A fixed-dose combination tablet of gemigliptin and metformin sustained release has comparable pharmacodynamic, pharmacokinetic, and tolerability profiles to separate tablets in healthy subjects

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Background: In type 2 diabetes mellitus, fixed-dose combination (FDC) can provide the complementary benefits of correction of multiple pathophysiologic defects such as dysfunctions in glycemic or metabolic control while improving compliance compared with separate tablets taken together. The objective of the study reported here was to compare the pharmacodynamic (PD), pharmacokinetic (PK), and tolerability profiles of gemigliptin and extended-release metformin (metformin XR) between FDC and separate tablets.

Methods: A randomized, open-label, single-dose, two-way, two-period, crossover study was conducted in 28 healthy male volunteers. Two FDC tablets of gemigliptin/metformin 25/500 mg or separate tablets of gemigliptin (50 mg ×1) and metformin XR (500 mg ×2) were orally administered in each period. Serial blood samples were collected up to 48 hours post-dose to determine dipeptidyl peptidase 4 (DPP-4) activity using spectrophotometric assay and concentrations of gemigliptin and metformin using tandem mass spectrometry. Geometric mean ratios (GMRs) of FDC to separate tablet formulations and their 90% confidence intervals (CIs) were calculated to compare the PD and PK parameters between the two formulations. Tolerability was assessed throughout the study.

Results: The plasma DPP-4 activity–time curves of the FDC and the separate tablets almost overlapped, leading to a GMR (90% CI) of the FDC to separate tablets for the plasma DPP-4 activity and its maximum inhibition of 1.00 (0.97–1.04) and 0.92 (0.82–1.05), respectively. Likewise, all of the GMRs (90% CIs) of FDC to separate tablets for the area under the plasma concentration–time curve and maximum plasma concentration of gemigliptin and metformin fell entirely within the conventional bioequivalence range of 0.80–1.25. Both the FDC and separate tablets were well tolerated.

Conclusion: The PD, PK, and tolerability profiles of gemigliptin and metformin XR in FDC and separate tablets were found to be comparable. The FDC tablet of gemigliptin and metformin sustained release can be a convenient therapeutic option in patients with type 2 diabetes mellitus requiring a combination approach.

Keywords: dipeptidyl peptidase 4, DPP-4 inhibitor, type 2 diabetes mellitus, T2DM

Introduction
Type 2 diabetes mellitus (T2DM) is a multifactorial disease threatening the health of all nations. Major pathophysiology of T2DM is characterized by insulin resistance and pancreatic β-cell failure. However, other mechanisms such as incretin deficiency

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or resistance to incretin in the gastrointestinal tract also play an important role in the development of glucose intolerance in T2DM patients. Therefore, effective treatment of T2DM may require an approach using two or more drugs in combination to correct those multiple pathophysiological defects.\(^1\)

Although metformin has been recommended as a first-line oral antidiabetic drug, combination therapy with other antidiabetic agents may offer additional glycemic control.\(^2\)

For this purpose, a dipeptidyl peptidase 4 (DPP-4) inhibitor has advantages in reducing the side effects of conventional antidiabetic agents such as weight gain (experienced with sulfonylureas, meglitinides, insulin, and thiazolidinediones), and hypoglycemia (with sulfonylureas, meglitinides, and insulin).\(^3\)

Furthermore, the additive antidiabetic effects of metformin and DPP-4 inhibitors may lead to better metabolic control. For example, in patients with T2DM who had been inadequately controlled by metformin alone, the addition of a DPP-4 inhibitor not only lowered glycated hemoglobin (HbA\(_1c\)), and fasting and 2-hour postprandial plasma glucose, but also improved \(\beta\)-cell function (homeostatic model assessment [HOMA]-\(\beta\)) and the proinsulin/insulin ratio.\(^4\)

Gemigliptin (Zemiglo\(^®\), LG Life Sciences, Seoul, South Korea) is a potent, selective, competitive, and long-acting DPP-4 inhibitor that was approved for use in patients with T2DM in June 2012 in Korea.\(^5\)

In a single ascending dose study, gemigliptin was rapidly absorbed after oral administration at 25–600 mg with a median time to peak concentration (T\(_{\text{max}}\)) of 2.0 hours (0.5–5.1 hour) post-dose and the mean terminal elimination half-life (t\(_{1/2}\)) ranged from 16.7 to 21.3 hours. Gemigliptin exhibited linear pharmacokinetic (PK) characteristics over the range of 50 to 400 mg in that study. The rate, but not the extent of absorption, appeared to be influenced by food intake.\(^6\)

Following a single oral dose of extended-release metformin (metformin XR) (Glucophage\(^®\), Bristol-Myers Squibb Company, Princeton, NJ, USA), a median value of T\(_{\text{max}}\) was 7 hours (4–8 hours) post-dose and approximately 90% of the absorbed dose was eliminated via the renal route within the first 24 hours, with a t\(_{1/2}\) of approximately 6.2 hours. Although the extent of absorption from the metformin XR tablet increased by approximately 50% when given with food, there was no effect of food on the maximum plasma concentration (C\(_{\text{max}}\)) and T\(_{\text{max}}\) of metformin.\(^7\)

In the dose-ranging Phase II clinical trial with gemigliptin, 50 mg was found to be the optimal dose based on a significant improvement in glycemic control and the overall safety profile.\(^8\)

Furthermore, in a previous drug–drug interaction study performed in healthy volunteers, multiple coadministration of gemigliptin (50 mg once-daily) and metformin (1,000 mg twice-daily) resulted in beneficial pharmacodynamic (PD) interactions such as an additive increase in the plasma concentration of active glucagon-like peptide-1 (GLP-1) without untoward PK interactions at steady state.\(^9\)

In this study, the tolerability profile was also comparable between gemigliptin alone and gemigliptin in combination with metformin.\(^9\) Therefore, 50 mg and 1,000 mg are likely to be the most preferred doses for gemigliptin and metformin, respectively, in combination therapy.

A novel fixed-dose combination (FDC) of gemigliptin/metformin sustained release (SR) 25/500 mg (Zemimet\(^®\) SR 25/500 mg, LG Life Sciences) has been developed, which may lead to better compliance than two separate tablets taken together. Two tablets of the FDC of gemigliptin/metformin SR, which slowly release metformin over the dosing interval can be a convenient treatment option with a once-daily regimen. Like other FDC formulations, however, the efficacy, tolerability, and PK profiles of gemigliptin and metformin given as FDC should be comparable to those of the individual drugs given as separate tablets. Based on this understanding, the objective of the present study was to compare the PD, PK, and tolerability profiles of gemigliptin/metformin SR between FDC and separate tablets.

To this end, a single-dose, two-way crossover, comparative PD and PK study was conducted in healthy volunteers.

**Methods**

**Subjects**

Healthy male volunteers aged 20–45 years with a body mass index of 18.0–27.0 kg/m\(^2\) and a fasting blood glucose level of 70–125 mg/dL were enrolled into the study if they presented no abnormalities based on medical history, physical examination, twelve-lead electrocardiogram, clinical laboratory tests, or urine drug screening (amphetamine, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and cotinine). Written informed consent was obtained before any study-related procedure was performed. The study was approved by the Institutional Review Board at Seoul National University Hospital, Seoul, South Korea, and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice standard (clinicaltrials.gov registration number: NCT01662674).

**Study design**

This was a randomized, open-label, single-dose, two-way, two-period, crossover study. Eligible subjects randomly received two tablets of FDC of gemigliptin/metformin SR 25/500 mg (Zemimet SR 25/500 mg) in one period, and a gemigliptin 50 mg tablet (Zemiglo) plus two metformin XR table
500 mg tablets (Glucophage) in the other period. There was a 7-day washout between the two periods, which was deemed appropriate given that this was longer than five-times the \( t_{1/2} \) of both gemigliptin and metformin XR and no significant PK interactions were observed between the two drugs.\(^9\)

In each period, subjects were hospitalized at the Clinical Trial Center at Seoul National University Hospital a day before administration of the study drug. After a high-fat meal (900 kcal; fat content of 50% or more), subjects orally took the study drug with 240 mL of water, and the study procedures were performed for 48 hours until discharge.

Within a week of completing Period II as planned, subjects reported to the Clinical Trials Center again for an end-of-study visit and laboratory tests.

### Sample-size calculation

The within-subject coefficient of variation for the PK parameters (\( C_{\text{max}} \) area under the time–concentration curve [AUC]) was assumed to be 20% for gemigliptin and metformin based on previous studies.\(^6,7\) The number of subjects required to detect a difference of 20% or more in the PK parameters between the treatments (ie, FDC vs separate tablets) at a significance level of 0.05 and a power of 90% was 24. Assuming a drop-out rate of ~20%, a total of 28 subjects were to be enrolled.

### Blood collection

Serial blood samples were collected at time zero (ie, pre-dose); 30 minutes; 1 hour; and 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0. and 48.0 hours post-dose using ethylenediaminetetraacetic acid and heparinized tubes for PD (DPP-4 activity) and PK (plasma concentrations of gemigliptin and metformin) analyses, respectively. Blood samples were centrifuged for 10 minutes at 4°C approximately at 1,550 and 1,910 g for PD and PK, respectively. Then 0.3 mL aliquots of plasma for gemigliptin analysis were placed into polypropylene tubes, which contained 0.3 mL of 5% formic acid in deionized water (high-performance liquid chromatography grade). Another 0.5 mL aliquot of plasma for metformin analysis was placed into a polypropylene tube (three tubes were prepared for each drug analysis). All plasma samples were stored at −20°C in the freezer for less than 24 hours. Then they were transferred to a deep freezer and stored at less than −70°C in the dark until required for sample analysis.

### Plasma dipeptidyl peptidase 4 activity

DPP-4 activity in plasma was determined using a continuous spectrophotometric assay with the substrate Gly-Pro-pNA (Bachem, Bubendorf, Switzerland), as has been reported previously.\(^9\) The assay was based on the ability of DPP-4 to cleave the substrate Gly-Pro-pNA into pNA, resulting in an increase in absorbance at 390 nm, where the absorbance was expressed as milli optical density (mOD). Enzymatic activity was calculated as the slope (in mOD/min) from 4 to 14 minutes. Intra- and inter-assay precisions were 2.28%–7.57% and 3.64%–12.75%, respectively. The lower limit of quantification was 1.43 mOD/min.

### Plasma concentrations of gemigliptin and metformin

Plasma concentrations of gemigliptin and metformin were determined using tandem mass spectrometry (MS/MS) (API™ 4000 LC/MS/MS system, AB Sciex, Framingham, MA, USA) with electrospray in positive ionization mode, coupled with high-performance liquid chromatography (Agilent 1100 series HPLC system, Agilent Technologies, Wilmington, DE, USA). Chromatographic separation was performed under gradient conditions using a Luna C8 column (30.0×2.0 mm, 3 µm; Phenomenex, Torrance, CA, USA) for gemigliptin and using a PC HILIC (hydrophilic interaction liquid chromatography column; 2.0 mm ID ×150 mm, Shiseido, Yokohama, Japan) for metformin, as reported previously.\(^9\) The calibration curves were linear over the range of 1–2,000 ng/mL for gemigliptin and 2–2,000 ng/mL for metformin \((r^2=0.9975\) and \(r^2=0.9983\), respectively). The between-run coefficients of variation (CV) of gemigliptin and metformin were all <14.2% and the accuracy ranged between 96% and 104%.

### Pharmacodynamic and pharmacokinetic data analyses

Plasma DPP-4 activity and plasma concentrations of gemigliptin and metformin were analyzed using a non-compartmental technique implemented in the Phoenix\® WinNonlin\® software (v 1.3, Pharsight, St Louis, MO, USA). The plasma DPP-4 activity–area under the effect-time curve from 0 to 48 hours post-dose \((\text{AUECl}_{0-48})\) was calculated using the linear trapezoidal rule. The observed values were used to estimate the maximum inhibition of plasma DPP-4 activity \((I_{\text{max}})\).

The areas under the plasma concentration–time curve from time 0 to 48 hours post-dose \((\text{AUC}_{0-48})\) were calculated for gemigliptin and metformin using the linear-up and log-down trapezoidal method. The observed values were used to estimate \( C_{\text{max}} \) of gemigliptin and metformin. The apparent clearance was calculated as the dose divided by the area under the plasma concentration–time curve from time
0 to infinity (AUC∞). The terminal elimination rate constant (λz) was estimated from a regression line of log-transformed plasma concentrations versus time over the terminal log-linear portion. The t1/2 was calculated as natural logarithm of 2 divided by λz. AUCinf was calculated as AUC$_{0-48\:h}$ + C$_{48}$/λz, where C$_{48}$ is the plasma concentration at 48 hours post-dose.

**Tolerability assessment**

The occurrence of adverse events (AEs) was recorded during the entire study period including at the end-of-study visit. Data from all the study participants who were administered the drug at least once were included for tolerability assessment, which also considered changes from baseline in physical examination, vital signs, twelve-lead electrocardiograms, and clinical laboratory tests.

**Statistical analysis**

The PD and PK parameters were summarized using descriptive statistics. Using log-transformed data, a general linear mixed effects model was developed to compare the PD (AUC$_{0-48\:h}$ and I$_{max}$) and PK (AUC$_{0-48\:h}$ and C$_{max}$) parameters between treatments, where period, sequence, and treatment were fixed effects, while subjects nested in sequence was a random effect. Using the model, the geometric mean ratio (GMR) and its 90% confidence interval (CI) of FDC to individual drug given as separate tablets were estimated for the PD and PK parameters. Comparability was concluded if the 90% CI of the GMRs (90% CI) of FDC to separate tablets for the PD and PK parameters was entirely contained within the conventional bioequivalence range of 0.80–1.25. P-values ≤0.05 were considered statistically significant. All statistical analyses were performed using SPSS software (v 18.0, IBM Corporation, Armonk, NY, USA).

## Results

**Demographic characteristics**

A total of 28 subjects were enrolled into the present study, one of whom withdrew consent during the washout period due to a personal reason. Therefore, the 27 subjects who completed the study as planned were included in PD and PK analyses, while all of the enrolled subjects (n=28) were included in the tolerability analysis population. The mean ± standard deviation of age, height, weight, and body mass index was 27.4±4.5 years, 174.3±6.4 cm, 69.4±8.8 kg, and 22.8±2.4 kg/m², respectively, none of which significantly differed between sequence groups (all P-values >0.05, Student’s t-test).

**Pharmacodynamics**

After a single oral administration of gemigliptin and metformin at 50 and 1,000 mg, respectively, the plasma DPP-4 activity was comparable between FDC and separate tablets as assessed by AUC$_{0-48\:h}$ and I$_{max}$ (Table 1). As a result, the GMR (90% CI) of FDC to separate tablets for AUC$_{0-48\:h}$ and I$_{max}$ was 1.00 (0.97–1.04) and 0.92 (0.82–1.05), respectively. Furthermore, the mean plasma DPP-4 activity profiles of FDC and the separate tablets over time almost overlapped (Figure 1A), and no trend or systematic deviation was found in individual comparison for AUC$_{0-48\:h}$ (Figure 1B) and I$_{max}$ (Figure 1C).

**Pharmacokinetics**

The systemic exposures to gemigliptin and metformin after a single oral administration of 50 and 1,000 mg, respectively, given as FDC were similar to those when they were taken together as separate tablets. The mean plasma concentration–time profiles of gemigliptin and metformin were superimposable (Figure 2A and B, respectively). Furthermore, all of the GMRs (90% CI) of FDC to separate tablets for the C$_{max}$ and AUC$_{0-48\:h}$ of gemigliptin and metformin fell entirely within the conventional bioequivalence range of 0.80–1.25 (Table 2). Other PK parameters, including apparent clearance and t$_{1/2}$, were also comparable between FDC and separate tablets for gemigliptin and metformin.

**Tolerability**

Only one drug-related AE (diarrhea) occurred after FDC administration, whereas three drug-related AEs (one

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**Table 1** Plasma dipeptidyl peptidase 4 (DPP-4) activity after a single oral administration of gemigliptin at 50 mg and metformin at 1,000 mg given as fixed-dose combination or separate tablets

<table>
<thead>
<tr>
<th>DPP-4 activity</th>
<th>Fixed-dose combination (N=27)</th>
<th>Separate tablets (N=27)</th>
<th>Geometric mean ratio* (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0-48:h}$ (mOD/min-h)</td>
<td>313.59±60.11</td>
<td>312.05±60.01</td>
<td>1.00 (0.97–1.04)</td>
</tr>
<tr>
<td>I$_{max}$ (mOD/min)</td>
<td>3.00±1.13</td>
<td>3.23±1.20</td>
<td>0.92 (0.82–1.05)</td>
</tr>
</tbody>
</table>

**Notes:** Data are presented as arithmetic mean ± standard deviation. *Geometric mean ratio of fixed-dose combination to separate tablets.

**Abbreviations:** AUC$_{0-48\:h}$, area under the plasma dipeptidyl peptidase 4 activity–time curve from 0 to 48 hours post-dose; CI, confidence interval; h, hours; I$_{max}$, maximum inhibition of DPP-4 activity; min, minutes; mOD, milli optical density.
Figure 1 Mean plasma dipeptidyl peptidase 4 (DPP-4) activity after a single oral administration of gemigliptin at 50 mg and metformin at 1,000 mg given as fixed-dose combination or separate tablets. (A) Mean percent inhibition–time profiles. (B) Area under the plasma DPP-4 activity–time curve from 0 to 48 hours post-dose (AUCC<sub>0–48 h</sub>); and (C) Maximum inhibition of DPP-4 activity (I<sub>max</sub>).

**Note:** The error bars in (A) denote the standard deviations. (B and C) The different symbols and lines represent different subjects assessed in the study.

**Abbreviations:** h, hours; min, minutes; mOD, milli optical density.

Figure 2 Mean plasma concentration–time profiles of (A) gemigliptin and (B) metformin after a single oral administration at 50 mg and 1,000 mg, respectively, given as fixed-dose combination or separate tablets.

**Notes:** The error bars denote the standard deviations. Insets show the linear scale.

**Abbreviation:** h, hours.
Table 2 Pharmacokinetic parameters of gemigliptin and metformin after a single oral administration at 50 mg and 1,000 mg, respectively, given as fixed-dose combination or separate tablets

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fixed-dose combination (N=27)</th>
<th>Separate tablets (N=27)</th>
<th>Geometric mean ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>0.84 (0.80–0.90)</td>
<td>0.94 (0.87–0.99)</td>
<td>0.89 (0.84–0.94)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (μg/L)</td>
<td>93 (30–50)</td>
<td>50 (13–100)</td>
<td>0.59 (0.39–0.90)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0–48 h&lt;/sub&gt; (μg⋅h/L)</td>
<td>2,348.2 ± 327.3</td>
<td>2,217.5 ± 224.4</td>
<td>1.06 (1.01–1.09)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>1.05 (1.00–1.08)</td>
<td>1.70 (1.50–1.91)</td>
<td>0.61 (0.57–0.64)</td>
</tr>
<tr>
<td>Vd/F (L)</td>
<td>292.0 ± 292.0</td>
<td>321.3 ± 327.3</td>
<td>1.07 (1.03–1.11)</td>
</tr>
</tbody>
</table>

Notes: Geometric mean ratio of fixed-dose combination to separate tablets (90% CI). C<sub>max</sub> = maximum plasma concentration of drug; h = hours; t<sub>1/2</sub> = terminal half-life; T<sub>max</sub> = time to reach the maximum blood concentration after administration of drug; Vd/F = apparent volume of distribution.

Discussion

This study indicates that an FDC tablet of gemigliptin and metformin SR has comparable PD, PK, and tolerability profiles to separate tablets taken together in healthy males. The comparability between the FDC of gemigliptin and metformin SR and their separate tablets was demonstrated in three ways in the present study. First, the GMRs and their 90% CIs of FDC and separate tablets for AUC<sub>0–48 h</sub> and I<sub>max</sub> were contained entirely within the conventional bioequivalence range of 0.80–1.25 (Table 1). Likewise, the mean plasma DPP-4 activity of FDC and the separate tablets was superimposable over time after dose (Figure 1A), and individual comparison of AUC<sub>0–48 h</sub> and I<sub>max</sub> did not reveal any systematic deviation (Figure 1B and C, respectively). Second, all of the PK parameters for gemigliptin and metformin were comparable between FDC and the separate tablets, again leading to the GMR and its 90% CI for FDC and separate tablets of each individual drug falling entirely within the conventional bioequivalence range of 0.80–1.25 for both C<sub>max</sub> and AUC<sub>0–48 h</sub> (Table 2). Lastly, both FDC and separate tablets were well tolerated.

Collectively, our results suggest that the FDC tablet of gemigliptin and metformin SR at 50 and 1,000 mg, respectively, can be a beneficial therapeutic option for patients with T2DM who require both gemigliptin and metformin for additional glycemic control. Therefore, the FDC of gemigliptin and metformin may act against multiple pathophysiological defects in T2DM such as pancreatic islet dysfunction and insulin resistance while keeping the convenience of a single-time administration, thereby improving the patient’s compliance.11,12 Whereas two different kinds of separate tablets should be concomitantly administered (eg, one tablet of gemigliptin 50 mg and two tablets of metformin XR 500 mg), only one tablet is needed in the case of FDC (eg, gemigliptin and metformin SR 25 mg/500 mg). Therefore, FDC can reduce pill burden to T2DM patients, which leads to increased convenience and higher compliance, while not affecting the PD, PK, or tolerability profile of individual drugs, as shown in our results.
In the present study, plasma DPP-4 activity was evaluated as a surrogate marker of PD parameters including fasting levels of glucose, HbA1c, insulin, and glucagon. Inhibition of DPP-4 activity results in the increase of the concentrations of both active GLP-1 and gastric inhibitory polypeptide (GIP) by stabilizing and preventing the degradation of these enzymes. In normoglycemic healthy subjects, increase in GLP-1 and GIP levels does not have clinically meaningful effects on glucose levels. However, in T2DM patients, elevated GLP-1 and GIP levels may lead to insulin release and lowering of glucose concentrations. The comparable degree of reduction in DPP-4 activity observed after administration of FDC of gemigliptin and metformin SR and separate tablets taken together in the present study (Table 1, Figure 1) is very much likely to give rise to similar efficacy profiles between the two formulations when administered in T2DM patients.

The present study was conducted on patients in the fed state – that is, after a high-fat meal of 900 kcal with a fat content ≥50% – because metformin is recommended to be taken with a meal to minimize its common gastrointestinal side effects such as diarrhea, whereas gemigliptin can be administered with or without food. The high-fat meal did not affect the PK profiles of gemigliptin and metformin XR when they were administered as FDC. Therefore, the comparable PK profiles of gemigliptin and metformin XR in FDC and separate tablets shown in the present study under the fed condition are likely to be reproduced in the fasting state as well.

Both the FDC and separate tablets of gemigliptin and metformin XR were well tolerated in this study. Diarrhea and nausea, two of the three drug-related AEs seen in the present study, are frequently associated with metformin. Another drug-related AE – blurred vision after separate tablets – was mild in intensity, and it recovered spontaneously.

Limitations

This study has several limitations. First, the PD and PK characteristics of FDC in healthy, relatively young, male subjects may not represent those in patients with T2DM. However, it is less likely that the PKs of either formulation would be affected more in a different subject population although further studies are warranted in populations with various disease statuses and demographic characteristics. Second, the comparability in the duration and extent of DPP-4 inhibition, PKs, and tolerability of the FDC and separate tablets of gemigliptin and metformin XR after a single administration seen in the present study may not necessarily hold after repeated administration. In this respect, further multiple dosing studies, preferably in patients with T2DM, are warranted to reflect real clinical settings.

Conclusion

The PD, PK, and tolerability profiles of gemigliptin and metformin XR after a single oral administration in healthy males were comparable between FDC and separate tablets. The FDC of gemigliptin and metformin SR can be a convenient therapeutic option in patients with T2DM who require a combined approach.

Disclosure

The present study was sponsored by a research grant from LG Life Sciences, Seoul, South Korea. Jeong-Ae Kim and Jong Hyuk Jung are employees of LG Life Sciences, Ltd., Seoul, South Korea. All the other authors declare no conflicts of interest in this work.

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