Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: BOEHRINGER INGELHEIM KOREA LTD.			
Name of finished medicinal product: JARDIANCE®			
Name of active ingredient: Empagliflozin			
Reporting Date: V1.0/ 01 Apr 2026	**Study Number:** 1245-0276	**Version / Revision:** Not applicable	**Version / Revision Date:** Not applicable
Tile of study:	A Post-Marketing Surveillance Study to Monitor the Safety and Efficacy of Jardiance® (Empagliflozin, 10mg) in Korean Patients with Chronic Heart Failure (NYHA class II-IV)		
Keywords:	Jardiance®, safety, effectiveness, post-market surveillance (PMS), Koreans		
Rationale and Background:	This survey is a Post-Marketing Surveillance (PMS) nce as an in-country post-authorization safety study (PASS), as stipulated in the relevant regulations for domestic post-marketing surveillance. PMS is a study conducted by the marketing authorization holder (MAH) to submit real-world clinical data to the Korean health authorities during the re-examination period by observing the safety and effectiveness of already approved and marketed new drugs. over a set period (4–6 years) and the outcomes will be reflected in the product labeling. The Korean health authorities approved chronic heart failure as a new indication for Jardiance® and imposed a post-approval obligation on Boehringer Ingelheim Korea to submit safety data from a single-arm cohort of over 600 patients in a real-world clinical setting over a four-year period until 22 November, 2025 as a minimum requirement to satisfy the risk management plan (RMP) regulations. This PASS can provide supplementary data to monitor the safety of new chemical entities (NCEs) in real-world situations. Data collected from randomised controlled studies, which include strict inclusion/exclusion criteria and thorough monitoring plans, had limitations.		
Research question and objectives:	The primary and secondary outcomes are to observe the safety and effectiveness of Jardiance® (empagliflozin, 10 mg), respectively, in Korean patients with chronic heart failure (NYHA class II-IV), regardless of the presence of type 2 diabetes, in a routine clinical practice setting.		
Study design:	Prospective observational, single-arm, non-interventional, open-label, multicentre study		
Setting:	Korean patients with chronic heart failure (NYHA class II-IV) Jardiance® is prescribed for adult patients with chronic heart failure (NYHA class II-IV). Inclusion criteria:		

	• Patients initiating Jardiance® treatment for the first time in accordance with the domestic label; • Chronic heart failure (NYHA class II-IV); • Aged ≥ 19 years at the time of enrollment; • Patients who have signed the data release consent form. Exclusion criteria: • Patients previously exposed to Jardiance®, • Known allergy or hypersensitivity to the active ingredient empagliflozin or excipient(s); • Patients with type 1 diabetes mellitus or a history of diabetic ketoacidosis (DKA); • Patients with renal impairment, with eGFR < 20 mL/min/1.73 m²; • Patients with rare hereditary disorders of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption; • Patients who are pregnant, breastfeeding, or planning to become pregnant during the study period; • Patients for whom empagliflozin is contraindicated according to the domestic label for Jardiance®.
Patients and study size, including dropouts:	Total number of patients enrolled: 676 - Number of patients in the safety set: 629* - Number of patients in the effectiveness set: 519 - Number of excluded patients: 47 * Target number of patients: 600 (based on the safety set)
Variables and data sources:	**Safety endpoints:** All adverse events (AEs) reported in patients who received at least one dose of Jardiance® were recorded. The primary outcomes are the safety outcomes calculated as the incidence of: - 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 **Effectiveness endpoints:** Secondary outcomes are the changes of effectiveness evaluation at 12 weeks and/or 24 weeks after treatment. - Occurrence of hospitalisation 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 Data source: New data collection via routine clinical practice (21 sites)
Statistical Methods:	Statistical analyses were performed using a version 9.4 64 bit (SAS Institute, Cary, NC, USA) on the SAS® Enterprise Guide (version 8.2) interface. Continuous variables were summarized using the number of subjects, mean, standard deviation (SD), median, minimum, maximum, 5th percentile, and 95th percentile. Categorical variables were summarized using frequency and percentage. Unless otherwise specified, statistical tests were performed at a two-sided significance level of 5% for baseline characteristics. The mean, median, 5th percentile, and 95th percentile were presented with one more significant digit than the original data, and the SD was presented with two more significant digits than the original data. The minimum and maximum values were presented with the same number of significant digits as the original data. However, 'Duration of disease (years)', 'Total duration of administration (day)', 'Total administered dose (mg)', 'Average daily dose (mg)', and 'Duration of hospitalisation' were presented assuming that the original data had two decimal places. The p-value was presented to four decimal places (rounded from the fifth digit), as <0.0001 if the p-value was less than 0.0001, and as >0.9999 if it was greater than 0.9999.
Results:	During the re-examination period, analysis of the demographics of the 629 patients in the safety set showed a mean age (standard deviation) of 66.2 years (14.68), with an age range of 22 to 93 years. The sex distribution showed 61.69% male (388/629 patients) and 38.31% female (241/629 patients), with a higher proportion of males. The incidence rate of all AEs reported among the 629 patients in the safety set was confirmed to be 18.44% (116 / 629 patients, 167 cases). The results of classifying them according to the PT criteria showed that 'dizziness' was most frequently reported, at 1.59% (10 / 629 patients, 10 cases), followed by 'heart failure' at 1.11% (7 / 629 patients, 9 cases), and 'dizziness postural' and 'dyspnea' each at 0.79% (5 / 629 patients, 5 cases). A total of nine reported cases of 'heart failure' were all identified as worsening of pre-existing heart failure and were coded under the higher-level PT 'heart failure' according to MedDRA coding rules. When classifying all 167 AEs reported according to their outcome, 'recovered' accounted for 54.49% (91/167 cases), 'not recovered' 40.72% (68/167 cases) and 'fatal' 4.79% (8/167 cases). There were no AEs whose outcome was reported as 'recovered with sequelae' or 'unknown'.

	The results of classifying all AEs that occurred during the re-examination period according to their causal relationship with Jardiance® showed that 'certain' accounted for 0.60% (1/167 cases), 'probable/likely' 1.20% (2/167 cases), 'possible' 16.77% (28/167 cases), and 'unlikely' 81.44% (136/167 cases). There were no AEs whose causality was reported as 'conditional/unclassified' or 'unassessable/unclassifiable'. The incidence of adverse drug reactions (ADRs) whose causal relationship with this drug could not be ruled out was 4.29% (27 / 629 patients, 31 cases). According to the results of classification by PT, 'dizziness' and 'dizziness postural' were reported most frequently, each at 0.64% (4 / 629 patients, 4 cases). The incidence rate of serious adverse events (SAEs) was found to be 5.25% (33 / 629 patients, 43 cases). The results of classifying them according to the PT criteria showed that 'heart failure' accounted for the highest proportion, at 1.11% (7 / 629 patients, 9 cases), and 'dilated cardiomyopathy' and 'cerebral infarction' were each reported at 0.48% (3 / 629 patients, 3 cases). There were no serious adverse drug reactions (SADRs) whose causal relationship with this drug could not be ruled out. Unexpected AEs accounted for 6.20% (39 / 629 patients, 54 cases). According to classifying them by PT, 'heart failure' accounted for the highest proportion, at 1.11% (7 / 629 patients, 16 cases), followed by 'hyperkalaemia' at 0.64% (4 / 629 patients, 4 cases), and 'COVID-19' and 'dilated cardiomyopathy' each at 0.48% (3 / 629 patients, 3 cases). Among these, unexpected ADRs whose causal relationship with this drug could not be ruled out were found to be 0.16% (1 / 629 patient, 1 case), which was classified as 'renal functional impairment' by PT criteria. Non-serious AE accounted for 14.94% (94/629 patients, 124 cases). According to classifying them by PT, 'dizziness' was reported with the highest rate, at 1.59% (10/629 patients, 10 cases), followed by 'dizziness postural' at 0.79% (5/629 patients, 5 cases), and 'headache' at 0.64% (4/629 patients, 4 cases). Non-serious ADRs accounted for 4.29% (27/629 patients, 31 cases. The results of classification by PT, 'dizziness' and 'dizziness postural' were reported with the highest rate, each at 0.64% (4/629 patients, 4 cases).Adverse events of special interest (AESI) accounted for 0.16% (1 / 629 patients, 1 case), which corresponded to “renal function deterioration” among the predefined categories and was 'myelodysplastic syndrome' at 0.16% (1 / 629 patient, 1 case) according to the results of classification by PT. AEs leading to discontinuation of the drug occurred in 2.54% (16 / 629 patients, 20 cases). The results of classifying them by PT showed that 'urticaria', 'rash', 'pruritus', and 'dizziness' accounted for the highest proportion, each at 0.32% (2 / 629 patients, 2 cases). During the re-examination period, the incidence of AEs was analysed in special populations among the 629 patients in the safety set, including pediatric patients aged < 19 years, elderly patients ≥ 65 years, pregnant women, breastfeeding women, and those with hepatic or renal impairment. The results showed statistically significant differences in the AE incidence rate in the 'patients with hepatic impairment (Yes: 31.43% (11/35 patients), No: 17.68% (105/594 patients), p-value=0.0415)'. To identify factors affecting safety, the incidence of AEs was analysed and presented according to demographic characteristics and baseline disease information of the 629 patients in the safety set. Factors that showed

	statistically significant differences were identified as 'prior medication use' (p-value=0.0132), 'long-term use status' (p-value=<0.0030), 'height' (p-value=0.0224), and 'body weight' (p-value=0.0007). The results of performing a multivariate logistic regression analysis to estimate the factors affecting safety showed that 'prior medication use status', defined as the use of concomitant medications before the first dose of Jardiance® and 'long-term use status', defined as used of Jardiance® for 24 weeks or longer, statistically significantly affected the incidence rate of AEs. The patients who received a prior medication had a slightly higher incidence of AEs compared to those who did not receive a prior medication (odds ratio=1.79 (95% CI: 1.10 – 2.93), p-value=0.0202). This is thought to be because the patients requiring a prior medication had more underlying diseases, or drug sensitivity, etc. influenced the occurrence of AEs. In addition, the incidence of AEs was slightly lower in patients who received long-term administration (≥ 24 weeks) of the drug under surveillance compared with patients who received the drug for < 24 weeks (odds ratio=0.43 (95% CI: 0.25 – 0.75), p-value=0.0028). This observation may be explained by a natural survivor bias, where AEs occurred relatively predominantly during the early phase of drug administration (< 24 weeks). Consequently, patients with comparatively low tolerability discontinued the treatment early, resulting in patients with good tolerability being included in the long-term administration group. It is also determined that the decreasing trend in AE occurrence in patients receiving long-term administration contributed to the lower incidence of AEs observed in this group,, as the body adapted to the drug with continuous administration over a certain period.As for effectiveness of Jardiance®, 519 patients in the effectiveness set, whose evaluations were completed after 12 or 24 weeks from the first dose of Jardiance®, were analysed for the occurrence of hospitalisation due to heart failure, CV death, changes in NYHA functional class, EF, BNP, NT-proBNP, HbA1c, FPG, eGFR, body weight, blood pressure (systolic/diastolic), and effectiveness rate according to the investigator's judgment (cases that were assessed as "improved" or "unchanged"). Among the 519 patients eligible for effectiveness evaluation, the overall assessment results in the 518 patients for whom the final effectiveness evaluation was conducted showed that 'improved' was 26.06% (135/518 patients), 'unchanged' 71.62% (371/518 patients), and 'worsening' 2.32% (12/518 patients). Since cases assessed as 'improved' or 'unchanged' were classified as 'effective', and cases as 'worsening' were classified as 'ineffective', the effectiveness rate of Jardiance® was found to be 97.68% (506/518 patients), and the ineffectiveness rate 2.32% (12/518 patients). It was also confirmed that the results for the 526 patients in the long-term effectiveness evaluation showed a consistent trend across all effectiveness evaluation parameters compared to the results from the patients in the effectiveness set. Among the 526 patients eligible for long-term effectiveness evaluation,the overall assessment results in the 525 patients for whom the final long-term effectiveness evaluation was conducted showed that 'improved' was 25.90% (136/525 patients), 'unchanged' 72.57% (381/525 patients), and 'worsening' 1.52% (8/525 patients). Accordingly, the effectiveness rate of Jardiance® was found to be 98.48% (517/525 patients), and the ineffectiveness rate 1.52% (8/525 patients).

	In addition to the main effectiveness outcomes mentioned in the synopsis, there are secondary effectiveness outcomes in the study, which are included in the text. No patients of special investigation including those aged < 19 years, elderly patients ≥ 65 years, pregnant women, breastfeeding women, and those with hepatic or renal impairment showed a statistically significant difference in effectiveness rates. During this re-examination period, the results of analysing the final effectiveness rates according to the characteristics of patients in the effectiveness set showed statistically significant differences in the 'presence of diabetes mellitus' (p-value=0.0183) and the 'long-term use status' (p-value=0.0417). Univariate logistic regression was performed on continuous variables representing patients' characteristics in the effectiveness set to assess their association with effectiveness status; no variables showed statistically significant associations.Meanwhile, a multivariate logistic regression analysis was performed to estimate the factors affecting the effectiveness. The results identified that the 'presence of diabetes mellitus' (p-value=0.0351) and the 'long-term use status' (p-value=0.0143) were statistically significant variables, indicating that higher effectiveness was observed in patients with type 2 diabetes and in those who received Jardiance for a longer duration. Regarding effectiveness by type 2 diabetes status, the effectiveness rate was 99.53% (213/214 patients) among those with type 2 diabetes mellitus and 96.38% (293/304 patients) among those without type 2 diabetes. The odds ratio for patients with type 2 diabetes compared to those without was 9.23 (95% CI: 1.17–72.96). While this suggests a potentially stronger drug response in patients with type 2 diabetes, interpretation is limited. The difference in effectiveness rates (99.53% vs 96.38%) is minimal, and the wide confidence interval indicates substantial uncertainty in the estimate. Therefore, these findings should not be considered evidence that diabetes status is an independent factor influencing effectiveness. Meanwhile, the effectiveness rate according to the long-term use status was confirmed to be 93.44% (57/61 patients) in patients who did not use the drug for a long-term period (< 24 weeks), and 98.25% (449/457 patients) in patients who used the drug for a long-term period (≥ 24 weeks). The odds ratio for long-term use compared to non-long-term use was 4.81 (95% CI: 1.37 – 16.91). This suggests the possibility that the characteristics of the therapeutic effect gradually accumulating or stabilizing with continued drug administration for a certain period have been reflected. However, since the absolute difference in effectiveness rates according to the long-term use status is not big and the confidence interval is wide, there are also limitations to considering the long-term administration status as an independent factor affecting effectiveness, along with the possibility that the odds ratio was calculated to be high relative to the actual difference in the effectiveness results, so interpretation of the results requires caution.
Discussion:	According to this PMS for Jardiance®, no particular trends regarding safety and effectiveness that require close observation were found, and no significant new information that could influence the risk-benefit assessment was identified. The safety profile observed in this study was in line with the current approved label. As part of its ongoing safety surveillance and management plan, Boehringer Ingelheim plans to continuously monitor and collect spontaneous reports and

	relevant research findings to identify factors affecting safety and will make every effort to supervise the safety of the product.
Interim Reports:	According to local PMS and RMP requirements, five interim reports were submitted during the re-examination period. Interim reports were submitted every six months for the first two years following the indication approval and annually thereafter. As no data had been collected by the time of the third interim report, data analysis was not performed. Interim analyses of PMS data were included in the fourth and fifth interim reports.
Marketing Authorisation Holder(s):	Boehringer Ingelheim Korea
Name and affiliations of principal investigators: