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Original Article

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Evaluation of pharmacokinetic interactions between lobeglitazone, empagliflozin, and metformin in healthy subjects

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ABSTRACT

Concomitant administration of lobeglitazone, empagliflozin, and metformin is expected to enhance blood glucose-lowering effects and improve medication compliance in patients with diabetes mellitus. In this study, we investigated the pharmacokinetic (PK) interactions and safety of lobeglitazone and co-administered empagliflozin and metformin, which are approved agents used in clinical settings. Two randomized, open-label, multiple-dose, 2-treatment, 2-period, 2-sequence crossover clinical trials (parts 1 and 2) were conducted independently. In part 1, lobeglitazone monotherapy or lobeglitazone, empagliflozin, and metformin triple therapy was administered for 5 days. In part 2, empagliflozin and metformin dual therapy or the abovementioned triple therapy were administered for 5 days. Serial blood samples were collected up to 24 hours after the last dose in each period for PK evaluation. The primary PK parameters ($AUC_{tau,ss}$, $C_{max,ss}$) of treatment regimens in each study part were calculated and compared. For lobeglitazone, the geometric mean ratios (GMRs) with 90% confidence intervals (CI) for triple therapy over monotherapy were 1.08 (1.03–1.14) for $C_{max,ss}$ and 0.98 (0.90–1.07) for $AUC_{tau,ss}$. For empagliflozin, the GMRs and 90% CIs for triple therapy over dual therapy were 0.87 (0.78–0.97) for $C_{max,ss}$ and 0.97 (0.93–1.00) for $AUC_{tau,ss}$. For metformin, the GMRs and 90% CIs for triple therapy over dual therapy were 1.06 (0.95–1.17) for $C_{max,ss}$ and 1.04 (0.97–1.12) for $AUC_{tau,ss}$. All reported adverse events were mild. The triple therapy consisting of lobeglitazone, empagliflozin, and metformin did not show any clinically relevant drug interactions in relation to the PKs and safety of each drug substance.

Trial Registration: ClinicalTrials.gov Identifier: NCT04334213

Keywords: Diabetes Mellitus; Drug Interactions; Pharmacokinetics; Thiazolidinediones

INTRODUCTION

Diabetes mellitus is characterized by abnormal carbohydrate metabolism and hyperglycemia. Among several different types of diabetes, type 2 diabetes accounts for over 90% of diabetes in adults. Diabetes ultimately leads to microvascular damage (e.g., retinopathy,

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nephropathy, and neuropathy) and macrovascular events such as myocardial infarction and stroke. High plasma glucose concentration is the most deterministic risk factor for diabetes complications. Therefore, glycemic control is the mainstay of managing diabetes [1]. The general target of glycemic control is to maintain a blood hemoglobin A1c (HbA1c) level of < 6.5%. However, to date, in Korea, only 24.5% of patients with diabetes achieve the desired glycemic control [2].

In addition to lifestyle changes, metformin is the first-line treatment for glycemic control in patients with type 2 diabetes mellitus (T2DM). In patients with T2DM who fail to reach the target HbA1c level with metformin monotherapy, the use of hypoglycemic drugs with different mechanisms of action is recommended. However, various clinical endpoints such as efficacy, cardiovascular risk, hypoglycemic risk, and body weight loss should be considered [3]. Metformin mainly inhibits gluconeogenesis by directly acting on the liver via various molecular mechanisms [4]. Empagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor that inhibits glucose absorption from the kidney, thus increasing glucose excretion in urine [5]. For metformin-based combination regimens, second-line agents such as thiazolidinediones (TZDs) and dipeptidyl peptidase-4 inhibitors can be added. These agents can also be used as monotherapy [6].

Lobeglitazone is a novel TZD that enhances insulin sensitivity by acting as a peroxisome proliferator activated receptor gamma agonist; it improves insulin resistance of muscle and fat tissue by selectively increasing gene expressions related to gluconeogenesis [7]. TZDs and SGLT2 inhibitors have different mechanisms of action, and both have a low risk of hypoglycemia. When these 2 drug classes are administered together, they attenuate the progression of early-phase diabetic nephropathy. The number of metformin + TZD or metformin + SGLT2 inhibitor users had gradually increased for treatment of T2DM [8]. Also, combination therapy with SGLT2 inhibitors and TZDs is one of the preferred treatment options for T2DM [9]. Therefore, it is predicted that the combination treatment consists of metformin, TZDs, and SGLT2 inhibiters would be increased.

T2DM is a chronic progressive disease, and there is a need for diverse treatment option [10]. Theoretically, a pharmacological synergy can be expected if drugs with different mechanisms of action are used. Thus, a combination of various T2DM treatment agents is often used in clinical settings [8]. The results of this study can serve as a basis for the safe use of empagliflozin, metformin, and lobeglitazone co-treatment in patients with T2DM.

Previous studies reported that there was no clinically significant drug interaction between empagliflozin and metformin [11]. Further, no significant changes were observed in the pharmacokinetics (PK) of lobeglitazone when it was administered with either metformin or dapagliflozin [11,12]. However, the possible occurrence of drug interactions when empagliflozin, metformin, and lobeglitazone are concomitantly administered remains unknown. Therefore, this study aimed to evaluate the safety and PK interactions of triple therapy consisting of lobeglitazone, empagliflozin, and metformin.

METHODS

Ethics

This study was conducted at the Clinical Trials Center, Severance Hospital, Yonsei University College of Medicine in Seoul, Korea. The protocol was approved by the Institutional Review Board of Severance Hospital (approval number: 4-2020-0154) and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The clinical trial is registered on clinicaltrials.gov (NCT Number: NCT04334213).

Subjects

Healthy Korean male volunteers aged 19–55 years, with a body weight of at least 55 kg and a body mass index (BMI) ranging 18.5–27.0 kg/m^2 were included in this study. The participants received a full study explanation from the researchers and voluntarily signed an informed consent form. The screening tests consisted of medical history documentation, physical examination, electrocardiography, vital signs, and clinical laboratory tests. Subjects with gastrointestinal diseases or surgery that could influence the absorption of investigational products (IPs) or those who were hypersensitive to the IPs were excluded.

Study design

Two independent (parts 1 and 2) randomized, open-label, multiple-dose, 2-treatment, 2-period, 2 × 2 crossover design clinical trials were conducted with a washout period of at least 7 days between treatments.

In part 1, 24 participants were randomly assigned to one of 2 treatment groups. Treatments were consisted of lobeglitazone 0.5 mg (Duvie; Chong Kun Dang Co., Ltd, Seoul, Korea) once daily for 5 days (LOB), empagliflozin 25 mg (Jardiance; Boehringer Ingelheim, Seoul, Korea) once daily for 5 days (EMP) and 2 tablets of metformin 1,000 mg (Glucophage XR; Merck Co., Ltd, Seoul, Korea) once daily for 5 days (MET). In group 1, the treatment of each period was in the following order: LOB then LOB + EMP + MET. The treatment of each period in group 2 was in the following order: LOB + EMP + MET then LOB.

In part 2, 24 participants were randomly assigned to one of 2 treatment groups, group 3 and group 4. Same treatments with part 1 study were applied. In group 3, the treatment of each period was in the following order: EMP + MET then LOB + EMP + MET. The treatment of each period in group 4 was in the following order: LOB + EMP + MET then EMP + MET. The study regimens are presented in **Table 1**.

Blood sample collection and analysis

Pre-dose PK sampling was conducted on days 1, 3, and 4 before the administration of the study drug. Intensive PK sampling on day 5 of each period, which was expected to be the

Table 1. Study design

Part	Group	No. of subjects	Period 1	Washout period (days)	Period
1	1	12	LOB	17	LOB + EMP + MET
	2	12	LOB + EMP + MET	17	LOB
2	3	12	EMP + MET	10	LOB + EMP + MET
	4	12	LOB + EMP + MET	10	EMP + MET

LOB, lobeglitazone 0.5 mg, once daily for 5 days; EMP + MET, empagliflozin 25 mg and metformin 1,000 mg 2 tablets, once daily for 5 days; LOB + EMP + MET, lobeglitazone 0.5 mg, empagliflozin 25 mg, and metformin 1,000 mg 2 tablets, once daily for 5 days.

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steady state, was conducted before the pre-dosing on day 5 at the following time points: 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 hours after dosing on day 5.

Blood samples were collected in EDTA K2 tubes. Thirty minutes after sampling, samples were centrifuged at 12,470 *g* for 10 minutes at 4°C. The supernatants were separated from samples and stored below –70°C until further analysis. Plasma concentrations of lobeglitazone, empagliflozin, and metformin were measured using a validated ultra-performance liquid chromatography (UPLC) with tandem mass spectrometry method. For UPLC, a Waters ACQUITY UPLC system (Waters Corporation, Milford, MA, USA) was used. Tandem mass spectrometry was conducted using a mass spectrometer connected to the Waters ACQUITY UPLCTM system. The developed analytical method was linear over the range of 1–250 ng/mL (relative standard deviation %:1.0–2.4%) for lobeglitazone, 5–1,000 ng/mL (1.0–2.6%) for empagliflozin, and 20–5,000 ng/mL (0.9–2.1%) for metformin. The coefficients of variation ranged 1.0–2.1% for lobeglitazone, 0.7–2.6% for empagliflozin, and 0.4–2.1% for metformin. The accuracy ranges were 94.2–103.1%, 95–103.3%, and 95.2–107.5%, respectively. Plasma concentrations were analyzed by BioInfra Co. (Suwon, Korea).

PK data assessment

PK parameters were calculated by a non-compartmental analysis using the WinNonlin® software (ver. 8.2; Certara, Princeton, NJ, USA). The maximum concentration of drug in plasma at steady state ($C_{max,ss}$) and time to maximum plasma concentration at steady state ($T_{max,ss}$) were directly derived from the observed values. The area under the plasma drug concentration-time curve within a dosing interval(τ) at steady state ($AUC_{tau,ss}$) was calculated using the trapezoidal rule (linear up/log down) without weighting. The apparent plasma clearance at steady state (CL_{ss}/F) was calculated using the following equation: $CL_{ss}/F = dose/AUC_{tau,ss.}$

Safety assessment

Safety monitoring was conducted for all the participants who received the drugs at least once throughout the study. Safety was monitored by assessing vital signs (blood pressure, heart rate, and body temperature) and performing physical examinations, 12-lead electrocardiograms, and clinical laboratory tests (hematology, serum chemistry, blood sugar tests, and urinalysis). Adverse events (AEs) detected by investigators or reported by the participants were recorded and evaluated by the former.

Statistical analysis

The demographics of each group, including age, weight, height, and BMI, were summarized using descriptive statistics and analyzed with Student's *t*-test using SAS statistical software version 9.4 (SAS Institute Inc. Cary, NC, USA) according to the treatment sequences of each study. The primary PK parameters ($AUC_{tau,ss}$ and $C_{max,ss}$ of lobeglitazone (part 1 study), empagliflozin, and metformin (part 2 study)) were converted to natural logarithms to obtain point estimates of the geometric least square mean difference with 90% confidence intervals (CIs) of triple therapy (LOB + EMP + MET) to monotherapy (LOB) for part 1 study and triple therapy (LOB + EMP + MET) to dual therapy (EMP + MET) for part 2 study with 90% CIs using analysis of variance test. The range of 0.80–1.25 was considered to determine the absence of a PK interaction [13]. WinNonlin® (ver. 8.2; Certara) was used for statistical analysis of PK parameters.

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RESULTS

Study participants

A total of 48 healthy subjects (24 subjects in each study) were enrolled, and all of them were administered the study drug(s) at least once during the whole study period. Three participants withdrew during part 1, and one withdrew during part 2 of the study. Data on subjects who withdrew from the study were not included in PK analyses but were included in the safety analyses. The demographic characteristics of the treatment groups are summarized in **Table 2**. No statistical or clinical differences were observed between the sequencing groups in both parts of the study.

PK analysis

The mean lobeglitazone, empagliflozin and metformin plasma concentration-time profiles of monotherapy (or dual therapy) and triple therapy are depicted in **Figs. 1-3** and were comparable. The PK parameters of lobeglitazone, empagliflozin and metformin in each treatment group are summarized in **Table 3**. The differences between triple therapy with monotherapy (or dual therapy) based on the point estimates and 90% CI of the log-transformed $C_{max,ss}$ and $AUC_{tau,ss}$ were within bioequivalence range except the $C_{max,ss}$ of empagliflozin whose lower margin of 90% CI was slightly lower than 0.8.

Table 2. Demographic characteristics

Characteristics	Part 1				Part 2			
	Group 1 (n = 12)	Group 2 (n = 12)	Total (n = 24)	*p*-value*	Group 3 (n = 12)	Group 4 (n = 12)	Total (n = 24)	*p*-value*
Age (yr)	30.3 ± 8.3	29.4 ± 7.1	29.8 ± 7.6	0.8192	29.3 ± 8.3	28.3 ± 5.5	28.8 ± 6.9	0.7474
Body weight (kg)	73.5 ± 5.0	74.1 ± 7.0	73.8 ± 5.9	0.8205	68.9 ± 8.6	66.9 ± 4.5	67.9 ± 6.8	0.5005
Height (cm)	172.1 ± 3.1	175.4 ± 7.5	173.7 ± 5.8	0.2349	174.1 ± 6.1	175.6 ± 4.8	174.8 ± 5.4	0.4942
BMI (kg/m^2)	24.8 ± 1.6	24.0 ± 1.6	24.4 ± 1.6	0.3266	22.6 ± 2.0	21.7 ± 1.9	22.2 ± 1.9	0.3325

All given figures are mean ± standard deviation (range).
Group 1: LOB – (LOB + EMP + MET); Group 2: (LOB + EMP + MET) – LOB; Group 3: (EMP + MET) – (LOB + EMP + MET); Group 4: (LOB + EMP + MET) – (EMP + MET).
LOB, lobeglitazone 0.5 mg, once daily for 5 days; EMP + MET, empagliflozin 25 mg 1 tablet, and metformin 1,000 mg 2 tablets, once daily for 5 days; LOB + EMP + MET, lobeglitazone 0.5 mg 1 tablet, empagliflozin 25 mg 1 tablet, and metformin 1,000 mg 2 tablets, once daily for 5 days.
*Comparison between 2 groups using independent *t*-tests.

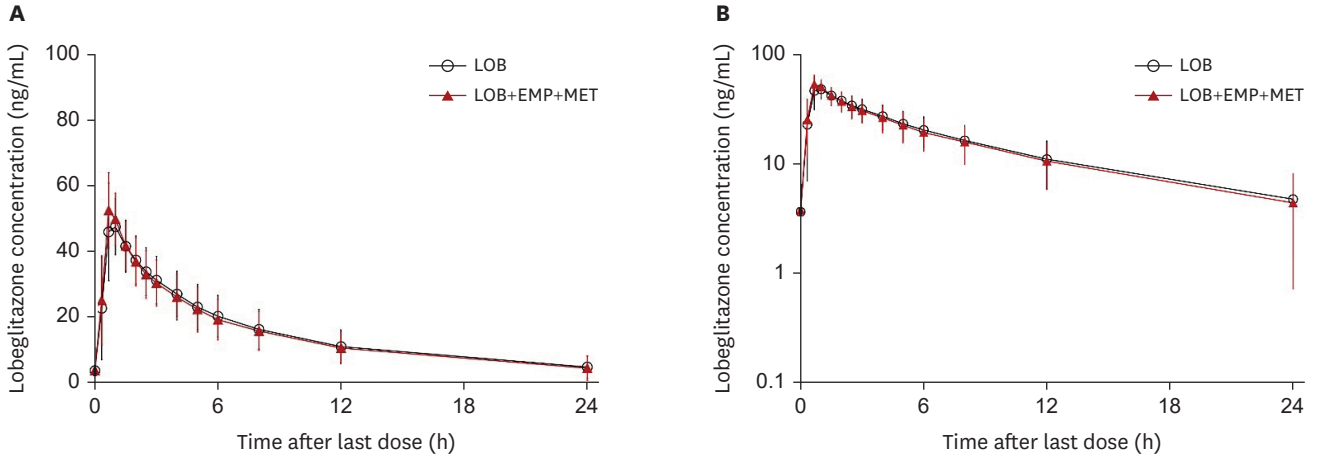

Figure 1. Mean (standard deviation) plasma concentration-time profiles at steady state of lobeglitazone when administered as monotherapy and as part of triple therapy. (A) Linear scale; (B) Semi-log scale.
LOB, administration of lobeglitazone 0.5 mg, once daily for 5 days; LOB + EMP + MET, administration of lobeglitazone 10 mg, empagliflozin 25 mg and metformin 1,000 mg 2 tablets, once daily for 5 days.

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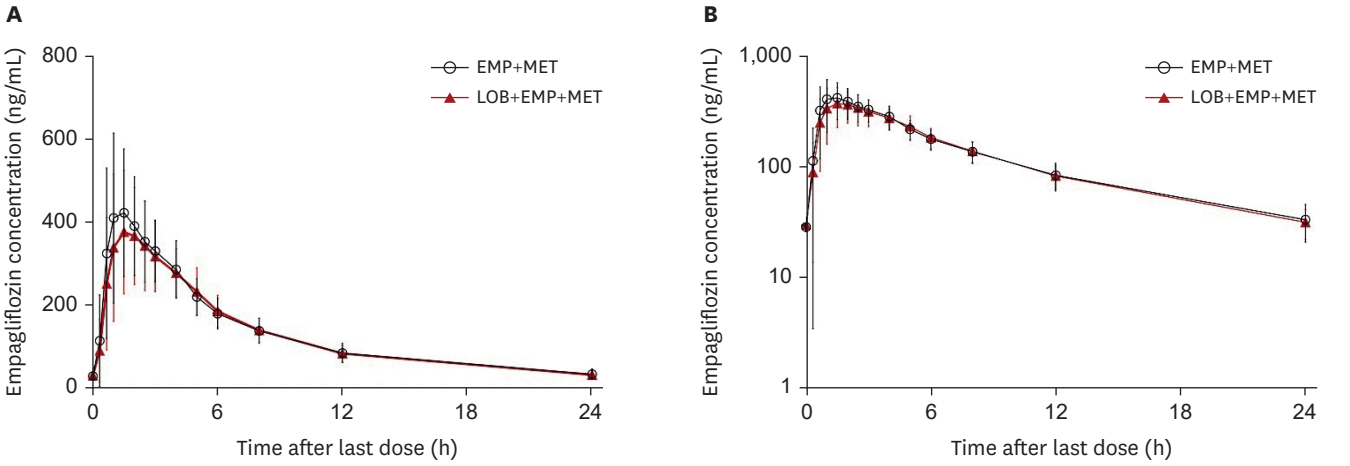

Figure 2. Mean (standard deviation) plasma concentration-time profiles at steady state of empagliflozin when administered as dual therapy and as part of triple therapy. (A) Linear scale; (B) Semi-log scale.
EMP + MET, administration of empagliflozin 25 mg and metformin 1,000 mg 2 tablets, once daily for 5 days; LOB + EMP + MET, administration of lobeglitazone 10 mg, empagliflozin 25 mg, and metformin 1,000 mg 2 tablets once daily for 5 days.

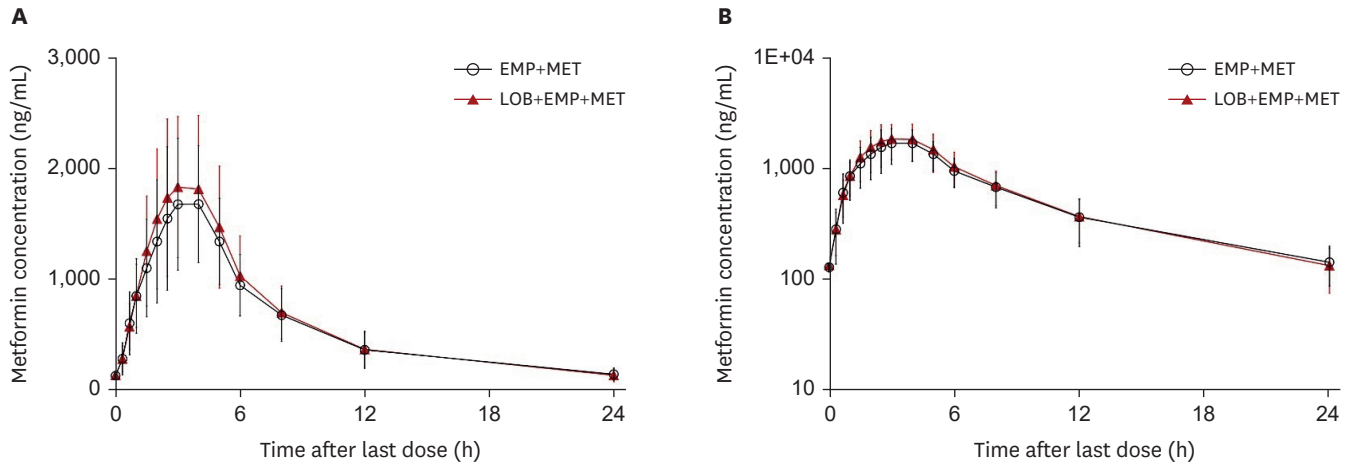

Figure 3. Mean (standard deviation) plasma concentration-time profiles at steady state of metformin when administered as dual therapy and as part of triple therapy. (A) Linear scale; (B) Semi-log scale.
EMP + MET, administration of empagliflozin 25 mg and metformin 1,000 mg 2 tablets, once daily for 5 days; LOB + EMP + MET, administration of lobeglitazone 10 mg, empagliflozin 25 mg, and metformin 1,000 mg 2 tablets, once daily for 5 days.

Safety

A total of 21 participants (87.5%) in part 1 and 17 (70.8%) in part 2 of the study experienced at least one AE. All AEs were considered to be related to the study drugs. Diarrhea was the most frequently reported AE in both parts of the study. All the reported AEs are summarized according to the "system of class" of AEs in **Table 4**.

In part 1, there was a statistically significant difference in the number of subjects with AEs between the 2 different treatments (generalized estimating equations: $p < 0.001$): 3 subjects (13.6%, 3 cases) after lobeglitazone monotherapy and 21 subjects (87.5%, 38 cases) after lobeglitazone, empagliflozin, and metformin triple therapy. The statistically significant difference between the treatment groups was not considered clinically significant. The most reported AE was diarrhea (9 subjects); diarrhea was not reported after monotherapy, but 13 subjects (54.2%, 13 cases) reported diarrhea after triple therapy. In part 2, there was no statistically significant difference in the number of subjects with AEs between the 2

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Table 3. Summary of plasma PK parameters of lobeglitazone, empagliflozin and metformin by treatment group

Drug	PK parameters	LOB (n = 21)		EMP + MET (n = 23)		LOB + EMP + MET (n = 21)		LOB + EMP + MET (n = 23)		GMR (90% CI)	
		Mean ± SD	GeoLSM	Mean ± SD	GeoLSM	Mean ± SD	GeoLSM	Mean ± SD	GeoLSM	LOB+EMP+MET/ LOB	LOB+EMP+MET/ EMP+MET
Lobeglitazone	$C_{max,ss}$ (ng/mL)	51.26 ± 10.71	50.22			55.11 ± 8.67	54.44			1.08 (1.03–1.14)	
	$AUC_{tau,ss}$ (h·ng/mL)	360.81 ± 124.69	344.40			352.83 ± 122.19	338.62			0.98 (0.90–1.07)	
	$C_{min,ss}$ (ng/mL)	0.94 ± 0.32	-			3.56 ± 3.67	-			-	
	$T_{max,ss}$ (h)*	1.00 (0.67–1.50)	-			0.67 (0.67–1.00)	-			-	
	CL_{ss}/F(L/h)	1.53 ± 0.48	-			1.53 ± 0.39	-			-	
Empagliflozin	$C_{max,ss}$ (ng/mL)			520.96 ± 127.15	506.26			455.17 ± 117.03	439.51		0.87 (0.78–0.97)
	$AUC_{tau,ss}$ (h·ng/mL)			3143.61 ± 687.88	3,071.28			3,025.86 ± 602.24	2,965.98		0.97 (0.93–1.00)
	$C_{min,ss}$ (ng/mL)			28.38 ± 10.48	-			28.28 ± 9.34	-		-
	$T_{max,ss}$ (h)*			1.50 (0.67–4.00)	-			2.00 (1.00–5.00)	-		-
	CL_{ss}/F(L/h)			8.30 ± 1.75	-			8.59 ± 1.79	-		-
Metformin	$C_{max,ss}$ (ng/mL)			1,885.87 ± 574.28	1,791.12			2,018.39 ± 708.40	1,891.53		1.06 (0.95–1.17)
	$AUC_{tau,ss}$ (h·ng/mL)			13,783.58 ± 3,770.42	13,311.12			14,544.38 ± 4,461.17	13,859.32		1.04 (0.97–1.12)
	$C_{min,ss}$ (ng/mL)			112.22 ± 54.27	-			103.41 ± 43.58	-		-
	$T_{max,ss}$ (h)*			3.00 (1.50–5.00)	-			4.00 (2.50–5.00)	-		-
	CL_{ss}/F (L/h)			154.63 ± 39.10	-			151.08 ± 50.02	-		-

LOB, lobeglitazone 0.5 mg, once daily for 5 days; EMP + MET, empagliflozin 25 mg 1 tablet, and metformin 1,000 mg 2 tablets, once daily for 5 days; LOB + EMP + MET, lobeglitazone 0.5 mg 1 tablet, empagliflozin 25 mg 1 tablet, and metformin 1,000 mg 2 tablets, once daily for 5 days; SD, standard deviation; GeoLSM, geometric least squares mean; GMR, geometric mean ratio; CI, confidence interval; $C_{max,ss}$, maximum concentration of drug in plasma at steady state; $AUC_{tau,ss}$, area under the plasma concentration-time curve within a dosing interval(tau) at steady state; $C_{min,ss}$, minimum concentration of drug in plasma at steady state; $T_{max,ss}$, time to maximum plasma concentration; CL_{ss}/F, apparent clearance at steady state.
*Values are presented as median (range).

Table 4. Summary of adverse events by system organ class

System organ class	No. of subjects (percentage of subjects with adverse events) [No. of adverse events]					
	Part 1			Part 2		
	LOB (n = 24)	LOB + EMT + MET (n = 24)	Total (n = 24)	EMT + MET (n = 24)	LOB + EMT + MET (n = 24)	Total (n = 24)
Total	3 (13.6) [3]	21 (87.5) [38]	21 (87.5) [41]	15 (62.5) [22]	13 (56.5) [23]	17 (70.8) [45]
Gastrointestinal disorders	2 (9.1) [2]	17 (70.8) [26]	17 (70.8) [28]	13 (54.2) [17]	11 (47.8) [16]	15 (62.5) [33]
Metabolism and nutrition disorders	-	2 (8.3) [2]	2 (8.3) [2]	3 (12.5) [3]	3 (13.0) [4]	6 (25.0) [7]
General disorders and administration site conditions	-	5 (20.8) [5]	5 (20.8) [5]	-	-	-
Renal and urinary disorders	1 (4.5) [1]	3 (12.5) [3]	4 (16.7) [4]	1 (4.2) [1]	1 (4.3) [1]	2 (8.3) [2]
Blood and lymphatic system disorders	-	1 (4.2) [1]	1 (4.2) [1]	-	1 (4.3) [1]	1 (4.2) [1]
Hepatobiliary disorders	-	1 (4.2) [1]	1 (4.2) [1]	-	1 (4.3) [1]	1 (4.2) [1]
Nervous system disorders	-	-	-	1 (4.2) [1]	-	1 (4.2) [1]

LOB, lobeglitazone 0.5 mg, once daily for 5 days; EMP + MET, empagliflozin 25 mg 1 tablet, and metformin 1,000 mg 2 tablets, once daily for 5 days; LOB + EMP + MET, lobeglitazone 0.5 mg 1 tablet, empagliflozin 25 mg 1 tablet, and metformin 1,000 mg 2 tablets, once daily for 5 days.

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treatments: 15 subjects (62.5%, 22 cases) after empagliflozin and metformin dual therapy and 13 subjects (56.5%, 23 cases) after lobeglitazone, empagliflozin, and metformin triple therapy. The most reported AE was diarrhea: 9 subjects (37.5%, 9 cases) reported diarrhea after dual therapy and 8 subjects (38.4%, 8 cases) reported diarrhea after triple therapy. No severe AEs were reported, and all the subjects fully recovered from the AEs.

DISCUSSION

Two separate multiple-dose crossover part-studies were conducted to evaluate the PK drug–drug interactions among empagliflozin, metformin, and lobeglitazone at steady state. The 5-day drug dosing period and designed 24 hours blood sampling schedule were considered to be appropriate for estimating drug exposure at steady state and adequate for precluding the carryover effect considering the known elimination half-lives of empagliflozin, metformin, and lobeglitazone, which are 12.4 hours, 5 hours, 7.8–9.8 hours, respectively [12,14,15]. The washout periods were set to 10 days (part 1) and 17 days (part 2), which were adequate to preclude the carry-over effect, considering that there were no subjects whose pre-dose plasma concentrations of empagliflozin, metformin, and lobeglitazone were detectable in period 2 of each sequence group.

Lobeglitazone is mainly metabolized by cytochrome P450 enzymes such as CYP1A2, 2C9, and 2C19, and only a small amount is excreted unchanged via the renal pathway [16,17]. The main metabolic pathway of empagliflozin is glucuronidation by UGT1A3, 1A8, 1A9, and 2B7 isozymes, and the contributions of the hepatic and renal excretion pathways are known to be similar [18]. In the case of metformin, the main elimination pathway is via the renal route, with approximately 90% of the absorbed drug being eliminated in this way [19]. Several studies also reported no significant PK drug interactions and tolerability of lobeglitazone with other antidiabetic drugs whose classes were similar to those investigated in this study [20-24]. Therefore, it was expected that the PK interactions on the metabolism, and excretion of lobeglitazone, empagliflozin, and metformin triple therapy would be negligible because the metabolic pathways of lobeglitazone, empagliflozin and metformin are different. In this study, the $AUC_{tau,ss}$ and $C_{max,ss}$ of lobeglitazone were similar regardless of its sole or concomitant administration with empagliflozin and metformin. The primary PK parameters of empagliflozin and metformin were also consistent with or without co-administration of lobeglitazone. Hence, these results implied that there were no meaningful PK drug interactions when empagliflozin, metformin, and lobeglitazone were concomitantly administered.

Although, in the case of empagliflozin, the lower margin of 90% CI for $C_{max,ss}$ of triple therapy to dual therapy was not within the 80 to 125 percent range, it was not judged to be significant as the geometric mean ratio difference was not enough to be assessed for considering lobeglitazone and metformin as weak inducers according to guideline [13]. In addition, $AUC_{tau,ss}$, which reflects the total amount of drug absorbed into the body and reaching the systemic circulation, was similar between the triple therapy group and the dual therapy group.

There was statistically significant difference in the number of subjects with AEs between monotherapy and triple therapy in part 1 study. The difference was presumed to be due to metformin based on the reported safety profiles of metformin that gastrointestinal AE was frequently occurred after administering metformin [25]. This hypothesis can be supported by the result that there was no statistically significant difference in the incidence of AEs between

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the dual therapy and the triple therapy groups in part 2 study, which contained metformin therapy. The statistical difference in the incidence of AEs in the part 1 study was considered clinically insignificant considering the clinical perspective since the AEs were all mild and recovered without sequelae.

This study has 2 limitations. First, the objective was not confirmatory, so the sample size was not calculated considering inter- or intra-individual variability; therefore, the study results could not be used to declare that drug interactions among empagliflozin, metformin, and lobeglitazone are totally negligible. Second, this study recruited healthy male volunteers and not patients with T2DM. Therefore, it is necessary to confirm the efficacy and safety of the 3-agent combination therapy of empagliflozin, metformin, and lobeglitazone in patients with T2DM through a follow-up study.

In conclusion, the drug interactions between lobeglitazone, empagliflozin, and metformin following their co-administration were not clinically significant. Based on these results, triple therapy consisting of empagliflozin, metformin, and lobeglitazone may be used without the consideration of dose adjustment owing to PK interaction.

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