Non-Interventional Study (NIS) Protocol

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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
Brief lay title:	Esgliteo PMS in Korean patients with type 2 diabetes mellitus
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Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	[redacted]
Joint PASS:	Not applicable

Research question and objectives:	To monitor the safety profile and effectiveness of Esgliteo in Korean patients with type 2 diabetes mellitus in a routine clinical practice setting
Country(-ies) of study:	South Korea
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Marketing authorisation holder(s):	[redacted]
MAH contact person:	[redacted]
EU-QPPV:	[redacted]
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2. LIST OF ABBREVIATIONS

ACR	Albumin Creatinine Ratio
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CA	Competent Authority
CCDS	Company Core Data Sheet
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
HbA1c	Glucosylated Hemoglobin
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
KIMS	Korea Index of Medical Specialties
LPVM	Local PV Manager
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	The Ministry of Food and Drug Safety
NCE	New Chemical Entity

NIS	Non-Interventional Study
NSADR	Non Serious Adverse Drug Reaction
OPU	Operative Unit
PASS	Post-Authorization Safety Study
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGLT2	Sodium-dependent Glucose Co-transporter 2
SOP	Standard Operating Procedure
T2DM	Type 2 Diabetes Mellitus
TCM	Trial Clinical Monitor
TMF	Trial Master File

3. RESPONSIBLE PARTIES

Boehringer Ingelheim (BI) has appointed a Trial Clinical Monitor (TCM), responsible for coordinating all required activities, in order to

- manage the study in accordance with applicable regulations and internal standard operating procedures (SOPs).
- direct the study team in the preparation, conduct, and reporting of the trial,
- order the materials as needed for the study,
- ensure appropriate training and information of Local Clinical Monitors (CMLs), Clinical Research Associate (CRAs), and Investigators of participating countries.

Data Management and Statistical Evaluation will be done by CRO according to CRO's SOPs.

The organization of the study in the participating countries will be done by the respective local BI- operative unit (OPU) or by a Contract Research Organization (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the study. In each local BI OPU participating in this study, a CML will be appointed responsible for coordinating the activities required in order to manage the study in accordance with applicable regulations and internal SOPs in the countries covered by the respective BI OPU. On-site monitoring will be performed by BI or a CRO appointed by BI.

An Investigator Site File (ISF) containing all relevant study related documentation will be maintained according to local regulations and BI SOPs at each study site. A copy of the ISF documents will also be kept as an electronic Trial Master File (TMF) at BI according to BI SOPs. Documents related to participating physician and other important participants, especially their curricula vitae, will be filed in the TMF.

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: ESGLITEO®.			
Name of active ingredient: empagliflozin/linagliptin			
Protocol date: 26 Apr2021	**Study number:** 1275-0028	**Version/Revision:** 5.0	**Version/Revision date:** 28 Oct 2022
Title of study:	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		
Rationale and background:	According to the local regulations, when a new chemical entity (NCE) is registered, a regulatory non-interventional study (NIS) should be conducted. Such NIS can provide supplementary data to monitor the safety of NCEs in a real-world situation. Data collected in randomized clinical study with strict inclusion/exclusion criteria and rigorous monitoring schemes have limitations. This is a non-interventional, multi-centre single national study. It will provide additional safety information of Esgliteo in Korean patients with type 2 diabetes mellitus in a routine clinical practice setting.		
Research question and objectives:	The objectives of this study are to monitor the safety and effectiveness of Esgliteo in Korean patients with type 2 diabetes mellitus in a routine clinical practice setting.		
Study design:	Non-interventional, multi-center and single national study based on newly collected data		
Population:	Patients diagnosed with type 2 diabetes mellitus in Korea. Esgliteo is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. <u>Inclusion criteria:</u> • 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 <u>Exclusion criteria:</u> • 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		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: ESGLITEO®.			
Name of active ingredient: empagliflozin/linagliptin			
Protocol date: 06 Apr 2021	**Study number:** 1275-0028	**Version/Revision:** 5.0	**Version/Revision date:** 28 Oct 2022
	• 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 local label of Esgliteo		
Variables:	Endpoints of safety All reported adverse events in patients who take at least one dose of Esgliteo will be noted. Endpoints of effectiveness Change from baseline in HbA1c, fasting plasma glucose (FPG), body weight, blood pressure (SBP, DBP) after 12weeks and/or 24 weeks of treatment and the final effectiveness evaluation at the end of the last visit will be noted.		
Data sources:	Field study with new data collection		
Study size:	Single arm (N=600 approximately)		
Data analysis:	In this non-interventional study, all statistical analyses will be descriptive. Data of characteristics and other status of patients will be described and proportions including the confidence intervals will be provided.		
Milestones:	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.		

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	11 May 2021	9.2.2.3 Exclusion criteria	• Patients with eGFR < 30 mL/min/1.73m^2, end stage renal disease, or patient on dialysis • Patients with moderate renal impairment (eGFR >/= 30 and < 60 mL/min/1.73m^2) not yet treated with empagliflozin at time of enrolment	Changed and Added eGFR cut-off criteria for Contraindication and Renal Impairment Patient according to local label
2	12 Oct 2021	9.2.2.3 Exclusion criteria	• Patients with eGFR < ~~30~~45 mL/min/1.73m^2, end stage renal disease, or patient on dialysis • ~~Patients with moderate renal impairment (eGFR >/= 30 and < 60 mL/min/1.73m^2) not yet treated with empagliflozin at time of enrolment~~	Comment from Korea HA (MFDS) : Amend the exclusion criteria according to Korea LPI.
3	23 May 2022	9.2.3.3 Visit 2; 12 weeks from Visit 1	• Effectiveness assessment: HbA1c, FPG (Within 1month prior to Visit 2)	Add assessment period
4	23 May 2022	9.2.3.4 Visit 3; 24 weeks from Visit 1	• Effectiveness assessment: HbA1c, FPG (Within 1month prior to Visit 3)	Add assessment period
5	23 May 2022	9.7.1Analysis of Demographic Data	① Basic information and disease information Age, Gender, Pregnancy, Family history of T2DM, Allergy, Smoking status, Body weight, Diabetes mellitus complications (if available), Other medical history, Disease period, Elderly (Age ≥ 65 years), Renal impairment and Hepatic impairment, Long term use(over 24 weeks)	Collect data if available
6	28 Oct 2022	9.1.2 Dosage and Administration	In patients tolerating this drug 10 mg/5 mg once daily and requiring additional glycaemic control, the dose can be increased to empagliflozin 25 mg/linagliptin 5 mg once daily.	Update in accordance with the product label updated on September 28, 2022.
7	28 Oct 2022	11.1 DEFINITIONS OF ADVERSE EVENTS	Delete the Always Serious Adverse Events	Not applicable for NIS studies including local PMS studies
8	28 Oct 2022	11.1 DEFINITIONS OF ADVERSE EVENTS	Update definitions for AESI hepatic injury	In accordance with the changes concerning the hepatic injury definition as AESI.

9	28 Oct 2022	11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING	Delete the report timeline of ASAE	Not applicable for NIS studies including local PMS studies

6. 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

7. RATIONALE AND BACKGROUND

7.1 RATIONALE

According to the local regulations, when a new chemical entity (NCE) is registered, a regulatory non-interventional study (NIS) should be conducted. Such NIS can provide supplementary data to monitor the safety of NCEs in a real-world situation. Data collected in randomized clinical study with strict inclusion/exclusion criteria and rigorous monitoring schemes have limitations.

This is a non-interventional, multi-centre single national study. It will provide additional safety information of Esgliteo (empagliflozin/linagliptin) in Korean patients with type 2 diabetes mellitus in a routine clinical practice setting.

7.2 BACKGROUND

Diabetes mellitus is an increasingly prevalent disease. Recent estimates suggest that the number of people worldwide with diabetes is currently 382 million and is expected to reach at least 592 million within the next 25 years [R14-1408]. The most common form is type 2 diabetes, which is characterized by insulin resistance, impaired insulin secretion, and increased blood glucose levels. Type 2 diabetes is also associated with microvascular complications [R09-6405, R09-6406] and elevated cardiovascular risks [R12-2906].

Diabetes and its complications have become a major cause of morbidity and mortality in Korea. Although diabetes-related mortality has recently decreased from 25.1 per 100,000 persons in 2002 to 19.6 per 100,000 persons in 2009, diabetes is still the fifth-leading cause of death in Korea. Diabetic complications such as renal failure, neuropathy, retinopathy, coronary and cerebral artery diseases, and amputations are associated with increased medical costs and reduced life expectancy [R13-1653].
The number of patients with T2DM is expected to increase dramatically from about 3.2 million in 2011 (8.8% of the national population) to about 4.25 million (11.1%) by 2030 [R12-1019].

Treatment of type 2 diabetes usually involves lifestyle interventions, such as diet and exercise, as well as the administration of antidiabetic drugs. Although initially effective, currently available oral antidiabetic agents often fail to maintain long-term glycemic control or are associated with side effects that may limit their use. Hence, there is an ongoing need for new therapeutic options to provide sustained improvements in glycemic control. [c03606501-02]

In the EMPA-REG OUTCOME trial (1245.25), empagliflozin demonstrated significant benefit in patients with T2DM with established cardiovascular (CV) disease by reducing overall mortality mostly due to CV death and hospitalisation for heart failure. Furthermore, empagliflozin significantly reduced the risk for the combined endpoint of new onset or worsening of nephropathy (new onset of macroalbuminuria, 2x serum creatinine accompanied by eGFR(Estimated Glomerular Filtration Rate) ≤45 mL/min/1.73 m^2, initiation

of continuous renal replacement therapy, and death due to renal disease) compared to placebo [c02695839-01].

In the CARMELINA trial, linagliptin did not increase the risk of the combined endpoint of CV death, non-fatal myocardial infarction or non-fatal stroke (3-point MACE), or the risk of combined endpoint of renal death, ESRD, 40% or more sustained decrease in eGFR, when added to standard of care in adult patients with T2DM with increased CV risk evidenced by a history of established macrovascular or renal disease. In addition, linagliptin did not increase the risk of hospitalisation for heart failure. No increased risk of CV death or all-cause mortality was observed [c22196815-01].

Thus, the FDC of linagliptin with empagliflozin provides clinically meaningful treatment benefits by lowering glucose and reducing HbA1c further than monotherapy with either component at corresponding doses. Combining linagliptin with empagliflozin simplifies the antidiabetic therapy by decreasing the number of tablets to be taken and is expected to improve patients' compliance with medication; FDC therapy has resulted in improved compliance in patients previously treated with oral antidiabetics [s00083671-01].

For a detailed description of the drug profile refer to the local prescribing information of Esgliteo.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 PRIMARY OBJECTIVE

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

8.2 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, blood pressure (SBP, DBP) and the final effectiveness evaluation at the end of the last visit in Korean T2DM patients.

9. RESEARCH METHODS

This study is a national multi-centre non-interventional study (NIS). 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. Before initiation of the study, any newly reported adverse events collected from other sources such as spontaneous cases, literature cases etc. will be closely monitored.

This study will be carried out by enrolling patients in a consecutive manner into the study requiring completion of 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. Prior to initiation of the study, written contract shall be concluded, and this contract shall be concluded with the head of the site or the investigator with his/her consent.

Patients will be managed according to the local practice guidelines. The choice of treatment will be solely at the discretion of the participating physician. Esgliteo will be administered according to the approved label in Korea. Hence there are no additional risks to patients by participating in this NIS.

9.1 STUDY DESIGN

This is a NIS based on single arm with Esgliteo. Esgliteo will be prescribed according to the local label and at the discretion of the treating physician. Since this is a non-interventional study, the drug will not be supplied by the sponsor. Furthermore, the sponsor will not cover the expenses related to other medications taken by the patient, interventions, procedures, or diagnostic test.

9.1.1 Method of Assigning Patients to Treatment Groups

The choice of treatment is fully at the discretion of the physician and the patient. There is no treatment assignment by a third party.

9.1.2 Dosage and Administration

The starting dose and the dose escalation schedule are based on the current authorized label in Korea.

The recommended dose is one tablet once daily as follows;

- In patients tolerating this drug 10 mg/5 mg once daily and requiring additional glycaemic control, the dose can be increased to empagliflozin 25 mg/linagliptin 5 mg once daily.
- In patients switching from separate tablets of empagliflozin and linagliptin to Esgliteo should receive the same dose already being taken.

The tablets can be taken with or without food, swallowed whole. If a dose is missed, it should be taken as soon as the patient remembers. If a dose is missed, and it is less than 12 hours

until the next dose, the dose should be skipped and the next dose should be taken at the usual time. A double dose should not be taken at once.

9.1.3 Concomitant Therapy, Restrictions, Rescue

The protocol will allow additional drugs considered necessary for the patient's welfare to be prescribed at the discretion of the treating physician. It is required, however, to record the details of all concomitant medication administered to the patient during the course of treatment in eCRF. This includes concomitant therapies started one month prior to Esgliteo initiation until the patient completes the final follow-up visit.
For more detailed information, please refer to the current local label.

9.2 SETTING

Enrolled patients will be followed up after 12 or/and 24 weeks of treatment period.

9.2.1 Study Sites

Approximately 20 sites by as many as 20 or more NIS investigators will participate. To minimize the selection bias at the site level, the goal is to have participating centers reflect a balance between general hospitals and clinics for surveillance. The treating physicians will mainly be internists.

As provided in the 『Standards for Re-examination of New Drugs』of the Ministry of Food and Drug Safety Notification, BI OPU should select study site according to the following requirements;

① Equipment/facility, and manpower capable of fully achieving the goal of investigation should be held;
② The investigator should have specialized knowledge of the drug subject to investigation and the indication, have completed education/training necessary for performing the investigation, or have practical experience;
③ Study site and the investigator should strictly keep confidential the record of subject's personal data
④ The investigator should be fully aware of the『Standards for Re-examination of New Drugs』and study protocol.

9.2.2 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.

9.2.2.1 Main diagnosis for study entry

Patients diagnosed with type 2 diabetes mellitus in Korea. Esgliteo is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are appropriate to take a combination of empagliflozin and linagliptin.

9.2.2.2 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

9.2.2.3 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

9.2.2.4 Subjects of special investigation

The patient who have signed on the data release consent form, subjects of special investigation (Geriatric (Older than 65 years), Pregnant Women, renal impairment, hepatic impairment and other special population) among the patients who conducted investigation for safety assessment after the administration of Esgliteo can be further investigation into cases collected from this study may be taken into account according to the outcome of retrospective analysis.

9.2.3 Study Visits

9.2.3.1 Screening and run-in periods

This section is not applicable as this is a non-interventional study.

9.2.3.2 Visit 1; Baseline Visit

Upon patient enrolment, the following will be recorded on the patient's eCRF.

- Visit date
- Diagnosis: date of the diagnosis of T2DM, Family history of T2DM
- Inclusion / Exclusion criteria
- Data release consent form: Date of data release consent form

- Demographic data: Year of birth(age), Gender, Pregnancy, Previous allergy, Height, Smoking status
- Diabetes mellitus related complication(Retinopathy, Neuropathy, Nephropathy, Vasculopathy, Others)
- Medical history: Renal impairment, Hepatic impairment, Others. (history of concomitant disease within 6 months prior to baseline)
- Physical examination: Body weight, Blood pressure (SBP, DBP)
- Renal function test: Serum creatinine, eGFR, Urine ACR if blood test result is available(the most recent data prior to baseline)
- Effectiveness assessment: HbA1c, FPG (within 1 month prior to baseline)
- Concomitant anti-hyperglycemic agent: record any anti-hyperglycemic agents that have been taken at least once (within 1 month prior to baseline)
- Concomitant medications: record all medications that have been taken at least once (within 1 month prior to baseline)
- Dose of Esgliteo given (Daily dose, Start date)

At visit 1, the patient will be requested to contact the treating physician in the event of any adverse events noted after initiating Esgliteo treatment.

9.2.3.3 Visit 2; 12 weeks from Visit 1

After 12 weeks from Visit 1, the patients will return for follow-up. The followings will be noted and recorded in the eCRF.

- Visit date
- Physical examination: Body weight, Blood pressure (SBP, DBP)
- Any changes of Esgliteo given
- Effectiveness assessment: HbA1c, FPG (Within 1month prior to Visit 2)
- Renal function test: Serum creatinine, eGFR, Urine ACR if blood test result is available (The most recent data since last visit, except previously entered data)
- Concomitant anti-hyperglycemic agent including new medications taken since last visit: any changes in the concomitant medications (dose and dosing intervals)
- Concomitant medications including new medications taken since last visit: any changes in the concomitant medications (dose and dosing intervals)
- Any changes in laboratory tests if there is any lab result which was clinically significant compared to data before Esgliteo therapy (This data is collected on the basis of medical need, i.e. independent of the NIS)
- Any adverse events noted, AESI (Adverse Event of Special interest)
- Study completion status (if necessary)

- The final effectiveness evaluation(if necessary)
- NIS physician's electronic signature for data integrity (if necessary)

9.2.3.4 Visit 3; 24 weeks from Visit 1

After 24 weeks from Visit 1, the patients will return for follow-up. The followings will be noted and recorded in the eCRF.

- Visit date
- Physical examination: body weight, blood pressure(SBP, DBP)
- Any changes of Esgliteo given
- Effectiveness endpoints: HbA1c, FPG (Within 1month prior to Visit 3)
- Renal function test: Serum creatinine, eGFR, Urine ACR if blood test result is available (The most recent data since last visit, except previously entered data)
- Concomitant anti-hyperglycemic agent including new medications taken since last visit: any changes in the concomitant medications (dose and dosing intervals)
- Concomitant medications including new medications taken since last visit: any changes in the concomitant medications (dose and dosing intervals)
- Any changes in laboratory tests if there is any lab result which was clinically significant compared to data before Esgliteo therapy (This data is collected on the basis of medical need, i.e. independent of the NIS)
- Any adverse events noted, AESI (Adverse Event of Special interest)
- Study completion status(if necessary)
- The final effectiveness evaluation
- NIS physician's electronic signature for data integrity

9.2.3.5 End of study and follow-up period

Patients with adverse events noted at the final follow-up visit or upon premature discontinuation of Esgliteo will be monitored further until the study completion. Alternatively, those patients will be followed up until the NIS physician and sponsor agree that no further follow-up is necessary.

9.2.4 Study Discontinuation

Boehringer Ingelheim reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular study site

2. Emergence of any effectiveness/safety information that could significantly affect continuation of the study
3. Violation of Good Pharmacoepidemiology Practice (GPP), the study protocol, or the contract by a study site, investigator or research collaborator, disturbing the appropriate conduct of the study

The investigator/the study site/research collaborator will be reimbursed for reasonable expenses incurred in case of study/site termination (except in case of the third reason).

9.2.5 Flow Chart

Data points	**Baseline**	**Follow-up 1**	**Follow-up 2**
Visit Number	1	2	3
Week/s	0	12	24
Informed consent	X		
Diagnosis	X		
Inclusion / exclusion criteria	X		
Demographics	X		
Family history of T2DM	X		
Diabetes mellitus complications	X		
Medical history	X		
Physical examination	X	X	X
Anti-diabetic agents	X	X	X
Concomitant medications	X	X	X
Esgliteo administration status	X	X	X
Renal function	X [A]	X [A]	X [A]
Effectiveness endpoints	X	X	X
Overall effectiveness evaluation			X
Changes in lab tests		X [A]	X [A]
Adverse events		X	X
Study completion		X	X

[A]: If applicable

9.3 VARIABLES

9.3.1 Analysis Sets

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 (12weeks) period, all patients will be enrolled for long-term (24weeks) surveillance.

9.3.1.1 Number of cases subject who entered the study

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

9.3.1.2 Number of cases subject to CRF collection

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.

9.3.1.3 Number of cases subject to safety evaluation

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 Ministry of Food & Drug Safety (MFDS) guideline, the cases below shall be excluded from safety analysis (defined below) set in the following order:

a. Patients who did not signed or signed on the data release consent form of Esgliteo PMS prior to the contract date
b. Patients administrated Esgliteo prior to the contract date
c. Patients administrated Esgliteo prior to the signed on the data release consent form
d. Patients who have not taken Esgliteo
e. Follow-up failure: Patients whose safety information cannot be obtained due to follow-up Loss
f. Patients who were prescribed for other indications except indications in the local label

9.3.1.4 Number of cases subject to effectiveness evaluation

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, and were evaluated for the effectiveness.
Reflecting Ministry of Food & Drug Safety (MFDS) guideline, the cases below shall be excluded from effectiveness analysis (defined below) set in the following order:

a. Patients excluded from safety analysis set listed in section 9.3.1.3
b. Patients with missing information of assessment of effectiveness set listed in section 9.3.2.2 at visit 2, visit 3

9.3.2 Endpoints

9.3.2.1 Endpoints of safety

All reported adverse events in patients who take at least one dose of Esgliteo will be noted. Endpoints pertaining to safety will be presented as frequency of adverse events and will include:

- Adverse events
- Unexpected adverse events
- Serious adverse events
- Drug-related adverse events
- Non-serious adverse drug reaction
- Adverse event of special interest
- Adverse events leading to discontinuation
- Adverse events by intensity, outcome of the events, causality

9.3.2.2 Endpoints of effectiveness

9.3.2.2.1 Primary endpoints

- Change from baseline in HbA1c after 12 weeks and/or 24 weeks of treatment

9.3.2.2.2 Secondary endpoints

- Occurrence of treat to target effectiveness response that is an HbA1c under treatment of < 7% after 12 weeks and/or 24 weeks of treatment
- Occurrence of relative effectiveness response (HbA1c lowering by at least 0.5% after 12 weeks and/or 24 weeks)
- Change from baseline in fasting plasma glucose (FPG) 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.

9.3.2.2.3 The final effectiveness evaluation

Records by performing the final effectiveness evaluation at the end of the last visit

① Improved: If determined as there is any effect of maintaining or improving disease related factors.
② Unchanged: If disease related factors have not been changed compared with before administration, and not determined as there is any effect of maintaining symptoms.
③ Aggravated: If disease related factors are worse than before administration.

④ Unassessable: If it cannot be determined due to insufficient information collected. (Even though there are any objective indicators present, it is possible to belong to this grade.)

'Improved' is assessed as "Effective", 'Unchanged' and 'Aggravated' are assessed as "Invalid".

9.3.3 Assessment Criteria

9.3.3.1 Assessment of safety

- Adverse events (event name/ symptoms/ sign/ identify hypoglycemia symptoms)
- Onset date, End date
- Intensity (Mild/ Moderate/ Severe)
- Serious (Serious/ Non-Serious)
- Outcome of the event (Recovered/ Not yet recovered/ Sequela/ Fatal/ Unknown)
- Causality (Certain/ Probable·Likely/ Possible/ Unlikely/ Conditional· Unclassified/ Unassessable·Unclassifiable)
- Action taken with study drug due to AE (Dose not changed/ Dose reduced/ Dose increased/ Drug withdrawn/ Not applicable)
- Adverse Event of Special interest (Hepatic injury/ Decreased renal function/ Metabolic acidosis, ketoacidosis and diabetic ketoacidosis (DKA)/ Lower limb amputation)

9.3.3.2 Assessment of effectiveness

① HbA1c(%):
HbA1c should be collected within 1 month prior to baseline and after 12 weeks, 24 weeks of treatment.

② Fasting Plasma Glucose (FPG)(mg/dL):
FPG should be collected within 1 month prior to baseline and after 12 weeks, 24 weeks of treatment.

③ Body Weight(kg):
Body weight should be collected within 1 month prior to baseline and after 12 weeks, 24 weeks of treatment.

④ Blood Pressure (SBP, DBP)(mmHg):
Blood pressure(SBP, DBP) should be collected within 1 month prior to baseline and after 12 weeks, 24 weeks of treatment.

⑤ Final effectiveness evaluation: Final effectiveness evaluation should be accessed and recorded at the end of the last visit.

9.4 DATA SOURCES

This study will be carried out by enrolling patients in a consecutive manner into the study requiring completion of 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. Prior to initiation of the study, written contract shall be concluded, and this contract shall be concluded with the head of the site or the investigator with his/her consent.

9.5 STUDY SIZE

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.

9.6 DATA MANAGEMENT

Patients' data will be collected by eCRF. The data management procedures to ensure the quality of the data are described in detail in the data management plan (DMP) available in TMF. Data management and statistics will be outsourced to a qualified contract research organization (CRO).

9.7 DATA ANALYSIS

9.7.1 Analysis of Demographic Data

Demographic data and the health status of subjects for the safety evaluation will be analysed descriptively. For continuous data, mean, standard deviation, minimum value, and maximum value will be described, while for categorical data, frequency will be shown.

Parameters corresponding to demographic data are as mentioned below.

① Basic information and disease information
Age, Gender, Pregnancy, Family history of T2DM, Allergy, Smoking status, Body weight, Diabetes mellitus complications (if available), Other medical history, Disease period, Elderly (Age ≥ 65 years), Renal impairment and Hepatic impairment, Long term use(over 24 weeks)

② Medication information
Concomitant medication, Any anti-diabetic agents, Study drug administration status (total period of drug use, average of daily dose), Reason for early interruption

9.7.2 Analysis of Safety

① Among the subjects of safety evaluation, the number of subjects with adverse event incurred and the number of adverse events incurred should be calculated, and the frequency of adverse events and the 95% confidence interval should be presented.
② The number and percentage of adverse events by type and category should be presented.
③ Analysis should be made using Chi-square test or Fisher's Exact test on the adverse event onset status by demographic data of subjects of safety evaluation.
④ To estimate any factors that are thought to influence the analyzed frequency of adverse events, logistic regression analysis should be conducted, and for statistically significant parameters, the meaning should be described.

Adverse Events (AEs) excluding the AEs whose 'Causality' is "Unlikely" will be treated as AEs whose causality cannot be excluded (hereafter "Adverse Drug Reaction (ADR)").

AEs will be coded according to the latest version of Medical Dictionary for Drug Regulatory Affairs (MedDRA) coding system. Concomitant medications will be coded according to the latest version of KIMS(Korea Index of Medical Specialties) coding system. The study database will not be locked until coding is complete.

Safety analyses will be based on all patients treated, i.e. all patients who received at least one dose of Esgliteo. However, if data for patients who have been treated with Esgliteo beyond the scope of approved label are collected, separate safety analyses will be performed. Patients lost to follow up will be characterized compared to the remaining patients and reason and time point of loss to follow up will be evaluated.

9.7.3 Analysis of Effectiveness

① Mean, standard deviation, minimum value, maximum value, and median of changes in glycosylated hemoglobin(HbA1c) and fasting plasma glucose(FPG), weight, and blood pressure, which were measured at the last visit versus baseline, should be presented, and if there is a difference before administration versus after administration should be analyzed using paired t-test.
② If there is difference in the change of glycosylated hemoglobin (HbA1c) according to demographic parameters mentioned in 9.7.1 should be analyzed using t-test or ANOVA (Analysis of Variance).
③ The frequency and percentage of patients who had glycosylated hemoglobin(HbA1c) reaching less than 7% (target effectiveness response rate) at the last visit should be calculated, and the frequency and percentage of patients with glycosylated hemoglobin(HbA1c) decreased by at least 0.5% at the last visit should be calculated.
④ For final effectiveness evaluation (improved, unchanged, aggravated, unassessable) and 'effective(improved)'/'ineffective(unchanged, aggravated)', the number and

percentage of subjects should be mentioned. The final effectiveness evaluation of "Improved" will be classified as "Effective", "Unchanged" and "Aggravated" will be classified as "Ineffective". The effectiveness rate and its 95% confidence intervals will be estimated with exact method.

⑤ To estimate any factors that are thought to influence an effective ratio, logistic regression analysis should be conducted, and for statistically significant parameters, the meaning should be described.

9.7.4 Interim Analyses

In accordance with local regulation for NIS, interim analyses are planned biannually for the initial two years and annually thereafter.

9.7.5 Handling of Missing Data

Maximum attempt will be made to ensure the completeness of data collection. All available data will be used in the data analysis.

9.8 QUALITY CONTROL

All entries in the eCRF and the existing codings will be stored in a database. The structure of the database is based on the division into sections and entry fields defined in the eCRF. To improve and ensure data quality, data checks will be performed automatically in the eCRF directly on electronic entry at the study site.
Plausible value ranges for numerical data entries and logical data and list entries will be filed in the eCRF. The tests for consistency and completeness based on this will be performed during entry in the eCRF. The validity of the recorded data will therefore be ensured by the validations incorporated in the documentation system, which highlight incorrect or implausible entries to the data entry.
All changes after initial data entry will be documented in an audit trail. An additional inspection/quality assurance check of the data collected within this NIS can be performed in case of any deviation.

9.9 LIMITATIONS OF THE RESEARCH METHODS

9.9.1 Loss to Follow-up

All efforts will be made to minimize loss to follow up, particularly in the tracking of lost patients. To the extent possible, occurrence of adverse event, at minimum, for patients lost to follow up will be obtained via patient visit/telephone/letter/email and others. Also, patients lost to follow up will be characterized compared to the completed patients and reason and time point of loss to follow up will be evaluated.

9.9.2 Channeling Bias

Channeling bias can occur due to access to product depending on reimbursement circumstances or preferential prescribing in relation to different risks for the events of interest: e.g., if Esgliteo would be more often prescribed to higher risk patients compared to other treatments, higher frequency of outcome events were then expected in the Esgliteo group. To assess the extent of preferential prescribing of Esgliteo and the potential for channeling bias, baseline data from the Jardiance Duo (empagliflozin /metformin) PMS would be used to provide context for the Esgliteo PMS data.

9.9.3 Confounding

As in any observational study, confounding may affect the estimation of associated between drug exposure and outcome of interest and statistical techniques. However, as only major confounders for selected research questions can be captured, residual (unmeasured) confounding may remain.

9.10 OTHER ASPECTS

The International Conference on Harmonization/Harmonized Tripartite Guideline for Good Clinical Practice (ICH/GCP) does not often apply to NIS as most elements are relevant for controlled clinical trials. However, in this NIS, all attempts will be made to adhere, as close as possible, to the standards of ICH/GCP.

The protocol of this regulatory required NIS will be submitted to the Ministry of Food and Drug Safety (MFDS) for notification. Also, the protocol of this NIS will be submitted to Institutional Review Board (IRB) whenever required or requested by these institutions. This study will be conducted in accordance with the Standards for Re-examination of New Medicines notified by MFDS, Korean Pharmaceutical Affairs Code (KPAC), Enforcement Regulation of KPAC and other applicable local laws and industry code (including but not limited to the Regulations on Fair Competition in the Trade of Medicines of KPMA and KRPIA).

[redacted] will submit periodic reports during re-examination period, and the final report to MFDS upon study completion. The periodic report for the final year will be substituted with the final report. When required, the interim reports and the final report will be submitted to the IRBs as well.

9.10.1 Data Quality Assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Board (IRBs) / Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the data release consent form documentation of this study.

9.10.2 Study Records

All of the clinical data will be captured via a web-based EDC (Electronic Data Capture) System. The site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained. The treating physician will approve the data using an electronic signature.
Patients will not be identified on the eCRF by name. Appropriate code identification (i.e., patient number) will be used. The treating physician will make a separate confidential record of these details (patient identification code list) to permit identification of all patients enrolled in this study in case follow-up is required. Likewise, any supporting documentation will be redacted of any patient identifying information, and the patient ID number clearly written on the documents.

9.10.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

For the eCRF, the following data need to be derived from source documents:

- Patient identification (gender, age)
- Patient participation in the study (study number, patient number, date patient was informed)
- Dates of Patient's visits, including dispensing of study medication
- Medical history (including study indication and concomitant diseases, if applicable)
- Medication history
- Physical examination (body weight, blood pressure (SBP, DBP))
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Laboratory results (if available)
- Completion of Patient's Participation in the study

9.10.2.2 Direct access to source data and documents

The investigator/institution will permit study-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents.
CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. US Food and Drug Administration

(FDA)). BI study staff and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.1.

9.10.2.3 Storage period of records

The NIS physician and the site are jointly responsible for maintaining essential study documents for 3 years after completion of the study (defined as termination date of re-examination period) by the Pharmaceutical Affairs Law and shall take measures to prevent accidental or premature destruction of these documents.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, Guidelines for Good Pharmacoepidemiology Practice (GPP), and the relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This NIS will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Competent Authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the study, written data release consent must be obtained from each patient (or the patient's legally accepted representative) according to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the data release consent retained by the investigator as part of the study records. A signed copy of the data release consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by BI in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (MPMs) or Clinical Quality Assurance auditors appointed by BI, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
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
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.

Serious adverse event
A serious adverse event 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, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse Event of Special Interest (AESI)

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

The following are considered as AESIs:

- Hepatic injury
  - An elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured at the same visit, or in samples drawn with in 30 days of each other, OR
  - An elevation of AST and/or ALT ≥3-fold ULN and INR ≥1.5-fold ULN measur ed at the same visit, or in samples drawn within 30 days of each other, OR
  - An elevation of AST and/or ALT ≥3-fold ULN with new onset, or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, an d/or eosinophilia (>5%), OR
  - An isolated elevation of AST and/or ALT ≥5-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).
    Each lower limb amputation, disarticulation, or auto-amputation should be report ed separately. The SAE report should include the date of the procedure, the level of amputation or disarticulation, the medical condition(s) leading to the procedur e and if the patient had some of the known risk factor(s) for lower limb amputati on.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs
The study is a non-interventional study in real-world situation and will be conducted within the conditions of the approved marketing authorization. For this reason, the following AE collection and reporting requirements have been defined.

All adverse events occurred from the signing date on data release consent form to last visit date of monitoring period need to be collected, documented and reported to the sponsor using the AE page of eCRF(14.1).

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:
- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**
- A **plausible time to onset of the event** relative to the time of drug exposure
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:
- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)

- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

The causal relationship must be provided by the Investigator for all potential study drugs, i.e. the BI study drug and for all other study drugs.
The reason for the decision on causal relationship needs to be provided in the eCRF and on the NIS AE form (if applicable).

Related

a. Certain : An event occurring in a plausible time relationship to drug administration and that cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

b. Probable/Likely : An event with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

c. Possible: An event with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

d. Conditional/Unclassified: Case of requiring more data or reviewing the additional data for the appropriate assessment

e. Unassessable/Unclassifiable: Case that it cannot be judged and complemented or confirmed due to the insufficient or contradictory information

Unrelated
Unlikely : An event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Intensity of adverse event
The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Expedited Reporting of AEs and Drug Exposure during Pregnancy to BI Pharmacovigilance

The following must be reported by the investigator on the NIS AE form and/or Pregnancy Monitoring Form(14.3) from signing the data release consent onwards until the end of the study and provide to the LPVM of [redacted]

Contact details:
Local PV Manager (LPVM)
Tel: [redacted]
Fax: [redacted]
Address: [redacted]

Type of Report	Timeline
All **Serious Adverse Events** (SAEs)	immediately within 24 hours
All **AEs with fatal outcome**	immediately within 24 hours
All **protocol specified Adverse Event of Special Interest** (AESIs)	Immediately within 24 hours
All non-serious adverse events	7 calendar days
Drug exposure during pregnancy	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete the AE page of the eCRF and/or the NIS AE form.

Pregnancy:

In rare cases, pregnancy might occur in a NIS. Once a patient has been enrolled in the study and has taken study medication, the investigator must report any drug exposure during pregnancy in a study participant within 7 days by means of Part A of the Pregnancy Monitoring Form (14.3) to the LPVM of [redacted]

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the LPVM of [redacted] on the Pregnancy Monitoring Form (Part B).

The ISF will contain the Pregnancy Monitoring Form (Part A and B). As pregnancy itself is not to be reported as an AE, in the absence of an accompanying serious ADR and/or AESI, only the Pregnancy Monitoring Form and not the NIS AE form is to be completed. If there is a serious ADR and/or AESI associated with the pregnancy a NIS AE form must be completed in addition.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate eCRF page and the NIS AE form.

For each AE, the investigator will provide the onset, end, intensity, outcome, seriousness and action taken with Esgliteo. The investigator will determine the relationship of Esgliteo to all AEs as defined in the 'Adverse Event Reporting' section of the investigator binder.

Reporting of related AEs associated with any other BI drug
The investigator is encouraged to report all adverse events related to any BI drug other than Esgliteo according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES AND IEC/IRB

Adverse event reporting to regulatory agencies and IEC/IRB will be done by the Marketing Authorization Holder (MAH) according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

13. REFERENCES

13.1 PUBLISHED REFERENCES

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13.2 UNPUBLISHED REFERENCES

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c22196815-01 A multicenter, international, randomized, parallel group, double-blind, placebo-controlled Cardiovascular Safety & Renal Microvascular outcome study with LINAgliptin, 5 mg once daily in patients with type 2 diabetes mellitus at high vascular risk. CARMELINA. 03 Aug 2018.

s00083671-01 Empagliflozin/linagliptin Periodic Benefit-Risk Evaluation Report, 13 Dec 2019

14. APPENDICES

14.1 ELECTRONIC CASE REPORT FORM

Please refer to “ELECTRONIC CASE REPORT FORM” in site file or in electronic CRF web page for the latest version.

14.2 NON-INTERVENTIONAL STUDY (NIS) ADVERSE EVENT FORM

Please refer to “Non-Interventional Study (NIS) Adverse Event Form” in site file or in electronic CRF web page for the latest version.

14.3 PREGNANCY MONITORING FORM

Please refer to “PREGNANCY MONITORING FORM” in site file or in electronic CRF web page for the latest version.

14.4 ESGLITEO PRESCRIPTION INFORMATION FOR KOREA

Please refer to “ESGLITEO PRESCRIPTION INFORMATION FOR KOREA” in site file or in electronic CRF web page for the latest version.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
None	None	None	None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Please refer to “ENCePP Checklist for Study Protocols” in separate file