Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

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Name of company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
Name of finished medicinal product: Jardiance Duo 5/500mg, 5/850mg, 5/1000mg, 12.5/500mg, 12.5/850mg, 12.5/1000mg			
Name of active ingredient: empagliflozin, metformin HCl			
Report date: 27Jan2021	**Study number:** 1276-0039	**Version/Revision:** 1.0/Not applicable	**Version/Revision date:** Not applicable

Title of study:	A regulatory requirement non interventional study to monitor the safety and effectiveness of JARDIANCE DUO® (empagliflozin/metformin, 5/500mg, 5/850mg, 5/1000mg, 12.5/500mg, 12.5/850mg, 12.5/1000mg) in Korean patients with type 2 diabetes mellitus
Keywords:	Non-interventional based on newly collected data, Open-label, Single arm, Multi-center and single national study
Rationale and background:	According to the local regulations, when a new chemical entity (NCE) is registered, a regulatory non interventional study (NIS) of an extended period (4 or 6 years) should be conducted. Such NIS can provide supplementary data to monitor the safety of NCEs in a real-life situation. Data collected in randomized clinical study with strict inclusion/exclusion criteria and rigorous monitoring schemes have limitations.
Research question and objectives:	To monitor the safety profile and effectiveness of JARDIANCE DUO® (empagliflozin/metformin, 5/500mg, 5/850mg, 5/1000mg, 12.5/500mg, 12.5/850mg, 12.5/1000mg) in Korean patients with type 2 diabetes mellitus in a routine clinical practice setting. Primary Objective The primary objective of this study is to monitor the safety profile of JARDIANCE DUO® in Korean patient with type 2 diabetes mellitus (T2DM) in a routine clinical setting. Secondary Objective The secondary objective of this study is to monitor the effectiveness of JARDIANCE DUO® by evaluation of the change from baseline after 12 weeks and/or 24 weeks in the glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG), body weight, blood pressure (SBP, DBP) and the final effectiveness evaluation at the end of the last visit in Korean T2DM patients.
Study design:	This is a single arm study with JARDIANCE DUO®. JARDIANCE DUO® 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.

Setting:	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 DUO® will be administered according to the approved label in Korea. JARDIANCE DUO® is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus who are appropriate to take a combination of empagliflozin and metformin. • When the patients never experienced prior treatments and monotherapy would not provide appropriate glycaemic control, or • When metformin monotherapy does not provide adequate glycemic control, or • As add-on therapy to sulphonylurea in patients with insufficient glycemic control despite treatment with metformin in combination with SU, or • As add-on therapy to pioglitazone in patients with insufficient glycemic control despite treatment with metformin in combination with pioglitazone, or • As add-on therapy to linagliptin in patients with insufficient glycemic control despite treatment with metformin in combination with linagliptin • As add-on therapy to insulin in patients with insufficient glycemic control despite treatment with insulin in combination with metformin, or • As add-on therapy to insulin in combination with sulphonylurea in patients with insufficient glycemic control despite treatment with insulin in combination with metformin plus sulphonylurea, or • As replacement therapy of empagliflozin plus metformin (Patients switching from separate tablets of empagliflozin (10 mg or 25 mg total daily dose) and metformin to JARDIANCE DUO® should receive the same daily dose of empagliflozin and metformin already being taken.) <u>Inclusion criteria:</u> • Patients who have started at first time on JARDIANCE DUO® in accordance with the approved label in Korea • Age ≥19 years at enrolment • Patients who have signed on the data release consent form <u>Exclusion criteria:</u> • Patients with previous exposure to JARDIANCE DUO® • Hypersensitivity to active ingredients empagliflozin and/or metformin or to any of the excipients • Moderate (stage 3b) and severe renal failure (CrCl < 45 ml/min or eGFR < 45 ml/min/1.73m^2) • Acute conditions with the potential to alter renal function such as: dehydration, severe infection, cardiovascular collapse (shock), acute myocardial infarction, sepsis • Type 1 diabetes, acute or chronic metabolic acidosis, including diabetic ketoacidosis with or without coma, history of a ketoacidosis

	(type 1 diabetes and diabetic ketoacidosis should be treated with insulin). • Congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure • Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials) - Intravascular administration of iodinated contrast media may lead to acute renal failure and has been associated with lactic acidosis in patients receiving metformin. Therefore, in patients with eGFR > 60ml/min/1.73m^2, JARDIANCE DUO® must be discontinued prior to, or at the time of the test and not be reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further. In patients with moderate renal impairment (eGFR 45-60 ml/min/1.73m^2), JARDIANCE DUO® must be discontinued 48 hours before administration of iodinated contrast media and not be reinstituted until at least 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further. • In patients with severe infections or severe traumatic systemic disorders, JARDIANCE DUO® should be temporarily suspended, and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal. • JARDIANCE DUO® should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) before 48 hours, and not be reinstituted until 48 hours afterwards, after renal function has been evaluated as normal. • Patients with malnutrition, starvation, hypostheniam pituitary or adrenal insufficiency • Impaired hepatic function (since impaired hepatic function has been associated with some cases of lactic acidosis, JARDIANCE DUO® should generally be avoided in patients with clinical or laboratory evidence of hepatic disease), pulmonary infarction, severe respiratory impairment, any condition associated with hypoxemia, excessive alcohol intake, GI disorders such as dehydration, diarrhoea or vomiting • Pregnant women, women who may be pregnant, nursing women • Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock • Patients for whom empagliflozin/metformin is contraindicated according local label of JARDIANCE DUO® • Current participation in other clinical trials
Subjects and study size, including dropouts:	A total of 600 patients will be entered in this study, and each patient will be followed for total three times (baseline, short term 12 weeks follow up, long term 24 weeks follow up). Since T2DM is chronic disease it might be restrictive to collect safety and effectiveness data in short-term (12weeks) period, all patients will be enrolled for long-term (24weeks) surveillance.
Variables and data sources:	<u>Endpoints of safety</u>

	All reported adverse events in patients who take at least one dose of JARDIANCE DUO® will be noted. Endpoints pertaining to safety will be presented as incidence rates of adverse events and will include: • Adverse events • Unexpected adverse events • Serious adverse events • Drug-related adverse events • Non serious adverse drug reaction • Adverse event of special interest • Adverse events leading to discontinuation <u>Endpoints of effectiveness</u> Change from baseline in HbA1c, fasting plasma glucose (FPG), body weight, blood pressure (SBP, DBP) after 12weeks and/or 24 weeks of treatment and the final effectiveness evaluation at the end of the last visit will be noted. • Change from baseline in HbA1c after 12 weeks and/or 24 weeks of treatment • Occurrence of treat to target effectiveness response that is an HbA1c under treatment of < 7% after 12 weeks and/or 24 weeks of treatment • Occurrence of relative effectiveness response (HbA1c lowering by at least 0.5% after 12 weeks and/or 24 weeks) • Change from baseline in fasting plasma glucose (FPG) after 12 weeks and/or 24 weeks of treatment • Change from baseline in body weight after 12 weeks and/or 24 weeks of treatment • Change from baseline in blood pressure (SBP, DBP) after 12 weeks and/or 24 weeks of treatment • Records by performing the final effectiveness evaluation at the end of the last visit: 'Improved' is assessed as "Effective", "Unchanged" and "Aggravated "are assessed as "Invalid"
Statistical Methods:	<u>Safety analysis</u> • Among the subjects of safety evaluation, the number of subjects with adverse event incurred and the number of adverse events incurred should be calculated, and the incidence rate of adverse events and the 95% confidence interval should be presented. • The number and percentage of adverse events by type and category should be presented. • Analysis should be made using Chi-square test or Fisher's Exact test on the adverse <u>event onset status by demographic data of subjects of safety evaluation.</u> • <u>To estimate any factors that are thought to influence the analysed incidence rate of adverse events, logistic regression analysis should be conducted, and for statistically significant parameters, the meaning should be described.</u> <u>Effectiveness analysis</u>

	• Mean, standard deviation, minimum value, maximum value, and median of changes in glycosylated hemoglobin(HbA1c) and fasting plasma glucose(FPG), weight, and blood pressure, which were measured at the last visit versus baseline, should be presented, and if there is difference before administration versus after administration should be analysed using paired t-test. • If there is difference in the change of glycosylated haemoglobin (HbA1c) according to demographic parameters should be analysed using t-test or ANOVA(Analysis of Variance). • The frequency and percentage of patients who had glycosylated hemoglobin(HbA1c) reaching less than 7% (target effectiveness response rate) at the last visit should be calculated, and the frequency and percentage of patients with glycosylated hemoglobin(HbA1c) decreased by at least 0.5% at the last visit should be calculated. • For final effectiveness evaluation (improved, unchanged, aggravated, unassessable) and 'effective(improved)'/'ineffective(unchanged, aggravated)', the number and percentage of subjects should be mentioned. The final effectiveness evaluation of "Improved" will be classified as "Effective", "Unchanged" and "Aggravated" will be classified as "Ineffective". The effectiveness rate and its 95% confidence intervals will be estimated with exact method. • 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.
Results:	**Subjects and Compliance with Protocol:** During this re-examination period, case report forms (CRFs) were retrieved from a total of 658 subjects. Of these, 620 subjects were included in safety analysis set excluding 3 'subjects who have taken study drug prior to the contract date', 2 'subjects who lost to safety follow-up', and 33 'subjects who have been violated the inclusion/exclusion criteria'. Of these, 497 subjects were included in the effectiveness assessment set excluding 60 'subjects with missing information of HbA1c before or after administration' and 63 'subjects with 'Unassessable' of HbA1c before or after administration'.

Number of subjects whose CRFs were retrieved	658
Number of subjects included in the safety analysis set	620
Number of subjects included in the effectiveness analysis set	497

Demographic information:

Among the 620 subjects in the safety analysis set, 64.35% (399/620 subjects) were 'male' and 35.65% (221/620 subjects) were 'Female'. The mean age of the subjects was 56.39±12.78 years, from minimum 19.00 years to maximum 83.00 years. The age distribution was 45.48% (282/620 subjects) in '≥ 60 years', followed by 28.23% (175/620 subjects) in '50 ~ < 60 years', and 26.29% (163/620 subjects) in '< 50 years' in order. Classifying geriatric subjects as those aged '65 years or more', 28.06%

	(174/620 subjects) of the subjects were found to be geriatrics. There was no pregnant subject. **Race and Ethnicity:** Not collected **Safety Results:** Among 620 subjects during the re-examination period, 11.94% (74/620 subjects, 90cases) of AEs, 5.48% (34/620 subjects, 40 cases) of ADRs, 1.61% (10/620 subjects, 11 cases) of serious AEs, 0.16% (1/620 subjects, 1 case) of SADRs, 9.03% (56/620 subjects, 65 cases) of unexpected AEs, 3.23% (20/620 subjects, 23 cases) of SADRs, 1.61% (10/620 subjects, 11 cases) of unexpected SAEs, and 0.16% (1/620 subjects, 1 case) of unexpected SADRs were reported. The one case of reported unexpected SADR was 'Cerebral infarction' under "Nervous system disorders". It was in 'Other comparable medical criteria' category, not recovered yet but the administration of study drug was continued. During the re-examination period, the frequency of non-SADR was 5.32% (33/620 subjects, 39 cases) among 620 subjects in the safety analysis set and the most frequent non-SADRs was 'Hypoglycaemia' in 1.29% (8/620 subjects, 8 cases). The frequency of AESI was 0.65% (4/620 subjects, 4 cases) and the most frequent AE was 'Increased urination' in 0.48% (3/620 subjects, 3 cases). The frequency of AEs leading to discontinuation of the drug was 2.90% (18/620 subjects, 21 cases) and the most frequent AEs were 'Dizziness' and 'Pollakiuria' each in 0.48% (3/620 subjects, 3 cases). Among 219 subjects whose administration period were less than 24 weeks during the re-examination period, 15.07% (33/219 subjects, 40 cases) of AEs, 7.76% (17/219 subjects, 20 cases) of ADRs, 2.74% (6/219 subjects, 7 cases) of serious AEs, 12.33% (27/219 subjects, 30 cases) of unexpected AEs, 5.02% (11/219 subjects, 12 cases) of unexpected ADRs, and 2.74% (6/219 subjects, 7 cases) of unexpected SAEs were reported, and there were no SADRs and unexpected SADRs. During this re-examination period, of 399 long-term use subjects who received the study drug for 24 weeks or longer in the safety analysis set, the frequency of AE was 10.28% (41/399 subjects, 50 cases), the frequency of ADRs was 4.26% (17/399 subjects, 20 cases), the frequency of SAEs was 1.00% (4/399 subjects, 4 cases), the frequency of SADRs was 0.25% (1/399 subjects, 1 case), the frequency of unexpected AEs was 7.27% (29/399 subjects, 35 cases), the frequency of unexpected ADRs was 2.26% (9/399 subjects, 11 cases), the frequency of unexpected SAEs was 1.00% (4/399 subjects, 4 cases), the frequency of unexpected SADRs was 0.25% (1/399 subjects, 1 case). When the severity of AEs was classified into 3 categories of 'Mild', 'Moderate', and 'Severe', 79 cases were 'Mild', 8 cases were 'Moderate', and 3 cases were 'Severe'. All severe cases had no causality with the study drug, and the outcome of AEs were 1 case (Pancreatic carcinoma) of not

	yet recovered and 2 cases (‘Ankle fracture’ and ‘Facial bones fracture’) of recovered. During this re-examination period, there were no AEs leading to deaths or death reported from PMS and non-PMS in Korea. **Effectiveness / Other Results:** In the results of analyzing the mean of change in HbA1c at the last visit versus baseline among 497 subjects in effective analysis set, the mean changed from 7.96±1.49% at baseline to 7.24±1.17% at the last visit. The mean of the change in HbA1c at the last visit versus baseline was -0.72±1.47%. This was statistically significant (p<0.0001). Target effectiveness response was defined as HbA1c of lower than 7% at the last visit. Of the 497subjects in the effectiveness analysis set, 48.09% (239/497 subjects) reached the target effectiveness response while 51.91% (258/497 subjects) did not reach the target effectiveness response. Relative effectiveness response was defined as HbA1c decrease of 0.5% or more at the last visit. Of the 497subjects in the effectiveness analysis set, 48.69% (242/497 subjects) reached the relative effectiveness response while 51.31% (255/497 subjects) did not reach the relative effectiveness response. In the results of analyzing the mean of change in FPG at the last visit versus baseline among 497 subjects in effective analysis set, the mean changed from 160.08±53.78 mg/dL at baseline in 460 subjects to 130.84±36.98 mg/dL at the last visit in 436 subjects. The mean of change in FPG at the last visit versus baseline was -26.86±50.91 mg/dL in 417 subjects. This was statistically significant (p<0.0001). In the results of analyzing the mean of the change in body weight at the last visit versus baseline among 497 subjects in effective analysis set, the mean changed from 74.72±14.38 kg at baseline in 440 subjects to 72.73±13.64 kg at the last visit in 386 subjects. The mean of the change in body weight at the last visit versus baseline was -2.18±3.53 kg. This was statistically significant (p<0.0001). In the results of analyzing the mean of change in SBP at the last visit versus baseline among 497 subjects in effective analysis set, the mean changed from 129.29±14.59 mmHg at baseline in 464 subjects to 127.44±13.78 mmHg at the last visit in 459 subjects. The mean of change in SBP at the last visit versus baseline was -1.96±15.45 mmHg in 448 subjects in the effectiveness analysis set. This was statistically significant (p=0.0076). In the results of analyzing the mean of change in DBP at the last visit versus baseline among 497 subjects in the effectiveness analysis set, the mean changed from 76.95±10.91 mmHg at baseline in 464 subjects to 75.03±10.09 mmHg at the last visit in 459 subjects. The mean of change in DBP at the last visit versus baseline was -2.04±10.80 mmHg in 448 subjects. This was statistically significant (p<0.0001).

	The investigators conducted the final effectiveness assessment by classifying the result as 4 categories of 'Improved', 'Unchanged', 'Aggravated', or 'Unassessable'. The final effectiveness assessment result was 'Improved' in 66.40% (330/497 subjects), 'Unchanged' in 20.72% (103/497 subjects), 'Aggravated' in 9.05% (45/497 subjects), and 'Unassessable' in 3.82% (19/497 subjects). Reclassifying the results of the final effectiveness as "Effective" for 'Improved' and as "Ineffective" for 'Unchanged' and 'Aggravated' in 478 subjects excluding 19 subjects who were included 'Unassessable' among 497 subjects in the final effectivenss assessment, the result was "Effective" for 69.04% (330/478 subjects).
Discussion:	As a result of this re-examination period, in conclusion, no unusual tendency or significant new information were found for Jardiance Duo® compared to safety and effectiveness of existing marketing approval. However, since this surveillance is a non-interventional, single-arm study, the analysis was conducted only on the data that can be collected and confounding variables were not controlled. Therefore, the limitation should be considered on the aspect of the study design. Unexpected AEs and SAEs will be continuously monitored subsequently further.
Marketing Authorisation Holder(s):	[redacted] [redacted] Korea
Names and affiliations of principal investigators:	[redacted]