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# Dual add-on therapy of gemigliptin and dapagliflozin in patients with type 2 diabetes inadequately controlled with metformin alone: The SOLUTION 2 study

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## Abstract

**Aim:** To evaluate the efficacy and safety of gemigliptin and dapagliflozin dual add-on therapy (GEMI + DAPA) to metformin in type 2 diabetes (T2D) patients who had inadequate glycaemic control on metformin alone, compared with a single add-on of either gemigliptin (GEMI) or dapagliflozin (DAPA) to metformin.

**Materials and Methods:** In this randomized, double-blind, double-dummy, active-controlled, parallel-group, phase 3 study, 469 T2D patients treated with a stable dose of metformin for 8 weeks or longer were randomized to receive GEMI + DAPA ($n = 157$) and either GEMI ($n = 156$) or DAPA ($n = 156$). The primary endpoint was change in HbA1c levels from baseline at week 24.

**Results:** Baseline characteristics including body mass index and T2D duration were similar among groups. At week 24, the least square mean changes in HbA1c from baseline were −1.34% with GEMI + DAPA, −0.90% with GEMI (difference between GEMI + DAPA vs. GEMI −0.44% [95% confidence interval {CI}: −0.58%

  

to −0.31%], $P < .01$) and −0.78% with DAPA (difference between GEMI + DAPA vs. DAPA −0.56% [95% CI: −0.69% to −0.42%], $P < .01$). Both upper CIs were less than 0, demonstrating the superiority of GEMI + DAPA for lowering HbA1c. The rates of responders achieving HbA1c less than 7% and less than 6.5% were greater with GEMI + DAPA (84.9%, 56.6%) than with GEMI (55.3%, 32.2%) and DAPA (49.3%, 15.3%). The incidence rate of adverse events was similar across groups, with low incidence rates of hypoglycaemia, urinary tract infection and genital infection.

**Conclusions:** These results suggest that the addition of GEMI + DAPA to metformin as triple combination therapy was effective, safe and well-tolerated, especially for T2D patients who experienced poor glycaemic control on metformin alone.

**KEYWORDS**
dapagliflozin, DPP-4 inhibitor, metformin, SGLT-2 inhibitor, type 2 diabetes

## 1 | INTRODUCTION

Type 2 diabetes (T2D) is characterized by a complex pathophysiology, involving multiple underlying defects leading to impaired glucose homeostasis and various complications. Over the past few decades, an increased understanding of T2D pathophysiology has led to the development of various antihyperglycaemic agents with different mechanisms, providing an opportunity to choose the appropriate medication for each T2D patient.[1,2] The recent guidelines[3,4] highlight the importance of early intensified management of T2D patients who do not meet their treatment goals. This approach positively influences disease progression management, decreases the risk of complications and extends the treatment failure time. Additionally, these guidelines emphasize a holistic approach, including not only glycaemic control, but also the management of cardiovascular risk and weight.[3,4]

Therefore, early intensification after the failure of metformin monotherapy, which is generally recommended as the first-line therapy, can be beneficial for achieving better glycaemic control and extending the duration of sustained glycaemic control in T2D patients.[3,4]

In the context of the comprehensive management emphasized by recent guidelines, intensified therapy using sodium-glucose co-transporter-2 (SGLT-2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors may be a useful treatment option. SGLT-2 inhibitors are widely used for their glucose-lowering properties, achieved by suppressing glucose reabsorption and increasing its excretion at the renal proximal tubule. Additionally, they offer known cardiovascular and renal benefits, while carrying a low risk of weight gain.[5,6] DPP-4 inhibitors are also widely used for their ability to reduce fasting and postprandial glucose levels, which is accomplished by inhibiting the degradation of incretin peptides (e.g. glucagon-like peptide-1), resulting in increased insulin secretion and reduced glucagon secretion. They offer the added advantages of minimal risk of hypoglycaemia and weight neutrality.[7–9] Considering the different mechanisms of action and benefits of the drugs, the dual combination of SGLT-2 and DPP-4 inhibitors with metformin is complementary and expected to result in an improved glucose-lowering effect, with low risks of hypoglycaemia and weight gain. In addition, the beneficial effect of SGLT-2 inhibitors[10–14] and the neutral effect of DPP-4 inhibitors[15,16] on cardiovascular or renal risk/progression, proven in large clinical trials, support their combination therapy.[3]

Gemigliptin is a potent DPP-4 inhibitor, and its efficacy and safety have been evaluated in clinical trials,[17–22] including a study that showed the additive glycaemic effect of gemigliptin in patients with T2D that was inadequately controlled with metformin and dapagliflozin.[23] In this study, the primary objective was to demonstrate the superiority of dual gemigliptin and dapagliflozin add-on compared with the single add-on of either gemigliptin or dapagliflozin in patients with inadequately controlled T2D receiving metformin alone. Additionally, we investigated whether the combination of gemigliptin and dapagliflozin exhibited similar benefits and characteristics as other drugs in the DPP-4 and SGLT-2 inhibitor classes.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design and population

This was a randomized, double-blind, double-dummy, active-controlled, parallel-group, phase 3 study. Major inclusion criteria included T2D patients aged 19 years or older, HbA1c of 7%-11%, and on stable metformin treatment (≥ 1000 mg/day) alone for 8 weeks or longer before screening. Major exclusion criteria included patients with an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m$^2$, New York Heart Association Class II-IV congestive heart failure, acute and unstable heart failure or arrhythmia requiring treatment, hepatic disease, body mass index (BMI) more than 40 kg/m$^2$ and uncontrolled hypertension. The detailed inclusion and exclusion criteria are presented in Table S1.

## 2.2 | Treatment and intervention

Eligible patients participated in the 2-week run-in period and received one tablet each of the placebo gemigliptin and dapagliflozin once daily in a single-blinded manner. After the run-in period, those patients who met the randomization criteria (on a stable dose of metformin ≥ 1000 mg/day and a run-in medication adherence rate ≥ 70% during the run-in period) were randomized to receive 50 mg of gemigliptin and 10 mg of dapagliflozin (GEMI + DAPA) and either 50 mg of gemigliptin (GEMI) or 10 mg of dapagliflozin (DAPA) in a 1:1:1 ratio. Stratified block randomization with two stratification factors (HbA1c [< 8.5% or ≥ 8.5%] and eGFR [< 90 or ≥ 90 mL/min/1.73m$^2$] at screening) was performed using an interactive web response system. After randomization, the patients received investigational products, which were assigned to each group once daily for 24 weeks. Along with the investigational products, a consistent dose of metformin was administered prior to screening as a background treatment without any dose adjustment. Visits were scheduled at screening, at the start of the single-blind run-in, at randomization, and at week 6, 12, 18 and 24. Efficacy and safety were evaluated at week 6, 12, 18 and 24. During the study, if the patients were inadequately controlled with the investigational drugs, the investigators were allowed to provide rescue therapy at their discretion. The SOLUTION 2 study (NCT04255238) was conducted in compliance with the International Council for Harmonization Good Clinical Practice and the Declaration of Helsinki and was approved by the Institutional Review Board (Seoul National University Hospital, H-2003-015-1106, etc.). All patients or their designees signed an informed consent form before participation.

## 2.3 | Study endpoints

The primary endpoint was the change in HbA1c level from baseline at week 24. Secondary endpoints included evaluations of changes in HbA1c, fasting plasma glucose (FPG), fasting lipid variables, eGFR, albuminuria (data not presented), body weight and waist circumference during the 24-week treatment period (hereafter, treatment period). Additionally, secondary endpoints encompassed the proportion of patients achieving HbA1c less than 7% (< 53.0/mol) or less than 6.5% at week 24, and the proportion of patients who received rescue therapy. Safety, including treatment-emergent adverse events (TEAEs), the incidence of hypoglycaemia, and vital signs, was assessed.

## 2.4 | Statistical analyses

In total, 468 patients (156 per group) were planned, allowing for a 15% dropout rate. The assumed effect size of the change in HbA1c at week 24 was −0.40%, calculated based on previous clinical studies of gemigliptin monotherapy[17] and DPP-4 inhibitors and SGLT-2 inhibitors in T2D patients,[24] with a common standard deviation of HbA1c change estimated at 1.0%. Given these assumptions, the planned sample size would yield greater than 80% power with a significance level of .025 to detect the superiority of the GEMI + DAPA group over the GEMI and DAPA groups. Demographic and efficacy analyses were performed using the full analysis set, which included all patients who received at least one dose of the study treatment and underwent assessment of their HbAc1 levels assessed at baseline and at least once thereafter, following the intent-to-treat principles. Patients who received the study treatment at least once were included in the safety analysis set, which was used for safety analyses.

A mixed-effects model was used to analyse the difference in HbA1c reduction between each group, with HbA1c change as a dependent variable; treatment group, baseline HbA1c, baseline eGFR, visit and interaction (between visit and treatment group) as fixed effects; and patient as a random effect. HbA1c changes from baseline (least square [LS] mean and standard error), two-sided 95% confidence interval [CI], and *P* value for the mean difference between treatment groups (GEMI + DAPA vs. GEMI, GEMI + DAPA vs. DAPA), were calculated. The superiority of the GEMI + DAPA-group compared with the GEMI and DAPA groups was proven if both upper limits of the 95% CIs were less than 0.

For the HbA1c responder rates, odds ratio, 95% CI and *P* value for the responder rate difference between groups were calculated using logistic regression with baseline HbA1c and baseline eGFR as covariates. All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC). Comparisons between groups were performed using a two-sample *t*-test or Wilcoxon rank-sum test, and comparisons among groups were performed using analysis of variance or the Kruskal–Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. The Shapiro–Wilk test was used to assess data normality.

# 3 | RESULTS

## 3.1 | Disposition and baseline characteristics

From June 2020 to March 2022, 469 patients who met the inclusion and exclusion criteria were randomized. Of the 469 randomized patients from 39 study sites in the Republic of Korea, 467 (155 [98.7%], 156 [100.0%] and 156 [100.0%] patients in the GEMI + DAPA, GEMI and DAPA groups, respectively) received the study treatment at least once. More than 90% of patients in each group completed the treatment period (Figure 1). Baseline characteristics were generally similar across the groups. Their mean age ranged from 57.9 to 58.5 years. The mean baseline HbA1c ranged from 7.80% to 7.87%, T2D duration ranged from 7.8 to 8.9 years and the background metformin dose ranged from 1280.8 to 1362.7 mg/day (Table 1).

## 3.2 | Efficacy endpoints

After the treatment period, the addition of GEMI + DAPA to metformin resulted in a significant reduction in HbA1c levels compared with

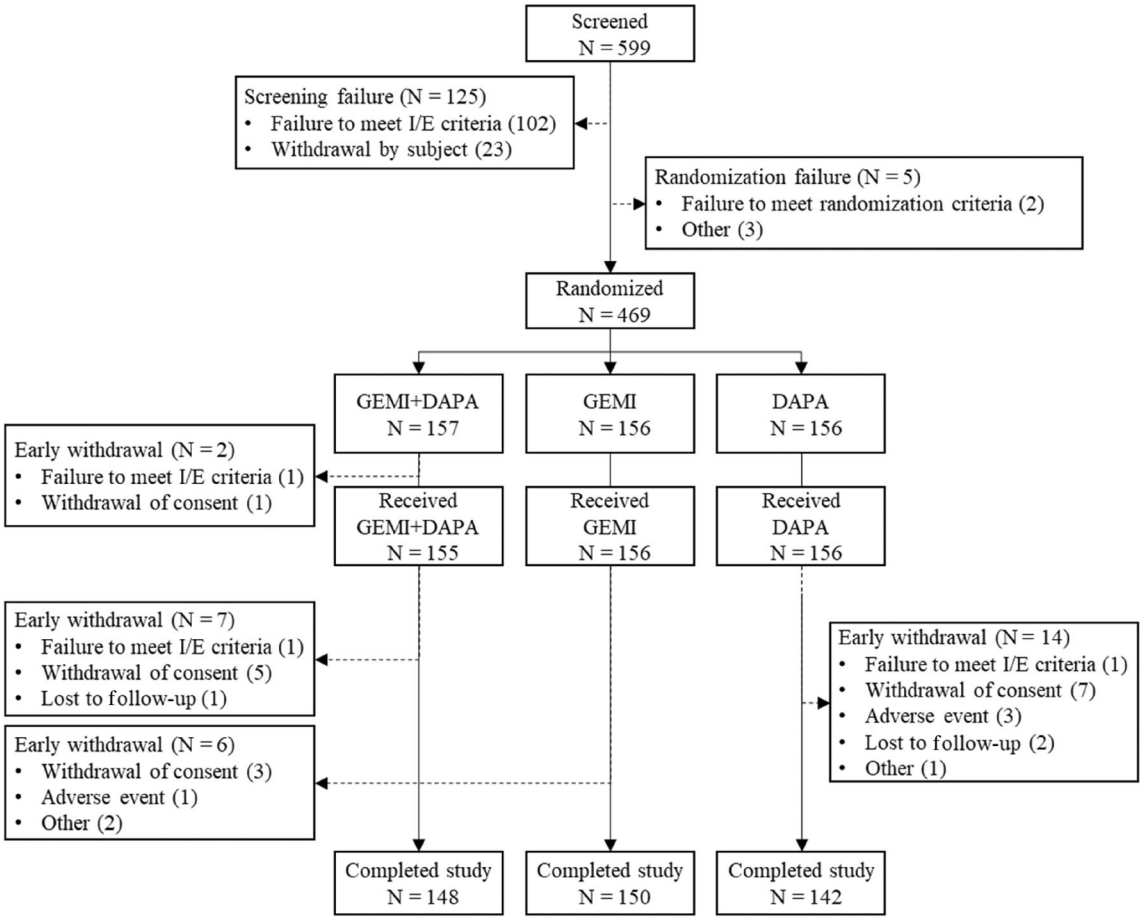


**FIGURE 1** Study disposition. DAPA, dapagliflozin; GEMI, gemigliptin; I/E, inclusion/exclusion.

**TABLE 1** Demographics and baseline characteristics – FAS.

| | GEMI + DAPA (*N* = 152) | GEMI (*N* = 152) | DAPA (*N* = 150) | *P* value[a] |
|---|---|---|---|---|
| Age (y)[b] | 57.9 ± 10.4 | 58.5 ± 10.9 | 58.1 ± 9.9 | Not significant |
| Male (%) | 83 (54.6) | 84 (55.3) | 83 (55.3) | |
| Weight (kg) | 69.3 ± 13.0 | 69.0 ± 11.2 | 69.0 ± 11.4 | |
| BMI (kg/m$^2$)[b] | 25.7 ± 3.6 | 25.7 ± 3.4 | 25.7 ± 3.7 | |
| HbA1c (%) | 7.80 ± 0.86 | 7.85 ± 0.85 | 7.87 ± 0.83 | |
| HbA1c (mmol/mol) | 61.8 ± 9.4 | 62.4 ± 9.3 | 62.6 ± 9.1 | |
| FPG (mg/dL) | 149.7 ± 34.6 | 150.8 ± 32.9 | 151.7 ± 33.1 | |
| Duration of T2D (y)[b] | 7.8 ± 5.7 | 8.8 ± 6.7 | 8.9 ± 6.4 | |
| eGFR (mL/min/1.73m$^2$) | 94.8 ± 19.6 | 94.6 ± 16.7 | 98.0 ± 23.8 | |
| Metformin dose (mg/day) | 1304.8 ± 359.1 | 1280.8 ± 409.8 | 1362.7 ± 392.6 | |

*Note*: Data are means ± SD or *n* (%).
Abbreviations: ANOVA, analysis of variance; BMI, body mass index; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; FAS, full analysis set; FPG, fasting plasma glucose; GEMI, gemigliptin; SD, standard deviation; T2D, type 2 diabetes.
[a]The *P* value for mean difference among groups was obtained from ANOVA or the Kruskal–Wallis test for continuous variables and the chi-square test or Fisher's exact test for categorical variables.
[b]Values from screening.

either GEMI or DAPA to metformin. The LS means for HbA1c change from baseline were −1.34% (−14.6 mmol/mol), −0.90% (−9.8 mmol/mol) and −0.78% (−8.6 mmol/mol) for the GEMI + DAPA, GEMI and DAPA groups, respectively, and HbA1c was significantly reduced at week 24 in all three treatment groups ($P < .01$). The 95% CI for between-group differences in HbA1c change was −0.58% to −0.31%

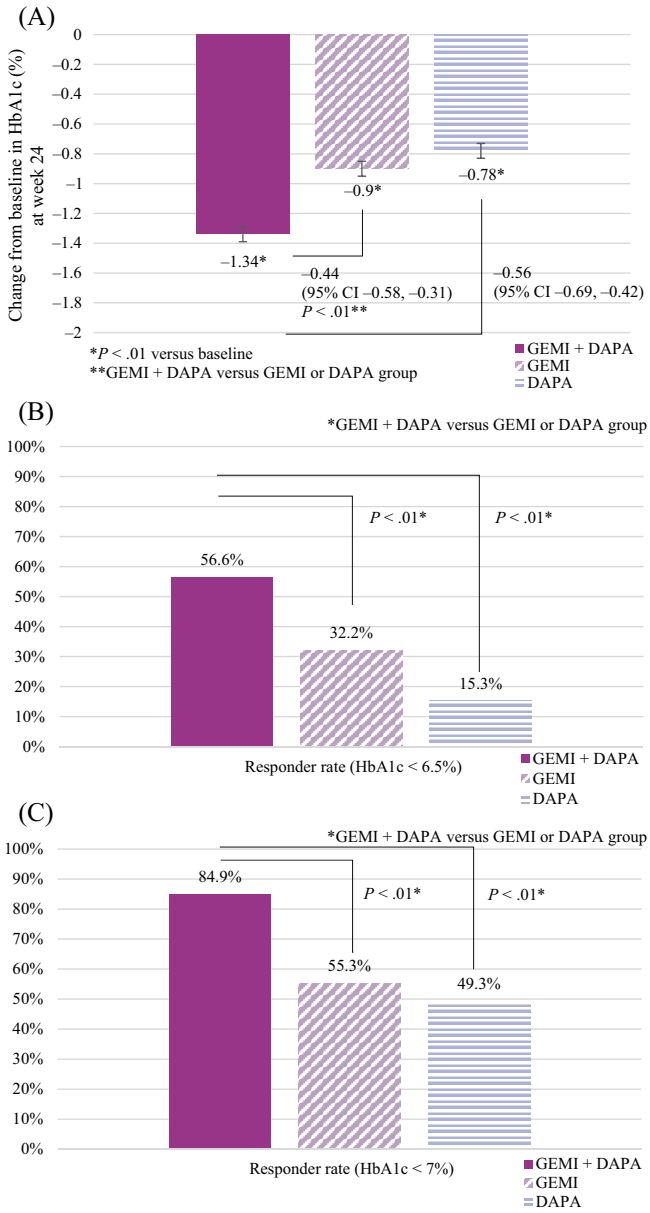


**FIGURE 2** A, LS mean (SE) of HbA1c change at week 24 B, Responder rate of patients who achieved HbA1c less than 6.5%, and C, Responder rate of patients who achieved HbA1c less than 7% at week 24 – FAS. CI, confidence interval; DAPA, dapagliflozin; FAS, full analysis set; GEMI, gemigliptin; LS, least square; SE, standard error.

(−6.3 to −3.4 mmol/mol) in GEMI + DAPA versus GEMI and −0.69% to −0.42% (−7.5 to −4.6 mmol/mol) in GEMI + DAPA versus DAPA. Both upper CIs were less than 0, showing the superiority of GEMI + DAPA as an add-on to metformin (Figure 2A, Table 2). The mixed-effects model suggested that all prespecified fixed effects, except for baseline eGFR, significantly affected the changes in the HbA1c level ($P < .01$).

In addition to the HbA1c change from baseline at week 24, the HbA1c and FPG changes during the treatment period also supported the superior glycaemic control observed in the GEMI + DAPA group. HbA1c and FPG levels in the GEMI + DAPA group were significantly reduced compared with those in the GEMI and DAPA groups at all evaluated time points up to week 24 ($P < .01$ for all time points) (Figure S1A,B).

Additionally, the percentage of patients who achieved HbA1c less than 6.5% after the 24-week treatment period was significantly greater in the GEMI + DAPA group than in the GEMI and DAPA groups (56.6%, 32.2% and 15.3% in the GEMI + DAPA, GEMI and DAPA groups, respectively; $P < .01$ for both comparisons) (Figure 2B). Similarly, 84.9% of patients on GEMI + DAPA achieved HbA1c less than 7.0% at week 24, and the percentages were significantly greater than those in patients on either GEMI (55.3%) or DAPA (49.3%) (both $P < .01$) (Figure 2C). During the treatment period, only a few patients received rescue therapy (two patients [1.32%] in the GEMI + DAPA group and one patient [0.66%] in the GEMI group). Regarding fasting lipid variables, a significant increase in high-density lipoprotein cholesterol and a decrease in triglycerides were observed in the GEMI + DAPA and DAPA groups; however, a significant increase in total cholesterol was observed in the DAPA group (Table 2).

Compared with that in patients treated with GEMI (LS mean of −0.2 kg), the change in body weight at week 24 was significant in patients treated with GEMI + DAPA (LS mean of −2.4 kg), similar to the weight loss in those treated with DAPA (LS mean of −2.6 kg). Similarly, patients in the GEMI + DAPA group, similar to those in the DAPA group, exhibited a notable reduction in waist circumference compared with those in the GEMI group (Table 2).

Mean baseline eGFR was 94.8, 94.6 and 98.0 mL/min/1.73m$^2$ in the GEMI + DAPA, GEMI and DAPA groups, respectively, and most of the patients exhibited normal kidney function at baseline. After the treatment period, mean eGFRs were 90 mL/min/1.73m$^2$ or higher in all groups, and no specific changes in renal function were identified in patients from any group (Table 2).

## 3.3 | Safety

The proportion of patients who experienced at least one TEAE during the treatment period was similar across groups. Most of the reported TEAEs were mild or moderate in intensity, and only a few patients experienced severe TEAEs. The proportion of patients who experienced at least one adverse drug reaction and serious adverse event was similar across the groups; no death was reported. Despite the significant decrease in HbA1c levels in the GEMI + DAPA group compared with those in either the GEMI or DAPA groups, the incidence of hypoglycaemia reported by patients was low and generally consistent across all treatment groups. Four (2.6%), three (1.9%) and one (0.6%) patients in the GEMI + DAPA, GEMI and DAPA groups, respectively, experienced hypoglycaemia. Most events were classified as level 1 (Table 3); all hypoglycaemic events recovered on the same day that occurred and none required additional treatment. No patients discontinued treatment because of a hypoglycaemic event.

Events in accordance with urinary tract infection (UTI) were reported in two patients each on GEMI (1.3%) and DAPA (1.3%), and

**TABLE 2** Efficacy endpoints – FAS.

| | GEMI + DAPA (*N* = 152) | GEMI (*N* = 152) | DAPA (*N* = 150) |
|---|---|---|---|
| HbA1c (%) | | | |
| Baseline | 7.80 ± 0.86 | 7.85 ± 0.85 | 7.87 ± 0.83 |
| Change from baseline at week 24[c] | −1.34 ± 0.05 | −0.90 ± 0.05 | −0.78 ± 0.05 |
| *P* value[a] | < .01 | < .01 | < .01 |
| Difference[c] | | −0.44 ± 0.07 | −0.56 ± 0.07 |
| 95% CI of difference | | (−0.58, −0.31) | (−0.69, −0.42) |
| *P* value[b] | | < .01 | < .01 |
| HbA1c (mmol/mol) | | | |
| Baseline | 61.8 ± 9.4 | 62.4 ± 9.3 | 62.6 ± 9.1 |
| Change from baseline at week 24[c] | −14.6 ± 0.5 | −9.8 ± 0.5 | −8.6 ± 0.5 |
| *P* value[a] | < .01 | < .01 | < .01 |
| Difference[c] | | −4.8 ± 0.7 | −6.1 ± 0.7 |
| 95% CI of difference | | (−6.3, −3.4) | (−7.5, −4.6) |
| *P* value[b] | | < .01 | < .01 |
| FPG (mg/dL) | | | |
| Baseline | 149.7 ± 34.6 | 150.8 ± 32.9 | 151.7 ± 33.1 |
| Change from baseline at week 24[c] | −39.1 ± 1.6 | −19.8 ± 1.6 | −28.4 ± 1.6 |
| *P* value[a] | < .01 | < .01 | < .01 |
| Difference[c] | | −19.4 ± 2.3 | −10.7 ± 2.3 |
| 95% CI of difference | | (−23.8, −14.9) | (−15.2, −6.3) |
| *P* value[a] | | < .01 | < .01 |
| TC (mg/dL) | | | |
| Baseline | 147.0 ± 30.2 | 151.1 ± 33.2 | 149.9 ± 32.5 |
| Change from baseline at week 24[c] | 1.6 ± 1.9 | 1.2 ± 2.0 | 6.3 ± 2.0 |
| *P* value[a] | NS | NS | < 0.01 |
| Difference[c] | | 0.4 ± 2.8 | −4.7 ± 2.8 |
| 95% CI of difference | | (−5.0, 5.8) | (−10.1, 0.8) |
| *P* value[b] | | NS | NS |
| LDL-C (mg/dL) | | | |
| Baseline | 81.2 ± 24.9 | 84.1 ± 29.8 | 83.2 ± 28.0 |
| Change from baseline at week 24[c] | −1.0 ± 1.7 | −1.5 ± 1.7 | 2.7 ± 1.7 |
| *P* value[a] | NS | NS | NS |
| Difference[c] | | 0.5 ± 2.4 | −3.8 ± 2.4 |
| 95% CI of difference | | (−4.2, 5.2) | (−8.5, 1.0) |
| *P* value[b] | | NS | NS |
| HDL-C (mg/dL) | | | |
| Baseline | 49.1 ± 13.3 | 49.3 ± 12.3 | 49.1 ± 11.7 |
| Change from baseline at week 24[c] | 2.5 ± 0.6 | −0.2 ± 0.6 | 3.6 ± 0.6 |
| *P* value[a] | < .01 | NS | < .01 |
| Difference[c] | | 2.7 ± 0.8 | −1.0 ± 0.8 |
| 95% CI of difference | | (1.0, 4.3) | (−2.7, 0.6) |
| *P* value[b] | | < .01 | NS |
| Triglycerides (mg/dL) | | | |
| Baseline | 144.9 ± 120.3 | 145.2 ± 70.3 | 143.0 ± 75.5 |
| Change from baseline at week 24[c] | −17.2 ± 9.6 | 17.1 ± 9.6 | −11.2 ± 9.6 |
| *P* value[a] | < .01 | NS | < .05 |

**TABLE 2** (Continued)

| | GEMI + DAPA (*N* = 152) | GEMI (*N* = 152) | DAPA (*N* = 150) |
|---|---|---|---|
| Difference[c] | | −34.3 ± 13.6 | −6.0 ± 13.6 |
| 95% CI of difference | | (−60.9, −7.6) | (−32.7, 20.7) |
| *P* value[c] | | < .05 | NS |
| Body weight (kg) | | | |
| Baseline | 69.3 ± 13.0 | 69.0 ± 11.2 | 69.0 ± 11.4 |
| Change from baseline at week 24[c] | −2.4 ± 0.2 | −0.2 ± 0.2 | −2.6 ± 0.2 |
| *P* value[a] | < .01 | NS | < .01 |
| Difference[c] | | −2.2 ± 0.2 | 0.2 ± 0.2 |
| 95% CI of difference | | (−2.7, −1.8) | (−0.3, 0.7) |
| *P* value[b] | | < .01 | NS |
| Waist circumference (cm) | | | |
| Baseline | 89.3 ± 9.7 | 88.6 ± 9.1 | 88.7 ± 9.4 |
| Change from baseline at week 24[c] | −2.1 ± 0.3 | −0.4 ± 0.3 | −2.3 ± 0.3 |
| *P* value[a] | < .01 | NS | < .01 |
| Difference[c] | | −1.7 ± 0.4 | 0.3 ± 0.4 |
| 95% CI of difference | | (−2.5, −1.0) | (−0.5, 1.1) |
| *P* value[b] | | < .01 | NS |
| eGFR (mL/min/1.73m$^2$) | | | |
| Baseline | 94.8 ± 19.6 | 94.6 ± 16.7 | 98.0 ± 23.8 |
| Change from baseline at week 24[c] | −2.8 ± 0.9 | −3.2 ± 0.9 | −2.8 ± 1.0 |
| *P* value[a] | < .01 | < .01 | < .01 |
| Difference[c] | | 0.3 ± 1.3 | −0.1 ± 1.3 |
| 95% CI of difference | | (−2.3, 2.9) | (−2.7, 2.6) |
| *P* value[b] | | NS | NS |

*Note*: Data are means ± SD or otherwise specified.

Abbreviations: CI, confidence interval; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; FAS, full analysis set; FPG, fasting plasma glucose; GEMI, gemigliptin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LS, least square; NS, not significant; SD, standard deviation; SE, standard error; TC, total cholesterol.

[a]The *P* value for the mean difference within groups obtained from a paired *t*-test or Wilcoxon signed rank test.

[b]The *P* value for the mean difference between groups was obtained from the mixed-effects model.

[c]LS means ± SE; difference: GEMI + DAPA − GEMI or DAPA.

none were reported in patients who received GEMI + DAPA (Table 3). Except for one patient in the DAPA group, all the other events were mild in intensity. One patient in the DAPA group reported severe acute pyelonephritis 22 days after the initiation of study treatment, and the investigator considered this event to be related to the study treatment. The patient recovered after appropriate treatment, but withdrew from the study. All UTI-related events were resolved during the treatment period.

The adverse events associated with genital infection were assessed, including not only reported cases explicitly categorized as genital infections, but also symptoms such as perineal pruritus suggestive of a potential genital infection. Events in accordance with genital infection were reported in three female patients on GEMI + DAPA (1.9%) and six female patients on DAPA alone (3.8%) (Table 3). In the DAPA group, a patient who reported mild vaginal infection recovered after treatment and continued the study without treatment interruption. All genital and vulvovaginal pruritus cases in the DAPA group resolved without further treatment. However, one patient in the DAPA group who reported vulvovaginal candidiasis and genital pruritus with moderate intensity discontinued the study treatment, despite recovery after treatment for vulvovaginal candidiasis. In the GEMI + DAPA group, all cases of genital infection, including genital pruritus and vulvovaginal pruritus, resolved during the treatment period, and no patients in the GEMI + DAPA group discontinued treatment because of genital infection. No patients reported volume depletion (Table 3).

Regarding blood pressure, both systolic blood pressure (SBP) and diastolic blood pressure (DBP) significantly decreased in patients on GEMI + DAPA (means of −4.7 and −2.1 mmHg, respectively) and in patients on DAPA alone (means of −4.4 and −2.9 mmHg, respectively) at week 24, whereas no change in SBP and DBP was observed in patients on GEMI alone (means of −1.6 and −1.4 mmHg, respectively).

**TABLE 3** Summary of treatment-emergent adverse events – SAF.

| | GEMI + DAPA (*N* = 155) | GEMI (*N* = 156) | DAPA (*N* = 156) |
|---|---|---|---|
| Patients with at least one AE | 38 (24.5) | 51 (32.7) | 43 (27.6) |
| Patients with at least one ADR | 10 (6.5) | 7 (4.5) | 20 (12.8) |
| Patients with at least one SAE | 4 (2.6) | 2 (1.3) | 2 (1.3) |
| Patients with at least one SADR | 0 | 0 | 1 (0.6) |
| Patients with at least one AE leading to discontinuation | 0 | 1 (0.6) | 3 (1.9) |
| Patients with at least one AE in accordance with UTI | 0 | 2 (1.3) | 2 (1.3) |
| Considered related by investigator | 0 | 1 (0.6) | 2 (1.3) |
| Cystitis | 0 | 2 (1.3) | 1 (0.6) |
| Pyelonephritis acute | 0 | 0 | 1 (0.6) |
| Patients with at least one AE in accordance with genital infection | 3 (1.9) | 0 | 6 (3.8) |
| Considered related by investigator | 3 (1.9) | 0 | 6 (3.8) |
| Vaginal infection | 0 | 0 | 1 (0.6) |
| Vulvovaginal candidiasis[a] | 0 | 0 | 1 (0.6) |
| Pruritus genital[a] | 2 (1.3) | 0 | 3 (1.9) |
| Vulvovaginal pruritus | 1 (0.6) | 0 | 2 (1.3) |
| Patients with at least one AE in accordance with volume depletion | 0 | 0 | 0 |
| Patients with at least one hypoglycaemia[b] | 4 (2.6) | 3 (1.9) | 1 (0.6) |
| Level 1 | 4 (2.6) | 3 (1.9) | 0 |
| Level 2 | 0 | 1 (0.6)[c] | 1 (0.6) |
| Level 3 | 0 | 0 | 0 |

*Note*: Data are *n* (%).

Abbreviations: ADR, adverse drug reaction; AE, adverse event; DAPA, dapagliflozin; GEMI, gemigliptin; SADR, serious adverse drug reaction; SAE, serious adverse event; SAF, safety analysis set; UTI, urinary tract infection.

[a]One patient in the DAPA group reported both vulvovaginal candidiasis and genital pruritus.

[b]Hypoglycaemia was classified into three levels with level 1 (plasma glucose level of ≤ 70 mg/dL), level 2 (plasma glucose level of < 54 mg/dL) and level 3 (events with severe cognitive impairment requiring external assistance for recovery).

[c]Level 2 hypoglycaemia was reported by the patient in the GEMI group who had previously reported level 1 hypoglycaemia. Both events recovered on the same day they occurred.

## 4 | DISCUSSION

T2D is a progressive condition,[25] necessitating timely treatment intensification to aid in the long-term management of T2D patients requiring intensified treatment.[3,4] This study suggests that a triple combination of the dual add-on of gemigliptin and dapagliflozin to metformin may be an effective treatment option because of its effectiveness and tolerance.

The primary objective of this study was to show the superior glycaemic control of GEMI + DAPA compared with that of either GEMI or DAPA in terms of HbA1c change from baseline at week 24. After the treatment period, the addition of GEMI + DAPA to metformin significantly reduced HbA1c levels compared with either GEMI or DAPA to metformin. Additionally, the probability of having patients who achieved HbA1c less than 7.0% and less than 6.5% was significantly greater in the GEMI + DAPA group than in the GEMI and DAPA groups. A significant FPG reduction was observed in patients treated with GEMI + DAPA compared with those treated with either GEMI or DAPA during the treatment period.

The use of SGLT-2 inhibitors promotes glucosuria, thus reducing glucose toxicity and body weight, and enhancing natriuresis, thereby lowering blood pressure.[3,26] At week 24, a significant reduction in weight and waist circumference was observed in both the GEMI + DAPA and DAPA groups, which included dapagliflozin in combination. This suggests that the weight-reducing effect of dapagliflozin persists even when combined with gemigliptin, which is known to be weight-neutral.[3] Additionally, the reduction in blood pressure observed with dapagliflozin was maintained when combined with gemigliptin, which was associated with nearly neutral changes in blood pressure.[26] Both SBP and DBP were significantly reduced in patients treated with GEMI + DAPA or DAPA.

These results are generally consistent with those of other clinical trials on the triple combination of DPP-4 and SGLT-2 inhibitors as a dual add-on to metformin.[24,27] The HbA1c reduction at week 24 in empagliflozin (10 and 25 mg) and linagliptin as an add-on to metformin was −1.08% and −1.19% (baseline HbA1c: 7.95% and 7.90%), respectively.[24] The adjusted mean HbA1c reduction from baseline at week 24 was −1.47% when 5 mg of saxagliptin and 10 mg of

dapagliflozin were added to metformin in T2D patients with a mean baseline HbA1c of 8.93%.[27] In addition, a similar trend of decrease in body weight and blood pressure was observed with the dual add-on of DPP-4 and SGLT-2 inhibitors and the single add-on of a SGLT-2 inhibitor.[24,27]

The incidence rates of events associated with UTI and genital infections were low in all groups. The use of SGLT-2 inhibitors is associated with an increased risk of genital infection or UTI compared with other classes of antidiabetic medications.[3,4] Incidences of UTI and genital infection are commonly reported with the use of dapagliflozin and are listed in the warnings and precautions of the dapagliflozin label.[28] According to clinical trials, this risk of genital infection is more frequently reported in women than in men and is generally not severe.[26] Additionally, studies have suggested that an increase in glucosuria caused by SGLT-2 inhibitors is associated with an increased risk of genital infections, and to a lesser degree, UTIs.[29] In this study, the incidence rate of UTI and genital infection was low in the triple combination group where GEMI + DAPA was added to metformin, consistent with the results of a trial on the triple combination of saxagliptin and dapagliflozin as a dual add-on to metformin.[27]

Intensified treatment offers the potential for more rapid attainment of glycaemic goals and longer-lasting glycaemic control. However, the increased risk of hypoglycaemia can pose a significant barrier to its adoption.[3,4] Hypoglycaemia is one of the factors that affects treatment burden, leading to a negative impact on adherence to therapy.[30] DPP-4 and SGLT-2 inhibitors are antidiabetic medications with a low risk of hypoglycaemia.[3,4] In a previous study on the triple combination of gemigliptin, dapagliflozin and metformin, gemigliptin was added to dapagliflozin and metformin for T2D patients, and a significant glycaemic reduction was achieved with a low incidence rate of hypoglycaemia (0.6%).[23] Similarly, triple therapy with GEMI + DAPA added to metformin resulted in a significant number of patients achieving a target HbA1c level (< 6.5% or < 7%) with a lower risk of mild hypoglycaemia.

These results suggest that triple combination therapy with GEMI + DAPA can be an effective intensified treatment option with favourable safety and tolerability profiles. However, it is important to weigh the potential benefits of triple combination therapy in terms of cost and risk. Clinicians may decide whether or when to start triple combination therapy on a case-by-case basis, considering the patient's individual needs, preferences and response to treatment, as well as financial considerations and the presence of national/regional reimbursement policies.

This study had a few limitations. Although this study showed a potent glycaemic effect over a short period, long-term glycaemic durability could not be assessed because of the short follow-up period. Further studies are warranted to investigate the glycaemic durability of triple combination therapy as an early and intensified treatment. Additionally, this study excluded patients with an eGFR of less than 60 mL/min/1.73m$^2$, following the label recommendations in 2019. This exclusion criterion may limit the generalizability of the findings to patients with impaired renal function. However, it is worth mentioning that patients who had an eGFR of less than 60 mL/min/1.73m$^2$ during the treatment period continued to receive the study treatment. Additionally, triple combination is prescribed to patients with an eGFR of 45 mL/min/1.73m$^2$ or higher in a real-life setting, and its clinical outcomes will be updated accordingly. Despite these limitations, this was the first study to use a randomized, double-blind and active-controlled design with a large sample size to evaluate and compare the efficacy and safety of the dual add-on of GEMI + DAPA as an early intensified treatment with a single add-on of either GEMI or DAPA in patients with poor glycaemic control treated with metformin alone.

Taken together, in T2D patients who had inadequate glycaemic control when on metformin alone (≥ 1000 mg/day), the intensified treatment—addition of GEMI + DAPA to metformin—provided robust glycaemic control with no noticeable safety issues. Therefore, the GEMI + DAPA add-on to metformin may offer a safe and superior glycaemic-lowering efficacy in those patients who experience inadequate control with metformin alone as an early initiation of combination therapy.

## AUTHOR CONTRIBUTIONS

Conception and design/acquisition of data: KAH and KSP. Analysis: KAH, JK and KSP. Interpretation of data: KAH, Y-CH, SJM, HCC, HJY, SHC, SC, K-AK, TNK, JGK, C-YP, JCW, EC and KSP.

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## CONFLICT OF INTEREST STATEMENT

JK and EC are employees of LG Chem, Ltd. All other authors declare no conflicts of interest.

## PEER REVIEW

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## DATA AVAILABILITY STATEMENT

Research data are not shared.

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## REFERENCES


1. Ahmad E, Lim S, Lamptey R, Webb DR, Davies MJ. Type 2 diabetes. *Lancet*. 2022;400:1803-1820. doi:10.1016/S0140-6736(22)01655-5
2. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *Lancet*. 2014;383(9922):1068-1083. doi:10.1016/S0140-6736(13)62154-6
3. American Diabetes Association. Standards of Care in Diabetes—2023. *Diabetes Care*. 2023;46(Supplement_1):S140-S157.
4. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2022;45(11):2753-2786. doi:10.2337/dci22-0034
5. Shah NK, Deeb WE, Choksi R, Epstein BJ. Dapagliflozin: a novel sodium-glucose cotransporter type 2 inhibitor for the treatment of type 2 diabetes mellitus. *Pharmacotherapy*. 2012;32(1):80-94. doi:10.1002/PHAR.1010
6. Bailey CJ, Gross JL, Pieters A, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double blind, placebo controlled trial. *Lancet*. 2010;375(9733):2223-2233.
7. Holst JJ, Deacon CF. Glucagon-like peptide 1 and inhibitors of dipeptidyl peptidase IV in the treatment of type 2 diabetes mellitus. *Curr Opin Pharmacol*. 2004;4(6):589-596. doi:10.1016/j.coph.2004.08.005
8. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch C. Emerging role of dipeptidyl peptidase-4 inhibitors in the management of type 2 diabetes. *Vasc Health Risk Manag*. 2008;4(4):753-768. doi:10.2147/vhrm.s1707
9. Vella A. Mechanism of action of DPP-4 inhibitors—new insights. *J Clin Endocrinol Metab*. 2012;97(8):2626-2628. doi:10.1210/jc.2012-2396
10. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128. doi:10.1056/NEJMoa1504720
11. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657. doi:10.1056/NEJMoa1611925
12. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357. doi:10.1056/NEJMoa1812389
13. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-1446. doi:10.1056/NEJMoa2024816
14. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995-2008. doi:10.1056/NEJMoa1911303
15. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;373(3):232-242. doi:10.1056/NEJMoa1501352 Erratum in: N Engl J Med 2015 Aug 6;373(6):586.
16. Rosenstock J, Perkovic V, Johansen OE, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *JAMA*. 2019;321(1):69-79. doi:10.1001/jama.2018.18269
17. Yang SJ, Min KW, Gupta SK, et al. A multicentre, multinational, randomized, placebo-controlled, double-blind, phase 3 trial to evaluate the efficacy and safety of gemigliptin (LC15-0444) in patients with type 2 diabetes. *Diabetes Obes Metab*. 2013;15(5):410-416.
18. Rhee EJ, Lee WY, Min KW, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor gemigliptin compared with sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Obes Metab*. 2013;15(6):523-530.
19. Lim S, Han KA, Yu J, et al. Efficacy and safety of initial combination therapy with gemigliptin and metformin compared with monotherapy with either drug in patients with type 2 diabetes: a double-blind randomized controlled trial (INICOM study). *Diabetes Obes Metab*. 2017;19(1):87-97.
20. Ahn CH, Han KA, Yu JM, et al. Efficacy and safety of gemigliptin, a dipeptidyl peptidase-4 inhibitor, in patients with type 2 diabetes mellitus inadequately controlled with combination treatment of metformin and sulphonylurea: a 24-week, multicentre, randomized, double-blind, placebo-controlled study (TROICA study). *Diabetes Obes Metab*. 2017;19(5):635-643.
21. Yoon SA, Han BG, Kim SG, et al. Efficacy, safety and albuminuria-reducing effect of gemigliptin in Korean type 2 diabetes patients with moderate to severe renal impairment: a 12-week, double-blind randomized study (the GUARD study). *Diabetes Obes Metab*. 2017;19(4):590-598.
22. Cho YM, Deerochanawong C, Seekaew S, et al. Efficacy and safety of gemigliptin as add-on therapy to insulin, with or without metformin, in patients with type 2 diabetes mellitus (ZEUS II study). *Diabetes Obes Metab*. 2020;22(1):123-127.
23. Lee BW, Min KW, Hong E, et al. Efficacy of gemigliptin add-on to dapagliflozin and metformin in type 2 diabetes patients: a randomized, double-blind, placebo-controlled study (SOLUTION). *Endocrinol Metab*. 2023;38(3):328-337.
24. DeFronzo RA, Lewin A, Patel S, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. *Diabetes Care*. 2015;38(3):384-393.
25. Bailey CJ, Day C. Treatment of type 2 diabetes: future approaches. *Br Med Bull*. 2018;126(1):123-137. doi:10.1093/brimed/ldy013
26. Scheen AJ. Cardiovascular effects of new oral glucose-lowering agents: DPP-4 and SGLT-2 inhibitors. *Circ Res*. 2018;122(10):1439-1459. doi:10.1161/CIRCRESAHA.117.311588
27. Rosenstock J, Hansen L, Zee P, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. *Diabetes Care*. 2015;38(3):376-383.
28. AstraZeneca Pharmaceutical. *Farxiga [Internet]*. Silver Spring; 2023.
29. Geerlings S, Fonseca V, Castro-Diaz D, List J, Parikh S. Genital and urinary tract infections in diabetes: impact of pharmacologically-induced glucosuria. *Diabetes Res Clin Pract*. 2014;103(3):373-381. doi:10.1016/j.diabres.2013.12.052
30. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence*. 2016;10:1299-1307. doi:10.2147/PPA.S106821


## SUPPORTING INFORMATION

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

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