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ARTICLE

Pharmacokinetic and pharmacodynamic drug–drug interactions between evogliptin and empagliflozin or dapagliflozin in healthy male volunteers

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Abstract

Evogliptin (EV) is a novel dipeptidyl peptidase-4 inhibitor (DPP4i) for glycemic control in patients with type 2 diabetes mellitus (T2DM). This study evaluated the pharmacokinetic (PK) and pharmacodynamic (PD) interactions between EV and sodium glucose cotransporter-2 inhibitors (SGLT2i) in healthy volunteers since combination therapy of DPP4i and SGLT2i has been considered as an effective option for T2DM treatment. A randomized, open-label, multiple-dose, two-arm, three-period, three treatments, two-sequence crossover study was conducted in healthy Korean volunteers. In arm 1, subjects were administered 5 mg of EV once daily for 7 days, 25 mg of empagliflozin (EP) once daily for 5 days, and the combination once daily for 5 days (EV + EP). In arm 2, subjects were administered 5 mg of EV once daily for 7 days, 10 mg of dapagliflozin (DP) once daily for 5 days, and the combination once daily for 5 days (EV + DP). Serial blood samples were collected for PK analysis, and oral glucose tolerance tests were conducted for PD analysis. In each arm, a total of 18 subjects completed the study. All adverse events (AEs) were mild with no serious AEs. The geometric mean ratio and confidence interval of the main PK parameters (maximum concentration of the drug in plasma at steady state and area under the plasma drug concentration-time curve within a dosing interval at a steady state) between EV and either EP or DP alone were not significantly altered by co-administration. Administration of EV + EP or EV + DP did not result in significant PD changes, as determined by the glucose-lowering effect. Administration of EV + EP or EV + DP had no significant effects on the PK profiles of each drug. All treatments were well-tolerated.

Dasohm Kim and Minkyu Choi contributed equally to this work.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Evogliptin (EV) is a novel and potent, selective DPP-4 inhibitor (DPP4i), approved in Korea for use in type 2 diabetes mellitus (T2DM) with comparable efficacy and safety as sitagliptin and linagliptin. Several SGLT-2 inhibitors (SGLT2is) have been recommended for second- or third-line treatment of T2DM. DPP4i and SGLT2i given together have shown adequate efficacy without safety concern, resulting in an increased use of the combination therapy.

WHAT QUESTION DID THIS STUDY ADDRESS?

EV has not been tested for interaction with SGLT2i. We evaluated the pharmacokinetic (PK) and pharmacodynamic profiles of EV and commonly used SGLT2i, empagliflozin (EP) and dapagliflozin (DP), when given alone and in combination in healthy adult volunteers.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Co-administration of EV with either EP or DP had no significant effect on the PKs of each drug. In healthy adult volunteers in our study, glucose lowering effect of EV was not significantly altered when combined with SGLT2i. Additionally, EV and EP or DP when administered alone or in combination were well-tolerated.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study serves as evidence for safety and stable PK profiles of co-administration of EV and EP or DP.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder caused by a progressive insulin secretory defect resulting from insulin resistance. T2DM treatments aim to improve glycemic control, correct metabolic abnormalities, and reduce risk factors for potential complications.[1]

Currently available antidiabetic therapies include metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 inhibitors (DPP4is), glucagon-like peptide-1 agonists, and insulin.[2] Because T2DM progresses over time, novel treatment options or combination therapies are needed to maintain adequate glycemic control.[3] Although the combination therapy of metformin and sodium glucose cotransporter-2 inhibitor (SGLT2i) has been widely used for the treatment of type 2 diabetes, the combination therapy of DPP4i and SGLT2i is also considered as an effective treatment option.[4–6]

Evogliptin (EV; DA-1229) is a novel, potent, and selective DPP4i developed by Dong-A ST Co., Ltd. EV (5 mg) administration in addition to metformin monotherapy effectively improved blood glucose control.[7,8] Additionally, EV was noninferior to sitagliptin and well-tolerated in patients with T2DM whose blood glucose was insufficiently controlled by metformin.[7,8]

Inhibition of SGLT2 is a new approach for treating diabetes, which inhibits the reabsorption of glucose in the renal tubule and excretes glucose into the urine, leading to glucosuria.[9,10] SGLT2is are not dependent on insulin levels and reduce plasma glucose levels without causing hypoglycemia. Additionally, they may lead to weight loss and blood pressure reduction.[11] Dapagliflozin (DP) and empagliflozin (EP) are SGLT2is currently available for the treatment of T2DM.

SGLT2i and DDP4i are currently recommended for use in addition to other oral antidiabetic drugs for second- or third-line treatment. Combination therapy with SGLT2i and DPP4i may provide adequate efficacy without increasing adverse events (AEs).[12]

Even though combination therapy of EV and DP or EP is considered an effective treatment option, there has not been formal studies to clarify pharmacokinetic/pharmacodynamic (PK/PD) interactions between these drugs so far. This study aimed to investigate the PK and PD interactions between EV and EP or DP following multiple-dose administration in healthy Korean male participants.

METHODS

Study participants

Healthy Korean male volunteers aged 19–55 years were eligible to participate in this study. All volunteers

weighed greater than 55 kg, and their body mass index ranged from 18.5–25.0 kg/m^2 at the time of screening. The health of all participants was screened and assessed by the investigators based on their medical history, physical examinations, vital signs, 12-lead electrocardiography (ECG), and laboratory tests, including hematology, serum chemistry, serology tests, and urinalysis. Participants who met any of the following criteria were excluded from the study: clinically significant hypersensitivity or a history of hypersensitivity to any of the investigational products (IPs) used in this study and other drugs, such as aspirin and antibiotics; a history of or currently having a clinically significant disease or gastrointestinal disorder; and a history of genetic disorders, such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

Study design

This study was a randomized, open-label, multiple-dose, two-arm, crossover clinical trial. Each arm was conducted in a crossover manner with three treatments and two sequence groups at the Clinical Trials Center of Severance Hospital, Yonsei University College of Medicine, between November 2018 and January 2019. This study was conducted in accordance with the Declaration of Helsinki and Korean Good Clinical Practice. The protocol was approved by the Institutional Review Board of Severance Hospital (Seoul, South Korea, IRB number: 4-2018-0654) and the Ministry of Food and Drug Safety. This study was registered at clinicaltrials.gov (Identifier number: NCT03766724). Written informed consent was obtained from all participants before screening and enrollment in the study. All IPs used in this study were administered at standard doses for clinical use. All participants received IPs with 150 mL of water after at least 10 h of fasting.

Arm 1: Empagliflozin study

In arm 1 of the trial, 20 participants were randomly assigned to one of the two sequence groups. The three treatments used were 5 mg of EV (Suganon; Dong-A ST Co., Ltd.) by mouth (p.o.) once daily for 7 days, 25 mg of EP (Jardiance; Boehringer Ingelheim) p.o. once daily for 5 days, and 5 mg of EV with 25 mg of EP p.o. once daily for 5 days (EV + EP). In sequence group A, the order of treatments was EV, EV + EP, and EP. The order of treatments in sequence group B was EP, EV, and EV + EP (Table 1).

TABLE 1 Study design.

Sequence A	Period 1	Period 2	Washout	Period 3
	EV	EV + EP	12 days	EP
Sequence B	Period 1	Washout	Period 2	Period 3
	EP	12 days	EV	EV + EP
Sequence C	Period 1	Period 2	Washout	Period 3
	EV	EV + DP	12 days	DP
Sequence D	Period 1	Washout	Period 2	Period 3
	DP	12 days	EV	EV + DP

Abbreviations: DP, dapagliflozin (10 mg) once daily for 5 days; EP, empagliflozin (25 mg) once daily for 5 days; EV, evogliptin (5 mg) once daily for 7 days; EV + DP, co-administration of evogliptin (5 mg) and dapagliflozin (10 mg) once daily for 5 days; EV + EP, co-administration of evogliptin (5 mg) and empagliflozin (25 mg) once daily for 5 days.

Arm 2: Dapagliflozin study

In arm 2 of the trial, 20 participants were randomly assigned to one of the two sequence groups. The three treatments used were 5 mg of EV p.o. once daily for 7 days, 10 mg of DP (Forxiga; AstraZeneca) p.o. once daily for 5 days, and 5 mg of EV with 10 mg of DP p.o. once daily for 5 days (EV + DP). In sequence group C, the order of treatments was EV, EV + DP, and DP. The order of treatments in sequence group D was DP, EV, and EV + DP (Table 1).

Pharmacokinetic assessment

Serial blood samples were collected for the PK evaluation. To evaluate EV in both arms, blood samples were obtained predose on days 5, 6, and 7, and 1, 2, 3, 4, 5, 6, 8, 12, and 24 h postdose on day 7. To evaluate EP and EV + EP in arm 1, blood samples were obtained predose on days 3, 4, and 5, and 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 h postdose on day 5. To evaluate DP and EV + DP in arm 2, blood samples were obtained predose on days 3, 4, and 5, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 h postdose on day 5.

The PK primary end points in arm 1 were the maximum concentration of the drug in plasma at steady-state ($C_{max,ss}$) and the area under the plasma drug concentration-time curve within a dosing interval at a steady-state ($AUC_{\tau,ss}$) of EV and EP. The PK primary end points in arm 2 were the $C_{max,ss}$ and $AUC_{\tau,ss}$ of EV and DP.

The secondary end points were time to $C_{max,ss}$, minimum concentration of drug in plasma at a steady-state, apparent clearance at a steady-state of EV, EP (arm 1), and DP (arm 2), and the $C_{max,ss}$, $AUC_{\tau,ss}$, and metabolite ratio of EV metabolites (M7 and M8).

To quantify the plasma concentration of EV in the EV group, ~8 mL of blood were drawn into an EDTA-K2-coated blood-drawing tube. For quantification of EP or DP plasma concentration in the EP and DP group, ~5 mL of blood were drawn into an EDTA-K2-coated blood-drawing tube. To quantify plasma concentrations of EV and EP or DP in the EV + EP and EV + DP groups, ~9 mL of blood were drawn into an EDTA-K2-coated blood-drawing tube. The samples were centrifuged at 1800 *g* and 4°C for 10 min within 30 min of sampling. Plasma aliquots were stored at −70°C or lower until analysis.

Plasma concentrations of EV, EP, and DP were determined separately using a validated liquid-chromatography tandem mass spectrometry assay. The lower limit of quantification of each IP in plasma was 0.1 ng/mL with linearity to 60 ng/mL (EV), 2 ng/mL with linearity to 1500 ng/mL (EP), and 0.5 ng/mL with linearity to 500 ng/mL (DP).

Pharmacodynamic assessment

For PD analysis, an oral glucose tolerance test (OGTT) was conducted the day before the first dosing of period 1 to evaluate baseline values. An OGTT was also conducted 2 h after drug administration on day 6 (EV) and day 4 (EP, DP, EV + EP, and EV + DP). To analyze serum glucose and plasma insulin levels, serial blood samples were collected predose and 0.25, 0.5, 1, 1.5, 2, and 3 h after glucose administration.

For PD evaluation, urine samples were collected after treatment. For the analysis of urine glucose levels, urine samples were collected over a 24-h period on day 5 in the EV, EP, DP, EV + EP, and EV + DP groups. The PD parameters were the area under the time-effect curve at a steady-state of serum glucose ($AUEC_{glu}$), the change in AUEC of blood glucose from baseline ($\Delta AUEC_{glu}$), area under the time-effect curve at a steady-state of plasma insulin ($AUEC_{ins}$), the change in AUEC of blood insulin from baseline ($\Delta AUEC_{ins}$), and urinary glucose excretion (UGE) over 24 h. The $\Delta AUEC_{glu}$ and $\Delta AUEC_{ins}$ were calculated by subtracting the baseline glucose and insulin levels at each timepoint from the corresponding timepoints of glucose and insulin levels.

Safety analysis

All AEs were monitored throughout the study period. Safety evaluations included physical examination, vital signs, 12-lead ECGs, and laboratory tests, including hematology, serum chemistry, and urinalysis. All AEs were recorded using MedDRA (version 22.0).

Statistical analysis

Continuous demographic data were analyzed to compare the two sequence groups using an independent *t*-test.

PK and PD data were analyzed to compare the treatment groups in each arm. Primary PK parameters were evaluated using a noncompartmental method. To evaluate the PK interaction between EV and EP or DP, the PK parameters were log-transformed and analyzed by point estimates and 90% confidence intervals (CIs) to generate geometric mean ratios (GMRs) using a mixed-effects model. Each model included the participant and formulation effects. The PD parameters were analyzed using a paired *t*-test to evaluate the glucose-lowering effect of EV and SGLT2i when compared to the baseline.

All statistical analyses were performed using SAS statistical software version 9.3 (SAS Institute) and Phoenix WinNonlin (version 8.0; Certara). Statistical significance was set at $p < 0.05$.

RESULTS

Study participants

In both arms 1 and 2 of the study, a total of 20 participants were enrolled, and 10 were randomly assigned to each sequence group. Two participants (one from each arm) withdrew before IP administration. Two participants (one from each arm) were withdrawn during the study and were not included in the PK and PD analysis set but were included in the demographics and safety analysis set.

Demographic data of the study participants are shown in Table S1. All study participants were men. There were no significant differences in demographics between the two sequence groups in each arm of the study, except for age (p value < 0.001) in arm 1.

Pharmacokinetics

Arm 1 of the study

The PK parameters of EV and EP in each treatment group are summarized in Table 2. The mean plasma concentrations of EV and EP over time after multiple administrations are shown in Figure 1. The $C_{max,ss}$ and $AUC_{\tau,ss}$ values of EV were similar between the EV + EP and EV groups. The point estimate (90% CI) of the GMR (EV + EP/EV) of the $C_{max,ss}$ and $AUC_{\tau,ss}$ were 1.01 (0.89–1.15) and 1.00 (0.88–1.14), respectively.

Additionally, the $C_{max,ss}$ and $AUC_{\tau,ss}$ values of EP were similar for the EV + EP and EP groups. The point

TABLE 2 PK parameters and comparison of evogliptin and empagliflozin (arm 1).

Evogliptin	EV + EP[a] (*N* = 18)	EV[a] (*N* = 18)	GMR (90% CI) EV + EP/EV
$C_{max,ss}$ (ng/mL)	6.09 ± 1.65	5.93 ± 1.16	1.01 (0.89–1.15)
$AUC_{\tau,ss}$ (h ng/mL)	94.80 ± 21.93	94.16 ± 20.34	1.00 (0.88–1.14)
$T_{max,ss}$ (h)	1.50 (0.33, 8.00)	4.00 (1.00, 5.00)	
$t_{1/2}$ (h)	22.22 ± 4.08	22.29 ± 6.31	
CL_{ss}/F (L/h)	55.67 ± 13.96	55.51 ± 12.82	
Vd_{ss}/F (L)	1782.06 ± 505.39	1739.60 ± 409.58	
Empagliflozin	**EV + EP[a] (*N* = 18)**	**EP[a] (*N* = 18)**	**GMR (90% CI) EV + EP/EP**
$C_{max,ss}$ (ng/mL)	473.45 ± 116.51	475.45 ± 115.85	0.99 (0.88–1.12)
$AUC_{\tau,ss}$ (h ng/mL)	3036.54 ± 655.56	2912.09 ± 598.97	1.04 (1.00–1.08)
$T_{max,ss}$ (h)	1.50 (0.67, 4.00)	1.50 (0.67, 4.00)	
$t_{1/2}$ (h)	6.68 ± 0.81	7.12 ± 0.69	
CL_{ss}/F (L/h)	8.64 ± 2.04	8.99 ± 2.13	
Vd_{ss}/F (L)	86.08 ± 18.42	91.55 ± 18.81	

Abbreviations: $AUC_{\tau,ss}$, area under the plasma drug concentration-time curve within a dosing interval (τ) at steady-state; CI, confidential interval; CL_{ss}/F, apparent clearance at steady-state; $C_{max,ss}$, maximum concentration of drug in plasma at steady-state; EP, empagliflozin (25 mg) once daily for 5 days; EV, evogliptin (5 mg) once daily for 7 days; EV + EP, co-administration of evogliptin (5 mg) and empagliflozin (25 mg) once daily for 5 days; GMR, geometric least squares mean ratio; PK, pharmacokinetic; $t_{1/2}$, elimination half-life; $T_{max,ss}$, time to maximum plasma concentration at steady state; Vd_{ss}/F, apparent volume of distribution at steady-state.

[a]Data are shown as mean ± standard deviation except for $T_{max,ss}$ where data are shown as median (minimum, maximum).

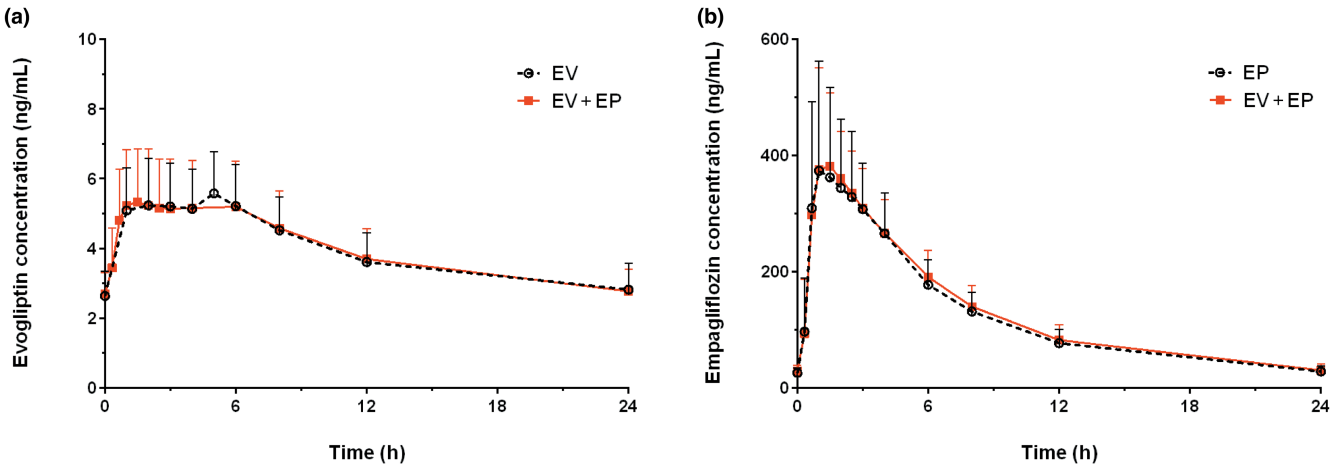

FIGURE 1 Mean plasma EV (a) and EP (b) concentration-time profiles at steady-state in arm 1 of the study. The error bars are standard deviations. EP, empagliflozin; EV, evogliptin.

estimate (90% CI) of the GMR (EV + EP/EP) of the $C_{max,ss}$ and $AUC_{\tau,ss}$ were 0.99 (0.88–1.12) and 1.04 (1.00–1.08), respectively.

The main metabolites of EV are M7 and M8, which are primarily produced by CYP3A4. The mean $AUC_{\tau,ss}$ values of M7 in the EV and EV + EP groups were 8828.26 and 9257.54 h pg/mL, respectively, whereas those of M8 in the EV and EV + EP groups were 11,775.33 and 12,211.19 h pg/mL, respectively. The metabolic ratios, $AUC_{\tau,ss}$ of M7/$AUC_{\tau,ss}$ of EV, were similar between the EV and EV + EP groups (=0.10). Simultaneously, the metabolic ratios, $AUC_{\tau,ss}$ of M8/$AUC_{\tau,ss}$ of EV, were similar between the EV and EV + EP groups (=0.13).

Arm 2 of the study

The PK parameters of EV and DP for each treatment group are summarized in Table 3. The mean plasma concentrations of EV and DP over time after multiple

TABLE 3 PK parameters and comparison of evogliptin and dapagliflozin (arm 2).

Evogliptin	EV + DP[a] (*N* = 18)	EV[a] (*N* = 18)	GMR (90% CI) EV + DP/EV
$C_{max,ss}$ (ng/mL)	5.80 ± 0.78	5.61 ± 0.70	1.03 (0.96–1.11)
$AUC_{\tau,ss}$ (h ng/mL)	91.77 ± 9.54	91.37 ± 9.62	1.00 (0.95–1.06)
$T_{max,ss}$ (h)	2.00 (0.50, 6.00)	2.00 (1.00, 6.00)	
$t_{1/2}$ (h)	25.46 ± 3.77	24.68 ± 4.36	
CL_{ss}/F (L/h)	55.03 ± 5.59	55.13 ± 5.46	
Vd_{ss}/F (L)	2005.80 ± 260.45	1956.10 ± 352.32	
Dapagliflozin	**EV + DP[a] (*N* = 18)**	**DP[a] (*N* = 18)**	**GMR (90% CI) EV + DP/DP**
$C_{max,ss}$ (ng/mL)	189.24 ± 58.55	170.56 ± 37.54	1.09 (0.95–1.25)
$AUC_{\tau,ss}$ (h ng/mL)	500.49 ± 100.40	493.47 ± 108.21	1.02 (0.99–1.05)
$T_{max,ss}$ (h)	0.52 (0.50, 2.00)	0.77 (0.50, 1.50)	
$t_{1/2}$ (h)	10.87 ± 4.42	10.43 ± 3.17	
CL_{ss}/F (L/h)	20.67 ± 3.71	21.11 ± 4.21	
Vd_{ss}/F (L)	321.75 ± 152.53	320.20 ± 128.57	

Abbreviations: $AUC_{\tau,ss}$, area under the plasma drug concentration-time curve within a dosing interval (τ) at steady-state; CI, confidential interval; CL_{ss}/F, apparent clearance at steady-state; $C_{max,ss}$, maximum concentration of drug in plasma at steady-state; DP, dapagliflozin (10 mg) once daily for 5 days; EV, evogliptin (5 mg) once daily for 7 days; EV + DP, co-administration of evogliptin 5 mg and dapagliflozin (10 mg) once daily for 5 days; GMR, geometric least squares mean ratio; $t_{1/2}$, elimination half-life; $T_{max,ss}$, time to maximum plasma concentration at steady-state; Vd_{ss}/F, apparent volume of distribution at steady state.

[a]Data are shown as mean ± standard deviation except for $T_{max,ss}$ where data are shown as median (minimum – maximum).

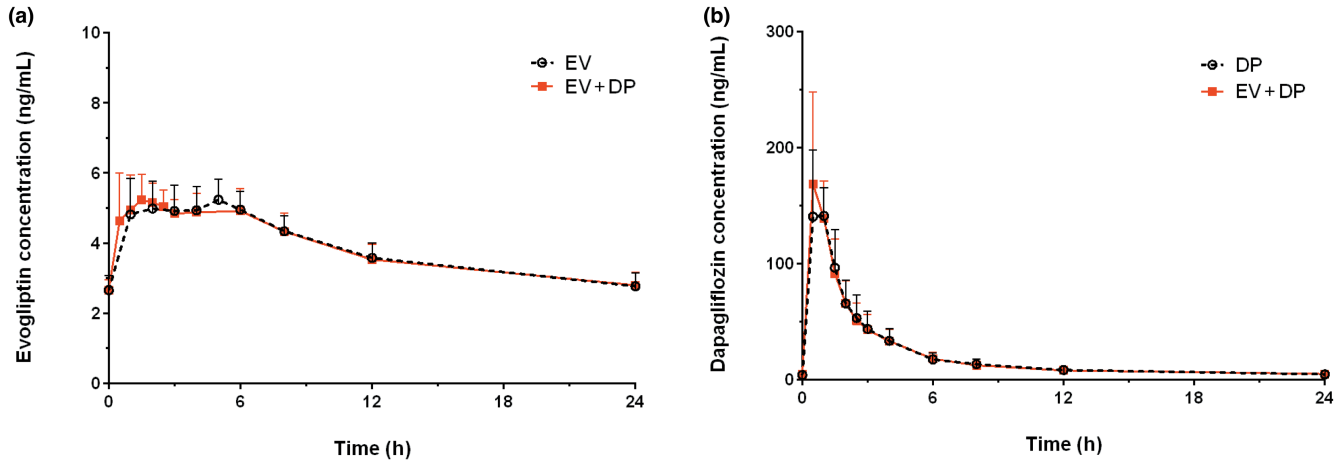

FIGURE 2 Mean plasma EV (a) and DP (b) concentration-time profiles at steady-state in arm 2 of the study. The error bars are standard deviations. DP, dapagliflozin; EV, evogliptin.

administrations are shown in Figure 2. The $C_{max,ss}$ and $AUC_{\tau,ss}$ values of EV were similar between the EV + DP and EV groups. The point estimate (90% CI) of the GMR (EV + DP/EV) of the $C_{max,ss}$ and $AUC_{\tau,ss}$ were 1.03 (0.96–1.11) and 1.00 (0.95–1.06), respectively.

Additionally, the $C_{max,ss}$ and $AUC_{\tau,ss}$ values of DP were similar for the EV + DP and DP groups. The point estimate (90% CI) of the GMR (EV + DP/DP) of the $C_{max,ss}$ and $AUC_{\tau,ss}$ were 1.09 (0.95–1.25) and 1.02 (0.99–1.05), respectively.

The main metabolites of EV are M7 and M8, which are primarily produced by CYP3A4. The mean $AUC_{\tau,ss}$ values of M7 in the EV and EV + DP groups were 8483.96 and 9124.99 h pg/mL, respectively, whereas those of M8 were 11,632.99 and 12,221.73 h pg/mL, respectively. The metabolic ratios, $AUC_{\tau,ss}$ of M7/$AUC_{\tau,ss}$ of EV, were

similar between the EV and EV + DP groups (EV = 0.09; EV + DP = 0.10). In parallel, the metabolic ratios, $AUC_{\tau,ss}$ of M8/$AUC_{\tau,ss}$ of EV, were similar between the EV and EV + DP groups (=0.13).

Pharmacodynamics

The PD parameters of EV and EP or DP in each treatment group are summarized in Table 4. For all treatment groups, the $AUEC_{glu}$ showed a statistically significant difference compared to the baseline AUEC levels except for DP. The $\Delta AUEC_{glu}$ for EV + EP was lower only by 4.1% and 10.3% than that of EV and EP alone, respectively ($p > 0.05$). The $AUEC_{\Delta glu}$ for EV + DP was lower only by 1.2% and 10.2% than that of EV and DP alone, respectively ($p > 0.05$). All treatment groups showed no statistically significant differences in $\Delta AUEC_{ins}$ ($p > 0.05$).

In addition, there were no statistically significant differences between EV + EP and EP/EV + DP and DP in UGE over 24 h (Table S2).

Safety and tolerability

In arm 1 of the study, 12 participants (63.2%) reported at least one AE. Five participants experienced an AE while receiving EV alone and six while receiving EP alone. Eight participants reported AEs during the co-administration of EV and EP. All AEs were drug-related, as determined by the investigator. In arm 2 of the study, seven participants (36.8%) reported at least one AE. Two participants experienced an AE while receiving EV alone, and five experienced an AE while receiving DP alone. One participant reported an AE during the co-administration of EV and DP. All AEs were drug-related, as determined by the investigator. The most frequently reported AEs were leukopenia, pharyngitis and "aspartate aminotransferase increased." The severity of all AEs was mild, and most patients recovered without the need for special treatment (Table S3).

DISCUSSION

This study aimed to investigate the interaction of EV with EP or DP. According to previous studies and US Food and Drug Administration (FDA) labels, the elimination half-life of EV, EP, and DP is 32.9–38.8, 12.4, and 12.9 h, respectively.[13–15] A steady-state would be achieved at approximately day 5 after administration of EP or DP once daily, whereas it would take ~7 days to achieve a steady-state condition for EV. The sampling schedule and

TABLE 4 PD parameters for blood glucose and insulin levels during oral glucose tolerance test at steady-state.

		Arm 1				Arm 2			
		Treatment				Treatment			
Parameters[a]		Baseline (*N* = 18)	EV (*N* = 18)	EP (*N* = 18)	EV + EP (*N* = 18)	Baseline (*N* = 18)	EV (*N* = 18)	DP (*N* = 18)	EV + DP (*N* = 18)
Blood glucose	AUEC (h mg/dL)	408.75 ± 68.03	344.51 ± 40.23*	368.27 ± 41.93*	330.44 ± 36.36*	400.11 ± 64.63	346.70 ± 70.80*	381.49 ± 61.24	342.69 ± 51.43*
	ΔAUEC (h mg/dL)	-	−67.09 ± 50.61	−43.64 ± 48.92	−80.67 ± 49.15	-	−54.46 ± 64.28	−19.00 ± 57.46	−58.85 ± 61.74
Blood insulin	AUEC (h μU/mL)	139.42 ± 65.46	131.45 ± 60.77	100.40 ± 26.14	114.32 ± 44.87	122.47 ± 50.78	121.47 ± 62.38	92.94 ± 39.18	97.24 ± 46.92
	ΔAUEC (h μU/mL)	-	−10.39 ± 37.75	−42.68 ± 66.62	−26.18 ± 40.43	-	−3.29 ± 47.16	−30.47 ± 33.36	−25.65 ± 42.89

Abbreviations: AUEC, area under the time-effect curve at steady state; ΔAUEC, change in AUEC from baseline; DP, dapagliflozin (10 mg) once daily for 5 days; EP, empagliflozin (25 mg) once daily for 5 days; EV, evogliptin (5 mg) once daily for 7 days; EV + DP, co-administration of evogliptin (5 mg) and dapagliflozin (10 mg) once daily for 5 days; EV + EP, co-administration of evogliptin (5 mg) and empagliflozin (25 mg) once daily for 5 days.

[a]Data are shown as mean ± standard deviation.

*Statistically significant difference in AUEC when compared to the baseline (p value < 0.05), p values were calculated using a paired t-test.

intervals used in the present study were appropriately planned to investigate the PK profiles of the study drugs. The OGTT permits the assessment of insulin secretion and glucose processing capacity without inducing unnecessary pressure on the subjects.[16] Therefore, to better understand which medication would be more beneficial with less toxicity, changes in blood glucose and insulin levels were compared during the OGTT to assess the antidiabetic effects of EV and SGLT2i. For the baseline measurement, OGTT was performed on the day before the first dosing in period 1. Considering the steady-state condition of each study drug and the PK sampling schedule, OGTT was conducted on day 6 (EV) and day 4 (EP, DP, EV + EP, and EV + DP) to analyze changes from baseline.

The PK results from the present study showed that EV + EP did not significantly alter the PKs of EV or EP. Similarly, EV + DP did not significantly alter the PKs of EV or DP.

According to in vitro studies, EV does not induce or inhibit other CYP enzymes. The major metabolites of EV are known to be formed by CYP3A4. Among the major metabolites, M7 and M8 are primary metabolites with unknown activities.[17,18] Therefore, the PKs of M7 and M8 were measured to confirm whether co-administration with SGLT2i affected the metabolism of EV. EP is mainly metabolized by glucuronidation by the uridine 5′-diphospho-glucur onosyltransferases "UGT2B7, UGT1A3, UGT1A8, and UGT1A9." EP did not inhibit or induce CYP enzymes in vitro. Similarly, EP did not inhibit UGT enzymes, such as UGT1A1, UGT1A3, UGT1A8, UGT1A9, and UGT2B7.[14] DP is mainly metabolized by UGT1A9, but CYP-mediated metabolism in humans is not well understood.[15] DP is a weak substrate of P-gp and not a substrate of OAT1 or OCT.[19] Moreover, it has been reported that DP does not inhibit or induce CYP enzymes.[15] The co-administration of EV with DP or EP did not affect the formation of M7 and M8 in this study.

DPP4i mainly acts on GLP-1, which contributes to the increase in insulin secretion by upregulating β-cell proliferation and downregulating β-cell apoptosis.[20] SGLT2is are known to inhibit renal tubular glucose reabsorption.[21] Considering the mechanisms of action, combination therapy of DPP4i and SGLT2i would elicit additive PD effects in patients with T2DM. Previous clinical trials have demonstrated that the co-administration of DPP4i, EV, sitagliptin or saxagliptin, and SGLT2i resulted in additive effects on glucose-lowering activity in patients with T2DM, when compared to monotherapy.[4–6,22,23] On the other hand, in our study, co-administration of EV and SGLT2i in healthy volunteers did not show additive PD effects on glucose lowering. This can be explained by the study design, which included healthy participants with undamaged glucose homeostasis. We assumed that because healthy subjects have a normal endocrine system that can regulate blood glucose levels within the normal range, the antidiabetic effect of the co-administration of EV and SGLT2i could have been attenuated.[24] Another possibility is the difference in renal threshold between healthy subjects and patients with T2DM.[25] SGLT2is are known to effectively reduce the threshold of patients with T2DM (200 and 250 mg/dL) to as low as 40–120 mg/dL. However, the normal renal threshold for re-absorption of glucose corresponds to a serum glucose concentration of 180 mg/dL, which is lower than that of patients with T2DM (200 and 250 mg/dL). Thus, EV might not show additive medical effects when co-administered with SGLT2i in healthy subjects due to normal glucose homeostasis and renal threshold differences. In addition, GLP-1 did not increase insulin-mediated blood glucose uptake in healthy young subjects.[26]

Considering the mechanism of action of SGLT2i, which do not affect insulin secretion, decreased insulin levels were predicted for SGLT2i monotherapy. However, contrary to the expectation that DPP4i would increase the secretion of insulin by upregulating GLP-1, EV-treated groups receiving either monotherapy or co-administration with SGLT2i also showed decreased insulin levels. This can be attributed to the high degree of fluctuation in insulin levels in healthy subjects.[27] Another possibility is that insulin levels in healthy subjects after OGTT could have been significantly influenced by the insulin-regulatory effect of glucose rather than by the effects of GLP-1, which can induce insulinotropic effects.[13] A comparable result was obtained in previous studies that administered EV and other drugs of the same class, including sitagliptin, to healthy subjects. In the case of sitagliptin, there was no significant increase in blood insulin levels in healthy subjects.[28] However, when the same dose of sitagliptin was administered to patients with DM, an insulinotropic effect was observed.[29] Based on previous studies, it was presumed that the PD effect would not be evident in healthy subjects. However, this analysis was necessary because a PD study of EV had not been performed in healthy subjects, including EV and SGLT2i. Therefore, it is possible that the PD findings in healthy subjects should be carefully interpreted with the premise that the responses could be quite different for patients with T2DM.

UGE over 24 h was analyzed as a PD parameter. Considering the mechanism of action of EV, we hypothesized that it would have no effect on the UGE of EP and DP. There was no statistically significant difference in UGE between arm 1 (EV + EP and EP) and arm 2 (EV + DP and DP).

As co-administration of EV and SGLT2i did not show PK interactions, it is unlikely that these drugs used in combination would raise the possibility of increased toxicities or diminished effects through PK-based alterations

in exposure. In addition, co-administration of EV and DP has shown additive PD effect and safety profiles in patients with T2DM.[6] Therefore, combination therapy of EV and EP or DP would be an effective and safe treatment option, which can facilitate therapy of patients with T2DM.

AUTHOR CONTRIBUTIONS

D.K., M.C., and M.S.P. wrote the manuscript. D.K., T.H., C.O.K., B.W.Y., and M.S.P. designed the study. D.K., B.H.J., T.H., C.O.K., B.W.Y., and M.S.P. performed the research. D.K., M.C., and M.S.P. analyzed the data. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

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REFERENCES

1. Galicia-Garcia U, Benito-Vicente A, Jebari S, et al. Pathophysiology of type 2 diabetes mellitus. *Int J Mol Sci*. 2020;21(17):6275.
2. Association, A.D. Standards of medical care in diabetes—2013. *Diabetes Care*. 2012;36(Suppl 1):S11-S66.
3. Tahrani AA, Bailey CJ, Del Prato S, Barnett AH. Management of type 2 diabetes: new and future developments in treatment. *Lancet*. 2011;378(9786):182-197.
4. Jabbour SA, Hardy E, Sugg J, Parikh S. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled studys. *Diabetes Care*. 2014;37:740-750.
5. Rosenstock J, Hansen L, Zee P, et al. Dual add-on therapy in poorly controlled type 2 diabetes on metformin: randomized, double-blind trial of saxagliptin + dapagliflozin vs saxagliptin and dapagliflozin alone. *Diabetes Care*. 2015;38:376-383.
6. Jeong IK, Choi KM, Han KA, et al. Dapagliflozin improves glycemic control and liver function with body weight loss as add-on therapy to metformin plus Evogliptin: a 24-week, randomized, double-blind, clinical trial. *Endocrine Abstracts*. 2023;90:335.
7. Hong SM, Park CY, Hwang DM, et al. Efficacy and safety of adding evogliptin versus sitagliptin for metformin-treated patients with type 2 diabetes: a 24-week randomized, controlled trial with open label extension. *Diabetes Obes Metab*. 2017;19(5):654-663.
8. Ajmani AK, Agrawal A, Prasad BLN, et al. Efficacy and safety of evogliptin versus sitagliptin as an add-on therapy in Indian patients with type 2 diabetes mellitus inadequately controlled with metformin: a 24-week randomized, double-blind, non-inferiority, EVOLUTION India study. *Diabetes Res Clin Pract*. 2019;157:107860.
9. Bailey CJ. Renal glucose reabsorption inhibitors to treat diabetes. *Trends Pharmacol Sci*. 2011;32(2):63-71.
10. Abdul-Ghani MA, Norton L, Defronzo RA. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. *Endocr Rev*. 2011;32(4):515-531.
11. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. *Diabetes Care*. 2009;32(4):650-657.
12. Li D, Shi W, Wang T, Tang H. SGLT2 inhibitor plus DPP-4 inhibitor as combination therapy for type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2018;20(8):1972-1976.
13. Gu N, Park MK, Kim TE, et al. Multiple-dose pharmacokinetics and pharmacodynamics of evogliptin (DA-1229), a novel dipeptidyl peptidase IV inhibitor, in healthy volunteers. *Drug des Devel Ther*. 2014;8:1709-1721.
14. FDA. *JARDIANCE® (empaglilfozin) [package insert]*. 2014. Accessed November 15, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/204629s026lbl.pdf
15. FDA. *FARXIGA® (dapagliflozin) [package insert]*. 2014. Accessed November 15, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202293s020lbl.pdf
16. Ernsberger P, Koletsky RJ. The glucose tolerance test as a laboratory tool with clinical implications. *Glucose Tolerance*. 2012;1:1-14.
17. Oh ES, Choi C, Kim CO, et al. Effects of clarithromycin on the pharmacokinetics of evogliptin in healthy volunteers. *J Clin Pharm Ther*. 2017;42(6):689-694.
18. Kim HJ, Kwak WY, Min JP, et al. Discovery of DA-1229: a potent, long acting dipeptidyl peptidase-4 inhibitor for the treatment of type 2 diabetes. *Bioorg Med Chem Lett*. 2011;21(12):3809-3812.
19. Obermeier M, Yao M, Khanna A, et al. In vitro characterization and pharmacokinetics of dapagliflozin (BMS-512148), a potent sodium-glucose cotransporter type II inhibitor, in animals and humans. *Drug Metab Dispos*. 2010;38(3):405-414.
20. Ahrén B. DPP-4 inhibitors. *Best Pract Res Clin Endocrinol Metab*. 2007;21(4):517-533.
21. Chao EC. SGLT-2 inhibitors: a new mechanism for glycemic control. *Clin Diabetes*. 2014;32(1):4-11.
22. 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.
23. 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.

24. Hwang I, Kim Y, Yoo H, Jang IJ, Yu KS, Lee S. Pharmacokinetic/pharmacodynamic interaction between evogliptin and pioglitazone in healthy male subjects. *Drug Des Devel Ther*. 2020;14:4493-4502.
25. Yue XD, Wang JY, Zhang XR, et al. Characteristics and impact factors of renal threshold for glucose excretion in patients with type 2 diabetes mellitus. *J Korean Med Sci*. 2017;32(4):621-627.
26. Ryan AS, Egan JM, Habener JF, Elahi D. Insulinotropic hormone glucagon-like peptide-1-(7-37) appears not to augment insulin-mediated glucose uptake in young men during euglycemia. *J Clin Endocrinol Metab*. 1998;83(7):2399-2404.
27. Gerich J, Becker RH, Zhu R, Bolli GB. Fluctuation of serum basal insulin levels following single and multiple dosing of insulin glargine. *Diabetes Technol Ther*. 2006;8(2):237-243.
28. Bergman AJ, Stevens C, Zhou Y, et al. Pharmacokinetic and pharmacodynamic properties of multiple oral doses of sitagliptin, a dipeptidyl peptidase-IV inhibitor: a double-blind, randomized, placebo-controlled study in healthy male volunteers. *Clin Ther*. 2006;28(1):55-72.
29. Herman GA, Bergman A, Stevens C, et al. Effect of single oral doses of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on incretin and plasma glucose levels after an oral glucose tolerance test in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2006;91(11):4612-4619.

SUPPORTING INFORMATION

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

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