NON-INTERVENTIONAL STUDY PROTOCOL

Document Number:	**c09963608-06**
BI Study Number:	1245.116
BI Investigational Product:	JARDIANCE® (empagliflozin)
Title:	A regulatory requirement non interventional study to monitor the safety and effectiveness of JARDIANCE® (empagliflozin 10mg, 25mg) in Korean patients with type 2 diabetes mellitus
Brief lay title	JARDIANCE® rPMS in Korean patients with type 2 diabetes mellitus
Protocol version identifier:	6.0
Date of last version of protocol:	21 Aug 2017
PASS:	Yes
EU PAS register number:	EUPAS13627
Active substance:	empagliflozin
Medicinal product:	JARDIANCE® film-coated tablets 10mg, 25mg
Product reference:	*Not applicable*
Procedure number:	*Not applicable*
Marketing authorisation holder:	Boehringer Ingelheim Korea
Joint PASS:	*Not applicable*
Research question and objectives:	To monitor the safety profile and effectiveness of JARDIANCE® in Korean patients with type 2 diabetes mellitus in a routine clinical practice setting
Country of study:	Multi-Centre study conducted in Korea

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MAH contact person:	[redacted]
EU-QPPV:	[redacted]
Signature of EU-QPPV:	*Not applicable*
Date:	23 Nov 2017

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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
ASAE	Always Serious Adverse Events
ASD	Absolute Standardized Differences
BI	Boehringer Ingelheim
BP	Blood Pressure
CA	Competent Authority
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRO	Contract Research Organization
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DKA	Diabetic Ketoacidosis
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EU	European Union
EU PAS	European Union electronic register of post-authorization studies
EU-QPPV	European Union-Qualified Person for Pharmacovigilance
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GLUT	Glucose Transporter
GPP	Good Pharmacy Practice
HbA1c	Glucosylated Hemoglobin
HDL-C	High Density Lipoprotein Cholesterol
IC50	Inhibitory Concentration
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

IRB	Institutional Review Board
ISF	Investigator Site File
LDL-C	Low Density Lipoprotein Cholesterol
LPVM	Local PV Manager
MAH	Marketing Authorisation Holder Activities
MedDRA	Medical Dictionary for Drug 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 Studies
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGLT2	Sodium-dependent Glucose Co-transporter 2
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
T2DM	Type 2 Diabetes Mellitus
TC	Triglycerides
T-Chol	Total Cholesterol
TCM	Trial Clinical Monitor
TMF	Trial Master File
TMM	Team Member Medicine
UTI	Urinary Tract Infection

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 Korea.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

The organization of the study will be done 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. 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 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 Korea			
Name of finished medicinal product: JARDIANCE®			
Name of active ingredient: empagliflozin			
Protocol date: 27 May 2016	**Study number:** 1245.116	**Version/Revision:** 6.0	**Version/Revision date:** 23 Nov 2017
Title of study:	A regulatory requirement non interventional study to monitor the safety and effectiveness of JARDIANCE® (empagliflozin, 10mg, 25mg) 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) of an extended period (6 years) should be conducted. A rNIS can provide supplementary data to monitor the safety of NCEs in a real-life situation. Data collected in randomized clinical study with strict inclusion/exclusion criteria and rigorous monitoring schemes have limitations.		
Research question and objectives:	To monitor the safety profile and efficacy of JARDIANCE® (empagliflozin, 10mg, 25mg) in Korean patients with type 2 diabetes mellitus in a routine clinical practice setting		
Study design:	Observational prospective, non-interventional, open-label, multi-centre study		
Population:	Patients diagnosed with type 2 diabetes mellitus in Korea <u>Inclusion criteria:</u> • Patients who have started at first time on JARDIANCE® 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> • Known hypersensitivity to empagliflozin or any of its excipients • Patients with type 1 diabetes or for the treatment of diabetic ketoacidosis • Patients with persistent eGFR<60 mL/min/1.73 m^2,end stage renal disease or on dialysis • Patients with rare hereditary conditions of galactose intolerance, the Lapp lactase deficiency or glucose-galactosemalabsorption • Patients for whom empagliflozin is contraindicated according local label of JARDIANCE®		
Variables:	<u>Endpoints of safety</u>		

Name of company: Boehringer Ingelheim Korea			
Name of finished medicinal product: JARDIANCE®			
Name of active ingredient: empagliflozin			
Protocol date: 27 May 2016	**Study number:** 1245.116	**Version/Revision:** 6.0	**Version/Revision date:** 23 Nov 2017
	All reported adverse events in patients who take at least one dose of JARDIANCE® will be noted. <u>Endpoints of effectiveness</u> 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 efficacy evaluation at the end of the last visit will be noted.		
Data sources:	Field study with new data collection		
Study size:	Single arm (N=3,000 approximately) A total of 3000 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 restrictive to collect safety and effectiveness data in short-term (12weeks) period, all patients will be enrolled for long-term (24weeks) surveillance.		
Study sites:	A total of 3,000 patients will be enrolled at approximately 70 sites by as many as 70 or more NIS physicians. 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. To minimize the selection bias, consecutive patients from each site who meet inclusion criteria will be enrolled in this study.		
Data analysis:	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. 2) Safety analysis : In the safety assessment population, the number of subjects to whom AE occurred and the number of AEs will be calculated. Also, the incidence proportion of AEs will be estimated with its 95% confidence interval. 3) Efficacy analysis: Mean, standard deviation, minimum value, maximum value, and median of changes in glycosylated hemoglobin(HbA1c) and fasting		

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	plasma glucose(FPG), body weight, and blood pressure (SBP, DBP), which were measured at the last visit versus baseline, should be presented, and if there is difference before administration versus after administration should be analyzed using paired t-test. The number and percentage of subjects for final efficacy evaluation 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.		
Milestones:	Study duration: 6 years (MFDS set JARDIANCE® re-examination period from 12 August 2014 to 11 August 2020). Interim reports: biannually for the first two years and annually thereafter by November 2020.		

4.1 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-hyperglycemic agents	X	X	X
Concomitant medications	X	X	X
JARDIANCE® administration status	X	X	X
Renal function	X [A]	X [A]	X [A]
Effectiveness endpoints	X	X	X
The final efficacy evaluation			X
Changes in lab tests		X [A]	X [A]
Adverse events		X	X
Study completion		X	X

A : If available

5. MILESTONES

Milestone	Planned Date
Start of data collection	01 Aug 2016
End of data collection	11 Aug 2020
Interim report 1	11 Oct 2016
Interim report 2	11 Oct 2017
Interim report 3	11 Oct 2018
Interim report 4	11 Oct 2019
Registration in the EU PAS register	TBD
Final report of study results:	11 Nov 2020

6. RATIONALE AND BACKGROUND

6.1 RATIONALE

According to the local regulations, when a new chemical entity (NCE) is registered, a regulatory non interventional study (NIS) of an extended period (6 years) should be conducted. Such rNIS can provide supplementary data to monitor the safety of NCEs in a real-life situation. Data collected in randomized clinical study with strict inclusion/exclusion criteria and rigorous monitoring schemes have limitations.

This is an observational prospective, non-interventional, open-label, multi-centre national study. It will provide additional safety information of JARDIANCE® (empagliflozin) in Korean patients with type 2 diabetes mellitus in a routine clinical practice setting.

6.2 BACKGROUND

Type 2 diabetes mellitus (T2DM) is characterized by increased peripheral insulin resistance and an insulin-secretory defect that varies in severity leading to raised blood glucose levels.

T2DM constitutes 90% to 95% of the diabetic population with an estimated 387 million people affected worldwide. It is now a common and serious global health problem, which for most countries has evolved in association with rapid cultural and social changes, ageing populations, increasing urbanization, dietary changes, reduced physical activity and other unhealthy lifestyle and behavioural patterns. The incidence of T2DM is expected to increase to approximately 592 million patients over the next 20 years [R14-4616].

The prevalence of type 2 diabetes mellitus (T2DM) in Korea is estimated to be 7.3% (in those over 20 years of age), and it has increased about 5-fold over the past 30 years according to a report of the Korea National Health and Nutrition Examination Survey (KNHNES III, 2005) [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].

JARDIANCE® is a reversible, highly potent and selective competitive inhibitor of SGLT2 with an IC50 of 1.3 nM. It has a 5000-fold selectivity over human SGLT1 (IC50 of 6278 nM), responsible for glucose absorption in the gut. Furthermore high selectivity could be shown toward other glucose transporters (GLUTs) responsible for glucose homeostasis in the different tissues. [P11-13842]

Empagliflozin improves glycemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent upon the blood glucose concentration and GFR [P12-00692, R11-4288]. Through inhibition of SGLT2 in patients with T2DM and hyperglycemia, excess glucose is excreted in the urine.

SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low [P11-13842]. It is responsible as the predominant transporter for reabsorption of glucose from the glomerular filtrate back into the circulation [P12-00692]. In patients with type 2 diabetes mellitus and hyperglycaemia a higher amount of glucose is filtered and reabsorbed. [ra00656956]

The phase III studies have shown that treatment with empagliflozin 10 mg or 25 mg once daily for up to 24 weeks results in a reduction of HbA1c up to 0.85%, body weight up to 2.2 kg and SBP up to 4.8 mmHg compared to placebo. This was consistently observed with empagliflozin as monotherapy, add on to metformin, to metformin + sulphonylurea, to pioglitazone with or without metformin, to multiple daily insulin injection with or without metformin, and to basal insulin with metformin and/or sulphonylurea.

Empagliflozin was well tolerated in patients with T2DM up to maximum treatment duration of 104 weeks in completed studies. Treatment with empagliflozin resulted in a similar percentage of overall AEs, severe AEs, and serious AEs compared to placebo and/or active comparators. Treatment with empagliflozin showed a higher frequency of genital infections and increased urination. In general a small increase in overall urinary tract infections frequency was observed with empagliflozin compared to comparators, especially in females. The overall hypoglycaemic events were similar with empagliflozin compared to placebo. There was a reduction in eGFR which gradually returned toward baseline values over the treatment period in the trials. Furthermore, eGFR returned to baseline when empagliflozin was discontinued. [c01838761-15]

6.3 DRUG PROFILE

JARDIANCE® is a novel antidiabetic drug that induces dose-dependent glucose excretion by inhibiting re-uptake of glucose by the sodium-dependent glucose co-transporter 2 in renal proximal tubules.

Treatment with JARDIANCE® as monotherapy and in combination with metformin, pioglitazone, sulfonylurea, and insulin lead to clinically relevant improvements in HbA1c, fasting plasma glucose, body weight, systolic and diastolic blood pressure (SBP, DBP).

For a more detailed description of the drug profile refer to the local prescribing information of JARDIANCE®.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 PRIMARY OBJECTIVE

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

7.2 SECONDARY OBJECTIVE

The secondary objective of this study is to monitor the effectiveness of JARDIANCE® 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 efficacy evaluation at the end of the last visit in Korean T2DM patients.

8. RESEARCH QUESTION AND OBJECTIVES

This rNIS is an observational prospective, non-interventional, open-label, multi-centre national study. As per regulation, the re-examination period extends from 12 August 2014 until 11 August 2020. However, active enrolment is to be initiated in 2016 after 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. The last patient follow up is expected in Aug 2020.

This study will be carried out in the manner of successive survey that the investigator will be asked to successively write in the case report forms (CRFs) from the subject who was initially administered the drug following the study start date to the requested number of subjects without omission. Prior to initiation of the study, a written contract shall be concluded, and this contract shall be executed among BI OPU, CRO 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. JARDIANCE® will be administered according to the approved label in Korea. Hence there are no additional risks to patients by participating in this rNIS.

8.1 STUDY DESIGN

This is a single arm study with JARDIANCE®.
JARDIANCE® 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.

8.1.1 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.

8.1.2 Dosage and Administration

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

The recommended dose of JARDIANCE® is 10 mg once daily. In patients tolerating JARDIANCE® 10 mg once daily and requiring additional glycemic control, the dose can be increased to 25 mg once daily.

When JARDIANCE® is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia.

JARDIANCE® can be taken with or without food and tablets should be swallowed whole. If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

Please refer to the current local label for about Special populations (*Patients with renal impairment, Patients with hepatic impairment, Elderly patients).*

8.1.3 Concomitant therapy, Restrictions, And rescue

Additional drugs are allowed as 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 in the eCRF of all concomitant medication administered to the patient during the course of treatment. This includes concomitant therapies started one month prior to JARDIANCE® initiation until the patient completes the final follow-up visit.

8.1.3.1 Rescue medication, emergency procedures, and additional treatments

Please refer to the current local label.(13.4)

8.2 SETTING

As per regulations, enrolled patients will be followed up for 12 or/and 24 weeks treatment period.

8.2.1 Study sites

A total of 3,000 patients will be enrolled at approximately 70 sites by as many as 70 or more NIS physicians. 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. To minimize the selection bias, consecutive patients from each site who meet inclusion criteria will be enrolled in this study.

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』 and study protocol.

8.2.2 Study population

8.2.2.1 Main diagnosis for study entry

Patients diagnosed with T2DM will be included.

8.2.2.2 Inclusion criteria:

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

8.2.2.3 Exclusion criteria:

- Known hypersensitivity to empagliflozin or any of its excipients
- Patients with type 1 diabetes or for the treatment of diabetic ketoacidosis (DKA)
- Patients with persistent eGFR<60 mL/min/1.73 m^2, end stage renal disease or on dialysis
- Patients with rare hereditary conditions of galactose intolerance, the Lapp lactase deficiency or glucose-galactosemalabsorption
- Patients for whom empagliflozin is contraindicated according local label of JARDIANCE®

8.2.2.4 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 JARDIANCE® can be further investigation into cases collected from this study may be taken into account according to the outcome of retrospective analysis.

8.2.3 Study visits

8.2.3.1 Screening and run-in periods

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

8.2.3.2 Visit 1; Baseline Visit

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

- Information on the site (Hospital name, Department, Physician name, Contract date)
- Visit date

- Diagnosis: date of the diagnosis of T2DM, Family history of T2DM
- Inclusion / Exclusion criteria
- Informed consent form: Date of Informed consent
- Demographic data: Age, gender, pregnancy, height, smoking status
- Diabetes mellitus related complication (Retinopathy, Neuropathy, Nephropathy, Vasculopathy, etc)
- Medical history: Hypertension, Dislipidemia, Coronary artery disease, Stroke, Liver disease, Renal failure, Allergy, Nephropathy, etc (history of concomitant disease within 6 months)
- Physical examination: body weight, blood pressure (SBP, DBP)
- Renal Function: record Serum creatinine, eGFR, urin ACR if blood test result is available (the most recent data prior to baseline)
- Effectiveness endpoints: HbA1c, FPG (Lab data should be collected within 1month prior to baseline)
- Concomitant anti-hyperglycemic agent : record any anti-hyperglycemic agents have been taken prior to the baseline visit (within 1 month prior to baseline)
- Concomitant medications: record all medications have been taken at least once since one month prior to the baseline visit.
- Dose of JARDIANCE® given(Daily dose(Dosage/Administration), 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 JARDIANCE® treatment.

8.2.3.3 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 change of JARDIANCE® given(Daily dose(Dosage/Administration), Start date, Date of discontinuation or continuation, Action taken, Causality)
- Effectiveness endpoints: HbA1c, FPG
- Renal Function: record 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 change in the concomitant medications (dose and dosing intervals)
- Concomitant medications including new medications taken since last visit : any change 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 JARDIANCE® 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

8.2.3.4 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 change of JARDIANCE® given(Daily dose(Dosage/Administration), Start date, Date of discontinuation or continuation, Action taken, Causality)
- Effectiveness endpoints : HbA1c, FPG
- Renal Function: record 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 change in the concomitant medications (dose and dosing intervals)
- Concomitant medications including new medications taken since last visit : any change 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 JARDIANCE® 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

8.2.3.5 End of study

- Visit date
- Discontinuation or continuation (if interruption, date of last administration, reason for interruption)
- The final efficacy evaluation
- NIS physician’s electronic signature for data integrity

8.2.3.6 Follow-up period

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

8.2.4 Study discontinuation

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

- Emergence of any effectiveness/safety information that could significantly affect continuation of the study
- Violation of applicable local regulations, the NIS protocol, or the contract by a study site or participating physician, disturbing the appropriate conduct of the study.

8.3 VARIABLES

8.3.1 Analysis sets

A total of 3000 patients will be entered in this study, and each patient will be followed for total three times (baseline, short term 12weeks follow up, long term 24weeks follow up). 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.

8.3.1.1 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.

8.3.1.2 Number of cases subject to CRF collection

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

8.3.1.3 Number of cases subject to safety evaluation

These include those who signed the informed consent form to participate in this study as subject, took JARDIANCE® 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 signed on the data release consent form of JARDIANCE® rPMS prior to the contract date
b. Patients administrated JARDIANCE® prior to the contract date
c. Patients administrated JARDIANCE® prior to the signed on the data release consent form
d. Patients who have not taken JARDIANCE®
e. Follow-up failure: Patients whose safety information can not be obtained due to follow-up Loss
f. Patients who were prescribed for other indications except indications in the local label

8.3.1.4 Number of cases subject to efficacy evaluation

These cases include those who signed the informed consent form to participate in this study as subject, visited as per the study schedule, took JARDIANCE®, and were evaluated for the efficacy.
Reflecting Ministry of Food & Drug Safety (MFDS) guideline, the cases below shall be excluded from efficacy analysis (defined below) set in the following order:

a. Patients excluded from safety analysis set listed in section 8.3.1.3
b. Patients with missing information of assessment of efficacy set listed in section 8.3.2.2 at visit 2, visit 3.

8.3.2 Endpoints

8.3.2.1 Endpoints of safety

All reported adverse events in patients who take at least one dose of JARDIANCE® will be noted.
Endpoints pertaining to safety will be presented as incidence rates of 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

8.3.2.2 Endpoints of effectiveness

8.3.2.2.1 Main endpoint

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

8.3.2.2.2 Other 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.

8.3.2.2.3 The final efficacy evaluation

Records by performing the final efficacy 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".

8.3.3 Assessment criteria

8.3.3.1 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/ Recovering/ Not yet recovered/ Sequela/ Unknown)
- Causality (Certain/ Probable·Likely/ Probable/ Possible/ Unlikely/ Conditional·Unclassified/ Unaccessible·Unclassifiable)
- Factors other than JARDIANCE® (None/ Concomitant medication/ Concomitant disease/ etc)
- Action taken with study drug due to AE (Discontinued/ Reduced/ Increased/ Continue/ Unknown/ Not applicable)
- Recurrence in reintroduced (Recurrence/ Do not recur/ Unknown/ Not applicable)
- Adverse Event of Special interest (Not applicable/Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection/Increased urination/Urinary tract infection/Volume depletion/ Diabetic Ketoacidosis, Decreased renal function, Hepatic injury defined by the alterations of liver parameters/Lower limb amputation)
- Investigator’s comments(if needed)

8.3.3.2 Assessment of efficacy

① <u>HbA1c:</u>

HbA1c should be collected within 1 month prior to baseline and after 12 weeks and 24 weeks of treatment.

② Fasting Plasma Glucose (FPG):

FPG should be collected within 1 month prior to baseline and after 12 weeks and 24 weeks of treatment.

③ Body Weight:

Body weight should be collected within 1 month prior to baseline and after 12 weeks and 24 weeks of treatment.

④ Blood Pressure (SBP, DBP) :

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

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

8.3.4 Items of Investigation

8.3.4.1 Demographic data

For demographic evaluation, following background information of subjects shall be recorded:

- Subject signed date
- Subject study number
- Age
- Gender
- Pregnancy (current status)
- Height
- Body weight
- Smoking status

8.3.4.2 Medical/Surgical history and pre-treatment experience

The medical/surgical history to be collected and the treatment experience prior to administration of this drug includes:

- Date of diagnosis
- Family history of T2DM
- Diabetes mellitus related complication (including but not limited to Retinopathy, Neuropathy, Nephropathy, Vasculopathy, etc.)

- Medical history : Hypertension, Dislipidemia, Coronary artery disease, Stroke, Liver disease, Renal failure, Allergy, Nephropathy, etc.

8.3.4.3 Concomitant medication

Information on concomitant medication that is to be collected includes:

- Brand name or generic name
- Daily dose
- Unit
- Indication
- Start date
- Date of discontinuation or continuation

8.3.4.4 Drug administration status

Information on the study drug administration status includes:

- Dose
- Unit
- Start date
- Date of discontinuation or continuation

8.3.4.5 Information on the site

Information on the site includes:

- Hospital name
- Department
- Physician name

8.4 DATA SOURCES

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

8.5 STUDY SIZE

The sample size of 3,000 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.

8.6 DATA MANAGEMENT

Patients' data will be gathered 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).

8.7 DATA ANALYSIS

8.7.1 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, body weight, smoking status, diabetes mellitus complications, other medical history, disease period, Family history of T2DM, elderly (Age ≥ 65 years), renal impairment and hepatic impairment, allergy, long term use(over 24 weeks)

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

To assess the extent of preferential prescribing and the potential for channeling bias, data from the TRAJENTA® (linagliptin) rPMS will be used as a comparator. The baseline characteristics of patients starting JARDIANCE® for the first time will be compared to the baseline characteristics of patients who started TRAJENTA® for the first time. Proportions and means (SD) of the baseline characteristics will be compared using absolute standardized differences (ASD), where an ASD of at least 10% will be considered a meaningful difference. p-values will also be calculated.

8.7.2 Safety analysis

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 incidence rate 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 incidence rate of adverse events, logistic regression analysis should be conducted, and for statistically significant parameters, the meaning should be described.

8.7.2.1 Adverse Events by preferred Terms (AEs/ADRs/SAEs)

All AEs recorded in the CRF will be classified by body organs and terms under the classification standard of MedDRA terms, and all AEs excluding the AEs whose 'Causality' is "Unlikely" will be treated as AEs whose causality cannot be excluded (hereafter "Adverse Drug Reaction (ADR)"). The study database will not be locked until coding is complete.

① The number of AE according to Severity (Mild, Moderate, Severe), Outcome of the event (Recovered, Not yet recovered, Sequelae, Fatal, Unknown), Action taken with trial drug due to AE (Continue, Reduced, Discontinued, Increased, Discontinued and reintroduced, Not applicable), Causality (Certain/ Probable·Likely/ Probable/ Possible/ Unlikely/ Conditional· Unclassified/ Unaccessible·Unclassifiable),Therapy for the event (Yes, No) will be calculated.

② All AEs will be classified into the preferred terms according to Severity (Mild, Moderate, Severe), Outcome of the event, (Recovered, Not yet recovered, Sequelae, Fatal, Unknown), Action taken with trial drug due to AE (Continue, Reduced, Discontinued, Increased, Discontinued and reintroduced, Not applicable), Causality (Certain, Probable/Likely, Possible, Unlikely), Therapy for the event (Yes, No). Also, the number of each AE will be calculated.

③ The number of patients and the number of Serious AE/Serious ADR (SADR), unexpected AE/ADR, unexpected Serious AE/unexpected Serious ADR, AE/ADR will be calculated according to the preferred terms. Also, the incidence proportion and its 95% confidence interval will be estimated.

④ For subjects excluded from safety analysis set ‡, the number of patients and the number of Serious AE/Serious ADR (SADR), unexpected AE/unexpected ADR, unexpected Serious AE/unexpected Serious ADR, AE/ADR will be calculated according to the preferred terms. Also, the incidence proportion and its 95% confidence interval will be estimated.

‡Patients excluded from safety analysis sets: 'Patients who have not taken JARDIANCE®' and 'Follow-up failure' of patients excluded from safety analysis sets will be excluded (This term reflects the Ministry of Food & Drug Safety (MFDS) guideline).

Safety analyses will be based on all patients treated, i.e. all patients who received at least one dose of JARDIANCE® except those who are found to have no observation after enrolment, invalid registration, or invalid contract with the site. However, if data for patients who have been treated with JARDIANCE® 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.

8.7.3 Efficacy analysis

① Mean, standard deviation, minimum value, maximum value, and median of changes in glycosylated hemoglobin(HbA1c) and fasting plasma glucose(FPG), body weight, and blood pressure (SBP, DBP), which were measured at the last visit versus baseline, should be presented, and if there is 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 8.7.1 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 efficacy 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 efficacy 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.

8.7.4 Interim analyses

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

8.7.5 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.

8.8 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 clerk/doctor.
If corrections are necessary after the data are saved, these will be documented in an audit trail.
For the further quality assurance of the documented patient observations, a sample-based source data comparison will be performed on about 10% of the sites. An additional inspection/quality assurance check of this NIS can be performed in case of any deviation.

8.9 LIMITATIONS OF THE RESEARCH METHODS

8.9.1 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 etc. This allows assessing the impact of informative censoring due to treatment discontinuation. Also, 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.

8.9.2 Channeling bias

Channeling bias can occur due to preferential prescribing in relation to different risks for the events of interest: e.g., if empagliflozin would be more often prescribed to higher risk patients compared to other treatments, higher incidences of outcome events were then expected in the empagliflozin group. To assess the extent of preferential prescribing of JARDIANCE® and the potential for channeling bias, baseline data from the TRAJENTA® (linagliptin) rPMS will be used to provide context for the JARDIANCE® rPMS data.

8.9.3 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.

8.10 DATA PROTECTION, STUDY RECORDS

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 requisite NIS will be submitted to the Ministry of Food And Drug Safety (MFDS) for notification. It is not a local requirement in Korea to obtain Institutional Review Board (IRB) approval for the conduct of regulatory requisite NIS.

However, the protocol of this NIS will be submitted to IRBs 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).

Boehringer Ingelheim Korea will submit interim reports during the re-examination period, and the final report to MFDS upon study completion. The interim 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.

8.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by IRBs/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 informed consent documentation of this non-interventional study.

8.10.2 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.

8.10.2.1 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 reported on the eCRFs must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study; current medical records must also be available.

For the eCRF, the following data need to be derived from source documents:
- Patient participation in the study (study number, patient number, date patient was informed)
- Patient identification (gender, age)
- Physical examination (body weight, blood pressure(SBP, DBP))

- Dates of Patient's visits, including dispensing of study medication
- Medical history (including study indication and concomitant diseases, if applicable)
- Medication history
- 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 If available)
- Completion of Patient's Participation in the study

8.10.2.2 Direct access to source data and documents

The Investigator / institution will permit study-related monitoring, audits, IRB review and regulatory inspection, providing direct access to all related source data / documents. eCRF and all source documents must be available at all times for review by the Sponsor's Medical Project Manager(MPM), auditor and inspection by health authorities (e.g. MFDS). The MPM and auditor may review all eCRF, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in section 8.10.2.1.

8.10.2.3 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.

9. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the applicable sections of GCP, relevant BI Standard Operating Procedures and local regulations. Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in 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/International Conference on Harmonization (ICH) GCP / GPP if applicable.
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.

9.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

Prior to patient participation in the study, written informed 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 informed consent retained by the investigator as part of the study records. A signed copy of the informed 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.

9.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study will be considered confidential and disclosure to third parties will be prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers. Treatment data will be made available to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated from the study will be made available for inspection on request by the participating physicians, the sponsor and/or its representatives and/or designees, by the IRBs/IECs and the regulatory authorities.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An 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 AE 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 reaction
An adverse reaction 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 authorisation 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 (SAE) is defined as any AE which:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity,
- 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 jeopardise 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.

Non Serious Adverse Drug Reaction
Non Serious Adverse Drug Reaction (NSADR) is defined as any adverse reaction which does not meet the SAE criteria.

ASAE (Always Serious Adverse Events)
BI has defined a list of adverse events that are considered as "always serious" by fulfilling the criterion "medically important event" by definition and are therefore judged as serious. If a non-serious AE meets this definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the item "serious" needs to be ticked and an SAE has to be reported in expedited fashion. The list of these adverse events can be found via the eCRF system.

AESI (Adverse Event of Special interest)

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. The adverse events below reported from patients who were administered this drug in a placebo-controlled study in accordance with the approved labeling fall under any adverse events of special interest. The following are considered as AESIs:

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

  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).

Besides, Diabetic Ketoacidosis, which may be observed in patients treated with SGLT-2 inhibitors, also corresponds to an adverse event of special interest in this investigation, and these adverse events of special interest should be closely monitored and reported during the investigation period.

10.2 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 design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorization. Sufficient data from controlled interventional studies are available to support the evidence on the safety and efficacy of the studied JARDIANCE®. For this reason the following AE collection and reporting requirements have been defined.

All adverse events occurred from the signing date on ICF to 30 days after last administration date of medication need to be collected, documented and reported to the sponsor using the AE reporting form of eCRF (13.1).

All SAEs, ASAEs and AESIs must be reported with details of relevant non serious AEs, occurring at the same time, within 24 hours of occurrence and via telephone/fax to the Local PV Manager (LPVM) of BI Korea using the NIS AE form (13.2). All non-serious Adverse Reactions associated with JARDIANCE® (empagliflozin) and pregnancy monitoring forms must be reported within 7 calendar days of occurrence and via telephone/fax to the LPVM of BI Korea. If any new or further information to these events is available, a follow-up NIS AE report has to be sent to BI. All SAEs and non-serious AEs must include a causal relationship assessment from the physician.

All ADRs (serious and non-serious), including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

Contact details:

Local PV Manager (LPVM)

Address: BoehringerIngelheim Korea, Medical Dept.
15F, Yonsei Severance Bldg.10, Tongil-ro, Jung-gu, Seoul, Korea (Postal code : 04527)

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

Causal relationship of AEs
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an AE. An adverse reaction, in contrast to an AE, is characterised 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 (e)CRF 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

a. 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 AE

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

Pregnancy

In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken study medication, JARDIANCE® the investigator must report any drug exposure during pregnancy which occurred in a female subject or in a partner to a male subject to the Sponsor's LPVM by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE/AESI, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded as well within the respective timelines.

The ISF will contain the Pregnancy Monitoring Form (Part A and B).

Expedited Reporting of AEs and Drug Exposure During Pregnancy

The following must be reported by the investigator on the NIS AE form from signing the informed consent onwards until the end of the study:

Type of Report	Timeline
All **Serious Adverse Events** (SAEs), **Always Serious Adverse Events** (ASAEs) and **Adverse Event of Special interest** and non-serious AEs relevant to the SAEs/ASAEs/AESI * *13.2 SAE/ Non-Serious Adverse Reaction Report*	immediately within 24 hours
All **AEs with fatal outcome** * *13.2 SAE/ Non-Serious Adverse Reaction Report*	immediately within 24 hours
All **non-serious Adverse Reactions** associated with JARDIANCE® (empagliflozin) * *13.2 SAE/ Non-Serious Adverse Reaction Report*	7 calendar days
All pregnancy monitoring forms * *13.3 Pregnancy Monitoring Form A, B*	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 and fax the NIS AE form.

All other Adverse Events must be reported using eCRF within 2weeks to the Sponsor.

Information required
For each reportable AE, the investigator should provide the information requested on the appropriate (e)CRF pages and the NIS AE form.
For each AE, the investigator will provide the onset, end, intensity, outcome, seriousness and action taken with JARDIANCE® tablets. The investigator will determine the relationship of JARDIANCE® tablets to all AEs as defined in the 'Adverse Event Reporting' section of the physician 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 JARDIANCE® 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.

10.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements.

11. 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.

12. REFERENCES

12.1 PUBLISHED REFERENCES

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12.2 UNPUBLISHED REFERENCES

ra00656956 JARDIANCE® Company Core Data Sheet, 09 January 2015

c01838761-15 empagliflozin Investigator's Brochure, 23 July 2015

13. APPENDICES

13.1 ELECTRONIC CASE REPORT FORM

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

13.2 SAE/ NON-SERIOUS ADVERSE REACTION REPORT

Please refer to "SAE/ NON-SERIOUS ADVERSE REACTION REPORT" in site file or in electronic CRF web page for the latest version.

13.3 PREGNANCY MONITORING FORM

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

13.4 JARDIANCE® PRESCRIPTION INFORMATION FOR KOREA

Please refer to "JARDIANCE® Prescription Information for Korea" in site file or in electronic CRF web page for the latest version.

14. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	30 May 2016	Version number and date	Update of version number and date	Change of protocol version
2	12 Jul 2016	8.7.2 Safety analysis 8.7.3 Efficacy analysis	8.7.2 Safety analysis was added to; Logistic regression analysis 8.7.3 Efficacy analysis regression analysis was changed to; logistic regression analysis	MFDS comments
3	06 Feb 2017	Version number and date	Update of version number and date	Change of protocol version
4	21 Aug 2017	8.2.3.2 Visit 1; Baseline Visit 8.2.3.3 Visit 2 8.2.3.4 Visit 3 10.1 Definitions of adverse events 13.Appendices	8.2.3.2 Change of data collection period 8.2.3.3, 8.2.3.4 Addition of Renal function test on Follow up visit 10.1 Addition of 'Always Serious Adverse Events' 10.1 Addition of 'AESI' case (Lower limb amputation)	- Period adjustment for completeness of data collection - Follow up for renal function - Addition of AE collection and method classification method according to BI PV process
5	23 Nov 2017	Abstract 8.2.3.2 Visit 1; Baseline Visit	Addition to Study size and study sites, Final effectiveness evaluation 8.2.3.2 Change of data collection period 13. Appendices are attached separately	- Period adjustment for completeness of data collection - Attached appendix separately

APPROVAL / SIGNATURE PAGE

Document Number: c09963608 **Technical Version Number:6.0**

Document Name: clinical-trial-protocol

Title: A regulatory requirement non interventional study to monitor the safety and effectiveness of JARDIANCE® (empagliflozin 10mg, 25mg) in Korean patients with type 2 diabetes mellitus

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Monitor	[redacted]	29 Nov 2017 06:05 CET
Approval-Pharmacovigilance		29 Nov 2017 06:22 CET
Approval-Safety		29 Nov 2017 07:48 CET
Approval-Medical Monitor		29 Nov 2017 08:04 CET
Approval-EU Qualified Person Pharmacovigilance		29 Nov 2017 08:22 CET
Approval-Team Member Medicine		29 Nov 2017 12:31 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed