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Efficacy and Safety of Fixed-Dose Combinations of Sitagliptin and Empagliflozin as Add-On to Metformin in Korean Patients With Type 2 Diabetes: A Randomised, Double-Blind, Multi-Centre, Placebo-Controlled, Phase III Trial

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a progressive, multi-organ disorder that often requires intensive combination therapy. This Phase III, randomised, double-blind, placebo-controlled study evaluated the efficacy and safety of two fixed-dose

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combinations (FDCs) of sitagliptin 100 mg with empagliflozin 10 mg (DW1026C1) or empagliflozin 25 mg (DW1026C2) as add-on therapy for patients with inadequately controlled T2DM.

Methods: Two hundred thirty adults with T2DM inadequately controlled by metformin (≥ 1000 mg/day) and sitagliptin (100 mg) were 1:1:1 randomised to receive DW1026C1 (E10 group, $n = 77$), DW1026C2 (E25 group, $n = 76$), or a placebo ($n = 77$). Treatment was administered for 24 weeks, followed by a 28-week extension period. The primary endpoint was the change in HbA1c from baseline to Week 24.

Results: Baseline characteristics were similar among groups. At Week 24, both active treatments demonstrated statistically significant HbA1c reductions versus the placebo. The least square mean differences [95% CI] versus the placebo were −0.54% [−0.78, −0.29] for E10 group and −0.61% [−0.85, −0.36] for E25 group (both $p < 0.0001$). Fasting plasma glucose (FPG), insulin resistance, body weight, systolic blood pressure, albumin-creatinine ratio and high-density lipoprotein cholesterol also improved in the active groups. Reductions in HbA1c, FPG and insulin resistance were sustained in Week 52. Safety profiles were favourable with adverse events similar in frequency and no increased hypoglycaemia risk.

Conclusion: Sitagliptin/empagliflozin FDC doses achieved improvements in glycaemic control at 24 weeks, which was maintained through 52 weeks. These benefits were accompanied by a favourable safety profile, including a very low risk of hypoglycaemia.

Trial Registration: NCT07076056

1 | Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, complex metabolic condition marked by reduced pancreatic insulin production and heightened peripheral insulin resistance [1, 2]. In Korea, diabetes affects a high proportion of adults aged 30 and older (approximately 15.5%), totalling about 5.3 million individuals. The prevalence of diabetes among adults aged ≥ 65 years is 29.3%, with control rates of only 31.2% achieving the optimal haemoglobin A1c (HbA1c) target of < 6.5% [3].

Metformin remains the cornerstone of initial therapy for T2DM, and DPP-4 inhibitors such as sitagliptin are commonly added because of their complementary mechanism and favourable safety profile. However, due to the progressive nature of T2DM, dual therapy frequently fails to achieve or sustain glycaemic targets, particularly in patients with markedly elevated HbA1c, thereby providing a strong rationale for early intensification with triple combination therapy [4–7].

Empagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor that works via an insulin-independent mechanism that increases renal glucose excretion and contributes to significant glycaemic control [8]. In addition to its efficacy in lowering blood glucose and weight, empagliflozin demonstrated significant cardiorenal protective effects in large-scale outcome trials [9–11]. Therefore, owing to the complementary mechanisms of SGLT2 and DPP-4 inhibitors, their concurrent administration represents an attractive therapeutic pathway [12]. The fixed-dose combination (FDC) of empagliflozin and linagliptin was an early oral therapy integrating two complementary drug classes. This FDC demonstrated clinically meaningful reductions in HbA1c and body weight when used either as initial therapy or as an add-on to metformin [13].

Similarly, the empagliflozin/sitagliptin FDC provides a compelling therapeutic option by harnessing complementary mechanisms for synergistic efficacy. Combining these agents into a single formulation may improve adherence by simplifying treatment and reducing pill burden [12].

This Phase III trial was designed to evaluate the efficacy and safety of sitagliptin (100 mg) and empagliflozin (10 or 25 mg) add-on therapy as an FDC to metformin in patients with T2DM whose glycaemic control was inadequately managed with metformin and sitagliptin combination therapy. Furthermore, the study aimed to provide robust, long-term data (up to 52 weeks) on the sustained effects and comprehensive safety profile of this triple therapy.

2 | Methods

2.1 | Study Design and Procedures

This was a multicentre, randomised, double-blind, placebo-controlled, three-arm parallel-group Phase III trial conducted at 25 sites in Korea from October 27, 2022, to June 19, 2024 (ClinicalTrials.gov identifier: NCT07076056). The study was conducted in accordance with the Declaration of Helsinki and ICH-GCP guidelines and was approved by the institutional review boards (IRBs) of the coordinating investigator's institution, Yeouido St. Mary's Hospital (IRB no. SC22MDDT0118), and all the participating 25 institutions. Study approval was also obtained from the Ministry of Food and Drug Safety. All participants provided written informed consent.

The protocol comprised screening, an 8-week stabilisation period, a 2-week run-in period, a 24-week treatment period and a 28-week extension period.

Eligible patients at screening were adults with T2DM who had received metformin at a stable dose (≥ 1000 mg/day) for at least 8 weeks, either as monotherapy or in combination with another drug (regardless of formulation type). All patients were required to maintain the same metformin dose throughout the study.

During the stabilisation period, patients received metformin and sitagliptin 100 mg. Those who had been on a stable regimen of both drugs for ≥ 8 weeks prior to screening could skip this period. In the run-in period, patients received metformin,

sitagliptin 100 mg, and matched placebos for sitagliptin/empagliflozin FDCs. Patients who demonstrated medication adherence of 70%–130% and met the eligibility criteria at baseline were 1:1:1 randomised to:

- E10 group: metformin + sitagliptin placebo + DW1026C1 (sitagliptin 100 mg/empagliflozin 10 mg FDC) + DW1026C2 placebo
- E25 group: metformin + sitagliptin placebo + DW1026C2 (sitagliptin 100 mg/empagliflozin 25 mg FDC) + DW1026C1 placebo
- Placebo group: metformin + sitagliptin 100 mg + DW1026C1 placebo + DW1026C2 placebo

Randomisation was stratified by baseline HbA1c levels (< 8.5% vs. ≥ 8.5%) and estimated glomerular filtration rate (eGFR) (< 90 mL/min/1.73 m^2 vs. ≥ 90 mL/min/1.73 m^2). During the treatment period, visits were scheduled for Weeks 12 and 24 for efficacy and safety assessments. Rescue medication was permitted during the treatment and extension periods for patients with uncontrolled hyperglycaemia, defined as a fasting plasma glucose (FPG) level > 240 mg/dL between baseline and Week 12, or > 200 mg/dL between Week 12 and Week 52. Glimepiride was used as rescue medication and could be administered up to a maximum daily dose of 4 mg. After the treatment period, eligible patients who provided informed consent entered the extension period. While patients who belonged to the E10 or E25 group continued their respective treatments, those in the placebo group were re-randomised (1:1) to receive either DW1026C1 (PE10) or DW1026C2 (PE25) as follows:

- PE10 group: metformin + DW1026C1 (sitagliptin/empagliflozin 10 mg FDC) + DW1026C2 placebo
- PE25 group: metformin + DW1026C2 (sitagliptin/empagliflozin 25 mg FDC) + DW1026C1 placebo

The extension period was designed primarily to provide additional assessment of long-term safety and durability of glycaemic control in patients who continued study treatment. Visits were scheduled for Weeks 38 and 52, with continued monitoring of efficacy and safety (Figure S1).

2.2 | Study Patients

A total of 299 patients were screened, and 230 patients were randomised (E10 group: $n = 77$, E25 group: $n = 76$, placebo group: $n = 77$). Of these, 215 completed the treatment period. During the extension period screening, 26 patients were excluded (22 did not provide written consent, 2 received rescue medication during the treatment period, 1 was deemed unsuitable by the investigator, and 1 met multiple exclusion criteria), and 4 withdrew consent, resulting in 185 patients entering the extension period (Figure S2). The inclusion and exclusion criteria are presented in Table S1. The inclusion criteria for the treatment period comprised HbA1c level ≥ 7.0% and ≤ 10.5% during the run-in period, whereas that for the extension period was providing written consent to participate in the extension study. Patients with a history of acute coronary syndrome, stroke, transient ischemic attack, acute or unstable heart failure within 12 weeks prior to screening were not eligible. Four patients, all in the placebo group, required rescue medication owing to uncontrolled hyperglycaemia during the treatment period were excluded from the extension study. No rescue medication use was observed during the extension period.

2.3 | Efficacy and Safety Endpoints

The primary efficacy endpoint was HbA1c change between baseline and Week 24. Secondary endpoints included changes in FPG, insulin, homeostasis model assessment of insulin resistance (HOMA-IR), homeostasis model assessment of β cell function (HOMA-β), quantitative insulin-sensitivity check index (QUICKI), body weight, eGFR, albumin-creatinine ratio (ACR), systolic/diastolic blood pressure (SBP/DBP), lipid profile at Weeks 12, 24, 38 and 52, and safety.

2.4 | Statistical Analyses

The sample size to detect a difference in the primary efficacy endpoint, defined as the change in HbA1c from baseline to Week 24 between each of the E10 and E25 groups and placebo group was determined. Based on previous studies, the mean HbA1c difference was conservatively assumed to be −0.59%, with a pooled standard deviation (SD) of 0.98 [14–17]. Using a two-sided significance level of 5%, 90% power, and a gatekeeping strategy to control multiplicity, 59 patients per group were required. Allowing for a 20% dropout rate, it was necessary to enrol 74 patients per group, totalling 222 participants.

Baseline characteristics were compared using appropriate parametric or nonparametric tests for continuous variables and Chi-square or Fisher's exact tests for categorical variables. Efficacy and safety were analysed in the full analysis set (FAS) and in the safety set (SS), respectively. FAS for the treatment and extension periods included patients who satisfied the period-specific inclusion and exclusion criteria; for the treatment period, at least one HbA1c assessment after baseline was required, and for the extension period, at least one HbA1c assessment after Week 24 was required. SS for each period consisted of patients who received at least one dose of the investigational product during the corresponding period. Continuous outcomes were summarised as mean ± SD, with treatment effects during the treatment period assessed using a mixed-effects model for repeated measures that included group, visit, group by visit interaction, baseline HbA1c, and baseline eGFR as fixed effects, patient as a random effect, and an unstructured covariance structure. The primary treatment effect was defined as the mean difference between groups in change from baseline in HbA1c at Week 24 in the FAS. Use of rescue medication was considered an intercurrent event and handled using a hypothetical strategy, whereby HbA1c measurements obtained after initiation of rescue therapy were treated as missing. The primary endpoint was analysed using MMRM based on observed data without imputation under a missing at random. Missing data was handled using endpoint-specific approaches, which are described in detail in Table S2. Within-group changes were evaluated using paired t-tests or Wilcoxon signed-rank tests, as appropriate.

TABLE 1 | Demographics and baseline characteristics.

Variable	Total ($N=226$)	E10 ($N=76$)	E25 ($N=74$)	Placebo ($N=76$)
Age, year	60.60 ± 9.69	61.71 ± 9.24	59.93 ± 10.27	60.14 ± 9.58
$p^{\dagger}$	0.5936[K]			
Sex (male)	117 (51.77)	44 (57.89)	39 (52.70)	34 (44.74)
$p^{\dagger}$	0.2627 [C]			
Body weight, kg	66.67 ± 11.38	67.14 ± 10.72	67.27 ± 12.62	65.60 ± 10.81
$p^{\dagger}$	0.4005[K]			
BMI, kg/m^2	25.12 ± 3.21	24.73 ± 2.98	25.57 ± 3.58	25.07 ± 3.04
$p^{\dagger}$	0.7183[K]			
HbA1c, %	7.78 ± 0.79	7.73 ± 0.86	7.74 ± 0.77	7.87 ± 0.74
$p^{\dagger}$	0.1263[K]			
HbA1c < 8.5%	190 (84.07)	64 (84.21)	63 (85.14)	63 (82.89)
$p^{\dagger}$	0.9314[C]			
FPG, mg/dL	158.00 ± 33.22	158.08 ± 36.04	156.64 ± 31.98	159.26 ± 31.82
$p^{\dagger}$	0.7934[K]			
Insulin, μU/mL	9.42 ± 7.53	8.40 ± 6.04	10.51 ± 10.00	9.37 ± 5.85
$p^{\dagger}$	0.2257[K]			
HOMA-IR	3.73 ± 3.25	3.27 ± 2.33	4.24 ± 4.41	3.70 ± 2.61
$p^{\dagger}$	0.3701[K]			
HOMA-ß	39.00 ± 33.42	36.40 ± 32.16	42.04 ± 39.86	38.65 ± 27.46
$p^{\dagger}$	0.2155[K]			
QUICKI	0.33 ± 0.03	0.33 ± 0.03	0.33 ± 0.03	0.33 ± 0.03
$p^{\dagger}$	0.4109 [K]			
SBP, mmHg	126.18 ± 12.23	124.66 ± 10.71	127.24 ± 12.97	126.66 ± 12.91
$p^{\dagger}$	0.3979[A]			
DBP, mmHg	74.35 ± 8.61	74.53 ± 8.64	74.26 ± 8.76	74.28 ± 8.53
$p^{\dagger}$	0.9774[A]			
Triglyceride, mg/dL	140.12 ± 85.94	137.47 ± 68.34	146.58 ± 118.64	136.47 ± 61.02
$p^{\dagger}$	0.6414[K]			
HDL-C, mg/dL	51.43 ± 12.67	52.04 ± 12.61	52.28 ± 12.99	49.99 ± 12.46
$p^{\dagger}$	0.3355[K]			
Triglyceride/HDL-C	3.07 ± 2.64	2.91 ± 1.79	3.28 ± 3.86	3.02 ± 1.79
$p^{\dagger}$	0.6561[K]			
LDL-C, mg/dL	82.25 ± 28.57	86.82 ± 29.79	77.84 ± 28.29	81.97 ± 27.23
$p^{\dagger}$	0.1840[K]			
eGFR, < 90 mL/min/1.73m^2	119 (52.65)	39 (51.32)	40 (54.05)	40 (52.63)
$p^{\dagger}$	0.9452[C]			
ACR, mg/g	54.03 ± 172.52	44.51 ± 142.25	33.69 ± 46.38	83.34 ± 256.11
$p^{\dagger}$	0.5462[K]			

(Continues)

TABLE 1 | (Continued)

Variable	Total ($N=226$)	E10 ($N=76$)	E25 ($N=74$)	Placebo ($N=76$)
Diabetes duration, year	11.33 ± 7.02	12.41 ± 7.27	10.65 ± 6.98	10.92 ± 6.75
$p^{\dagger}$	0.2528[K]			
Metformin dosage, mg	1337.28 ± 464.01	1330.92 ± 464.76	1367.23 ± 450.59	1314.47 ± 480.47
$p^{\dagger}$	0.5569[K]			

Note: Values are presented as mean ± standard deviation or number (%). Presented data are based on the full analysis set of treatment period. p value[†]: Test among the E10, E25 and placebo groups. [A]: Analysis of variance, [C]: Chi-square test, [K]: Kruskal–Wallis test. There was no statistically significant difference among the three groups.

Abbreviations: ACR, albumin-creatinine ratio; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; HDL-C, high density lipoprotein cholesterol; HOMA-β, homeostatic model assessment of β cell function; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol; QUICKI, quantitative insulin–sensitivity check index; SBP, systolic blood pressure.

Between-group comparisons of categorical outcomes used logistic regression with stratification factors, baseline HbA1c (< 8.5%, ≥ 8.5%), and eGFR (< 90 mL/min/1.73 m^2, ≥ 90 mL/min/1.73 m^2) as covariates, and results are presented as odds ratios (ORs) with 95% CIs and p values. Safety data were summarised as numbers and proportions (%), and group differences were tested with Chi-square or Fisher's exact tests. Subgroup analyses as post hoc analyses were performed by sex, age (< 65, ≥ 65 years), baseline BMI (< 25, ≥ 25 kg/m^2), hypertension and dyslipidaemia, which affect glycaemic control [18] for change in HbA1c from baseline to Week 24, and for changes in ACR from baseline to Week 24 according to baseline categories (< 30 mg/g and 30–300 mg/g). Efficacy analyses through 52 weeks were performed descriptively using observed efficacy data from the extension period. Only patients who entered the extension period were included in Week 52 efficacy analyses. Therefore, achievement rates of target HbA1c level in extension period were calculated using the number of extension entrants as the denominator. Accordingly, these rates represent descriptive outcomes among extension participants and should not be interpreted as estimates for the originally randomised population. Changes in HbA1c from baseline to Weeks 24 and 52 were also analysed based on baseline HbA1c (< 8.0%, ≥ 8.0%). A two-sided p value of < 0.05 was considered statistically significant. For the secondary efficacy endpoints, no gatekeeping strategy or adjustment for multiplicity was applied and all reported p values are nominal. Statistical analyses were conducted using SAS version 9.3.1 (SAS Institute Inc., Cary, NC, USA).

3 | Results

3.1 | Baseline Characteristics

The baseline characteristics of the participants were similar among the three groups. The mean age was 60.60 ± 9.69 years, and the proportion of males was 51.77%. The average body weight was 66.67 ± 11.38 kg. The mean HbA1c level was 7.78%, the mean FPG was 158.00 mg/dL and the mean diabetes duration was 11.33 ± 7.02 years (Table 1).

3.2 | Efficacy

At Week 24, the mean ± SD change from baseline in HbA1c was −0.76% ± 0.09% in the E10 group and −0.83% ± 0.09% in the E25 group, compared to −0.22% ± 0.09% in the placebo group. The estimated difference in mean change [95% CI] in HbA1c level from baseline in each group versus the placebo group was −0.54 [−0.78, −0.29] for the E10 group and −0.61 [−0.85, −0.36] for the E25 group (both $p < 0.0001$) (Table 2, Figure 1B). At Week 12, the E10 and E25 groups exhibited average reductions in HbA1c of 0.68 and 0.78, respectively, and these were sustained throughout the study. Furthermore, at Week 52, PE10 and PE25 groups showed marked reductions of 0.87% and 1.01% on average, respectively, following the switch to active treatment (Figure 1A).

In the pooled analysis of the E10 and E25 groups, the change in HbA1c at Week 24 consistently showed differences compared with the placebo group across all defined subgroups (sex, age [< 65, ≥ 65 years], BMI [< 25, ≥ 25 kg/m^2], baseline HbA1c [≤ 8.0%, > 8.0%] and the presence of comorbid hypertension and dyslipidaemia) (Table S3, Figure 1C,D).

The proportion of patients who achieved the strict HbA1c target of < 6.5% in the E10 and E25 groups ranged from 9.46% to 18.42% during the 24-week treatment period (Figure S3A). Achievement of the clinically relevant HbA1c target of < 7.0% was observed in 48.68% of E10 patients and 60.81% of E25 patients at Week 12. These response rates were maintained at Week 24 (53.95% for E10 and 55.41% for E25), with similar favourable trends continuing throughout the extension period (Figure 1G, Figure S3B,D). Because the assessments during the extension period were available only for participants who entered the extension period, the outcomes in the extension period represent descriptive outcomes among extension participants. Furthermore, composite response rates, defined as achieving either HbA1c < 6.5% or a reduction of > 0.5%, or achieving either HbA1c < 7.0% or a reduction > 0.5%, increased markedly, ranging from 52.63% to 81.08% in the E10 and E25 groups and showed an advantage in these composite responses compared to the placebo group at both Weeks 12 and 24 (nominal $p < 0.0001$) (Figure 1H and S3C). Gradual changes in FPG mirrored the pattern observed with HbA1c. At Week 24, the E10 and E25 groups achieved greater LS mean reductions in FPG compared to the placebo group (nominal $p < 0.0001$, Table 2, Figure 1E,F).

HOMA-IR demonstrated reductions in the E10 and E25 groups at Weeks 12 and 24, with the magnitude of the reductions at Week 24 revealing differences between these groups and the

TABLE 2 | Changes in efficacy parameters from baseline to Week 24.

	E10 ($N=76$)	E25 ($N=74$)	Placebo ($N=76$)
HbA1c, %			
LS mean ± SE	−0.76 ± 0.09	−0.83 ± 0.09	−0.22 ± 0.09
LS mean difference [95% CI]	−0.54 [−0.78, −0.29]	−0.61 [−0.85, −0.36]	
$p^{\dagger}$	< 0.0001	< 0.0001	
FPG, mg/dL			
LS mean ± SE	−28.16 ± 3.53	−30.32 ± 3.56	−0.32 ± 3.70
LS mean difference [95% CI]	−27.84 [−37.93, −17.75]	−30.00 [−40.13, −19.87]	
$p^{\dagger}$	< 0.0001	< 0.0001	
Insulin, μU/mL			
LS mean ± SE	−1.80 ± 0.65	−2.18 ± 0.66	0.54 ± 0.69
LS mean difference [95% CI]	−2.34 [−4.22, −0.47]	−2.72 [−4.61, −0.83]	
$p^{\dagger}$	0.0146	0.0049	
HOMA-IR			
LS mean ± SE	−0.95 ± 0.39	−1.38 ± 0.39	0.19 ± 0.41
LS mean difference [95% CI]	−1.15 [−2.26, −0.04]	−1.58 [−2.69, −0.46]	
$p^{\dagger}$	0.0421	0.0057	
HOMA-β			
LS mean ± SE	1.02 ± 2.52	6.40 ± 2.56	2.42 ± 2.69
LS mean difference [95% CI]	−1.40 [−8.68, 5.87]	3.98 [−3.34, 11.30]	
$p^{\dagger}$	0.7042	0.2853	
QUICKI			
LS mean ± SE	0.0289 ± 0.0042	0.0271 ± 0.0042	−0.0000 ± 0.0044
LS mean difference [95% CI]	0.0290 [0.0170, 0.0410]	0.0272 [0.0151, 0.0392]	
$p^{\dagger}$	< 0.0001	< 0.0001	
Body weight, kg			
LS mean ± SE	−2.82 ± 0.25	−2.55 ± 0.25	−0.99 ± 0.26
LS mean difference [95% CI]	−1.83 [−2.54, −1.12]	−1.56 [−2.28, −0.85]	
$p^{\dagger}$	< 0.0001	< 0.0001	
eGFR, mL/min/1.73m^2			
LS mean ± SE	−1.39 ± 1.23	−3.56 ± 1.25	0.37 ± 1.30
LS mean difference [95% CI]	−1.76 [−5.30, 1.78]	−3.93 [−7.50, −0.37]	
$p^{\dagger}$	0.3280	0.0306	
ACR, mg/g			
LS mean ± SE	−7.98 ± 8.62	−6.12 ± 8.79	−12.20 ± 9.31
LS mean difference [95% CI]	4.22 [−20.88, 29.31]	6.07 [−19.29, 31.44]	
$p^{\dagger}$	0.7408	0.6373	
SBP, mmHg			
LS mean ± SE	−7.06 ± 1.45	−3.72 ± 1.46	0.75 ± 1.50

(Continues)

TABLE 2 | (Continued)

	E10 ($N=76$)	E25 ($N=74$)	Placebo ($N=76$)
LS mean difference [95% CI]	−7.81 [−11.92, −3.70]	−4.47 [−8.61, −0.34]	
$p^{\dagger}$	0.0002	0.0341	
DBP, mmHg			
LS mean ± SE	−3.99 ± 0.99	−2.21 ± 1.00	−1.35 ± 1.03
LS mean difference [95% CI]	−2.65 [−5.46, 0.17]	−0.86 [−3.70, 1.97]	
$p^{\dagger}$	0.0654	0.5484	
Triglyceride, mg/dL			
LS mean ± SE	47.79 ± 21.12	43.07 ± 21.12	48.67 ± 20.54
LS mean difference [95% CI]	−0.89 [−25.46, 23.68]	−5.60 [−30.06, 18.85]	
$p^{\dagger}$	0.9432	0.6519	
HDL-C, mg/dL			
LS mean ± SE	2.36 ± 0.81	3.46 ± 0.82	0.31 ± 0.86
LS mean difference [95% CI]	2.06 [−0.28, 4.39]	3.15 [0.80, 5.50]	
$p^{\dagger}$	0.0837	0.0088	
Triglyceride/HDL-C			
LS mean ± SE	−0.28 ± 0.24	−0.57 ± 0.24	−0.03 ± 0.25
LS mean difference [95% CI]	−0.25 [−0.93, 0.43]	−0.54 [−1.23, 0.14]	
$p^{\dagger}$	0.4715	0.1210	
LDL-C, mg/dL			
LS mean ± SE	−4.04 ± 2.25	3.47 ± 2.27	−0.93 ± 2.39
LS mean difference [95% CI]	−3.10 [−9.58, 3.37]	4.40 [−2.09, 10.89]	
$p^{\dagger}$	0.3459	0.1826	

Note: Presented results are based on the full analysis set of treatment period. *p* value†: Test between the E10 and placebo groups and between the E25 and placebo groups. *p* value for the efficacy endpoints other than HbA1c is reported as nominal. The difference between groups was determined by using a mixed effect model for repeated measures including baseline HbA1c, baseline estimated glomerular filtration rate, and baseline value as covariates; treatment-by-visit interaction as fixed effects, and patient as a random effect.

Abbreviations: ACR, albumin-creatinine ratio; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β cell function; LDL-C, low density lipoprotein cholesterol; LS mean, least squares mean; QUICKI, quantitative insulin-sensitivity check index; SBP, systolic blood pressure; SE, standard error.

placebo group (Figure 2A). In particular, the mean HOMA-IR in the E25 group decreased from 4.24 ± 4.41 at baseline to 2.57 ± 2.17 at Week 24. At Week 24, the E10 and E25 groups also showed improvements in fasting insulin levels and QUICKI compared with the placebo group. Conversely, changes in HOMA-β were not significantly different in either group compared with the placebo group at Week 24 (Table 2). Regarding metabolic parameters, while all groups experienced some degree of weight reduction, the E10 and E25 groups demonstrated greater reductions than the placebo group at Week 24 (−2.82 kg and −2.55 kg vs. −0.99 kg, respectively; both nominal $p < 0.0001$) (Table 2, Figure 2B). Both active treatment groups achieved within-group and between-group reductions in SBP at Weeks 12 and 24 compared to the placebo group (Figure 2C). For DBP, although within-group reductions were observed at Week 24, these changes were not significantly different from those in the placebo group (Table 2).

Regarding the lipid profile at Week 24, the E25 group demonstrated an increase in high density lipoprotein cholesterol (HDL-C) compared with the placebo group (LS mean difference 3.15 [0.80, 5.50]; nominal $p = 0.0088$). Additionally, the triglyceride (TG)/HDL-C ratio showed a reduction from baseline at Week 24 in both the E10 and E25 groups (Data not presented). However, TG, low density lipoprotein cholesterol (LDL-C), and the TG/HDL-C ratio did not differ significantly between the active treatment and placebo groups (Table 2).

ACR showed within-group reductions in the E25 group at Week 12 and in both the E10 and E25 groups at Week 24. However, no significant between-group differences versus placebo were observed at either time point (Figure 2D). Patients with baseline microalbuminuria (30–300 mg/g) in the E25 group achieved a reduction from baseline at Week 12 (LS mean −34.64 ± 14.56), which was also different from that in the placebo group (nominal $p = 0.0434$). At Week

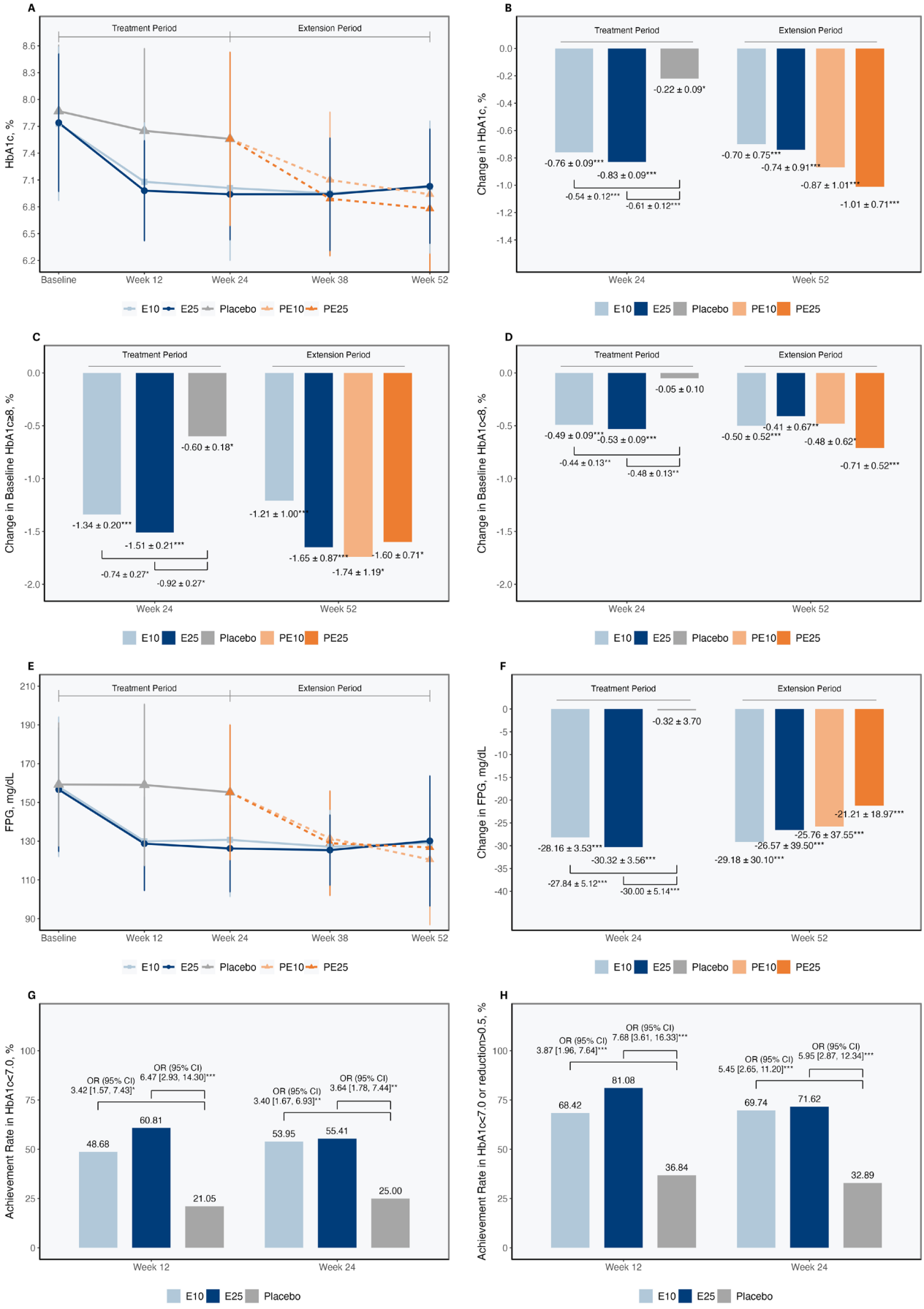

FIGURE 1 | Legend on next page.

FIGURE 1 | Changes in HbA1c and FPG (A) HbA1c, % at Weeks 12, 24, 38 and 52; (B) changes in HbA1c from baseline to Weeks 24 and 52; (C) change in HbA1c from baseline (≥8.0%) to Weeks 24 and 52; (D) changes in HbA1c from baseline (<8.0%) to Weeks 24 and 52; (E) FPG, mg/dL at Weeks 12, 24, 38 and 52; (F) changes in FPG from baseline to Weeks 24 and 52; (G) achievement rate of target HbA1c <7.0% at Weeks 12 and 24; (H) achievement rate of target HbA1c <7.0% or reduction >0.5% at Weeks 12 and 24. HbA1c and FPG values at each week are presented with mean and SD denoted with error bar. Changes from baseline are presented with LS mean ± SE for treatment period, and with mean ± SD for extension period. LS means and group comparisons during extension period based on changes were not performed due to treatment re-randomisation of placebo group at Week 24. Within-group change was analysed by paired *t*-test or Wilcoxon signed rank test. Changes were compared between groups using mixed effect model for repeated measures. Achievement rates of target HbA1c level were compared between groups by logistic regression. *$p < 0.01$; **$p < 0.001$; ***$p < 0.0001$. *p* values for efficacy endpoints other than change in HbA1c at Week 24 are reported as nominal. CI, confidence interval; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; LS mean, least squares mean; OR, odds ratio; SD, standard deviation; SE, standard error.

24, the E10 and E25 groups showed within-group improvements in this subgroup (LS mean −12.64 ± 20.69 and −23.29 ± 16.99, respectively), but the changes were not statistically significant compared to those in the placebo group (Table S4).

At Week 24, the E25 group showed a difference in eGFR change compared with the placebo group (nominal $p = 0.0306$). The E25 group exhibited an LS mean change of −3.56 ± 1.25 mL/min/1.73 m^2, differing from the change of 0.37 ± 1.30 mL/min/1.73 m^2 in the placebo group (Figure 2E). In subgroup analyses, patients with normal baseline eGFR (≥90 mL/min/1.73 m^2) in the E10 and E25 groups showed within-group improvements at Week 24 (nominal $p = 0.0171$ and nominal $p = 0.0049$), although they did not show between-group differences versus placebo (E10: nominal $p = 0.1924$; E25: nominal $p = 0.0526$). In contrast, patients with mildly reduced baseline eGFR (60–89 mL/min/1.73 m^2) showed no significant changes from baseline or versus placebo at Weeks 12 or 24 (Figure S4A,B).

Throughout the extension period (Weeks 24 to 52), eGFR changes were relatively small in the groups whose treatment was maintained (E10 and E25) (Table S4). Conversely, the groups switched from placebo to active treatment (PE10 and PE25) experienced the initial eGFR reduction, resulting in larger decreases in mean eGFR from baseline compared to the sustained treatment groups (Figure 2F). All groups (E10, E25, PE10 and PE25) showed a downward change in eGFR from baseline at Week 52 (Table S5).

By Week 52, most glycaemic and metabolic parameters showed within-group improvements across all treatment groups (E10, E25, PE10, PE25). Specifically, HbA1c, FPG, HOMA-IR, insulin, QUICKI, HOMA-β, body weight and HDL-C were improved in most treatment groups. An within-group increase in HOMA-β from baseline was observed in both active treatment groups only by Week 52. Conversely, changes in SBP and LDL-C were not statistically significant in any group. DBP reached substantial changes in the sustained treatment groups (E10 and E25) but was not consistent in the groups with switched regimens (Table S5).

3.3 | Safety

The proportion of the incidences of TEAEs were 16.88%, 23.68%, 24.68% in the E10, E25 and placebo groups, respectively, during the treatment period ($p = 0.7158$). In the E10 group, ADRs included dyspepsia, abdominal pain, thirst and rash in one patient each, and vaginal infection in two patients. In the E25 group, a case of dyspepsia and two cases of vulvovaginal pruritus were reported. In the placebo group, abdominal pain and vulvovaginal pruritus occurred in one patient each, while inadequate diabetes mellitus control was reported in four patients. A total of eight SAEs were reported, none of which were assessed as related to the study treatment (Table 3). During the extension period, one case of vulvovaginal dryness was reported as an ADR in the (PE25) group, and no SAE was observed. During the treatment period, no substantial hypoglycaemia occurred in any patient; however, one case of hypoglycaemia was observed during the extension period, which was attributable to device malfunction.

4 | Discussion

In this Phase III trial, sitagliptin/empagliflozin FDCs added to metformin provided durable glycaemic control with a favourable safety profile in inadequately controlled T2DM.

At Week 24, both FDCs led to statistically significant HbA1c reductions from baseline, demonstrating superior glycemia-lowering ability compared to the placebo (both groups $p < 0.0001$). The observed HbA1c lowering efficacy was robust, starting from Week 12 and persisting through to Week 52, highlighting the durability of this triple combination. The sustained maintenance of glycaemic control beyond the primary endpoint (Week 24) is critical for preventing or delaying long-term diabetes complications [19].

A greater proportion of patients in the active treatment groups achieved glycaemic targets, particularly for HbA1c <7.0%. Considering that the mean disease duration exceeded 10 years, achievement rates of 50% or higher at Week 24 are remarkable. Importantly, while only 25% of placebo-group patients reached this target at Week 24, more than 50% achieved HbA1c <7.0% by Week 38 after switching to active treatment. These findings suggest that timely intensification from dual therapy to triple therapy with the sitagliptin/empagliflozin FDC to facilitate more rapid glycaemic target attainment in patients with T2DM.

Beyond HbA1c, key secondary endpoints showed improvements. FPG declined in both active treatment groups at Weeks 12 and 24, with no meaningful change in the placebo group. Reductions in HOMA-IR and increases in QUICKI indicate amelioration of insulin resistance, a core pathophysiological defect in T2DM [1], with improvements maintained through 52 weeks. Consistent with improved insulin sensitivity, insulin

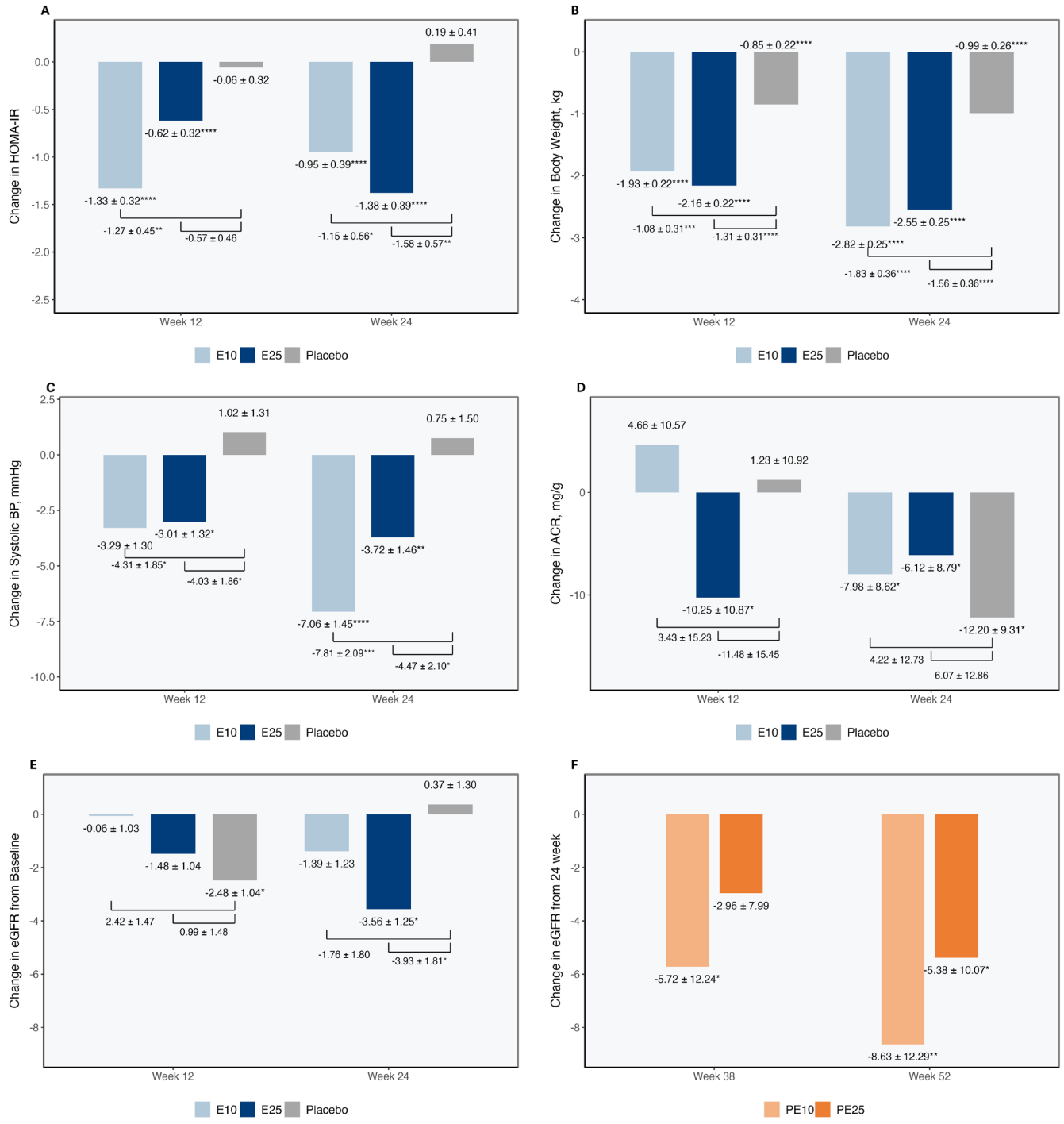

FIGURE 2 | Other glycaemic parameter and metabolic parameters. (A) Changes in HOMA-IR from baseline to Weeks 12 and 24; (B) Changes in body weight from baseline to Weeks 12 and 24. (C) Changes in SBP from baseline to Weeks 12 and 24. (D) Changes in ACR from baseline to Weeks 12 and 24. (E) Changes in eGFR from baseline to Weeks 12 and 24. (F) Changes in eGFR from Week 24 to Weeks 38 and 52. Changes from baseline are presented with least squares mean ± standard error. Within-group change was analysed by paired t-test or Wilcoxon signed rank test. Changes were compared between groups using mixed effect model for repeated measures. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$. All p values are reported as nominal. ACR, albumin-creatinine ratio; eGFR, estimated glomerular filtration rate; HOMA-IR, homeostasis model assessment of insulin resistance; SBP, systolic blood pressure.

levels also showed reductions in the active treatment groups and were maintained through 52 weeks. While changes in HOMA-β were modest during the initial 24 weeks, they became more apparent by Week 52, suggesting that β-cell functional recovery may require longer exposure to SGLT2 inhibition as glucotoxic stress is progressively relieved [20].

While all groups experienced weight reduction, the E10 and E25 groups showed greater decreases than the placebo group. This enhanced weight loss is primarily attributable to the SGLT2 inhibitor component, which induces caloric loss through increased urinary glucose excretion [5, 21]. Consistent with these findings, previous studies of SGLT2 and DPP-4 inhibitor combinations

TABLE 3 | Safety outcomes during the treatment period.

	E10 ($N=77$)	E25 ($N=76$)	Placebo ($N=77$)
TEAEs	13 (16.88) [17]	18 (23.68) [27]	19 (24.68) [29]
ADRs	6 (7.79) [6]	3 (3.95) [3]	6 (7.79) [6]
Dyspepsia	1 (1.30) [1]	1 (1.32) [1]	1 (1.30) [1]
Abdominal pain	1 (1.30) [1]	0 (0.00) [0]	0 (0.00) [0]
Diabetes mellitus inadequate control	0 (0.00) [0]	0 (0.00) [0]	4 (9.09) [4]
Vulvovaginal pruritus	0 (0.00) [0]	2 (2.63) [2]	1 (1.30) [1]
Vaginal infection	2 (2.60) [2]	0 (0.00) [0]	0 (0.00) [0]
Thirst	1 (1.30) [1]	0 (0.00) [0]	0 (0.00) [0]
Rash	1 (1.30) [1]	0 (0.00) [0]	0 (0.00) [0]
SAEs	1 (1.30) [1]	3 (3.95) [3]	4 (5.19) [4]
Lower limb fracture	0 (0.00) [0]	0 (0.00) [0]	1 (1.30) [1]
Radius fracture	0 (0.00) [0]	1 (1.32) [1]	0 (0.00) [0]
Aggravated concomitant disease	0 (0.00) [0]	1 (1.32) [1]	0 (0.00) [0]
Urinary tract infection	0 (0.00) [0]	0 (0.00) [0]	1 (1.30) [1]
Rotator cuff syndrome	1 (1.30) [1]	0 (0.00) [0]	0 (0.00) [0]
Malignant thymic neoplasm	0 (0.00) [0]	0 (0.00) [0]	1 (1.30) [1]
Cerebral infarction	0 (0.00) [0]	0 (0.00) [0]	1 (1.30) [1]
Endometrial hyperplasia	0 (0.00) [0]	1 (1.32) [1]	0 (0.00) [0]
Hypoglycaemia	0 (0.00) [0]	0 (0.00) [0]	0 (0.00) [0]

Note: Values are presented as number (%) [number of events]. Treatment-emergent adverse events were coded using the Medical Dictionary for Regulatory Activities version 27.0. There was no statistically significant difference between the three groups. All SAEs were not related to the investigational product.
Abbreviations: ADR, adverse drug reaction; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

have reported favourable or modest reductions in body weight [10, 11].

Furthermore, the FDC therapy demonstrated beneficial effects on blood pressure and lipid profiles during the treatment period. The significant reductions in SBP, increases in HDL-C, and reductions in the TG/HDL-C ratio in the FDC treatment groups contribute to a more favourable cardiometabolic risk profile [22].

A notable finding from the subgroup analysis was the consistent efficacy across demographic and clinical characteristics. In the pooled analysis, HbA1c reductions were significantly greater across all subgroups compared to the placebo group. Critically, efficacy was maintained even in elderly patients (aged ≥ 65 years), supporting the broad applicability of this FDC in the diverse T2DM population [20].

In this study, a modest decline in eGFR was observed in the E25 group compared with the placebo group during the treatment period. The magnitude of this decline was within the range of approximately −2 to −5 mL/min/1.73 m^2, which is consistent with the early hemodynamic changes commonly reported following initiation of SGLT2 inhibitors and has been attributed to restoration of tubuloglomerular feedback [23]. During the extension phase, eGFR values remained relatively stable in the groups that continued active treatment, whereas participants who switched from placebo to active treatment exhibited an initial decrease in eGFR after treatment initiation.

Regarding albuminuria, numerical reductions in ACR were observed within the active treatment groups during the treatment period, although overall differences versus placebo were not observed at Week 24. Among patients with baseline microalbuminuria, a reduction in ACR was observed in the E25 group at Week 12. However, this pattern was not consistently maintained at later time points. Similar temporal patterns in eGFR and albuminuria following SGLT2 inhibitor therapy have been reported in previous large clinical trials [24].

The overall safety profile of the FDCs was favourable and comparable to that of the placebo. The incidence of adverse events did not differ meaningfully between the groups, consistent with expectations for these drug classes [10, 11, 25]. Hypoglycaemic events were not observed during the study, a finding that aligns with the glucose-dependent mechanisms of action of these agents and is clinically relevant when considering treatment intensification. No serious adverse drug reactions were reported in any group. Overall, the observed tolerability profile was acceptable within the study population defined by the eligibility criteria [12, 25].

The combination of an SGLT2 inhibitor and a DPP-4 inhibitor in an FDC leverages their complementary mechanisms of action.

SGLT2 inhibitors provide insulin-independent glucose lowering, renal and cardiovascular benefits and modest weight loss [5]. DPP-4 inhibitors enhance endogenous incretin-mediated, glucose-dependent insulin secretion and glucagon suppression, with a neutral effect on weight and low hypoglycaemia risk [14]. This combination synergistically targets multiple pathophysiological defects of T2DM, addressing hyperglycaemia, improving insulin sensitivity and potentially preserving beta-cell function. The fixed-dose format simplifies the regimen, which may enhance adherence and support sustained therapeutic success [10, 12].

This study's strengths include its randomised, double-blind, placebo-controlled design and the 52-week follow-up, providing robust evidence for sustained efficacy and safety of the FDCs. However, re-randomisation of the placebo group after 24 weeks limited placebo-controlled comparisons beyond this point. In addition, extension period efficacy results should be interpreted with caution, as they are based on patients who completed the treatment period and entered the extension period, and therefore may be subject to selection bias. Finally, the exclusive inclusion of Korean patients may restrict the generalizability of the findings to other ethnic populations.

In summary, sitagliptin/empagliflozin FDCs (DW1026C1 and DW1026C2) represent an effective and well-tolerated triple therapy option for patients with inadequately controlled T2DM. In addition to durable glycemic control, these FDCs offer favourable metabolic effects, including weight reduction, SBP lowering and HDL-C improvement, as well as early renal benefits in patients with microalbuminuria. The simplified single-tablet regimen may enhance adherence while providing comprehensive cardiometabolic benefits for long-term diabetes management.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70669.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Study design. **Figure S2:** Study disposition. **Figure S3:** HbA1c goal achievement. (A) Achievement rate of target HbA1c $< 6.5\%$ at Weeks 12 and 24. (B) Achievement rate of target HbA1c $< 6.5\%$ at Weeks 38 and 52. (C) Achievement rate of target HbA1c $< 6.5\%$ or reduction $> 0.5\%$ at Weeks 12 and 24. (D) Achievement rate of target HA1c $< 7.0\%$ at Weeks 38 and 52. **Figure S4:** eGFR subgroup analysis based on baseline eGFR. (A) Changes in eGFR from baseline to Weeks 12 and 24 ($60 \leq$ baseline eGFR < 90). (B) Changes in eGFR from baseline to Weeks 12 and 24 (baseline eGFR ≥ 90). **Table S1:** Inclusion and exclusion criteria. **Table S2:** Methods for handling missing data. **Table S3:** HbA1c subgroup analysis based on sex, BMI, age, hypertension and dyslipidemia. **Table S4:** ACR subgroup analysis based on baseline ACR. **Table S5:** Changes from baseline to Week 52 in efficacy parameters.