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Address for Correspondence:

Kyun-Seop Bae, MD, PhD

Department of Clinical Pharmacology and Therapeutics, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.  
E-mail: ksbae@amc.seoul.kr

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ORCID iDs

Yong-Soon Cho

<https://orcid.org/0000-0003-1424-1123>

Shi Hyang Lee

<https://orcid.org/0000-0002-5565-8278>

Hyeong-Seok Lim

<https://orcid.org/0000-0002-0352-6599>

Kyun-Seop Bae

<https://orcid.org/0000-0001-7399-5879>

Trial Registration

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# Pharmacokinetic Equivalence of the High Dose Strength Fixed-Dose Combination Tablet of Gemigliptin/Metformin Sustained Release (SR) and Individual Component Gemigliptin and Metformin XR Tablets in Healthy Subjects

Yong-Soon Cho , Shi Hyang Lee , Hyeong-Seok Lim , and Kyun-Seop Bae

Department of Clinical Pharmacology and Therapeutics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

## ABSTRACT

**Background:** In type 2 diabetes mellitus therapy, fixed-dose combination (FDC) can offer not only benefits in glucose control via the combined use of agents, but also increase patient compliance. The aim of this study was to assess the pharmacokinetic equivalence of the high dose of the FDC tablet (gemigliptin/metformin sustained release [SR] 50/1,000 mg) and a corresponding co-administered dose of individual tablets.

**Methods:** This study was randomized, open-label, single dose, two treatments, two-period, crossover study, which included 24 healthy subjects. Subjects received the FDC or individual tablets of gemigliptin (50 mg) and metformin XR (1,000 mg) in each period. Geometric mean ratios (GMRs) and 90% confidence intervals (CIs) of maximum plasma concentration ( $C_{max}$ ) and area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration ( $AUC_{last}$ ) of the FDC tablet and co-administration of individual tablet for both gemigliptin and metformin were calculated.

**Results:** The GMRs (FDC tablets/co-administration; 90% CIs) for  $C_{max}$  and  $AUC_{last}$  of gemigliptin were 1.079 (0.986–1.180) and 1.047 (1.014–1.080), respectively. For metformin, the GMRs for  $C_{max}$  and  $AUC_{last}$  were 1.038 (0.995–1.083) and 1.041 (0.997–1.088), respectively. The 90% CIs for GMRs of  $C_{max}$  and  $AUC_{last}$  for gemigliptin and metformin fell entirely within bounds of 0.800–1.250. Both administration of FDC tablet and co-administration of individual tablets were well tolerated.

**Conclusion:** FDC tablet exhibited pharmacokinetic equivalence and comparable safety and tolerability to co-administration of corresponding doses of gemigliptin and metformin XR as individual tablets.

**Trial Registration:** ClinicalTrials.gov Identifier: NCT02056600

**Keywords:** Gemigliptin/Metformin-SR; FDC; Pharmacokinetic Equivalence; Pharmacokinetics

**Disclosure**

The authors have no potential conflicts of interest to disclose.

**Author Contributions**

Conceptualization: Cho YS, Bae KS. Data curation: Cho YS, Lee SH. Formal analysis: Cho YS. Methodology: Lee SH. Writing - original draft: Cho YS, Bae KS. Writing - review & editing: Cho YS, Lim HS, Bae KS.

**INTRODUCTION**

Type 2 diabetes mellitus (T2DM) is a chronic progressive disease caused by a complex pathophysiology that includes insufficient insulin production, insulin resistance, increased hepatic glucose output, and other mechanisms such as incretin deficiency or resistance to incretin in the gastrointestinal tract.<sup>1</sup> Monotherapy with metformin, a biguanide agent that primarily acts to lower hepatic glucose output, is the most widely prescribed first-line oral anti-hyperglycemic agent.<sup>2</sup> However, recent studies reported that monotherapy with metformin or other traditional anti-diabetic agents is frequently unsuccessful in the attainment or maintenance of target glucose level.<sup>2</sup> Combination therapy with one or more oral anti-diabetic agents is often required to achieve therapeutic goals and effectively manage the treatment of patients with T2DM.

Dipeptidyl peptidase (DPP)-4 inhibitors are a relatively new class of oral anti-diabetic agents and are widely used in various combination therapies because of their robust efficacy, good tolerability, and overall favorable safety profile. They increase the concentration of the endogenous active form of incretin hormones, glucagon-like peptide-1 (GLP-1), and glucose dependent insulinotropic peptide (GIP) by preventing the degradation of their intact forms.<sup>3-5</sup> GLP-1 and GIP are both released from L and K cells, respectively, into the systemic circulation in response to a meal. Both hormones stimulate glucose-dependent insulin secretion from pancreatic beta cells, leading to glucose uptake by peripheral tissues. GLP-1 also acts on pancreatic alpha cells to block glucagon secretion, reducing glucose production in the liver.<sup>6-9</sup> Consequently, DPP-4 inhibitors improve overall glycemic control with a low risk of hypoglycemia and weight gain owing to the incretin-based mechanism of action.

Gemigliptin (Zemiglo®; LG Chem, Ltd., Seoul, Korea) is a synthetic, potent, reversible, orally active DPP-4 inhibitor that was approved for treatment of T2DM in Korea.<sup>10</sup> In a single ascending-dose study on healthy volunteers, gemigliptin was rapidly absorbed, possessing a the time to reach maximum plasma concentration ( $C_{max}$ ) ( $T_{max}$ ) of 0.5–5.1 hours, following oral administration, while its elimination was slower, as indicated by its long half-life (16.7–21.3 hours). It also exhibited dose-linear  $C_{max}$  and area under the curve (AUC) that were in the range of 50–400 mg, and inhibited plasma DPP-4 activity by > 80% 24 hours after the administration of a  $\geq 200$  mg dose.<sup>11</sup> Gemigliptin is primarily metabolized by hydroxylation to the metabolite LC15-0636 via cytochrome P450 (CYP) 3A4 in humans.<sup>12</sup> The efficacy and safety of gemigliptin for T2DM treatment have been demonstrated in many clinical trials. Gemigliptin significantly not only reduces the glycemic parameters, including hemoglobin A1c (HbA1c), fasting plasma glucose, and post-prandial plasma glucose but also improves insulin sensitivity, when compared with a placebo.<sup>10-13</sup> This drug was well tolerated in T2DM patients and the tolerability profiles were similar to placebo profiles in phase II and III trials.<sup>10-13</sup>

The combined use of gemigliptin and metformin is effective in the treatment of T2DM, which is consistent with the mechanism of action by which gemigliptin and metformin improve glucose control. A phase II study conducted in patients with T2DM demonstrated that the addition of a 50 mg dose of gemigliptin to a daily dose of 1,000 mg metformin significantly improved glycemic control relative to metformin monotherapy in patients whose parameters were inadequately controlled with metformin alone. The treatment was also found not to increase the risk of adverse events (AEs).<sup>14</sup> Additionally, in a drug-drug interaction study performed in (executed on) healthy subjects, co-administration of 50 mg gemigliptin and

1,000 mg metformin resulted in an increase in active GLP-1 concentration and a decrease in serum glucose levels without any significant effect on the pharmacokinetic profile of gemigliptin or metformin.<sup>15</sup>

The use of fixed-dose combination (FDC) formulations of two or more therapeutic agents with complementary mechanisms of action has been increasing in the clinical setting. With the goal of optimizing patient compliance, gemigliptin/metformin sustained release (SR) FDC tablets (Zemimet® SR; LG Chem, Ltd.) consisting of 25 mg or 50 mg gemigliptin and 500 mg or 1,000 mg metformin administered as two tablets of gemigliptin/metformin SR 25/500 mg qd, one tablet of gemigliptin/metformin SR 50/500 mg qd and one tablet of gemigliptin/metformin SR 50/1,000 mg qd have been developed for the treatment of T2DM. A recent study reported that the pharmacokinetics, pharmacodynamics, and tolerability profile of gemigliptin and metformin were comparable in healthy subjects who were administered a FDC (gemigliptin/metformin SR 25 mg/500 mg) and co-administered two individual tablets.<sup>16</sup> The objective of this study was to establish pharmacokinetic equivalence between the higher dose strength FDC tablet (gemigliptin/metformin SR 50/1,000 mg) and the corresponding co-administered doses of gemigliptin and metformin as individual tablets in healthy male volunteers.

## METHODS

### Study population

This study enrolled healthy Korean male volunteers aged between 20 and 45 years, with body mass indices (calculated from height and weight) between 18 and 27 kg/m<sup>2</sup> and a fasting glucose level between 70 and 125 mg/dL. All volunteers were assessed by physicians based on their medical histories, physical examination results, laboratory test results (e.g., hematology, blood chemistry, urinalysis, human immunodeficiency virus antibody test, hepatitis B surface antigen, hepatitis C virus, and syphilis high-quality reagent test), electrocardiography (ECG) results, and vital signs. The following volunteer candidates were excluded: participants with chronic, clinically significant medical histories, including drug hypersensitivity, those having donated blood less than 60 days prior to study drug administration, those having taken any drugs that could influence drug metabolism (e.g., barbiturates) less than 30 days prior to dosing and/or prescription drugs less than 14 days prior, those testing positive for opiates, barbiturates, amphetamines, cocaine, and/or benzodiazepines at screening, those with abnormal liver function test results (e.g., aspartate aminotransferase, alanine aminotransferase, total bilirubin > 1.5 times the upper normal limit), those with low or high blood pressure (BP; systolic BP < 90 or > 145 mmHg; diastolic BP < 60 or > 95 mmHg), those with abnormal creatinine clearance (< 80 mL/min as calculated using the Cockcroft-Gault equation) and those exhibiting abnormal results on ECG, especially corrected QT > 450 ms. All laboratory tests were performed at the Department of Laboratory Medicine of Asan Medical Center (Seoul, Korea), which is accredited by the Korean Association of Quality Assurance for Clinical Laboratories and certified by the College of American Pathologists.

### Study design

This randomized, open-label, two-period, two-sequence crossover study was conducted at the Asan Medical Center. Twenty-four eligible volunteers were randomized to receive a single oral dose of the FDC tablet (gemigliptin/metformin SR 50 mg/1,000 mg) in one

period, and a co-administration of both a single oral dose of a 50 mg gemigliptin tablet (Zemiglo) and a 100 mg metformin XR tablet (Glucophage XR) in another period. To our best knowledge, depending on the manufacturer, XR, a more comprehensive term, can be used for the same product instead of SR and metformins used in most clinical studies are those marketed as XR. For these reasons, we used XR formulations for metformin of the co-administration of individual tablets whereas SR formulations for metformin of the FDC. The random assignment was performed according to a randomization table that was generated using R<sup>®</sup> version 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria). There was a 7-day washout between the two periods, which was deemed appropriate given that this was over five times the half-life ( $t_{1/2}$ ) of both gemigliptin and metformin XR and no significant pharmacokinetic interactions were observed between the two drugs.<sup>15</sup> In each period, subjects were admitted to hospital on Day 1 and discharged on Day 2 after all the blood samples were collected at 48 hours post-dose. In clinical practice, gemigliptin can be administered irrespective of diet, and metformin is administered after meals. Furthermore, because both of them have some food effect, the study was conducted under fed conditions. After an overnight fast lasting a minimum of 10 hours, participants were started on a high-fat meal (900 kcal; fat content of 50% or more) 30 minutes prior to administration of study medication. The tablets were administered with 240 mL of water within 5 minutes of finishing breakfast. Subjects were seated on a bed at 45° for 4 hours. Food was restricted for 4 hours and water was not allowed for 2 hours following study drug administration. Throughout the study period, smoking, the ingestion of beverages containing caffeine or alcohol, and heavy exercise were not allowed.

### Blood sampling

Blood samples (8 mL) for determination of plasma concentrations of gemigliptin and metformin were collected prior to and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 24, 32, and 48 hours after dosing. Samples were collected in heparinized tubes, and 1.5 mL blood was discarded before obtaining samples from an inserted angiocatheter. Plasma was extracted by centrifugation at 1,800 g for 8 minutes at 4°C, and 0.5 mL each was immediately transferred to two Eppendorf tubes and mixed by vortexing with 5% formic acid (FA; 98%) in 0.5 mL water. The remaining plasma was divided and 1 mL each was transferred to two Eppendorf tubes. The four Eppendorf tubes containing plasma were frozen at -70°C until they were shipped to the Chemical Structure Analysis Team of LG Chem, Ltd., (Daejeon, Korea), where gemigliptin and metformin concentrations were assayed.

### Bioanalytical methods

Plasma concentrations of gemigliptin and metformin were determined by the Chemical Structure Analysis Team of LG Chem, Ltd., using a validated liquid chromatography (LC, for gemigliptin and Shiseido NASCA; Shiseido, Tokyo, Japan and for metformin, Agilent 1,100 series; Agilent Technologies, Wilmington, DE, USA)–tandem mass spectrometry (MS/MS, AB Sciex, Framingham, MA, USA). For gemigliptin, chromatographic separation was performed at 40°C using a Unison UK-C18<sup>®</sup> column (3  $\mu$ m, 50.0  $\times$  2.0 mm; Imtakt, Kyoto, Japan) operated under reverse-phase conditions with the mobile phase consisting of solvent A (water with 0.1% formic acid) and solvent B (methanol with 0.1% formic acid). Calibration standards covered the theoretical concentration range of 0.5–200 ng/mL gemigliptin ( $R^2 > 0.996$ ). Using this assay, the accuracy of the calibration standard curve for gemigliptin was between 98.0% and 102.0%, and the coefficient of variation (CV) of the back-calculated concentration was < 6.58%. The accuracy of the quality control (QC) samples for gemigliptin, for the low (1.5 ng/mL), middle (12 ng/mL) and high (160 ng/mL) concentrations were 106%, 106%, and 101%, with CVs 2.75%,

3.44%, and 4.27%, respectively. The lower limits of quantification (LLOQ) for gemigliptin were 0.5 ng/mL.

Chromatographic separation for metformin was performed at 40°C using a phosphorylcholine (PC) hydrophilic interaction LC (HILIC) column (2.0 mm ID × 150 mm; Shiseido, Yokohama, Japan) operated under reverse-phase conditions consisting of mobile phase A (10 mM ammonium acetate) with 0.1% FA and mobile phase B (acetonitrile) with 0.1% formic acid. The standard curve range of metformin was 2.0–2,000.0 ng/mL. The accuracy of the calibration standard curve was between 98.2% and 105.0%, and the CV of the back-calculated concentration was < 7.2%. The accuracy of the QC samples for metformin for the low (6.00 ng/mL), mid (200 ng/mL) and high (1,600 ng/mL) concentrations were 103%, 103%, and 104%, with CVs 6.04%, 2.70%, and 3.14% respectively. The LLOQ for metformin was 2.0 ng/mL. All assays were conducted in a blinded manner in terms of treatment, sequence, and period.

### Safety and tolerability assessments

All subjects who received more than one dose of the study drug were included in the tolerability analyses. All AEs were noted regardless of the suspected relationship with the study drugs. Evaluation of safety was accomplished through subject-reported adverse experiences, investigator observations and assessment, and pre-specified study evaluations (clinical laboratory tests — serum chemistry, hematology, and urinalysis, 12-lead ECG, vital sign measurements, and physical examinations). All AEs were rated by investigators for severity (mild, moderate, and severe) and relationships to study drugs (definitely not, probably not, possibly, probably, and definitely). If abnormal vital signs, ECGs, and/or clinical laboratory test results were observed, the investigators subsequently assessed the clinical significance and relationship to the study drug and considered further evaluation and/or treatment if needed.

### Statistical analysis

The pharmacokinetic parameters of gemigliptin and metformin were derived from plasma concentration-time data, using non-compartmental analysis with Phoenix® WinNonlin® version 6.3 (Pharsight, San Diego, CA, USA). Actual, rather than scheduled blood sampling time were used to determine the pharmacokinetic parameters while scheduled (nominal) times were used to present the results in the figures. The pharmacokinetic parameters for both gemigliptin and metformin, which were used to assess pharmacokinetic equivalence between the FDC tablet (gemigliptin/metformin SR 50 mg/1,000 mg) and their individual components, included the  $C_{max}$  and the AUC from time zero to the time of the last measurable concentration ( $AUC_{last}$ ). The log-transformed individual  $C_{max}$  and  $AUC_{last}$  were compared using mixed-effect model analysis of variance (SAS® version 9.3; SAS institute Inc., Cary, NC, USA). Sequence, period, and treatment were considered fixed effect, and subjects were nested within the sequence as random effects. The 90% confidence intervals (CIs) of the geometric mean ratios (GMRs) for the pharmacokinetic parameters of each treatment, gemigliptin and metformin, were compared using pharmacokinetic equivalence limits of 0.8 and 1.25. The following for all analytes after administration were also calculated:  $T_{max}$  and the elimination half-life ( $t_{1/2}$ ).

### Ethics statement

This is a randomized clinical trial, registered at ClinicalTrials.gov (<https://clinicaltrials.gov/>), number NCT02056600. All volunteers provided written informed consent prior to

screening, and this trial was conducted in accordance with the International Conference of Harmonization (ICH) guidelines for good clinical practice.<sup>17</sup> The Institutional Review Board of Asan Medical Center approved the study protocol prior to the start of the trial in 2014 (approval No. 2014-0101).

## RESULTS

### Demographics

In the present study, 24 subjects were enrolled, but one discontinued in the washout period because of the development of an AE (corneal abrasion) and consequent medication. Therefore, 23 subjects completed the study according to the protocol and were evaluated as part of the pharmacokinetic analysis, whereas all of the enrolled subjects (n = 24) were included in the safety analysis. The mean (standard deviation [SD]) age of study participants was 25.88 (3.17) years, the mean (SD) height was 175.16 (5.61) cm, and the mean (SD) weight was 68.18 (7.40) kg, none of which significantly differed between sequence groups ( $P > 0.05$ ; **Table 1**).

### Pharmacokinetics

The mean plasma concentration versus time profiles for gemigliptin and metformin obtained from a single administration of the FDC tablet (gemigliptin/metformin SR 50 mg/1,000 mg) under fed conditions, as well as co-administration of a gemigliptin 50 mg tablet and a metformin XR 1,000 mg tablet in the fed state, are illustrated in **Fig. 1**. Following administration of single gemigliptin/metformin SR FDC tablets and co-administration of the corresponding doses of gemigliptin and metformin as individual tablets, the plasma concentrations of gemigliptin and metformin were virtually superimposable. Summary statistics for  $C_{max}$ ,  $T_{max}$ ,  $AUC_{last}$ ,  $AUC_{inf}$ , and  $t_{1/2}$  for gemigliptin and metformin are provided in **Table 2** (gemigliptin) and **Table 3** (metformin). Individual  $C_{max}$  and  $AUC_{last}$  values and box-and-whisker plot for FDC tablet and co-administration of separate tablets in gemigliptin and metformin are presented in **Fig. 2**. GMRs for FDC tablet/co-administration of the individual components and the associated 90% CIs for the  $C_{max}$  and  $AUC_{last}$  of gemigliptin and metformin are shown in the same tables. The GMRs (FDC tablets/co-administration; 90% CIs) for  $C_{max}$  and  $AUC_{last}$  of gemigliptin were 1.079 (0.986–1.180) and 1.047 (1.014–1.080), respectively (**Table 2**). The GMRs (FDC tablets/co-administration; 90% CIs) for  $C_{max}$  and

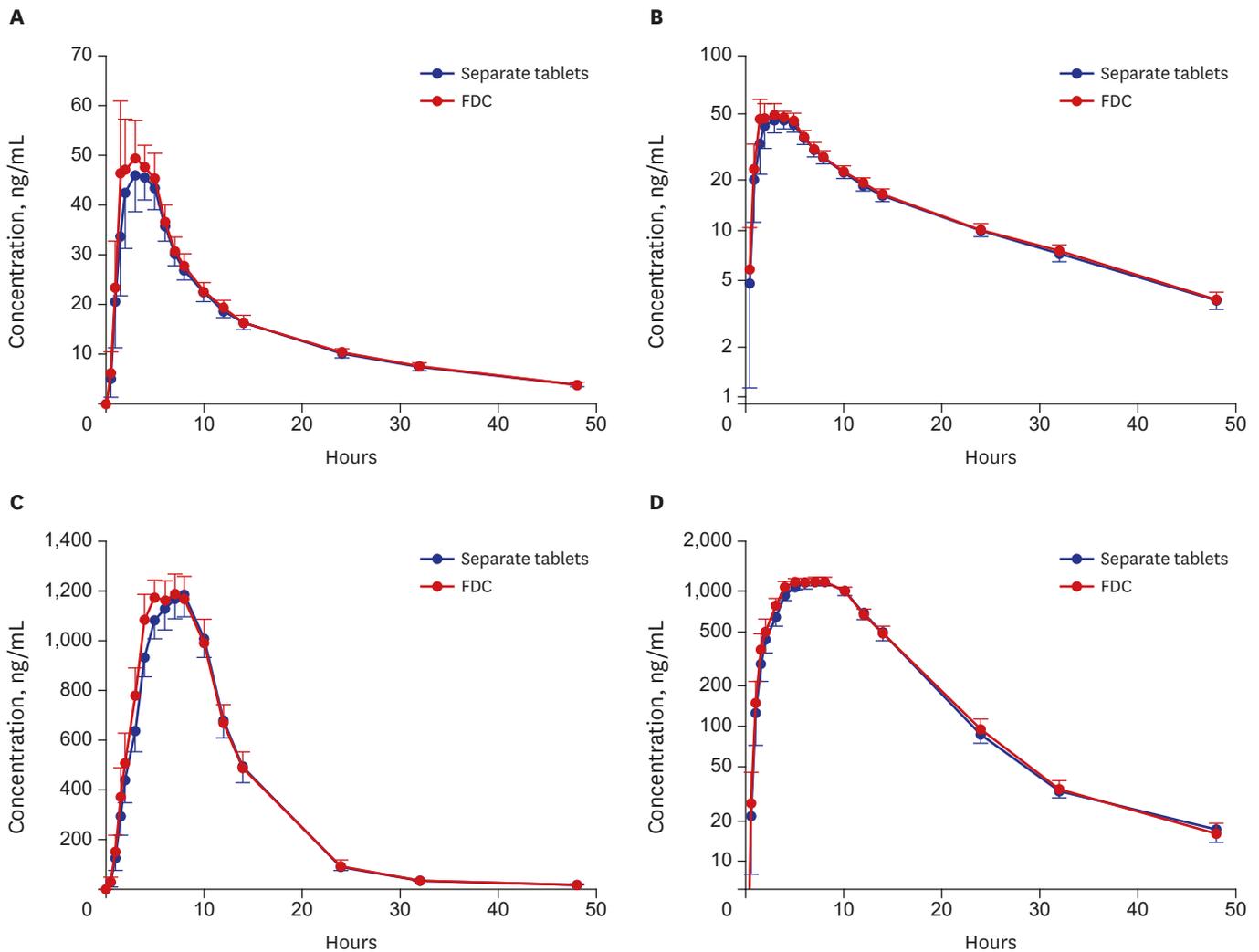
**Table 1.** Baseline characteristics of the present study

Characteristics		Sequence		Total (n = 24)	P value <sup>c</sup>
		1 (R <sup>a</sup> →T <sup>b</sup> , n = 12)	2 (T→R, n = 12)		
Age, yr	Mean	25.58	26.17	25.88	0.7059
	SD	2.71	3.66	3.17	
	Min–Max	22.00–32.00	20.00–32.00	20.00–32.00	
	Med	25	27.5	25	
Height, cm	Mean	175.87	174.45	175.16	0.5833
	SD	4.46	6.7	5.61	
	Min–Max	168.40–183.30	162.70–184.60	162.70–184.60	
	Med	175.8	174.5	175.75	
Weight, kg	Mean	67.53	68.84	68.18	0.7728
	SD	6.42	8.5	7.4	
	Min–Max	57.40–80.10	55.85–86.70	55.85–86.70	
	Med	67.73	67.95	67.73	

SD = standard deviation, Min = minimum, Max = maximum, Med = median, FDC = fixed-dose combination, SR = sustained release.

<sup>a</sup>Co-administration of a single oral dose of gemigliptin 50 mg and metformin 1,000 mg; <sup>b</sup>A single oral dose of the FDC tablet (gemigliptin/metformin SR 50/1,000 mg);

<sup>c</sup>Obtained by Wilcoxon's rank sum test.



**Fig. 1.** Mean plasma concentration-time profile of gemigliptin and metformin following administration of a single dose of FDC tablet (gemigliptin/metformin SR 50/1,000 mg) and co-administration of gemigliptin 50 mg+metformin XR 1,000 mg. Plasma concentrations of gemigliptin are plotted on a (A) linear or (B) log scale and those of metformin are plotted on a (C) linear or (D) log scale. The error bars indicate standard deviations. FDC = fixed-dose combination, SR = sustained release.

$AUC_{last}$  of metformin were 1.038 (0.995–1.083) and 1.041 (0.997–1.088), respectively (Table 3). The 90% CIs for GMRs of gemigliptin and metformin  $C_{max}$  and  $AUC_{last}$  fell entirely within the pre-specified bounds of 0.800 and 1.250 necessary to confirm pharmacokinetic equivalence (Tables 2 and 3).

**Table 2.** Plasma pharmacokinetic parameters of gemigliptin given as an FDC or as individual components

Parameters	Individual components (n = 23)	FDC (n = 3)	GMR <sup>a</sup>
$C_{max}$ , ng/mL	61.86 ± 17.16	67.78 ± 23.91	1.079 (0.986–1.180)
$AUC_{last}$ , ng·hr/mL	676.45 ± 114.23	707.57 ± 123.14	1.047 (1.014–1.080)
$AUC_{inf}$ , ng·hr/mL	770.41 ± 140.82	800.75 ± 140.94	-
$T_{max}$ , hr	3.00 (1.00–5.00)	3.00 (1.00–5.00)	-
$t_{1/2}$ , hr	16.48 (13.01–22.70)	15.81 (11.98–22.73)	-

Summarized as arithmetic mean ± standard deviation except for  $T_{max}$  and  $t_{1/2}$ , for which median (minimum–maximum). FDC = fixed-dose combination, GMR = geometric mean ratio,  $C_{max}$  = maximum plasma concentration,  $AUC_{last}$  = area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration,  $AUC_{inf}$  = area under the plasma concentration-time curve extrapolated to infinity,  $T_{max}$  = time to the maximum plasma concentration,  $t_{1/2}$  = elimination half-life, CI = confidence interval. <sup>a</sup>GMR of FDC to individual tablets (90% CI).

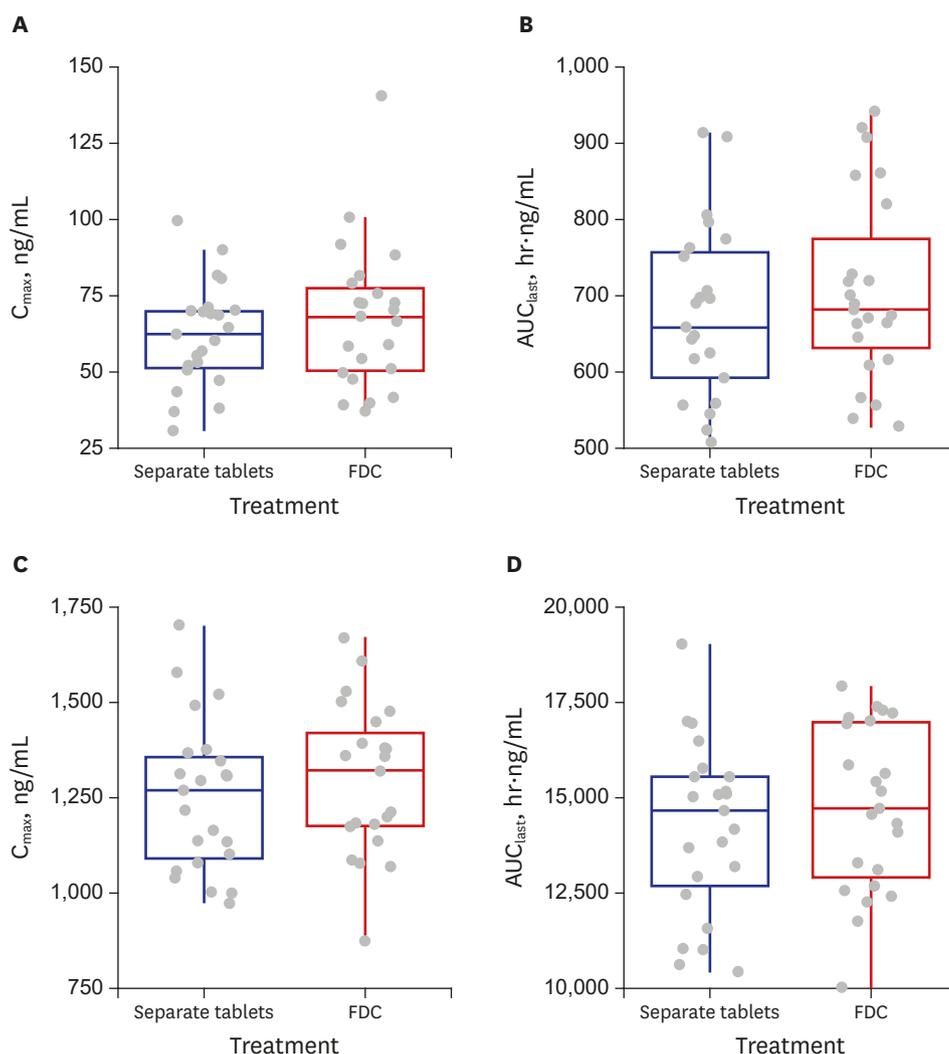
**Table 3.** Plasma pharmacokinetic parameters of metformin given as an FDC or as individual components

Parameters	Individual components (n = 23)	FDC (n = 23)	GMR <sup>a</sup>
C <sub>max</sub> , ng/mL	1,250.61 ± 197.86	1,297.09 ± 194.74	1.038 (0.995-1.083)
AUC <sub>last</sub> , ng·hr/mL	14,184.39 ± 2,269.01	14,726.80 ± 2,186.28	1.041 (0.997-1.088)
AUC <sub>inf</sub> , ng·hr/mL	14,359.66 ± 2,248.86	14,881.53 ± 2,217.91	
T <sub>max</sub> , hr	8.00 (5.00-10.02)	7.00 (4.00-9.97)	
t <sub>1/2</sub> , hr	6.42 (4.90-14.48)	6.23 (4.69-10.59)	

Summarized as arithmetic mean ± standard deviation except for T<sub>max</sub> and t<sub>1/2</sub>, for which median (minimum–maximum).

FDC = fixed-dose combination, GMR = geometric mean ratio, C<sub>max</sub> = maximum plasma concentration, AUC<sub>last</sub> = area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration, AUC<sub>inf</sub> = area under the plasma concentration-time curve extrapolated to infinity, T<sub>max</sub> = time to the maximum plasma concentration, t<sub>1/2</sub> = elimination half-life, CI = confidence interval.

<sup>a</sup>GMR of FDC to individual tablets (90% CI).



**Fig. 2.** Systemic exposure comparison between FDC tablet and co-administration of separate tablets. C<sub>max</sub> values (A) and AUC<sub>last</sub> values (B) of gemigliptin and C<sub>max</sub> values (C) and AUC<sub>last</sub> values (D) of metformin are presented as gray points and box-and-whisker plots. Each box shows the 25th, 50th (median) and 75th percentiles of individual values. FDC = fixed-dose combination, C<sub>max</sub> = maximum plasma concentration, AUC<sub>last</sub> = area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration.

### Safety and tolerability

Eight subjects (33.33%) experienced at least one AE during the present study (Table 4).

Four AEs, i.e., neutrophil count decrease, creatine kinase increase, dizziness, and corneal

Table 4. AEs during the study

MedDRA preferred terms	Individual component (n = 24)		FDC (n = 24)		Total	
	N <sup>a</sup> /n <sup>b</sup>	P, % <sup>c</sup>	N/n	P, %	N/n	P, %
Alanine aminotransferase increase	0/0	0.0	1/1	4.17	1/1	4.17
Aspartate aminotransferase increase	0/0	0.0	1/1	4.17	1/1	4.17
Neutrophil count decrease	1/1	4.17	1/1	4.17	2/2	8.33
Creatine kinase increase	1/1	4.17	0/0	0.0	1/1	4.17
Dizziness	1/1	4.17	0/0	0.0	1/1	4.17
Rhinorrhea	0/0	0.0	2/2	8.33	2/2	8.33
Upper abdominal discomfort	0/0	0.0	1/1	4.17	1/1	4.17
Corneal abrasion	1/1	4.17	0/0	0.0	1/1	4.17
Total	4/4	16.67	4/6	16.67	8/10	33.33

AE = adverse event, FDC = fixed-dose combination, MedDRA = medical dictionary for regulatory activities.

<sup>a</sup>Number of subjects with AEs; <sup>b</sup>Number of AEs; <sup>c</sup>Percent based on the subjects within each treatment group.

abrasion, were reported for 4 subjects following co-administration of gemigliptin and metformin as individual tablets, while six AEs, i.e., alanine aminotransferase increase, aspartate aminotransferase increase, neutrophil count decrease, rhinorrhea, and upper abdominal discomfort, were reported in 4 subjects following administration of the FDC tablet. All reported AEs were considered mild to moderate in severity by the study investigator and were resolved by the end of the study without additional treatment, except one case of a corneal abrasion: this AE occurred in the washout period following co-administration of gemigliptin and metformin as individual tablets, and the subject took the necessary medication and was withdrawn from study by the investigator because of violation of the condition prohibiting concomitant medication. However, this case was assessed as definitely not related to the study drug and he recovered after 1 month of treatment and finished the study. Overall, 7 AEs were considered possibly related to the study drug, including alanine aminotransferase increase, aspartate aminotransferase increase, neutrophil count decrease, rhinorrhea, and upper abdominal discomfort. Other AEs were assessed as unlikely or definitely not related to the study drug. No deaths or serious AEs were reported in this study. There was no apparent imbalance between treatment groups with regard to AEs.

## DISCUSSION

Clinical studies have shown that the addition of gemigliptin to the treatment regimen for patients with T2DM inadequately controlled with metformin alone provides clinically significant reduction in glycosylated hemoglobin (HbA1c).<sup>14</sup> Co-administration of gemigliptin and metformin also produces a meaningful decrease in fasting and postprandial glycemic parameters and an increase in GLP-1 and  $\beta$ -cell sensitivity to glucose, while maintaining an adequate safety and tolerability profile.<sup>14</sup> High-dose-strength FDC tablets combining gemigliptin and metformin, two oral anti-hyperglycemic agents with different but complementary mechanisms of action are available for the treatment of T2DM. The purpose of the current study was to establish pharmacokinetic equivalence between the high dose strength FDC tablet (gemigliptin/metformin SR 50/1,000 mg) available and co-administration of the corresponding doses of gemigliptin and metformin XR as individual tablets in order to support the bridging of all relevant clinical safety and efficacy data from prior studies of co-administration of gemigliptin and metformin to the FDC tablet. In this study,  $C_{max}$  and  $AUC_{last}$  GMRs of FDC tablet/co-administration for both gemigliptin and metformin were close to unity and the associated 90% CIs fell entirely within the bounds required to establish pharmacokinetic equivalence. Therefore, the results from the study

demonstrate that the FDC tablet is pharmacokinetically equivalent to co-administration of the corresponding dose of gemigliptin and metformin XR as individual tablets. Furthermore, these results are consistent with a similarly designed study comparing two tablets of the FDC (gemigliptin/metformin SR 25/500 mg), collectively, 50 mg and 1,000 mg, and the separate tablets.<sup>16</sup> The reference tablets used in this study were the same as those used in the pivotal safety and efficacy studies for each agent, thus providing a direct link with the FDC tablet. Additionally, the peak and total exposures of LC15-0636 (metabolite of gemigliptin) were similar in both the FDC tablet and the individual tablets, further supporting the interchangeability of the FDC tablet and the individual tablets (data not shown).

A single dose of the FDC tablet (gemigliptin/metformin SR 50/1,000 mg) and co-administration of gemigliptin and metformin XR as individual tablets were generally well tolerated in healthy adult subjects in the present study and observed AEs were transient and mild to moderate. There were no serious AEs in this study. Only one subject discontinued the treatment because of an AE and a consequent violation of the prohibition of concomitant medication, but this case was assessed as definitely not related to the study drug. No treatment-related trends were observed in AEs, clinical laboratory results, vital sign measurements, 12-lead ECG results or physical examination findings.

The dose strengths of the gemigliptin/metformin SR FDC tablet are gemigliptin/metformin SR 25/500 mg (which was used in the previous study<sup>16</sup>), gemigliptin/metformin SR 50/500 mg (which has not been examined in a pharmacokinetic equivalence study), and gemigliptin/metformin SR 50/1,000 mg (which was used in the present study). From the present study, for common clinical settings such as a case requiring the high daily dose of gemigliptin (50 mg) and an intermediate dose of metformin (1,000 mg), only one FDC tablet used in this study is needed whereas two different kinds of separate tablets (e.g., one tablet of 50 mg gemigliptin and one of 1,000 mg metformin) or two FDC tablets (e.g., gemigliptin/metformin SR 25/500 mg) should be concomitantly administered. Hence, the FDC (gemigliptin/metformin SR 50/1,000 mg) can reduce pill burden for T2DM patients, which leads to increased convenience and improved compliance, while not affecting safety or efficacy.

In the present study, repeated-dose administration was not assessed. In this respect, additional multiple dosing studies, preferably in patients with T2DM, are warranted to reflect a real clinical setting.

In conclusion, FDC tablet (gemigliptin/metformin SR 50/1,000 mg) showed pharmacokinetic equivalence with individual tablets of gemigliptin and metformin XR co-administered at the corresponding strengths, and was generally well tolerated by healthy adult subjects. These results are consistent with those observed in previous evaluations of administration of lower-dosage-strength FDC tablets (gemigliptin/metformin SR 25/500 mg), supporting the use of FDC tablets as a convenient therapeutic option in patients with T2DM who require a combination of both components.

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