STATISTICAL ANALYSIS PLAN

Study Title

A regulatory requirement non-interventional study to monitor the safety and effectiveness of Esgliteo (empagliflozin/linagliptin, 10/5mg, 25/5mg) in Korean patients with type 2 diabetes mellitus

Protocol No./Version/Date

1275-0028/4.0/2022.05.23 (Kor.)

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Prepared by

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STATISTICAL ANALYSIS PLAN

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STATISTICAL ANALYSIS PLAN

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VERSION INFORMATION (DOCUMENT REVISION HISTORY)

Version	Date	Prepared by	Details
1.0	20-SEP-2022	[redacted]	First Version
2.0	19-APR-2023		[6.3 HANDLING OF DERIVED VARIABLES] - 'Total period of drug use(days)', '10/5mg, 25/5mg Sum of total period of drug use(days)': Correcting typos - 'Total number of administrations': Adding description [8.5 SUMMARY OF ADVERSE EVENTS FOR SUBJECTS NOT TREATED ACCORDING TO THE APPROVED LABEL] - Deleted the contents for analysis of 'subjects excluded from safety set' and added contents for analysis of 'subjects not treated according to the approved label'.

ABBREVIATION

Term	Definition
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ANOVA	Analysis of variance
DB	Database
DBP	Diastolic blood pressure
FPG	Fasting plasma glucose
HbA1c	Glucosylated hemoglobin
MedDRA	Medical dictionary for drug regulatory activities
MFDS	Ministry of food and drug safety
NIS	Non-interventional Study
OC	Observed case
PMS	Post-market surveillance
PT	Preferred term
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
T2DM	Type 2 diabetes mellitus
UADR	Unexpected adverse drug reaction
UAE	Unexpected adverse events
VIF	Variance Inflation factor
WHO ATC index	World health organization anatomical therapeutic chemical index

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STATISTICAL ANALYSIS PLAN

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STATISTICAL ANALYSIS PLAN

1. INTRODUCTION

The purpose of this statistical analysis plan(SAP) 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's guidelines (2021.11) for final analysis of <1275-0028, 4.0, A regulatory requirement non-interventional study (NIS) to monitor the safety and effectiveness of Esgliteo (empagliflozin/linagliptin, 10/5mg, 25/5mg) in Korean patients with type 2 diabetes mellitus (T2DM), 2022.05.23>,. The table shell and list, 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.

2. STUDY OVERVIEW

2.1 STUDY OBJECTIVE

2.1.1 Primary objective

The primary objective of this study is to monitor the safety profile of Esgliteo in Korean patient with T2DM in a routine clinical setting.

2.1.2 Secondary objective

The secondary objective of this study is to monitor the effectiveness of Esgliteo by evaluation of the change from baseline after 12 weeks and/or 24 weeks in the glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG), body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP) and the final effectiveness evaluation at the end of the last visit in Korean T2DM patients.

2.2 STUDY SIZE

The sample size of 600 patients is based on the requirement of the local regulatory authority, Ministry of Food & Drug Safety (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 MILESTONES

In accordance with local regulation for NIS, interim analyses are planned biannually for the initial two years and annually thereafter.
As per regulation, the re-examination period extends from 31 March 2017 until 30 March 2023. However, active enrolment is to be initiated in 2021 before finalizing the re-imbursement agreement with the authority. Actual study period will be for about 2 years.

Table 1 Milestones

Milestone	Planned Date
Start of data collection	30 Oct 2021
End of data collection	30 Nov 2022
Interim report	30 May 2022
Final report of study results:	30 Jun 2023

3. STUDY POPULATION

A total of 600 patients will be enrolled at approximately 20 sites by as many as 20 or more NIS physicians. To minimize the selection bias, consecutive patients from each site who meet inclusion criteria will be enrolled in this study.

3.1 MAIN DIAGNOSIS FOR STUDY ENTRY

Patients diagnosed with T2DM in Korea. Esgliteo is indicated as an adjunct to diet and exercise to improve glycemic control in patients with T2DM who are appropriate to take a combination of empagliflozin and linagliptin.

3.2 INCLUSION CRITERIA

- Patients who have started at first time on Esgliteo in accordance with the approved label in Korea
- Age ≥19 years at enrolment
- Patients who have signed on the data release consent form

3.3 EXCLUSION CRITERIA

- Patients with previous exposure to Esgliteo
- Patients with hypersensitivity to the empagliflozin and/or linagliptin or any of the excipients
- Patients with type 1 diabetes or diabetic ketoacidosis
- Patients with eGFR < 45 mL/min/1.73m^2, end stage renal disease, or patient on dialysis
- Patients for whom empagliflozin/linagliptin is contraindicated according to the local label of Esgliteo

3.4 SUBJECTS OF SPECIAL INVESTIGATION

Among the patients who have signed on the data release consent form and the patients who conducted investigation for safety assessment after the administration of Esgliteo, subjects of special investigation (geriatric population (65 years or more), pregnant women, renal impairment, hepatic impairment and other special population, long-term use etc.) will be analyzed.

4. COMPOSITION OF SUBJECTS

A total of 600 patients will be entered in this study, and each patient will be followed for total three times (baseline, short term 12 weeks follow up, Long-term 24 weeks follow up). Since T2DM is chronic disease it might be too restrictive to collect safety and effectiveness data in short-term (12 weeks) period, all patients will be enrolled for long-term (24 weeks) surveillance.

4.1 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 Esgliteo once at least.

4.2 SAFETY SET

These include those who signed the data release consent form to participate in this study as subject, took Esgliteo once at least, and were followed up by the physician once or more. Reflecting MFDS guideline, the cases below shall be excluded from safety analysis set (defined below) in the following order:

a. Cases not signed or signed on the data release consent form of Esgliteo post-market surveillance (PMS) prior to the contract date
b. Cases administrated Esgliteo prior to the contract date
c. Cases administrated Esgliteo prior to the signed on the data release consent form
d. Not administrated an Esgliteo
e. Follow-up failure: Patients whose safety information cannot be obtained due to follow-up loss
f. Violation of efficacy·effectiveness, Dosage
g. Dual registration
h. Violation of Inclusion/Exclusion criteria

4.3 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 Esgliteo once at least, and were evaluated for the effectiveness.
Reflecting MFDS's guideline, the cases below shall be excluded from effectiveness analysis (defined below) set in the following order.

a. Cases excluded from safety set
b. Cases with missing information of effectiveness assessment
c. Cases omitted in final effectiveness evaluation
d. Cases whose final effectiveness evaluation was found to be 'Unassessable'

4.4 LONG-TERM SAFETY SET

Long-term safety set will include safety set who took Esgliteo for 24 weeks or more and include cases followed up at 24 weeks or more after the date of first Esgliteo administration.

4.5 LONG-TERM EFFECTIVENESS SET

Among long-term safety set, the cases below shall be excluded from long-term effectiveness set.

a. Cases excluded from long-term safety set
b. Cases with missing information of effectiveness assessment
c. Cases omitted in final effectiveness evaluation

d. Cases whose final effectiveness evaluation was found to be 'Unassessable'

4.6 SUBJECTS OF SPECIAL INVESTIGATION

Subjects of special investigation include geriatric population (65 years or more), pregnant women, patients with renal impairment, patients with hepatic impairment, long-term use of Esgliteo (24 weeks or more) among the subjects who conducted investigation for safety assessment after the Esgliteo administration.

5. GENERAL ANALYSIS CONSIDERATIONS

5.1 STATISTICAL ANALYSIS SOFTWARE

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

5.2 GENERAL CONSIDERATIONS

Continuous variables will be summarized with number of subjects, means, standard deviation (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 all tests. 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, and the percentage, confidence interval, and Odd ratio are presented in two decimal places (rounded from the third position). However, duration of disease, total administration period, and the average number of administrations per day are presented by 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.

6. DATA HANDLING CONVENTIONS

6.1 HANDLING OF MISSING DATA

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

6.2 HANDLING OF MISSING DATES

If there are missing dates which are needed in calculations, they will be imputed as described in the following.

If date of last safety assessment is missing when processing missing values on end date of administration of Esgliteo, it is replaced with date of last visit.

Table 2 Handling of missing dates

Types of Dates	Missing	Imputation	Examples
Diagnosed date	DD	01	Collected date: 2021-12-UK Imputed date: 2021-12-01
End date of Esgliteo administration	DD	1. [Year-Month] is the same as date of last safety assessment [Year-Month]: date of last safety assessment [Day] 2. [Year-Month] is different from date of last safety assessment [Year-Month]: 31	1. Date of last safety assessment: 2021-12-21 Collected date: 2021-12-UK Imputed date: 2021-12-21 2. Date of last safety assessment: 2021-12-21 Collected date: 2021-11-UK Imputed date: 2021-11-31
Start date of other anti-diabetic agent/	MM-DD	01-01	Collected date: 2021-UK-UK Imputed date: 2021-01-01
Prior/concomitant medications administration	DD	01	Collected date: 2021-12-UK Imputed date: 2021-12-01
End date of other anti-diabetic agent/	MM-DD	12-31	Collected date: 2021-UK-UK Imputed date: 2021-12-31
Prior/concomitant	DD	Last [day] of the month	Collected date: 2021-12-UK

Types of Dates	Missing	Imputation	Examples
medications administration			Imputed date: 2021-12-31

6.3 HANDLING OF DERIVED VARIABLES

The baseline is considered to be the start date of the first administration of Esgliteo and the baseline value is defined as the last value measured before the first administration.

Derivation/imputation of variables will be performed as in the following.

Table 3 Derived variables

Variable	Derivation Method
Change from baseline	Post-baseline value – Baseline value
Age group	Less than 19 years 19 years or older and less than 30 years 30 years or older and less than 40 years 40 years or older and less than 50 years 50 years or older and less than 60 years 60 years or older
Duration of disease (years)	(Date of data release consent – Diagnosed date) / 365.25
Geriatric population	65 years or older, Less than 65 years
Total period of drug use(days)	End date of Esgliteo final administration – Start date of Esgliteo first administration+1 If [Continuing] is checked on CRF [DISPENSING OF ESGLITEO] page, end date of Esgliteo final administration will be replaced with date of last safety assessment, and if date of last safety assessment is missing, it is replaced with date of last visit.
10/5mg, 25/5mg Sum of total period of drug use(days)	Sum of ((End date of Esgliteo administration - Start date of Esgliteo administration +1) per duration of visit) If [Continuing] is checked on CRF [DISPENSING OF ESGLITEO] page, end date of Esgliteo final administration will be replaced with date of last safety assessment, and if date of last safety assessment is missing,

Variable	Derivation Method
	it is replaced with date of last visit.
Total number of administrations	Sum of (Administration frequency[1]×period of drug use) per duration of visit [1] QD: Once a day, BID: Twice a day, TID: Three times a day, QID: Four times a day, PRN: Whenever necessary But, the value collected with PRN is excluded from analysis.
Average number of administrations per day	Total number of administrations / Total period of drug use
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 date of last safety assessment, and if date of last safety assessment is missing, it is replaced with date of last visit, and will mark ≥ (e.g. ≥15).
Onset duration of AE	AE onset date – Date of first Esgliteo administration
Less than 7% of HbA1c	yes: HbA1c < 7% no: HbA1c ≥ 7%
Decreased by at least 0.5% of HbA1c	yes: HbA1c measurements at baseline – HbA1c measurements after baseline ≥ 0.5% no: HbA1c measurements at baseline – HbA1c measurements after baseline < 0.5%

6.4 DEFINITION OF ANALYSIS VISIT

Analysis visits for effectiveness set are defined as follows.

If more than one visit result exists in the visit 2 analysis acceptance range, the results closer to the planned visit in protocol are considered as the visit result and the visit result(e.g. -3 days) investigated previously is included in the analysis if the absolute value of the visit day difference is the same (e.g. -3 days, +3 days).

If more than one visit result exists in the visit 3 analysis visit acceptance range, the visit result with a larger visit date interval is included in the analysis.

Table 4 Definition of analysis visit

Analysis visit	Period	Visit window (day)	Analysis acceptance range (day)
Baseline	1		
Visit 2	84	+83	84 ≤ Visit 2-Baseline+1 < 168
Visit 3	168		168 ≤ Visit 3-Baseline+1

6.5 HOW TO HANDLE DATA ERRORS AFTER DB LOCK

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

7. SUBJECT INFORMATION

7.1 STUDY PERIOD AND NUMBER OF SUBJECTS

The study year and study period 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.

7.2 POST-MARKET SURVEILLANCE TABLES

The study sites and study Principal Investigator 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.

7.3 SUBJECT CHARACTERISTICS

Subject characteristics will be performed on safety set.

7.3.1 Demographics

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

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

7.3.2 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, and the categorical variables will be summarized using number of subjects and percentages.

- Continuous variable: Duration of disease (years)
- Categorical variable: Family history of T2DM, Previous allergy, Diabetes mellitus complications (Retinopathy, Neuropathy, Nephropathy, Vasculopathy, Other), Medical history, Comorbidities, Prior/Concomitant medication, Other anti-diabetic agent

7.3.3 Subjects of special investigation

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

- Geriatric population (65 years or more, Less than 65 years)
- Pregnant women (Yes, No, Not applicable)
- Renal impairment (Yes, No)
- Hepatic impairment (Yes, No)
- Long-term use (24 weeks or more)

7.3.4 Medical history and comorbidities

Previous medical history is defined as those that are blanked for the question “Ongoing” under [Medical History] page of the CRF, and comorbidities are defined as those that are checked “1” for the same question.

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

7.3.5 Prior and concomitant medication

Prior medication is defined as any medication that the subjects took before the first dose of Esgliteo. Concomitant medication is defined as any medication that the subjects took on or after the first dose of Esgliteo.

Prior medication is any medication that can be classified into the following category.

- Medication start date ＜ Start date of first Esgliteo administration

Concomitant medication is any medication that can be classified into the following category.

- Medication start date ≥ Start date of first Esgliteo administration

Table 5 Examples of categorization

Medication start date	Medication end date	Date of first Esgliteo 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

If there is a missing date, Prior/concomitant medication is classified by processing according to [6.2 Handling of Missing Dates].

Prior and concomitant medications will be summarized with number of subjects, percentages and number of cases. Prior and concomitant medications will be coded using the World Health Organization Anatomical Therapeutic Chemical index (WHO ATC index) latest version and

will be summarized with Level 1 (anatomical main group) and Level 5 (chemical substance) using number of subjects, percentages and number of cases. However, if level 5 is 'Combinations', 'Various' or 'various combinations', then level 4 will be used instead. (If level 5 doesn't exist then a higher level will be used.) The frequency is counted as one person in each classification (Subjects investigated with prior and concomitant medication, level 1 and level 5) even if one subject has multiple prior/concomitant medications.

7.3.6 Other anti-diabetic agent

Subjects who used other anti-diabetic agent during the study will be summarized with number of subjects, percentages and number of cases and will be coded using the World Health Organization Anatomical Therapeutic Chemical index (WHO ATC index) latest version and will be summarized with Level 1 (anatomical main group) and Level 5 (chemical substance) using number of subjects, percentages and number of cases. However, if level 5 is 'Combinations', 'Various' or 'various combinations', then level 4 will be used instead. (If level 5 doesn't exist then a higher level will be used.) The frequency is counted as one person in each classification even if one subject use multiple other anti-diabetic agent.

7.4 ESGLITEO ADMINISTRATION STATUS

Total period of drug use, Total number of administrations, Average number of administration per day will be summarized using number of subjects, mean, SD, median, minimum, maximum, 5th percentile and 95th percentile.
In addition, the frequency and percentage of reasons for early interruption are presented when the subjects prematurely withdraw the study.

8. 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.

An 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.

ADR is defined as the case where the causal relationship with Esgliteo evaluated by the investigator falls under the following.

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

The following Aes are defined as serious adverse event (SAE).

- 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 medical criteria

Unexpected adverse event (UAE) means any adverse event not listed in the permit.

Adverse events of special interest (AESI) refer to any of the following cases.

- Hepatic injury
  - 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)
- Decreased renal function
  - Creatinine value shows a >2-fold increase from baseline and is above the ULN
- Metabolic acidosis, ketoacidosis and diabetic ketoacidosis (DKA)
- 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)

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).

Adverse events leading to discontinuation refers to all adverse events in which action taken with study drug due to AE is 'Drug withdrawn'.

8.1 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 and 95% exact confidence intervals.

- AE
- ADR
- SAE
- Serious adverse drug reaction (SADR)

- UAE
- Unexpected adverse drug reaction (UADR)
- Non-serious adverse drug reaction
- AESI
- Adverse events leading to discontinuation

8.2 ANALYSES OF ADVERSE EVENTS

The following types of AEs will be coded with MedDRA 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.

- AE/ADR
- SAE/SADR
- UAE/UADR
- Non-serious adverse drug reaction
- AESI
- Adverse events leading to discontinuation
- AE classified by Outcome of the event
- AE classified by Therapy for the event
- AE classified by Action taken with Esgliteo
- AE classified by Intensity
- AE classified by Causal relationship

In the analysis for re-examination application, the following AEs of rare (less than 0.1%) or occasional (less than 0.1%~5%) occurrence will be coded with MedDRA 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.

- SAE/SADR
- UAE/UADR

8.3 SAFETY ANALYSES BY FACTORS

8.3.1 Univariate analysis

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. (However, if [Diabetes mellitus complications] responds with [Not applicable], [Pregnancy] responds with [Not applicable], [Height] responds with [Not done], it is excluded from Pearson′s chi-square test or Fisher′s exact test.)

- Gender (Male, Female)
- Smoking status (Never smoked, Ex-smoked, Currently smokes)
- Family history of T2DM (Yes, No)
- Previous allergy (Yes, No)
- Diabetes mellitus complications (Retinopathy, Neuropathy, Nephropathy, Vasculopathy, Other) (Yes, No, Not applicable)
- Medical history (Yes, No)
- Comorbidities (Yes, No)
- Prior medication (Yes, No)
- Concomitant medication (Yes, No)
- Other anti-diabetic agent (Yes, No)

For the following continuous variables AE Occurrence will be summarized using odds ratio and 95% confidence interval for an increase or decrease per defined unit of the variable based on using simple logistic regression.

- Age (years)
- Height (cm)
- Weight (kg)

- Duration of disease (years)
- Total period of drug use (days)
- Total number of administrations
- Average number of administration per day

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-squire test or Fisher's exact test to confirm statistically significant differences.

- Geriatric population (65 years or more, Less than 65 years)
- Pregnant women (Yes, No, Not applicable)
- Renal impairment (Yes, No)
- Hepatic impairment (Yes, No)
- Long term use (24 weeks or more)

8.3.2 Multivariable analysis

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.

8.4 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 exact 95% confidence intervals. The details of AEs for each subject of special investigation will also be presented in a listing.

- AE
- ADR
- SAE
- SADR
- UAE
- UADR
- Non-serious adverse drug reaction
- AESI
- Adverse events leading to discontinuation

8.5 SUMMARY OF ADVERSE EVENTS FOR SUBJECTS NOT TREATED ACCORDING TO THE APPROVED LABEL

The following types of AEs for each subject who is treated with Esgliteo beyond the scope of approved label will be summarized with the number of subjects and proportion of the number of subjects with AE and exact 95% confidence intervals. The details of AEs for the subjects will also be presented in a listing.

- AE
- ADR
- SAE
- SADR
- UAE
- UADR
- Non-serious adverse drug reaction
- AESI
- Adverse events leading to discontinuation

8.6 SUMMARY OF ADVERSE EVENTS FOR LONG-TERM SAFETY SET

The following types of AEs for Long-term safety set will be summarized with the number of

subjects and proportion of the number of subjects with AE and exact 95% confidence intervals.

- AE
- ADR
- SAE
- SADR
- UAE
- UADR
- Non-serious adverse drug reaction
- AESI
- Adverse events leading to discontinuation

8.7 ANALYSES OF ADVERSE EVENTS FOR LONG-TERM SAFETY SET

The following types of AEs for Long-term safety set will be coded with MedDRA 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. The details of SAEs will also be presented in a listing.

- AE/ADR
- SAE/SADR
- UAE/UADR
- Non-serious adverse drug reaction
- AESI
- Adverse events leading to discontinuation

9. EFFICACY ANALYSIS

Efficacy analyses will be performed on Effectiveness set.

9.1 PRIMARY ENDPOINT

For HbA1c, the changes from baseline to 12 and 24 weeks will be summarized using number of subjects, mean, SD, median, minimum, maximum, 5th percentile and 95th percentile, and will be compared using paired t-test.

9.2 SECONDARY ENDPOINTS

1) The frequency, percentage and 95% confidence interval of the changes from baseline to 12 and 24 weeks will be summarized for patients who had HbA1c reaching less than 7% (target effectiveness response rate).
2) The frequency, percentage and 95% confidence interval of the changes from baseline to 12 and 24 weeks will be summarized for patients whose HbA1c was decreased by at least 0.5% at the last visit (relative effectiveness response rate).
3) For FPG, Weight, SBP and DBP, the changes from baseline to 12 and 24 weeks will be summarized using number of subjects, mean, SD, median, minimum, maximum, 5th percentile and 95th percentile, and will be compared using paired t-test.
4) Mean difference in the change of HbA1c from baseline to latest value according to following variables will be analyzed using t-test or ANOVA (Analysis of Variance).

- Age group (Less than 19 years, 19 years or older and less than 30 years, 30 years or older and less than 40 years, 40 years or older and less than 50 years, 50 years or older and less than 60 years, 60 years or older)
- Gender (Male, Female)
- Height (<median, ≥median)
- Weight (<median, ≥median)
- Smoking status (Never smoked, Ex-smoked, Currently smokes)
- Duration of disease (<median, ≥median)
- Family history of T2DM (Yes, No)
- Previous allergy (Yes, No)
- Diabetes mellitus complications (Retinopathy, Neuropathy, Nephropathy, Vasculopathy, Other) (Yes, No, Not applicable)
- Medical history (Yes, No)

- Comorbidities (Yes, No)
- Prior medication (Yes, No)
- Concomitant medication (Yes, No)
- Other anti-diabetic agent (Yes, No)
- Geriatric population (65 years or more, Less than 65 years)
- Pregnant women (Yes, No, Not applicable)
- Renal impairment (Yes, No)
- Hepatic impairment (Yes, No)
- Long-term use (24 weeks or more)
- Total period of drug use (<median, ≥median)
- Total number of administration (<median, ≥median)
- Average number of administration per day (<median, ≥median)
- Reasons for early interruption (Change to other antidiabetics, Consent withdrawal, Adverse events, Patient refusal to continue taking study medication, Follow up loss, Others)

9.3 THE FINAL EFFECTIVENESS EVALUATION

For the final effectiveness evaluation, the three items ([Improved, Unchanged, Aggravated]) evaluated at the end of the last visit will be summarized using number of subjects, percentage, 95% confidence intervals. In addition, if final effectiveness is evaluated as [Improved], it is classified as [Efficacy]. And If final effectiveness is evaluated as [Unchanged, Aggravated], it is classified as [Inefficacy].

9.4 UNIVARIATE ANALYSIS

The following categorical variables will be summarized using number of subjects, number of efficacy, efficacy rate and 95% confidence interval. Efficacy will be analyzed using Pearson′s chi-square test or Fisher′s exact test to determine if statistically significant differences exist. (However, if [Diabetes mellitus complications] responds with [Not applicable], [Pregnancy]

responds with [Not applicable], [Height] responds with [Not done], it is excluded from Pearson′s chi-square test or Fisher′s exact test.)

- Gender (Male, Female)
- Smoking status (Never smoked, Ex-smoked, Currently smokes)
- Family history of T2DM (Yes, No)
- Previous allergy (Yes, No)
- Diabetes mellitus complications (Retinopathy, Neuropathy, Nephropathy, Vasculopathy, Other) (Yes, No, Not applicable)
- Medical history (Yes, No)
- Comorbidities (Yes, No)
- Prior medication (Yes, No)
- Concomitant medication (Yes, No)
- Other anti-diabetic agent (Yes, No)

The following continuous variables will be summarized using number of subjects. Efficacy 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)
- Total period of drug use (days)
- Total number of administrations
- Average number of administration per day

Subjects of special investigation will be summarized using number of subjects, number of efficacy, efficacy rate and 95% confidence interval. Efficacy will be analyzed by using Pearson's chi-square test or Fisher's exact test to determine if statistically significant differences

exist.

- Geriatric population (65 years or more, Less than 65 years)
- Pregnant women (Yes, No, Not applicable)
- Renal impairment (Yes, No)
- Hepatic impairment (Yes, No)
- Long-term use (24 weeks or more)

9.5 MULTIVARIABLE ANALYSIS

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 per 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 multivariate logistic regression model.

9.6 PRIMARY ENDPOINT FOR LONG-TERM EFFECTIVENESS SET

The change from baseline after 12 weeks and/or 24 weeks in HbA1c will be summarized using number of subjects, mean, SD, median, minimum, maximum, 5th percentile, 95th percentile, and will be compared using paired t-test.

9.7 SECONDARY ENDPOINTS FOR LONG-TERM EFFECTIVENESS SET

1) The frequency, percentage and 95% confidence interval of the changes from baseline to 12 and 24 weeks will be summarized for Long-term effectiveness set who had HbA1c reaching less than 7% (target effectiveness response rate).
2) The frequency, percentage and 95% confidence interval of the changes from baseline to 12 and 24 weeks will be summarized for Long-term effectiveness set whose HbA1c was decreased by at least 0.5% at the last visit (relative effectiveness response rate).
3) For FPG, Weight, SBP and DBP, the changes from baseline to 12 and 24 weeks 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.

4) Mean difference in the change of HbA1c according to following variables will be analyzed for Long-term effectiveness set using t-test or ANOVA (Analysis of Variance).

- Age group (Less than 19 years, 19 years or older and less than 30 years, 30 years or older and less than 40 years, 40 years or older and less than 50 years, 50 years or older and less than 60 years, 60 years or older)
- Gender (Male, Female)
- Height (<median, ≥median)
- Weight (<median, ≥median)
- Smoking status (Never smoked, Ex-smoked, Currently smokes)
- Duration of disease (<median, ≥median)
- Family history of T2DM (Yes, No)
- Previous allergy (Yes, No)
- Diabetes mellitus complications (Retinopathy, Neuropathy, Nephropathy, Vasculopathy, Other) (Yes, No, Not applicable)
- Medical history (Yes, No)
- Comorbidities (Yes, No)
- Prior medication (Yes, No)
- Concomitant medication (Yes, No)
- Other anti-diabetic agent (Yes, No)
- Geriatric population (65 years or more, Less than 65 years)
- Pregnant women (Yes, No, Not applicable)
- Renal impairment (Yes, No)
- Hepatic impairment (Yes, No)
- Total period of drug use (<median, ≥median)
- Total number of administration (<median, ≥median)
- Average number of administration per day (<median, ≥median)

- Reasons for early interruption (Change to other antidiabetics, Consent withdrawal, Adverse events, Patient refusal to continue taking study medication, Follow up loss, Others)

9.8 THE FINAL EFFECTIVENESS EVALUATION FOR LONG-TERM EFFECTIVE-NESS SET

For the final effectiveness evaluation, the three items ([Improved, Unchanged, Aggravated]) at the time of week 24 will be summarized for Long-term effectiveness set using number of subjects, percentage, 95% confidence intervals. In addition, if final effectiveness is evaluated as [Improved], it is classified as [Efficacy]. And If final effectiveness is evaluated as [Unchanged, Aggravated], it is classified as [Inefficacy].

10. APPENDIX

10.1 APPENDIX 2

Appendix 2 will be prepared for the Use Result Surveillance. The number of subjects whose CRF was retrieved, safety set, effectiveness set by year of the study will be presented. The number of subjects excluded from the safety evaluation, efficacy evaluation and their specific reasons will be presented.

10.2 APPENDIX 3

ADR collected in use result surveillance will be summarized using the 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, SADRs, Not SAEs, Not SADRs collected from use result surveillance, special study (Pharmacoepidemiology study, etc.), clinical trials and Spontaneous reporting will be coded with MedDRA and will be summarized with SOC and PT using the number of subjects and proportion of the number of subjects with AE.

10.3 APPENDIX 5

SAEs, SADRs, UADRs collected from use result surveillance, special study (Pharmacoepidemiology study, etc.), clinical trials and Spontaneous reporting will only be presented for Re-examination according to the format

10.4 DETAILS OF SAES LEADING TO DEATH

The details of Serious AEs leading to death collected from use result surveillance, special study (Pharmacoepidemiology study, etc.), clinical trials and Spontaneous reporting will be presented in a listing.

10.5 DETAILS OF SERIOUS UNEXPECTED AEs

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

11. Changes to the planned analysis method

In the 9.7.1 demographic analysis item of Protocol (version 4.0), it is described that the administration status of this drug (average daily dose) is analyzed, but since Esgliteo is a composite, the average number of administrations per day will be analyzed.

12. SAS program code

The following SAS program codes will be used.

Table 6 SAS program code

Analysis method	SAS program code
Pearson's chi-square test or Fisher's exact test	PROC FREQ DATA=dataset; TABLE ae*factor/CHISQ EXACT; RUN;
Paired t-test	PROC UNIVARIATE DATA=dataset; VAR diff;

Analysis method	SAS program code
	RUN;
t-test	PROC TTEST DATA=dataset; CLASS factor; VAR chg; RUN;
ANOVA	PROC MIXED DATA=dataset; CLASS treatment; MODEL variable=treatment; LSMEANS treatment / PDIFF CL; RUN;
Simple logistic regression	PROC LOGISTIC DATA=dataset; CLASS factor; MODEL ae=factor; RUN;
Multiple logistic regression	PROC LOGISTIC DATA=dataset; CLASS factor1 factor2 factor3; MODEL ae= factor1 factor2 factor3 factor4; RUN;

13. TABLE SHELLS

The following are the lists of tables for this study.

Table 7 List of Tables

Table Number	Table Description
A1	Study period and number of subjects
A2	Post-Market Surveillance tables
B1	Demographics
B2	Disease information

Table Number	Table Description
B3	Subjects of special investigation
B4	Medical history
B5	Comorbidities
B6	Prior medication
B7	Concomitant medication
B8	Other anti-diabetic agent
B9	Esgliteo administration status
C1	Summary of AEs
C2	Frequency of AEs and ADRs
C3	Frequency of SAEs and SADRs
C4	Frequency of UAEs and UADRs
C5	Frequency of non-serious adverse drug reaction
C6	Frequency of AESI
C7	AEs leading to discontinuation
C8	Details of SAEs
C9	AE classified by Outcome of the event
C10	AE classified by Therapy for the event
C11	AE classified by Action taken with Esgliteo
C12	AE classified by Intensity
C13	AE classified by Causal relationship
C14	SAEs and SADRs by frequency of occurrence
C15	UAEs and UADRs by frequency of occurrence
C16	Status of AEs by subject characteristics – categorical variables
C17	Status of AEs by subject characteristics – continuous variables
C18	Status of AEs for subjects of special investigation
C19	Status of AEs by subjects of special investigation – Multivariable analysis
C20	Summary of AEs for subjects of special investigation
C21	Details of AEs for subjects of special investigation
C22	Summary of AEs for subjects who are not treated according to the approved label

Table Number	Table Description
C23	Details of AEs for subjects who are not treated according to the approved label
C24	Summary of AEs for subjects of long term safety set
C25	Frequency of AEs and ADRs for long term safety set
C26	Frequency of SAEs and SADRs for long term safety set
C27	Frequency of UAEs and UADRs for long term safety set
C28	Frequency of non-serious adverse drug reaction for long term safety set
C29	Frequency of AESI for long term safety set
C30	Frequency of AEs leading to discontinuation for long term safety set
C31	Details of SAEs for long term safety set
D1	Main outcome – the change of HbA1c from baseline
D2	Other outcome – HbA1c reaching less than 7% (target effectiveness response rate) from baseline
D3	Other outcome – HbA1c decreased by at least 0.5% at the last visit(relative effectiveness response rate)
D4	Other outcome – the change of FPG, Weight, SBP, DBP from baseline
D5	Other outcome – the change of HbA1c from baseline by subject characteristics
D6	The final effectiveness evaluation
D7	The final effectiveness evaluation by subject characteristics – categorical variables
D8	The final effectiveness evaluation by subject characteristics – continuous variables
D9	The final effectiveness evaluation for subjects of special investigation
D10	The final effectiveness evaluation by subject characteristics – multivariable analysis
D11	Main outcome for long term effectiveness set – the change of HbA1c from baseline
D12	Other outcome for long term effectiveness set – HbA1c reaching less than 7% (target effectiveness response
D13	Other outcome for long term effectiveness set – HbA1c decreased by at least 0.5% at the last visit (relative effectiveness response rate)
D14	Other outcome for long term effectiveness set – the change of FPG, Weight, SBP, DBP from baseline

Table Number	Table Description
D15	Other outcome for long term effectiveness set – the change of HbA1c from baseline by subject characteristics
D16	The final effectiveness evaluation for long term effectiveness set

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Signing Complete	Security Checked	4/19/2023 4:16:02 PM
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