[English Version_For Reference]

Statistical Analysis Plan

Protocol Identification No.	1276.39
Title	A regulatory requirement non interventional study to monitor the safety and effectiveness of JARDIANCE DUO (empagliflozin/metformin, 5/500mg, 5/850mg, 5/1000mg, 12.5/500mg, 12.5/850mg, 12.5/1000mg) in Korean patients with type 2 diabetes mellitus
Protocol Date and Version	31-JAN-2019/Version 3.0
Sponsor	[redacted]
Author	
Approver	
Approver	
Date and Version	15-APR-2019/Version 1.0

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1. Purpose of the Statistical Analysis Plan

The purpose of this Statistical Analysis Plan is to be documented the details for analyzing collected data from Post-marketing Surveillance of 1276.39.

This document is based on the statistical analysis method described in this plan, and the results of the analysis will be included in the final Re-examination report.

If any post-analysis or unplanned analysis is required that is not defined in this document, it will be reflected in a separate document (e.g., the Additional Analysis Plan).

2. Study Features

2.1 Study Objective

Primary Objective
The primary objective of this study is to monitor the safety profile of JARDIANCE DUO in Korean patient with type 2 diabetes mellitus (T2DM) in a routine clinical setting.

Secondary Objective
The secondary objective of this study is to monitor the effectiveness of JARDIANCE DUO by evaluation of the change from baseline after 12 weeks and/or 24 weeks in the glycosylated hemoglobin (HbA1c), [redacted] in Korean T2DM patients.

2.2 Number of Subjects

The sample size of 600 patients is based on the requirement of the local regulatory authority (MFDS). As per regulation, long-term surveillance is necessary for the T2DM indication. Since T2DM is chronic disease it might be restrictive to collect safety and effectiveness data in short-term (12weeks) period, all patients will be enrolled for long-term (24weeks) surveillance.

2.3 Study Period

Minister of Food and Drug Safety (MFDS) set JARDIANCE DUO re-examination period from 21 January 2016 to 11 August 2020. The study period is granted as the remaining period of JARDIANCE (empagliflozin) according to the Standards for Re-examination of New Drugs.

2.4 Study Method

This study will be carried out in the manner of successive survey that the investigator will be asked to successively write in the case report forms (CRFs) from the subject who was initially administered the drug following the study start date to the requested number of subjects without omission.

3. Sequence of Planned Analyses

In the 'Guidelines for Re-examination of New Drugs, etc.', study reporting period is defined as follows (section 1 of Chapter 4).

> B. Periodic reports are submitted to the Minister of Food and Drug Safety (MFDS) with results of use-result surveillance and special surveillance that are conducted for 6 months in first 2 years from the license date and for 1 year thereafter within 2 months after the expiration of surveillance period and the final periodic report may be replaced with the re-examination application.

In accordance with the above local regulation, interim analysis will be carried out at the time of the 5th, re-examination of review reporting. However, statistical analysis may not proceed if;

- When the brief report is prepared as a reason for not being executed due to lack of number of cases of reporting;
- If a regular report is prepared as a case study report due to a small number of subjects;

4. Analysis Sets

In this study, the analysis sets for statistical analysis consist of the safety analysis set (section 4.1), the effectiveness analysis set (section 4.2), and the long-term safety analysis set (section 4.3).

4.1 Safety Analysis Set

In the 'Guidelines for Re-examination of New Drugs, etc.', study subject is defined as follows (section 3 of Chapter 3).

> 2) Patient group to be study subjects
> A) Patients who have decided to receive the investigational product based on the medical judgment of the investigator are included in the subjects.
> B) In principle, those who fall under off-label use of the drug are not included in the subjects. However, if the data of off-label use subjects are collected, they are analyzed as a separate item.
> C) The actual method of selecting study subjects should be described in detail.

In this study, the safety analysis set is defined as follows.
The safety analysis set consists of subjects who signed the informed consent form to participate in this study, took the drug at least once, and then received follow-up at least once by the study investigator.

4.2 Effectiveness Analysis Set

In the 'Guidelines for Re-examination of New Drugs, etc.', the effectiveness analysis set is defined as follows (section 3 of Chapter 3).

> (1) Composition of study subjects
> Effectiveness analysis set: Among subjects in the safety analysis set, subjects whose effectiveness evaluation records are collected as specified in the protocol.

In this study, the effectiveness analysis set is defined as follows.
The effectiveness analysis set consists of subjects who received effectiveness evaluation among those in the safety analysis set.

5. General Specifications for Statistical Analyses

5.1 Analysis Software

Each statistical analysis will be carried out with SAS Software version 9.4 or more recent version.

5.2 Planned Covariate

No covariate analysis is planned for this study.

5.3 Summary Statistics

For continuous data, the number of subjects, mean, standard deviation, median, minimum, and maximum are presented, and for categorical data, the frequency and percentage (%) are presented.

5.4 Methods for Missing Data and Incomplete Data

If missing or incomplete data exists, they are processed as follows. However, if separate processing for missing data is required depending on the analysis item, the information will be described in the relevant item of '7.1 Derivation'.

- If there are missing data other than those related to this drug, the collected data will be analyzed as they are without any replacement.
- Among the continuous data used for analysis, data containing inequality signs and symbols (Ex: 'over 20', '>20') are excluded from the analysis.
- If only some information (Ex: '2017-03-UK', '20UK') of the date used in the analysis (Ex: total administration period) exists, and the other part cannot be calculated, it is excluded from the analysis.

5.5 Other Statistical Considerations

The analysis will be conducted in consideration of the following matters, and if separate considerations are needed depending on the analysis item, the contents will be described in the relevant item of '7.1 Derivation'.

- The standard for converting Day into Month or Year is as follows: 1 month = 30.4375 days, 1 year = 365.25 days
- For all data analyses, the test statistic is a two-sided test, and the statistical significance level is based on 0.05.
- When calculating percentages from categorical demographics and baseline data, the denominator is defined as the sum of the number of subjects in each category. However, for analysis by detailed medical history/medication type, the denominator is defined as the number of subjects with medical history/medication.
- When calculating percentages of the incidence of adverse events and valid/invalid by demographics and baseline data, the denominator is defined as the number of subjects in each category. However, upon analyzing by detailed medical history/medication type, the denominator is defined as the number of subjects with medical history/medication in each category.
- When calculating the percentage of the incidence for each type of adverse event, the denominator for analyzing the safety analysis set is defined as the number of subjects in the safety analysis set. However, in the analysis of subjects excluded from safety evaluation, the denominator is defined as the number of subjects excluding those who were investigated in duplicate, those who did not receive this drug, or those who did not undergo follow-up for safety.

- In categorical data, if the cells with an expected frequency of less than 5 are more than 20% of all cells in the between group test, Fisher's exact test is used for analysis instead of the Chi-square test.
- For the confidence interval, a 95% two-sided confidence interval is calculated by applying the exact confidence interval method.
- If the total number of adverse events is 10 or less, the analysis of the incidence of adverse events by demographics and baseline data can be replaced with the list of adverse events.
- Multiple logistic regression analysis is not performed when there are two or less variables that show significant differences in the analysis of the incidence of adverse events by demographics and baseline data.

5.6 Reporting Conventions

- P-value is rounded and presented to 4 decimal places.
- If the calculated p-value is less than 0.0001, it is presented as '<0.0001'.
- Descriptive statistics (mean, standard deviation, median, minimum, maximum, percentage) are rounded and presented to 2 decimal places.
- If the calculated percentage is less than 0.01, it is presented as '<0.01'.

6. Evaluation of Study Data

The analysis set will be applied as analysis group as followings:

Analyses	Safety Analysis Set	Excluded from Safety Analysis Set	Effectiveness Analysis Set
Demographics	✓		✓
Medical History	✓		✓
Prior and Concomitant Medication	✓		✓
Study Medication Treatment Status	✓		✓
Safety Evaluation	✓	✓†	
Effectiveness Evaluation			✓

† analysis only for 6.8.4 section

6.1 Disposition of Subjects

The frequency and percentage of subjects who enrolled in this surveillance are calculated as followings:

- Total number of enrolled subjects
- The number of subjects in the safety analysis set
- The number of subjects excluded from safety analysis set and reasons
- The number of subjects in the effectiveness analysis set
- The number of subjects excluded from effectiveness analysis set and reasons

6.3 Demographics

- Continuous Data:
    - Birth of year
    - Body weight

- Categorical Data:
    - Gender
    - Birth of year
    - Smoking status
    - Early termination and reasons

6.4 Medical History

- Continuous Data:
    - Duration of disease[a]

- Categorical Data:
    - Duration of disease
    - Family history of Type 2 diabetes mellitus
    - Diabetes mellitus related complication
    - Other Medical history
    - Allergy history
    - Renal impairment

[a] Duration of disease: Total period from date of the diagnosis to start date of this study drug
[b] Other Medical history: history of concomitant disease within 6 months prior to baseline
[c] Allergy history: history of allergy within 6 months prior to baseline

Detailed disease names of other medical history will be summarized in SOC using the latest version of MedDRA. At this time, even if one subject has two or more medical histories, if they fall under one category, they will be analyzed as one person within the category. Also, one subject may be presented in duplicate in different medical history categories.

In addition, detailed disease names of diabetes complications are analyzed by type as collected in the CRF. At this time, even if one subject has two or more medical histories, if they fall under one category, they will be analyzed as one person within the category. Also, one subject may be presented in duplicate in different medical history categories.

6.5 Prior and Concomitant Medications

- Categorical Data:
    - Concomitant medications[a]
    - Concomitant anti-hyperglycemic agent[b]

[a] Concomitant medications: within 1 month prior to baseline
[b] Concomitant anti-hyperglycemic agent: within 1 month prior to baseline except study drug

The presence or absence of medication history of concomitant medications and other antidiabetic agents is presented as descriptive statistics.

The detailed drug names of concomitant medication history will be summarized using KIMS with a major category name and a subcategory name. At this time, even if one subject took two or more drugs, if they fall under one category, they will be analyzed as one person within the category. Also, one subject may be presented in duplicate in different drug categories.

In addition, the detailed drug names of the medication history of other antidiabetic agents are analyzed by type as collected in the CRF. At this time, even if one subject took two or more drugs, if they fall under one category, they will be analyzed as one person within the category. Also, one subject may be presented in duplicate in different drug categories.

6.7 Study Medication Treatment Status

- Continuous Data:
    - Total period of study drug
    - Total dose of study drug (empagliflozin)
    - Total dose of study drug (metformin)
    - Average of daily dose (empagliflozin)
    - Average of daily dose (metformin)

- Categorical Data:
    - Total period of study drug
    - Average of daily dose (empagliflozin)
    - Average of daily dose (metformin)

6.8 Safety Evaluation

Safety analysis set will be analyzed following the section 6.8.1, 6.8.2, 6.8.3, 6.8.5 and excluded from safety analysis set will be analyzed following the section 6.8.4.

6.8.1 Summary of Adverse Events

The number of subjects with adverse events and their incidence (%) for each SOC and PT, 95% confidence interval for the incidence, and the number of cases will be included.

- Adverse events, Adverse drug reactions[a]
- Serious adverse events, Serious adverse drug reactions
- Unexpected adverse events[b], Unexpected adverse drug reactions
- Unexpected serious adverse events, Unexpected serious adverse drug reactions
- Non serious adverse drug reaction[c]
- Adverse event of special interest(AESI)[d]
- Adverse events leading to discontinuation[e]

[a] Adverse Drug Reaction (ADR): any adverse drug reaction with causality (Certain/ Probable·Likely/ Possible/ Conditional·Unclassified/ Unassessable)
[b] Unexpected adverse event: the event is not included in the latest approved local label
[c] Non serious adverse drug reaction: any adverse reaction which does not meet the SAE criteria
[d] Adverse event of special interest(AESI) is as following 8 events:

AESI (Adverse Event of Special interest)

- Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection
- Increased urination
- Urinary tract infection (UTI)
- Volume depletion
- Diabetic Ketoacidosis (DKA)
- Decreased renal function:
  - Creatinine value shows a >2-fold increase from baseline and is above the ULN
- Hepatic injury defined by the following alterations of liver parameters:
  - An elevation of AST and/or ALT >3-fold ULN combined with an elevation of total bilirubin >2-fold ULN measured in the same blood draw sample.
  - An isolated elevation of AST and/or ALT >5-fold ULN (without an elevation of total bilirubin >2-fold ULN)
- Lower limb amputation
  - Amputation (i.e. resection of a limb through a bone)
  - Disarticulation (i.e. resection of a limb through a joint)
  - Auto-amputations (i.e. spontaneous separation of non-viable portion of the lower limb)

[e] Adverse events leading to discontinuation: Reason of early termination is a ′due to Adverse event′ and also action taken with study drug is ′Discontinued′

6.8.2 Adverse Events by Preferred Term

For the safety analysis set, the adverse event incidence status for the following items will be presented in detail. Using the latest version of MedDRA, the number of subjects with adverse events and their incidence (%) for each SOC and PT, 95% confidence interval for the incidence, and the number of cases will be included. At this time, even if two or more adverse events were expressed in one subject, if they fall under one category, they will be analyzed as one person within the category. In addition, one subject may be presented in duplicate in different adverse event categories.

- Adverse events, Adverse drug reactions
- Serious adverse events, Serious adverse drug reactions
- Unexpected adverse events, Unexpected adverse drug reactions
- Unexpected serious adverse events, Unexpected serious adverse drug reactions
- Non serious adverse drug reaction
- Adverse event of special interest(AESI)
- Adverse events leading to discontinuation

For the short-term use (< 24 weeks) and long-term use (≥ 24 weeks) subjects in the safety analysis set, the adverse event incidence status for the following items will be presented in detail. Using the latest version of MedDRA, the number of subjects with adverse events and their incidence (%) for each SOC and PT, 95% confidence interval for the incidence, and the number of cases will be included. At this time, even if two or more adverse events were

expressed in one subject, if they fall under one category, they will be analyzed as one person within the category. In addition, one subject may be presented in duplicate in different adverse event categories.

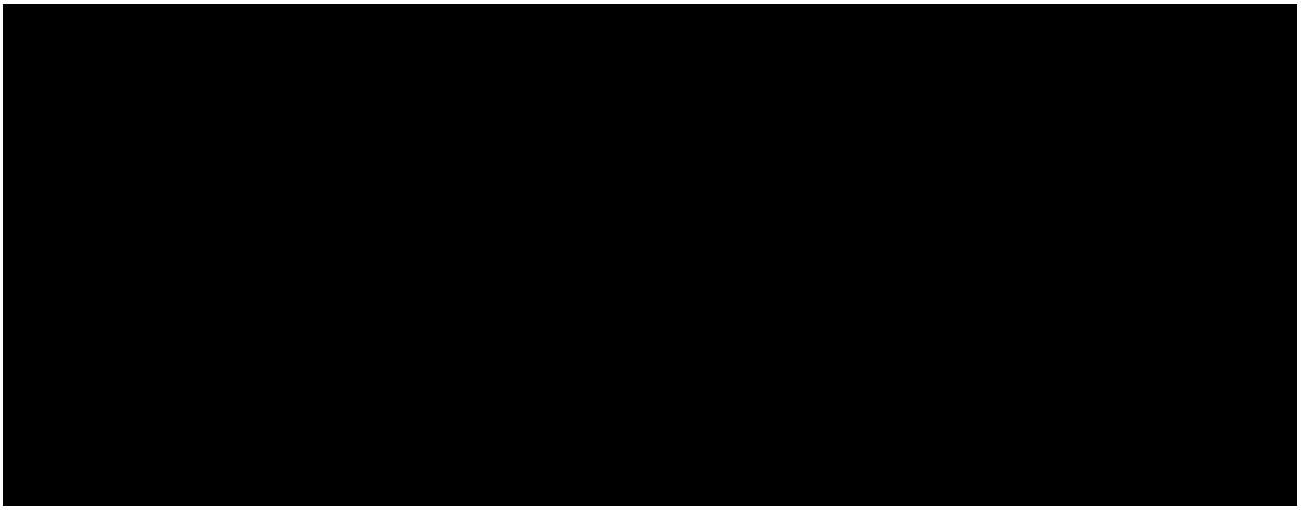
- Adverse events, Adverse drug reactions
- Serious adverse events, Serious adverse drug reactions
- Unexpected adverse events, Unexpected adverse drug reactions
- Unexpected serious adverse events, Unexpected serious adverse drug reactions

For all adverse events that have occurred, the number of cases by the following adverse event investigation items is presented. Additionally, the incidence status of adverse events by investigation item is presented in detail. Using the latest version of MedDRA, the number of cases of adverse events by SOC and PT will be included. At this time, even if two or more adverse events were expressed in one subject, if they fall under one category, they will be analyzed as one person within the category. In addition, one subject may be presented in duplicate in different adverse event categories.

- Severity of Adverse events
- Action taken with study drug due to Adverse events
- Recurrence according to reintroduced
- Causality
- Factor other than study drug
- Outcome of the event
- Therapy for the event

For the following categories, a list of events will be included:

- Serious adverse events
- Unexpected adverse events
- Unexpected serious adverse events
- Adverse events with Renal impairment
- Adverse events with Hepatic impairment



6.8.4 Adverse Events for Subjects Excluded from Safety Analysis Set

In accordance with section 3 of Chapter 3 in the ‘Guidelines for Re-examination of New Drugs, etc.’, the incidence status of adverse events in off-label use subjects is presented. However, those who were investigated in duplicate, those who did not receive this drug, or those who did not undergo follow-up for safety are excluded from this analysis.

For the following items, the incidence status of adverse events will be presented in a summary table. The summary table will include the number of subjects with adverse events and their incidence (%), 95% confidence interval for the incidence and the number of cases.

In addition, for the following items, the incidence status of adverse events is presented in detail. Using the latest version of MedDRA, the number of subjects with adverse events and their incidence (%) for each SOC and PT, 95% confidence interval for the incidence, and the number of cases will be included.

- Adverse events, Adverse drug reactions
- Serious adverse events, Serious adverse drug reactions
- Unexpected adverse events, Unexpected adverse drug reactions
- Unexpected serious adverse events, Unexpected serious adverse drug reactions

For the following categories, a list of events will be included:

- Serious adverse events
- Unexpected adverse events
- Unexpected serious adverse events
- Adverse events with Renal impairment
- Adverse events with Hepatic impairment

6.8.5 Other Safety Analyses

When reporting for re-examination, the following items will be categorized based on the incidence (%) by PT (Preferred Term), and information on SOC (System Organ Classes) and PT (Preferred Term) will be presented in a table.

- Serious adverse events, Serious adverse drug reactions
- Unexpected adverse events, Unexpected adverse drug reactions

At the time of reporting for re-examination, descriptive statistics of serum creatinine, glomerular filtration rate, and albumin-creatinine-ratio measured before administration of this drug and at the final visit are presented. In order to analyze whether there is a difference at the final visit compared to before administration of this drug, the paired t-test is used.

6.9 Effectiveness Evaluation

6.9.1 Effectiveness Assessment

For the effectiveness analysis set, descriptive statistics of glycated hemoglobin (HbA1c), [redacted] measured before administration of this drug and at the final visit are presented. In order to analyze whether there is a difference at the final visit compared to before administration of this drug, the paired t-test is used.

[redacted]

7. Derivation and Categorization for Variable

7.1 Derivation

The items that need to be calculated in this study are as follows, but the following matters may be considered.

- If an additional calculated variable related to the variables defined below is required during statistical analysis, SAP may not be revised, but the variable will be specified in TLFs.
- Depending on the data actually collected, the item units defined in SAP may change (Ex. duration of disease: months → years)

Age

- If the birthday has passed from the date of signing the consent form: (Year of signing the consent form – Year of birth)
- If the birthday has not passed since the date of signing the consent form: (Year of signing consent – Year of birth – 1)

Duration of disease (days)

- (Start date of initial dose of this drug – Date of diagnosis + 1)
- For continuous analysis, if the date is not complete, it is excluded from the analysis.
- For categorical analysis, if the diagnosis date is partially collected, it is analyzed according to the following rules.
  - If 'day' of the diagnosis date is missing: (Year & month of the start date of initial dose of this drug – Year & month of diagnosis date)
  - If there is only 'year' in the diagnosis date: (Year of the start date of initial dose of this drug – Year of the diagnosis date)

Total administration period of this drug (days)

- $\sum_{i=1}^{n}[(\text{End date of drug})_i - (\text{Start date of drug})_i + 1]$,
  i: The i^{th} administration period of the subject in the n times of administration period of this drug
- If the end date of the i^{th} dose is "in progress" or is missing, other than the end date of the last dose:
  - [(one day before start date of $i+1^{th}$ dose) – (dose start date) + 1]
- If the end date of the last dose is 'in progress' or missing, it is substituted in the following order.
  - [(Date of Last visit) – (Start date of drug) + 1]
  - [(Start date of drug) – (Start date of drug) + 1

Total dose of this drug (empagliflozin/metformin)(mg)

- $\sum_{i=1}^{n}[(\text{End date of drug})_i - (\text{Start date of drug})_i + 1]$ * Daily dose
  i: The i^{th} administration dose of the subject in the n times of administration dose of this drug

Average of daily dose drug (empagliflozin/metformin)(mg/days)

- Total dose(mg) / Total administration period (days)

7.2 Categorization

The categories for each item for categorical analysis are as follows. However, categories defined for categorical analysis of continuous data may be added or changed according to the distribution of the actually collected data.

Items	Category
• Children	< 19 years, ≥ 19 years
• Elderly	< 65 years, ≥ 65 years
• Pregnancy	Yes, No, Not Applicable
• Renal impairment	Yes, No
• Hepatic impairment	Yes, No
• Long-term follow-up	< 24 weeks,

Items	Category
	≥ 24 weeks
• Age	19 years ~ 29 years, 30 years ~ 39 years, 40 years ~ 49 years, 50 years ~ 59 years, ≥ 60 years
• Gender	Male, Female
• Smoking status	Never smoked, Ex-smoker, Currently smokes
• Family history of T2DM	Yes, No
• Disease period	< 1 year, 1 year ~ < 5 years, 5 years ~ < 10 years, ≥ 10 years
• Diabetes mellitus complications	Retinopathy, Neuropathy, Nephropathy, Vasculopathy, Etc.
• Medical history	Yes, No
• Allergy	Yes, No
• Renal failure	Yes, No
• Total administration period of JardianceDuo	< 12 weeks, 12 weeks ~ ≥ 24 weeks, ≥ 24 weeks
• Average of daily dose (Empagliflozin)	< 10 mg, 10 mg ~ ≥ 25 mg, ≥ 25 mg
• Average of daily dose (Metformin)	< 1,000 mg, 1,000 mg ~ ≥ 1,700 mg, 1,700 mg ~ ≥ 2,000 mg, ≥ 2,000 mg
• Other anti-diabetic agent	Yes, No
• Concomitant medications	Yes, No
• Discontinuation of study medication	Yes, No
• Severity	Mild, Moderate, Severe
• Serious AE	Yes, No
• SAE Category	Results in death, Immediately life-threatening, Persistent or significant disability/ incapacity, Requires patient hospitalization, Prolongs patient hospitalization, Congenital anomaly/ birth defect, Other comparable medical criteria
• Action taken	Continue, Reduced, Discontinued, Increased, discontinued and reintroduced, Unknown, Not applicable
• Recurrence according to reintroduced	Recurrence, No-recurrence, Unknown,

Items	Category
	Not applicable
• Causality	Certain, Probable/Likely, Possible, Unlikely, Conditional / Unclassified, Unassessable / Unclassifiable
• Factors other than JARDIANCE DUO	None, Concomitant medication, Concomitant diagnoses, Other
• Outcome	Recovered, Not yet recovered, Sequelae, Fatal, Unknown
• Therapy for the event	Yes, No
[redacted]	
• Effectiveness	Effectiveness, Ineffectiveness