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

Document Number:	228892_979562_1.0
Boehringer Ingelheim Study Number:	1245-0276
Boehringer Ingelheim Product(s):	Jardiance® (empagliflozin, 10mg)
Title:	A regulatory requirement non-interventional study to monitor the safety and effectiveness of Jardiance® (empagliflozin, 10mg) in Korean patients with chronic heart failure (NYHA class II-IV)
Brief lay title:	Jardiance® PMS in Korean patients with chronic heart failure
Protocol version identifier:	8.0
Date of last version of protocol:	08 Feb 2023 (V7.0)
PASS:	Yes
EU PAS register number:	EUPAS44641
Active substance:	empagliflozin
Medicinal product:	JARDIANCE® film-coated tablets 10mg
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	[redacted]
Joint PASS:	Not applicable
Research question and objectives:	To monitor the safety profile and effectiveness of JARDIANCE® in Korean patients with chronic heart failure (NYHA class II-IV)
Country(-ies) of study:	South Korea
Author:	[redacted]

	Phone: [redacted] Fax: [redacted]
Marketing authorisation holder(s):	[redacted]
MAH contact person:	[redacted]
EU-QPPV:	
Signature of EU-QPPV:	The signature of the EU-QPPV is provided electronically
Date:	10 Jan 2025

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

ACR	Albumin Creatinine Ratio
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ASAE	Always Serious Adverse Events
AST	Aspartate Aminotransferase
CA	Competent Authority
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practice
HbA1c	Glucosylated Hemoglobin
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
KIMS	Korea Index of Medical Specialties
LPSL	Local Patient Safety Lead
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	The Ministry of Food and Drug Safety
NCE	New Chemical Entity
ONIS	Observational and Non-Interventional Study
OPU	Operative Unit
PASS	Post-Authorization Safety Study
SAE	Serious Adverse Event
SGLT2	Sodium-dependent Glucose Co-transporter 2
SOP	Standard Operating Procedure
T2DM	Type 2 Diabetes Mellitus
TCM	Trial Clinical Monitor
TMF	Trial Master File

3. RESPONSIBLE PARTIES

Boehringer Ingelheim 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 CRO according to Boehringer Ingelheim's and/or CRO's SOPs.

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

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

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: JARDIANCE®			
Name of active ingredient: empagliflozin			
Protocol date: 31 Aug 2021	**Study number:** 1245-0276	**Version/Revision:** 8.0	**Version/Revision date:** 06 Jan 2025
Title of study:	A regulatory requirement non-interventional study to monitor the safety and effectiveness of Jardiance® (empagliflozin, 10mg) in Korean patients with chronic heart failure (NYHA class II-IV)		
Rationale and background:	This is a PMS (Post Marketing Surveillance) Study as a local PASS (post authorized safety study), which is stipulated in local PMS regulation: A surveillance that the MAH (Marketing Authorization Holder) conducts to submit real world data during the re-examination period for Korea Health Authority to observe for the defined period (4-6 years) for the safety/ effectiveness of new drugs etc. that were already licensed and were in market and reflect the results to the licensed information. Jardiance® for the chronic heart failure indication was submitted to Korea Health Authority and Korea Health Authority imposed this mandatory post-approval commitment for [redacted] to submit safety data of more than 600 patients in single arm under real world environment for 4 years until December 2025, which are minimum requirements to meet Risk Management Plan (RMP) regulation. Such ONIS can provide supplementary data to monitor the safety of NCE (New chemical entity) 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:	The primary and secondary outcomes are to observe respectively safety and effectiveness of Jardiance® (empagliflozin, 10 mg) in Korean patients with chronic heart failure (NYHA class II-IV), in a routine clinical practice setting.		
Study design:	Observational prospective, single arm, non-interventional, open-label, multi-centre study		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: JARDIANCE®			
Name of active ingredient: empagliflozin			
Protocol date: 31 Aug 2021	**Study number:** 1245-0276	**Version/Revision:** 8.0	**Version/Revision date:** 10 Jan 2025
Population:	Patients diagnosed with chronic heart failure (NYHA class II-IV) Jardiance® is indicated in adult patients with chronic heart failure (NYHA class II-IV) <u>Inclusion criteria:</u> • Patients who have started at first time on Jardiance® in accordance with the approved label in Korea • Chronic heart failure (NYHA class II-IV) • Age ⩾ 19 years at enrolment • Patients who have signed on the data release consent form <u>Exclusion criteria:</u> • Patients with previous exposure to Jardiance ® • Known allergy or Hypersensitivity to active ingredients empagliflozin or to any of the excipients • Patients with type 1 diabetes or with prior history of diabetic ketoacidosis (DKA) • Patient with renal impairment with eGFR < 20 mL/min/1.73 m^2 • Patients with rare hereditary conditions of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption • Patient who are pregnant or are nursing or who plan to become pregnant while in the trial • Patients for whom empagliflozin is contraindicated according local label of Jardiance ®		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: JARDIANCE®			
Name of active ingredient: empagliflozin			
Protocol date: 31 Aug 2021	**Study number:** 1245-0276	**Version/Revision:** 8.0	**Version/Revision date:** 10 Jan 2025
Variables:	Endpoints of safety All reported adverse events in patients who take at least one dose of Jardiance® will be noted. Endpoints of effectiveness Occurrence of hospitalization for heart failure, occurrence of cardiovascular death, Changes from baseline in NYHA functional class, Changes in EF (if available), Changes in BNP or NT-proBNP (if available), Changes in HbA1c or FPG, Change from baseline in eGFR (if available), Change from baseline in Body weight, Change from baseline in blood pressure (SBP, DBP) after 12 weeks and/or 24 weeks of treatment, The investigator's overall evaluation at last visit		
Data sources:	Field study with new data collection		
Study sites	Approximately 21 sites		
Study size:	Single arm (N=600 approximately)		
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, the number of patients, mean, standard deviation, minimum value, maximum value, and median 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) Effectiveness analysis: Mean, standard deviation, minimum value, maximum value, and median of changes in HbA1c or FPG (if available), eGFR (if available), Body weight, and blood pressure, which were measured at the last visit versus baseline, should be presented, and analyzed using paired t-test. It will analyze by using the occurrence of hospitalization for heart failure, the occurrence of cardiovascular death, and variables of NYHA functional class, EF (if available), BNP or NT-proBNP (if available).		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: JARDIANCE®			
Name of active ingredient: empagliflozin			
Protocol date: 31 Aug 2021	**Study number:** 1245-0276	**Version/Revision:** 8.0	**Version/Revision date:** 10 Jan 2024
Milestones:	As per local PMS(Post Marketing Surveillance) regulation and Risk Management Plan (RMP) regulation, safety data will be collected for about 4 years until December 2025.		

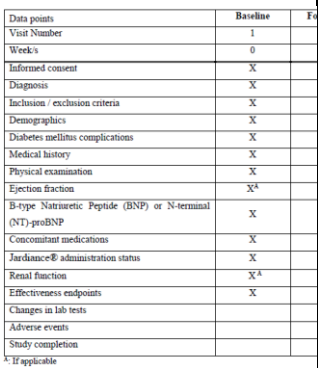
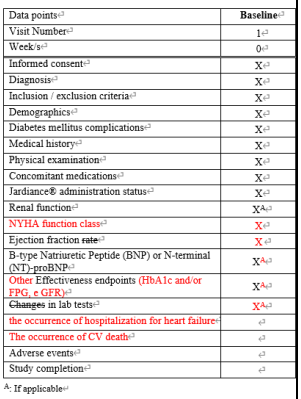
5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update (before)	Amendment or update (After)	Reason
1	10Nov 2021 (v2.0)	Abstract _ 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. --- --- 3) Effectiveness analysis: Mean, standard deviation, minimum value, maximum value, and median of changes in ~~eGFR if available, Body weight, blood pressure, and HbA1 if available~~ which were measured at the last visit versus baseline, should be presented, and analyzed using paired t-test.	1) Analysis of demographic data: Demographic data and the health status of subjects for the safety evaluation will be analysed descriptively. For continuous data, the number of patients, mean, standard deviation, minimum value, maximum value, and median will be described, while for categorical data, frequency will be shown. --- 3) Effectiveness analysis: Mean, standard deviation, minimum value, maximum value, and median of changes in HbA1c or FPG (if available), eGFR (if available), Body weight, and blood pressure, which were measured at the last visit versus baseline, should be presented, and analyzed using paired t-test The occurrence of hospitalization for heart failure, the occurrence of cardiovascular death will be displayed by frequencies, EF (if available), BNP or NT-proBNP (if available) will be analyzed using paired t-test. For NYHA class a shift table will be provided for change from baseline to last value.	Updated contexts according to the changes in protocol
2	10Nov 2021 (v2.0)	9.2.3.2 Visit 1 ; Baseline Visit	--- --- --- --- • Concomitant medications: record all medications that have been taken at least once (within 1 month prior to baseline) • Dose of Jardiance® g	--- • history of diabetes mellitus --- • Concomitant medications: Record all medications including trade name, daily dose, unit, purpose of administration, start date, and end date that have been taken at least once (within 1 month prior to baseline)	history of diabetes mellitus' update protocol text aligned with CRF update protocol text

<table>
<tr><td></td><td></td><td></td><td>iven (~~Daily~~ dose, Start date)

Effectiveness endpoints: NYHA functional class, EF ~~(if available)~~, BNP or NTproBNP level (if available), HbA1c and/or FPG(if available in T2D patients), eGFR(if available), Lab data should be collected within 1 month prior to baseline.</td><td>• Dose of Jardiance® given (Dose of Administration, The Frequency of Administration, Start Date, End Date)

Effectiveness endpoints: NYHA functional class, EF (mandatory), BNP or NT-proBNP level (if available), HbA1c and/or FPG (if available in T2D patients), eGFR (if available), Lab data should be collected within 1 month prior to baseline.</td><td>aligned with CRF

Modify the EF from ‘if available’ to ‘mandatory’.</td></tr>
<tr><td>3</td><td>10Nov 2021
(v2.0)</td><td>9.2.5 Flow Chart</td><td> 
<table>
<tr><th>Data points</th><th>Baseline</th><th>Fo</th></tr>
<tr><td>Visit Number</td><td>1</td><td></td></tr>
<tr><td>Week/s</td><td>0</td><td></td></tr>
<tr><td>Informed consent</td><td>X</td><td></td></tr>
<tr><td>Diagnosis</td><td>X</td><td></td></tr>
<tr><td>Inclusion / exclusion criteria</td><td>X</td><td></td></tr>
<tr><td>Demographics</td><td>X</td><td></td></tr>
<tr><td>Diabetes mellitus complications</td><td>X</td><td></td></tr>
<tr><td>Medical history</td><td>X</td><td></td></tr>
<tr><td>Physical examination</td><td>X</td><td></td></tr>
<tr><td>Ejection fraction</td><td>X[A]</td><td></td></tr>
<tr><td>B-type Natriuretic Peptide (BNP) or N-terminal (NT)-proBNP</td><td>X</td><td></td></tr>
<tr><td>Concomitant medications</td><td>X</td><td></td></tr>
<tr><td>Jardiance® administration status</td><td>X</td><td></td></tr>
<tr><td>Renal function</td><td>X[A]</td><td></td></tr>
<tr><td>Effectiveness endpoints</td><td>X</td><td></td></tr>
<tr><td>Changes in lab tests</td><td></td><td></td></tr>
<tr><td>Adverse events</td><td></td><td></td></tr>
<tr><td>Study completion</td><td></td><td></td></tr>
</table>
[A]: If applicable</td><td> 
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<tr><td>Informed consent</td><td>X</td></tr>
<tr><td>Diagnosis</td><td>X</td></tr>
<tr><td>Inclusion / exclusion criteria</td><td>X</td></tr>
<tr><td>Demographics</td><td>X</td></tr>
<tr><td>Diabetes mellitus complications</td><td>X</td></tr>
<tr><td>Medical history</td><td>X</td></tr>
<tr><td>Physical examination</td><td>X</td></tr>
<tr><td>Concomitant medications</td><td>X</td></tr>
<tr><td>Jardiance® administration status</td><td>X</td></tr>
<tr><td>Renal function</td><td>X[A]</td></tr>
<tr><td>NYHA function class</td><td>X</td></tr>
<tr><td>Ejection fraction ~~rate~~</td><td>X</td></tr>
<tr><td>B-type Natriuretic Peptide (BNP) or N-terminal (NT)-proBNP</td><td>X[A]</td></tr>
<tr><td>Other Effectiveness endpoints (HbA1c and/or FPG, e GFR)</td><td>X[A]</td></tr>
<tr><td>~~Changes~~ in lab tests</td><td>X[A]</td></tr>
<tr><td>the occurrence of hospitalization for heart failure</td><td></td></tr>
<tr><td>The occurrence of CV death</td><td></td></tr>
<tr><td>Adverse events</td><td></td></tr>
<tr><td>Study completion</td><td></td></tr>
</table>
[A]: If applicable</td><td>Ejection fraction rate -> Ejection fraction, modify the visit 1 to mandatory.

Add the NYHA function class’

Partially changes in sequence.

Modify Effectiveness endpoints -> other effectiveness endpoints X[A]

Add the occurrence of hospitalization, CV death</td></tr>
<tr><td>4</td><td>10Nov 2021
(v2.0)</td><td>9.3.2.1 Endpoints of safety</td><td>• Adverse events
• Unexpected adverse events
• Serious adverse events
• Drug-related adverse events
• Non-serious adverse drug reaction</td><td>• Adverse events
• Unexpected adverse events
• Unexpected adverse drug reaction
• Serious adverse events
• Serious adverse drug reaction</td><td>Add “unexpected adverse drug reaction, serious adverse drug reaction”</td></tr>
</table>

			• Adverse event of special interest • Adverse events leading to discontinuation	• Drug-related adverse events • Non-serious adverse drug reaction • Adverse event of special interest • Adverse events leading to discontinuation	
5	10Nov 2021 (v2.0)	9.3.3.1 Assessment Criteria	• The important potential risk (Urinary tract carcinogenicity / Liver injury / Amputation risk / Pancreatitis)	• The important potential risks (Urinary tract carcinogenicity / Liver injury / Amputation risk / Pancreatitis / bone fracture) • Missing information (NYHA Class IV Heart Failure)	Add 'bone fracture', missing information (NYHA class IV HF) according to the RMP update
6	10Nov 2021 (v2.0)	9.3.2.3 Endpoints of effectiveness after 12 and/or 24 weeks	• Changes in HbA1c or FPG (if available in T2D patients)	• Changes in HbA1c or FPG (if available in T2D patients) after 12 weeks and/or 24 weeks of treatment	State the period
7	10Nov 2021 (v2.0)	9.7.1 Analysis of Demographic Data	Demographic data and the health status of subjects for the safety evaluation will be analysed descriptively. For continuous data, mean, standard deviation, minimum value, ~~and~~ maximum value will be described, while for categorical data, frequency will be shown. Parameters corresponding to demographic data are as mentioned below. ① Basic information and disease information Age, Gender, Pregnancy, ~~Family history of Heart Failure, Allergy~~, Smoking status, Body weight, Diabetes mellitus complications, Other medical history, Disease period, Elderly (Age ≥ 65 years), Renal impairment and Hepatic impairment, Long term use (over 24 weeks)	Demographic data and the health status of subjects for the safety evaluation will be analysed descriptively. For continuous data, the number of patients, mean, standard deviation, minimum value, maximum value, and median 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 Year of birth (age), Gender, Pregnancy, Previous allergy, Height, Smoking Status, Body weight, blood pressure, history of diabetes mellitus, diabetes mellitus complications, history of heart failure, medical history, Other medical history, Disease period, Elderly (Age≥65 years), Renal impairment and	Add "the number of patients, median" Identically reflect the section 9.2.3.2 Visit 1

			② Medication information Concomitant medication, Study drug administration status (total period of drug use, average of daily dose), Reason for early interruption	Hepatic impairment, Long term use (over 24 weeks), NYHA class, EF. ② Medication information Concomitant medication, Study drug administration status (total period of drug use, average of daily dose), Reason for early interruption	
8	10Nov 2021 (v2.0)	9.7.2 Analysis of Safety	③ The important identified risks and the important potential risks will be analyzed separately for each AE (The important identified risks (Complicated urinary tract infection/Genital infection/Diabetic ketoacidosis with atypical presentation/Necrotizing fasciitis of the perineum (Fournier´s gangrene)), the important potential risks (Urinary tract carcinogenicity/Liver injury/Amputation risk/Pancreatitis)) --- --- --- ⑤ To estimate any factors that are thought to influence the analyzed frequency of adverse events, logistic regression analysis should be conducted, and for statistically significant parameters, the meaning ~~should be described.~~ --- --- 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. --- ---	③ The important identified risks and the important potential risks will be analyzed separately for each AE (The important identified risks (Complicated urinary tract infection/Genital infection/Diabetic ketoacidosis with atypical presentation/Necrotizing fasciitis of the perineum (Fournier´s gangrene)), the important potential risks (Urinary tract carcinogenicity/Liver injury/Amputation risk/Pancreatitis/bone fracture), missing information (NYHA Class IV Heart Failure)) --- ⑤ To estimate any factors that are thought to influence the analyzed frequency of adverse events, logistic regression analysis should be conducted, and for statistically significant parameters, the meaning will be described in medically. --- 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 in accordance with protocol to the relevant data. ---	Add 'bone fracture', missing information (NYHA class IV HF) according to the RMP update. Modify the phrase
9	10Nov 2021 (v2.0)	9.7.3 Analysis of Effectiveness	① Mean, standard deviation, minimum value, maximum value, and median of changes in ~~eGFR if available, Body weight, blood pressure, and HbA1 if available~~ which were measured at the last visit versus baseline, should be	① Mean, standard deviation, minimum value, maximum value, and median of changes in HbA1c or FPG (if available), eGFR (if available), Body weight, and blood pressure, which were measured at the last visit	Reflect the section 9.3.2.3 Endpoints of effectiveness and modify.

			presented, and if there is difference before administration versus after administration should be analyzed using paired t-test. ② 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.	versus baseline, should be presented, and if there is difference before administration versus after administration should be analyzed using paired t-test. It will be analyzed by using the occurrence of hospitalization for heart failure, the occurrence of cardiovascular death, and variables of NYHA functional class, EF (if available), BNP or NT-proBNP (if available). ② 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.	
10	10Nov 2021 (v2.0)	9.10.2.1 Source documents	• Adverse events and outcome events (onset date (mandatory), and end date (~~if available~~)) • Serious adverse events (onset date (mandatory), and end date ~~(if available))~~	• Adverse events and outcome events (onset date (mandatory), and end date (mandatory, last date if continues)) • Serious adverse events (onset date (mandatory), and end date (mandatory, last date if continues))	Modify the end date of adverse events to mandatory
11	08Dec 2021 (v3.0)	Title page - Title	A regulatory requirement non-interventional study to monitor the safety and effectiveness of Jardiance® (empagliflozin, 10mg) in Korean patients with heart failure (NYHA class II-IV) ~~and reduced ejection fraction (HFrEF), with or without type 2 diabetes mellitus~~	A regulatory requirement non-interventional study to monitor the safety and effectiveness of Jardiance® (empagliflozin, 10mg) in Korean patients with chronic heart failure (NYHA class II-IV) independent of left ventricular ejection fraction	Indication update
12	08Dec 2021 (v3.0)	Title page - Brief lay title:	Jardiance® PMS in Korean patients with heart failure ~~and reduced ejection fraction~~	Jardiance® PMS in Korean patients with chronic heart failure independent of left ventricular ejection fraction	Indication update
13	08Dec 2021 (v3.0)	Title page - Research Question and objectives	To monitor the safety profile and effectiveness of JARDIANCE® in Korean patients with heart failure (NYHA class II-IV) ~~and reduced ejection fraction (HFrEF), with or without type 2 diabetes mellitus~~	To monitor the safety profile and effectiveness of JARDIANCE® in Korean patients with chronic heart failure (NYHA class II-IV) independent of left ventricular ejection fraction	Indication update
14	08Dec 2021	Abstract – Title of study	A regulatory requirement non-interventional study to monitor the safety and effectiveness of	A regulatory requirement non-interventional study to monitor the safety and	Indication update

	(v3.0)		Jardiance® (empagliflozin, 10mg) in Korean patients with heart failure (NYHA class II-IV) ~~and reduced ejection fraction (HFrEF~~), with or without type 2 diabetes mellitus	effectiveness of Jardiance® (empagliflozin, 10mg) in Korean patients with chronic heart failure (NYHA class II-IV) independent of left ventricular ejection fraction,	
15	08Dec 2021 (v3.0)	Abstract – Rationale and background	--- Jardiance® for the ~~HFrEF~~ indication was submitted to Korea Health Authority ---	--- Jardiance® for the chronic heart failure indication was submitted to Korea Health Authority ---	Indication update
16	08Dec 2021 (v3.0)	Abstract - Research Question and objectives	The primary and secondary outcomes are to observe respectively safety and effectiveness of Jardiance® (empagliflozin, 10 mg) in Korean patients with heart failure (NYHA class II-IV) ~~and reduced ejection fraction (HFrEF~~), with or without type 2 diabetes mellitus in a routine clinical practice setting.	The primary and secondary outcomes are to observe respectively safety and effectiveness of Jardiance® (empagliflozin, 10 mg) in Korean patients with chronic heart failure (NYHA class II-IV) independent of left ventricular ejection fraction, in a routine clinical practice setting.	Indication update
17	08Dec 2021 (v3.0)	Abstract – population	Patients diagnosed with heart failure (NYHA class II-IV) ~~and reduced ejection fraction (~~HFrEF), with or without type 2 diabetes mellitus in Korea. Jardiance® is indicated in adult patients with heart failure (NYHA class II-IV) ~~and reduced ejection fraction (HFrEF), with or without type 2 diabetes mellitus.~~ Inclusion criteria: • Patients who have started at first time on Jardiance® in accordance with the approved label in Korea • Heart failure ~~and reduced ejection fraction~~ (NYHA class II-IV) • Age ≥ 19 years at enrolment Patients who have signed on the data release consent form	Patients diagnosed with chronic heart failure (NYHA class II-IV) independent of left ventricular ejection fraction. Jardiance® is indicated in adult patients with chronic heart failure (NYHA class II-IV) independent of left ventricular ejection fraction. Inclusion criteria: • Patients who have started at first time on Jardiance® in accordance with the approved label in Korea • Chronic heart failure independent of left ventricular ejection fraction (NYHA class II-IV) • Age ≥ 19 years at enrolment Patients who have signed on the data release consent form	Indication update
18	08Dec 2021 (v3.0)	7.1 RATIONALE	--- Jardiance® for the ~~HFrEF~~ indication was submitted to Korea Health Authority ---	--- Jardiance® for the chronic heart failure indication was	Indication update

				submitted to Korea Health Authority ---	
19	08Dec 2021 (v3.0)	7.2 BACKGROUND	--- They consist of heart failure with reduced EF (HFrEF) ~~<~~ 40% ~~and heart failure with preserved EF (HFpEF) ≥40%.~~ --- --- Despite advances in therapy and management, HF remains a deadly clinical syndrome. After ~~HHF~~, --- For HFpEF, however, control of congestive symptoms during acute episodes is the mainstay of management of these patients and no class of drugs have shown to increase survival or reduce ~~hospitalisations for HF~~ ---	--- They consist of heart failure with reduced EF (HFrEF) ≤ 40%, heart failure with mildly reduced EF 41~49%, and heart failure with preserved EF ≥ 50%. --- Despite advances in therapy and management, HF remains a deadly clinical syndrome. After hospitalisations for HF (HHF), --- For HFpEF, however, control of congestive symptoms during acute episodes is the mainstay of management of these patients and no class of drugs have shown to increase survival or reduce HHF ---	Heart failure classification update (rEF, mrEF, pEF) Amend description
20	08Dec 2021 (v3.0)	8.1 PRIMARY OBJECTIVE	The primary objective of this study is to monitor the safety profile of Jardiance® in Korean patient with heart failure (NYHA class II-IV) ~~and reduced ejection fraction (HFrEF~~), with or without type 2 diabetes mellitus in a routine clinical setting.	The primary objective of this study is to monitor the safety profile of Jardiance® in Korean patient with chronic heart failure (NYHA class II-IV) independent of left ventricular ejection fraction in a routine clinical setting.	Indication update
21	08Dec 2021 (v3.0)	9.2.2.1 Main diagnosis for study entry	Patients diagnosed with heart failure (NYHA class II-IV) ~~and reduced ejection fraction (~~HFrEF), with or without type 2 diabetes mellitus in Korea.	Patients diagnosed with chronic heart failure (NYHA class II-IV) independent of left ventricular ejection fraction in Korea.	Indication update
22	08Dec 2021 (v3.0)	9.2.2.2 Inclusion criteria	• Patients who have started at first time on Jardiance® in accordance with the approved label in Korea • Heart failure ~~and reduced ejection fraction~~ (NYHA class II-IV) • Age ≥ 19 years at enrolment • Patients who have signed on the data release consent form	• Patients who have started at first time on Jardiance® in accordance with the approved label in Korea • Chronic Heart failure independent of left ventricular ejection fraction (NYHA class II-IV) • Age ≥ 19 years at enrolment • Patients who have signed on the data release consent form	Indication update

23	08Dec 2021 (v3.0)	9.2.3.2 Visit 1; Baseline Visit	○ Diagnosis: date of the diagnosis of heart failure (NYHA class II-IV) ~~and reduced ejection fraction (HFrEF~~), with or without type 2 diabetes mellitus --- ○ Effectiveness endpoints: NYHA functional class, EF (mandatory), BNP or NT-proBNP level (if available), HbA1c and/or FPG(if available in T2D patients), eGFR (if available), Lab data should be collected within 1 month prior to baseline.	□ Diagnosis: date of the diagnosis of chronic heart failure (NYHA class II-IV) independent of left ventricular ejection fraction --- ○ Effectiveness endpoints: NYHA functional class, EF (mandatory), BNP or NT-proBNP level (if available), HbA1c and/or FPG (if available in T2D patients), eGFR (if available), Lab data should be collected within 1 month prior to baseline except EF. The EF data should be collected from the most recent echocardiography, within 12 months prior to baseline.	Indication update Update EF data collecting time point by considering local clinical environment.
24	08Dec2021 (v3.0)	9.3.3.1 Assessment Criteria	• The important potential risks (Urinary tract carcinogenicity / Liver injury / ~~Amputation risk /~~ Pancreatitis / Bone fracture)	• The important potential risks (Urinary tract carcinogenicity / Liver injury / Pancreatitis / Bone fracture)	RMP update
25	08Dec2021 (v3.0)	9.7.2 Analysis of Safety	③ The important identified risks and the important potential risks will be analyzed separately for each AE (The important identified risks (Complicated urinary tract infection / Genital infection / Diabetic ketoacidosis with atypical presentation / Necrotizing fasciitis of the perineum (Fournier´s gangrene)), the important potential risks (Urinary tract carcinogenicity / Liver injury ~~/ Amputation risk~~ / Pancreatitis / Bone fracture)), missing information (NYHA Class IV Heart Failure)).	③ The important identified risks and the important potential risks will be analyzed separately for each AE (The important identified risks (Complicated urinary tract infection / Genital infection / Diabetic ketoacidosis with atypical presentation / Necrotizing fasciitis of the perineum (Fournier´s gangrene)), the important potential risks (Urinary tract carcinogenicity / Liver injury / Pancreatitis / Bone fracture)), missing information (NYHA Class IV Heart Failure)).	RMP update
26	08Dec 2021 (v3.0)	9.7.3 Analysis of Effectiveness	① Mean, standard deviation, minimum value, maximum value, and median of changes in HbA1c or FPG (if available), eGFR (if available), Body weight, and blood pressure, 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. ~~It~~	① Mean, standard deviation, minimum value, maximum value, and median of changes in HbA1c or FPG (if available), eGFR (if available), Body weight, and blood pressure, 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.	Update analysis method

			~~will be analyzed by using the occurrence of hospitalization for heart failure, the occurrence of cardiovascular death, and variables of NYHA functional class, EF (if available), BNP or NT-proBNP (if available).~~ ② 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.	The occurrence of hospitalization for heart failure, the occurrence of cardiovascular death will be displayed by frequencies, EF (if available), BNP or NT-proBNP (if available) will be analyzed using paired t-test. For NYHA class a shift table will be provided for change from baseline to last value. ② To estimate any factors that are thought to influence an effective ratio, logistic regression and/or poisson regression analysis should be conducted, and for statistically significant parameters, the meaning should be described.	
27	08Dec 2021 (v3.0)	9.9.2 Channeling Bias	To assess the extent of preferential prescribing of Jardiance® and the potential for channeling bias, baseline data from the Jardiance® T2DM PMS would be used to provide context for the Jardiance® ~~HFrEF~~ PMS data.	To assess the extent of preferential prescribing of Jardiance® and the potential for channeling bias, baseline data from the Jardiance® T2DM PMS would be used to provide context for the Jardiance® chronic heart failure PMS data.	Indication update
28	25May 2022 (v4.0)	Title page - Title	A regulatory requirement non-interventional study to monitor the safety and effectiveness of Jardiance® (empagliflozin, 10mg) in Korean patients with chronic heart failure (NYHA class II-IV) ~~independent of left ventricular ejection fraction~~	A regulatory requirement non-interventional study to monitor the safety and effectiveness of Jardiance® (empagliflozin, 10mg) in Korean patients with chronic heart failure (NYHA class II-IV)	Update according to approved indication on 24May2022
29	25May 2022 (v4.0)	Title page - Brief lay title:	Jardiance® PMS in Korean patients with chronic heart failure ~~independent of left ventricular ejection fraction~~	Jardiance® PMS in Korean patients with chronic heart failure	Update according to approved indication on 24May2022
30	25May 2022 (v4.0)	Title page - Research Question and objectives	To monitor the safety profile and effectiveness of JARDIANCE® in Korean patients with chronic heart failure (NYHA class II-IV) ~~independent of left ventricular ejection fraction~~	To monitor the safety profile and effectiveness of JARDIANCE® in Korean patients with chronic heart failure (NYHA class II-IV)	Update according to approved indication on 24May2022
31	25May 2022 (v4.0)	Abstract – Title of study	A regulatory requirement non-interventional study to monitor the safety and effectiveness of Jardiance® (empagliflozin, 10mg) in Korean patients with chronic heart failure (NYHA class II-IV) ~~independent of left ventricular ejection fraction~~	A regulatory requirement non-interventional study to monitor the safety and effectiveness of Jardiance® (empagliflozin, 10mg) in Korean patients with chronic heart failure (NYHA class II-IV)	Update according to approved indication on 24May2022

32	25May 2022 (v4.0)	Abstract - Research Question and objectives	The primary and secondary outcomes are to observe respectively safety and effectiveness of Jardiance® (empagliflozin, 10 mg) in Korean patients with chronic heart failure (NYHA class II-IV) ~~independent of left ventricular ejection fraction~~, in a routine clinical practice setting.	The primary and secondary outcomes are to observe respectively safety and effectiveness of Jardiance® (empagliflozin, 10 mg) in Korean patients with chronic heart failure (NYHA class II-IV), in a routine clinical practice setting.	Update according to approved indication on 24May2022
33	25May 2022 (v4.0)	Abstract – population	Patients diagnosed with chronic heart failure (NYHA class II-IV) ~~independent of left ventricular ejection fraction~~. Jardiance® is indicated in adult patients with chronic heart failure (NYHA class II-IV) ~~independent of left ventricular ejection fraction.~~ Inclusion criteria: • Patients who have started at first time on Jardiance® in accordance with the approved label in Korea • Chronic heart failure ~~independent of left ventricular ejection fraction~~ (NYHA class II-IV) • Age ≥ 19 years at enrolment Patients who have signed on the data release consent form	Patients diagnosed with chronic heart failure (NYHA class II-IV). Jardiance® is indicated in adult patients with chronic heart failure (NYHA class II-IV). Inclusion criteria: • Patients who have started at first time on Jardiance® in accordance with the approved label in Korea • Chronic heart failure (NYHA class II-IV) • Age ≥ 19 years at enrolment Patients who have signed on the data release consent form	Update according to approved indication on 24May2022
34	25May 2022 (v4.0)	8.1 PRIMARY OBJECTIVE	The primary objective of this study is to monitor the safety profile of Jardiance® in Korean patient with chronic heart failure (NYHA class II-IV) ~~independent of left ventricular ejection fraction~~, in a routine clinical setting.	The primary objective of this study is to monitor the safety profile of Jardiance® in Korean patient with chronic heart failure (NYHA class II-IV), in a routine clinical setting.	Update according to approved indication on 24May2022
35	25May 2022 (v4.0)	9.2.2.1 Main diagnosis for study entry	Patients diagnosed with chronic heart failure (NYHA class II-IV) ~~independent of left ventricular ejection fraction~~ in Korea.	Patients diagnosed with chronic heart failure (NYHA class II-IV) in Korea.	Update according to approved indication on 24May2022
36	25May 2022 (v4.0)	9.2.2.2 Inclusion criteria	• Patients who have started at first time on Jardiance® in accordance with the approved label in Korea	• Patients who have started at first time on Jardiance® in accordance with the approved label in Korea	Update according to approved indication on 24May2022

			• Chronic heart failure ~~independent of left ventricular ejection fraction~~ (NYHA class II-IV) • Age ≥ 19 years at enrolment • Patients who have signed on the data release consent form	• Chronic Heart failure (NYHA class II-IV) • Age ≥ 19 years at enrolment • Patients who have signed on the data release consent form	
37	25May 2022 (v4.0)	9.2.3.2 Visit 1; Baseline Visit	○ Diagnosis: date of the diagnosis of chronic heart failure (NYHA class II-IV) ~~independent of left ventricular ejection fraction~~	○ Diagnosis: date of the diagnosis of chronic heart failure (NYHA class II-IV)	Update according to approved indication on 24May2022
38	30Jun2022 (v5.0)	6. Milestone	-Start of data collection : 28, Feb 2022 -End of data collection : 30, Apr 2025 -Final report of study results : 31, Dec 2025	-Start of data collection : 23, Nov 2021 (Approval date of Product) -End of data collection : 31, May 2025 -Final report of study results : 22, Feb 2025 (Expected date of MFDS submission)	Update the milestone
39	30Jun2022 (v5.0)	MAH contact person:	[redacted]	[redacted]	Update the MAH contact person
40	30Jun2022 (v5.0)	9.2.3.2 Visit 1; Baseline Visit	• Demographic data: Year of birth(age), Gender, Pregnancy, Previous allergy, Height, Smoking status	• Demographic data: Year and month of birth(age), Gender, Pregnancy, Previous allergy, Height, Smoking status	Update the month of birth to calculate the age
41	30Jun2022 (v5.0)	9.2.3.2 Visit 1; Baseline Visit	Not applicable	• History of Diabetic ketoacidosis	Add the item
42	22Nov2022 (v6.0)	9.3.3.1 Assessment Criteria	• The important identified risks (Complicated urinary tract infection / Genital infection / Diabetic ketoacidosis with atypical presentation / Necrotizing fasciitis of the perineum (Fournier´s gangrene)) • The important potential risks (Urinary tract carcinogenicity / Liver injury / Pancreatitis / Bone fracture)	• The important identified risks (Complicated urinary tract infection / Genital infection / Diabetic ketoacidosis with atypical presentation) • The important potential risks (Urinary tract carcinogenicity / Liver injury / Pancreatitis)	Update per local RMP v3.0
43	22Nov2022 (v6.0)	9.7.2 Analysis of Safety	③ The important identified risks and the important potential risks will be analyzed separately for each AE (The important identified risks (Complicated urinary tract infection / Genital infection /	③ The important identified risks and the important potential risks will be analyzed separately for each AE (The important identified risks (Complicated urinary tract infection / Genital	Update per local RMP v3.0

			Diabetic ketoacidosis with atypical presentation / Necrotizing fasciitis of the perineum (Fournier´s gangrene)), the important potential risks (Urinary tract carcinogenicity / Liver injury / Pancreatitis / Bone fracture)), missing information (NYHA Class IV Heart Failure)).	infection / Diabetic ketoacidosis with atypical presentation), the important potential risks (Urinary tract carcinogenicity / Liver injury / Pancreatitis), missing information (NYHA Class IV Heart Failure)).	
44	22Nov2022 (v6.0)	11.1 DEFINITIONS OF ADVERSE EVENTS _Adverse Event of Special Interest (AESI)	Hepatic injury A hepatic injury is defined by the following alterations of hepatic laboratory parameters: •an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or in samples drawn within 30 days of each other, or, •aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN. These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.	Hepatic injury - An elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured at the same visit, or in samples drawn 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	Update per changed definition of AESI 'hepatic injury'
45	08Feb2023 (v7.0)	9.2.3.3 Visit 2; 12 weeks from Visit 1	Not applicable	• The investigator's overall evaluation (if necessary)	Add the evaluation item for effectiveness

46	08Feb2023 (v7.0)	9.2.3.4 Visit 3; 24 weeks from Visit 1	Not applicable	• The investigator's overall evaluation	Add the evaluation item for effectiveness
47	08Feb2023 (v7.0)	9.2.5 Flow Chart	Not applicable	Add the investigator's overall evaluation under the visits for Follow-up1 and Follow-up 2	Add the evaluation item for effectiveness
48	08Feb2023 (v7.0)	9.3.2.2.1 Endpoints of effectiveness after 12 and/or 24 weeks	Not applicable	• The result of investigator's overall evaluation after 12weeks and/or 24weeks of treatment	Add the evaluation item for effectiveness
49	08Feb2023 (v7.0)	9.3.3.2 Assessment of effectiveness	Not applicable	⑦The investigator's overall evaluation Records by performing the overall effectiveness evaluation at the end of the last visit ①Improved: If determined as there is any effect of maintaining or improving disease related factors. ②Unchanged: If disease related factors have not been changed compared with before administration, and not determined as there is any effect of maintaining symptoms. ③Aggravated: If disease related factors are worse than before administration. ④Unassessable: 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 "Ineffective".	Add the evaluation item for effectiveness
50	08Feb2023 (v7.0)	9.7.3 Analysis of Effectiveness	① Mean, standard deviation, minimum value, maximum value, and median of changes in	① Mean, standard deviation, minimum value, maximum value, and median of changes	Add the details about effectiveness analysis

			HbA1c or FPG (if available), eGFR (if available), Body weight, and blood pressure, 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 occurrence of hospitalization for heart failure, the occurrence of cardiovascular death will be displayed by frequencies, EF (if available), BNP or NT-proBNP (if available) will be analyzed using paired t-test. For NYHA class a shift table will be provided for change from baseline to last value. ② To estimate any factors that are thought to influence an effective ratio, logistic regression analysis and/or poisson regression should be conducted, and for statistically significant parameters, the meaning should be described.	in HbA1c or FPG (if available), eGFR (if available), Body weight, and blood pressure, 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 occurrence of hospitalization for heart failure, the occurrence of cardiovascular death will be displayed by frequencies, EF (if available), BNP or NT-proBNP (if available) will be analyzed using paired t-test. For NYHA class a shift table will be provided for change from baseline to last value. ② **The effectiveness evaluation will be determined by comparing the NYHA functional class at the baseline and at the last value. If the last value of the NYHA class is the same or lower than baseline value, the evaluation will be deemed "effective". If the last value of NYHA class is higher than the baseline value, the evaluation will be considered "ineffective". The effectiveness rate, along with its 95% confidence intervals, will be calculated using the exact method.** ③ **The NYHA classification is subject to ceiling effects, since those with class IV cannot worsen. Therefore, the additional sensitivity analysis will also be performed**	

				by excluding the patients with NYHA class IV at baseline. **④ For the final effectiveness evaluation(improved, unchanged, aggravated, unassessble) 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 and/or poisson regression should be conducted, and for statistically significant parameters, the meaning should be described.	
51	10Jan2025 (v8.0)	All	Non-Interventional Study (NIS)	Observational and Non-Interventional Study (ONIS)	Wording change
52	10Jan2025 (v8.0)	All	BI	Boehringer Ingelheim	Deleted abbreviation(BI) and replaced with 'Boehringer Ingelheim' for sponsor's name
53	10Jan2025 (v8.0)	All	Local PV manager	Local Patient Safety Lead	Wording change

54	10Jan2025 (v8.0)	9.3.3.1 Assessment of Safety	• The important identified risks (Complicated urinary tract infection / Genital infection / Diabetic ketoacidosis with atypical presentation • The important potential risks (Urinary tract carcinogenicity / Liver injury / Pancreatitis)	• The important potential risks (Urinary tract carcinogenicity)	Update per recent local RMP v7.1 (deleted all of the important identified risks and 'liver injury', 'Pancreatitis' of the important potential risks)
55	10Jan2025 (v8.0)	9.7.2 Analysis of Safety	③ The important identified risks and Tthe important potential risks will be analyzed separately for each AE (The important identified risks (Complicated urinary tract infection / Genital infection / Diabetic ketoacidosis with atypical presentation), the important potential risks (Urinary tract carcinogenicity / Liver injury / Pancreatitis), missing information (NYHA Class IV Heart Failure)).	③ The important potential risks will be analyzed separately for each AE (the important potential risks (Urinary tract carcinogenicity), missing information (NYHA Class IV Heart Failure)).	Update per recent local RMP v6.1 (deleted all of the important identified risks and 'liver injury', 'Pancreatitis' of the important potential risks)
56	10Jan2025 (v8.0)	11.2 Adverse event and Serious Adverse Event Collection and Reporting	**Collection of AEs** The study is a non-interventional study in real-world situation and will be conducted within the conditions of the approved marketing authorization. For this reason, the following AE collection and reporting requirements have been defined. All 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(section 14.1).	**Collection of AEs** The study is a non-interventional study in real-world situation and will be conducted within the conditions of the approved marketing authorization. For this reason, the following AE collection and reporting requirements have been defined. All 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 and documented by the investigator on the AE page of the eCRF. Expedited reporting requirements including reporting method and timelines are defined below.	Revise instruction for the safety collection and reporting in more detail

			Expedited Reporting of AEs and Drug Exposure during Pregnancy to BI Pharmacovigilance The following must be reported by the investigator on the NIS AE form(section 14.2) and/or Pregnancy Monitoring Form(section 14.3) from signing the data release consent onwards until the end of the study and provide to the LPVM of [redacted]	**Expedited Reporting of AEs and Drug Exposure during Pregnancy to BOEHRINGER INGELHEIM Patient Safety and Pharmacovigilance** All adverse events noted from signing on the data release consent form onwards until the end of the study must be reported by the investigator to the LPSL of [redacted] using the ONIS AE form created through the eCRF system AE page. In exceptional circumstances, investigator can submit using the paper ONIS AE form (Appendix 14.2). For pregnancy case, it should be reported by the Pregnancy Monitoring Form (Appendix 14.3).	

6. MILESTONES

Milestone	**Planned Date**
Start of data collection	23, Nov 2021 (Approval date of Product)
End of data collection	31, May 2025
Interim reports of study results	As per regulation
Final report of study results	22, Feb 2026 (Expected date of MFDS submission)

7. RATIONALE AND BACKGROUND

7.1 RATIONALE

According to the local regulations, when a new chemical entity (NCE) is registered, a PMS (Post Marketing Surveillance) Study as a local PASS (post authorized safety study), which is stipulated in local PMS regulation: A surveillance that the MAH (Marketing Authorization Holder) conducts to submit real world data during the re-examination period for Korea Health Authority to observe for the defined period (4-6 years) for the safety/ effectiveness of new drugs etc. that were already licensed and were in market and reflect the results to the licensed information.
Jardiance® for the chronic heart failure indication was submitted to Korea Health Authority and Korea Health Authority imposed this mandatory post-approval commitment for [redacted] to submit safety data of more than 600 patients in single arm under real world environment for 4 years until December 2025, which are minimum requirements to meet Risk Management Plan (RMP) regulation. Such NIS can provide supplementary data to monitor the safety of NCE (New chemical entity) in a real-life situation. Data collected in randomized clinical study with strict inclusion/exclusion criteria and rigorous monitoring schemes have limitations.

7.2 BACKGROUND

Chronic heart failure (HF) is a progressive syndrome characterised by the inability of the heart to provide adequate blood supply to meet the metabolic demand of different tissues or to be able to do so only at the expense of elevated left ventricle filling pressure. HF is a prevalent disease affecting an estimated 26 million people worldwide. In the United States alone the prevalence is 5.7 million, and there are 670,000 new cases per year [R16-1527]. HF is associated with premature mortality and frequent hospitalisation. Approximately 50% of patients who develop HF die within 5 years after diagnosis [P16-03952]. Annually, more than 1 million patients are hospitalised with a primary diagnosis of HF. HF is the most common cause of hospitalisation among individuals above 65 years of age in the western countries [P16-03760]. Two types of HF have been defined mainly based on the LV ejection fraction (EF) and also other structural changes in heart muscle. They consist of heart failure with reduced EF (HFrEF) $\leq$40%, heart failure with mildly reduced EF 41~49%, and heart failure with preserved EF $\geq$ 50%.. Relative prevalence of HFrEF among HF patients is approximately 50% [R16-1528]. Amongst patients with HF who require hospitalisation, the proportion of HFpEF is rising. The rate of rehospitalisation among patients with HFrEF is close to 29% within 60-90 days of discharge from hospital [P16-03760].
Despite advances in therapy and management, HF remains a deadly clinical syndrome. After hospitalisations for HF (HHF), the one year mortality rate is high and not different between patients with preserved or reduced left ventricular ejection fraction (LVEF) [R16-2217], underscoring a high unmet medical need in this population.
About 25 to 45% of patients with HF have concomitant type 2 diabetes mellitus (T2DM), and nearly 15-25% has borderline diabetes (pre-diabetes), indicating a potential link between the HF syndromes and glucometabolic disturbances [R16-2382, R16-2384].

Despite the current standard of care for treatment of HFrEF such as medical therapy [angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta blockers, mineralocorticoid receptor antagonists (MRA), ivabradine and angiotensin receptor blocker-neprilysin inhibitor (ARNI)] or device therapy the mortality and morbidity remains high in HF patients. For HFpEF, however, control of congestive symptoms during acute episodes is the mainstay of management of these patients and no class of drugs have shown to increase survival or reduce HHF [P16-03760, P16-05920].
Empagliflozin is an orally available inhibitor of the renal dependent glucose co-transporter 2 (SGLT-2) indicated for, reduction of blood glucose in patients with T2DM by promoting urinary glucose excretion. It also reduces blood pressure, arterial stiffness and measures of the myocardial workload, likely through various mechanisms, as well as improving other CV risk factors (uric acid, visceral fat mass, albuminuria) [P15-00589, P15-09541].
In 2010 Boehringer Ingelheim initiated the EMPA-REG OUTCOME trial to explore CV benefit of the drug as well as to establish the safety profile of empagliflozin [P15-09840]. This trial completed in 2015 and showed empagliflozin, when given in addition to standard care treatment in high CV risk patients with T2DM, reduces the risk of 3-point MACE by 14% mostly driven by a 38% reduction in CV death. Furthermore this trial demonstrated reduction in the prespecified and adjudicated composite outcome of "CV death or hospitalisation for heart failure (HHF)" and HHF by 34%.
Consistent with the main results of the EMPA-REG OUTCOME trial, in approximately 10% of the trial population who had investigator-reported heart failure at baseline, empagliflozin showed significant reduction in CV death, HHF, and composite of "HHF or CV death" [P16-01253].

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

8. RESEARCH QUESTION AND OBJECTIVES

8.1 PRIMARY OBJECTIVE

The primary objective of this study is to monitor the safety profile of Jardiance® in Korean patient with chronic heart failure (NYHA class II-IV), in a routine clinical setting.

8.2 SECONDARY OBJECTIVE

The secondary objective of this study is to monitor the occurrence of hospitalization for heart failure(first and recurrent) or cardiovascular death within 12 weeks and/or 24 weeks from baseline.

9. RESEARCH METHODS

This study is an observational prospective, single arm, non-interventional, open-label, multi-centre study (ONIS). As per local PMS(Post Marketing Surveillance) regulation and Risk Management Plan (RMP) regulation, safety data will be collected for about 4 years until December 2025.

This study will be carried out by enrolling patients in a consecutive manner into the study requiring completion of case report forms(CRFs) from the subject who was initially administered the drug following the study start date to the requested number of subjects without omission. Prior to the initiation of the study, written contract shall be concluded, and this contract shall be concluded among BOEHRINGER INGELHEIM OPU, CRO(if applicable) and 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 ONIS.

9.1 STUDY DESIGN

This is a ONIS based on single arm 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.

9.1.1 Method of Assigning Patients to Treatment Groups

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

9.1.2 Dosage and Administration

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

9.1.3 Concomitant Therapy, Restrictions, Rescue

The 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 of all concomitant medication administered to the patient during the course of treatment in eCRF. This includes concomitant therapies started one month prior to Jardiance® initiation until the patient completes the final follow-up visit.
For more detailed information, please refer to the current local label.

9.2 SETTING

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

9.2.1 Study Sites

Approximately 21 sites by as many as 21 or more ONIS investigators will participate. To minimize the selection bias at the site level, the goal is to have participating centers reflect a balance between general hospitals and clinics for surveillance. The treating physicians will mainly be internists.

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

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

9.2.2 Study Population

A total of 600 patients will be enrolled at approximately 21 sites by as many as 21 or more ONIS physicians. To minimize the selection bias, consecutive patients from each site who meet inclusion criteria will be enrolled in this study.

9.2.2.1 Main diagnosis for study entry

Patients diagnosed with chronic heart failure (NYHA class II-IV) in Korea.

9.2.2.2 Inclusion criteria

- Patients who have started at first time on Jardiance® in accordance with the approved label in Korea for HF
- Chronic heart failure (NYHA class II-IV)
- Age ⩾ 19 years at enrolment
- Patients who have signed on the data release consent form

9.2.2.3 Exclusion criteria

- Patients with previous exposure to Jardiance ®
- Known allergy or Hypersensitivity to active ingredients empagliflozin or to any of the excipients
- Patients with type 1 diabetes or with prior history of diabetic ketoacidosis (DKA)
- Patient with renal impairment with eGFR < 20 mL/min/1.73 m^2
- Patients with rare hereditary conditions of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
- Patient who are pregnant or are nursing or who plan to become pregnant while in the trial
- Patients for whom empagliflozin is contraindicated according local label of Jardiance ®

9.2.2.4 Investigation for subjects of special interest

The patient who have signed on the data release consent form, subjects of special interest (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 summarized into subgroups collected from this.

9.2.3 Study Visits

9.2.3.1 Screening and run-in periods

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

9.2.3.2 Visit 1; Baseline Visit

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

- Visit date (visit 1, week 0)
- Data release consent form: Date of data release consent form
- Diagnosis: date of the diagnosis of chronic heart failure (NYHA class II-IV)
- Cause of HF (ischemic, non-ischemic)
- Inclusion / Exclusion criteria

- Demographic data: Year and month of birth(age), Gender, Pregnancy, Previous allergy, Height, Smoking status
- History of diabetes mellitus
- History of Diabetic ketoacidosis
- Diabetes mellitus related complication (Retinopathy, Neuropathy, Nephropathy, Vasculopathy, Others)
- Cardiovascular history (hospitalization for HF≦12 months, atrial fibrillation, hypertension)
- Medical history: Renal impairment, Hepatic impairment, Others. (history of concomitant disease within 6 months prior to baseline)
- Physical examination: Body weight, Blood pressure (SBP, DBP)
- Concomitant medications: Record all medications including trade name, daily dose, unit, purpose of administration, start date, and end date that have been taken at least once (within 1 month prior to baseline)
- Dose of Jardiance® given (Dose of Administration, The Frequency of Administration, Start Date, End Date)
- Renal function test: Serum creatinine, eGFR, Urine ACR if blood test result is available (the most recent data prior to baseline)
- Effectiveness endpoints: NYHA functional class, EF (mandatory), BNP or NT-proBNP level (if available), HbA1c and/or FPG (if available in T2D patients), eGFR (if available), Lab data should be collected within 1 month prior to baseline except EF. The EF data should be collected from the most recent echocardiography, within 12 months prior to baseline.

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.

9.2.3.3 Visit 2; 12 weeks from Visit 1

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

- Visit date (visit 2, 12weeks)
- Physical examination: Body weight, Blood pressure (SBP, DBP)
- Concomitant medications
- Any changes of Jardiance® given
- Renal function test: Serum creatinine, eGFR, Urine ACR if blood test result is available (the most recent data prior to Visit 2)
- Effectiveness endpoints: Occurrence of hospitalization for heart failure (first and recurrent), Occurrence of cardiovascular death, NYHA functional class, EF (if

available), BNP or NT-proBNP level (if available), HbA1c and/or FPG (if available in T2D patients), eGFR (if available), Lab data.

- 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 ONIS)
- Any adverse events noted, AESI (Adverse Event of Special interest)
- Study completion status (if necessary)
- The investigator's overall evaluation (if necessary)
- ONIS physician's electronic signature for data integrity (if necessary)

9.2.3.4 Visit 3; 24 weeks from Visit 1

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

- Visit date (visit 3, 24weeks)
- Physical examination: Body weight, Blood pressure (SBP, DBP)
- Concomitant medications
- Any changes of Jardiance® given
- Renal function test: Serum creatinine, eGFR, Urine ACR if blood test result is available (the most recent data prior to Visit 3)
- Effectiveness endpoints: Occurrence of hospitalization for heart failure (first and recurrent), Occurrence of cardiovascular death, NYHA functional class, EF (if available), BNP or NT-proBNP level (if available), HbA1c and/or FPG (if available in T2D patients), eGFR (if available), Lab data.
- 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 ONIS)
- Any adverse events noted, AESI (Adverse Event of Special interest)
- Study completion status
- The investigator's overall evaluation
- ONIS physician's electronic signature for data integrity

9.2.3.5 End of study and follow-up period

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

9.2.4 Study Discontinuation

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

1. Failure to meet expected enrolment goals overall or at a particular study site
2. Emergence of any effectiveness/safety information that could significantly affect continuation of the study
3. Violation of Good Pharmacoepidemiology Practice (GPP), the study protocol, or the contract by a study site, investigator or research collaborator, disturbing the appropriate conduct of the study

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

9.2.5 Flow Chart

Data points	**Baseline**	**Follow-up 1**	**Follow-up 2**
Visit Number	1	2	3
Week/s	0	12	24
Informed consent	X		
Diagnosis	X		
Inclusion / exclusion criteria	X		
Demographics	X		
Diabetes mellitus complications	X		
Medical history	X		
Physical examination	X	X	X
Concomitant medications	X	X	X
Jardiance® administration status	X	X	X
Renal function	X[A]	X[A]	X[A]
NYHA function class	X	X	X
Ejection fraction	X	X[A]	X[A]
B-type Natriuretic Peptide (BNP) or N-terminal (NT)-proBNP	X[A]	X[A]	X[A]
Other Effectiveness endpoints (HbA1c and/or FPG, e GFR)	X[A]	X[A]	X[A]
lab tests	X[A]	X[A]	X[A]
the occurrence of hospitalization for heart failure		X[A]	X[A]

Data points	**Baseline**	**Follow-up 1**	**Follow-up 2**
The occurrence of CV death		X[A]	X[A]
The investigator's overall evaluation		X[A]	X
Adverse events		X	X
Study completion		X	X

[A]: If applicable

9.3 VARIABLES

9.3.1 Analysis Sets

A total of 600 patients will be entered in this study, and each patient will be followed for baseline, short term 12 weeks follow up, and long term 24 weeks follow up. The safety analysis will comprise all patients who is administered Jardiance® and is completed at least one time of safety follow-up. Since heart failure is chronic disease it might not be sufficient to collect safety and effectiveness data in short-term (12weeks) period, therefore, most of patients will be enrolled for long-term (24weeks) surveillance.
It is expected that approximately 80% (480 cases) will be enrolled for long-term surveillance, and approximately 50% (300 cases) will be enrolled as geriatric (older than 65 years).

9.3.1.1 Number of cases who entered the study

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

9.3.1.2 Number of cases to CRF collection

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

9.3.1.3 Number of cases to safety evaluation

These include those who signed the data release 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 did not signed (sign missing), or patients who signed on the data release consent form of Jardiance® PMS 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 cannot be obtained due to follow-up Loss
f. Patients who were prescribed for other indications except indications in the local label

9.3.1.4 Number of cases to effectiveness evaluation

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

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

9.3.2 Endpoints

9.3.2.1 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 patients with adverse events and will include:

- Adverse events
- Unexpected adverse events
- Unexpected adverse drug reaction
- Serious adverse events
- Serious adverse drug reaction
- Drug-related adverse events
- Non-serious adverse drug reaction
- Adverse event of special interest
- Adverse events leading to discontinuation

9.3.2.2 Endpoints of effectiveness

9.3.2.2.1 Endpoints of effectiveness after 12 and/or 24 weeks

- Occurrence of hospitalization for heart failure (first and recurrent) after 12 weeks and/or 24 weeks of treatment from baseline
- Occurrence of cardiovascular death after 12 weeks and/or 24 weeks of treatment
- Changes from baseline in NYHA functional class after 12 weeks and/or 24 weeks of treatments.
- Changes in EF (if available) at 12 weeks and 24 weeks compared to baseline
- Changes in BNP or NT-proBNP (if available) at 12 weeks and 24 weeks compared to baseline
- Changes in HbA1c or FPG (if available in T2D patients) after 12 weeks and/or 24 weeks of treatment
- Change from baseline in eGFR (if available) 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

- The result of investigator's overall evaluation after 12weeks and/or 24weeks of treatment

9.3.3 Assessment Criteria

9.3.3.1 Assessment of safety

- Adverse events (event name/ symptoms/ sign/ identify hypoglycemia symptoms)
- Onset date, End date
- Intensity (Mild/ Moderate/ Severe)
- Serious (Serious/ Non-Serious)
- Outcome of the event (Recovered/ Not yet recovered/ Sequela/ Fatal/ Unknown)
- Causality (Certain/ Probable·Likely/ Possible/ Unlikely/ Conditional· Unclassified/ Unassessable·Unclassifiable)
- Action taken with study drug due to AE (Dose not changed/ Dose reduced/ Dose increased/ Drug withdrawn/ Not applicable)
- Adverse Event of Special interest (Hepatic injury/ Decreased renal function/ Ketoacidosis/ Events leading to Lower limb amputation)
- The important potential risks (Urinary tract carcinogenicity)
- Missing information (NYHA Class IV Heart Failure)

9.3.3.2 Assessment of effectiveness

① NYHA (New York Heart Association) functional class:
The New York Heart Association (NYHA) functional classification will be used to classify the severity of the patients' heart failure.

NYHA FUNCTIONAL CLASSIFICATION

Class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath)
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath)
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases

The investigator should place the patients in one of the four categories based on how limited their physical activity are. Candidates for screening are required to have a NYHA functional class II, III or IV. The classification of patient's physical activity according to NYHA will be performed at all on-site until end of the trial. If

a visit is designated as an on-site visit but is conducted by phone, the NYHA functional classification must be performed.

② BNP or NT-proBNP (if available):
The Investigator would collect BNP or NT-proBNP data (if available) in accordance with the test method of each site.

③ HbA1c (%):
HbA1c should be collected within 1 month prior to baseline and after 12 weeks, 24 weeks of treatment (if available in T2D patients).

④ Fasting Plasma Glucose (FPG)(mg/dL):
FPG should be collected within 1 month prior to baseline and after 12 weeks, 24 weeks of treatment (if available in T2D patients).

⑤ Body Weight(kg):
Body weight should be collected within 1 month prior to baseline and after 12 weeks, 24 weeks of treatment at visiting site.

⑥ Blood Pressure (SBP, DBP) (mmHg):
Blood pressure (SBP, DBP) should be collected within 1 month prior to baseline and after 12 weeks, 24 weeks of treatment.

⑦ The investigator's overall evaluation
Records by performing the overall effectiveness evaluation at the end of the last visit

a. Improved: If determined as there is any effect of maintaining or improving disease related factors.
b. Unchanged: If disease related factors have not been changed compared with before administration, and not determined as there is any effect of maintaining symptoms.
c. Aggravated: If disease related factors are worse than before administration.
d. 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 "Ineffective".

9.4 DATA SOURCES

For this ONIS based on newly collected data, the site selection will be done with feasibility questionnaire including phone or visit to potential investigator who can prescribe the drug under his/her clinical practice. To minimize the selection bias at the site level, the goal is to have participating centers reflecting a balance between general hospitals and clinics for surveillance. The treating physicians will mainly be cardiologist. To minimize the selection bias, consecutive patients from each site who meet inclusion criteria will be enrolled in this study.
This study will be carried out in the manner of successive observation that the investigator will be asked to put clinical data in the local EDC (electronic data capture) system from the subject who was initially administered the drug following the study start date to the requested number of subjects without omission. Prior to initiation of the study, written contract shall be concluded, and this contract shall be concluded with the head of the site or the investigator with his/her consent.

9.5 STUDY SIZE

According to the local RMP and PMS regulation, it's required to submit more than 600 patient of safety analysis in this study, and each patient will be followed for baseline, short term 12 weeks follow up, and long term 24 weeks follow up. The requirement of the number of safety analysis is defined as patient who is administered Jardiance® and is completed at least one time of safety follow-up. Since heart failure is chronic disease it might not be sufficient to collect safety and effectiveness data in short-term (12 weeks) period, therefore, most of patients will be enrolled for long-term (24 weeks) surveillance.
It is expected that approximately 80% (480 cases) will be enrolled for long-term surveillance, and approximately 50% (300 cases) will be enrolled as geriatric (older than 65 years).

9.6 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). Though this task is outsourced to CRO, DMP will be developed following BOEHRINGER INGELHEIM and/or CRO relevant SOPs.

9.7 DATA ANALYSIS

9.7.1 Analysis of Demographic Data

Demographic data and the health status of subjects for the safety evaluation will be analysed descriptively. For continuous data, the number of patients, mean, standard deviation, minimum value, maximum value, and median 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
Year of birth (Age), Gender, Pregnancy, Previous allergy, Height, Smoking status, Body weight, Blood pressure, History of diabetes mellitus, Diabetes mellitus complications, History of heart failure, Medical history, Other medical history, Disease period, Elderly (Age ≥ 65 years), Renal impairment and Hepatic impairment, Long term use (over 24 weeks), NYHA class, EF

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

9.7.2 Analysis of Safety

① 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.
② The number and percentage of adverse events by type and category should be presented.
③ The important potential risks will be analyzed separately for each AE (the important potential risks (Urinary tract carcinogenicity), missing information (NYHA Class IV Heart Failure)).
④ 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.
⑤ To estimate any factors that are thought to influence the analyzed frequency of adverse events, logistic regression analysis should be conducted, and for statistically significant parameters, the meaning will be described medically.

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

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

Safety analyses will be based on all patients treated, i.e. all patients who received at least one dose of Jardiance®. 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 in accordance with protocol to the relevant data. Patients lost to follow up will be characterized compared to the remaining patients and reason and time point of loss to follow up will be evaluated.

9.7.3 Analysis of Effectiveness

① Mean, standard deviation, minimum value, maximum value, and median of changes in HbA1c or FPG (if available), eGFR (if available), Body weight, and blood pressure, 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 occurrence of hospitalization for heart failure, the occurrence of cardiovascular death will be displayed by frequencies, EF (if available), BNP or NT-proBNP (if available) will be analyzed using paired t-test. For NYHA class a shift table will be provided for change from baseline to last value.

② The main effectiveness evaluation will be determined by comparing the NYHA functional class at the baseline and at the last value. If the last value of the NYHA class is the same or lower than baseline value, the evaluation will be deemed "effective". If the last value of NYHA class is higher than the baseline value, the evaluation will be considered "ineffective". The effectiveness rate, along with its 95% confidence intervals, will be calculated using the exact method.

③ The NYHA classification is subject to ceiling effects, since those with class IV cannot worsen. Therefore, the additional sensitivity analysis will also be performed by excluding the patients with NYHA class IV at baseline.

④ For the effectiveness in patients with NYHA class IV, it should be assessed through the investigator's overall evaluation and the number and percentage of subjects should be presented. If the result of overall evaluation is 'improved' at last visit, it will be classified as 'effective'. If the result of overall evaluation is 'unchanged' or 'aggravated', it will be classified as 'ineffective'.

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

9.7.4 Interim Analyses

There will be interim analyses in accordance with local regulation.

9.7.5 Handling of Missing Data

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

9.8 QUALITY CONTROL

All entries in the eCRF and the existing codings will be stored in a database. The structure of the database is based on the division into sections and entry fields defined in the eCRF. To improve and ensure data quality, data checks will be performed automatically in the eCRF directly on electronic entry at the study site.
Plausible value ranges for numerical data entries and logical data and list entries will be filed in the eCRF. The tests for consistency and completeness based on this will be performed during entry in the eCRF. The validity of the recorded data will therefore be ensured by the

validations incorporated in the documentation system, which highlight incorrect or implausible entries to the data entry.
All changes after initial data entry will be documented in an audit trail. An additional inspection/quality assurance check of the data collected within this 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 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.

9.9.2 Channeling Bias

Channeling bias can occur due to access to product depending on reimbursement circumstances or preferential prescribing in relation to different risks for the events of interest: e.g., if Jardiance® would be more often prescribed to higher risk patients compared to other treatments, higher frequency of outcome events were then expected in the Jardiance® group. To assess the extent of preferential prescribing of Jardiance® and the potential for channeling bias, baseline data from the Jardiance® T2DM PMS would be used to provide context for the Jardiance® chronic heart failure PMS data.

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. However, as only major confounders for selected research questions can be captured, residual (unmeasured) confounding may remain.

9.10 OTHER ASPECTS

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

The protocol of this regulatory required ONIS will be submitted to the Ministry of Food and Drug Safety (MFDS) for notification. Also, the protocol of this ONIS will be submitted to Institutional Review Board (IRB) whenever required or requested by these institutions. This

study will be conducted in accordance with the Standards for Re-examination of New Medicines notified by MFDS, Korean Pharmaceutical Affairs Code (KPAC), Enforcement Regulation of KPAC and other applicable local laws and industry code (including but not limited to the Regulations on Fair Competition in the Trade of Medicines of KPMA and KRPIA).

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

9.10.1 Data Quality Assurance

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

9.10.2 Study Records

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

9.10.2.1 Source documents

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

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

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

- Patient 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 (mandatory, last date if continues))
- Serious adverse events (onset date (mandatory), and end date (mandatory, last date if continues))
- Concomitant therapy (start date, changes)
- Laboratory results (if available)
- Completion of Patient's Participation in the study

9.10.2.2 Direct access to source data and documents

The investigator/institution will permit study-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. Ministry of Food and Drug Safety (MFDS)). BOEHRINGER INGELHEIM study staff and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.1.

9.10.2.3 Storage period of records

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

10. PROTECTION OF HUMAN SUBJECTS

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

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

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

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

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

The patient must be informed that his/her personal study-related data will be used by BOEHRINGER INGELHEIM 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 BOEHRINGER INGELHEIM , by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

10.2 STATEMENT OF CONFIDENTIALITY

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

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the

study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse drug reaction
An adverse drug reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

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

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

The term AESI relates to any specific AE that has been identified at the substance level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs.

The following are considered as AESIs for empagliflozin:

Hepatic injury

- An elevation of AST and/or ALT ⩾3-fold ULN combined with an elevation of total bilirubin ⩾2-fold ULN measured at the same visit, or in samples drawn 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

Decreased renal function

Decreased renal function is defined by a creatinine value showing a ⩾ 2 fold increase from baseline and is above the ULN.
For the AESI "decreased renal function" the patient needs to be followed-up appropriately based on local clinical guidance.

Ketoacidosis

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 and measurement of serum beta-hydroxybutyrate levels. Other diagnostic criteria which can support the diagnosis of KA are urine ketones and anion gap >10.
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.

Events leading to 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.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

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

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

All 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 and documented by the investigator on the AE page of the eCRF.
Expedited reporting requirements including reporting method and timelines are defined below.

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

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

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

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

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

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

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

The causal relationship of related or unrelated will be collected considering the 6 categories in accordance with the Korea Health Authority requirement.

Related

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

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

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

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

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

Unrelated

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

Intensity of adverse event

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

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

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

All adverse events noted from signing on the data release consent form onwards until the end of the study must be reported by the investigator to the LPSL of [redacted] using the ONIS AE form created through the eCRF system AE page. In exceptional circumstances, investigator can submit using the paper ONIS AE form (Appendix 14.2). For pregnancy case, it should be reported by the Pregnancy Monitoring Form (Appendix 14.3).

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/or the ONIS AE form.

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(Appendix 14.3) to the LPSL of [redacted]

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

The ISF will contain the Pregnancy Monitoring Form (Part A and B). As pregnancy itself is

not to be reported as an AE, in the absence of an accompanying AE, only the Pregnancy Monitoring Form and not the NIS AE form is to be completed. If there is an AE associated with the pregnancy a ONIS AE form must be completed in addition.

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

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

11.3 REPORTING TO HEALTH AUTHORITIES AND IEC/IRB

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

13. REFERENCES

13.1 PUBLISHED REFERENCES

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14. APPENDICES

14.1 ELECTRONIC CASE REPORT FORM

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

14.2 OBSERVATIONAL AND NON-INTERVENTIONAL STUDY (ONIS) ADVERSE EVENT FORM

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

14.3 PREGNANCY MONITORING FORM

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

14.4 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.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	**Document Reference Number**	**Date**	**Title**
None	None	None	None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

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