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ORIGINAL ARTICLE

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Efficacy and safety of combining empagliflozin in people with type 2 diabetes mellitus uncontrolled with metformin and sitagliptin: A randomised, double-blind, multicentre, therapeutic confirmatory phase 3 clinical trial

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Abstract

Aim: This study evaluated the efficacy and safety of empagliflozin 10 and 25 mg compared to placebo as add-on treatment for people with type 2 diabetes mellitus (T2DM) uncontrolled after ≥8 weeks of treatment with metformin and sitagliptin.

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Materials and Methods: A randomised, double-blind, multicentre, therapeutic confirmatory, phase 3 clinical trial was conducted in 172 patients with T2DM. Participants with glycosylated haemoglobin (HbA1c) levels 7%–10% receiving sitagliptin and metformin were randomised 1:1:1 to empagliflozin 10 mg, empagliflozin 25 mg, or placebo. The primary endpoint was the change in HbA1c from baseline to week 24.

Results: After 24 weeks of treatment, HbA1c levels were significantly decreased in the empagliflozin 10 and 25 mg group versus the placebo group; the adjusted mean differences with empagliflozin 10 and 25 mg versus placebo were −0.7% (95% CI −1.0, −0.4; p <.0001) and −0.8% (95% CI −1.1, −0.5; p <.0001), respectively. Fasting plasma glucose levels were also significantly decreased in both empagliflozin groups compared to the placebo group (both p <.0001). More patients reached HbA1c <7% or <6.5% after 24 weeks in the empagliflozin 10 and 25 mg groups versus the placebo group (both p <.05). Efficacy was maintained in the empagliflozin groups during a 28-week extension period. Empagliflozin add-on was associated with improvements in albuminuria and body weight. The incidence of adverse events was similar across groups; add-on empagliflozin was well tolerated.

Conclusions: These results suggest that coadministration of empagliflozin safely improves glycemic control in Korean patients with T2DM uncontrolled by sitagliptin and metformin.

KEYWORDS
clinical trial, empagliflozin, metformin, sitagliptin, type 2 diabetes mellitus

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterised by elevated levels of blood glucose and various complications. According to the Diabetes Fact Sheets in Korea 2024, the prevalence of diabetes mellitus was 15.5% among Korean adults. Among these patients with diabetes mellitus, only 32.4% achieved glycosylated haemoglobin (HbA1c) levels <6.5%, despite the use of antidiabetic drugs.[1] Because prolonged hyperglycemia can lead to microvascular and macrovascular complications, continuous blood glucose management is an essential component of diabetes care. To effectively control blood glucose in patients with T2DM, combination therapy may be an adequate treatment approach for patients who do not respond to monotherapy.[2,3] The treatment strategy of combining multiple drugs with different mechanisms of action could lead to more stable glycemic control and help prevent or delay diabetic complications.

Empagliflozin is a selective inhibitor of sodium glucose cotransporter 2 (SGLT2) that reduces blood glucose by enhancing the urinary excretion of glucose. It has the highest SGLT2 specificity among all the clinically used or currently tested SGLT2 inhibitors.[4–6] In a clinical trial of empagliflozin monotherapy, empagliflozin significantly reduced HbA1c levels.[7] In addition, due to the proven cardiovascular and renal benefits, treatment with an SGLT2 inhibitor is the recommended choice for people with heart failure, atherosclerotic cardiovascular disease, albuminuria, and decreased estimated glomerular filtration rate (eGFR).[3,8–9]

A previous study reported that the combination of the SGLT2 inhibitor empagliflozin and dipeptidyl peptidase-4 (DPP-4) inhibitor linagliptin significantly reduced HbA1c levels compared to monotherapy in patients whose hyperglycemia was not adequately controlled on metformin.[10] This suggests that the combination of SGLT2 inhibitors and DPP-4 inhibitors, which act through different mechanisms and pathways, synergistically controls blood glucose in patients with T2DM. Although several fixed-dose combinations of SGLT2 inhibitors and DPP-4 inhibitors are available, a fixed-dose combination of empagliflozin, sitagliptin, and metformin has not been developed yet. Empagliflozin and sitagliptin offer numerous benefits and are commonly prescribed as preferred antidiabetic agents in Korea. Therefore, the development of a fixed-dose combination of empagliflozin, sitagliptin, and metformin is expected to enhance the blood glucose-lowering effect while improving the burden of the number of drugs and the complexity of pharmacotherapy, thereby improving patient adherence with treatment.

In this phase 3 clinical trial, we aimed to evaluate the efficacy and safety of empagliflozin add-on therapy in patients with T2DM who are uncontrolled with the dual combination of metformin and sitagliptin.

2 | MATERIALS AND METHODS

2.1 | Study participants

Eligible participants were adults aged ≥19 and ≤85 years with T2DM treated with oral hypoglycemic agents for at least 8 weeks. Participants with an HbA1c level of 7%–10% and body mass index (BMI) of 18.5–40 kg/m^2 at the screening visit were included in this trial. After

a 2-week placebo run-in period, patients with an HbA1c of 7%–10% could be entered into the treatment period. Key exclusion criteria included: history of type 1 diabetes or secondary diabetes; history of severe diabetic complications such as proliferative diabetic retinopathy; fasting plasma glucose (FPG) >270 mg/dL; eGFR <45 mL/min/1.73 m^2, history of end-stage renal disease, or treatment with dialysis. Full inclusion and exclusion criteria are listed in Supplementary Table 1.

2.2 | Study design

This was a randomised, double-blind, multicentre, therapeutic confirmatory, phase 3 study consisting of 24 weeks of treatment and a 28-week extension period (ClinicalTirals.gov NCT05566028). The study was conducted at 26 sites in South Korea, starting on 14 September 2022 and with the last patient completed on 23 July 2024. This study was conducted following the ethical principles of the Declaration of Helsinki and Good Clinical Practice. The study protocol was approved by the Ministry of Food and Drug Safety (MFDS) and the Institutional Review Boards (IRBs) of all sites (Supplementary Table 2).

Patients receiving metformin at a dose of ≥1000 mg in combination with sitagliptin 100 mg without a change in dose for at least 8 weeks were eligible to enter a 2-week single-blind run-in period. After the run-in period, eligible patients were randomised to empagliflozin 10 mg add-on group, empagliflozin 25 mg add-on group, or placebo add-on group in a 1:1:1 ratio. Randomisation was conducted using an interactive web response system, with stratification based on baseline HbA1c levels (≤8.5% or >8.5%) and baseline eGFR categories (45–< 60, 60–< 90, ≥90 mL/min/1.73 m^2). The metformin and sitagliptin regimen was maintained throughout the study. Patients who completed the 24-week treatment period entered the extension period and continued the study for up to 52 weeks, except for those who met the dropout criteria or did not consent to participate in the extension period. The empagliflozin 10 mg and empagliflozin 25 mg groups maintained their regimen, while the placebo group switched to empagliflozin 10 mg (Supplementary Figure 1). Patients, investigators, and the sponsor remained blind during the 24-week treatment period. Only members of the sponsor related to analysing the data and reporting to MFDS were unblinded after the week 24 database lock; the investigators, patients, and the other members of the sponsor remained blinded during the 28-week extension period. Throughout the study, patients with FPG >240 mg/dL at least twice or as determined by the investigator were considered to require rescue therapy. The investigator advised the participant to improve lifestyle habits or administer up to 4 mg of glimepiride per day at the investigator's discretion.

2.3 | Outcome measures

The primary efficacy endpoint was the change in HbA1c from baseline to week 24. The key secondary endpoints were the change in HbA1c and FPG from baseline up to week 52 and the proportion of patients with HbA1c <7% or <6.5% at week 24 and 52. Other exploratory endpoints were the change in body weight, waist circumference, and urine albumin to creatinine ratio (UACR) and the resolution rate of metabolic syndrome at week 24 and 52. Safety was assessed by monitoring the overall incidence of treatment-emergent adverse events (TEAEs), adverse drug reactions (ADRs), serious adverse events (SAEs), serious ADRs, vital signs, clinical laboratory (haematology, blood chemistry, urinalysis), and physical examination.

2.4 | Measurements and definitions

Physical examinations, including height, body weight, and waist circumference, were measured using a scale and measuring tape, respectively. Blood pressure was measured in a seated position following at least 5 min of rest to ensure adequate stabilisation. Participants were instructed to fast for at least 9 h prior to the visit for laboratory tests (including blood and urine tests). Except for laboratory tests performed during the screening period, all subsequent analyses were conducted by a central laboratory. HbA1c was measured using a turbidimetric inhibition immunoassay on a Cobas c513 analyser (Hitachi, Japan), and FPG was measured by an enzymatic colorimetric method using a Cobas c502 analyser (Hitachi, Japan). Serum insulin (Elecsys insulin, Roche, Germany) and C-peptide (Elecsys C-peptide, Roche, Germany) levels were determined by electrochemiluminescence immunoassay on a Cobas e801 (Roche, Germany). Aspartate transaminase (AST), alanine transaminase (ALT), and gamma-glutamyl transferase (γ-GT) were measured by enzymatic colorimetric methods using a Cobas c502 analyser (Hitachi, Japan). High-sensitivity C-reactive protein (hsCRP) was measured by immunoturbidimetric assay using Cardiac CRP-Latex reagent (Roche, Germany), and serum creatinine was assessed using a colorimetric test. UACR was calculated as follows: UACR = urine microalbumin/urine creatinine (mg/g). eGFR was calculated using the 2009 CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation.[11]

Metabolic syndrome was defined as the presence of at least three out of the following five criteria: (1) Hyperglycemia: assumed to meet the hyperglycemia criterion in all participants; (2) Abdominal Obesity: waist circumference ≥90 cm (men), ≥85 cm (women); (3) Hypertension: blood pressure ≥130/85 mmHg or currently taking antihypertensive medication; (4) Elevated Triglycerides: triglycerides ≥150 mg/dL or currently taking medication to lower triglycerides; (5) Low HDL Cholesterol: HDL-C <40 mg/dL (men), <50 mg/dL (women).

2.5 | Statistical analysis

The primary purpose of the study was to demonstrate the superiority of empagliflozin 10 mg and 25 mg over placebo in reducing HbA1c at week 24. The difference in HbA1c between empagliflozin and placebo was assumed to be −0.7%, with a standard deviation of 0.93%. A 90% statistical power and a two-sided significance level of 5% were used. The drop-out rate was assumed to be 15%. The sample size was estimated to be 165 patients (55 patients per group).

For the analysis of the primary efficacy endpoint, analysis of covariance (ANCOVA) was performed with stratification factors at randomisation included as covariates. To control the family-wise type I error rate (FWER), prespecified gatekeeping was applied to the primary efficacy endpoint (change in HbA1c from baseline to week 24 in the full analysis set [FAS]). The testing hierarchy was: (1) empagliflozin 10 mg versus placebo, followed—only if the first null hypothesis was rejected—by (2) empagliflozin 25 mg versus placebo. All other endpoints (secondary/exploratory) were analysed without multiplicity adjustment. For secondary and exploratory efficacy endpoints, ANCOVA or the Cochran–Mantel–Haenszel test (CMH test) was used, as appropriate. Within-group comparisons for efficacy endpoints during the extension period were performed using paired t tests or, if normality assumptions were not met, the Wilcoxon signed-rank test. For safety endpoints, adverse events (AEs) were compared between groups using Pearson's chi-square test or Fisher's exact test. Vital signs were analysed within groups using paired t tests or Wilcoxon signed-rank tests. These methods were applied consistently across both the treatment and extension periods. Demographics and efficacy were analysed in the FAS, which consisted of patients who were exposed to at least one dose of the study drug and had at least one HbA1c measurement after taking the study drug. Safety was analysed in the safety analysis set, which included patients who were exposed to at least one dose of the study drug. Efficacy was also analysed in the Per-Protocol Set (PPS) who completed the 24-week treatment period as specified in the protocol. Participants were excluded if they terminated early, had major protocol violations regarding inclusion/exclusion criteria or prohibited concomitant medications/therapies, received rescue therapy, or had less than 80% treatment adherence, as well as any other major protocol violations that could significantly impact safety or efficacy assessments.

For the extension period, efficacy was analysed in the extension-period FAS, which included patients who were exposed to at least one dose of the study drug and had at least one HbA1c measurement after taking the study drug during the extension period, among patients who completed the treatment period. Safety during the extension period was analysed in the extension-period safety analysis set, which consisted of patients exposed to at least one dose of the study drug during the extension period. For efficacy and exploratory analyses, missing values in the FAS were imputed using the last observation carried forward (LOCF) method. All safety analyses were performed using observed data, and there was no imputation of missing data. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Study population and baseline characteristics

A total of 230 patients were screened, of whom 172 patients were randomised (Figure 1). Among the randomised patients, 10 patients (5.8%) dropped out of the study, and 162 patients (94.2%) completed the treatment period. The safety analysis set and FAS each comprised 171 patients. Of the patients who completed the treatment period, 4 patients who did not consent to participate in the extension period were excluded; thus, 158 patients entered the extension period. During the extension period, 7 patients (4.4%) dropped out of the study, and 151 patients (95.6%) completed the study. The extension period safety analysis set included 157 patients, and the Extension Period FAS comprised 154 patients.

Baseline demographics and characteristics in FAS were generally well balanced between the treatment groups (Table 1). The mean age of the patients was 60.4 ± 11.1 years, and 63.7% were men. The mean duration of T2DM was 134.3 ± 81.0 months. The mean HbA1c and FPG were 7.8% ± 0.6% and 152.1 ± 34.7 mg/dL, respectively. The mean BMI and waist circumference were 25.5 ± 3.1 kg/m^2 and 89.8 ± 8.3 cm, respectively. In addition, all other laboratory parameters and major chronic diseases (hypertension and dyslipidemia) were well balanced between the treatment groups.

3.2 | Efficacy endpoints

At week 24, the empagliflozin 10 and 25 mg groups had significantly lower HbA1c levels compared with the placebo group. The adjusted mean differences in the change from baseline in HbA1c for the empagliflozin 10 and 25 mg group versus the placebo group were −0.7% (95% CI −1.0, −0.4; p <.0001) and − 0.8% (95% CI −1.1, −0.5; p <.0001), respectively. Decreases in HbA1c levels with empagliflozin 10 and 25 mg were maintained over 52 weeks with mean changes from baseline of −0.7% ± 0.7% and −0.7% ± 0.8%, respectively. Among patients who switched from placebo to empagliflozin 10 mg during the extension period, the mean change in HbA1c level was −0.6% ± 0.8%, which was similar to the glycemic improvement observed in the empagliflozin 10 mg group during the treatment period (Figure 2A).

As shown above, reductions in mean HbA1c levels were similar between the empagliflozin 10 and 25 mg groups. However, in the subgroup of patients with a baseline HbA1c ≥8.5%, empagliflozin 25 mg showed numerically greater reductions in HbA1c compared to empagliflozin 10 mg at both week 24 (empagliflozin 25 mg −1.5% ± 0.3%, empagliflozin 10 mg −1.1% ± 0.3%) and week 52 (empagliflozin 25 mg −1.6% ± 0.4%, empagliflozin 10 mg −0.8% ± 0.5%), although these differences did not reach statistical significance (Supplementary Figure 2).

Mean FPG levels were also reduced significantly at week 24 in the empagliflozin 10 mg and 25 mg groups compared with the placebo group. The adjusted mean differences in change from baseline in FPG with empagliflozin 10 and 25 mg versus placebo were −32.2 mg/dL (95% CI −41.4, −23.1; p <.0001) and −32.6 mg/dL (95% CI −42.0, −23.1; p <.0001), respectively (Figure 2B). The proportion of patients who reached HbA1c <7% or <6.5% at week 24 in the empagliflozin 10 mg and 25 mg groups was significantly higher compared with the placebo group (all p <.05) (Figure 3).

Consistent with the FAS analysis, the PPS analysis also demonstrated statistically significant reductions in HbA1c and FPG, as well

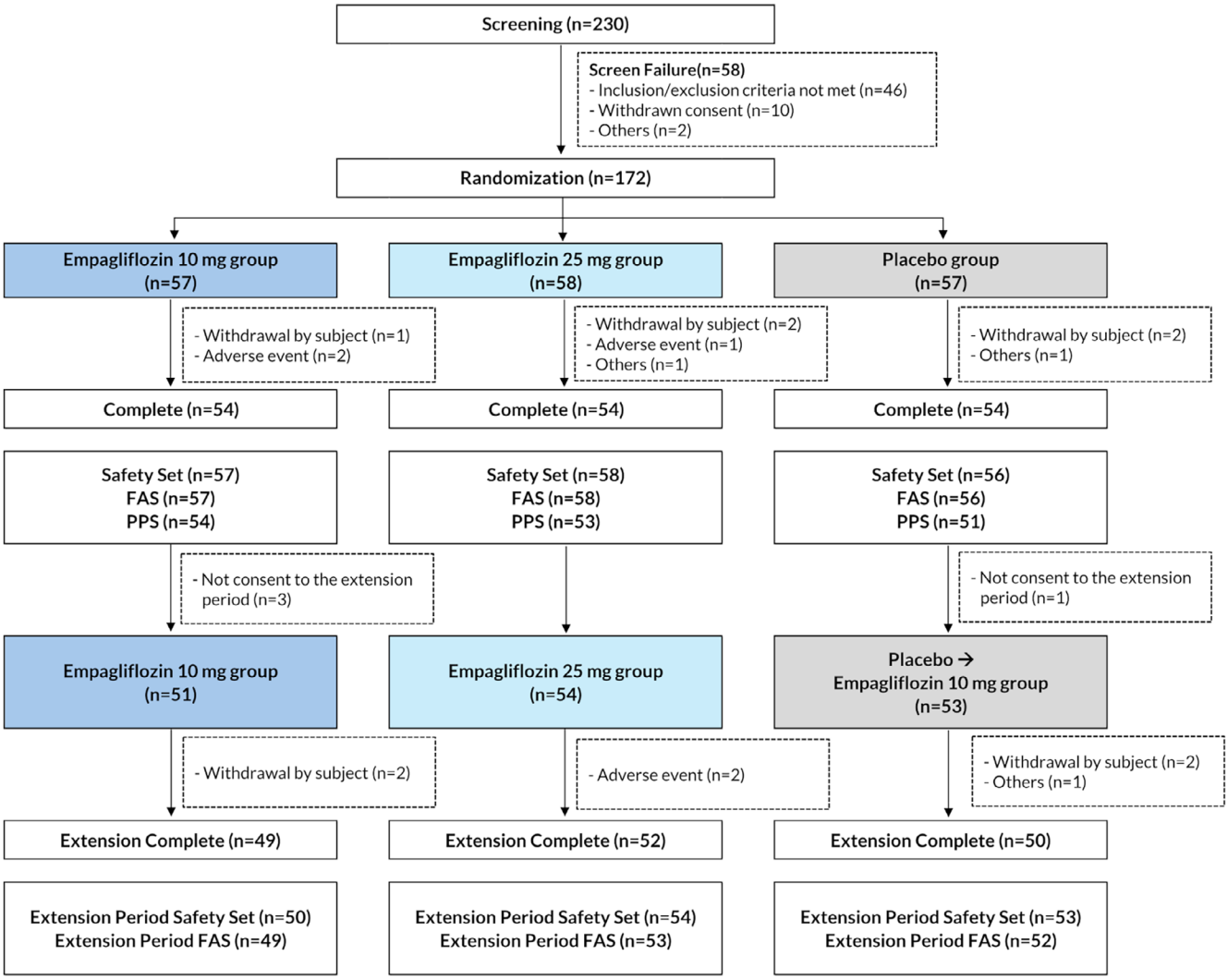

FIGURE 1 Patient disposition.

as a higher proportion of patients achieving the target HbA1c level in the empagliflozin 10 mg and 25 groups compared with the placebo group (all p <.05). These improvements were sustained in the empagliflozin groups during the extension period.

Glycemic rescue therapy was administered to three patients during the 24-week treatment period and to two patients during the extension period, including one patient who required therapy in both periods. All four patients were in the placebo (or switch) group. No patients in the empagliflozin 10 or 25 mg groups received rescue therapy during either period.

3.3 | Exploratory endpoints

Significantly greater reductions in body weight and waist circumference were observed at week 24 and 52 in the empagliflozin 10 and 25 mg groups compared to baseline. These reductions were significantly greater in the empagliflozin groups than in the placebo group at week 24 (Table 2). Body weight changes were analysed according to baseline BMI. Subgroup analysis revealed that empagliflozin reduced body weight in patients with BMI ≥25 kg/m^2 and those with BMI <25 kg/m^2, with a greater reduction observed in patients with BMI ≥25 kg/m^2 (Supplementary Table 3).

In addition, UACR tended to increase in the placebo group but decreased in the empagliflozin groups. The proportion of patients receiving angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers during the study was comparable among groups (placebo 55.4%, empagliflozin 10 mg 35.1%, and empagliflozin 25 mg 39.7%; $p = .0744$), indicating that observed differences in UACR changes were unlikely due to variations in background RAS blockade. Both the empagliflozin 10 and 25 mg groups had numerically greater reductions in UACR from baseline at week 24 compared with the placebo group, but the difference was only statistically significant in the empagliflozin 25 mg group versus the placebo group. Significantly greater reductions in UACR were observed at week 52 in the empagliflozin 10 and 25 mg groups compared to baseline (Table 2).

Mean SBP and DBP were reduced from baseline at week 24 with empagliflozin during the treatment period. The mean reductions in

TABLE 1 Baseline characteristics of study participants.

	Empagliflozin 10 mg ($n = 57$)	Empagliflozin 25 mg ($n = 58$)	Placebo ($n = 56$)	Total ($n = 171$)	p-value[a]
Age (years)[b]	61.1 (11.2)	61.4 (9.3)	58.8 (12.7)	60.4 (11.1)	0.5788[K]
Height (cm)[b]	165.3 (8.2)	163.4 (8.6)	164.1 (8.7)	164.2 (8.5)	0.4719[A]
Weight (kg)[b]	69.1 (11.9)	67.2 (10.9)	70.3 (13.0)	68.9 (12.0)	0.3697[A]
BMI (kg/m^2)[b]	25.3 (3.3)	25.2 (2.6)	26.1 (3.5)	25.5 (3.1)	0.3710[K]
Waist circumference (cm)[b]	89.5 (8.4)	89.1 (7.4)	90.7 (9.0)	89.8 (8.3)	0.5600[A]
Sex[c]					
Male	40 (70.2)	38 (65.5)	31 (55.4)	109 (63.7)	0.2462[C]
Female	17 (29.8)	20 (34.5)	25 (44.6)	62 (36.3)	
Duration of type 2 diabetes mellitus (months)[b]	139.8 (86.8)	138.5 (74.0)	124.4 (82.5)	134.3 (81.0)	0.3041[K]
Hypertension[c]	28 (49.1)	30 (51.7)	38 (67.9)	96 (56.1)	0.0943[C]
Dyslipidemia[c]	52 (91.2)	47 (81.0)	48 (85.7)	147 (86.0)	0.2894[C]
HbA1c (%)[b]	7.8 (0.6)	7.8 (0.6)	7.7 (0.7)	7.8 (0.6)	0.2805[K]
FPG (mg/dL)[b]	152.1 (35.1)	151.5 (35.7)	152.8 (34.0)	152.1 (34.7)	0.8823[K]
Fasting insulin (uU/mL)[b]	8.0 (5.8)	7.4 (4.1)	10.7 (12.3)	8.7 (8.2)	0.5310[K]
C-peptide (ng/mL)[b]	2.0(0.9)	2.1(0.8)	2.4(1.4)	2.2(1.0)	0.4885[K]
UACR (mg/g)[b]	60.8 (199.0)	69.4 (241.5)	27.7 (72.1)	52.9 (186.0)	0.1230[K]
Serum creatinine (mg/dL)[b]	0.9 (0.2)	0.8 (0.1)	0.8 (0.2)	0.8 (0.2)	0.6080[K]
eGFR (mL/min/1.73 m^2)[b]	88.5 (13.7)	89.1 (12.0)	90.4 (15.1)	89.3 (13.6)	0.7513[A]
AST (IU/L)[b]	26.2 (15.7)	23.6 (14.8)	28.3 (23.8)	26.0 (18.5)	0.3599[K]
ALT (IU/L)[b]	24.5 (14.8)	26.7 (21.4)	27.2 (17.7)	26.1 (18.1)	0.6614[K]
γ-GT (IU/L)[b]	30.1 (19.4)	29.2 (21.9)	45.8 (75.5)	34.9 (46.8)	0.5384[K]
hsCRP (mg/L)[b]	0.9 (1.1)	1.3 (3.4)	1.6 (4.6)	1.3 (3.4)	0.2599[K]
SBP (mmHg)[b]	127.1 (12.7)	127.1 (11.0)	127.0 (12.6)	127.0 (12.0)	0.9993[A]
DBP (mmHg)[b]	74.8 (8.6)	74.3 (8.8)	75.2 (10.5)	74.8 (9.3)	0.8914[A]
Heart rate (bpm)[b]	78.6 (9.4)	77.6 (9.0)	78.8 (10.1)	78.3 (9.5)	0.7828[A]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; bpm, beats per minute; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; γ-GT, gamma glutamyltransferase; HbA1c. glycosylated haemoglobin; hsCRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio.
[a]ANOVA (A), Chi-square test (C), or Kruska–Wallis Test (K) for comparison between treatment groups.
[b]Mean (SD).
[c]*n* (%).

SBP in both empagliflozin groups were significantly greater than those in the placebo group at week 24 (Supplementary Table 4).

Additionally, based on data collected at baseline (including medical history and blood test results), patients were classified according to the presence of metabolic syndrome. Among those with metabolic syndrome at baseline, the metabolic syndrome resolution rate was significantly higher in the empagliflozin groups compared to the placebo group at week 24 (all p <.05) (Supplementary Figure 3).

3.4 | Safety

During the treatment period, the proportions of patients with one or more TEAEs were similar across groups: empagliflozin 10 mg, 19.3%; empagliflozin 25 mg, 20.7%; placebo, 26.8%. The incidence of ADRs and TEAEs leading to discontinuation was also similar across treatment groups. Among TEAEs leading to discontinuation (5 participants, 8 events), 5 events were considered to be ADRs (asthenia, decreased weight, chest pain, pollakiuria, cold sweat). All 5 events considered to be ADRs were mild in intensity. A total of 6 serious TEAEs (5 participants, 6 events) were reported in the empagliflozin 10 mg and 25 mg groups and none of them were considered to be ADRs (Table 3).

During the extension period, the proportions of patients experiencing one or more TEAEs were similar across groups: empagliflozin 10 mg, 16.0%; empagliflozin 25 mg, 16.7%; switched, 24.5%. The incidence of TEAEs reported in the switched group was similar to that observed in the empagliflozin 10 mg group during the treatment period. Only two ADRs were observed: 'weight decreased' in the empagliflozin 25 mg group and 'genital pruritus' in the placebo group. Only one TEAE, 'weight decreased' in the empagliflozin 25 mg group, resulted in study drug discontinuation (Table 3). No diabetic

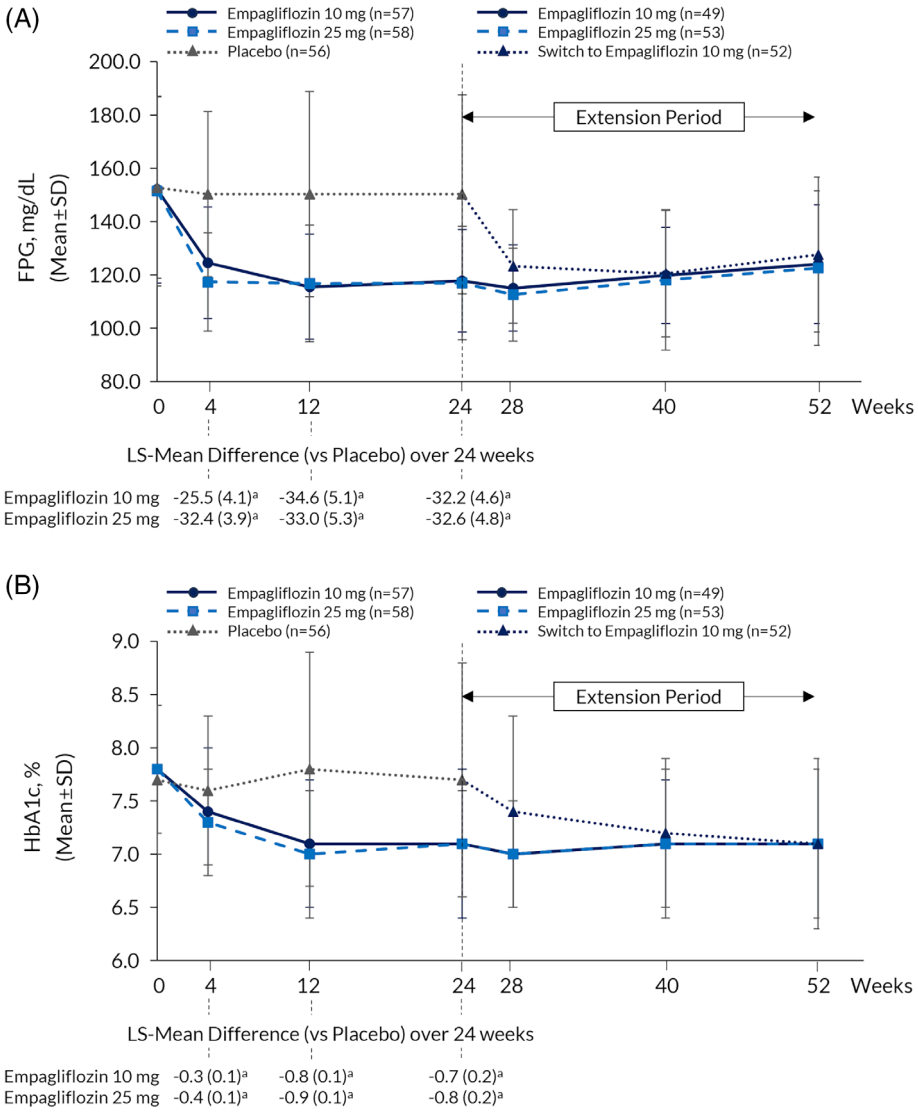

FIGURE 2 Changes in glycemic control over time: (A) Mean HbA1c from baseline to 52 weeks. (B) Mean fasting plasma glucose (FPG) from baseline to 52 weeks. Error bars are standard deviation (SD) of the mean. [a]Significant change compared to placebo (p <.0001).

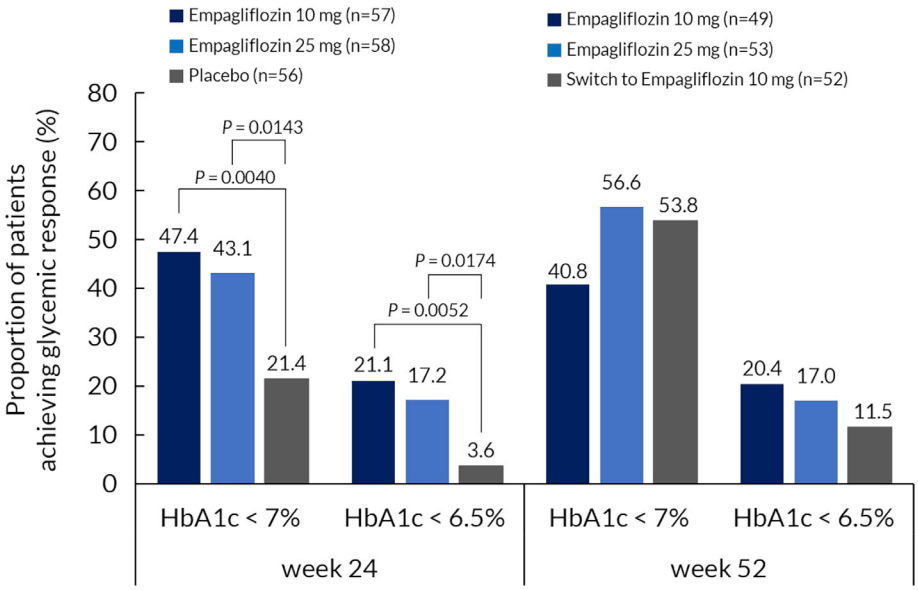

FIGURE 3 Proportion of patients achieving HbA1c less than 7.0% or 6.5% at 24 and 52 weeks.

TABLE 2 Mean changes in body weight, waist circumference and UACR from baseline to 24 and 52 weeks.

	Empagliflozin 10 mg		Empagliflozin 25 mg		Placebo → Empagliflozin 10 mg	
	△Week 24 ($n = 57$)	△Week 52 ($n = 49$)	△Week 24 ($n = 58$)	△Week 52 ($n = 53$)	△Week 24 ($n = 56$)	△Week 52 ($n = 52$)
Body weight (kg)	−3.0 (2.1)[b,d]	−2.8 (1.5)[b]	−2.9 (2.4)[b,d]	−2.8 (2.5)[b]	−0.4 (1.8)	−2.6 (2.2)[b]
Waist circumference (cm)	−2.7 (2.9)[b,c]	−2.9 (3.0)[b]	−2.1 (2.7)[b]	−2.3 (2.3)[b]	−1.2 (3.2)[a]	−3.0 (3.3)[b]
UACR (mg/g)	−8.7 (62.0)	−16.9 (55.2)[a]	−19.9 (83.0)[c]	−30.6 (144.2)[a]	6.1 (24.5)	29.1 (181.9)

Note: Significant change from baseline ([a]$p < .05$, [b]$p < .0001$), significant change compared to placebo group ([c]$p < .05$, [d]$p < .0001$).
Abbreviations: △, change from baseline; UACR, urine albumin-to-creatinine ratio.

TABLE 3 Summary of adverse events.

	Treatment period			Extension period		
	Empagliflozin 10 mg ($n = 57$)	Empagliflozin 25 mg ($n = 58$)	Placebo ($n = 56$)	Empagliflozin 10 mg ($n = 50$)	Empagliflozin 25 mg ($n = 54$)	Switch group ($n = 53$)
Adverse event (AE)	11 (19.3)	12 (20.7)	15 (26.8)	8 (16.0)	9 (16.7)	13 (24.5)
Adverse drug reaction (ADR)	4 (7.0)	3 (5.2)	1 (1.8)	0	1 (1.9)	1 (1.9)
Chest pain	0	2 (3.4)	0	0	0	0
Asthenia	1 (1.8)	0	0	0	0	0
Cervicitis	0	0	1 (1.8)	0	0	0
Vaginal infection	0	1 (1.7)	0	0	0	0
Weight decreased	2 (3.5)	0	0	0	1 (1.9)	0
Vulvovaginal pruritus	2 (3.5)	0	0	0	0	0
Pollakiuria	0	1 (1.7)	0	0	0	0
Cold sweat	0	1 (1.7)	0	0	0	0
Pruritus genital	0	0	0	0	0	1 (1.9)
Serious adverse event (SAE)	2 (3.5)	2 (3.4)	1 (1.8)	0	1 (1.9)	1 (1.9)
Serious adverse drug reaction	0	0	0	0	0	0
Adverse events leading to study drug discontinuation	2 (3.5)	3 (5.2)	0	0	1 (1.9)	0
Adverse drug reaction leading to study drug discontinuation	1 (1.8)	1 (1.7)	0	0	1 (1.9)	0

Note: Values are presented as number (%).

ketoacidosis events occurred in any group during the treatment or extension periods.

4 | DISCUSSION

This phase 3 clinical trial was conducted to evaluate the efficacy and safety of empagliflozin add-on therapy to sitagliptin and metformin in people with T2DM. The efficacy results showed that empagliflozin 10 and 25 mg significantly reduced HbA1c and FPG in patients with T2DM and more patients in the empagliflozin groups met HbA1c targets of <6.5% and <7%. In addition, decreases in body weight and waist circumference, and a reduction in UACR were observed. Both empagliflozin groups were well tolerated, and the reported AEs were similar to those known for the individual components.

T2DM is a multifactorial metabolic disorder characterised by heterogeneous and progressive pathophysiology. As such, monotherapy or even dual therapy may be insufficient to achieve optimal glycemic control or to reduce the risk of complications. The major conventional hypoglycemic agents act on distinct targets to address the complex mechanisms underlying T2DM. Combination therapy with these agents is often required to exert a synergistic effect by simultaneously targeting multiple underlying mechanisms of the disease, thereby improving glycemic outcomes.[2,12] Given that a substantial proportion of patients fail to meet glycemic targets with monotherapy or dual therapy, intensification to triple combination therapy may be necessary as an effective strategy to enhance treatment efficacy.[13–15]

The combination of metformin, DPP-4 inhibitors and SGLT2 inhibitors has emerged as a promising therapeutic strategy for the management of T2DM, as these drugs act through distinct

mechanisms: DPP-4 inhibitors enhance insulin secretion and inhibit glucagon secretion, while SGLT2 inhibitors promote urinary glucose excretion. The concomitant use of these agents has been shown to produce additive or potentially synergistic effects on glycemic control. Multiple clinical trials have evaluated the efficacy of DPP-4 inhibitors in combination with SGLT2 inhibitors, showing consistent improvement in glycemic control. In a recent updated systematic review and meta-analysis focusing on an Asian subpopulation, combination therapy with SGLT2 and DPP-4 inhibitors reduced HbA1c by 0.57% compared to DPP-4 inhibitor and by 0.46% compared to SGLT2 inhibitor. Moreover, meta-analyses indicate that combination therapy using DPP-4 and SGLT2 inhibitors offers not only significant glycemic benefits but also additional advantages, including a low risk of hypoglycemia, weight reduction, and decreased cardiovascular risk.[16–18]

In the present study, reductions in mean HbA1c levels were similar with empagliflozin 10 and 25 mg. This result was also observed in several previous studies of empagliflozin. However, in a subgroup analysis in patients with a baseline HbA1c ≥8.5%, empagliflozin 25 mg resulted in a numerically greater reduction in HbA1c levels compared to empagliflozin 10 mg at week 24 and 52 in the current study. Therefore, empagliflozin 25 mg add-on therapy might be more effective in controlling blood glucose than empagliflozin 10 mg in patients who have a higher HbA1c level before treatment.[19–22]

There are additional benefits to empagliflozin add-on therapy. First, empagliflozin add-on therapy reduces renal damage in patients with T2DM. Empagliflozin enhances urinary sodium excretion, activates tubuloglomerular feedback, and reduces glomerular hyperfiltration. Consequently, empagliflozin protects from renal damage and albuminuria.[23] The EMPA-KIDNEY trial confirmed the efficacy and safety of empagliflozin in patients with chronic kidney disease (CKD), suggesting that the use of empagliflozin could be prioritised in patients with CKD.[24] In the current study, UACR was assessed to confirm the renal protection effect of empagliflozin. Empagliflozin add-on therapies reduced UACR; in particular, empagliflozin 25 mg reduced UACR significantly compared to empagliflozin 10 mg. Secondly, empagliflozin add-on therapy reduces body weight and waist circumference in patients with T2DM. Obesity is a major risk factor for developing T2DM, and weight loss is associated with improved glycemic control.[25,26] Since the majority of patients with T2DM are overweight or obese, weight management is crucial for controlling blood glucose in these patients. In the current study, empagliflozin add-on therapies showed greater body weight reduction in patients with a BMI ≥25 kg/m^2. Despite this, reductions in mean body weight were similar with empagliflozin 10 and 25 mg doses, consistent with previous studies reporting similar dose-related effects of empagliflozin on body weight.[19–21] Previous research suggests that greater weight loss with the 25 mg dose occurs in participants with higher baseline body weight.[22] In our study, the relatively lower mean baseline weight and the smaller proportion of patients in the higher-weight categories (≥80 kg) likely limited the ability to observe dose-dependent effects on weight reduction.

This study confirmed that empagliflozin add-on therapy leads to improvements in glycemic control as well as in other metabolic parameters, such as waist circumference. Therefore, empagliflozin is expected to provide benefits in individuals with metabolic syndrome, which is characterised by a cluster of disorders that increase the risk of cardiovascular disease and T2DM.[27] Among patients who had metabolic syndrome at baseline, the resolution rate of metabolic syndrome was significantly higher in the empagliflozin groups compared with the placebo group at week 24. These results suggest that empagliflozin add-on therapy may help reduce the risk of cardiovascular disease by improving metabolic syndrome.

The combination of DPP-4 inhibitors and SGLT2 inhibitors has generally demonstrated a favourable safety profile, comparable to that of either agent used as monotherapy. Importantly, the incidence of hypoglycemia remains low due to the glucose-dependent mechanisms of both drug classes. Consistent with previous findings, only a single case of hypoglycemia was reported as an AE over the 52-week treatment period in this study. One notable adverse effect of SGLT2 inhibitors is an increased risk of genital or urinary tract infections, which can limit treatment adherence.[28] Interestingly, previous observations suggest that the addition of a DPP-4 inhibitor may attenuate this risk.[29,30] The proposed mechanism involves the immune-modulatory and anti-inflammatory effects of DPP-4 inhibition, although clear mechanistic data are limited. In our study, the rate of genital infection was very low in study participants. These findings indicate that the DPP-4 inhibitor/SGLT2 inhibitor combination is not only effective in improving glycemic control but may also mitigate one of the most common AEs associated with SGLT2 inhibitor use, thereby improving overall tolerability and patient adherence.

In conclusion, this study demonstrated that empagliflozin add-on therapy to sitagliptin and metformin safely improves glycemic control in Korean patients with T2DM, with the additional benefits of renal protection, weight control, and improvement in metabolic syndrome. Although this study was confined to the Korean population, the results are consistent with those from other studies, and the results are strengthened by the randomised, double-blind, placebo-controlled design and the long-term duration of treatment. Triple combination therapy with metformin, sitagliptin, and empagliflozin is a preferable treatment option with multifaceted effects for people with T2DM.

AUTHOR CONTRIBUTIONS

SHL and YMC conceptualised and designed the study. All authors conducted the clinical trial, collected the data, and contributed to data interpretation. SHL drafted the manuscript. YMC is the guarantor of this work. All authors significantly contributed to the manuscript and approved the final version for publication.

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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