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1. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CRF	Case Report Form
DAP	Definition of Analysis Population
DB	Database
DKA	Diabetic ketoacidosis
eGFR	Estimated Glomerular Filtration Rate
FPG	Fasting Plasma Glucose
HbA1c	Glucosylated Hemoglobin
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
NSADR	Non Serious Adverse Drug Reaction
NSAE	Non-Serious Adverse Event
OC	Observed Case
ONIS	Observational and Non-Interventional Study
PMS	Post Marketing Surveillance
PT	Preferred Term
RMP	Risk Management Plan
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SD	Standard Deviation
SD	Supporting Document
SEAP	Statistical and Epidemiological Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
UADR	Unexpected Adverse Drug Reaction
UAE	Unexpected Adverse Events
ULN	Upper Limits of Normal
VIF	Variance Inflation Factor
WHO ATC index	World Health Organization Anatomical Therapeutic Chemical index

2. RESPONSIBLE PARTIES

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3. PURPOSE AND SCOPE

The purpose of this statistical SEAP is to describe in detail the plan for statistical analysis method, processing method of data to be used for analysis, and definition of analysis datasets based on the Ministry of Food and Drug Safety (MFDS)'s guidelines for final analysis of <1245-0276, 9.0 (Effective date: 12-JUN-2025), A regulatory requirement non-interventional study to monitor the safety and effectiveness of Jardiance (empagliflozin, 10mg) in Korean patients with chronic heart failure (NYHA class II-IV)>. The table shell, which will record the analysis results, will be developed as a separate document. If the analysis is performed in a manner different from this document, the method of change and the reason for change will be recorded in detail in the final report.

4. AMENDMENTS AND UPDATES

Changes are as follows.

1. In the analyses of adverse events, the following contents are deleted due to amendments to Protocol version 8.0 and 9.0:

- Important identified risks (Complicated urinary tract infection / Genital infection /

- Diabetic ketoacidosis with atypical presentation) for AE
- Important potential risks (Urinary tract carcinogenicity / Liver injury / Pancreatitis) for AE

2. In the summary of adverse events, the following contents are added to analysed.

- Non-Serious AE

5. RESEARCH QUESTION AND OBJECTIVE

5.1 PRIMARY OBJECTIVE

The primary objective of this study is to monitor the safety profile of Jardiance® in Korean patients with chronic heart failure (NYHA class II-IV), in a routine clinical setting.

5.2 SECONDARY OBJECTIVE

The secondary objective of this study is to monitor the occurrence of hospitalization for heart failure (first and recurrent) or cardiovascular death within 12 weeks and/or 24 weeks from baseline.

6. RESEARCH METHODS

6.1 STUDY SIZE

According to the local RMP (Risk Management Plan) and PMS (Post Marketing Surveillance) regulation, it is required to submit data from more than 600 patients for the safety analysis in this study, and each patient will be followed from baseline for 12 weeks (short term), and 24 weeks (long term). The requirement of the number of safety analysis is defined as patient who is administered Jardiance® and is completed at least one time of safety follow-up. Since heart failure is chronic disease, it might not be sufficient to collect safety and effectiveness data in short-term (12 weeks) period, therefore, most of patients will be enrolled for long-term (24 weeks) surveillance.

It is expected that approximately 80% (480 cases) will be enrolled for long-term surveillance, and approximately 50% (300 cases) will be enrolled as geriatric (older than 65 years).

6.2 SETTING

A total of 600 patients will be enrolled at approximately 21 sites by as many as 21 or more ONIS physicians. To minimize the selection bias, consecutive patients from each site who meet inclusion criteria will be enrolled in this study.

6.2.1 Milestones

As per local PMS regulation and RMP regulation, safety data will be collected for about 4 years until May 31, 2025.

Table 1 Milestones

Milestone	Planned Date
Start of data collection	23, Nov 2021 (Approval date of Jardiance®)
End of data collection	31, May 2025
Interim reports of study results	As per regulation
Final report of study results	22, Feb 2026 (Expected date of MFDS submission)

6.2.2 Main diagnosis for study entry

- Patients diagnosed with chronic heart failure (NYHA class II-IV) in Korea.

6.2.3 Inclusion criteria

- Patients who have started at first time on Jardiance® in accordance with the approved label in Korea for HF
- Chronic heart failure (NYHA class II-IV)
- Age ≥ 19 years at enrolment
- Patients who have signed on the data release consent form

6.2.4 Exclusion criteria

- Patients with previous exposure to Jardiance®
- Known allergy or Hypersensitivity to active ingredients empagliflozin or to any of the excipients
- Patients with type 1 diabetes or with prior history of diabetic ketoacidosis (DKA)
- Patient with renal impairment with $\text{eGFR} < 20 \text{ mL/min/1.73 m}^2$
- Patients with rare hereditary conditions of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
- Patients who are pregnant or are nursing or who plan to become pregnant while in the surveillance

- Patients for whom empagliflozin is contraindicated according to the local label of Jardiance®

6.2.5 Subjects of special investigation

Among the patients who have signed on the data release consent form in order to conduct investigation for safety assessment after the administration of Jardiance®, subjects of special investigation (geriatric population (65 years or more), pregnant women, renal impairment, hepatic impairment and other special population) will be analyzed.

6.3 STUDY POPULATION

6.3.1 Subjects who entered the study

This number means the number of cases as specified in the contract concluded with the investigator (physician) prior to initiation of the study.

6.3.2 Subjects whose CRF was retrieved

This number means the number of cases who signed the data release consent form to participate in the study as subject, with a record of taking Jardiance® once at least.

6.3.3 Safety set

The safety set will include all patients who signed the data release consent form to participate in this study, took Jardiance® once at least after signing the data release consent form, and were followed up by the physician once or more for up to 24 weeks of follow up. Reflecting MFDS (Ministry of food and drug safety) guideline, the cases below shall be excluded from safety analysis set and analysed separately (defined below) in the following order:

- Patients did not sign (sign missing), or signed on the data release consent form of Jardiance® PMS prior to the contract date with institution/physician
- Duplicate registration
- Patients administered Jardiance® prior to the contract date with institution/investigator
- Patients administered Jardiance® prior to the signed on the data release consent form
- Violation of Inclusion/Exclusion criteria in protocol
- Patients who did not taken 10mg of Jardiance® (Not acceptable if patients took Jardiance® 25mg or JardianceDuo®)
- Failure of follow-up
- Violation of the approved indications and dosage in local label
(Patients who were prescribed for other indications except indications in the local label)

6.3.4 Effectiveness set

These cases include those who signed the data release consent form to participate in this study as subject, visited as per the study schedule, took Jardiance® once at least, and were evaluated for the effectiveness between 12 weeks (84 days) and less than 24 weeks (168 days) after treatment with at least 1 dose of Jardiance.

Reflecting MFDS's guideline, the cases below shall be excluded from effectiveness analysis (defined below) set in the following order.

- Patients excluded from safety set
- Patients who did not undergo effectiveness evaluation

6.3.5 Long-term safety set

The long-term safety set will include safety set who took Jardiance® for more than 24 weeks (168 days) and were followed up by the physician 24 weeks after the date of first Jardiance® administration.

The cases below shall be excluded from long term safety set in the following order.

- Patients excluded from safety set
- Patients who did not taken Jardiance® more than 24 weeks

6.3.6 Long-term effectiveness set

The long-term effectiveness set will include long-term safety set who were evaluated for the effectiveness up to 24 weeks (168 days) after the date of first Jardiance® administration at least once.

The cases below shall be excluded from effectiveness analysis (defined below) set in the following order.

- Patients excluded from long-term safety set
- Patients who did not undergo effectiveness evaluation

6.3.7 Subjects of special investigation

The subjects of special investigation will include pediatric population (<19y old), geriatric population (≥65y old), pregnant women, lactating women, hepatic impairment patients, and renal impairment patients.

6.4 STUDY VISITS

This study collects data from baseline visit and follow-up visit 1 and 2 at 12 weeks and 24 weeks, respectively, according to the protocol.

7. VARIABLES

7.1 EXPOSURES

Exposure to Jardiance® will be estimated as time from the day Jardiance® is initiated until last visit of the patient (or the final contact with the patient for the last regular observation/end of the study).

The treatment dose will be based on the doses that will be authorized. The recommended dose of Jardiance® is 10 mg once daily.

7.2 OUTCOME

7.2.1 Primary outcomes

Primary outcomes are all reported adverse events in patients who take at least one dose of Jardiance® will be noted. Endpoints pertaining to safety will be presented as incidence rates of patients with adverse events and will include:

- Adverse events
- Unexpected adverse events
- Unexpected adverse drug reaction
- Serious adverse events
- Serious adverse drug reaction
- Drug-related adverse events
- Non-serious adverse drug reaction
- Adverse event of special interest
- Adverse events leading to discontinuation

7.2.2 Secondary outcomes

Secondary outcomes are the changes of effectiveness evaluation at 12 weeks and/or 24 weeks after treatment.

- Occurrence of hospitalization for heart failure (first and recurrent) after 12 weeks and/or 24 weeks of treatment from baseline
- Occurrence of cardiovascular death after 12 weeks and/or 24 weeks of treatment
- Changes from baseline in NYHA functional class after 12 weeks and/or 24 weeks of treatments.
- Changes in EF (if available) at 12 weeks and 24 weeks compared to baseline
- Changes in BNP or NT-proBNP (if available) at 12 weeks and 24 weeks compared to baseline
- Changes in HbA1c or FPG (if available in T2D patients) after 12 weeks and/or 24 weeks of treatment
- Change from baseline in eGFR (if available) after 12 weeks and/or 24 weeks of

treatment

- Change from baseline in Body weight after 12 weeks and/or 24 weeks of treatment
- Change from baseline in blood pressure (SBP, DBP) after 12 weeks and/or 24 weeks of treatment
- The result of investigator's overall evaluation after 12weeks and/or 24weeks of treatment

7.3 COVARIATES

Not applicable.

8. DATA SOURCES

Data source covered in Protocol and DMRP.

9. DATA MANAGEMENT AND SOFTWARE / TOOLS

9.1 SOFTWARE/TOOLS

Statistical analyses will be performed using a version 9.4 64 bit () or higher on the SAS® Enterprise Guide (version 8.2 and later) interface.

9.2 HANDLING OF MISSING VALUES

All endpoints will be analyzed for OC (observed case) method. In other words, missing data is not replaced.

9.3 HANDLING OF INCONSISTENCIES IN DATA AND OUTLIERS

Not applicable.

9.4 HANDLING OF MISSING DATES

If there are missing dates and are used in calculations, they will be imputed as the following:

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Table 2 Handling of Missing Dates

Types of Dates	Missing	Imputation	Examples
1. Date of the diagnosis of chronic heart failure (NYHA class II-IV)	YYYY-MM-DD	The year of 'Data Release Consent'-01-01	Data Release Consent date: 2021-12-05 Collected date: UKUK-UK-UK Imputed date: 2021-01-01
2. Prior/ Concomitant medication start date	MM-DD	01-01	Collected date: 2021-UK-UK Imputed date: 2021-01-01
	DD	01	Collected date: 2021-12-UK Imputed date: 2021-12-01
Prior/ Concomitant medication end date	MM-DD	12-31	Collected date: 2021-UK-UK Imputed date: 2021-12-31
	DD	Last day of the month [day]	Collected date: 2021-12-UK Imputed date: 2021-12-31
Adverse event onset date	YYYY-MM-DD	Jardiance [®] administration start date	Administration start date: 2018-12-05 Collected date: UK-UK-UK Imputed date: 2018-12-05
	MM-DD	1. If [Year] is same as the year of Jardiance [®] administration start date: [Month-Day] of Jardiance [®] administration start date 2. If [Year] is not same as the year of Jardiance [®] administration start date: 01-01	1. Administration start date: 2018-12-05 Collected date: 2018-UK-UK Imputed date: 2018-12-05 2. Administration start date: 2018-12-05 Collected date: 2019-UK-UK Imputed date: 2019-01-01
	DD	1. If [Year-Month] is same as the [year-month] of Jardiance [®] administration	1. Administration start date: 2018-12-05

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Types of Dates	Missing	Imputation	Examples
		start date: [Day] of Jardiance® administration start date	Collected date: 2018-12- UK Imputed date: 2018-12-05
		2. If [Year-Month] is not same as the [Year-Month] of Jardiance® administration start date: 01	2. Administration start date: 2018-12-05 Collected date: 2019-05- UK Imputed date: 2019-05-01

9.5 HANDLING OF DRIVED VARIABLES

Derived variables will be imputed as the following.

Table 3 Derived Variables

Variable	Derivation Method
Change from baseline	Post-baseline value – Baseline value
Rate of change (%)	$\frac{\text{Post} - \text{baseline value} - \text{Baseline value}}{\text{Baseline value}} \times 100$
Age group	age ≥ 19y old and age < 30y old age ≥ 30y old and age < 40y old age ≥ 40y old and age < 50y old age ≥ 50y old and age < 60y old age ≥ 60y old
Duration of disease (years)	(Date of data release consent – Date of first diagnosis)/365.25
Duration of hospitalization (days)	Hospitalization stop date – Hospitalization start date + 1 * When patients have more than 2 hospitalizations, duration of hospitalization will be the sum of each hospitalization days. * If the hospitalization stop date is not collected and collected as ‘Continuing’, replace it with the [Date of last visit] on the CRF ‘Study Completion’ page.
Pediatric population	<19y old, ≥19y old
Geriatric population	<65y old, ≥65y old
Duration of AE (days)	AE end date – AE onset date +1 If [Continuing] is checked on CRF [ADVERSE EVENTS] page, AE end date will be replaced with the [Date of last visit] on CRF ‘Study Completion’ page, and will mark ≥ (e.g. ≥15).

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Variable	Derivation Method
Onset duration of AE (days)	AE onset date – Date of first Jardiance® administration

9.6 HOW TO HANDLE DATA ERRORS AFTER DB LOCK

If an 'Error List After DB Lock' (SD 0314 D) document according to 'SOP 0314' Database Lock is created after DB lock, the related content is not reflected in the analysis and will be written in the comments.

10. DATA ANALYSIS

10.1 MAIN ANALYSIS

Continuous variables will be summarized with number of subjects, mean, SD, median, minimum, maximum, 5th percentile and 95th percentile. Categorical variables will be summarized with frequency and percentage. Unless otherwise specified, statistical tests will be performed at two-sided significance level of 5% for baseline characteristics.

The mean, median, 5th percentile and 95th percentile present one more significant digit than the original data, and SD presents two more significant digits than the original data. The minimum, maximum values are presented in the same significant digits as the original data. However, 'Duration of disease (years)', 'Total duration of administration (day)', 'Total administered dose (mg)', 'Average daily dose (mg)' and 'Duration of hospitalization' are presented considering the original data as two decimal places.

The p-value is presented to four decimal places (rounded from the fifth digit), <0.0001 if the p-value is less than 0.0001, and >0.9999 if it is greater than 0.9999.

10.3 STUDY PERIOD AND NUMBER OF SUBJECTS

The study year and study period will be presented. The number of subjects who entered the study will be presented. The number of subjects whose CRF was retrieved, safety set, effectiveness set, long-term safety set, long-term effectiveness set by year of the study will be presented.

10.4 POST-MARKET SURVEILLANCE TABLES

The details related to study sites and study Principal Investigator will be presented. The number of subjects who entered the study, the number of subjects whose CRF was retrieved, safety set, effectiveness set, long-term safety set, long-term effectiveness set by study sites of the study will be presented.

10.5 SUBJECT CHARACTERISTICS

10.5.1 Demographics

For the following variables, the continuous variables will be summarized using number of subjects, mean, standard deviation (SD), median, minimum, maximum, 5th percentile and 95th percentile. Categorical variables will be summarized using number of subjects and percentages.

- Continuous variables: Age (years), Height (cm), Weight (kg)
- Categorical variables: Age group, Gender, Smoking status

10.5.2 Disease information

For the following variables, the continuous variables will be summarized using number of subjects, mean, SD, median, minimum, maximum, 5th percentile and 95th percentile. Categorical variables will be summarized using number of subjects and percentages.

- Continuous variables: Duration of disease (years), EF (%)
- Categorical variables: Cause of heart failure, History of Diabetes Mellitus, History of Diabetic ketoacidosis, History of Diabetes Mellitus Complications, History of hospitalization, History of Atrial fibrillation, Patient's major limitation to exertion, History of Hypertension, Medical History, Previous allergy, Comorbidities, Prior medication, Concomitant medication, NYHA functional class

10.5.3 Subjects of special investigation

The following variables will be summarized using number of subjects and percentages.

- Pediatric population (<19y old, ≥19y old)
- Geriatric population (<65y old, ≥65y old)
- Pregnant women (Yes, No)
- Lactating women (Yes, No)
- Hepatic impairment (Yes, No)
- Renal impairment (Yes, No)

10.5.4 Medical history and comorbidities

Comorbidities are defined as those that are checked “Yes” for question “Ongoing” under [Medical History] page of the CRF. All other medical conditions that are checked “No” for the question “Ongoing” under medical history page of the CRF are to be considered as medical history.

Medical history and comorbidities will be summarized with number of subjects, percentages and cases. Medical history and comorbidities will be coded with Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or latest major version and will be summarized with system organ class (SOC) and preferred term (PT) using number of subjects, percentages and cases.

10.5.5 Prior and concomitant medications

Prior medication is defined as any medication discontinued prior to the first dose of Jardiance®. Concomitant medication is defined as any medication that the subjects took with Jardiance®. Specifically, medications will be classified as the following:

Prior medication is a medication that can be classified into the following category:

- Medication end date < Date of first Jardiance® administration

Concomitant medication is a medication that can be classified into the following category:

- Medication end date ≥ Date of first Jardiance® administration
- Ongoing

Table 4 Examples of Categorization

Medication start date	Medication end date	Date of first Jardiance® administration	Prior medication	Concomitant medication
2020-01-01	2020-01-14	2020-01-15	Y	
2020-01-01	2020-01-15	2020-01-15		Y
2020-01-01	2020-01-20	2020-01-15		Y
2020-01-01	Ongoing	2020-01-15		Y
2020-01-15	2020-01-15	2020-01-15		Y
2020-01-15	2020-01-20	2020-01-15		Y
2020-01-15	Ongoing	2020-01-15		Y
2020-01-20	2020-01-25	2020-01-15		Y
2020-01-20	Ongoing	2020-01-15		Y

In the case of [Date of first Jardiance® administration = medication start date = medication end

date], it is included only as the concomitant medication. If it is clearly possible to classify as Prior medication, it is classified only as Prior medication.

If there is a missing date, Prior/concomitant medication is classified according to [8.4 HANDLING OF MISSING DATES].

Prior and concomitant medications will be summarized with number of subjects, percentages and cases. Prior and concomitant medications will be coded using the World Health Organization Anatomical Therapeutic Chemical index (WHO ATC index) version 2022 or latest major version and will be summarized with Level1(anatomical main group) and Level 5 (chemical substance) using number of subjects, percentages and cases. However, if level 5 (chemical substance) doesn't exist or 'Combinations', 'Various' then level 4 (chemical subgroup) will be used instead. (If level 5 doesn't exist then a higher level will be used.)

10.5.6 Jardiance administration status

Total duration of administration (day), Total administered dose (mg), and Average daily dose (mg) will be summarized using number of subjects, mean, SD, median, minimum, maximum, 5th percentile and 95th percentile. Long term (<24weeks, ≥24weeks) use will be summarized using number of subjects and percentages.

If the date of last administration is missing or Jardiance® administration status is "continuing", then the date of last administration will be replaced with date of last visit.

Each variable is defined as follows.

- Total duration of administration (day): Date of last administration – Date of first administration + 1
- Total number of days administered (day): Sum of number of days administered by timepoint (Date of last administration by timepoint - Date of first administration by timepoint + 1)
- Total administered dose (mg): Sum of administered dose by timepoint (Single dose × Frequency per Day × number of days administered by timepoint)
- Average daily dose (mg): Total administered dose (mg) / Total number of days administered (day).

10.6 SAFETY ANALYSIS

Safety analyses will be performed on Safety set.

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally

associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Drug Reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

The following relationship categories will be considered as ADR:

- Certain
- Probable/Likely
- Possible
- Conditional/Unclassified
- Unassessable/Unclassifiable

Serious adverse event (SAE) is defined as any AE which:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Other important medical events

Unexpected adverse event (UAE) is AE not listed in the local label.

The term Adverse Event of Special Interest (AESI) relates to any specific AE that has been identified at the substance level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs.

The following are considered as AESIs for empagliflozin:

- 1) Hepatic injury
 - An elevation of AST and/or ALT $\geq$ 3-fold ULN combined with an elevation of total bilirubin $\geq$ 2-fold ULN measured at the same visit, or in samples drawn within 30 days of each other, or
 - An elevation of AST and/or ALT $\geq$ 3-fold ULN and INR $\geq$ 1.5-fold ULN measured at the same visit, or in samples drawn within 30 days of each other, or
 - An elevation of AST and/or ALT $\geq$ 3-fold ULN with new onset, or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$), or

- An isolated elevation of AST and/or ALT $\geq$ 5-fold ULN
- 2) Decreased renal function
Decreased renal function is defined by a creatinine value showing a $\geq$ 2 fold increase from baseline and is above the ULN.
- 3) Ketoacidosis
The diagnosis of KA(Ketoacidosis) can be based on arterial pH $\leq$ 7.30, serum bicarbonate levels $<$ 15 and measurement of serum beta-hydroxybutyrate levels. Other diagnostic criteria which can support the diagnosis of KA are urine ketones and anion gap $>$ 10.
Investigators should note that not all criteria mentioned above need to apply for the diagnosis of KA, and clinical judgment should also be taken into consideration.
- 4) Events leading to lower limb amputation
Any event leading to a lower limb procedure of amputation, auto-amputation or disarticulation as defined below is considered as an AESI.
Amputation is a resection of a limb through a bone. Disarticulation is a resection of a limb through a joint. Auto-amputation is a spontaneous separation of non-viable portion of the lower limb.
Not included in this definition are debridement (removal of callus or dead tissue), procedures on a stump (like stump revision, drainage of an abscess, wound revision etc.) and other procedures (e.g., nail resection or removal) without a concomitant resection of a limb (amputation or disarticulation).” (International Working Group of Diabetic Foot, 2015).
Each lower limb amputation, disarticulation, or auto-amputation should be reported separately. The SAE report should include the date of the procedure, the level of amputation or disarticulation, the medical condition(s) leading to the procedure and if the patient had some of the known risk factor(s) for lower limb amputation.

Adverse events leading to discontinuation refer to a case where the action taken with study drug due to AE is discontinued. Case can be found in CRF ‘Adverse event’ pages whose ‘Action taken with study drug’ is ‘Drug withdrawn’.

Non-Serious Adverse Event (NSAE) is defined as AE which does not meet the SAE criteria. Non-Serious Adverse Drug Reaction (NSADR) is defined as any ADR which does not meet the SAE criteria.

10.6.1 Summary of adverse events

The following types of AEs will be summarized with the number of subjects and proportion of the number of subjects with AE, number of cases with AE and exact 95% confidence intervals.

- Adverse event (AE)

- Adverse drug reaction (ADR)
- Serious adverse event (SAE)
- Serious adverse drug reaction (SADR)
- Unexpected adverse event (UAE)
- Unexpected adverse drug reaction (UADR)
- Adverse events of special interest (AESI)
- Adverse events leading to discontinuation
- Non-serious adverse event (NSAE)
- Non-serious adverse drug reaction (NSADR)

10.6.2 Analyses of adverse events

The following types of AEs will be coded with MedDRA version 25.0 or latest major version and will be summarized with SOC and PT using the number of subjects and proportion of the number of subjects with AE, number of cases. The details of SAEs will also be presented in a listing. However, AE classified by intensity, outcome, causal relationship, action taken with Jardiance®, therapy for the event will be summarized using the number of AE cases and proportion of the number of cases.

- AE/ADR
- SAE/SADR
- UAE/UADR
- AESI
- AE leading to discontinuation
- NSAE/NSADR
- AE classified by Intensity
- AE classified by Outcome of the event
- AE classified by Causal Relationship
- AE classified by Action taken with Jardiance®
- AE classified by Therapy for the event

When applying for the re-examination, the following AEs of rare (less than 0.1%) or Occasional (less than 0.1%~5%) occurrent will be coded with MedDRA version 25.0 or latest major version and will be summarized with SOC and PT using the number of subjects and proportion of the number of subjects with AE, number of cases.

- SAE/SADR
- UAE/UADR

10.6.3 Univariate factor analysis (RE-EXAMINATION)

The following categorical variables will be summarized using number of subjects, the number of subjects and proportion of the number of subjects with AE and 95% confidence interval. AE

Occurrence will be analyzed using Pearson's chi-square test or Fisher's exact test to determine if statistically significant differences exist.

- Cause of heart failure (Ischemic, Non-ischemic)
- Gender (Male, Female)
- History of Diabetes Mellitus (Yes (Type 1 diabetes), Yes (Type 2 diabetes), No)
- History of Diabetic ketoacidosis (Yes, No)
- History of Diabetes Mellitus Complications (Yes, No)
- Smoking status (Never smoked, EX-smoker, Current)
- History of Atrial fibrillation (Yes, No)
- History of Hypertension (Yes, No)
- Medical History (Yes, No)
- Previous allergy (Yes, No)
- Comorbidities (Yes, No)
- Prior medication (Yes, No)
- Concomitant medication (Yes, No)
- Long term use (≥ 24 weeks, < 24 weeks)
- NYHA functional class (Class I, Class II, Class III, Class IV)

For the following continuous variables, AE Occurrence will be summarized using odds ratio and 95% confidence interval by using simple logistic regression.

- Age (years)
- Height (cm)
- Weight (kg)
- Duration of disease (years)
- Average daily dose (mg)
- EF (%)

Subjects of special investigation will be summarized using number of subjects, number of subjects with AE, proportion of subjects with AE and 95% confidence interval. AE Occurrence will be analyzed by using Pearson's chi-square test or Fisher's exact test to confirm statistically significant differences.

- Pediatric population (< 19 y old, ≥ 19 y old)
- Geriatric population (< 65 y old, ≥ 65 y old)
- Pregnant women (Yes, No)
- Lactating women (Yes, No)
- Hepatic impairment (Yes, No)
- Renal impairment (Yes, No)

10.6.4 Multivariable factor analysis (RE-EXAMINATION)

As a result of simple logistic regression, statistically significant variables will be included in a multivariable logistic regression and odds ratio and 95% confidence interval will be provided for each variable. (However, Variables with the Variance Inflating Factor (VIF) exceeding 10 can be excluded from the model.) The complete case analysis will be used to handle missing values of variables in the multivariable logistic regression model.

10.6.5 Univariate factor analysis (PERIODIC REPORT)

Subjects of special investigation will be summarized using number of subjects, number of subjects with AE, proportion of subjects with AE and 95% confidence interval.

- Pediatric population (< 19y old, ≥ 19y old)
- Geriatric population (< 65y old, ≥ 65y old)
- Pregnant women (Yes, No)
- Lactating women (Yes, No)
- Hepatic impairment (Yes, No)
- Renal impairment (Yes, No)

10.6.6 Summary of adverse events for subjects of special investigation

The following types of AEs for each subject of special investigation will be summarized with the number of subjects and proportion of the number of subjects with AE and cases of AE and exact 95% confidence intervals. The details of AEs for each subject of special investigation will also be presented in a listing.

- Adverse event (AE)
- Adverse drug reaction (ADR)
- Serious adverse event (SAE)
- Serious adverse drug reaction (SADR)
- Unexpected adverse event (UAE)
- Unexpected adverse drug reaction (UADR)
- Adverse events of special interest (AESI)
- Adverse events leading to discontinuation
- Non-serious adverse event (NSAE)
- Non-serious adverse drug reaction (NSADR)

10.6.7 Summary of adverse events for subjects who are excluded from safety set

The following types of AEs for each subject who are excluded from safety set will be summarized with the number of subjects and proportion of the number of subjects and cases of AE and exact 95% confidence intervals. The details of AEs for each subject who are not eligible

will also be presented in a listing. However, subjects who didn't take any one time with Jardiance®, failure to follow-up, and dual registration are excluded.

- Adverse event (AE)
- Adverse drug reaction (ADR)
- Serious adverse event (SAE)
- Serious adverse drug reaction (SADR)
- Unexpected adverse event (UAE)
- Unexpected adverse drug reaction (UADR)
- Adverse events of special interest (AESI)
- Adverse events leading to discontinuation
- Non-serious adverse event (NSAE)
- Non serious adverse drug reaction (NSADR)

10.6.8 Summary of adverse events for subjects with missing information (NYHA class IV heart failure)

The following types of AEs for each subject whose NYHA class is IV will be summarized with the number of subjects and proportion of the number of subjects and cases of AE and exact 95% confidence intervals. The details of AEs for each subject whose NYHA class is IV will also be presented in a listing.

- Adverse event (AE)
- Adverse drug reaction (ADR)
- Serious adverse event (SAE)
- Serious adverse drug reaction (SADR)
- Unexpected adverse event (UAE)
- Unexpected adverse drug reaction (UADR)
- Adverse events of special interest (AESI)
- Adverse events leading to discontinuation
- Non-serious adverse event (NSAE)
- Non-serious adverse drug reaction (NSADR)

10.6.9 Summary of adverse events for long-term safety set

The following types of AEs will be summarized with the number of subjects and proportion of the number of subjects with AE, number of cases with AE and exact 95% confidence intervals. The details of SAEs will also be presented in a listing.

- Adverse event (AE)
- Adverse drug reaction (ADR)
- Serious adverse event (SAE)
- Serious adverse drug reaction (SADR)
- Unexpected adverse event (UAE)

- Unexpected adverse drug reaction (UADR)
- Adverse events of special interest (AESI)
- Adverse events leading to discontinuation
- Non-serious adverse event (NSAE)
- Non-serious adverse drug reaction (NSADR)

10.7 EFFECTIVENESS ANALYSIS

Effectiveness analyses will be performed on Effectiveness set.

The 12 weeks timepoint corresponds to the evaluation results collected 12 weeks (84 days) or after and less than 24 weeks (168 days) of treatment, and the 24 weeks timepoint corresponds to the evaluation results collected after 24 weeks (168 days) of treatment.

10.7.1 Main outcome

- 1) Occurrence of hospitalization for heart failure (first and recurrent) after 12 weeks from baseline and after 24 weeks from baseline will be summarized using number of subjects, percentage, and 95% confidence. Also, the duration of hospitalization will be summarized using number of subjects, mean, SD, median, minimum, maximum, 5th percentile, 95th percentile.
- 2) Occurrence of cardiovascular death (CV death) after 12 weeks from baseline and after 24 weeks from baseline will be summarized using number of subjects, percentage, and 95% confidence.
- 3) For NYHA functional class, a shift table will be provided with frequency and percentage for change from baseline to 12 weeks, 24 weeks and final visit. However, since subjects with NYHA class IV at baseline cannot worsen, an additional sensitivity analysis will be conducted excluding the subjects with NYHA class IV at baseline.
- 4) For EF (%), the changes from baseline to 12 weeks, 24 weeks and final visit will be summarized using number of subjects, mean, SD, median, minimum, maximum, 5th percentile, 95th percentile, and will be compared using paired t-test.
- 5) For BNP or NT-proBNP, a log scale will be applied, the changes from baseline to 12 weeks, 24 weeks and final visit will be summarized using number of subjects, mean, SD, median, minimum, maximum, 5th percentile, 95th percentile, and will be compared using paired t-test. Also, the ratio of NT-proBNP change from baseline to 12 weeks, 24 weeks and final visit will be summarized using number of subjects, percentage, 95% confidence intervals.
- 6) For HbA1c (%) or FPG (mg/dL), the changes from baseline to 12 weeks, 24 weeks and final visit will be summarized using number of subjects, mean, SD, median, minimum, maximum, 5th percentile, 95th percentile, and will be compared using paired t-test.
- 7) For eGFR (mL/min/1.73m²), the changes from baseline to 12 weeks, 24 weeks and final visit will be summarized using number of subjects, mean, SD, median, minimum, maximum, 5th percentile, 95th percentile, and will be compared using paired t-test.

- 8) For Weight (kg), the changes from baseline to 12 weeks, 24 weeks and final visit will be summarized using number of subjects, mean, SD, median, minimum, maximum, 5th percentile, 95th percentile, and will be compared using paired t-test.
- 9) For Systolic blood pressure (SBP) (mmHg) and Diastolic blood pressure (DBP) (mmHg), the changes from baseline to 12 weeks, 24 weeks and final visit will be summarized using number of subjects, mean, SD, median, minimum, maximum, 5th percentile, 95th percentile, and will be compared using paired t-test.
- 10) For patients with NYHA class IV, investigator's overall evaluation at final visit will be summarized using the number of subjects, percentage, and 95% confidence. If the investigator's overall evaluation is collected as [Improved], it is classified as [Effective]. And if the investigator's overall evaluation is collected as [Unchanged] or [Aggravated], it is classified as [Ineffective]. The number of subjects, percentage, and 95% confidence will be presented for Effective/Ineffective.

10.7.2 The final effectiveness evaluation

For the final effectiveness evaluation, the three items ([Improved, Unchanged, Aggravated]) are evaluated by the changes from baseline of the NYHA Class at the end of last visit and will be summarized using number of subjects, percentage, 95% confidence intervals. In addition, if final effectiveness is evaluated as [Improved, Unchanged], it is classified as [Effective]. And if final effectiveness is evaluated as [Aggravated], it is classified as [Ineffective].

10.7.4 Multivariable analysis (RE-EXAMINATION)

As a result of simple logistic regression, statistically significant variables will be included in a multivariable logistic regression and odds ratio and 95% confidence interval will be provided for each variable. (However, Variables with the VIF exceeding 10 can be excluded from the model.) The complete case analysis will be used to handle missing values of variables in the multivariate logistic regression model.

10.7.5 Main outcome for long-term effectiveness set

- 1) Occurrence of hospitalization for heart failure (first and recurrent) after 12 weeks from baseline and after 24 weeks from baseline will be summarized for long-term effectiveness set using number of subjects, percentage, and 95% confidence. Also, the duration of hospitalization will be summarized for long-term effectiveness set using number of subjects, mean, SD, median, minimum, maximum, 5th percentile, 95th percentile.
- 2) Occurrence of cardiovascular death (CV death) after 12 weeks from baseline and after 24 weeks from baseline will be summarized for long-term effectiveness set using number of subjects, percentage, and 95% confidence.
- 3) For NYHA functional class, a shift table will be provided with frequency and percentage for long-term effectiveness set for change from baseline to 12 weeks, 24

weeks and final visit. However, since subjects with NYHA class IV at baseline cannot worsen, an additional sensitivity analysis will be conducted excluding the subjects with NYHA class IV at baseline.

- 4) For EF (%), the changes from baseline to 12 weeks, 24 weeks and final visit will be summarized for long-term effectiveness set using number of subjects, mean, SD, median, minimum, maximum, 5th percentile, 95th percentile, and will be compared using paired t-test.
- 5) For BNP or NT-proBNP, a log scale will be applied, the changes from baseline to 12 weeks, 24 weeks and final visit will be summarized for long-term effectiveness set using number of subjects, mean, SD, median, minimum, maximum, 5th percentile, 95th percentile, and will be compared using paired t-test. Also, the ratio of NT-proBNP change from baseline to 12 weeks, 24 weeks and final visit will be summarized using number of subjects, percentage, 95% confidence intervals.
- 6) For HbA1c (%) or FPG (mg/dL), the changes from baseline to 12 weeks, 24 weeks and final visit will be summarized for long-term effectiveness set using number of subjects, mean, SD, median, minimum, maximum, 5th percentile, 95th percentile, and will be compared using paired t-test.
- 7) For eGFR (mL/min/1.73m²), the changes from baseline to 12 weeks, 24 weeks and final visit will be summarized for long-term effectiveness set using number of subjects, mean, SD, median, minimum, maximum, 5th percentile, 95th percentile, and will be compared using paired t-test.
- 8) For Weight (kg), the changes from baseline to 12 weeks, 24 weeks and final visit will be summarized for long-term effectiveness set using number of subjects, mean, SD, median, minimum, maximum, 5th percentile, 95th percentile, and will be compared using paired t-test.
- 9) For Systolic blood pressure (SBP) (mmHg) and Diastolic blood pressure (DBP) (mmHg), the changes from baseline to 12 weeks, 24 weeks and final visit will be summarized for long-term effectiveness set using number of subjects, mean, SD, median, minimum, maximum, 5th percentile, 95th percentile, and will be compared using paired t-test.
- 10) For patients with NYHA class IV, investigator's overall evaluation at final visit will be summarized using the number of subjects, percentage, and 95% confidence. If the investigator's overall evaluation is collected as [Improved], it is classified as [Effective]. And if the investigator's overall evaluation is collected as [Unchanged] or [Aggravated], it is classified as [Ineffective]. The number of subjects, percentage, and 95% confidence will be presented for Effective/Ineffective.

10.7.6 The final effectiveness evaluation for long-term effectiveness set

For the final effectiveness evaluation of long-term effectiveness set, the three items ([Improved, Unchanged, Aggravated]) are evaluated by the changes from baseline of the NYHA Class at the end of last visit and will be summarized using number of subjects, percentage, 95% confidence intervals. In addition, if final effectiveness is evaluated as [Improved, Unchanged], it is classified as [Effective]. And if final effectiveness is evaluated as [Aggravated], it is

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Version 3.0

classified as [Ineffective].

11. QUALITY CONTROL

In accordance with [REDACTED] SOP 0401, the designated reviewer will perform QC on all generated datasets and tables.

12. REFERENCES

12.1 PUBLISHED REFERENCES

Not applicable.

12.2 UNPUBLISHED REFERENCES

Not applicable.

ANNEX

ANNEX 1. DEFINITION OF ANALYSIS POPULATION

Definition of Analysis Population (DAP) creates criteria for subjects excluded from the defined analysis group. An analysis group is defined by creating a subject list based on the DAP.

ANNEX 2. TABLE SHELL

The table shell represents the models of the tables in which the results of the analysis will be presented. In principle, the analysis results are basically in accordance with the table shell.

ANNEX 3. SUBJECT LIST OF PMS (Regulatory template Appendix no. 2)

Annex 3 will be prepared for the PMS. The number of subjects whose CRF was retrieved, safety set, effectiveness set, long-term safety set, long-term effectiveness set by year of the study will be presented. The number of subjects excluded from the safety evaluation, effectiveness evaluation, long-term safety evaluation, long-term effectiveness evaluation and their specific reasons will be presented.

ANNEX 4. SUMMARY TABLE OF DOMESTIC ADVERSE EVENT OCCURENCES (Regulatory template Appendix no. 3)

ADR collected in PMS will be summarized using number of study sites, the number of safety set, the number of subjects with ADR and cases of ADRs, proportion of the number with ADR according to the appendix format. SAEs, SADR, Not SAEs, Not SADR collected from PMS, special study (Pharmacoepidemiology study, etc.), clinical trials and Spontaneous reporting will be coded with Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized with system organ class (SOC) and preferred term (PT) using the number of subjects and proportion of the number of subjects with AE.

ANNEX 5. TABLE OF SERIOUS ADVERSE EVENTS, ADVERSE DRUG REACTIONS, AND UNEXPECTED ADVERSE DRUG REACTIONS

SAEs, SADR, UADR collected from PMS, special study (Pharmacoepidemiology study, etc.), clinical trials and Spontaneous reporting will only be presented for Re-examination according to the format.

ANNEX 6. DETAILS OF SAES IN DEATH OR LEADING TO DEATH

The details of SAEs in death or leading to death collected from PMS, special study (Pharmacoepidemiology study, etc.), clinical trials and Spontaneous reporting will be presented in a listing.

**ANNEX 7. DETAILS OF SERIOUS UNEXPECTED AES (Regulatory template
Appendix no. 5)**

The details of Serious Unexpected AEs collected from PMS, special study (Pharmacoepidemiology study, etc.), clinical trials and Spontaneous reporting will be presented in a listing.

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ANNEX 8. REVIEWERS AND APPROVAL SIGNATURES

Study Title: A regulatory requirement non-interventional study to monitor the safety and effectiveness of Jardiance® (empagliflozin, 10mg) in Korean patients with chronic heart failure (NYHA class II-IV)

Study Number: 1245-0276

Protocol Version: 9.0

I herewith certify that I agree to the content of the study SEAP and to all documents referenced in the study SEAP.

Position: _____ Name/Date: _____ /
designee

Position: _____ Name/Date: _____ /

Position: _____ Name/Date: _____ /
ONIS Lead

Signature: _____ 서명인: _____ "!" "Ä" "\$
서명인 이름: _____
서명 사유: 이 문서의 작성자임
서명 시간: 21-8-2025 | 5:13:25 오후 KST

Signature: _____ 서명인: _____ "!" "Ä" "\$
서명인 이름: _____
서명 사유: 이 문서를 검토함
서명 시간: 21-8-2025 | 5:15:11 오후 KST

Signature: _____ 서명인: _____ "!" "Ä" "\$
서명인 이름: _____
서명 사유: 이 문서를 승인함
서명 시간: 21-8-2025 | 5:19:30 오후 KST

Certificate Of Completion

Envelope Id: D7F7296F-DA84-49E1-9DD8-5A294E8F9EDB		Status: Completed
Subject: Complete with Docusign: 1245-0276_SEAP_v3_0_2025-08-21_clean_re.pdf		
Source Envelope:		
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	Signature Adoption: Pre-selected Style	
	Signature ID: [Redacted]	
	Using IP Address: [Redacted]	
	With Signing Authentication via Docusign password With Signing Reasons (on each tab): 이 문서의 작성자임	
Electronic Record and Signature Disclosure: Accepted: 8/21/2025 5:11:58 PM ID: [Redacted] Company Name: Boehringer Ingelheim [Redacted] [Redacted] Security Level: Email, Account Authentication (Required)	[Redacted]	Sent: 8/21/2025 5:13:44 PM Viewed: 8/21/2025 5:14:25 PM Signed: 8/21/2025 5:15:23 PM
	Signature Adoption: Pre-selected Style	
	Signature ID: [Redacted]	
	Using IP Address: [Redacted]	
	With Signing Authentication via Docusign password With Signing Reasons (on each tab): 이 문서를 검토함	
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Signer Events	Signature	Timestamp
Security Level: Email, Account Authentication (Required)	Signature Adoption: Pre-selected Style Signature ID: Using IP Address: With Signing Authentication via DocuSign password With Signing Reasons (on each tab): 이 문서를 승인함	Sent: 8/21/2025 5:15:25 PM Viewed: 8/21/2025 5:19:05 PM Signed: 8/21/2025 5:19:45 PM

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Company Name: Boehringer Ingelheim

In Person Signer Events	Signature	Timestamp
Editor Delivery Events	Status	Timestamp
Agent Delivery Events	Status	Timestamp
Intermediary Delivery Events	Status	Timestamp
Certified Delivery Events	Status	Timestamp
Carbon Copy Events	Status	Timestamp
Witness Events	Signature	Timestamp
Notary Events	Signature	Timestamp
Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	8/21/2025 5:05:04 PM
Certified Delivered	Security Checked	8/21/2025 5:19:05 PM
Signing Complete	Security Checked	8/21/2025 5:19:45 PM
Completed	Security Checked	8/21/2025 5:19:45 PM
Payment Events	Status	Timestamps
Electronic Record and Signature Disclosure		

Parties agreed to: [REDACTED]

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Boehringer Ingelheim Consent to Proceed with Electronic Signatures

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- I can print on paper the disclosure or save or send the disclosure to a place where I can print it, for future reference and access; and
- Until or unless I have notified my respective Company contact as described above, I consent to receive through electronic means all contractual documents, notices and other documents that are required to be provided or made

available to me by the Company during the course of the business relationship with you.