapy entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked 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 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 GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject 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 Clinical Research Associates (CRA) organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject 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 subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

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 subjects 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

The following population will be used for the statistical analyses:

The Safety Set (SAF): comprises all patients who received at least one dose of study treatment.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively for all subjects for the SAF.

Continuous variables will be summarized using n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency and percentage. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by overall.

12.3 Treatments

The Safety set will be used for the analyses below.

The overall duration on the study drug will be summarized using mean, standard deviation, median, minimum, and maximum. Mean doses and dose levels will be summarized by visit. 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 for all subjects.

12.4 Analysis of the primary endpoint(s)

The primary objective of this study will be to evaluate further the safety and tolerability of long-term treatment with LCZ696 in eligible HFpEF patients who completed PARAGON-HF in Japan.

12.4.1 Definition of primary endpoint(s)

All safety data, including vital signs, adverse

events, are considered primary endpoints.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary objective of this study is to evaluate safety and tolerability so in this study there is no statistical model/hypothesis defined however the assessment of safety will be based primarily on the frequency of AEs and SAEs.

12.4.2.1 Primary analysis

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

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

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

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

12.4.3 Handling of missing values/censoring/discontinuations

There will be no imputation done on any parameter or variable in this study.

12.4.4 Sensitivity and Supportive analyses

Sensitivity analyses

Not applicable.

Supportive analyses

Not applicable.

12.5 Analysis of secondary endpoints

Not applicable.

12.6 Interim analyses

Not applicable.

12.7 Sample size calculation

12.7.1 Primary endpoint(s)

The study population will consist of Japanese patients who completed PARAGON-HF. It is anticipated that approximately 70 patients will survive to the end of PARAGON-HF, of which approximately 80% are anticipated to enrol into this study.

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

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 etc.) .

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 standard operational procedures (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 subjects 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 subject 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 subject 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.

15 References

References are available upon request

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

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

Hematology

Hematocrit >50% increase, >20% decrease

Hemoglobin >50% increase, >20% decrease

Platelet count >75% increase, >50% decrease

RBC count >50% increase, >20% decrease

WBC count >50% increase, >50% decrease

Blood Chemistry

Alkaline phosphatase >100% increase

ALT(SGPT) >150% increase

AST(SGOT) >150% increase

BUN >50% increase

Calcium >10% increase, >10% decrease

Chloride >10% increase, >10% decrease

Creatinine >50% increase

Potassium >20% increase, >20% decrease

Total bilirubin >100% increase

Uric acid >50% increase

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
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.

Alb: Albumin, LFT: Liver Function test

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

General principles

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

Any patient with a serum potassium > 5.3 mmol/L (mEq/L) at any time in treatment period requires the Investigator to confirm the potassium concentration in a non-hemolyzed sample via an immediate repeat lab sample to both the clinic local lab and the study central lab.

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

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

Corrective action for management of hyperkalemia

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

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

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

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

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

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

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

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

16.4 Appendix 4: Guidelines for the management of blood pressure

Guidelines

1. Investigator should monitor BP closely
2. If symptomatic hypotension occurs:
   a. Correct any treatable cause, e.g. hypovolemia
   b. If hypotension persists, any antihypertensive drug such as diuretics, calcium channel blockers (CCBs), nitrates, beta blockers, aldosterone antagonists and α-blockers, should be down-titrated or stopped first before down-titration of the study drug is considered. Any non-antihypertensive drug (such as nitrates) should be considered for down-titration prior to study drug as determined by the best judgment of the investigator.
   c. If hypotension persists, the study drug should be down-titrated or even temporarily withdrawn. The dose re-challenge and medications adjust guidelines described in Section 6.5.2 should be adhered to as much as possible.

16.5 Appendix 5: Guidelines for the management of renal dysfunction

General principles:Glomerular filtration rate in HF patients depends on intrinsic renal function and on a balance between afferent and efferent glomerular arterial tonicity. This tonicity is partly regulated by astimulation 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 situationIf, at any time in treatment period, eGFR decreases by ≥25% from baseline (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

Action situation

If a patient's eGFR decreases by ≥40% from baseline (Visit 101) (or if serum creatinine concentration rises above 3 mg/dL (265μmol/L), the investigator will check for potentially reversible causes of renal dysfunction (see above).

The investigator may consider down-titration of study 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.