NOVARTIS

Clinical Development

LCZ696

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)

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section impacted (Current)
22APR2019	Prior to FPFV	Initial Version		
12DEC2019	Before DBL	The CTT suggested few updates	Few of the summary tables will be performed for Overall and removed by treatment group.	2.3.1, 2.3.2, 2.4.2
			For vital signs, added the change from baseline.	2.7.3.2

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List of abbreviations

ACEi	angiotensin converting enzyme inhibitor
AE	adverse event
ARB	angiotensin receptor blocker
ATC	anatomical therapeutic classification
Bid	twice a day
BP	blood pressure
CRF	case report form
CSR	clinical study report
DBP	diastolic blood pressure
DMC	data monitoring committee
eGFR	estimated glomerular filtration rate
HFpEF	heart failure with preserved ejection fraction
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mg	milligram(s)
NYHA	New York Heart Association
RAAS	Renin angiotensin aldosterone system
SAE	serious adverse event
SAF	safety set
SAP	statistical analysis plan
SBP	systolic blood pressure
SMQ	Standardized MedDRA query
SOC	system organ class
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse event

1 Introduction

The statistical analysis plan (SAP) describes the detailed methodology and implementation of the planned statistical analyses outlined in the study protocol v00 for CLCZ696D1301E1. The analysis results will be summarized in the clinical study report (CSR).

1.1 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 ACEi's, 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.

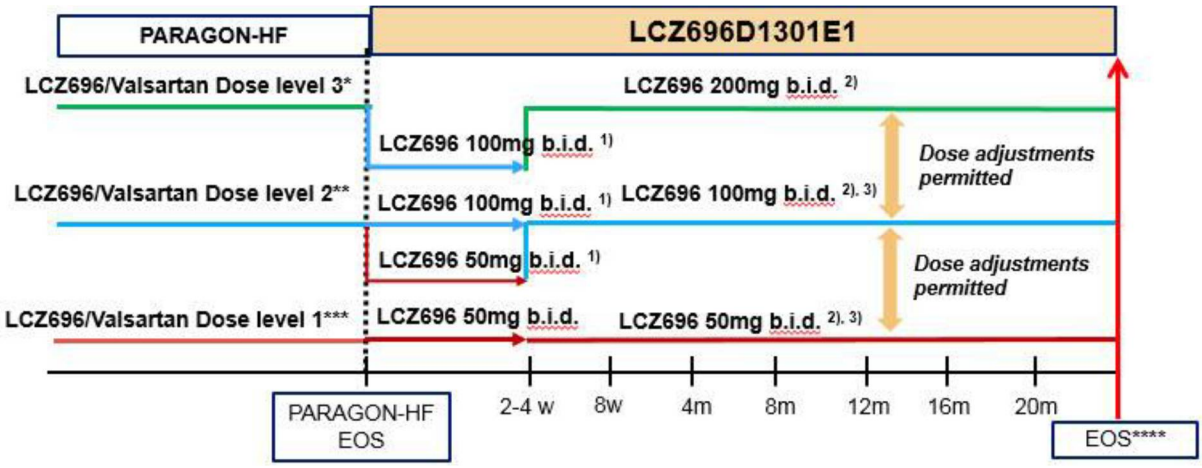
Patients will start on open-label LCZ696 at a dose that is equivalent to the last dose level (or dose of other renin angiotensin aldosterone syste (RAAS) inhibitors if patient switched) taken at the time of completing PARAGON-HF, but no higher than dose level 2 (Figure 1-1, Table 1-1). The dose and regimen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

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 of protocol 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 of protocol.

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.

Figure 1-1 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 1-1 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.

Final dose level of study medication of PARAGON-HF	**LCZ696**
***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 in the protocol. 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)	

1.2 Study objectives and endpoints

Table 1-2 presents the objectives and related endpoints

Table 1-2 Objectives and related endpoints

Objective(s)	Endpoint(s)
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.	**Endpoint(s) for primary objective(s)** • All safety data, including vital signs, adverse events, are considered primary endpoints.

2 Statistical methods

The following section contain important information on detailed statistical methodology used for analysis and reporting purposes.

2.1 Data analysis general information

Unless otherwise specified, data will be analyzed by [redacted] according to the protocol for CLCZ696D1301E1, using SAS 9.4 or higher. Further details on planned statistical analyses will be presented in the following section and in CSR Appendix 16.1.9.

An established program level data monitoring committee (DMC) independent of Novartis that reviews safety data from LCZ696 studies will be used for this study. The DMC will review patient safety data in an unblinded manner approximately every six months and determine if it is safe to continue the study. Any major recommendation from the DMC will be communicated to the Executive Committee and must be reviewed and ratified by the Executive Committee in consultation with Novartis prior to its enactment.

In general, the continuous variables will be summarized using number of observations, mean, standard deviation, median, quartiles, minimum and maximum; the categorical variables will be summarized using frequencies and percentages.

The analysis will be conducted on all data at the end of trial.

2.1.1 General definitions

Baseline assessment and study day

Unless otherwise specified, the baseline assessment is defiend as below.

- For safety variables, the baseline assessment is defined as the last non-missing assessment (scheduled or unscheduled) prior to or on the first dose date of the study drug.

In the listings, the study day will be displayed, as applicable.

- In the listings of safety data, the study day is defined as the date of assessment (event/visit) minus the date of first dose plus one day, i.e., Day 1 is the first dose date.

Post-baseline assessment

Unless otherwise specified, for safety variables, the post-baseline assessments are defined as those assessments taken later than the first dose date of the study drug.

Unscheduled assessments

Unscheduled assessments will be included in over period minimum/maximum, and in over period shift table, but will not be included in by-visit summary and longitudinal modelling.

2.2 Analysis sets

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

- **Screened set (SCR)** – All patients who signed the informed consent for CLCZ696D1301E1
- **Safety set (SAF)** – All patients who received at least one dose of study drug. Patients will be analyzed according to the treatment actually received. Patients without valid written informed consent will be excluded from safety set.

Rules leading to exclusion from the analysis sets are given in section 5.2 of protocol

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Disposition for the screening epoch

The number and percentage of patients who completed the screening visit will be provided. Besides, the primary reason for not completing the screening visit will be summarized, using the number and percentage of patients not qualifying for such reasons. For any patient who was screened more than once, the data from the last screening will be used in the summary.

The SCR will be used for the above analyses.

Disposition for the study treatment

The numbers and percentages of patients who took at least one dose of the study drug, who completed the study treatment and who permanently discontinued from the study treatment will be provided for overall; the primary reason for permanent discontinuation from the study drug will be summarized for overall and, using the number and percentage of patients discontinued for such reasons.

The SAF will be used for the above analyses.

Protocol deviations

The protocol deviations will be summarized for overall and protocol deviation category, using the numbers and percentages of patients with at least one protocol deviation within the protocol deviation category.

The SAF will be used for the above analyses.

Analysis set dispositions

The numbers and percentages of patients within each analysis set will be for overall.

In addition, the number and percentage of patients satisfying each criteria leading to exclusion from analysis sets will be provided for overall.

2.3.2 Background and demographic characteristics

For overall, summary statistics will be provided for demographics and baseline characteristics, including age, age group (< 65 years, ≥ 65 years), age group (< 75 years, ≥ 75 years), sex, region, race, ethnicity, pulse rate, sitting pulse, sitting systolic blood pressure (SBP), and sitting diastolic blood pressure (DBP). If an above variable is scheduled at screening. Few parameters like height, weight and BMI for all the subjects will be taken from the screening visit of the CLCZ696D2301 study. Also parameters includes BMI group (<=30 (kg/m2), >30-<=35 (kg/m2), >35 (kg/m2)), pulse pressure, eGFR, eGFR group (<60 mL/min/1.73m^2, >=60 mL/min/1.73m^2) and MMSE total score will be taken from the CLCZ696D2301 study.

Continuous variables will be summarized using number of observations, mean, standard deviation, median, minimum, the first quartile (Q1), the third quartile (Q3), and maximum.

Categorical variables will be summarized using frequencies and percentages.

The SAF will be used for the above analyses.

2.3.3 Medical history

Any condition entered on the relevant medical history/current medical conditions CRF will be coded using the most updated version of MedDRA dictionary. Medical history will be collected only for patients with SAE. A listing of such patients will be provided.

The SAF will be used for the above analyses.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The study drug administration will be recorded on the CRF page: “Study Treatment” using start date, end date and dispensing level of the study drug. Each pair of start date and end date will be considered as a dosing interval.

For each patient, the dosing intervals will be sorted according to the start date and the end date from the earliest to the latest. It is expected that, for each patient, there should be no gaps and overlaps among dosing intervals, with the exception that, the end date of a dosing interval can

be the same as the start date of its next dosing interval, when the patient may take the previous dispensing level in the morning and start a different dispensing level in the evening.

For patients who permanently discontinue from the study treatment, the date of premature treatment discontinuation will be their study end date.

For each dosing interval, the dispensing level of the study drug will be recorded together with the start date and end date. The dose level and the daily dose (mg/day) are defined based on the dispensing level according to Table 2-1.

Table 2-1 Dose levels and daily doses of the study drug

Dispensing Level	Dose Level	Dose	Daily Dose
		LCZ696	LCZ696
Dose level 1	1	50 mg bid.	100 mg/day
Dose level 2	2	100 mg bid.	200 mg/day
Dose level 3	3*	200 mg bid.	400 mg/day

* 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.

Dispensing level, dose level and daily dose at each visit

For a given visit, the visit associated dosing interval is defined as the dosing interval with its start date prior to or equal to the date of visit AND its end date later than or equal to the date of visit; the dispensing level, dose level and daily dose (mg/day) at the visit are defined as the dispensing level, dose level and daily dose (mg/day) for the visit associated dosing interval. In the case that, the visit date is equal to the end date of an earlier dosing interval as well as the start date of a later dosing interval, the later dosing interval will be taken as the visit associated dosing interval.

The dispensing level will be summarized by treatment and visit, for overall using the number and percentage of patients on each level; the dose level will be summarized by treatment and visit, using number of observations, mean, standard deviation, median, minimum, Q1, Q3, and maximum; the daily dose (mg/day) will be summarized by treatment and visit, using number of observations, mean, standard deviation, median, minimum, Q1, Q3, and maximum.

The SAF will be used for the above analyses.

Duration of treatment

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.

The SAF will be used for the above analyses.

Duration on each dose level

For a given dose level, the duration (day) on this dose level is defined as the number of days on this dose level during the period from the date of the first dose of the study drug to the date of the last dose of the study drug. In the case that, the end date of an earlier dosing interval is the same as the start date of a later dosing interval, the day will be counted as 0.5 day on both the earlier dose level and the later dose level. In the case that, the date of permanent discontinuation of the study drug is the same as the date of the last dose the study drug, the day will be counted as 0.5 day on the dose level of the last dose but not counted on dose level 0.

The duration (week) will be converted from the duration (day) using a factor of 7 day/week, and will be summarized by overall.

The SAF will be used for the above analyses.

Duration of study drug exposure

The duration (day) of study drug exposure is defined as the sum of the duration (day) on dose level 1 to 3, excluding interruptions.

The duration (week) of study drug exposure will be converted from the duration (day) of study drug exposure using a factor of 7 day/week, and will be summarized by treatment, overall using number of observations, mean, standard deviation, median, minimum, Q1, Q3, and maximum.

The duration (week) of study drug exposure will be categorized into the following categories.

- < 4 weeks
- 4 weeks to < 8 weeks
- 8 weeks to < 16 weeks
- 16 weeks to < 32 weeks
- 32 weeks to < 52 weeks (12 months)
- ≥ 52 weeks (12 months)

The categorized duration of study drug exposure will be summarized by treatment, using the number and percentage of patients within each category.

The SAF will be used for the above analyses.

Percentage of study drug exposure

For each patient, the percentage of study drug exposure is defined as the percentage of the duration (day) of study drug exposure out of the duration (day) of treatment.

The percentage of study drug exposure will be summarized by treatment, using number of observations, mean, standard deviation, median, minimum, Q1, Q3, and maximum.

The SAF will be used for the above analyses.

Study treatment permanent discontinuation at each visit

For a given visit, a patient is considerred as permanently discontinued from the study treatment at this visit, if the patient permanently discontinued from the study treatment prior to or on the date of this visit.

For overall, the number and percentage of patients who permanently discontinued from the study treatment will be provided for each scheduled visit in the treatment period.

Mean daily dose and mean dose level

Mean daily dose and mean daily dose level for each patient will be computed as follows.

$$\text{Mean daily dose (mg)} = \frac{\sum_{i=0}^{3}(number\ of\ days\ on\ dose\ level\ i)\times(dose\ level\ i\ )}{number\ of\ days\ upto\ end\ of\ treatment}$$

$$\text{Mean daily dose level} = \frac{\sum_{i=0}^{3}(number\ of\ days\ on\ dose\ level\ i)\times i}{number\ of\ days\ upto\ end\ of\ treatment}$$

Frequency and percentage of patients at each dose level will be summarized by visit.

The SAF will be used for the above analyses.

Duration of study exposure

The duration (day) of study exposure is defined as the date of last visit minus the date of randomization plus one day.

The duration (week) of study exposure will be derived from the duration (day) of study exposure using a factor of 7 day/week, and will be summarized by treatment, using number of observations, mean, standard deviation, median, minimum, Q1, Q3, and maximum.

The duration (week) of study exposure will be categorized into the following categories.

- < 4 weeks
- 4 weeks to < 8 weeks
- 8 weeks to < 16 weeks
- 16 weeks to < 32 weeks
- 32 weeks to < 52 weeks (12 months)
- ≥ 52 weeks (12 months)

The categorized duration of study exposure will be summarized by treatment, using the number and percentage of patients within each category.

The SAF will be used for the above analyses.

Last recorded dose level

The last recorded dose level is defined as the dose level for the last dosing interval.

The last recorded dose level will be summarized by treatment, using the number and percentage of patients on each dose level.

The SAF will be used for the above analyses.

Dose down-titration

A down-titration dosing interval is defined as a dosing interval whose dose level is changed to a lower dose level from its previous dosing interval.

The dose down-titration will be summarized by treatment, using the number and percentage of patients with at least one down-titration dosing interval.

The SAF will be used for the above analyses.

Dose interruption

A dose-interruption dosing interval is defined as a dosing interval whose dose level is 0.

The number and percentage of patients with at least one dose-interruption dosing interval will be provided by treatment.

The duration of dose interruption is defined as the sum of (the end date minus the start date plus one day) among all dose-interruption dosing intervals.

The number and percent of patients will be summarize by treatment interruption episodes such as none, at least once interruption.

The SAF will be used for the above analyses.

2.4.2 Prior and concomitant therapies

Prior and concomitant medications will be recorded on the CRF page: “Prior and Concomitant Medications”. Procedures and significant non-drug therapies (prior and concomitant) will be recorded on the CRF page “Surgical and Medical Procedures”.

The missing or partially missing start/end date for prior/concomitant therapies will be imputed based on the Novartis ADaM Governance Board (AGB) global standards.

Prior and concomitant medications/non-drug therapies will be identified based on recorded or imputed start dates and end dates.

Prior medications are defined as any recorded medication with its start date (recorded or imputed) prior to the date of the first dose of the study drug.

Concomitant medications are defined as any recorded medication with its end date (recorded or imputed) later than or equal to the date of the first dose of the study drug AND its start date (recorded or imputed) prior to or equal to the end date of the study.

Prior non-drug therapies are defined as any procedure/significant non-drug therapy with its start date (recorded or imputed) prior to the date of the first dose of the study drug.

Concomitant non-drug therapies are defined as any recorded procedure/significant non-drug therapy with its end date (recorded or imputed) later than or equal to the date of the first dose of the study drug AND its start date (recorded or imputed) prior to or equal to the end date of the study.

For overall, prior and concomitant medications will be summarized separately by treatment, anatomical therapeutic classification (ATC) and PT; prior and concomitant non-drug therapies will be summarized separately for overall, SOC, PT.

The SAF will be used for the above analyses.

2.5 Analysis of the primary objective

2.5.1 Primary endpoints

The primary endpoints for this study includes all safety data (adverse events and vital signs).

No statistical analyses for primary endpoints will be done and summaries for adverse events and serious adverse events will be provided 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.

Additional details regarding safety analysis are included in Section 2.7.

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

SAF will be used for analysis of primary endpoints.

2.5.2 Statistical hypothesis, model, and method of analysis

There will be no formal statistical inferential analysis.

2.5.3 Handling of missing values/censoring/discontinuations

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

2.5.4 Supportive and sensitivity analyses

No additional sensitivity/supportive analysis will be performed for this study.

2.6 Analysis of secondary efficacy objective(s)

Not applicable.

2.7 Safety analyses

The SAF will be used for all safety analyses.

2.7.1 Adverse events (AEs)

All AEs will be recorded on the CRF page “Adverse Events” and be identified using Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA version used for reporting the study will be described in a footnote.

An AE with its severity increased should be considered and recorded as a new AE.

The missing or partially missing start/end date for AEs will be imputed based on the Novartis AGB global standards.

Treatment emergent adverse events (TEAEs) are defined as any recorded AE with its start date (recorded or imputed) later than or equal to the date of the first dose of the study drug.

Study drug related AEs are defined as any recorded AE with "Relationship to study treatment" answered as "RELATED".

AEs leading to permanent discontinuation of study treatment are defined as any recorded AE with "Action taken with study treatment" answered as "DRUG WITHDRAWN".

AEs leading to dose adjustment or temporarily interruption of study treatment are defined as any recorded AE with "Action taken with study treatment" answered as "DOSE REDUCED", "DOSE INCREASED" or "DRUG INTERRUPTED".

Most common TEAEs are defined as any recorded TEAE corresponding to a PT.

SAEs are defined as any recorded AE with "Was the adverse event serious" answered as "Yes".

The following rules are applicable to the summaries.

- If a patient reported more than one AE with the same PT, the patient will be counted only once with the greatest severity at the PT level
- If a patient reported more than one AE within the same SOC, the patient will be counted only once with the greatest severity at the SOC level, where applicable.

The following summaries will be performed.

- TEAEs will be summariesed for overall by primary SOC and PT. Additional summaries along with maximum severity will be produced.
- Study drug related TEAEs will be summariesed for overall by primary SOC and PT.
- TEAEs leading to treatment discontinuation will be summariesed for overall by primary SOC and PT.
- TEAEs leading to dose adjustment or temporarily interruption of study treatment will be summariesed for overall by primary SOC and PT.
- Most common TEAEs will be summariesed for overall by primary SOC and PT.
- Treatment emergent SAEs (TESAEs) will be summariesed for overall by primary SOC and PT.
- Most common TESAEs will be summariesed for overall by primary SOC and PT.
- Study drug related TESAEs will be summariesed for overall by primary SOC and PT.

The SAF will be used for the above analyses.

The search paths for the related preferred terms (PTs), high level group term (HLGT), high level term (HLT), in Standard Medical Queries (SMQs), or NMQ in MedDRA for the are store in the LCZ696 Case Retrieval Strategy.

The following standard analyses will be applied to all risks.

- Numbers and percentages of patients with any TEAE within the risk name (or SOC/PT within risk name) will be provided for dose level and overall by risk name, SOC, PT and maximum severity.
- Exposure adjusted incidence rates per 100 patient-years for TEAEs within the risk name will be provided for dose level and overall by risk name.
- Listing of patients numbers per risk.

2.7.1.1 Adverse events of special interest / grouping of AEs

AEs of special interest will also be summarized. AEs of special interest and their further specified events include the followings.

Hypotension

- SBP <90 mmHg
- SBP decline by ≥30 mmHg
- Simultaneous SBP <90 mmHg and SBP decline by ≥30 mmHg

Angioedema (adjudicated)

- No treatment or antihistamines only
- Treated with catecholamines or steroids
- Hospitalized but no mechanical airway protection, without airway compromise
- Hospitalized but no mechanical airway protection, with airway compromise
- Mechanical airway protection or death from airway compromise

Drug-related hepatic disorders

- all preferred terms listed in the Standardized Med-DRA Query(SMQ) module "drugrelated hepatic disorders – comprehensive search SMQ code 20000006 - broad search"

Cough

Summary tables that summarize the numbers and percentages of subjects experienced the above events at least once during study will be presented by event or SMQ (when drug-related hepatic disorders).

Summary tables that summarize the numbers and percentages of subjects experienced the above events at least once throughout the study will be presented by event or SMQ (when drug-related hepatic disorders).

The search paths for the related preferred terms (PTs), high level group term (HLGT), high level term (HLT), in Standard Medical Queries (SMQs), or NMQ in MedDRA for hypotension, hyperkalaemia, renal impairment and cough are stored in the latest LCZ696 Case Retrieval Strategy (CREDI directory: /CREDI Projects/L/LCZ696A/Integrated Medical Safety)).

Numbers and percentages of subjects with adjudicated angioedema events with the adjudicated maximum severity and angioedema-like (i.e. investigator-reported) events will be presented.

2.7.2 Death

Death and primary cause of death (reported as SAE) will be reported by the investigator.

The investigator reported death and primary cause of death will be recorded on the CRF page: "SAE_Death Information".

Any finding determined by AUTOPSY will also be reported and recorded in description of the event CRF page.

The investigator reported death and primary cause of death will be summarized for overall, using the number and percentage of patients who died, as well as the numbers and percentages of patients whose primary cause of death is in each category.

The SAF will be used for the above analyses.

2.7.3 Laboratory data

2.7.3.1 General laboratory data

Laboratory evaluations serum potassium and creatinine will be performed locally every visit. Additional laboratory evaluation should be performed by Investigator's judgement. 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. The laboratory results are not collected in this study. If abnormal laboratory values fulfill the AE criteria (protocol section 10.1.1), the investigator should report the labolatory values as AE.

2.7.3.2 Vital signs

Vital signs (BP [systolic blood pressure (SBP) and diastolic blood pressure (DBP)] and pulse will be summarized by parameter, for overall , using number of observations, mean, standard deviation, median, minimum, Q1, Q3, and maximum, including changes from baseline. By-visit summary will only include scheduled assessments.

Change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as:

- change from baseline = post-baseline value – baseline value

The SAF will be used for the above analyses.

2.8 Pharmacokinetic endpoints

Not applicable.

2.9 PD and PK/PD analyses

Not applicable.

2.10 Patient-reported outcomes

Not applicable

2.11 Biomarkers

Not applicable

2.12 Other Exploratory analyses

Not applicable.

2.13 Interim analysis

No formal interim efficacy analysis is planned.

3 Sample size calculation

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.

4 Change to protocol specified analyses

No change from protocol.

5 Appendix

5.1 Imputation rules

The missing or partially missing start/end date for AEs and prior/concomitant therapies will be imputed based on the Novartis AGB global standards. Details will be provided in the study PDS.

6 Reference