# Non-Interventional Study Protocol

# A6141122

# Drug Use Investigation of Selara® Tablets
# (An investigation for chronic heart failure)

# STATISTICAL ANALYSIS PLAN

**Version**: 7.0

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**TABLE OF CONTENTS**

1. REVISION HISTORY ..... 4
2. INTRODUCTION ..... 8
2.1. Study Design ..... 8
2.2. Objective ..... 8
3. INTERIM AND FINAL ANALYSES ..... 8
4. HYPOTHESES AND DECISION RULES ..... 8
4.1. Statistical Hypotheses ..... 8
4.2. Statistical Decision Rules ..... 8
5. ANALYSIS POPULATIONS ..... 8
5.1. Safety Analysis Set ..... 8
5.2. Effectiveness Analysis Set ..... 9
5.3. Other Analysis Sets ..... 9
5.4. Subgroup Analyses ..... 9
6. ENDPOINTS AND COVARIATES ..... 10
6.1. Safety Endpoints ..... 10
6.2. Effectiveness Endpoints ..... 11
6.3. Other Endpoints ..... 11
6.4. Covariates ..... 11
7. HANDLING OF MISSING DATA ..... 11
8. STATISTICAL METHODS AND ANALYSES ..... 12
8.1. Statistical Methods ..... 12
8.1.1. Continuous Variables ..... 12
8.1.2. Categorical Variables ..... 12
8.1.3. Binary Variables ..... 12
8.1.4. Time-to-event Data ..... 12
8.2. Statistical Analyses ..... 13
8.2.1. Patient Description ..... 13
8.2.2. Patient Characteristics and Medical History ..... 13
8.2.3. Safety Analysis ..... 16
8.2.3.1. Adverse Reactions ..... 16
8.2.3.2. Adverse Events ..... 17

8.2.3.3. Other Endpoints ..... 18
8.2.3.4. Subgroup Analyses ..... 18
8.2.3.5. Exploratory Analyses ..... 18
8.2.4. Effectiveness Analyses ..... 18
8.2.4.1. Death ..... 18
8.2.4.2. NYHA Class ..... 19
8.2.4.3. Clinical Effectiveness (as assessed by the physician) ..... 19
8.2.4.4. Subgroup Analyses ..... 19
8.2.4.5. Exploratory Analyses ..... 19
9. LISTINGS ..... 20
10. REFERENCES ..... 21
11. APPENDICES ..... 22
11.1. Appendix 1: Details of Data Extraction ..... 22
A1.1 Definition of Visits for the Assessment of Dosing Status and Safety Endpoints ..... 22
A1.2 Definition of Visits for Cardiac Function Classification ..... 23
A1.3 Definition of Visits for the Assessment of Plasma BNP and Serum NT-proBNP ..... 23
11.2. Appendix 2: An Example of Table Showing Risk Ratios Regarding the Incidence of Adverse Reaction ..... 24

## 1. REVISION HISTORY

| Version/ Date/ Author(s) | Summary of Changes/Comments |
|---|---|
| 7.0<br>19-Nov-2020<br>PPD | **Status of Observation: Completed**<br><br>5.4. Subgroup Analyses<br><br>Use of diuretics (excluding potassium-sparing diuretics) in a relevant treatment for CHF/hypertension (present, absent) was added for subgroup analyses of patient characteristics.<br><br>8.2.2. Patient Characteristics<br><br>Subgroup Analyses of patient characteristics were added.<br><br>Other editorial revisions. |
| 6.0<br>28-Sep-2020<br>PPD | **Status of Observation: Completed**<br><br>5.4. Subgroup Analyses<br><br>For effectiveness analyses, additional subgroups were defined with respect to presence or absence of hepatic impairment, presence or absence of renal impairment, and estimated creatinine clearance (eCLCr).<br><br>8.2.4.5.5. Plasma BNP and Serum NT-proBNP<br><br>Serum NT-proBNP was added.<br><br>A1.3 Definition of Visits for the Assessment of Plasma BNP and Serum NT-proBNP<br><br>Serum NT-proBNP was added.<br><br>Other editorial revisions. |
| 5.0<br>03-Jul-2020<br>PPD | **Status of Observation: Completed**<br><br>5.4. Subgroup Analyses<br><br>Changes were made for the category “unknown” in some categorizations.<br><br>8.2.2. Patient Characteristics<br><br>Handling of concomitant drugs was specified. |

| Version/ Date/ Author(s) | Summary of Changes/Comments |
|---|---|
| | In "Dosing Status of Selara Tablets", handling of treatment-discontinued patients with unknown date of last observed administration was specified.<br><br>Other editorial revisions. |
| 4.0<br>30-Mar-2020<br>PPD | **Status of Observation: Ongoing**<br><br>5.4. Subgroup Analyses<br><br>Age categorization was revised.<br><br>6.1. Safety Endpoints<br><br>• Other Investigation Items<br><br>Definition of renal impairment-related events was revised.<br><br>8.2.1. Patient Description<br><br>Summarization of participating sites and patients by type of site was deleted.<br><br>8.2.2. Patient Characteristics and Medical History<br><br>The part "Patient Characteristics" was updated to include estimated glomerular filtration rate (eGFR).<br>Description was updated to include handling of concomitant drugs.<br>Scatter plotting of estimated creatinine clearance (eCLCr) vs. eGFR was added.<br><br>8.2.3.1. Adverse Reactions<br><br>• Details of Adverse Reactions<br>• Major Investigation Items<br>• Other Investigation Items<br><br>Summarization by SOC was removed from the summarizations with respect to seriousness, known/unknown, action taken, and outcome.<br>Categorization of action taken was updated to include "others (none, dose increase)".<br><br>• Onset Time of Adverse Reaction<br><br>Summarization of all adverse reactions was added.<br><br>11.1. Appendix 1: Details of Data Extraction |

| Version/ Date/ Author(s) | Summary of Changes/Comments |
|---|---|
| | A1.1 Definition of Visits for the Assessment of Dosing Status and Safety Endpoints<br>A1.2 Definition of Visits for Cardiac Function Classification<br>A1.3 Definition of Visits for the Assessment of Plasma BNP<br><br>Description was updated to include handling of cases in which multiple values are reported on the same day.<br><br>Other editorial revisions. |
| 3.0<br>01-Feb-2019<br>PPD | **Status of Observation: Ongoing**<br><br>9. LISTINGS<br>Listing of contraindication violators was added.<br><br>Other editorial revisions. |
| 2.0<br>17-Oct-2018<br>PPD | **Status of Observation: Ongoing**<br><br>5.4. Subgroup Analyses<br><br>Reference subgroups for the calculation of risk ratios were specified.<br><br>6.1. Safety Endpoints<br><br>Definition of an adverse reaction was revised so that no company judgement is used. Definitions of a serious adverse reaction and a serious adverse event (SAE) were added.<br><br>8. STATISTICAL METHODS AND ANALYSES<br><br>The data to be included in analyses were revised with respect to their time.<br><br>8.1.4. Time-to-event Data<br><br>Description of the determination of the observation time was revised to refer to another part.<br><br>8.2.2. Patient Characteristics and Medical History<br><br>In “Patient Characteristics”, categories for NYHA class were specified.<br><br>In “Dosing Status of Selara Tablets”, the summarization item “Daily dose [25 mg, 50 mg, 25 mg every 2 days, others]” was deleted because the dosage of the drug is adjusted as appropriate. |

| Version/ Date/ Author(s) | Summary of Changes/Comments |
|---|---|
| | In "Follow-up Status", determination of the duration of follow-up for a patient was described for each of possible cases.<br><br>8.2.3.4. Subgroup Analyses<br><br>Regarding the calculation of a risk ratio for the incidence of adverse reactions, the action taken when the number of patients in one subgroup is small was described.<br><br>8.2.4.1. Death<br><br>Regarding the analysis of time-to-event data, handling of deaths with unknown date was described for each of possible cases.<br><br>11.1. Appendix 1: Details of Data Extraction<br><br>A1.1 Definition of Visits for the Assessment of Dosing Status and Safety Endpoints<br>A1.2 Definition of Visits for Cardiac Function Classification<br>A1.3 Definition of Visits for the Assessment of Plasma BNP<br><br>The representative date for baseline was revised from Day 0 to Day 1.<br><br>The start date of the time window for Week 1 was revised from one day after treatment start to the date of treatment start (after dosing).<br><br>11.2 Appendix 2: An Example of Table Showing Risk Ratios Regarding the Incidence of Adverse Reaction<br><br>An example of table was added.<br><br>Other editorial revisions. |
| 1.0<br>29-Jun-2017<br>PPD | Original version |

## 2. INTRODUCTION

This document describes the statistical analysis plan (SAP) of the drug use investigation of Selara® Tablets. In this SAP, citations from the corresponding study protocol are indicated in *italics*.

### 2.1. Study Design

*This study is a multi-center cohort study of patients with chronic heart failure (CHF) receiving this drug. The investigators complete the case report form (CRF) based on source documents such as medical records that include data obtained in daily medical practice.*

### 2.2. Objective

*To confirm the safety of this drug when used in CHF patients with moderate renal impairment under actual medical practice.*

## 3. INTERIM AND FINAL ANALYSES

In this study, interim analysis will be performed on a regular basis for the purpose of periodic safety reporting. At the time of an interim analysis, among the analyses described in this SAP only those that are required for the periodic safety reporting will be performed. At the time of the final analysis, which is performed for the purpose of re-examination application, all analyses described in this SAP will be performed.

## 4. HYPOTHESES AND DECISION RULES

### 4.1. Statistical Hypotheses

Because of the non-confirmatory nature of this study, all statistical tests in this study are considered exploratory. Unless otherwise stated, any statistical test in this study will be performed at a two-sided significance level of 5%.

### 4.2. Statistical Decision Rules

Not applicable.

## 5. ANALYSIS POPULATIONS

### 5.1. Safety Analysis Set

The Safety Analysis Set is the Full Analysis Set that is as close to all patients treated with Selara tablets as possible. Specifically, the Safety Analysis Set consists of all registered or reported patients except those who meet at least one of the following conditions:

a. No CRF was collected. (Indicated as “CRF not collected” in the study report.)

b. Any violation or deficiency was found concerning the study contract. (Indicated as "Contract violation/deficiency" in the study report.)

c. The registration failed to meet all the requirements. (Indicated as "Invalid registration" in the study report.)

d. No dosing information is reported for the study drug. (Indicated as "No dosing information" in the study report.)

e. No information is reported for adverse events (AEs). (Indicated as "No AE information" in the study report.)

Details of each condition follow the Guidance for the Adoption/Rejection Criteria for Analysis Populations and Handling of Data in Drug Use Investigations.

**5.2. Effectiveness Analysis Set**

The Effectiveness Analysis Set is composed of the patients in the Safety Analysis Set excluding those who meet the following condition:

f. No effectiveness assessments are reported. (Indicated as "No effectiveness information" in the study report.)

**5.3. Other Analysis Sets**

Not applicable.

**5.4. Subgroup Analyses**

The safety of study drug will be analyzed for each of the subgroups defined according to the following patient characteristics. The underlined one in each categorization will be used as the reference when a risk ratio is calculated:

- Hepatic impairment (as assessed by the physician) (present, absent, unknown)
- Renal impairment (as assessed by the physician) (present, absent, unknown)
- Estimated creatinine clearance (eCLCr)
  (<30 mL/min, 30 mL/min - <50 mL/min, ≥50 mL/min, unknown)
- Not aged (<65 years old), Aged (≥65 years old)
- Children (<15 years old), Not children (≥15 years old)
- Young-old (≥65, <75 years old), Old-old + oldest-old (≥75 years old)
- Diabetes mellitus with microalbuminuria or proteinuria (present, absent, unknown)

Safety will also be analyzed for each of the subgroups defined according to the following factors:

- Use of a relevant treatment for CHF/hypertension (present, absent) (any of the 1st to 17th drug groups, except the 2nd and 15th which are contraindicated for coadministration, listed)
- Previous treatment with device therapy (present, absent, unknown)

- NYHA class (I, II, III, IV, not assessed/unknown)

As a subgroup analysis, patients who may have violated any of the contraindications indicated in the package insert of Selara Tablets ("contraindication violators", hereinafter) will be extracted according to the criteria defined separately and the safety will be assessed for this subgroup.

The effectiveness of study drug will be analyzed for each of the subgroups defined according to the following patient characteristics:

- Hepatic impairment (as assessed by the physician) (present, absent, unknown)
- Renal impairment (as assessed by the physician) (present, absent, unknown)
- Estimated creatinine clearance (eCLCr)
  (<30 mL/min, 30 mL/min - <50 mL/min, ≥50 mL/min, unknown)
- Not aged (<65 years old), Aged (≥65 years old)
- Children (<15 years old), Not children (≥15 years old)
- Young-old (≥65, <75 years old), Old-old + oldest-old (≥75 years old)
- Use of a relevant treatment for CHF/hypertension (present, absent)
- NYHA class (I, II, III, IV, not assessed/unknown)
- Treatment status (completed, discontinued)

If patients included in a subgroup for safety or effectiveness analysis are limited, reviewing individual patients will be considered instead of presenting a statistical summarization.

The patient characteristics will be analyzed for each of the subgroups defined according to the following patient characteristic:

- Use of diuretics (excluding potassium-sparing diuretics) in a relevant treatment for CHF/hypertension (present, absent)

## 6. ENDPOINTS AND COVARIATES

### 6.1. Safety Endpoints

- Adverse reactions: An adverse reaction is an AE related to study drug as judged by the physician.
- Serious adverse reactions: A serious adverse reaction is an adverse reaction that is serious as judged by the physician.
- AEs
- Serious adverse events (SAEs): A SAE is an AE that is serious as judged by the physician.
- Major investigation items: Events included in each major investigation item are defined as follows:
  - Hyperkalaemia: This includes all AEs indicated as "Hyperkalaemia-related event" or "Combination of the above two events ("Hypotension-related event" and "Hyperkalaemia-related event")" in the CRF.

  - Hypotension-related events: These include all AEs indicated as “Hypotension-related event” or “Combination of the above two events (“Hypotension-related event” and “Hyperkalaemia-related event”)” in the CRF.

- Other investigation items
  - Renal impairment-related events

  Renal impairment-related events are events coded as one of the following preferred terms (PTs):

  Acute kidney injury, Chronic kidney disease, Renal failure, or Renal impairment.

- Blood pressure (systolic, diastolic)
- Body weight
- Laboratory tests (serum creatinine, serum potassium, BUN)

**6.2. Effectiveness Endpoints**

- Death (all-cause death, cardiovascular death)
- Cardiac function tests
- NYHA class
- Clinical effectiveness (as assessed by the physician)
- Laboratory tests (plasma brain natriuretic peptide [BNP], serum N-terminal pro-BNP [NT-proBNP])

**6.3. Other Endpoints**

Not applicable.

**6.4. Covariates**

Not applicable.

**7. HANDLING OF MISSING DATA**

If the severity, treatment, or outcome of an AE is missing, it will be regarded as having a value of “unknown” at the time of a statistical summarization.

If an observation for the dosing status, a safety endpoint, an effectiveness endpoint, or a laboratory test was done outside its time window (Appendices A1.1, A1.2, and A1.3), the obtained data will be regarded as missing data and will not be imputed.

Cleaning-uncompleted data will be basically handled as follows. Detailed handling of individual items will be explained in separate lists.

- Items for which data are missing: For both summarization and listing, their values will be handled as missing data (or "unknown" in the case of a categorical variable).
- Items for which data are inconsistent: For both summarization and listing, their values will be handled as missing data.
- Items for which signature is missing: For both summarization and listing, any data in a CRF with no signature of the contract physician (including when the CRF is signed only by individuals other than the contract physician) will be handled as missing data.

## 8. STATISTICAL METHODS AND ANALYSES

Unless otherwise stated, for patients who completed treatment, data within the first 52 weeks (364 days) + 30 days (= 394 days) will be included in each statistical analysis. For patients who discontinued treatment, data until the first visit after discontinuation of treatment with Selara tablets, or the date 30 days after the last treatment, whichever comes first, will be included. For patients who died, all data will be included.

### 8.1. Statistical Methods

#### 8.1.1. Continuous Variables

For a continuous variable, its summary statistics (n, mean, standard deviation [SD], median, maximum, minimum) will be presented.

#### 8.1.2. Categorical Variables

For a categorical variable, patients included in each category will be summarized in terms of n and proportion (%).

#### 8.1.3. Binary Variables

For a binary variable, patients included in each binary category will be summarized in terms of n and proportion (%). When a confidence interval (CI) of the proportion is presented, the two-sided 95% CI (exact method) will be presented.

When subgroups are compared with respect to proportion, the risk ratio (RR) and its 95% CI will be presented (See Appendix 2).

#### 8.1.4. Time-to-event Data

Mortality at one year from the start of treatment will be estimated using the Kaplan-Meier method. Kaplan-Meier plots (displaying the number of at-risk patients every one month) will also be presented.

Analyses Based on the Person-Year Method

The incidence of an event per observation time will, if it is presented, be calculated using the formula:

Incidence (events/100 person-year) = 100 × $y/PT$
$y$: Number of events
$PT$: Total observation time (years),

where the observation time is determined in conformity with the part "Follow-up Status" in "8.2.2. Patient Characteristics and Medical History". In addition, its 95% CI will be presented according to the formula [1]:

$$\left[\frac{100}{PT}\times\frac{1}{2}\chi^2_{2y}(\alpha/2),\ \frac{100}{PT}\times\frac{1}{2}\chi^2_{2(y+1)}(1-\alpha/2)\right]$$

$y$: Number of events

$\chi^2_{2y}(\alpha/2)$: The $\alpha/2$ percentage point of the chi-square distribution of $2y$ degrees of freedom

## 8.2. Statistical Analyses

### 8.2.1. Patient Description

- **Constitution**

Among the registered patients, the registered patients themselves, patients with their CRF locked/collected, patients included in the Safety Analysis Set, and patients included in the Effectiveness Analysis Set will be summarized in terms of number of patients. In addition, patients with their CRF uncollected, patients excluded from the Safety Analysis Set, and patients excluded from the Effectiveness Analysis Set will be summarized in terms of total number of patients and number of patients by reason of exclusion.

- **Treatment Discontinuations and Dropouts**

The number and proportion of patients who discontinued treatment will be presented by Visit (See Appendix A1.1) in the Safety Analysis Set and the Effectiveness Analysis Set. The number and proportion of patients who discontinued treatment will also be presented by reason of discontinuation.

- **Patients Excluded from Analyses**

Patients excluded from the Safety Analysis Set and those excluded from the Effectiveness Analysis Set will be presented in a tabular form with their reason for exclusion.

### 8.2.2. Patient Characteristics and Medical History

- **Patient Characteristics**

For both Safety Analysis Set and Effectiveness Analysis Set, statistics will be presented according to Section 8.1 with respect to the following patient characteristics:

- Sex [male, female]
- Age (continuous)
- Age [<15 years, 15 - <65 years, ≥65 years, 65 - <75 years, ≥75 years]
- Patient status at the first prescription [hospitalized, outpatient]

- Past hospitalization due to cardiovascular events (before receiving Selara tablets) [present, absent, unknown]
- Past hospitalization due to cardiovascular events (before receiving Selara tablets) [if present, predefined categories]
- Body height (continuous)
- Body weight (continuous)
- Body mass index (BMI) (continuous)
- Underlying cardiovascular disease [predefined categories]
- Duration of disease (continuous)
- Duration of disease [<5 years, 5 - <10 years, ≥10 years, unknown]
- NYHA class [I, II, III, IV, not assessed/unknown]
- Reason of the administration of Selara tablets [predefined categories]
- Past history of device therapy [present, absent, unknown]
- Past history of device therapy [if present, predefined categories]
- Hepatic impairment (as assessed by the physician) [predefined categories]
- Renal impairment (as assessed by the physician) [predefined categories]
- Pregnancy [present, absent]
- Past history [predefined categories]
- Coexisting conditions [predefined categories]
- Pretreatments [predefined categories]
- Medications for CHF/hypertension [predefined categories]
- Estimated creatinine clearance (eCLCr) (continuous)
- eCLCr [<30 mL/min, 30 - <50 mL/min, ≥50 mL/min, unknown]
- Estimated glomerular filtration rate (eGFR) (continuous)
- eGFR [<30 mL/min/1.73m$^2$, 30 - <50 mL/min/1.73m$^2$, ≥50 mL/min/1.73m$^2$, unknown]

A concomitant drug is considered as a pretreatment if the end date of its use coincides with the start date of administration of Selara tablets. A drug is not considered as a concomitant drug if the start date of its use coincides with the end date of administration of Selara tablets.

The Cockcroft & Gault formula will be used to estimate CLCr. The Japanese Society of Nephrology's formula will be used to estimate GFR.

- **Dosing Status of Selara Tablets**

For both Safety Analysis Set and Effectiveness Analysis Set, the following dosing data of Selara tablets will be summarized for the overall population and by eCLCr (<30 mL/min, 30 - <50 mL/min, ≥50 mL/min, unknown):

- Duration of treatment (continuous)
- Duration of treatment [for each of the periods defined in Appendix A1.1 (excluding the Final Visit)]
- Mean daily dose (continuous)
- Mean daily dose [for each of the periods defined in Appendix A1.1 (excluding the Final Visit)]

– Reason for discontinuation [within 26 weeks: inadequate clinical response, AEs, others; after 26 weeks: inadequate clinical response, AEs, no revisit, others]

The duration of treatment is defined as the period from the first administration to the last administration in this study, including non-dosing periods. If the date of the last administration is unknown for a patient who discontinued treatment, the date on which the patient was first seen by the physician after the discontinuation will be considered as the date of the last administration.

- **Follow-up Status**

For the Effectiveness Analysis Set, the duration of follow-up (continuous) will be summarized. The duration of follow-up for a patient will be calculated as follows.

When the patient survived at Week 52,

Duration of follow-up = 52 weeks (364 days).

When the survival status of the patient is “unknown” at Week 52,

Duration of follow-up = date of final confirmation of survival − date of first administration in this study + 1 (days).

When the patient died by Week 52,

if the date of death is known,

Duration of follow-up = date of death − date of first administration in this study + 1 (days),

if the date of death is unknown,

Duration of follow-up = date of final confirmation of survival − date of first administration in this study + 1 (days).

- **Estimated Creatinine Clearance (eCLCr) and Estimated Glomerular Filtration Rate (eGFR)**

Scatter plots (x-axis: baseline eCLCr, y-axis: baseline eGFR) will be presented. The number of data and the Pearson product-moment correlation coefficient will be presented.

- **Subgroup Analyses**

For both Safety Analysis Set and Effectiveness Analysis Set, statistics will be presented according to Section 8.1 with respect to the following patient characteristics:

– Sex [male, female]
– Age [<15 years, 15 - <65 years, 65 - <75 years, ≥75 years]
– NYHA class [I, II, III, IV, not assessed/unknown]
– Diabetes mellitus with microalbuminuria or proteinuria [present, absent, unknown]

- Estimated creatinine clearance (eCLCr)
  [<30 mL/min, 30 mL/min - <50 mL/min, ≥50 mL/min, unknown]

### 8.2.3. Safety Analysis

#### 8.2.3.1. Adverse Reactions

- **All Adverse Reactions**

Adverse reactions will be summarized by system organ class (SOC) and preferred term (PT) in terms of number and proportion of patients.

- **Serious Adverse Reactions**

Serious adverse reactions will be summarized by SOC and PT in terms of number and proportion of patients.

- **Details of Adverse Reactions**

Adverse reactions will be summarized by each of the categorizations below for each PT in terms of number and proportion of patients:

- Seriousness [serious, non-serious]
- Known/unknown [known, unknown]
- Action taken [permanent discontinuation, temporary discontinuation or dose reduction, others (none, dose increase)]
- Outcome [not recovered, recovered with sequelae, improved, resolved/recovered, unknown, death]

If the same patient experienced the same adverse reaction (of the same PT) more than once, the patient will be counted as follows:

- Seriousness: If the events include both serious and non-serious ones, the patient is counted as a patient experiencing a serious reaction.
- Known/unknown: If the events include both known and unknown ones, the patient is counted as a patient experiencing an unknown reaction.
- Time to onset (days): The first onset will be counted.
- Action taken: If multiple actions were taken, a single action will be chosen according to the order of priority of (1) permanent discontinuation, (2) temporary discontinuation/dose reduction, and (3) others (none, dose increase).
- Outcome: The outcome of the last event will be used.

- **Major Investigation Items**

The major investigation items listed below will be summarized in terms of number and proportion of patients:

- Hyperkalaemia
- Hypotension-related events

In addition, each major investigation item will be summarized by action taken and by outcome for each PT in terms of number and proportion of patients.

- **Other Investigation Items**

Renal impairment-related events will be summarized in terms of number and proportion of patients. In addition, the events will be summarized by action taken and by outcome for each PT in terms of number and proportion of patients.

- **Onset Time of Adverse Reaction**

All adverse reactions, hyperkalaemia, hypotension-related events, and renal impairment-related events will be summarized by time of first onset [Appendix A1.1] for each SOC and PT in terms of number of patients.

- **Relationship Between Concomitant Drugs and Adverse Reactions**

To investigate the relationship between treatments for CHF/hypertension, or CYP3A4 inhibitors/other concomitant drugs requiring caution (any drug in the 3rd, 4th, 13th, 14th, 16th, or 17th drug groups, or a liskiren included in the 7th, listed) and adverse reactions of hyperkalaemia, hypotension-related events, or renal impairment-related events, patients experiencing hyperkalaemia, hypotension-related events, and renal impairment-related events will be summarized by PT in terms of number of patients, depending on whether they used CHF/hypertension treatments or whether they used CYP3A4 inhibitors/other concomitant drugs requiring caution (any drug in the 3rd, 4th, 13th, 14th, 16th, or 17th drug groups, or aliskiren included in the 7th, listed). Concomitant drugs used after the first onset of the relevant event will be excluded from the summarization.

- **Adverse Reactions in Patients Excluded from the Safety Analysis Set**

Adverse reactions occurring in CRF-collected patients who are excluded from the Safety Analysis Set will be presented in a tabular form. In addition, they will be summarized by SOC and PT in terms of number of patients.

**8.2.3.2. Adverse Events**

- **All Adverse Events**

AEs will be summarized by SOC and PT in terms of number and proportion of patients.

- **Serious/Non-Serious Adverse Events**

SAEs will be summarized by SOC and PT in terms of number and proportion of patients. Non-SAEs will also be summarized in the same manner.

#### 8.2.3.3. Other Endpoints

Observed values and changes from baseline at each Visit specified in Appendix A1.1 will be analyzed according to "8.1.1 Continuous Variables" for the following variables:

- Blood pressure (systolic, diastolic).

#### 8.2.3.4. Subgroup Analyses

For each of the categories defined in Section 5.4, the number and proportion of patients experiencing at least one adverse reaction will be presented. For each patient category, adverse reactions will also be summarized by SOC and PT in terms of number and proportion of patients.

According to Section 8.1.3, the risk ratio of one subgroup to the other will be presented for the incidence of adverse reactions (the proportion of patients experiencing adverse reactions) for each of the binary categorizations. The risk ratio will not be presented for a categorization if <10 patients are included in one category in the categorization and the analysis of risk ratio is determined to be difficult after the categorization is reviewed.

Similar subgroup analyses will be performed also for serious adverse reactions and SAEs.

Adverse reactions occurring in contraindication violators will be tabulated and, as necessary, will be summarized by SOC and PT in terms of number and proportion of patients.

#### 8.2.3.5. Exploratory Analyses

Not applicable.

### 8.2.4. Effectiveness Analyses

#### 8.2.4.1. Death

Deaths will be summarized in terms of number and proportion of patients by cause of death (cardiovascular, non-cardiovascular, unknown) and detailed cause of death (cardiovascular: cardiac failure, myocardial infarction, arrhythmia, stroke or cerebrovascular accident, others; non-cardiovascular: neoplasm malignant, infection, others).

All-cause deaths and cardiovascular deaths will be analyzed in the following manner:

"8.1.3. Binary Variables" will be followed for binary variables, and

"8.1.4. Time-to-event Data" will be followed for time-to-event data.

In the Kaplan-Meier analysis, a patient whose date of death is unknown will be handled as follows:

- If the date of final confirmation of survival is on Week 52 or earlier and the information of death was obtained on Week 52 or earlier,

the patient is handled as interval censored data between the date of final confirmation of survival and the date of death information;

- If the date of final confirmation of survival is on Week 52 or earlier and the information of death was obtained after Week 52,

  the patient is handled as a patient who was alive on the date of final confirmation of survival;

- If the date of final confirmation of survival is after Week 52 and the information of death was obtained after Week 52,

  the patient is handled as a patient who was alive at Week 52 (Day 364).

#### 8.2.4.2. NYHA Class

NYHA class data at baseline and final visit will be summarized in shift tables (I, II, III, IV, not assessed/unknown).

#### 8.2.4.3. Clinical Effectiveness (as assessed by the physician)

Clinical effectiveness (as assessed by the physician) will be analyzed by presenting the number and proportion of patients falling into each category (effective, not effective, inconclusive).

#### 8.2.4.4. Subgroup Analyses

According to the categorizations defined in Section 5.4, subgroup analyses will be performed regarding deaths and clinical effectiveness (as assessed by the physician).

#### 8.2.4.5. Exploratory Analyses

##### 8.2.4.5.1. Death

When results from this study are compared with those from the Japanese phase 3 clinical study or an epidemiologic study (e.g., Study CHART-1, CHART-2, or JCARE-CARD), a subpopulation close to the population of the Japanese phase 3 clinical study or the population defined in published articles of each epidemiologic study will be defined (according to inclusion criteria such as age and left ventricular ejection fraction [LVEF]) for the purpose of comparison. If, as a result, only a limited number of patients are included in the subpopulation of this study, relevance of the comparison will be reviewed. At present, the target populations for comparison are as follows:

For the purpose of comparisons with the Japanese phase 3 study, a subpopulation consisting of patients aged ≥55 years with LVEF ≤35% in this study is planned to be defined;

For the purpose of comparisons with Study CHART-1, a subpopulation consisting of patients aged ≥18 years with LVEF <50% or left ventricle internal dimensions in diastole (LVDd) ≥55 mm in this study is planned to be defined;

For the purpose of comparisons with Study CHART-2, the target population in the study is planned to be defined with patients with symptomatic heart failure registered in Study CHART-2 who meet eligibility criteria similar to those in Study CHART-1 (either LVEF <50%, LVDd ≥55 mm, or history of congestive heart failure). The corresponding subpopulation in this study is planned to be defined with patients aged ≥18 years with LVEF <50% or LVDd ≥55 mm;

For the purpose of comparisons with Study JCARE-CARD, the target population in the study is planned to be defined with patients with heart failure with reduced ejection fraction (LVEF <40%) registered in Study JCARE-CARD, excluding those with no LVEF data. The corresponding population in this study is planned to be a subpopulation consisting of patients with LVEF <40% who were hospitalized at the start of treatment with Selara tablets.

#### 8.2.4.5.2. Left Ventricular Ejection Fraction (LVEF)

Observed values of LVEF and changes from baseline at each Visit specified in Appendix A1.2 will be analyzed according to "8.1.1 Continuous Variables" in the entire population and in each of the 5 subgroups: (1) baseline LVEF <30%, (2) 30% - <40%, (3) 40% - <50%, (4) ≥50%, or (5) unknown.

#### 8.2.4.5.3. Left Ventricle Internal Dimensions in Diastole (LVDd)

Observed values of LVDd and changes from baseline at each Visit specified in Appendix A1.2 will be analyzed according to "8.1.1 Continuous Variables" in the entire population and in each of the 5 subgroups: (1) baseline LVDd ≥60 mm, (2) 55 mm - <60 mm, (3) 50 mm - <55 mm, (4) <50 mm, or (5) unknown.

#### 8.2.4.5.4. Left Atrial Dimension (LAD)

Observed values of LAD and changes from baseline at each Visit specified in Appendix A1.2 will be analyzed according to "8.1.1 Continuous Variables" in the entire population and in each of the 5 subgroups: (1) baseline LAD ≥55 mm, (2) 50 mm - <55 mm, (3) 45 mm - <50 mm, (4) <45 mm, or (5) unknown.

#### 8.2.4.5.5. Plasma BNP and Serum NT-proBNP

For plasma BNP and serum NT-proBNP, observed values and changes from baseline at each Visit specified in Appendix A1.3 will be analyzed according to "8.1.1 Continuous Variables" in the entire population and in each of the 3 subgroups: (1) baseline plasma BNP/serum NT-proBNP being the median or higher level, (2) less than the median, or (3) unknown.

## 9. LISTINGS

Following listings will be presented:

- Listing of patients included in this study
- Listing of patients experiencing AEs
- Listing of patients who experienced AEs outside the observation period

- Listing of patients experiencing adverse reactions
- Listing of patients excluded from the Safety Analysis Set who experienced adverse reactions
- Listing of contraindication violators experiencing adverse reactions
- Listing of patients experiencing serious adverse reactions
- Listing of patients experiencing SAEs
- Listing of patients with hepatic impairment (as assessed by the physician) who experienced adverse reactions
- Listing of patients with renal impairment (as assessed by the physician) who experienced adverse reactions
- Listing of patients with eCLCr 30 mL/min - <50 mL/min who experienced adverse reactions
- Listing of aged patients (≥65 years) experiencing adverse reactions
- Listing of events of each major investigation item
- Listing of adverse reactions of each major investigation item
- Listing of events of renal impairment
- Listing of adverse reactions of renal impairment
- Listing of patients who used a CYP3A4 inhibitor as a concomitant drug and experienced adverse reactions
- Listing of dosages in patients who experienced adverse reactions of hyperkalaemia
- Listing of data for blood pressure (systolic, diastolic), body weight, and laboratory tests
- Listing of data for cardiac function tests
- Listing of AEs leading to death
- Listing of AEs leading to hospitalization
- Listing of results of survival confirmations
- Listing of contraindication violators

In addition, tables of data for Attachment Forms specified in applicable notifications from the authority will be generated.

## 10. REFERENCES

1. Fay MP, Feuer RJ. Confidence intervals for directly standardized rates: a method based on the gamma distribution. *Statistics in Medicine* 1997; 16: 791-801.

# 11. APPENDICES

## 11.1. Appendix 1: Details of Data Extraction

### A1.1 Definition of Visits for the Assessment of Dosing Status and Safety Endpoints

| Visit | Endpoints | Representative date | Definition (time window) |
|---|---|---|---|
| Baseline | Dosing status, safety endpoints | Day 1 | From 30 days before the date of the first dose in this study (the date of the start of treatment) to the date of treatment start (before dosing) |
| Week 1 | Dosing status, safety endpoints | Day 7 | From the date of treatment start (after dosing) to 17 days after treatment start |
| Week 4 | Dosing status, safety endpoints | Day 28 | 18-42 days after treatment start |
| Week 8 | Dosing status, safety endpoints | Day 56 | 43-70 days after treatment start |
| Week 12 | Dosing status, safety endpoints | Day 84 | 71-98 days after treatment start |
| Week 16 | Dosing status, safety endpoints | Day 112 | 99-126 days after treatment start |
| Week 20 | Dosing status, safety endpoints | Day 140 | 127-154 days after treatment start |
| Week 36 | Dosing status, safety endpoints | Day 252 | 155-266 days after treatment start |
| Week 52 | Dosing status, safety endpoints | Day 364 | 267-394 days after treatment start |
| Final Visit | Dosing status, safety endpoints | | The time when the final visit for this study is made |

If multiple sets of observation data are reported on different dates within a time window, data on the date closest to the representative one will be used for summarization/analysis. If two sets of data are reported on two dates equally close to the representative one, the data on the later date will be adopted. If there are multiple values observed on the same day, the mean value of them will be used.

**A1.2 Definition of Visits for Cardiac Function Classification**

| Visit | Endpoints | Representative Date | Definition (time window) |
|---|---|---|---|
| Baseline | Left ventricular ejection fraction (LVEF), left ventricle internal dimensions in diastole (LVDd), left atrial dimension (LAD) | Day 1 | From 180 days before the date of the first dose in this study (the date of the start of treatment) to the date of treatment start (before dosing) |
| Week 26 | LVEF, LVDd, LAD | Day 182 | From the date of the start of treatment (after dosing) to 182 days after treatment start |
| Week 52 | LVEF, LVDd, LAD | Day 364 | 183-394 days after treatment start |

If multiple sets of observation data are reported on different dates within a time window, data on the date closest to the representative one will be used for summarization/analysis. If two sets of data are reported on two dates equally close to the representative one, the data on the later date will be adopted. If there are multiple values observed on the same day, the mean value of them will be used.

**A1.3 Definition of Visits for the Assessment of Plasma BNP and Serum NT-proBNP**

| Visit | Endpoints | Representative date | Definition (time window) |
|---|---|---|---|
| Baseline | Plasma BNP, serum NT-proBNP | Day 1 | From 90 days before the date of the first dose in this study (the date of the start of treatment) to the date of treatment start (before dosing) |
| Week 13 | Plasma BNP, serum NT-proBNP | Week 91 | From the date of treatment start (after dosing) to 91 days after treatment start |
| Week 26 | Plasma BNP, serum NT-proBNP | Day 182 | 92-182 days after treatment start |
| Week 39 | Plasma BNP, serum NT-proBNP | Day 273 | 183-273 days after treatment start |
| Week 52 | Plasma BNP, serum NT-proBNP | Day 364 | 274-394 days after treatment start |

If multiple sets of observation data are reported on different dates within a time window, data on the date closest to the representative one will be used for summarization/analysis. If two sets of data are reported on two dates equally close to the representative one, the data on the later date will be adopted. If there are multiple values observed on the same day, the mean value of them will be used.

## 11.2. Appendix 2: An Example of Table Showing Risk Ratios Regarding the Incidence of Adverse Reaction

| Event name: Increased XXX | Category 1 | | Category 2 | | Risk ratio (RR) | |
|---|---|---|---|---|---|---|
| | n/N | (%) | n/N | (%) | RR | 95% CI |
| Sex (male vs. female) | 18 / 2220 | (0.8) | 3 / 1099 | (0.3) | 2.97 | (0.88 - 10.06) |
| Aged (≥65 yrs) vs. Not aged (<65 yrs) | 19 / 2788 | (0.7) | 2 / 531 | (0.4) | 1.81 | (0.42 - 7.74) |
| Diagnosis (disease A vs. disease B) | 3 / 221 | (1.4) | 18 / 3098 | (0.6) | 2.34 | (0.69 - 7.87) |
| Duration of disease (<1 year vs. ≥1 year) | 9 / 771 | (1.2) | 7 / 866 | (0.8) | 1.44 | (0.54 - 3.86) |
| Concomitant use of drug A (present vs. absent) | 9 / 798 | (1.1) | 12 / 2521 | (0.5) | 2.37 | (1.00 - 5.60) |
| Pretreatment with drug A (present vs. absent) | 1 / 148 | (0.7) | 20 / 3171 | (0.6) | 1.07 | (0.14 - 7.93) |
| Coexistence of disease B (present vs. absent) | 16 / 1614 | (1.0) | 5 / 1703 | (0.3) | 3.38 | (1.24 - 9.20) |
| Past history of disease B (present vs. absent) | 7 / 674 | (1.0) | 14 / 2643 | (0.5) | 1.96 | (0.79 - 4.84) |
| Hepatic impairment (present vs. absent) | 0 / 80 | | 18 / 2056 | (0.9) | | |
| Renal impairment (present vs. absent) | 1 / 140 | (0.7) | 17 / 2004 | (0.8) | 0.84 | (0.11 - 6.28) |