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.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

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..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

# 1. ABSTRACT

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| **Name of company:** | | | |
| Boehringer Ingelheim | | | |
| **Name of finished medicinal product:** JARDIANCE® Tablets 10 mg, 25 mg | | | |
| **Name of active ingredient:** Empagliflozin | | | |
| **Report date:** | **Study number:** | **Version/Revision:** | **Version/Revision date:** |
| 07 Oct 2021 | 1245.94 | Version 1.0 | Not applicable |
| **Title of study:** | Post Marketing Surveillance in Japan on Long Term Drug Use of JARDIANCE® Tablets in Patients with type 2 Diabetes Mellitus | | |
| **Keywords:** | JARDIANCE®, Japan, PMS, type 2 diabetes mellitus | | |
| **Rationale and background:** | This PMS plan was conducted as additional pharmacovigilance plan of the Japanese RMP.<br>In Japan, post-approval execution of post marketing surveillance (PMS) is requested by the Japanese Pharmaceuticals and Medical Devices Act (J-PMD Act) in order to accumulate safety and effectiveness data for re-examination. Re-examination period is defined by J-PMD Act. Eight years after approval of a new substance, results of PMS need to be submitted as a part of re-examination dossier to the Japanese regulatory authority, the Ministry of Health, Labor and Welfare (MHLW).<br>SGLT-2 inhibitor was a drug class with a new mode of action. PMDA has indicated that it is necessary to further consider the safety of important identified risks, important potential risks and important missing information in post-marketing surveillance. | | |
| **Research question and objectives:** | Study objectives were to investigate the safety and effectiveness of long-term daily use of JARDIANCE® Tablets in Japanese patients with type 2 diabetes mellitus. | | |
| **Study design:** | Cohort study<br>Non-interventional, prospective, observational, single arm based on new data collection<br>Main criteria for inclusion was male and female Japanese patients with type 2 diabetes mellitus.<br>Patients with type 2 diabetes mellitus who had never received JARDIANCE® Tablets before enrollment were included in the surveillance.<br>Patients were observed for up to 156 weeks (approximately 36 months) after start of the treatment with JARDIANCE® Tablets or at premature discontinuation and dropout.<br>Descriptive statistics were summarized for safety and effectiveness.<br>A mixed model repeated measures analysis was performed for hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) over time. | | |

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| **Setting:** | Sites throughout entire country were equally listed according the size of the hospitals or general clinics at which JARDIANCE® Tablets were available for prescription. Patients were selected by using the continuous investigation system.<br>This study was conducted in 1,103 centers in Japan.<br>Study period: June 2015 – November 2020<br>Enrollment period: June 2015– May 2017 |
| **Subjects and study size, including dropouts:** | Male and female Japanese patients with type 2 diabetes mellitus who had never been treated with JARDIANCE® Tablets before the enrollment.<br>This PMS targeted to include 3,000 patients who completed a 3-year JARDIANCE® observation period including elderly patients, patients with renal dysfunction and hepatic dysfunction. |
| **Variables and data sources:** | Outcomes:<br><u>Primary outcome:</u><br>Frequencies of adverse drug reactions (ADRs)<br><u>Secondary outcomes:</u><br>Change from baseline in HbA1c to the last observation on treatment<br>Change from baseline in FPG to the last observation on treatment<br><u>Further outcomes:</u><br>Change from baseline in HbA1c to Week 26<br>Occurrence of effectiveness response (Patients with baseline HbA1c of ≥7.0% (≥6.5%), achieve under treatment of <7.0% (<6.5%) at Week 26)<br>Occurrence of relative effectiveness response (HbA1c lowering by at least 0.5% at Week 26)<br>Change from baseline in FPG to Week 26<br>Frequencies of serious adverse events (SAEs)<br>Frequencies of priority survey items<br><u>Others: baseline characteristics</u><br>Variables:<br>Demographics<br>Medical history/baseline conditions<br>Previous/concomitant therapies<br>Jardiance administration<br>Vital signs and laboratory test |

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| | Adverse event<br>Data sources:<br>Patients data were gathered by electronic Case Report Form (CRF) on electronic data capture (EDC) |
| **Results:** | In this PMS, a total of 8145 patients were enrolled in Japan. Of the 8145 patients enrolled, and clinical report forms of 8059 patients were collected. 7947 and 7459 patients were included in the safety and the effectiveness sets, respectively. A total of 4729 patients (58.68%) completed the study for 156 weeks, 3416 patients discontinued (41.94%).<br><br>Baseline characteristics<br>In the safety set, 63.02% of patients were male. The mean age was 58.8 years (range: 15 to 98) and 835 patients (10.51%) being to "75 years old or over". The mean baseline estimated glomerular filtration rate (eGFR) was 82.40 ± 24.56 mL/min/1.73m$^2$. A total of 121 patients had moderate or severe hepatic impairment.<br><br>Almost all patients were diagnosed as type 2 diabetes mellitus with mean disease duration of 8.23 years and 19.84% of the patients had diabetes for more than 10 years before they were enrolled in this study. The mean baseline HbA1c was 8.02%. Baseline HbA1c values in 1717 patients (21.61%) were <7.0%. The mean baseline FPG was 160.2 mg/dL.<br><br>Of the 7947 patients analyzed for safety, 1023 patients (12.87%) were treated with antidiabetic drugs before starting administration of JARDIANCE® Tablets.<br>The mean treatment duration of JARDIANCE® Tablets was 842.8 days. A total of 496 (6.58%) patients starting at lower dosages (10 mg) of JARDIANCE® Tablets increased to 25 mg. The mean duration at the time of dose increase was 344.3 days.<br><br>Primary outcome<br>A total of 1029 patients (12.95%) experienced at least 1 ADR throughout the PMS. The frequently reported ADRs were pollakiuria (68 patients, 0.86%), pruritus genital (44 patients, 0.55%) and urinary tract infection (41 patients, 0.52%).<br><br>Safety summary<br>A total of 1556 (19.58%) experienced at least 1 AE throughout the PMS. |

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The frequently reported AEs (≥0.50%) throughout the PMS were diabetes mellitus inadequate control (89 patients, 1.12%), pollakiuria (68 patients, 0.86%), diabetes mellitus (57 patients, 0.72%), hypertension (52 patients, 0.65%), nasopharyngitis and glycosylated haemoglobin increased (49 patients, 0.62% each), pruritus genital (45 patients, 0.57%), urinary tract infection (43 patients, 0.54%), constipation and hypoglycaemia (41 patients, 0.52% each). The most AEs were mild or moderate in intensity. Severe AEs were reported in 178 patients (2.24%).

A total of 667 SAEs were reported in 381 patients (4.79%). Of these, fatal SAEs were reported from 42 patient. The frequently reported SAEs were angina pectoris (19 patients, 0.24%), acute myocardial infarction and fall (13 patients, 0.16% each) and diabetes mellitus inadequate control (12 patients, 0.15%). A total of 242 serious ADRs were reported in 168 patients (2.11%). Of these, fatal serious ADRs were reported from 13 patients. The most frequently reported serious ADRs were cerebral infarction (17 patients, 0.21%).

ADRs leading to the discontinuation of JARDIANCE® Tablet were reported in 484 patients (6.09%). The most frequently reported ADRs leading to discontinuation were pollakiuria (49 patients, 0.62%), pruritus genital (34 patients, 0.43%).

The reported priority survey items were cardiovascular events (108 patients, 1.36%), excessive urination/frequent urination (102 patients, 1.28%), malignancy (93 patients, 1.17%), urinary tract infection (91 patients, 1.15%), liver injury (77 patients, 0.97%), the adverse events relating to volume depletion (56 patients, 0.70%), genital infections (55 patients, 0.69%), volume depletion (45 patients, 0.57%), the adverse events related to an increase in ketone (43 patient, 0.54%), hypoglycaemia (41 patients, 0.52%), bone fracture (39 patients, 0.49%), renal impairment (29 patients, 0.36%), diabetic ketoacidosis (1 patient, 0.01%).

Secondary outcomes

The mean change in HbA1c (%) from baseline to the last observation was –0.74 ± 1.34% (mean ± SD). The mean change in FPG (mg/dL) from baseline to the last observation was –30.1 ± 55.5 mg/dL. The data show a clinically relevant reduction in HbA1c and FPG.

Further outcomes

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| | The mean change in HbA1c (%) from baseline to Week 26 was –0.82 ± 1.24% (mean ± SD). The mean change in FPG (mg/dL) from baseline to Week 26 was –31.6 ± 51.3 mg/dL. The data show a clinically relevant reduction. Throughout the observation period during the PMS, mean HbA1c values were lower than the baseline value and decreases from baseline at the each time point were observed with the mean changes ranging –0.74 to – 0.82%. Also FPG value recorded lower than the baseline value and decreases from baseline at the each time point were observed with the mean changes ranging –30.0 to –34.0 mg/dL.<br>A total of 1768 (38.01%) with HbA1c ≥7.0% at baseline and 980 (17.86%) with HbA1c ≥6.5% at baseline were classified as responder (HbA1c <7.0% and <6.5%, respectively). At Week 26 3443 (57.69%) had the HbA1c response of 0.5% or more.<br><br>No interim analysis was conducted. |
| **Discussion:** | The PMS results showed safety, effectiveness and tolerability in daily use of JARDIANCE® Tablets in Japanese patients with type 2 diabetes mellitus.<br>The reported related AEs are in line with the safety profile of Empagliflozin and the experience from the Empagliflozin clinical trials.<br>The reported SAEs do not provide information about a potential causal association with JARDIANCE® Tablets. Overall the results do not raise a safety concern.<br>No new safety measure was required such as label change or additional risk minimization based on the study results.<br>The effectiveness of JARDIANCE® Tablets according to patient baseline characteristics do not indicate an effect modifier. |
| **Marketing Authorisation Holder(s):** | Nippon Boehringer Ingelheim Co., Ltd<br>2-1-1 Osaki, Shinagawa-ku, Tokyo 141-6017, Japan |
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