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Trial Registration ClinicalTrials.gov Identifier: NCT03355014 Pharmacokinetics and pharmacodynamics of a fixed-dose combination of gemigliptin/metformin sustained release 25/500 mg compared to the loose combination in healthy male subjects

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ABSTRACT

A fixed-dose combination (FDC) of gemigliptin/metformin can improve the medication adherence in patients with type 2 diabetes mellitus (T2DM). In this study, the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of gemigliptin and metformin were compared between FDC and the corresponding loose combination under fasted and fed states. A two-part, randomized, open label, single-dose, two-way crossover study was conducted in healthy male subjects. Under fasted (part 1) or fed (part 2) state, 2 FDC tablets of gemigliptin/ metformin sustained release (SR) 25/500 mg or loose combination with one tablet of gemigliptin 50 mg and two tablets of metformin extended release (XR) 500 mg were orally administered in each period with a 7-day washout. Serial blood samples were collected up to 48 hours to determine the drug concentration and the dipeptidyl peptidase 4 (DPP-4) activity. The concentration-time profiles of gemigliptin and metformin were similar between FDC and loose combination in both the fasted and fed states. Geometric mean ratios and 90% confidence intervals of FDC to loose combination for area under the concentration-time curve and maximum plasma concentration of gemigliptin and metformin were within the bioequivalence range (0.8–1.25) in both states. DPP-4 activity-time profiles of FDC were comparable to that of the loose combination, showing similar area under the DPP-4 inhibition-time curve and maximum DPP-4 inhibition between FDC and loose combination, regardless of the fasted or fed state. In conclusion, the PK/PD characteristics of gemigliptin and metformin were similar in FDC tablets and loose combination both in fasted and fed states.

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Keywords: Fixed-dose combination; Gemigliptin; Metformin

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Conflict of interest

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Conceptualization: Jin X, Kim E, Yu KS, Lee S; Formal analysis: Jin X, Kim E; Investigation: Jin X, Kim E, Huh KY, Hwang I, Cho JY, Yu KS, Lee S; Supervision: Yu KS, Lee S; Writing - original draft: Jin X, Lee S; Writing - review & editing: Kim E, Huh KY, Hwang I, Cho JY, Yu KS, Lee S.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic disease that is characterized by hyperglycemia [1]. The T2DM is caused due to various reasons, such as decrease in pancreatic insulin secretion, insulin resistance in target tissue, and unrestrained hepatic glucose production [2]. According to the treatment guideline for T2DM, metformin monotherapy is considered as the first-line treatment and dipeptidyl peptidase 4 (DPP-4) inhibitor, sodium glucose cotransporter 2 (SGLT2) inhibitor, or thiazolidinedione can be added as second line treatment [3]. DPP-4 inhibitor has satisfactory glycemic control with lower incidence of hypoglycemia when compared to conventional antidiabetic drug [4]. Furthermore, DPP-4 inhibitor is used commonly as add-on to metformin when metformin monotherapy is insufficient for glycemic control, particularly when there is a desire to minimize the risk for hypoglycemia [5].

Gemigliptin (Zemiglo[®]; LG Chem, Ltd., Seoul, Korea) is a synthetic, potent, reversible, orally active DPP-4 inhibitor that was approved for treatment of T2DM [6]. Gemigliptin can increase the secretion of insulin and regulates blood glucose by reducing glucagon-like peptide-1 (GLP-1) decompositions through inhibiting DPP-4 activity [7]. Gemigliptin was rapidly absorbed and the maximum concentration (C_{max}) was attained at 2 hours with a terminal half-life ($t_{1/2}$) of 17.1 hours [8]. The pharmacokinetic (PK) properties showed linearity over a dose range of 50–400 mg [7]. Gemigliptin is primarily metabolized by CYP3A4 and produce active metabolites of LC15-0636, which shows twice potent DPP-4 inhibitory activity compared with the parent drug and accounts for more than 10% of total drug-related systemic exposure [9]. Metformin, a biguanide antihyperglycemic drug, which reaches C_{max} within 4–8 hours, with a $t_{1/2}$ of approximately 6.2 hours in plasma with extended-release formulations [10]. The mechanism of action for metformin involves the lowering of glucose production by the liver and also improving insulin sensitivity by increasing peripheral glucose uptake and utilization [11].

The fixed-dose combination (FDC) therapy has greater efficacy compared with higher dose monotherapy and can improve the medication adherence [12]. Therefore, for people who are required to take multiple antihyperglycemic agents to achieve glycemic control, FDC is one of the good choices. A previous drug interaction study has shown that the coadministration of gemigliptin and metformin is expected to have beneficial anti-diabetic effects without PK drug-drug interactions [13,14]. Another previous study has elucidated that FDC of gemigliptin/metformin sustained release (SR) and corresponding loose combination have a similar PK/pharmacodynamic (PD) profile and are well tolerable [15]. Therefore, FDC of DPP-4 inhibitor of gemigliptin 25 mg and metformin 500 mg (Zemimet® SR; LG Chem, Ltd., Seoul, Korea) has been developed and marketed. Furthermore, to improve the patient's medication adherence, a new FDC of gemigliptin/metformin SR 25/500 mg with a small size and modified coating formulations was under development by LG Chem, Ltd., (Seoul, Republic of Korea).

In this study, the PK/PD and the safety profiles of gemigliptin and metformin were compared between the new FDC formulation of gemigliptin/metformin SR 25/500 mg and the loose combination of gemigliptin and metformin extended release (XR) (Glucophage XR[®]; Merck & Co., Inc., Seoul, Korea) under fasted and fed states.



METHODS

Subjects and study design

The study was approved by Korea Ministry of Food and Drug Safety and the Institutional Review Board at Seoul National University Hospital (SNUH), Seoul, Republic of Korea (NCT03355014). All procedures were conducted in the Clinical Trials Center of SNUH in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent from all participants was obtained prior to the enrollment.

All participants were healthy Korean male volunteers aged between 19–45 years with fasting glucose levels of 70–125 mg/dL. All the participants had no abnormalities with medical history, physical examination, clinical laboratory tests, 12-lead electrocardiogram (ECG) and urine drug screening. We excluded the subjects who have unusual eating habits, like vegetarians, or those who could not eat the diet provided in this study.

This was a 2-part, randomized, open label, single-dose, two-way crossover study conducted under fasted (part 1) and fed (part 2) states. Each of 40 and 30 eligible participants were enrolled in part 1 and part 2, respectively. In both parts, subjects were randomly assigned to one of the 2 sequences at a 1:1 ratio. The participants were administered either two FDC tablets of gemigliptin/metformin SR 25/500 mg or loose combination with one tablet of gemigliptin 50 mg and two tablets of metformin XR 500 mg in each period with a 7-day wash out. The dose was determined based on the approved dose of gemigliptin 50 mg and metformin 1,000 mg. In part 1, subjects were administered the investigational product (IP) after 10 hours overnight fasting. While, in part 2, subjects started to take high fat meal (900 kcal, fat content: more than 50%) 30 minutes before the IP administration, and consumed all of the meal within 20 minutes.

For the PK/PD analysis, the blood samples were obtained at 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 24, 32, and 48 hours post-dose during each period. Each blood sample was collected in heparinized and ethylenediaminetetraacetic acid (EDTA) tubes for PK (plasma concentrations of gemigliptin, metformin and LC15-0636 (active metabolite of gemigliptin)) and PD (DPP-4 activity) analysis, respectively. Blood samples for PK/PD analysis were centrifuged for 10 minutes at 4°C at 2,700 rpm. A 0.3 mL aliquot of the sample was placed into polypropylene tubes, which contained 0.3 mL of 5% formic acid (98%) in water for gemigliptin and LC15-0636 analysis. For PD analysis, a 0.3 mL aliquot was placed into the polypropylene tube. All the blood samples were stored at -70°C until analysis.

Determination of plasma concentrations of gemigliptin and metformin and plasma DPP-4 activity

The plasma concentrations of gemigliptin and LC15-0636 were determined using liquid chromatography tandem mass spectrometry (LC-MS/MS) (APITM 5500 UFLC system; SCIEX, Seoul, Korea) with electrospray in positive ionization mode. For gemigliptin and LC15-0636, the chromatographic separation was performed at 40°C using a Unison UK-C18 (50 × 2.0 mm, 3 µm; Shimadzu, Kyoto, Japan). The quantification was performed by using multiple reaction monitoring (MRM) mode of the transitions at m/z 490.039 \rightarrow 338.082 for gemigliptin, at m/z 506.083 \rightarrow 175.037 for LC15-0636, at m/z 380.300 \rightarrow 91.100 for donepezil (internal standard; IS). The standard curve range for gemigliptin was within 0.5–200.0 ng/mL. The within-run precision and between-run precision were 0.9%–6.7% and 5.0%–6.3%, respectively, and the

within-run and between-run accuracy were 87.3%–108.0% and 99.2%–100.1%, respectively. The standard curve for LC15-0636 was in the range of 0.25–100.0 ng/mL. The within-run precision and between-run precision of LC15-0636 were 1.2%–9.8% and 4.1%–6.3%, and the within-run and between-run accuracy were 91.7%–110.3% and 99.2%–104.2%, respectively.

The plasma concentration of metformin was determined using LC-MS/MS (APITM 4000; SCIEX) with electrospray in the positive ionization mode. The chromatographic separation for metformin was performed at 40°C using a Luna hydrophilic interaction liquid chromatography column (2.0 mm ID × 150 mm; Shimadzu). The quantification was performed using the MRM mode of the transitions at m/z 130.071 \rightarrow 60.108 for metformin, and m/z 136.425 \rightarrow 60.065 for metformin-d6 (IS). The standard curve range of metformin was 2.0–2,000.0 ng/mL. The within-run precision and between-run precision for metformin were 1.2%–6.6% and 4.2%–4.7%, respectively. The within-run and between-run accuracy for metformin were 91.9%–108.1% and 99.4%–101.6%, respectively.

The plasma DPP-4 activity was determined by a validated continuous spectrophotometric assay with Gly-Pro-pNA as the substrate (Bachem, Bubendorf, Switzerland), as has been reported previously [13].

Sample size calculation

The sample size was determined based on the maximum value of within-subject variability among the PK parameters of gemigliptin and metformin. According to the results of previous studies, among the C_{max} and the area under the curve (AUC) of gemigliptin and metformin, the C_{max} of gemigliptin showed the maximum value and the value was approximately 23.4% in the fasted state (unpublished previous study results, 2016). Accordingly, the minimum number of subjects required to show bioequivalence was calculated to 31 when coefficient of variation was 23.4% with significance level of 0.05 and 90% power. Assuming a dropout rate of 20%, a total of 40 subjects were required in fasted state. In fed state based on the results of previous studies, the C_{max} of gemigliptin was approximately 20.4% (unpublished previous study results, 2015). With the same calculation method as above, a total of 30 subjects were required in fed state.

PK/PD analysis

The PK/PD analysis was performed in the subjects who had completed all periods. The PK parameters were determined using non-compartmental analysis with Phoenix WinNonlin[®] software version 7.1 (Certara, Princeton, NJ, USA). AUC from 0 to the last quantifiable concentration (AUC_{last}), C_{max}, AUC from dosing to infinity (AUC_{inf}), time to reach C_{max} (T_{max}), t_{1/2} and apparent clearance (CL/F) of gemigliptin and metformin were obtained. For LC15-0636, AUC_{last}, C_{max} and metabolic ratio were calculated. C_{max} and T_{max} were directly estimated from the observed values and AUC_{last} was calculated using linear-up and log-down trapezoidal method. The t_{1/2} was calculated from the log-linear plot of the portion in the terminal phase of the individual plasma. AUC_{inf} was calculated as AUC_{last} plus last concentration of drug in plasma (C_{last})/ λ_z . CL/F was calculated as dose/AUC_{last}. Metabolic ratio was divided from AUC_{last} of metabolite by AUC_{last} of parent drug.

Area under the effect curve (AUEC) and the maximum inhibition of plasma DPP-4 activity (E_{max}) were obtained for PD evaluation. The PD parameter of AUEC was calculated using the linear trapezoidal and linear interpolation method. The E_{max} was calculated by dividing the difference in enzyme activity at pre-dose and at post-dose into the enzyme activity at pre-dose.

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Statistical analysis

The statistical analysis was performed using SAS® software version 9.4 (SAS Institute Inc., Cary, NC, USA). Linear mixed effect model was used to compare the PK/PD parameters between treatments, with log-transformed data. Period, sequence and treatment were set as fixed effects, and the subjects nested in sequence was set as a random effect. Using the model, the geometric mean ratios (GMRs) and 90% confidence intervals (CIs) for PK/PD parameters were calculated and assessed whether these values were entirely contained within the conventional bioequivalence range of 0.80–1.25.

Safety and tolerability assessment

The safety and tolerability were assessed in subjects who administered the treatment at least once. Adverse event (AE) monitoring, physical examinations, vital signs, 12-lead ECG and clinical laboratory tests were conducted to assess the safety and tolerability. All the AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA, ver.19.1), and summarized by treatment, severity and relationships with treatments.

RESULTS

Subjects

In fasted state (part 1), 40 subjects (included in the safety and tolerability assessments) were enrolled and 39 subjects (included in the PK/PD assessments) completed the study. In fed state (part 2), 30 subjects (included in safety and tolerability assessments and PK/PD assessments) were enrolled and completed the study. In the demographic characteristics, there were no significant differences between the sequences in part 1 and part 2 (**Table 1**).

PKs

In fasted state, the plasma concentration-time profiles of gemigliptin and metformin were similar between the 2 treatments (**Figure 1**), and PK parameters were also similar (**Table 2**). The GMRs (90% CIs) for C_{max} , AUC_{last} and AUC_{inf} of FDC to corresponding loose combination were within the conventional bioequivalence range of 0.8–1.25 (**Table 2**).

In fed state, gemigliptin and metformin also showed similar PK profiles between FDC and loose combination (**Figure 2**). The GMRs (90% CIs) of FDC to corresponding loose combination for C_{max} , AUC_{last} and AUC_{inf} of gemigliptin and metformin were within the range of 0.80–1.25 range (**Table 3**).

Table 1. Demographic of study subjects

Characteristics		Fasted state			Fed state	
	Sequence 1 (n = 20)	Sequence 2 (n = 20)	p-value*	Sequence 3 (n = 15)	Sequence 4 (n = 15)	p-value*
Age (yr)	32.9 ± 6.6	32.3 ± 6.6	0.7744	28.9 ± 5.7	28.0 ± 5.7	0.6550
Height (cm)	172.2 ± 6.5	173.2 ± 4.2	0.5686	172.7 ± 5.4	174.1 ± 3.0	0.3904
Weight (kg)	71.7 ± 7.5	70.7 ± 5.6	0.6252	71.0 ± 6.4	70.9 ± 5.4	0.9732
BMI (kg/m²)	24.2 ± 1.8	23.6 ± 1.7	0.2869	23.8 ± 1.5	23.4 ± 1.6	0.5063

Sequence 1: Loose combination (gemigliptin 50 mg + metformin XR 1,000 mg) \rightarrow Two tablets of FDC (gemigliptin/metformin SR 25/500 mg); Sequence 2: Two tablets of FDC (gemigliptin/metformin SR 25/500 mg) \rightarrow Loose combination (gemigliptin 50 mg + metformin XR 1,000 mg); Sequence 3: Loose combination (gemigliptin 50 mg + metformin XR 1,000 mg) \rightarrow Two tablets of FDC (gemigliptin/metformin SR 25/500 mg); Sequence 4: Two tablets of FDC (gemigliptin/metformin SR 25/500 mg) \rightarrow Loose combination (gemigliptin/metformin SR 25/500 mg); Sequence 4: Two tablets of FDC (gemigliptin/metformin SR 25/500 mg) \rightarrow Loose combination (gemigliptin 50 mg + metformin XR 1,000 mg). Data are expressed as mean \pm standard deviation. BMI, body mass index; XR, extended release; FDC, fixed-dose combination; SR, sustained release. *Two-sample *t*-test was performed.

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Figure 1. Mean plasma concentration-time profiles of (A) gemigliptin, (B) LC15-0636, and (C) metformin after a single administration of 2 fixed-dose combination of gemigliptin/metformin SR 25/500 mg or loose combination with gemigliptin 50 mg and metformin XR 1,000 mg in fasted state. The error bars denote the standard deviations.

SR, sustained release; XR, extended release.

For LC15-0636, which also showed the similar plasma concentration-time profile between two treatments both in fasted and fed states, and the GMRs (90% CIs) of the C_{max} , AUC_{last} and AUC_{inf} were within the bioequivalence range in both states (**Figures 2** and **3**, **Tables 2** and **3**).

Pharmacodynamics

The mean plasma DPP-4 activity-time profiles of FDC and loose combination almost overlapped in fasted and fed states (**Figure 3**). In fasted state, the E_{max} was approximately 80% in both FDC and loose combination, and the GMRs (90% CIs) of FDC to loose combination for E_{max} and AUEC_{last} were 0.9994 (0.9912–1.0077) and 1.0030 (0.9918–1.0142), respectively (**Table 4**). In fed state, the value of E_{max} was about 82%–83% in FDC and loose combination, and the GMRs (90% CIs) of FDC to loose combination, and the GMRs (90% CIs) of FDC to loose combination for E_{max} was about 82%–83% in FDC and loose combination, and the GMRs (90% CIs) of FDC to loose combination for E_{max} and AUEC_{last} were 0.9885

Variables		Gemigliptin			LC15-0636			Metformin
	FDC (n = 39)	Loose combination (n = 39)	Geometric mean ratio* (90% CI)	FDC (n = 39)	Loose combination (n = 39)	Geometric mean ratio* (90% CI)	FDC (n = 39)	Loose combination (n = 39)
T _{max} (h)	3.00 [0.52-6.00]	3.00 [0.50-5.00]		4.00 [2.00-6.02]	5.00 [1.50-6.00]		4.00 [1.00-6.02]	4.00 [2.00-5.00]
C _{max} (µg/L)	50.92 ± 12.81	51.69 ± 10.73	0.9759 (0.9249-1.0296)	8.14 ± 1.98	8.17 ± 1.70	0.9952 (0.9551-1.0370)	1,291.33 ± 402.61	1,203.59 ± 321.86
AUC _{last} (µg*h/L)	633.25 ± 108.38	644.13 ± 112.52	0.9827 (0.9611-1.0047)	178.10 ± 28.71	175.94 ± 23.80	1.0110 (0.9905-1.0320)	9,598.36 ± 2,999.26	8,667.30 ± 2,328.45
AUC _{inf} (µg*h/L)	711.83 ± 122.13	725.26 ± 132.63	0.9822 (0.9593-1.0056)	252.29 ± 42.43	249.59 ± 35.85	1.0073 (0.9879–1.0271)	9,925.88 ± 2,911.01	8,971.10 ± 2,364.9'
t _{1/2} (h)	16.02 ± 1.55	16.08 ± 1.97		27.16 ± 4.28	27.05 ± 4.65		14.20 ± 12.21	13.70 ± 9.64
CL/F (L/h)	72.46 ± 13.80	71.16 ± 12.93	ı	ı	ı	ı	109.06 ± 31.08	119.52 ± 33.40
Metabolic ratio [†]				0.29 ± 0.05	0.28 ± 0.05			

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"Geometric mean ratio is the ratio of the FDC to the loose combination. ⁴Metabolic ratio is AUC_{ust} of LC15-0636 (metabolite of gemigliptin)/AUC_{ust} of gemigliptin (parent drug).

concentration; AUC_{inf} area under the curve from dosing to infinity; t_{1/2}, half-life; CL/F, apparent clearance; CI, confidence interval.

metformin XR 1,000 mg in fed state	Gemiølintin
gemigliptin 50 mg and	Variahles

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Variables		Gemigliptin			LC15-0636			Metformin	
	FDC (n = 30)	Loose combination (n = 30)	Geometric mean ratio* (90% CI)	FDC (n = 30)	Loose combination (n = 30)	Geometric mean ratio* (90% CI)	FDC (n = 30)	Loose combination (n = 30)	Geometric mean ratio [*] (90% CI)
T _{max} (h)	3.00 [1.00-5.02]	2.50 [1.00-5.02]		5.00 [1.50-8.00]	5.00 [2.00-7.00]		6.04 [4.00-10.00]	6.00 [4.00-8.03]	
C _{max} (µg/L)	52.55 ± 13.58	59.95 ± 17.79	0.8861 (0.8242-0.9526)	6.93 ± 1.26	7.56 ± 1.43	0.9233 (0.8827-0.9659)	$1,348.73 \pm 216.68$	1,315.87 ± 217.98	1.0257 (0.9966–1.0557)
AUC _{last} (µg*h/L)	686.30 ± 100.45	694.84 ± 101.06	0.9874 (0.9631–1.0124)	170.31 ± 23.29	176.62 ± 25.82	0.9681 (0.9450–0.9918)	14,464.63 ± 2,609.18	13,982.36 ± 2,674.08	1.0372 (1.0078–1.0674)
AUC _{inf} (µg*h/L)	772.94 ± 119.71	777.48 ± 121.28	0.9940 (0.9691–1.0195)	253.66 ± 39.38	256.27 ± 40.90	0.9904 (0.9606-1.0212)	14,618.25 ± 2,619.42	14,151.09 ± 2,641.80	1.0349 (1.0058-1.0649)
t _{1/2} (h)	16.01 ± 2.13	15.84 ± 1.96	ı	29.25 ± 5.61	28.18 ± 5.13	,	7.47 ± 3.31	8.20 ± 4.04	ı
CL/F (L/h)	66.19 ± 10.14	65.76 ± 9.76	ı	ı	,		70.52 ± 12.54	73.14 ± 14.05	ı
Metabolic ratio ^{$†$}	I	ı	ı	0.25 ± 0.04	0.26 ± 0.04			ı	Ţ
Data are present FDC, fixed-dose	ed as mean ± stand combination; SR, su	dard deviation, unless ustained release; XR, in the runde from dosing t	Tmax; Tmax are presen extended release; C o infinity: t half-lii	ted as median [min ™, maximum plasn fe: CL/F_annarent c	iimum-maximum]. na concentration; T _{ma}	‰ time to reach C _{max} ; nce interval	AUC _{last} , area under the	curve from 0 to the las	t quantifiable
*Geometric mea	ratio is the ratio o	of the FDC to the loose	e combination. [†] Met	abolic ratio is AUC _{la}	_{st} of LC15-0636 (metal	bolite of gemigliptin))/AUC _{last} of gemigliptin ((parent drug)	

(1.0339-1.1698) (1.0273-1.1681)

ï .

(0.9825-1.1549)

1.0652 1.0955 1.0997

Geometric mean ratio* (90% CI)

mg or loose combination with

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Figure 2. Mean plasma concentration-time profiles of (A) gemigliptin, (B) LC15-0636, and (C) metformin after a single administration of 2 fixed-dose combination of gemigliptin/metformin SR 25/500 mg or loose combination with gemigliptin 50 mg and metformin XR 1,000 mg in fed state. The error bars denote the standard deviations.

SR, sustained release; XR, extended release.

(0.9740–1.0033) and 0.9774 (0.9682–0.9866), respectively. All the values were within the conventional bioequivalence range of 0.80–1.25 (**Table 4**).

Safety and tolerability

In fasted state, a total of 24 treatment-emergent adverse events (TEAEs) occurred in 12 subjects, and all the TEAEs were assessed as adverse drug reactions (ADRs); 17 ADRs (8 subjects) occurred in FDC group and 7 ADRs (5 subjects) occurred in loose combination group. In fed state, a total of 27 TEAEs occurred in 9 subjects, and 25 TEAEs in 8 subjects were related to the drug, 11 ADRs (6 subjects) for FDC group and 14 ADRs (5 subjects) for loose combination group (**Table 5**).

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Figure 3. Mean plasma concentration-time profiles for DPP-4 activity after a single administration of 2 fixed-dose combination of gemigliptin/metformin SR 25/500 mg and corresponding loose combination in (A) fasted and (B) fed states. The error bars denote the standard deviations. DDP-4, dipeptidyl peptidase 4; SR, sustained release; mOD, milli optical density.

Table 4. Inhibition of DPP-4 activity after a single administration of 2 tablets of FDC for gemigliptin/metformin SR 25/500 mg or loose combination with gemigliptin 50 mg and metformin XR 1,000 mg in fasted and fed states

Variables		Fasted state			Fed state	
	FDC (n = 39)	Loose combination	Geometric mean ratio*	FDC (n = 30)	Loose combination	Geometric mean ratio*
		(n = 39)	(90% CI)		(n = 30)	(90% CI)
E _{max} (%)	80.16 ± 3.25	80.26 ± 3.13	0.9994 (0.9912-1.0077)	82.40 ± 4.10	83.29 ± 2.39	0.9885 (0.9740-1.0033)
AUEC _{last} (%*h)	3,188.49 ± 179.53	3,182.95 ± 156.02	1.0030 (0.9918-1.0142)	3,238.70 ± 138.57	3,313.54 ± 133.90	0.9774 (0.9682-0.9866)

Data are presented as mean ± standard deviation.

DDP-4, dipeptidyl peptidase 4; FDC, fixed-dose combination; SR, sustained release; XR, extended release; E_{max}, maximum inhibition of plasma DPP-4 activity; AUEC, area under the effect curve; CI, confidence interval.

 * Geometric mean ratio is the ratio of the FDC to the loose combination.

No serious AEs occurred and all the AEs were mild in intensity. ADRs that were considered to be 'possible' related to the IP were dyspepsia, myalgia, rash generalized, nausea, and dyschezia, the other ADRs were considered to be 'unikely' to be related to the IP. All the AEs were resolved spontaneously without any intervention except one adverse event, which was dyschezia that occurred after the administration of FDC in fed state but was recovered after taking bisacodyl as a concomitant medication. Gemigliptin and metformin in both FDC and loose combination were well tolerated.

DISCUSSION

In this study, we compared the PK/PD and safety of the 2 tablets of FDC gemigliptin/ metformin 25/500 mg SR, and corresponding loose combination in both fasted and fed states. The two treatments of FDC and loose combination showed similar PK/PD profiles in both fasted and fed states in healthy male subjects. In addition, the incidence of adverse events between the two treatment groups was similar and any unexpected AEs did not occurred. These results suggested that the treatment of FDC was equivalent to the loose combination in aspect of PK/PD and safety.



Table 5. Summary	of adverse events
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/ariables		Fasted state		Fed state
	FDC (n = 39)	Loose combination (n = 39)	FDC (n = 30)	Loose combination $(n = 30)$
Abdominal pain lower	1 [1]	0 [0]	0 [0]	0 [0]
Acne	0 [0]	1 [1]	0 [0]	0[0]
Catheter site erythema*	0 [0]	0 [0]	1 [1]	0 [0]
Catheter site pruritus*	0 [0]	0 [0]	1 [1]	0[0]
Chills	2 [2]	0 [0]	0 [0]	1 [1]
Cough	3 [3]	1 [1]	1 [1]	1 [1]
Dizziness	0 [0]	0 [0]	1 [1]	0[0]
Dyschezia	0 [0]	0 [0]	1 [1]	0[0]
Dyspepsia	1 [1]	0 [0]	4 [4]	2 [2]
Dysphonia	0 [0]	0 [0]	0 [0]	1 [1]
eeling hot	1 [1]	0 [0]	0 [0]	0 [0]
Headache	1 [1]	0 [0]	1 [1]	0 [0]
nsomnia	0 [0]	0 [0]	1 [1]	0[0]
Myalgia	0 [0]	1 [1]	0 [0]	0 [0]
Nasal congestion	2 [2]	1 [1]	0 [0]	0[0]
Nausea	0 [0]	0 [0]	0 [0]	2 [2]
Dropharyngeal pain	1 [1]	2 [2]	1 [1]	1 [1]
Paraesthesia	1 [1]	0 [0]	0 [0]	0 [0]
Procedural dizziness	1 [1]	0 [0]	0 [0]	O [O]
Productive cough	0 [0]	0 [0]	0 [0]	1 [1]
Pyrexia	0 [0]	0 [0]	0 [0]	1 [1]
Rash generalised	0 [0]	0 [0]	0 [0]	1 [1]
Rhinorrhoea	3 [3]	1 [1]	1 [1]	3 [3]

Data are presented as number of subjects with adverse events [number of adverse events].

*Not related to the investigational product.

In the case of metformin XR, although the extent of metformin absorption increased by approximately 50% when given food, metformin is recommended to be administered with meals to minimize the common gastrointestinal side effects [10]. While genigliptin can be taken with or without meals, FDC of genigliptin/metformin 25/500 mg SR is expected to be taken without considering meals; therefore, PK/PD evaluation was conducted not only in fasted state but also in fed state. Although the results showed that the two formulations had similar PK/PD properties in each state, the FDC of genigliptin/metformin 25/500 mg SR is expected to be administered with meals to reduce the gastrointestinal symptoms related to metformin.

The recommended dose of gemigliptin is 50 mg regardless of co-administration with metformin [7]. The FDC of gemigliptin and metformin was developed for the patients who need to take both metformin 1,000 mg and gemigliptin 50 mg. However, the formulation containing 50 mg of gemigliptin and 1,000 mg of metformin is not easy to take because of the large size of the formulation. Therefore, an FDC formulation of gemigliptin/metformin 25/500 mg was developed to improve the convenience of taking the medication. However, the marketed dose of gemigliptin is 50 mg, so this study used two tablets of FDC.

The wash-out period was generally set as 4–5 times of the half-life of the drug. In this study, the reported terminal half-life of gemigliptin was found to be about 16 hours, which is longer than the half-life of metformin. Thus, 7 days was considered as sufficient wash-out period. The T_{max} of gemigliptin and metformin XR is approximately 2 hours in 50 mg and about 6 hours in 1,000 mg, respectively [15]. Therefore, the blood collection time points were set more tightly around the suspected T_{max} .

DPP-4 activity is a useful engagement biomarker for DPP-4 inhibitors. DPP-4 inhibitor can block the DPP-4 enzyme to increase the level of GLP-1 and glucose-dependent insulinotropic peptide (GIP) by attenuate the degradation of these incretins [16]. In healthy subjects, increase in GLP-1 and GIP levels does not have clinically meaningful effects on glucose levels [7,8]. However, in T2DM patients, increase GLP-1 and GIP concentrations may lead to increase insulin activity and lowering of blood glucose levels [6,13,16]. Although insulin and glucose were not measured in this study, it can be expected that the two treatments would have similar effects in T2DM patients in both fasted and fed states. Because the degree of the inhibition of DPP-4 activity was similar between two treatments regardless meal.

In conclusion, the PK/PD and safety profiles of new FDC formulation of gemigliptin/ metformin SR 25/500 mg and the loose combination of gemigliptin and metformin XR were similar under both in fasted and fed states. Therefore, new FDC of gemigliptin/metformin SR 25/500 mg can be used as a convenient therapeutic option for the combination therapy.

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