Pharmacokinetic/Pharmacodynamic Interaction between Evogliptin and Glimepiride in Healthy Male Subjects

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Abstract

Aims: Evogliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor and glimepiride, a sulfonylurea, have been used to treat type 2 diabetes mellitus. This study aimed at evaluating the pharmacokinetic (PK) and pharmacodynamic (PD) interactions between evogliptin and glimepiride. Methods: A randomized, open-label, 3-period, 3-treatment, 2-sequence crossover study was conducted in healthy male subjects. During each period, subjects received multiple doses of evogliptin 5 mg alone (EVO), glimepiride 4 mg alone (GLI), or co-administration of the two (EVO+GLI). Serial blood and urine samples for PK and PD analyses were collected 168 and 24 hours post-dosing, respectively. Results: Thirty-four subjects completed the study. Co-administration of evogliptin and glimepiride did not alter their plasma and urine PK profiles. For evogliptin, the geometric mean ratio (GMR) (90% confidence intervals) for the maximum plasma concentrations at steady-state ($C_{max,ss}$) and the area under the curve during dosing interval at steady-state ($AUC_{\tau,\sigma\varsigma}$) of EVO+GLI to E were 1.02 (0.98 – 1.06) and 0.97 (0.95 – 1.00), respectively. For glimepiride, the corresponding values of EVO+GLI to GLI were 1.08 (1.01 – 1.17) and 1.08 (1.02 – 1.14), respectively. All values were within the regulatory bioequivalence criteria of 0.80 – 1.25. Administration of EVO+GLI decreased the glucose excursion compared to evogliptin and glimepiride monotherapy, respectively. Conclusion: Evogliptin and glimepiride had no PK interactions when co-administered, while combination therapy showed an additive glucose lowering effect compared to those of evogliptin or glimepiride monotherapy.

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*The authors confirm that the Principal Investigator for this paper is Kyung-Sang Yu and that he had direct clinical responsibility for study participants.

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DATA SHARING: Please contact the corresponding author for questions concerning data sharing.

ABSTRACT

Aims: Evogliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor and glimepiride, a sulfonylurea, have been used to treat type 2 diabetes mellitus. This study aimed at evaluating the pharmacokinetic (PK) and pharmacodynamic (PD) interactions between evogliptin and glimepiride.

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Results: Thirty-four subjects completed the study. Co-administration of evogliptin and glimepiride did not alter their plasma and urine PK profiles. For evogliptin, the geometric mean ratio (GMR) (90% confidence intervals) for the maximum plasma concentrations at steady-state ($C_{max,ss}$) and the area under the curve during dosing interval at steady-state ($AUC_{\tau,\sigma\varsigma}$) of EVO+GLI to E were 1.02 (0.98 – 1.06) and 0.97 (0.95 – 1.00), respectively. For glimepiride, the corresponding values of EVO+GLI to GLI were 1.08 (1.01 – 1.17) and 1.08 (1.02 – 1.14), respectively. All values were within the regulatory bioequivalence criteria of 0.80 – 1.25. Administration of EVO+GLI decreased the glucose excursion compared to evogliptin and glimepiride monotherapy, respectively.

Conclusion: Evogliptin and glimepiride had no PK interactions when co-administered, while combination therapy showed an additive glucose lowering effect compared to those of evogliptin or glimepiride monotherapy.

What is already known

- Evogliptin is a DPP-4 inhibitor used as treatment for type 2 diabetes mellitus.
- Many guidelines recommend the use of combination therapy as treatment for type 2 diabetes mellitus.
- Unlike evogliptin and metformin, no data is available on the drug interaction of evogliptin and sulfonylurea.

What this study adds

- Co-administering evogliptin and glimepiride may be an alternative option for the treatment of type 2 diabetes mellitus, as they do not appear to interfere with each other's pharmacokinetics.
- Co-administering evogliptin and glimepiride showed an additive glucose lowering effect.

Keywords: evogliptin, glimepiride, pharmacokinetics, pharmacodynamics, drug interaction

INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors inhibit DPP-4, increasing active glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) levels. GLP-1 and GIP increase insulin concentrations in a glucose-dependent fashion by increasing the intracellular levels of cyclic adenosine , 5'-monophosphate (cAMP) and lowering glucagon concentrations. [1] Thereby, DPP-4 inhibitors lower blood glucose levels. Many clinical trials have proven that evogliptin, a DPP-4 inhibitor, lowers blood glucose, and it was approved in Korea in 2015. [2, 3] It is rapidly absorbed after oral administration and takes approximately 5 hours to reach maximal concentration (T_{max}). [4] Evogliptin is mainly eliminated by non-renal routes, involving the human cytochrome P450 3A (CYP3A) enzyme. [5] Especially, 4(S)-hydroxyevogliptin (evogliptin M7) and 4(R)-hydroxyevogliptin (evogliptin M8) which are main metabolites of evogliptin are produced by CYP3A4 and CYP3A5. [6]

Glimepiride is a third-generation sulfonylurea that stimulates insulin release. Because the main cause of type 2 diabetes mellitus (T2DM) in Asians is a predominant insulin secretory defect, sulfonylureas may be

an effective treatment option for Asian T2DM patients. Therefore, glimepiride has been used as an initial treatment for T2DM in many countries, including China and Japan. [7] It is rapidly absorbed after oral administration and reaches T_{max} within 3 hours. [8] It is mainly eliminated by non-renal routes, involving the CYP2C9 which metabolites glimepiride to hydroxy-glimepiride (glimepiride M1), its main metabolite. [8]

Monotherapy with metformin is the recommended initial pharmacotherapy for T2DM; however, the therapeutic failure of monotherapy is approximately 45% in Korea. [9] Many T2DM treatment guidelines recommend combination therapy with drugs that have different action mechanisms, if monotherapy fails to achieve the glycemic target. [10, 11] Therefore, combination therapy with a DPP-4 inhibitor and sulfonylurea can be an effective T2DM treatment option. Glimepiride has not shown any pharmacokinetic (PK) interaction with some DPP-4 inhibitors, including vildagliptin, sitagliptin, and linagliptin. [12, 13]. However its interaction with evogliptin remains unevaluated. Therefore, this study aimed at evaluating the PK and pharmacodynamic (PD) interactions between evogliptin and glimepiride.

METHODS

Subjects

Healthy Korean male subjects aged 19-45 years with a body mass index of 18-27 kg/m^2 were enrolled. They were defined by their previous medical and surgical history, physical examination, vital signs, 12-lead electrocardiography (ECG), and clinical laboratory tests. Those that had been exposed to any investigational products within 90 days prior to the first dosing in the study and those known to be hypersensitive to evogliptin or glimepiride, were excluded. All subjects provided a signed informed consent form before any study related procedure was performed.

Study design and procedures

The study was a randomized, open-label, 3-period, 3-treatment, 2-sequence crossover study in healthy Korean male subjects. It was conducted at Seoul National University Hospital Clinical Trials Center, Seoul, Republic of Korea. The study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (number, H-1607-042-774) and Korea Ministry of Food and Drug Safety. This study was registered with ClinicalTrials.gov (number, NCT02954822) and conducted in accordance with the major ethical principles of the Declaration of Helsinki and Korean Good Clinical Practice Guidelines.

Subjects were randomly assigned to the sequence A or B. In sequence A, 5 mg of evogliptin (EVO) (evogliptin tartate, Suganon®, Seoul, Korea) was orally administered once daily from day 1-7, 5 mg of evogliptin and 4 mg of glimepiride (EVO+GLI) (glimepiride, Amaryl®, Sanofi-Aventis Co. Ltd., France) were orally co-administered once daily on day 8 and 9, and then 4 mg of glimepiride (GLI) was orally administered once daily on day 21 and 22 followed by a 12-day wash-out period. In sequence B, 4 mg of glimepiride (GLI) was orally administered once daily on day 1 and 2, 5 mg of evogliptin (EVO) was orally administered once daily from day 14-20 followed by a 12-day wash-out period, and then 5 mg of evogliptin and 4 mg of glimepiride (EVO+GLI) were orally co-administered once daily on day 21 and 22 (Figure 1).

For determination of plasma evogliptin, evogliptin M7, and evogliptin M8 concentration, blood samples (10 mL) were collected at the following time points: pre-dose from day 1-9 and 1, 2, 3, 4, 5, 6, 8, and 12 hours post-dose on days 7 and 9 in sequence A; pre-dose from day 14-22 and 1, 2, 3, 4, 5, 6, 8, and 12 hours post-dose on days 20 and 22 in sequence B. For determination of plasma glimepiride and glimepiride M1 concentration, blood samples were collected at pre-dose on days 8, 9, 22, and 23 and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours post-dosing on days 9 and 22 in sequence A; and pre-dose on days 2, 3, 21, and 22 and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours post-dosing on days 2 and 22 in sequence B (Figure 1). The blood samples were centrifuged at 1,900 g at 4 for 10 minutes, and the plasma (4 mL) was transferred into 4 Eppendorf tubes. For determination of urine evogliptin concentration, urine samples were collected at the following periods: 0-24 hours on days 7, 9 and 22 in sequence A; and on days 2, 20 and 22 in sequence B. The obtained plasma and urine samples were frozen below -70 until the assay.

Oral glucose tolerance test (OGTT) was conducted for PD evaluation. After an overnight fast, each subject ingested a test solution with 75 g of glucose. Blood samples for determination of serum glucose level and insulin level were collected at the following time points: 0, 0.25, 0.5, 1, 1.5, 2, and 3 hours after solution ingestion on days -1, 6, 8, and 21 in sequence A and at the same time points on days -1, 1, 19, and 21 in sequence B.

Pharmacokinetic analysis

Liquid chromatography with tandem mass spectrometry was used to analyze plasma evogliptin, evogliptin M7, evogliptin M8, glimepiride, and glimepiride M1 and urine evogliptin concentrations. In blank human plasma and urine, no interference of endogenous compounds was observed. The calibration curves of undiluted samples were linear over the range of concentration from 0.1 μg/L to 60 μg/L for plasma evogliptin; from 10 ng/L to 10000 ng/L for plasma evogliptin M7 and evogliptin M8; from 5 μg/L to 2000 μg/L for plasma glimepiride; from 0.5 μg/L to 500 μg/L for plasma glimepiride M1; from 5 to 50000 μg/L for urine evogliptin. The within-run accuracy and precision were 97.2 - 105.5 % and 0.8 - 7.2 % for plasma evogliptin; 94.9 - 103.2 % and 0.2 - 6.9 % for plasma evogliptin M7; 86.7 -106.3 % and 0.1 - 11.2 % for plasma evogliptin M8; and for plasma glimepiride; and for plasma glimepiride M1; 97.5 - 104.6 % and 3.3 - 6.5 % for urine evogliptin.

The individual PK parameters were determined via noncompartmental methods using Phoenix WinNonlin® software version 8.0 (Certara, Princeton, NJ, USA). The maximum concentration at steady-state ($C_{max,ss}$) and T_{max} at steady state ($T_{max,ss}$) were determined by observing the plasma concentration-time data. The half-life at steady state ($T_{1/2,ss}$) was determined by fitting a linear regression for evogliptin, evogliptin M7, evogliptin M8, glimepiride, and glimepiride M1. The area under the plasma concentration-time curve over dosing interval at steady-state ($AUC_{\tau,\sigma\varsigma}$) and the total apparent clearance at steady-state (CL_{ss}) were determined using the linear-log trapezoidal method.

The fraction excreted unchanged in urine over dosing interval at steady-state ($fe_{\tau,\sigma\varsigma}$) was determined by dividing the amount excreted unchanged in urine over dosing interval at steady-state ($Ae_{\tau,\sigma\varsigma}$) by the total dose given on the day of urine collection. The renal clearance at steady-state ($CL_{R,ss}$) was determined as $Ae_{\tau,\sigma\varsigma}$ divided by the $AUC_{\tau,\sigma\varsigma}$ for evogliptin.

Pharmacodynamic analysis

The individual PD parameters at steady-state were determined via noncompartmental methods using Phoenix WinNonlin®software version 8.0 (Certara, Princeton, NJ, USA). The maximum serum glucose level (G_{max}) and two-hour postprandial blood glucose (2-h PBG) were determined by observation. The area under the glucose-time curve (AUGC) was determined using the linear trapezoidal method. The maximum effect (E_{max}) and AUEC of insulin were determined in the same manner.

The ΔG_{max} and ΔE_{max} were calculated by subtracting the serum glucose and insulin level of at each timepoint in baseline from the serum glucose and insulin level at the corresponding timepoint, respectively. ΔAUGC and ΔAUEC were calculated by subtracting the serum glucose and insulin level at each timepoint in baseline from the serum glucose and insulin level at the corresponding timepoint using the linear trapezoidal method, respectively.

Sample size and statistical analysis

Sample size was determined based on the intrasubject variability of $C_{max,ss}$ and $AUC_{\tau,\sigma\varsigma}$ of evogliptin and glimepiride from previous studies in healthy subjects. The sample size of 32 was calculated in order to detect 20% differences in PK parameters ensuring a statistical power of 80%, with a significance level of 5% under the assumptions that the maximum of intra-subject coefficient of variation for PK parameters of evogliptin or glimepiride was 33%. Considering possible dropouts, 36 subjects were chosen as the final sample size.

To evaluate the PK interactions between evogliptin and glimepiride, the geometric mean ratios (GMRs) and 90% confidence intervals (90% CIs) for the $C_{max,ss}$ and $AUC_{\tau,\sigma\varsigma}$ of the combination therapy to the

monotherapy (EVO+GLI/GLI or EVO+GLI/EVO) were calculated from the analyses of variance (ANOVA) model, with sequence, period and treatment as fixed effects.

Safety analysis

Safety and tolerability were evaluated throughout the study based on adverse events (AEs), physical examinations, vital signs, 12-lead electrocardiograms, and clinical laboratory tests. AEs were collected throughout the study and the investigators assessed their relationships with the treatment.

RESULTS

Demographics

Thirty-six healthy Korean male subjects were enrolled. Their mean age, height, weight, and body mass index were (mean ± standard deviation) 32.6 ± 6.1 years, 173.5 ± 5.8 cm, 68.5 ± 7.2 kg, and 22.7 ± 1.9 kg/m^2, respectively. The demographic characteristics between sequences showed no statistical difference.

One subject withdrew consent before the first dosing and another withdrew during the treatment period. Therefore, 35 subjects were included in the safety assessment, and 34 were included in the PK and PD analyses.

Pharmacokinetics

For evogliptin, steady-state was achieved on day 4. The mean plasma evogliptin concentration-time curves and PK parameters were similar between EVO and EVO+GLI (Figure 2). The GMR (90% CI) of EVO+GLI to EVO for $C_{max,ss}$ and $AUC_{\tau,\sigma\varsigma}$ of evogliptin were 1.02 (0.98 – 1.06) and 0.97 (0.95 – 1.00), respectively (Table 1). Likewise, the PK parameters of evogliptin M7 and evogliptin M8 were similar between EVO and EVO+GLI (Table 1).

For glimepiride, the mean plasma glimepiride concentration-time curves of GLI and EVO+GLI and the PK parameters were similar (Figure 2). The GMR (90% CI) of EVO+GLI to GLI for $C_{max,ss}$ and $AUC_{\tau,\sigma\varsigma}$ of glimepiride were 1.08 (1.01 – 1.17) and 1.08 (1.02 – 1.14), respectively (Table 2). Likewise, the PK parameters of glimepiride M1 were similar between GLI and EVO+GLI (Table 2).

Pharmacodynamics

Serum glucose level at OGTT after EVO+GLI was lower than that after EVO or GLI (Figure 3). G_{max} in the EVO+GLI was lower by 8.0% compared to that in EVO and 6.4% compared to that in GLI. Similar to G_{max}, AUGC in EVO+GLI was also lower by 20.4% and 8.6% compared to that in EVO and GLI, respectively. 2-h PBG showed a similar pattern to G_{max} and AUGC (Table 3). Likewise, ΔG_{max} and ΔAUGC in EVO+GLI were lower than those in EVO or GLI (Table 3).

Serum insulin level after EVO+GLI was higher than that after EVO or GLI (Figure 3). E_{max} in EVO+GLI was higher by 98.6% compared to that in EVO and 18.8% compared to that in GLI. AUEC in EVO+GLI was also higher by 81.2% and 16.5% compared to those in EVO and GLI, respectively (Table 3). Likewise, ΔE_{max} and ΔAUEC in EVO+GLI were higher than that in EVO or GLI (Table 3).

Safety

No serious AEs were reported, and no subject discontinued the study due to AEs. Twenty-four AEs in 10 subjects were considered to be related to the following investigational products: 1 AE (diarrhoea) in 1 subject after EVO, 5 AEs (blood bilirubin increased, hypoglycaemia, nausea, dizziness, and cold sweat) in 3 subjects after GLI and 18 AEs (abdominal discomfort, asthenia, blood bilirubin increased, cold sweat, dizziness, nausea, throat irritation, etc.) in 9 subjects after EVO+GLI (Table 4).

In clinical laboratory tests, no clinically significant changes were observed when compared to the baseline values, except for a case of total bilirubin increase. Furthermore, there were no clinically significant changes in physical examination, vital signs, and 12-lead electrocardiograms.

DISCUSSIONS

According to T2DM treatment guidelines, combinations of DPP-4 inhibitors and sulfonylureas are recommended due to their different action mechanisms. Nevertheless, clinical use of the evogliptin and sulfonylurea combination is limited, as the significant drug-drug interactions between evogliptin and sulfonylureas, including glimepiride, remain unevaluated. In this respect, this study is meaningful, as it explored the PK and PD interactions between evogliptin and sulfonylurea in humans.

In general, for drug-drug interaction studies, it is recommended to evaluate PK interaction at steady-state, as it is most similar to actual clinical settings and the maximum effect as a perpetrator is shown at steady-state. Therefore, investigational drugs are multiply administered (4 or 5 times) for their half-lives to reach the steady-state. However, a single dose of glimepiride was adopted in this study because a single dosing of glimepiride can be considered to have reached steady state considering its short half-life (1.2-1.5 hours). Similar to this study, previous PK interaction studies of glimepiride adopted a single-dose regimen of glimepiride. [8, 14, 15].

This study revealed that evogliptin and glimepiride have no significant PK interactions with each other. As previously mentioned, evogliptin is mainly metabolized by CYP3A, whereas glimepiride may be a CYP3A4 inhibitor, given that it increased the plasma concentration of sildenafil, mainly metabolized by CYP3A4 in rats. [5, 16]· Additionally, it is believed that there is no significant change in PK properties of glimepiride, mainly metabolized by CYP2C9, as evogliptin does not induce nor inhibit CYP enzymes (unpublished in-house data). This study actually revealed that the PK properties of glimepiride are not altered by evogliptin. In addition, evogliptin and glimepiride did not affect the formation of each major metabolite.

As expected, the combination therapy showed additive glycemic control compared to evogliptin or glimepiride monotherapy. However, the degree of the additive effect in this study is smaller than expected. The difference may be caused by differences in glycemic homeostasis in healthy subjects and T2DM patients; unlike in patients, GLP-1 does not augment insulin-mediated glucose uptake in young healthy subjects with euglycemia. [17]

Although DPP-4 inhibitors increase postprandial insulin secretion, insulin secretion in healthy subjects decreased after evogliptin monotherapy. [18, 19] This phenomenon difference in patients' results was already observed in previous healthy volunteer studies. [3, 20, 21], Although there are no reported clinical studies about the mechanism, it is suggested to have resulted from the difference between healthy volunteers and T2DM patients, including blood glucagon level. [22] Therefore, a further study can be considered to evaluate the PD interactions in T2DM patients.

CONCLUSION

In conclusion, co-administered evogliptin and glimepiride had no PK interactions, but exerted an additive glucose lowering effect compared to evogliptin or glimepiride monotherapy. Therefore, the combination therapy with evogliptin and glimepiride may be an alternative option for T2DM patients with inadequate glycemic control using either a DPP-4 inhibitor or sulfonylurea.

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CONFLICT OF INTEREST

The authors have no competing interests to declare.

REFERENCES

1. Ahren B. DPP-4 inhibitors. Best Pract Res Clin Endocrinol Metab. 2007;21(4):517-33.

2. Hong SM, Park CY, Hwang DM, Han KA, Lee CB, Chung CH, et al. Efficacy and safety of adding evogliptin versus sitagliptin for metformin-treated patients with type 2 diabetes: A 24-week randomized,

controlled trial with open label extension. Diabetes Obes Metab. 2017;19(5):654-63.

3. Park J, Park SW, Yoon KH, Kim SR, Ahn KJ, Lee JH, et al. Efficacy and safety of evogliptin monotherapy in patients with type 2 diabetes and moderately elevated glycated haemoglobin levels after diet and exercise. Diabetes, Obesity and Metabolism. 2017;19(12):1681-7.

4. Gu N, Park MK, Kim TE, Bahng MY, Lim KS, Cho SH, et al. Multiple-dose pharmacokinetics and pharmacodynamics of evogliptin (DA-1229), a novel dipeptidyl peptidase IV inhibitor, in healthy volunteers. Drug Des Devel Ther. 2014;8:1709-21.

5. Kim HJ, Kwak WY, Min JP, Lee JY, Yoon TH, Kim HD, et al. Discovery of DA-1229: a potent, long acting dipeptidyl peptidase-4 inhibitor for the treatment of type 2 diabetes. Bioorganic & medicinal chemistry letters. 2011;21(12):3809-12.

6. Oh E, Choi C, Kim C, Kim K, Kim Y, Kim S, et al. Effects of clarithromycin on the pharmacokinetics of evogliptin in healthy volunteers. Journal of clinical pharmacy and therapeutics. 2017;42(6):689-94.

7. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon K-H, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. Jama. 2009;301(20):2129-40.

8. Heather D. Langtry, Balfour JA. Glimepiride. Drugs. 1998;55(4):563-87.

9. Hotta N. A new perspective on the biguanide, metformin therapy in type 2 diabetes and lactic acidosis. Journal of diabetes investigation. 2019.

10. Ko S-H, Hur K-Y, Rhee SY, Kim N-H, Moon MK, Park S-O, et al. Antihyperglycemic agent therapy for adult patients with type 2 diabetes mellitus 2017: a position statement of the Korean Diabetes Association. Diabetes & metabolism journal. 2017;41(5):337-48.

11. McGuire H, Longson D, Adler A, Farmer A, Lewin I. Management of type 2 diabetes in adults: summary of updated NICE guidance. Bmj. 2016;353:i1575.

12. Serra D, He Y, Bullock J, Riviere G, Balez S, Schwartz S, et al. Evaluation of pharmacokinetic and pharmacodynamic interaction between the dipeptidyl peptidase IV inhibitor vildagliptin, glyburide and pioglitazone in patients with Type 2 diabetes. International journal of clinical pharmacology and therapeutics. 2008;46(7):349-64.

13. Friedrich C, Metzmann K, Rose P, Mattheus M, Pinnetti S, Woerle HJ. A randomized, open-label, crossover study to evaluate the pharmacokinetics of empagliflozin and linagliptin after coadministration in healthy male volunteers. Clinical therapeutics. 2013;35(1):A33-A42.

14. Niemi M, Backman JT, Neuvonen M, Laitila J, Neuvonen PJ, Kivistö KT. Effects of fluconazole and fluvoxamine on the pharmacokinetics and pharmacodynamics of glimepiride. Clinical Pharmacology & Therapeutics. 2001;69(4):194-200.

15. Macha S, Mattheus M, Pinnetti S, Seman L, Woerle HJ. Pharmacokinetics of empagliflozin, a sodium glucose cotransporter 2 inhibitor, and glimepiride following co-administration in healthy volunteers: a randomised, open-label, crossover study. Journal of Diabetes Research and Clinical Metabolism. 2012;1(1):14.

16. Tripathi AS, Timiri AK, Mazumder PM, Chandewar A. Does glimepiride alter the pharmacokinetics of sildenafil citrate in diabetic nephropathy animals: investigating mechanism of interaction by molecular modeling studies. Journal of molecular modeling. 2015;21(10):276.

17. Ryan AS, Egan JM, Habener JF, Elahi D. Insulinotropic hormone glucagon-like peptide-1-(7–37) appears not to augment insulin-mediated glucose uptake in young men during euglycemia. The Journal of Clinical Endocrinology & Metabolism. 1998;83(7):2399-404.

18. Nauck MA, Heimesaat MM, Orskov C, Holst JJ, Ebert R, Creutzfeldt W. Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients

with type-2 diabetes mellitus. The Journal of clinical investigation. 1993;91(1):301-7.

19. Holst JJ, Gromada J. Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans. American Journal of Physiology-Endocrinology And Metabolism. 2004;287(2):E199-E206.

20. Jung CH, Park CY, Ahn KJ, Kim NH, Jang HC, Lee MK, et al. A randomized, double-blind, placebo-controlled, phase II clinical trial to investigate the efficacy and safety of oral DA-1229 in patients with type 2 diabetes mellitus who have inadequate glycaemic control with diet and exercise. Diabetes Metab Res Rev. 2015;31(3):295-306.

21. Rhee SJ, Choi Y, Lee S, Oh J, Kim SJ, Yoon SH, et al. Pharmacokinetic and pharmacodynamic interactions between metformin and a novel dipeptidyl peptidase-4 inhibitor, evogliptin, in healthy subjects. Drug Des Devel Ther. 2016;10:2525-34.

22. Dunning B, Foley J, Ahrén B. Alpha cell function in health and disease: influence of glucagon-like peptide-1. Diabetologia. 2005;48(9):1700-13.

FIGURE LEGENDS

Figure 1. Study design. Abbreviation: PK, pharmacokinetics; PD, pharmacodynamic; OGTT, oral glucose tolerance test; EVO, evogliptin 5 mg once daily; GLI, glimepiride 4 mg once daily; EVO+GLI, evogliptin 5 mg + glimepiridpe 4 mg once daily

Figure 2. Mean plasma evogliptin and glimepiride concentration-time profiles at steady-state after EVO, GLI or EVO+GLI. Error bars represent standard deviations. (a) evogliptin, linear scale, (b) evogliptin, semilog scale, (c) glimepiride, linear scale, (d) glimepiride, semilog scale.

Figure 3. Mean (a) Δ serum glucose and (b) Δ serum insulin level-time profiles at steady-state after EVO, GLI after EVO+GLI. The Δ glucose and Δ insulin were calculated by subtracting the values at 0h from the values at each timepoint. The Error bars represent standard deviations.

Supplementary figure 1. Mean plasma (a) evogliptin M7, (b) evogliptin M8 and (c) glimepiride M1 concentration-time profiles at steady-state after EVO, GLI or EVO+GLI. Error bars represent standard deviations.

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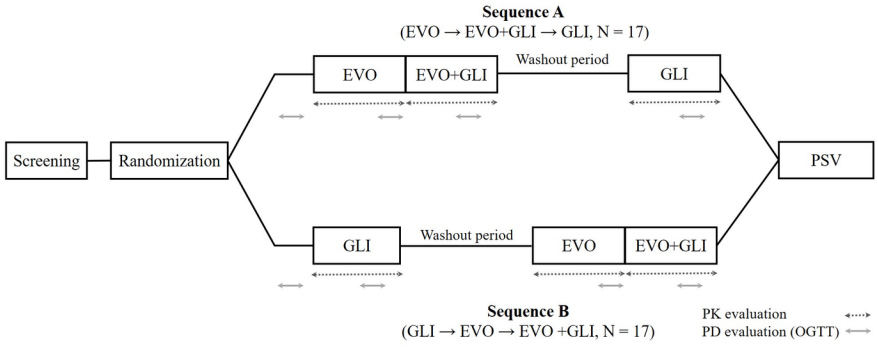

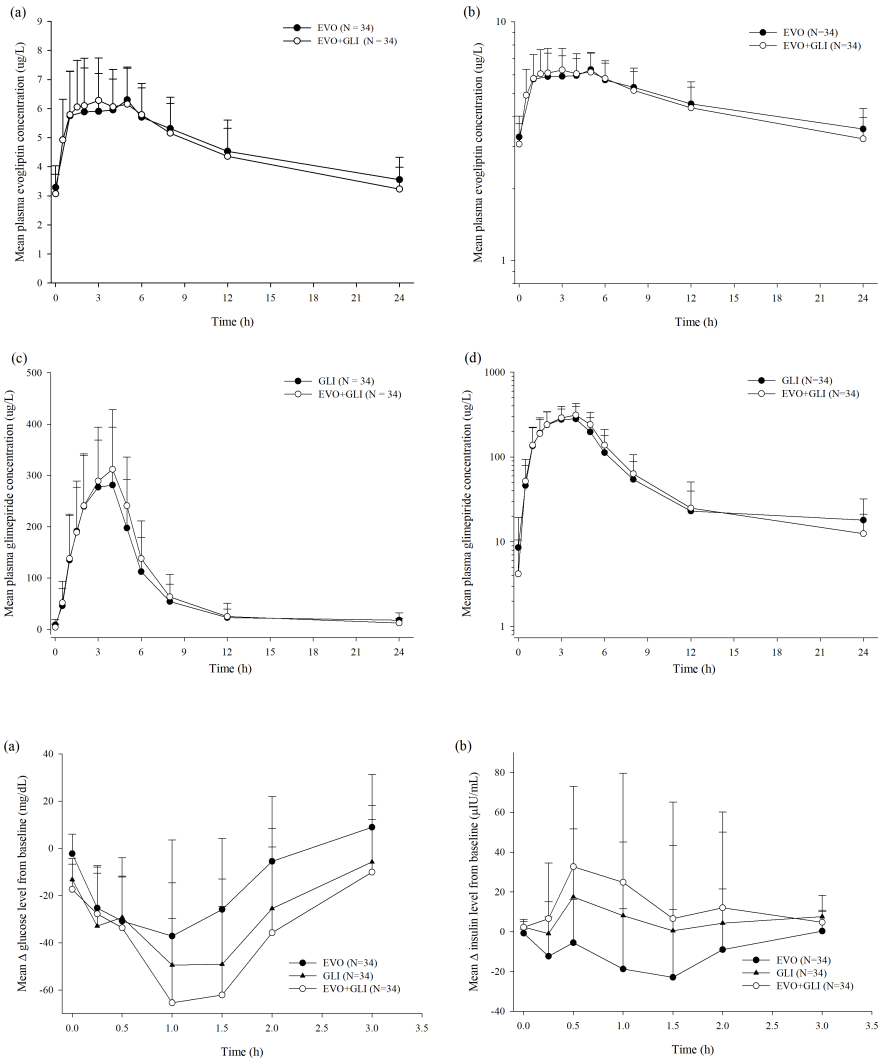

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