Observational and Non-Interventional Study (ONIS)
New Data Collection Protocol

Document Number:	c42645766-03
BI Study Number:	1245-0323
BI Investigational Product(s):	JARDIANCE®
Title:	A regulatory non-interventional study to monitor the safety and efficacy of JARDIANCE® (Empagliflozin 10 mg) in Korean patients with Chronic Kidney Disease (CKD)
Brief lay title:	JARDIANCE® Post Marketing Surveillance in Korean patients with Chronic Kidney Disease (CKD)
Protocol version identifier:	3.0
Date of previous version of protocol:	06 October 2023
PASS:	Yes
EU PAS register number:	EUPAS107293
Active substance:	SGLT-2 inhibitor (A10BK03) / Empagliflozin
Medicinal product:	Jardiance tablets 10mg
Product reference:	NA
Procedure number:	NA
Marketing authorisation holder(s):	[redacted]
Joint PASS:	No
Research question and objectives:	To monitor the safety profile and efficacy of JARDIANCE® in Korean patients with CKD in routine clinical practice

Country(-ies) of study:	Republic of Korea
Author:	[redacted] Email: [redacted]
Marketing authorisation holder(s):	[redacted]
MAH contact person:	
EU-QPPV:	Email: [redacted]
Signature of EU-QPPV:	The signature of the EU-QPPV is provided electronically.
Date:	28 February 2024

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BI	Boehringer Ingelheim
BMI	Body Mass Index
CA	Competent Authority
CDA	Confidentiality Agreement
CI	Confidence Interval
CKD	Chronic Kidney Disease
CRF	Case Report Form
CRO	Contract Research Organization
CV	Cardiovascular
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DMP	Data Management Plan
EC	Ethics Committee
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
HbA1c	Glycated Hemoglobin
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
KA	Ketoacidosis
KDIGO	Kidney Disease: Improving Global Outcomes
KIMS	Korea Index of Medical Specialties
KPAC	Korean Pharmaceutical Affairs Code
KPBMA	Korea Pharmaceutical and Bio-Pharma Manufacturers Association
KRPIA	Korean Research-based Pharma Industry Association
LPVM	Local Pharmacovigilance Manager
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities

MFDS	Ministry of Food and Drug Safety
ONIS	Observational and Non-Interventional Study
PASS	Post-Authorisation Safety Study
PMP	Project Management Plan
PMS	Post Marketing Surveillance
QV	Qualification Visit
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFQ	Site Feasibility Questionnaire
SGLT-2	Sodium Glucose Cotransporter 2
SOP	Standard Operating Procedure
UACR	Urine Albumin-Creatinine Ratio

3. RESPONSIBLE PARTIES

An ONIS lead who is appointed by [redacted] is 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 study,
- order the materials as needed for the study,
- ensure appropriate training and information of a Contract Research Organization (CRO) and site staff.

[redacted] delegate study tasks such as monitoring activities, data management, statistical analysis, etc. to a CRO and the delegated tasks are performed in accordance with the applicable SOPs of CRO or BI as described in a Project Management Plan (PMP).

Participating study sites are general hospitals or clinics. Contact details and the list of all investigators are kept in a stand-alone document.

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: JARDIANCE®			
Name of active ingredient: SGLT-2 inhibitor (A10BK03) / Empagliflozin			
Protocol date: 26 July 2023	**Study number:** 1245-0323	**Version/Revision:** 3.0	**Version/Revision date:** 28 February 2024
Title of study:	A regulatory non-interventional study to monitor the safety and efficacy of JARDIANCE® (Empagliflozin 10 mg) in Korean patients with Chronic Kidney Disease (CKD)		
Rationale and background:	This Post Marketing Surveillance (PMS) is a local Post Authorized Safety Study (PASS) stipulated in the local PMS regulation: A surveillance that the Marketing Authorization Holder (MAH) conducts during the re-examination period (4-6 years) in order to collect, review, confirm, or verify the information regarding the safety and efficacy of commercially licensed new drugs requiring the re-exmination. This real world data is submitted to the Ministry of Food and Drug Safety (MFDS) and the surveillance results are reflected in the approved information. JARDIANCE® was submitted for Chronic Kidney Disease (CKD) indication to MFDS and a mandatory post-approval study was requested to collect safety		

	data from 250 participants in a single arm study conducted in a real world environment for 2 years, which is now accepted to meet the Risk Management Plan (RMP) regulation. Although the safety profile of JARDIANCE® has been established in clinical trials, it is possible that patients with more diverse conditions than those enrolled in clinical trials will be treated with JARDIANCE® in routine clinical setting. Therefore, this PMS can provide supplementary data to monitor the safety of JARDIANCE® in Korean patients with CKD in a real-life clinical setting.
Research question and objectives:	The primary and secondary objectives are to monitor the safety and efficacy of JARDIANCE® in Korean patients with CKD in routine clinical practice.
Study design:	Single-arm, open-label, multi-centre, observational and non-interventional study based on newly collected data
Population:	Inclusion criteria: • Age ≧19 years at enrolment • Patients diagnosed with CKD • Patients with CKD starting JARDIANCE® for the first time in accordance with the approved label in Korea • Patients who have provided informed consent and signed the data release consent form Exclusion criteria: • Patients with previous exposure to JARDIANCE® • Patients with hypersensitivity to empagliflozin or to any of the excipients • Patients with type 1 diabetes • Patients with history of diabetic ketoacidosis (DKA) • Patients with rare hereditary conditions of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption • Patients who are pregnant or are breastfeeding or who plan to become pregnant during the study period
Variables:	Outcomes of safety: All reported adverse events (AEs) in participants who take at least one dose of JARDIANCE® Outcomes of efficacy: Change in Urine Albumin-Creatinine Ratio (UACR) from baseline to 12 weeks and/or 24 weeks of treatment
Data sources:	Participants' medical records
Study size:	250 participants
Data analysis:	All statistical analyses will be explorative in nature. Participant characteristics will be reported using measures of central tendency (e.g., mean, median) and variance (standard deviation, quartiles) for continuous variables and using frequencies and percentages for count data. Frequency

	of safety events will be reported using frequencies and incidence with 95% confidence interval (CI). The changes of the efficacy outcomes from baseline will be compared in an exploratory sense via paired t-test.
Milestones:	Start of data collection: March 2024 End of data collection: November 2025 Interim report 1: January 2024 Interim report 2: January 2025 Final study report: February 2026

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	06 October 2023	9.3.2.1 Primary outcomes	· Added liver injury and lower limb amputation as AESI. · Added a description of specific adverse events (Severe hypoglycaemia, Urinary tract infection, Genital infection, Bone fracture, Urinary tract malignancy, Volume depletion, Acute kidney injury, Gout, Hyperkalaemia).	According to the review comment of MFDS
2	06 October 2023	11.1 Deffinitions of adverse events	· Added definitions of liver injury and lower limb amputation. · Added a description of specific adverse events.	According to the review comment of MFDS
3	28 February 2024	Title page	Added EU PAS register number.	Add EU PAS register number
4	28 February 2024	4. Abstract	· Changed the study period and sample size. · Changed the milestones.	Reflection of MFDS approval

Number	Date	Section of study protocol	Amendment or update	Reason
5	28 February 2024	6. Milestones	Changed the milestones.	Reflection of MFDS approval
6	28 February 2024	7. Rationale and background	Changed the study period and sample size	Reflection of MFDS approval
7	28 February 2024	9.1 Study design	Changed the safety data collection period	According to the change in the study period
8	28 February 2024	9.2.2 Study population	Changed the sample size	Due to change in the study period
9	28 February 2024	9.2.2.3 Exclusion critera	Deleted “patients on dialysis”.	According to local label revision
10	28 February 2024	9.2.3 Study visits	Added “serum creatinine” to laboratory tests.	To collect serum creatinine levels
11	28 February 2024	9.5 Study size	Changed the study period and sample size.	Reflection of MFDS approval
12	28 February 2024	9.7.1 Analysis sets	Changed the sample size.	Due to change in the study period
13	28 February 2024	11.1 Deffinitions of adverse events	Added definitions of specific AEs.	To clarify the definitions of specific AEs
14	28 February 2024	11.2 Adverse event and serious adverse event collection and reporting	Added a description of study discontinuation of pregnant participants.	To clarify study discontinuation for pregnant participants

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	FEB 2024
Start of data collection	MAR 2024
End of data collection	NOV 2025
Interim report 1	JAN 2024
Interim report 2	JAN 2025
Registration in the EU PAS register	OCT 2023
Final report of study results:	FEB 2026

7. RATIONALE AND BACKGROUND

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health.[P22-08628] CKD is a major public health problem worldwide and also strongly interrelated with other major disease, including Diabetes and Cardiovascular (CV) disease, which remain the leading causes of morbidity and premature death in this patient population.[R13-0282]

CKD is a major, growing, health concern in Asia and the substantial burden of CKD in Asia may be prevalent at similar or even greater magnitudes as compared with those observed in other parts of the world including North America and Europe.[R22-3432]

Empagliflozin is an orally available, potent, and selective inhibitor of the renal dependent sodium glucose cotransporter 2 (SGLT-2). Its selective inhibition reduces renal reabsorption of sodium and glucose. This leads to both increased urinary sodium and glucose excretion.[c37800399-01] While urinary sodium excretion returns to normal within few days of empagliflozin administration, the effect on urinary glucose continues for as long as the medication is used.[c37800399-01] Empagliflozin also reduces blood pressure, arterial stiffness and measures of myocardial workload, likely through various proposed mechanisms, and improves other potential CV risk factors.[P15-00589, P15-09541]

The EMPA-KIDNEY trial showed that treatment with empagliflozin significantly reduced the risk of kidney disease progression or CV death by 28% compared with placebo. Treatment with empagliflozin demonstrated clinically meaningful cardio-renal benefits in a broad range of CKD patients. Empagliflozin was also superior to placebo in reducing the risk of hospitalisations for any cause by 14% and treatment effects were consistent regardless of diabetes status, estimated Glomerular Filtration Rate (eGFR) or albuminuria levels.

The frequencies of prespecified non-serious AE, AEs leading to treatment discontinuation, and SAEs were similar to placebo. The results from the AEs and safety laboratory analyses were generally consistent with the known safety profile of empagliflozin. [c37800399-01]

This PMS is a local PASS stipulated in the local PMS regulation: A surveillance that the MAH conducts during the re-examination period (4-6 years) in order to collect, review, confirm, or verify the information regarding the safety and efficacy of commercially licensed new drugs requiring the re-examination. This real world data is submitted to MFDS and the surveillance results are reflected in the approved information.

During the review of the CKD indication MFDS imposed this mandatory post-approval commitment to submit safety data of 250 participants under real world conditions for 2 years, which is now accepted to meet the RMP regulation.

Although the safety profile of JARDIANCE® has been established in clinical trials, it is possible that patients with more diverse conditions than those in clinical trials will be enrolled in routine settings. Therefore, this PMS can provide supplementary data to monitor the safety of JARDIANCE® in Korean patients with CKD in a real-life situation.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 PRIMARY OBJECTIVE

The primary objective is to monitor the safety profile of JARDIANCE® in Korean patient with CKD in routine clinical practice.

8.2 SECONDARY OBJECTIVE

The secondary objective is to monitor the efficacy of JARDIANCE® by evaluating changes in UACR after 12 and/or 24 weeks of treatment.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a single-arm, open-label, multi-centre ONIS based on newly collected data. As per local regulations, safety data will be collected for about 2 years.

This study will be carried out by enrolling patients in a consecutive manner into the study requiring completion of case report forms (CRFs) for all participants who initially administered JARDIANCE® following the study start date until the planned number of participants is reached. Prior to the initiation of the study, written contract shall be concluded, and this contract shall be concluded among [redacted], CRO (if applicable) and with the head of the site or the investigator with his/her consent.

Participants will be managed according to local practice guidelines. The choice of treatment will be solely at the discretion of the investigator. JARDIANCE® will be administered according to the approved label in Korea. Hence there are no additional risks to participants by participating in this ONIS.

9.2 SETTING

9.2.1 Study sites

Approximately 20 sites with approximately 20 or more investigators will participate in the study. To minimize selection bias at the site level, the goal is to have participating centers reflect a balance between general hospitals and clinics. The investigators will be mainly internists or nephrologists.

As provided in the 「Standards for Re-examination of New Drugs, etc. of MFDS Notification, [redacted] should select study sites according to the following requirements:

- Equipment/facility and personel support capable of fully achieving the goal of investigation should be available.
- The investigators 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.
- Study site and the investigators should strictly keep confidential the record of personal data of patients/participants.
- The investigators should be fully aware of the 「Standards for Re-examination of New Drugs, etc.」 and study protocol.

9.2.1.1 Managing Site and Physician/Investigator Selection, Contracting and Training

See Annex 3.

9.2.2 Study population

250 participants will be enrolled. To minimize the selection bias, consecutive participants 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 CKD in Korea
When diagnosing CKD, the criteria of Kidney Disease: Improving Global Outcomes (KDIGO) can be referred to (Annex 6).

9.2.2.2 Inclusion criteria

- Age ≧19 years at enrolment
- Patients diagnosed with CKD
- Patients with CKD starting JARDIANCE® for the first time in accordance with the approved label in Korea
- Patients who have provided informed consent and signed the data release consent form

9.2.2.3 Exclusion criteria

- Patients with previous exposure to JARDIANCE®
- Patients with hypersensitivity to empagliflozin or to any of the excipients
- Patients with type 1 diabetes

- Patients with history of Diabetic Ketoacidosis (DKA)
- Patients with rare hereditary conditions of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
- Patients who are pregnant or are breastfeeding or who plan to become pregnant during the study period

9.2.2.4 Investigation for participants of special interest

The participants who have signed the data release consent form, participants of special interest (geriatric (older than 65 years), pregnant women, hepatic impairment and other special population) among the participants who conducted investigation for safety assessment after the administration of JARDIANCE® can be further summarized into subgroups collected from this.

9.2.3 Study visits

9.2.3.1 Visit 1 (Baseline)

At Visit 1, the informed consent is obtained from the participant using the data release consent form. After obtaining written informed consent, the following data will be collected from the participant's medical record:

- Visit date
- Date of data release consent
- Diagnosis date of CKD
- Inclusion/exclusion criteria eligibility
- Demographics (age (month and year of birth), gender, current pregnancy status (female only), current breastfeeding status (female only), smoking status, alcohol intake status, history of type 2 Diabetes Mellitus (DM)
- Medical history (within 6 months)
- Past or concomitant medication use (within 1 month)
- Physical examination information (height, weight, Body Mass Index (BMI), blood pressure)
- Efficacy assessment: UACR (The measurement taken on the date closest to the visit date is collected. A value from up to 6 months prior to the visit date can be used as a baseline.)
- Other laboratory test results (Glycated Hemoglobin (HbA1c), eGFR, serum creatinine, etc.: if available)
- JARDIANCE® administration status (dose, frequency, total daily dose, start and end date)

At Visit 1, the participant will be requested to contact the investigator in the event of any AEs noted after initiating JARDIANCE® treatment.

9.2.3.2 Visit 2 (Follow-up 1: 12 weeks from Visit 1)

After 12 weeks from Visit 1, the participant returns for follow-up. The following data will be collected:

- Visit date
- Physical examination information (weight, BMI, blood pressure)
- Concomitant medication use
- Any changes in the JARDIANCE® administration status
- Efficacy assessment: UACR (The measurement taken on the date closest to the visit date is collected.)
- Any changes in the laboratory test results (HbA1c, eGFR, serum creatinine, etc.: if available) if there is any lab result which was clinically significant compared to data before JARDIANCE® treatment
- Safety assessment: any AEs noted
- Study completion status (if applicable)
- Investigator's overall efficacy assessment (if applicable)

9.2.3.3 Visit 3 (Follow-up 2: 24 weeks from Visit 1)

After 24 weeks from Visit 1, the participant returns for a final follow-up. The following data will be collected:

- Visit date
- Physical examination information (weight, BMI, blood pressure)
- Concomitant medication use
- Any changes in the JARDIANCE® administration status
- Efficacy assessment: UACR (The measurement taken on the date closest to the visit date is collected.)
- Any changes in the laboratory test results (HbA1c, eGFR, serum creatinine, etc.: if applicable) if there is any lab result which was clinically significant compared to data before JARDIANCE® treatment
- Safety assessment: any AEs noted
- Study completion status
- Investigator's overall efficacy assessment

9.2.4 Study discontinuation

BI 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, or any other administrative reasons
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	**1**	**2**	**3**
Week	**0**	**12**	**24**
Data release consent	X		
Diagnosis	X		
Inclusion/Exclusion criteria	X		
Demographics (initial, gender, age, smoking status, alcohol intake status, history of type 2 DM)	X		
Medical history[1)]	X		
Physical examination (blood pressure, height[2)], weight, BMI)	X	X	X
Past[3)] or concomitant therapies	X		
JARDIANCE® administration status	X	X	X
UACR[4)]	X	X	X
Investigator's overall efficacy assessment		X[A]	X
Other laboratory tests[5)]	X[B]	X[B]	X[B]
AEs		X	X
Study completion		X[A]	X

A: If applicable
B: If available
1) Medical history 6 months prior to Visit 1 is collected.
2) Height is measured only in Visit 1.
3) Past medications 1 month prior to Visit 1 are collected.
4) Data performed on the date closest to each visit date are collected.

5) Data performed on the date closest to each visit date can be collected. Laboratory test results such as eGRF, HbA1c, etc. are collected, if available.

9.3 VARIABLES

9.3.1 Exposures

Exposure to JARDIANCE® will be estimated as time from the first intake date to the last intake date of the participant during the study period.

The treatment dose is based on the current authorized label in Korea. The recommended dose of JARDIANCE® is 10mg once daily and it can be taken with or without food.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

The primary outcomes are the safety outcomes calculated as the incidence of:

- AEs
- Serious adverse event (SAEs)
- Non-serious adverse events
- Adverse drug reaction (ADR)s
- Serious adverse drug reactions
- Unexpected adverse events
- Adverse events of special interest (AESIs)
- Specific adverse events
- Adverse events leading to temporary or permanent discontinuation
- Adverse events by intensity
- Adverse events by outcome of the events
- Adverse events by causality
- Adverse events leading to death

Assessment of safety:

- Adverse events (event name/ symptoms/ sign)
- 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 events of special interest (Liver injury, Ketoacidosis in diabetic and non-diabetic population, Lower limb amputation)
- Specific adverse events (Severe hypoglycaemia, Urinary tract infection, Genital infection, Bone fracture, Urinary tract malignancy, Volume depletion, Acute kidney injury, Gout, Hyperkalaemia)

9.3.2.2 Secondary outcomes

The secondary outcome is the efficacy outcome as follows:

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

9.3.2.3 Further outcomes

The further outcomes are as follows:

- Progression or reduction in albuminuria* from baseline (defined as a worsening to a more severe UACR category)

*Albuminuria category [P22-08623] is assigned as follows:

		ACR (approximate equivalent)		
Category	AER (mg/24h)	(mg/mmol)	(mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased[a]
A3	>300	>30	>300	Severely increased[b]

ACR, albumin-creatinine ratio; AER, albumin excretion rate
[a]Relative to young-adult level.
[b]Including nephrotic syndrome (AER usually >2200 mg/24h [ACR >2200 mg/g; >220 mg/mmol]).

- Investigator's overall efficacy assessment after 12 weeks and/or 24 weeks of treatment

  The overall efficacy assessment is performed at the investigator's discretion. The information includes:

  - Improved: If determined as there is any effect of maintaining or improving clinical condition.
  - Unchanged: If clinical condition has not been changed compared with before administration, and not determined as there is any effect of maintaining clinical condition.
  - Aggravated: If clinical condition is worse than before administration.
  - Unassessable: If clincal condition cannot be determined.

9.3.3 Covariates

1) Participant characteristics
   - Demographics: age, gender, pregnancy status, breastfeeding status, smoking status, alcohol intake status, history of type 2 DM
   - Physical examination results: height, weight, blood pressure, BMI
   - Disease information: duration of disease, medical history, past or concomitant medications
2) JARDIANCE® administration status: total duration of administration, total administered dose, average daily dose
3) Participants of special investigation: pediatric population, geriatric population, pregnant women, lactating women, hepatic impairment
4) Laboratory test results
5) Study completion status: follow-up duration, reasons for stopping JARDIANCE® administration

9.4 DATA SOURCES

The source data will be captured from the medical records of the patients who have consented to data release. Details on how to capture the data are described in section 9.10.2.

9.5 STUDY SIZE

The enrolment target is 250 participants for a total of 2 years, considering the prevalence and market conditions in Korea.

9.6 DATA MANAGEMENT

Participants' data will be gathered by electronic Case Report Form (eCRF). The data management procedures to ensure the quality of the data are described in detail in the data management plan (DMP). Data management and statistics will be outsourced to a qualified CRO. DMP will be developed following BI and/or CRO relevant SOPs.

9.7 DATA ANALYSIS

The statistical analysis plan for the study is summarized below. Full details of the statistical analysis will be documented in the Statistical Analysis Plan (SAP), which will be finalized before the end of data collection.

9.7.1 Analysis sets

250 participants will be entered in this study, and each participant will be followed for baseline, short term (12 weeks) follow-up, and long term (24 weeks) follow-up. The safety analysis will comprise all participants who took JARDIANCE® with at least one time of safety follow-up.

9.7.1.1 Number of participants who entered the study

This number means the actual number of participants as specified in the contract concluded with the investigator prior to initiation of the study.

9.7.1.2 Number of participants of CRF collection

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

9.7.1.3 Number of participants for safety assessment

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

a. Participants who did not signed (signature missing), or participants who signed on the data release consent form of JARDIANCE® CKD PMS prior to the contract date
b. Participants who took JARDIANCE® prior to the contract date
c. Participants who took JARDIANCE® prior to signing the data release consent form
d. Participants who have not taken JARDIANCE®
e. Follow-up failure: Participants whose safety information cannot be obtained due to lost-to-follow-up
f. Participants who were prescribed Jardiance for indications outside the local label

9.7.1.4 Number of participants for efficacy assessment

These cases include those who signed the data release consent form to participate in this study, had at least one follow-up visit, took Jardiance®, and had at least some follow-up data for the efficacy.
Reflecting the MFDS guideline, the cases below shall be excluded from efficacy analysis (defined below) set in the following order:

a. Participants excluded from the safety analysis set listed in section 9.7.1.3.

b. Participants with missing information of efficacy assessment listed in section 9.3.2.2.

9.7.2 Safety analysis

Safety analyses will be performed on the safety set.

Frequency of safety events will be reported using numbers of participants with AEs, frequencies, incidence with 95% CIs. AEs will be tabulated by system organ class and preferred term for overall and for subgroup based on demographics and baseline characteristics.

Categorical variables will be reported using numbers of participants with AEs, frequencies, incidence with 95% CIs. Incidence will be analyzed using Pearson's chi-square or Fisher's exact test to determine if there are statistically significant differences.

Continuous variables will be reported using number of participants. Incidence will be reported using odds ratios and 95% CIs by simple logistic regression.

As a result of simple logistic regression, statistically significant variables will be reported using odds ratios and 95% CIs by multiple logistic regression.

AEs will be coded with the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Past / concomitant medications will be coded according to the current version of the Korea Index of Medical Specialties (KIMS) coding system.

Safety analyses will be based on all participants treated, i.e. all participants who received at least one dose of JARDIANCE®. However, if data for participants who have been treated with JARDIANCE® beyond the scope of approved label are collected, these will be listed separately.

9.7.3 Efficacy analysis

Efficacy analyses will be performed on the efficacy set.

Efficacy analyses will be performed by subgroup based on demographics and baseline characteristics.
The standard descriptive statistical parameters (number of participants, mean, standard deviation, median, minimum, maximum, etc.) will be summarized.

The changes of the efficacy outcomes from baseline will be compared in an exploratory sense via paired t-test.

For investigator's overall efficacy assessment, the number and percentage of participants will be presented. If the result of overall assessment is 'improved', it will be classified as 'effective'. If the result of overall assessment is 'unchanged' or 'aggravated', it will be classified as 'ineffective'.

'Effective' and 'ineffective' will be reported using numbers of participants, percentages with 95% CIs.

Categorical variable will be reported using numbers of participants, numbers of participants assessed as 'effective', effective rates and 95% CIs. Efficacy will be analyzed by Pearson's chi-squire test or Fisher's exact test to determine if there are statistically significant differences.

Continuous variable will be reported using numbers of participants. Odds ratio and 95% CIs by simple logistic regression will be summarized.

To estimate any factors that are thought to influence an effective rate, logistic regression analysis and/or poisson regression will be conducted, and for statistically significant covariates the meaning will be described.

9.7.4 Interim analysis

There will be interim analyses according to Korean regulations, see section 6.

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. Missing or incomplete dates of AEs are imputed according to BI standard.

9.8 QUALITY CONTROL

The quality control, review, and monitoring plan are summarized below. Greater details are documented in the DMP and PMP.

All entries in eCRFs and the existing coding will be stored in a database. The structure of the database is based on the division into sections and entry fields defined in the eCRFs. To improve and ensure data quality, data checks will be performed automatically in the eCRFs 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 eCRFs. The tests for consistency and completeness based on this will be performed during entry in the eCRFs. 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.

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 ONIS 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 participants. To the extent possible, occurrence of adverse event, at minimum, for participants lost to follow up will be obtained via pariticipant visit / telephone / letter / email etc. This allows assessing the impact of informative censoring due to treatment discontinuation. Also, participants lost to follow-up will be characterized compared to the remaining participants 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., a higher frequency of outcome events would be expected in the JARDIANCE® group if JARDIANCE® was prescribed more frequently to high-risk participants compared to other treatments. However, this will not be assessed since there is no comparator group.

9.9.3 Confounding

As in any observational study, confounding may affect the estimation of association between drug exposure and outcome of interest and statistical techniques. When the investigators assess the overall efficacy, different assessment criteria among them may affect the study outcome. Also, information bias may occur and cause a distortion in the observed association due to a lack of accurate measurements of key study variables. If key study variables (exposure, health outcome, or confounders) are inaccurately measured or classified (which may happen in real-world clinical settings), bias in the risk ratio, rate ratio, or odds ratio can be produced.

9.10 OTHER ASPECTS

The protocol of this regulatory required ONIS will be submitted to MFDS for approval. Also, the protocol will be submitted to Institutional Review Board (IRBs) whenever required or requested by these study sites. This study will be conducted in accordance with the 「Standards for Re-examination of New Drugs, etc.」 notified by MFDS, the 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 the Korea Pharmaceutical and Bio-Pharma Manufacturers Association (KPBMA) and the Korean Research-based Pharma Industry Association (KRPIA)).

[redacted] will submit interim reports during re-examination period, and the study 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.

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 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 informed consent documentation of this study.

9.10.2 Study records

CRFs for individual participants will be provided by the sponsor, either on paper or via remote data capture, if applicable.

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 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 eCRFs **all** data must be derived from source documents.

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.

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 GPP, Guidelines for Good Pharmacovigilance Practices (GVP) and the relevant BI 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 ONIS will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB / 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 informed consent must be obtained from each patient (or the patient's legally accepted representative) per GPP and according to the regulatory and legal requirements of the participating country, if applicable.

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 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 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 AE 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 (SAE) is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, 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
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 following are considered as AESIs:

Liver 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 within 30 days of each other, OR
- An elevation of AST and/or ALT ≧3-fold ULN and INR ≧1.5-fold ULN measured at the same visit, or in samples drawn within 30 days of each other, OR
- An elevation of AST and/or ALT ≧3-fold ULN with new onset, or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%), OR
- An isolated elevation of AST and/or ALT ≧5-fold ULN

Ketoacidosis (KA) in diabetic and non-diabetic population

If metabolic acidosis, KA and DKA is suspected, further investigations should be done according to the medical judgment and the clinical course until a diagnosis is made and/or the patient is recovered.
Due to its mechanism of action, empagliflozin may potentially modify the clinical presentation of KA which may occur at lower plasma glucose levels in patients with DM and potentially also in non-diabetic patient population. The diagnosis of KA in these patients can be based on arterial pH ≦7.30, serum bicarbonate levels <15 mmol/L and measurement of serum beta-hydroxybutyrate levels. Other diagnostic criteria which can support the diagnosis of KA are urine ketones and anion gap >10 mmol/L.
Investigators should note that not all criteria mentioned above need to apply for the diagnosis of KA, and clinical judgment should also be taken into consideration.

Lower limb amputation

Any event leading to a lower limb procedure of amputation, auto-amputation or disarticulation as defined below is considered as an AESI.
"Amputation is a resection of a limb through a bone. Disarticulation is a resection of a limb through a joint. Auto-amputation is a spontaneous separation of non-viable portion of the lower limb.
Not included in this definition are debridement (removal of callus or dead tissue), procedures on a stump (like stump revision, drainage of an abscess, wound revision etc.) and

other procedures (e.g., nail resection or removal) without a concomitant resection of a limb (amputation or disarticulation)." (International Working Group of Diabetic Foot, 2015). Each lower limb amputation, disarticulation, or auto-amputation should be reported separately. The SAE report should include the date of the procedure, the level of amputation or disarticulation, the medical condition(s) leading to the procedure and if the patient had some of the known risk factor(s) for lower limb amputation.

Specific Adverse Event

The following are considered as specific adverse events:
Severe hypoglycaemia (defined as low blood sugar causing severe cognitive impairment which requires assistance from another person for recovery), Urinary tract infection, Genital infection (see below for definition), Bone fracture, Urinary tract malignancy, Volume depletion (defined as whether or not a participant has experienced symptoms they attribute to dehydration, such as feeling faint or fainting), Acute kidney injury (see below for definition), Gout, Hyperkalaemia

Definitions:

Acute Kidney injury (AKI):

Confirmation of acute kidney injury requires evidence of one of the following:

i. An increase in serum creatinine to 1.5-times a recent historical value (which is presumed to have increased within about a week); OR
ii. Initiation of Renal Replacement Therapy for acute kidney injury

Note: Adapted from 2012 KDIGO staging guidance. Increase in serum creatinine of $\geq$27 µmol/L (or $\geq$0.3 mg/dL) within about 48 hours has been excluded from the definition of AKI stage 1 as this is likely to occur simply due to natural variation in these participants with advanced CKD. Similarly, serum creatinine $\geq$353.6 µmol/L (or $\geq$4.0mg/dl) has been excluded from the definition of AKI stage 3 as this may be less than their recent historical measurement.

Genital infections including Fournier's gangrene:

i. A genital infection is any bacterial or fungal infection of the genitals or perineum, including vulvovaginitis, balanitis and infections of skin between the genital and anus.
ii. Necrotising fasciitis of the perineum is a subset of all serious genital infections characterized by fulminant tissue destruction which may extend from a cellulitis to include fasciitis and myositis. In men, in which it is more common, it can affect the scrotum and penis. In both sexes, it can rapidly spread to involve the anterior abdominal wall and gluteal muscles.
iii. Necrotising fasciitis of the perineum is characterised by:

a. Perineal inflammation (erythema and oedema) with or without evidence of necrosis, severe pain (out of proportion to examination findings), and crepitus or bullous changes (indicating gas gangrene, evident in perhaps a half of cases);
b. Systemic features of infection;
c. A need for rapid surgical debridement and intravenous antibiotics; and
d. Histopathological evidence of extensive tissue destruction, inflammation with abundant bacteria along fascial planes and sometimes necrotising myositis.

Note: Necrotising fasciitis of the lower limb and infections developing from primary ano-rectal disease are not considered a serious genital infection.

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 adverse events

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 serious adverse events, non-serious adverse events and AESIs occurring from the signing date on data release consent form to the end of the study need to be collected, documented and reported to the sponsor using the AE page of eCRF.

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 AE. An adverse reaction, in contrast to an AE, 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 of related or unrelated will be collected considering the 6 categories in accordance with MFDS' requirements.

- **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

Pregnancy:

In rare cases, pregnancy might occur in a ONIS. 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 to the LPSL of [redacted] Pregnant participants should be discontinued from the study (exclusion criteria).

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

The Investigator Site File (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 AE, only the Pregnancy Monitoring Form and not the ONIS AE form is to be completed. If there is an AE associated with the pregnancy a ONIS AE form must be completed in addition.

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

The following must be reported by the investigator on the ONIS AE form (Annex 4) and / or Pregnancy Monitoring Form (Annex 5) from signing on the data release consent form onwards until the end of the study and provide the LPSL of [redacted]:

BI contact details
Local Patient Safety Lead (LPSL)
Tel: [redacted]
Fax:
Address: [redacted]

Type of Report	Timeline
All **Serious Adverse Events** (SAEs)	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 the ONIS AE form and report the ONIS AE form.

Information required

For each reportable AE, the investigator should provide the information requested on the appropriate (e)CRF page and the ONIS AE form.

11.3 REPORTING TO HEALTH AUTHORITIES

AE reporting to regulatory agencies will be done by 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

P15-00589 Inzucchi SE, Zinman B, Wanner C, Ferrari R, Fitchett D, Hantel S, Espadero RM, Woerle HJ, Broedl UC, Johansen OE. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcometrials. Diabetes Vasc Dis Res;12(2):90-100; 2015.

P15-09541 Chilton R, Tikkanen I, Cannon CP, Crowe S, Woerle HJ, Broedl UC, Johansen OE. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. Diabetes Obes Metab; 17(12); 1180-1193; 2015.

P22-08623 KDIGO Executive Committee. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease, Kidney Int.; p. S10 (Suppl); 2022.

P13-0282 Lozano R, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the GlobalBurden of Disease Study 2010. Lancet; 2012; 380(9859); 2095-2128.

R22-3432 Liyanage T, Toyama T, Hockham C, Ninomiya T, Perkovic V, Woodward M, Fukagawa M, Matsushita K, Praditpornsilpa K, Hooi LS, Iseki K, Lin MY, Stirnadel-Farrant HA, Jha V, Jun M. Prevalence of chronic kidney disease in Asia: a systematic review and analysis. BMJ Glob Health. 2022 Jan;7(1):e007525. doi: 10.1136/bmjgh-2021-007525. PMID: 35078812; PMCID: PMC8796212.

13.2 UNPUBLISHED REFERENCES

c37800399-01 A multicentre international randomized parallel group double-blind placebo-controlled clinical trial of EMPAgliflozin once daily to assess cardio-renal outcomes in patients with chronic KIDNEY disease. 1245-0137

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
A regulatory non-interventional study to monitor the safety and efficacy of JARDIANCE® (Empagliflozin 10 mg) in Korean patients with chronic kidney disease

EU PAS Register® number: EUPAS107293
Study reference number (if applicable): N/A

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

1.1.3: According to the local regulation, periodic reports will be submitted to the regulatory authority.

Section 2: Research question		Yes	No	N/A	Section Number
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
	2.1.2 The objective(s) of the study?	☒	☐	☐	8
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.2
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

2.1.4: This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

Section 3: Study design		Yes	No	N/A	Section Number
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

3.3, 3.4: This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	9.2.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.3.6
	4.2.2 Age and sex	☒	☐	☐	9.2.2
	4.2.3 Country of origin	☒	☐	☐	9.2.2
	4.2.4 Disease/indication	☒	☐	☐	9.2.2

Section 4: Source and study populations		Yes	No	N/A	Section Number
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.3.6
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

5.2, 5.3, 5.5, 5.6: This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

6.3, 6.4: This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

Section 7: Bias		Yes	No	N/A	Section Number
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.9.2
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.1, 9.2
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

7.3: This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

Section 8: Effect measure modification		Yes	No	N/A	Section Number
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

Section 9: Data sources		Yes	No	N/A	Section Number
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.2.3
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.2.3
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.2.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.7.1
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7.1
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.7.1

Section 9: Data sources		Yes	No	N/A	Section Number
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

9.1.1, 9.4: This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

Section 10: Analysis plan		Yes	No	N/A	Section Number
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☐	☐	☒	
10.3	Are descriptive analyses included?	☒	☐	☐	
10.4	Are stratified analyses included?	☐	☐	☒	
10.5	Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.4
10.8	Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

10.2, 10.4, 10.5, 10.6, 10.8: This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

Section 11: Data management and quality control		Yes	No	N/A	Section Number
11.1	Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6, 9.8
11.2	Are methods of quality assurance described?	☒	☐	☐	9.10.1
11.3	Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

11.3: This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

Section 12: Limitations		Yes	No	N/A	Section Number
12.1	Does the protocol discuss the impact on the study results of:				
	12.1.1 Selection bias?	☒	☐	☐	9.1, 9.2
	12.1.2 Information bias?	☒	☐	☐	9.9

Section 12: Limitations	Yes	No	N/A	Section Number
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☒	

Comments:

12.2: This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: [redacted]

Date: 07/July/2023

Signature: [redacted]

ANNEX 3. MANAGE SITE AND PHYSICIAN / INVESTIGATOR SELECTION, CONTRACTING, AND TRAINING

Sites may be identified several ways:

- Suggestions from internal colleagues. For instance, obtaining suggestions from local affiliates is crucial.
- Suggestions from external stakeholders, such as vendor if study is outsourced or key external experts
- Existing data such as externally accessed prescriber data, participating physician databases, commercial listings and / or EMR, national registries, marketing information or other secondary data sources.

A comprehensive site list, including contact information for the sites, should be developed well ahead of protocol finalization and the site selection strategy should be clearly outlined in the protocol and operational documents.

Conduct site feasibility questionnaire, if applicable

To ensure that the most appropriate sites will participate in the study, a Site Feasibility Questionnaire (SFQ) can be useful in order to ask sites about their interest and ability to conduct the study. This is especially the case if many sites need to be identified.

Sites may find it helpful to have the study summary so they have a background regarding the study. Depending on local requirements, some countries may require a phone call prior to any study documents being sent.

Obtain signed confidentiality agreement (CDA) first

Before sharing information with a site, a confidentiality agreement (CDA) with the site should be signed. Signatures may take time, so, this should considered in the study timelines.

Considerations when selecting a site:

Below are some criteria for selecting a site:

- **Ability to conduct the study**: Most importantly, the site should be able to conduct the study as outlined in the study summary or protocol.
- **Representativeness**: Sites should not only be restricted to only those with previous research experience but optimized to ensure broad representation of the sites that typically diagnosis and / or treat the indication of interest in a given country. This is to ensure the study provides a representative picture of the real-world practice setting. Thus, the team should evaluate criteria such as the representativeness of practice type, practice size, and professional qualifications. Local input is often crucial.
- **Enrolment rate:** It is important to ask the site how many patients they can enrol. The team should evaluate if this aligns with the requirements of the study summary or protocol. When considering number of patients per site, it is advisable to consider if

site enrollment caps are needed to be instituted to avoid the potential for center effects which drive results.

- **Resources:** It is important to confirm that the site has the needed resources (staff, computer equipment, etc) to conduct the study. Moreover, sites may have a heavy workload or may prioritize other studies, especially if they are conducting clinical trials at the same time.
- **Compliance:** A due-diligence review should be conducted to ensure there are no compliance issues with investigators.

Number of sites:

- The number of sites depends on several factors. Based on sample size needed, it is important to determine the how many patients can be enrolled per site within the timeline of the study. Having several sites will help avoid individual sites dominating the results and potentially compromising the representativeness. Moreover, the team should consider identifying more sites than needed, including “back-up sites” in case site(s) drop out or more sites are needed in case, enrolment rates are lower than expected.

Verification from stakeholders and OPU’s

- The study team should review the results of the SFQ, if done, to determine which sites may be selected for site qualification visits (QV) or phone calls (or “pre-study contact”).
- The list should be verified with each OPU in terms of the target physician specialties and site types that reflect standard of care for the indication under study (e.g. If patients are followed most often by cardiologists in a tertiary care / academic setting, this should be built into the final site breakdown for an OPU). Clear communication pathways should be discussed and agreed upon to ensure that sites are receiving consistent information not only during start-up, but throughout the study.
- The site list should also be reviewed by the local teams to determine if there are existing relationships with the site staff, or if similar studies in the same indication have been previously managed by the team.

Conduct qualification call:

- During the qualification call, the study staff should discuss the protocol (or study summary), patient population of interest, and reconfirm the site’s ability to conduct the study.
- Sites should be informed of the budget expectations, and relevant BI or vendor specific business processes that may impact the site
- The results of the site qualification calls / visits are reported to the study team, after that the final selection of the sites for the study can take place.

ANNEX 4. OBSERVATIONAL AND NON-INTERVENTIONAL STUDY (ONIS) ADVERSE EVENT FORM

Boehringer Ingelheim	**Observational and Non-Interventional Study (ONIS) Adverse Event Form**	BI Study No:	Country:
		Site No:	Subject No:

No. of pages, including this page:

To: Boehringer Ingelheim [*or CRO*] [Address] [Fax number]	From: [site stamp]

BY SIGNING THIS FORM, YOU ARE CONFIRMING THAT THE INFORMATION CONTAINED HEREIN IS ACCURATE.

Record all dates in ddmmmyyyy format (e.g. 01Jan2016)

Type of report	Date	Investigator's signature	Remarks
☐ Initial		_____	
☐ Follow-up		_____	
☐ Follow-up		_____	
☐ Follow-up		_____	
☐ Follow-up		_____	
☐ Follow-up		_____	
☐ Follow-up		_____	

SUBJECT DEMOGRAPHICS

Year of birth: Height __(cm) Weight __(kg)
If unknown, record 'UNK'

Sex: ☐ Male ☐ Female Pregnant: ☐ No ☐ Yes weeks
If pregnant, please submit completed Pregnancy Monitoring Form for Studies

Boehringer Ingelheim	**Observational and Non-Interventional Study (ONIS) Adverse Event Form**	BI Study No:	Country:
		Site No:	Subject No:

EVENT INFORMATION

Record all dates in ddmmmyyyy format (e.g. 01Jan2016). If ongoing, enter 'CONT.' Record all times in 24-hour (hh:mm) format. If time is unknown, record 'UNK.'

		Event No. [ ]	Event No. [ ]	Event No. [ ]	Event No. [ ]
Adverse Event term (If available, enter the diagnosis)					
Onset date					
Onset time					
End date					
End time					
Was the event serious?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
If serious, please mark reason for seriousness	Results in death	☐	☐	☐	☐
	Immediately life-threatening	☐	☐	☐	☐
	Persistent or significant disability / incapacity	☐	☐	☐	☐
	Requires / prolongs hospitalisation	☐	☐	☐	☐
	Congenital anomaly/birth defect	☐	☐	☐	☐
	Other comparable medical criteria (*specify in Description of Event section*)	☐	☐	☐	☐
Was the event a protocol-specified Adverse Event of Special Interest (AESI)?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Is there a reasonable causal relationship between the Adverse Event and: (*provide description of rationale, other possible causes on page 3*)					
BI studied medication or BI product given for the disease in scope of ONIS		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Concomitant medications: Please refer to concomitant medication section to document causal relationship.					
Outcome of event (*check only one*)					
Recovered (report AE end date above)		☐	☐	☐	☐
Not yet recovered		☐	☐	☐	☐
Recovered with sequelae (report AE end date above)		☐	☐	☐	☐
Unknown		☐	☐	☐	☐
Fatal		☐	☐	☐	☐
If fatal, was this event the primary cause of death?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
If subject died, record date of death:					
Was an autopsy performed?		☐ Yes	☐ No	☐ Unknown	
Was therapy for the event administered?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
If yes, specify therapy in Description of Event section.					
Was a dechallenge performed?		☐ Yes ☐ No ☐ NA	☐ Yes ☐ No ☐ NA	☐ Yes ☐ No ☐ NA	☐ Yes ☐ No ☐ NA
If yes, did the event disappear or significantly decrease in intensity after the BI product was stopped?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Was a rechallenge performed?		☐ Yes ☐ No ☐ NA	☐ Yes ☐ No ☐ NA	☐ Yes ☐ No ☐ NA	☐ Yes ☐ No ☐ NA
If yes, did the event reappear after reintroduction?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

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Boehringer Ingelheim	**Observational and Non-Interventional Study (ONIS) Adverse Event Form**	BI Study No:	Country:
		Site No:	Subject No:

RATIONALE FOR CAUSALITY ASSESSMENT

Please document the event(s) and provide your rationale for the causal assessment to BI product and include a rationale for any other causal relationships which are considered relevant. Rationale may include temporal relationships, confounding factors (i.e. disease/medication), positive dechallenge / rechallenge, interactions with other medications and/or pattern of reaction.

DESCRIPTION OF THE EVENT(S)

Please highlight any additional information (not otherwise provided on this form) which may contribute to the assessment of the case including but not limited to relevant diagnostic/lab test results (with reference ranges) and therapeutic measures given for event.

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Boehringer Ingelheim	**Observational and Non-Interventional Study (ONIS) Adverse Event Form**	BI Study No:	Country:
		Site No:	Subject No:

RELEVANT BASELINE CONDITIONS INCLUDING PAST MEDICAL HISTORY

Record all dates in ddmmmyyyy format (e.g. 01Jan 2015). If ongoing, enter 'CONT.'

☐ None ☐ Yes (*specify below*)	If concomitant, provide onset date	Past - Please check box only if ended prior to (S)AE onset
1.		☐
2.		☐
3.		☐
4.		☐
5.		☐
6.		☐

BOEHRINGER-INGELHEIM PRODUCT

Indication Lot Number

Name of BI studied medication or BI product given for the disease in scope of ONIS:		
Formulation		
Total daily dose at onset of event (*dose, unit*)		
Route		
Start date		
Start time		
Date of last administration prior to event		
End date		
End time		
Was the administration correct?	☐ Yes ☐ No	
If the administration was not correct, check all applicable boxes: overdose, abuse, misuse, medication error, other (i.e. occupational exposure, lack of effect, unexpected benefit)	☐ Misuse / Abuse ☐ Medication error ☐ Overdose ☐ Other:	
Action taken with BI studied medication or BI product administered for the disease in scope of ONIS as a result of the event (*check one*)	Dose not changed	☐
	Dose reduced	☐
	Dose increased	☐
	Drug withdrawn	☐
	Not applicable	☐

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Boehringer Ingelheim	**Observational and Non-Interventional Study (ONIS) Adverse Event Form**	BI Study No:	Country:
		Site No:	Subject No:

RELEVANT PAST AND CONCOMITANT MEDICATIONS

Please preferably provide trade name. Do not include medications used solely to treat the adverse event(s).

☐ None ☐ Yes (*specify below*)	Indication	Past	Start/end dates *dd/mmm/yyyy or cont.*	Total daily dose at onset of event (*dose/ unit*)	Route	Is there a reasonable causal relationship between the event and the past or concomitant therapy? If Yes, record event number from page 2
1.		☐	Start:			☐ No ☐ Yes
			End:			Event #
2.		☐	Start:			☐ No ☐ Yes
			End:			Event #
3.		☐	Start:			☐ No ☐ Yes
			End:			Event #
4.		☐	Start:			☐ No ☐ Yes
			End:			Event #
5.		☐	Start:			☐ No ☐ Yes
			End:			Event #
6.		☐	Start:			☐ No ☐ Yes
			End:			Event #
7.		☐	Start:			☐ No ☐ Yes
			End:			Event #
8.		☐	Start:			☐ No ☐ Yes
			End:			Event #

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ANNEX 5. PREGNANCY MONITORING FORM FOR STUDIES

Boehringer Ingelheim	Pregnancy Monitoring Form for Studies	BI Trial No.:
		Subject No.:

No. of pages, including cover page: .....

To: Boehringer Ingelheim *[or CRO]*	From: *[site stamp]* Site No.: .....
[Address] [redacted]	
[Fax No.] [redacted]	Country: [redacted]

Please use this cover page for each report

Date received at:

BI OPU or CRO Date (dd mon yyyy or date stamp)

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Boehringer Ingelheim	**Pregnancy Monitoring Form for Studies** **Part A**	BI Trial No.:
		Subject No.:

- This form is to be completed by the **investigator** for reporting any drug exposure during pregnancy after exposure to study medication. The form must be signed, dated and forwarded immediately to the **sponsor/CRO** (preferably by fax).
- If in addition a Serious Adverse Event or Adverse Event of Special Interest is experienced, an SAE form must also be completed.

Pregnancy occurred in	☐ Female study subject ☐ Female partner of a male study subject

Demographic Information:

Year of Birth (yyyy):	Height (cm):	Weight (kg):
_____	_____	_____

** Please leave blank, if regulations within your country prohibit the collection of this information.*

Medications: Please list all treatments given during pregnancy to date, if available.
Continue on a separate sheet if necessary.

Drug name		Route	Daily Dose	Indication for Use	Start Date (dd mmm yyyy)	End Date (dd mmm yyyy)
Trial Drug(s)	1.					
	2.					
	3.					
Concomitant Medication(s)	4.					
	5.					
	6.					
	7.					

Relevant Maternal History: *Any maternal health problems, underlying diseases and medications, smoking, drug and/or alcohol use during the pregnancy, previous infertility therapy, obstetric history including previous miscarriages and pertinent family history:*

_____
_____

First day of last menstrual period:	Date (dd mmm yyyy): _____
Estimated date of delivery:	Date (dd mmm yyyy): _____
Enter gestation at time of initial exposure (if known):	No. of weeks: _____ If weeks not known: ☐ 1st trimester ☐2nd trimester ☐3rd trimester

Date (dd mmm yyyy): Investigator's signature:

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Boehringer Ingelheim	**Pregnancy Monitoring Form for Studies**	BI Trial No.:
		Subject No.:

No. of pages, including cover page: .....

To: Boehringer Ingelheim ***[or CRO]***	**From:** ***[site stamp]*** **Site No.:** .....
[Address] [redacted]	
[Fax No.] [redacted]	**Country:** [redacted] .....

Please use this cover page for each report

Date received at:

BI OPU or CRO Date (dd mon yyyy or date stamp)

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Boehringer Ingelheim	**Pregnancy Monitoring Form for Studies** Part B	BI Trial No.: Subject No.:

- This form is to be completed by the **investigator** after delivery/termination of pregnancy. The form must be signed, dated and forwarded immediately to the **sponsor/CRO** (preferably by fax).
- If in addition a Serious Adverse Event or Adverse Event of Special Interest is experienced, an SAE form must also be completed.

Pregnancy occurred in	☐ Female study subject ☐ Female partner of a male study subject

Demographic Information:

Year of Birth (yyyy):	Height (cm):	Weight (kg):
_____	_____	_____

** Please leave blank, if regulations within your country prohibit the collection of this information.*

Pregnancy Information:

Birth Outcome (tick the appropriate box)		
Unknown	☐	
Induced Abortion	☐	Please complete SAE form
Live Birth		
Normal Newborn	☐	
Congenital Malformation/Anomaly	☐	Please complete SAE form
Spontaneous Abortion/Miscarriage	☐	Please complete SAE form
Still Birth	☐	Please complete SAE form

Multiple Pregnancy	no ☐	yes ☐	Enter gestational age at birth (weeks): _____

**If yes, please complete an additional page / additional pages for each additional newborn*

Year of Birth (yyyy):	Birth weight (grams):	Birth Height (cm)	APGAR Score (1-10):	Gender:
_____	_____	_____	_____	male ☐ female ☐

Date (dd mmm yyyy): Investigator's signature:

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ANNEX 6. CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. CKD is classified based on Cause, GFR category (G1–G5), and Albuminuria category (A1–A3), abbreviated as CGA.

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red: very high risk.