ABSTRACT

Name of company: [redacted]			
Name of finished medicinal product: ESGLITEO®			
Name of active ingredient: Empagliflozin/Linagliptin			
Report date: 1.0/29JUN2023	**Study number** 1275-0028	**Version/Revision:** 3.0	**Version/Revision date:** 02Aug2024
Title of study:	Post-Marketing Surveillance to Monitor the Safety and Effectiveness of ESGLITEO® (Empagliflozin/Linagliptin, 10/5mg, 25/5mg) in Korean patients with Type 2 Diabetes Mellitus		
Keyword:	ESGLITEO®, Safety, Effectiveness, Post-Marketing Surveillance, Korean		
Rationale and background:	In accordance with applicable laws and regulations, once a new chemical entity (NCE) is registered, post-marketing studies must be conducted. These studies can provide supplementary data to monitor the safety of NCEs in real-world settings. There are limitations in the data collected from randomized clinical trials conducted using stringent inclusion/exclusion criteria and stringent monitoring plans. This study is a non-interventional, multi-centre, single-country study. It also provides additional safety and effectiveness information for Korean patients with type 2 diabetes mellitus in routine clinical settings.		
Research question and objective:	To monitor the safety and effectivenessof ESGLITEO® in Korean patients with type 2 diabetes mellitus in routine clinical settings.		
Study design:	Prospective, Non-interventional, Multi-centre, Single-country Study		
Setting:	Patients diagnosed with type 2 diabetes mellitus in Korea ESGLITEO®is administered as an adjunct to diet and exercise therapy to improve glycaemic control in patients with type 2 diabetes mellitus. <u>Inclusion Criteria:</u> • Patients who have started treatment with ESGLITEO® for the first		

	time in accordance with the label approved in Korea • Patients aged 19 years or older at enrollment • Patients who have signed the Informed Consent Form for the Use of Personal Information <u>Exclusion Criteria:</u> • Patients with previous exposure to ESGLITEO® • Patients with hypersensitivity to the active ingredients of this drug, empagliflozin and/or linagliptin, or any of the excipients of this drug • Patients with type 1 diabetes or diabetic ketoacidosis • Patients with estimated Glomerular Filtration Rate (eGFR) < 45 mL/min/1.73m^2, end stage renal disease, or patients on dialysis • Patients for whom the use of empagliflozin/linagliptin is contraindicated according to the prescribing in formation of ESGLITEO®
Subjects and study size, including dropouts:	Total number of subjects entered: 1053 -number of subjects for safety evaluation: 616* -number of subjects for effectiveness evaluation: 342 -number of subjects excluded: 437 *Target number of subjects: 600 (safety set)
Variables and data sources:	Variables: <u>Safety Endpoint</u> All reported adverse events will be collected from subjects taking at least one dose of ESGLITEO®. <u>Effectiveness Endpoint</u> Changes from the baseline in glycosylated haemoglobin (HbA1c), fasting plasma glucose (FPG), body weight, and blood pressure (systolic, diastolic) after 12 and/or 24 weeks of treatment and final effectivenessevaluation data at the end-of-study visit will be collected. Data Sources: New data collection through routine care (35 institutions)
Results:	During this re-examination period, the incidence of the Adverse Event (AE) reported in 616 subjects for safety evaluation was 3.41%

	(21/616, 26 cases). Among these, the incidence of Adverse Drug Reactions (ADRs), in which a causal relationship with this drug could not be excluded, was 0.65% (4/616, 4 cases), and all were found to be non-serious ADRs. The incidence of Serious Adverse Event (SAE) was found to be 0.49% (3/616, 4 cases), and there was no Serious Adverse Drug Reaction (SADR). As a result of PT classification of AE, 'Diabetic neuropathy' and 'Hypoglycaemia' were reported in more than one subject (0.32%,2/616 subjects, 2 cases), respectively. As a result of PT classification of adverse drug reactions for which a causal relationship with ESGLITEO® could not be ruled out, 'Generalised oedema', 'Hypoglycaemia', 'Diabetic retinopathy', and 'Vulvovaginal pruritus' were each found to be 0.16% (1/616, 1 case). As a result of PT classification of reported serious adverse events, 'Adrenal insufficiency', 'Aortic thrombosis', 'Acute kidney injury', and 'Lung neoplasm malignant' were found to be 0.16% (1/616, 1 case), respectively, and none of these events resulted in death. For all reported serious adverse events, the causal relationship with Esgliteo was assessed as 'unlikely.' During this re-examination period, the incidence of adverse events reported in 269 subjects with long-term use for more than 24 weeks was 4.83% (13/269 subjects, 15 cases). Among these, the number of adverse drug reactions for which a causal relationship with the drug could not be ruled out was 1.12. % (3/269 subjects, 3 cases), all of which were reported as non-serious adverse drug reactions. The incidence of serious adverse events was 0.37% (1/269 subjects, 2 cases), and it was not related to Esgliteo. The incidence of unexpected adverse events was 1.86% (5/269 subjects, 5 cases), and there was no unexpected adverse drug reaction(UADR). To identify factors affecting safety, the incidence of adverse events was analyzed according to the demographic characteristics, basic disease information, medical history, presence of concomitant medications, and Esgliteo administration status of 616 subjects for safety evaluation. According to this analysis, the factors indicating a different risk were 'Complications of Diabetes (Others)',

	'Concomitant Medications', 'Age', 'Geriatric Patients', 'Total Duration of Treatment (day)' and 'Total number of administrations'. Among these, 'Geriatric Patients' was excluded from the model due to the high correlation with age and geriatric patients, and 'Total number of administrations', due to the high variability. Accordingly, multiple logistic regression analysis was conducted including all factors associated with a univariately different risk. As a result, all of these factors identified as statistically significantly associated with higher risk were included as factors to estimate the incidence of adverse events. (p-value<0.05) For the total administration period, the p-value was less than 0.05, which was indicating a statistically significant, but there was no significant difference in the AE incidenc estimated from odds ratio. Examining the factors that showed statistically significant differences in AE incidence, Diabetic complications (other) and concomitant medication were identified as statistically significantly associated with higher risk and were therefore included as factors to estimate the incidence of adverse events. However, with regard to the interpretation of the two factors, this data is very limited as only 4 patients in our dataset were available for assessment of 'diabetic complications (other)'. Additionally, use of concomitant medications implies a more complex clinical picture. Greater proportion of AEs in these participants could be related to underlying medical conditions as well as the effects of concomitant medications. In terms of age, nearly half of subjects in safety set were over 60 years of age (49.35%), and the AE incidence rate in geriatric population (65 years or more) was higher than those under the age of 65 (6.34% over the age of 65 vs 1.95% under the age of 65). In consideration of this, underlying medical conditions by aging and the effects of other concomitant medications administered could be related. Among the 342 subjects for effectiveness evaluation, the mean (SD) of the change in HbA1c for 303 subjects who had HbA1c tested 12 weeks after administration was -0.21% (1.126) (*p*-value=0.0011),

	indicating a statistically significant decrease. The mean (SD) of the change in HbA1c for 139 subjects who had HbA1c tested 24 weeks after administration was -0.27% (0.983) (*p*-value=0.0014), indicating a statistically significant decrease. Among the 342 subjects for effectiveness evaluation who were tested for HbA1c at 12 and/or 24 weeks after administration of ESGLITEO®, 49.50% (150/303) of the 303 subjects tested 12 weeks after administration and 53.24% (74/139) of the 139 subjects tested 24 weeks after administration achieved HbA1c < 7% (target effectiveness response rate). Among the 342 subjects for effectiveness evaluation who were tested for HbA1c at 12 and/or 24 weeks after administration of ESGLITEO®, 29.37% (89/303) of the 303 subjects tested 12 weeks after administration and 38.85% (54/139) of the 139 subjects tested 24 weeks after administration had a HbA1c decrease by at least 0.5% (relative effectiveness response rate). Among the 342 subjects for effectiveness evaluation, the mean (SD) of the FPG change for 302 subjects who were tested for fasting plasma glucose (FPG) 12 weeks after administration was -10.8mg/dL (54.90) (*p*-value=0.0008), indicating a statistically significant decrease. The mean (SD) of the FPG change for the 154 subjects who underwent testing 24 weeks after administration was -12.3mg/dL (55.76) (*p*-value=0.0068), indicating a statistically significant decrease. Among the 342 subjects for effectiveness evaluation, body weight was measured in 107 subjects 12 weeks after administration, and the mean (SD) of the body weight change for 85 subjects was -0.72kg (5.583) (*p*-value=0.1867), indicating a statistically insignificant decrease. The mean (SD) of the body weight change of the 93 subjects who underwent measurement 24 weeks after administration was -1.27kg (3.204) (*p*-value=0.0003), indicating a statistically significant decrease. Among the 342 subjects for effectiveness evaluation, 241 subjects had systolic blood pressure measured 12 weeks after administration, and the mean (SD) of the change for 237 subjects of them was -

	2.8mmHg (13.77) (*p*-value=0.0020), indicating a statistically insignificant decrease. The mean (SD) of the change for the 134 subjects who underwent measurement 24 weeks after administration was -0.4mmHg (16.59) (*p*-value=0.7591), not indicating a statistically significant decrease. Among the 342 subjects for effectiveness evaluation, 297 subjects had diastolic blood pressure measured 12 weeks after administration, and the mean (SD) of the change for 241 subjects was -1.6mmHg (9.91) (*p*-value=0.0132), indicating a statistically significant decrease. The mean (SD) of the change in the 134 subjects who underwent measurement 24 weeks after administration was -0.6mmHg (11.01) (*p*-value=0.5161), not indicating a statistically significant decrease. As a result of analysing the change in HbA1c at the last measurement from the baseline before administration of ESGLITEO® according to the characteristics of 342 subjects for effectiveness evaluation (demographic characteristics, basic disease information, medical history, concomitant medications, special populations, and drug administration information, reasons for premature discontinuation of the study), the factors indicated to be effect modifiers were identified as 'Prior Medications' (*p*-value=0.0111) and 'Concomitant Medications' (*p*-value=0.0405). The mean (SD) of the HbA1c change in 280 subjects with 'prior medications' was -0.18 % (0.988), and the mean (SD) of the HbA1c change in 62 subjects without 'prior medications' was -0.58% (1.583). The mean (SD) of the HbA1c change in 74 subjects with 'concomitant medications' was -0.49% (1.278), and the mean (SD) of the HbA1c change in 268 subjects without 'concomitant medications' was -0.19% (1.075). The results of the final effectiveness evaluation at 12 weeks after administration in 342 subjects for effectiveness evaluation showed that 52.92% (181/342 subjects) were 'Improved', 38.89% (133/342 subjects) were 'Unchanged', and 8.19% (28/342 subjects) were 'Aggravated'. When 'Improved' was classified as 'effective' and

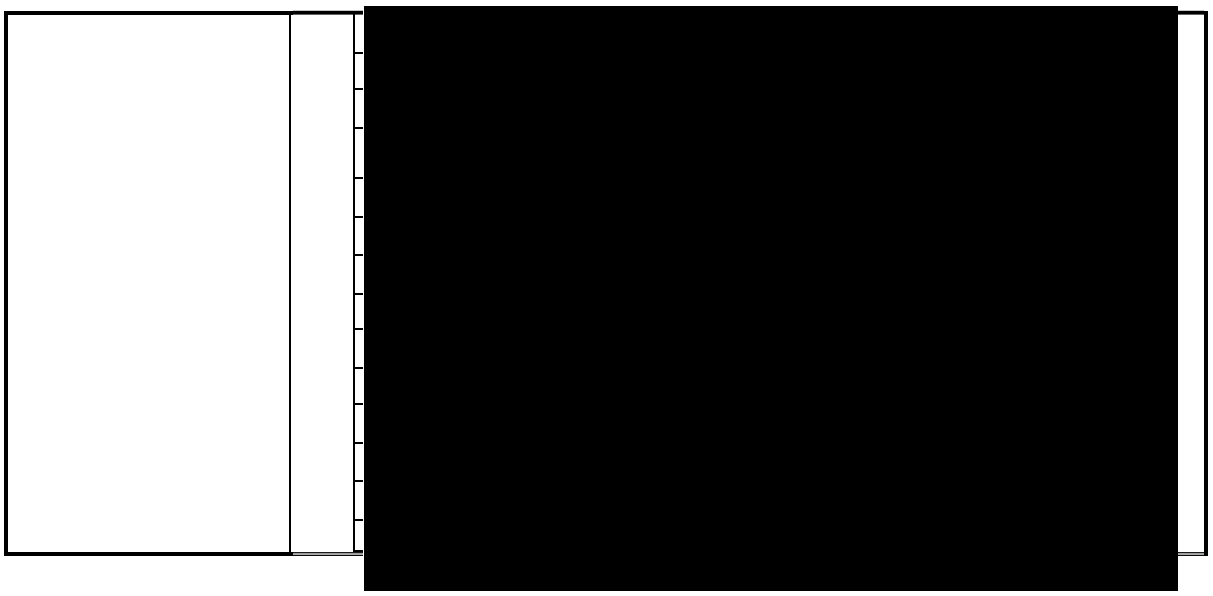
	'Unchanged' or 'Aggravated' as 'ineffective', the effective rate of ESGLITEO® was 52.92% (181/342 subjects). Long-term effectiveness evaluation was conducted in a total of 139 subjects who underwent the final effectiveness evaluation 24 weeks after the first administration date of ESGLITEO®. The mean (SD) of the HbA1c change in 100 subjects who had HbA1c tested 12 weeks after administration was -0.17% (0.906) (*p*-value=0.0666), indicating a statistically not significant trend. The mean (SD) of the HbA1c change in 139 subjects who had HbA1c tested 24 weeks after administration was -0.27% (0.983) (*p*-value=0.0014), indicating a statistically significant decrease. Among 139 subjects for long-term effectiveness evaluation, the subjects who achieved HbA1c< 7% (target effectiveness response rate) at 12 and/or 24 weeks after administration of ESGLITEO® were 51.00% (51/100) of the 100 subjects for long-term effectiveness evaluation who underwent testing 12 weeks after administration and 53.24% of the 139 subjects who underwent testing 24 weeks after administration. Among 139 subjects for long-term effectiveness evaluation, the subjects who had HbA1c decreased by at least 0.5% (relative effectiveness response rate) at 12 and/or 24 weeks after administration of ESGLITEO® were 30.00% (30/100) of the 100 subjects who underwent testing 12 weeks after administration and 38.85% (54/139) of the 139 subjects who underwent testing 24 weeks after administration. Among 139 subjects for long-term effectiveness evaluation, the mean (SD) of the FPG change in 112 subjects who were tested for the fasting plasma glucose (FPG) 12 weeks after administration was -11.1mg/dL (51.04) (*p*-value=0.0227), indicating a statistically significant decrease. The mean (SD) of the FPG change in 136 subjects who underwent testing 24 weeks after administration was -14.5mg/dL (50.86) (*p*-value=0.0012), indicating a statistically significant decrease.

	Among 139 subjects for long-term effectiveness evaluation, the mean (SD) of the body weight change in 67 subjects who had body weight measured 12 weeks after administration was -0.80kg (3.189) (*p*-value=0.0429), indicating a statistically significant decrease. The mean (SD) of the body weight change in 84 subjects who underwent measurement 24 weeks after administration was -1.15kg (3.244) (*p*-value=0.0017), indicating a statistically significant decrease. Among 139 subjects for long-term effectiveness evaluation, the mean (SD) of the SBP change in 104 subjects who had systolic blood pressure (SBP) measured 12 weeks after administration was -1.9mmHg (14.57) (*p*-value=0.1947), not indicating a statistically significant decrease. The mean (SD) of the SBP change in 110 subjects who underwent measurement 24 weeks after administration was -1.5mmHg (15.05) (*p*-value=0.3040), indicating a statistically insignificant decrease. Among 139 subjects for long-term effectiveness evaluation, the mean (SD) of the DBP change in 104 subjects who had diastolic blood pressure (DBP) measured 12 weeks after administration was -3.1mmHg (9.82) (*p*-value=0.0020), indicating a statistically significant decrease. The mean (SD) of the DBP change in 110 subjects who underwent measurement 24 weeks after administration was -1.8mmHg (10.62) (*p*-value=0.0829), which was indicating a statistically not significant trend. As a result of analysing the change in HbA1c at the last measurement from the baseline before administration of ESGLITEO® according to the characteristics of 139 subjects for long-term effectiveness evaluation (demographic characteristics, basic disease information, medical history, concomitant medications, special populations, and drug administration information, reasons for premature discontinuation of the study), the factors showing statistically significant changes were identified as 'Prior Medications' (*p*-value<0.0001), 'Concomitant Medications' (*p*-value=0.0058), and 'Hepatic Impairment' (*p*-value=0.0384). The mean (SD) of the HbA1c change in 116 subjects with 'prior medications' was -0.12% (0.907), and the mean (SD) of the HbA1c

	change in 23 subjects without 'prior medications' was -1.04% (1.008). The mean (SD) of the HbA1c change in 44 subjects with 'concomitant medications' was -0.61% (1.199), and the mean (SD) of the HbA1c change in 95 subjects without 'concomitant medications' was -0.12% (0.828). The mean (SD) of the HbA1c change in 10 subjects with 'hepatic impairment' was -0.89% (0.913), and the mean (SD) of the HbA1c change in 129 subjects without 'hepatic impairment' was -0.22% (0.976). In case of 'prior medication' and 'concomitant medication', these trends should be interpreted with caution due to the rather low sample size. In addition, since the liver is a major organ responsible for glucose metabolism and the breakdown of insulin and glucagon, it is closely related to diabetes, 'hepatic impairment' may have had an effect on the HbA1c change in the subjects. The results of the final effectiveness evaluation at 24 weeks after administration in 139 subjects for long-term effectiveness evaluation showed that 55.40% (77/139 subjects) were 'Improved', 41.73% (58/139 subjects) were 'Unchanged', and 2.88% (4/139 subjects) were 'Aggravated'. When 'Improved' was classified as 'effective' and 'Unchanged' or 'Aggravated' as 'ineffective', the effective rate of ESGLITEO® was 55.40% (77/139 subjects). In order to identify factors affecting the effectiveness, the effective rates were analysed and presented according to the demographic characteristics, basic disease information, medical history, presence of concomitant medications, and Esgliteo administration status in subjects for effectiveness evaluation. The factors that showed a statistically significant difference were 'Starting dose of Esgliteo (High dose)', 'Complications of diabetes (angiopathy)', 'Comorbidities' and 'Long-term use (24weeks more)'. As a result of performing multiple logistic regression analysis with the items as variables, the factor that was statistically significant was 'Starting dose of Esgliteo (High dose)' (p-value=0.0174), 'Complications of diabetes (angiopathy)' (p-value=0.0049) and 'Comorbidities' (p-value=0.0140).

	In the analysis of the effectiveness rate by starting dose of Esgliteo, it was the effectiveness rate in the subjects with low dose and high dose accounted for 44.07% (177/342 subjects) and 62.42% (165/342 subjects), respectively. The odds of effectiveness was 1.83 for the high dose compared to the low dose. Looking at the reasons for using high dose as starting dose, it was determined that most subjects started with high dose were not sufficient glucose control with low dose of SGLT2-I or needed active glucose control considering their previous antidiabetic treatment, and as a result, the use of high-dose as starting dose seems to have a more pronounced effect on the effectiveness rate. Accordingly, it is expected that an effective glucose control can be achieved when an appropriate starting dose should be selected in consideration of the subject's previous history and baseline condition. In the analysis of the effectiveness rate by angiopathy, it was investigated the effectiveness rate in the subjects with and without angiopathy accounted for 88.46% (26/342 subjects) and 49.81% (263/342 subjects), respectively. The difference in the effectiveness rate by angiopathy indicated significance, but the change of HbA1c level from baseline in the subjects with and without angiopathy accounted for -0.36% and -0.20%, not indicating a significant difference(p=0.4865). In the analysis of the effectiveness rate by comorbidities, it was investigated the effectiveness rate in the subjects with and without comorbidities accounted for 51.23% (324/342 subjects) and 83.33% (18/342 subjects), respectively and the subjects who had not comorbidities was higher. However, the change of HbA1c level from baseline in the subjects with and without comorbidities accounted for -0.23% and -0.69%, not indicating significance (p=0.0941). The lower effectiveness rate in subjects with comorbidities seems to have affected the outcome by the underlying conditions of subjects with comorbidities. As a result of the final effectiveness evaluation, an effective rate of 52.92% was estimated, and an effective rate of 55.40% was estimated in subjects for long-term effectiveness evaluation. According to this PMS protocol, only cases assessed as

	"Improved" excluding "Unchanged" and "Aggravated" were evaluated as effective, and the effective rate was estimated to exceed 50%.
Discussion:	According to this post-marketing surveillance for ESGLITEO®, no unusual tendency regarding safety and efficacy was found, and no significant new information that could affect risk versus benefit assessment was identified. Boehringer Ingelheim plan to continuously monitor and collect spontaneous reports and related research results to identify factors affecting safety as part of our ongoing safety surveillance and management plan, and every effort will be made to supervise the safety of the product.
Marketing Authorization Holder(s):	[redacted]
Names and affiliations of [redacted] investigators:	**Institution** / **Investigator** [redacted]



LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Events of Special Interest
CCDS	Company Core Data Sheet
cRMP	Core Risk Management Plan
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DKA	Diabetic ketoacidosis
DLP	Data Lock Point
DPP-4 Inhibitor	Dipeptidyl pepti- dase-4 inhibitors
EMA	European Medicines Agency
EU	European Union
EUPI	European Union Product-information
FDA	U.S. Food and Drug Administration
FPG	fasting plasma glucose
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MLE	Maximum Likelihood Estimation
OR	Odds Ratio
PAS	Prior approval supplement
PASS	Post authorization Safety Study