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

Inyoung Hwang[1], Yun Kim[2], Hyounggyoon Yoo[3], In-Jin Jang[3], Kyung-Sang Yu[4], and SeungHwan Lee[2]

[1]Affiliation not available
[2]Seoul National University College of Medicine and Hospital
[3]Seoul National University College of Medicine
[4]Seoul National University Hospital

June 15, 2020

Abstract

Aims: Evogliptin is a newly developed oral glucose-lowering medication of dipeptidyl peptidase 4 (DPP-4) inhibitor class for type 2 diabetes mellitus. Combination of DPP-4 inhibitor with pioglitazone is a promising therapeutic option. The aim of present study was to evaluate pharmacokinetic and pharmacodynamic interaction between evogliptin and pioglitazone. Methods: A randomized, open-label, multiple-dose, three-treatment, three-period, six-sequence crossover study was conducted in healthy Korean male subjects. All subjects received evogliptin 5 mg once daily for 7 days (EVO), pioglitazone 30 mg once daily for 7 days (PIO) and co-administration of evogliptin 5 mg and pioglitazone 30 mg once daily for 7 days (EVO+PIO) according to the assigned sequence and period. Serial blood samples were collected for 24 hours for pharmacokinetic analysis and 3 hours after oral glucose tolerance test for pharmacodynamic analysis. Results: Thirty-four subjects completed the study. EVO+PIO and EVO showed similar maximum plasma concentration at steady state ($C_{max,ss}$) and the area under the concentration-time curve during dosing interval at steady state ($AUC_{\tau,\sigma\varsigma}$) of evogliptin, with geometric mean ratios (GMRs) (90% confidence interval (CI)) of 1.01 (0.97-1.05) and 1.01 (0.98-1.04), respectively. EVO+PIO and PIO showed similar $C_{max,ss}$ and $AUC_{\tau,\sigma\varsigma}$ of pioglitazone, with GMRs (90% CI) of 1.07 (0.99-1.17) and 1.08 (0.99-1.17), respectively. Reduction of glucose level after EVO+PIO was larger compared to PIO, and similar with EVO. Conclusion: Concomitant administration of evogliptin and pioglitazone showed similar glucose lowering effects with those of evogliptin alone without pharmacokinetic interactions when compared to intake of each drug alone.

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.
- There are no pharmacokinetic nor pharmacodynamic data of co-administration of evogliptin and pioglitazone although many DPP-4 inhibitors showed no pharmacokinetic interactions with pioglitazone.

What this study adds

- Co-administering evogliptin and pioglitaozne showed no pharmacokinetic nor pharmacodynamic interaction.
- Co-administering evogliptin and pioglitaozne may show improved glucose reduction in type 2 diabetes mellitus patients.

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

INTRODUCTION

Type 2 diabetes mellitus (T2DM), which accounts for more than 90% of all DM cases, is a progressive disease resulting in gradual decline of insulin secretory capacity.[1, 2] As a result, patients often fail to achieve glycemic goal with monotherapy as treatment continues.[3] Current guidelines on management of T2DM recommend metformin as first-line medication, and glucose-lowering medications including oral agents and injectable medications as second-line if optimal glycemic target is not achieved.[4] Still, additional glucose-lowering medication is required in patients with inadequate glycemic control.

Dipeptidyl peptidase 4 (DPP-4) inhibitors prevent DPP-4 enzyme from degrading incretins including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP).[5] Increased incretins subsequently lower blood glucose level by stimulating insulin release and inhibit glucagon production.[6] Evogliptin is an orally bioavailable, selective DPP-4 inhibitor developed for the treatment of T2DM.[7] After repeated once daily administrations in healthy subjects in a first-in-human clinical trial (ClinicalTrials.gov Identifier: NCT00961025), evogliptin was well tolerated with time to reach maximum plasma concentration (T_{max}) of 4–5 hours after administration and terminal half-life ($t_{1/2}$) of 33–39 hours.[8] At steady state, evogliptin showed dose-proportional increase in systemic exposure and sustained inhibition of DPP-4 activity above 80% in dose range of 5–20 mg.[8] In *in vitro* study, evogliptin was mainly metabolized to 4(S)-hydroxyevogliptin (M7) and 4(R)-hydroxyevogliptin (M8) by CYP3A4 and CYP3A5.[9] Pharmacological activity of the metabolites is currently unknown.[10] The recommended dosage of evogliptin for T2DM is 5 mg once daily.[11]

Pioglitazone, on the other hand, is a thiazolidinedione (TZD) that increases insulin sensitivity by acting as an agonist of peroxisome proliferator–activated receptor gamma (PPAR-γ).[12] After once daily oral administration, T_{max} of pioglitazone is about 2 hours and $t_{1/2}$ is in range of 3–7 hours.[13] Pioglitazone is extensively metabolized, mainly by CYP2C8, CYP3A4 and CYP2C9 to form active metabolites (M3 and M4).[13, 14] The recommended starting dose of pioglitazone is 15 to 30 mg once daily.[13]

Combination of DPP-4 inhibitors with pioglitazone treatment for T2DM has shown potential as an effective treatment owing to their complementary mechanism of action.[15] Recent guideline of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) on T2DM suggests addition of DPP-4 or TZD to subjects who do not achieve target HbA_{1c} level with metformin monotherapy, in case compelling need to reduce hypoglycemia exists. If dual therapy with metformin plus one of DPP-4 and TZD fails to meet target, addition of the other one could be considered for triple therapy according to the guideline.[1]

Since evogliptin and pioglitazone have complementary mechanisms of action, combination of two medications is a promising therapeutic option for T2DM treatment. However, assessment of drug interaction between the two drugs has been lacking. The aim of present study was to evaluate pharmacokinetic and pharmacodynamic interaction between evogliptin and pioglitazone, along with safety profiles in healthy volunteers.

METHODS

Subjects

Healthy Korean male volunteers aged between 19 and 45 years with body mass index (BMI) between 18.0 and 27.0 kg/m^2 were eligible for inclusion in the study. Volunteers with fasting plasma glucose (FPG) $<$ 70 mg/dL or $>$ 125 mg/dL, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $>$ 60 IU/mL, creatinine clearance (MDRD equation) $<$ 80 mL/min, corrected QT interval (Bazett correction) $>$ 450 ms, known allergy or hypersensitivity to components of investigational drug (evogliptin, pioglitazone) were excluded. Other major reasons for exclusion were the followings; clinically significant abnormalities in medical history, vital sign measurements, physical examination, clinical laboratory tests (hematology, biochemistry, urinalysis), 12-lead electrocardiogram. According to results from previous studies, the largest intra-subject variability of selected pharmacokinetic parameters (C_{max}, $AUC_{\tau,\sigma\varsigma}$) of evogliptin, pioglitazone and their major metabolites were assumed to be 29%[8, 16]. Sample size of 30 was required to detect 20% difference in those pharmacokinetic parameters with a power of 80% and significance level of 0.05. Actual sample size of 36 was determined considering drop-out. Study protocol was approved by Institutional Review

Board (IRB) of Seoul National University Hospital (ClinicalTrials.gov identifier: NCT02753803, IRB number: 1604-135-757) and the Ministry of Food and Drug Safety, Republic of Korea. All volunteers provided written informed consent prior to study procedure.

Study design

This randomized, open-label, multiple-dose, three-treatment, three-period, six-sequence crossover study was conducted at Clinical Trials Center of Seoul National University Hospital (Seoul, Republic of Korea). Eligible subjects were randomly assigned to one of six treatment sequence groups (Figure 1). Subjects received either evogliptin 5 mg once daily for 7 days (EVO), pioglitazone 30 mg once daily for 7 days (PIO), or coadministration of evogliptin 5 mg and pioglitazone 30 mg once daily for 7 days (EVO+PIO) according to the assigned sequence and period. Each treatment period was separated by 7 days of washout period. Study drugs were administered with 150 mL of water under fasted state.

Pharmacokinetic assessment

For pharmacokinetic evaluation, serial blood samples were collected at 0 (pre-dose), 1, 2, 3, 4, 5, 6, 8, 12 and 24 hours after last dose for evogliptin and its metabolites (M7, M8), and at 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours after last dose for pioglitazone and its metabolites (M3, M4). Urine samples of evogliptin, pioglitazone and their metabolites were collected up to 24 hours after last dose.

Individual steady-state pharmacokinetic parameters of each period were calculated by non-compartmental methods using Phoenix WinNonlin® software version 8.0 (Certara, Princeton, NJ, USA) software. Maximum plasma concentration of each analyte at steady-state ($C_{max,ss}$) and the time to reach $C_{max,ss}$ ($T_{max,ss}$) was directly derived from observed data. Area under the plasma concentration-time curve during a dosing interval at steady-state ($AUC_{\tau,\sigma\varsigma}$) was calculated by the linear trapezoidal method when concentrations are increasing in the interval, and by the log trapezoidal method when concentrations are decreasing in the interval. Apparent clearance at steady-state (CL_{ss}/F) was calculated as administered dose / $AUC_{\tau,\sigma\varsigma}$. Renal clearance at steady-state ($CL_{R,ss}$) was calculated as amount of unchanged drug excreted into the urine during a dosing interval at steady state ($Ae_{\tau,\sigma\varsigma}$) / $AUC_{\tau,\sigma\varsigma}$. Metabolic ratio at steady state was calculated as $AUC_{\tau,\sigma\varsigma}$ of metabolite / $AUC_{\tau,\sigma\varsigma}$ of parent drug.

Plasma and urine concentrations of evogliptin, pioglitazone and their metabolites (M7, M8 of evogliptin and M3, M4 of pioglitazone) were analyzed with a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method (LC: Shimadzu UFLC, Shimadzu, Japan. MS: TQ5500(3)/5500QTRAP, SCIEX, USA). Internal standards (ISs) for evogliptin, M7 and M8 were evogliptin-d_9, M8-d_9 and M8-d_9, respectively, and ISs for pioglitazone, M3 and M4 were pioglitazone-d_4, M3-d_4 and M4-d_5, respectively.

For plasma sample analysis, mobile phase consists of 5 mM ammonium formate with 0.1 % formic acid and acetonitrile for evogliptin; deionized water with 0.1% formic acid and methanol for M7 and M8. Mobile phase consists of 10 mM ammonium formate with 0.1 % formic acid and acetonitrile for pioglitazone, M3 and M4. All plasma analytes and their ISs were separated in C_{18} column (evogliptin: 100 × 2.1 mm, 1.7 μm, M7/M8: 100 × 2.1 mm, 5 μm, pioglitazone/M3/M4: 50 × 2.1 mm, 3 μm). Positive electrospray ionization (ESI) mode with multiple reaction monitoring (MRM) was used to detect transition (m/z) of evogliptin (402.2 - 346.2), evogliptin-d_9 (411.2 - 347.2), M7 (418.2 - 362.2), M8 (418.2 - 362.2), M8-d_9(427.2 - 363.2), pioglitazone (357.2 - 134.1), pioglitzone-d_4 (361.2 - 138.2), M3 (371.2 - 148.1), M3-d_4 (375.3 - 152.3), M4 (373.2 - 150.2) and M4-d_5 (378.3 - 154.4). Calibration curves of plasma analytes were linear within the range of 0.1 – 60 ng/mL for evogliptin, 10 – 10,000 pg/mL for M7 and M8, 10 – 10,000 ng/mL for pioglitazone and 10 – 5,000 ng/mL for M3 and M4 (r [?] 0.9950). Accuracy and precision of intra-batch quality control (QC) is 98.0 – 106.3 % and < 8.3 % for evogliptin, 96.0 – 107.8 % and < 6.7 % for M7, 93.9 – 105.9 % and < 6.5 % for M8, 89.4 – 108.2 % and < 6.7 % for pioglitazone, 95.6 – 106.9 % and < 7.3 % for M3, and 92.6 – 111.2 % and < 6.2 % for M4.

For urine sample analysis, mobile phase consists of 5 mM ammonium formate with 0.1% formic acid and acetonitrile for evogliptin; 5 mM ammonium formate with 0.1% formic acid and methanol for M7 and M8.

Mobile phase consists of 10 mM ammonium formate with formic acid and acetonitrile for pioglitazone, M3 and M4. Other LC and MS/MS condition was same as in plasma sample analysis. Calibration curves of plasma analytes were linear within the range of 5 – 5,000 ng/mL for evogliptin, 0.5 – 500 ng/mL for M7 and M8, 30 – 10,000 ng/mL for pioglitazone and 30 – 10,000 ng/mL for M3 and M4 (r [?] 0.9950). Accuracy and precision of intra-batch quality control (QC) is 100.4 – 107.1 % and < 3.6 % for evogliptin, 95.3 – 99.4 % and < 5.2 % for M7, 97.4 – 110.8 % and < 6.2 % for M8, 92.4 – 105.4 % and < 9.9 % for pioglitazone, 103.3 – 109.1 % and < 4.3 % for M3, and 99.2 – 107.8 % and < 8.2 % for M4.

Pharmacodynamic assessment

For pharmacodynamic analysis, serial blood samples were collected during oral glucose tolerance test (OGTT); 0 (pre-OGTT), 0.25, 0.5, 1, 1.5, 2 and 3 hours after administration of glucose (75 g) for measurement of serum glucose and plasma insulin level. OGTT was conducted at the day before first study drug administration at period 1 (baseline) and 2 hours after study drug administration at sixth day of each period.

Individual steady-state serum glucose and plasma insulin parameters of each period were calculated by non-compartmental methods using Phoenix WinNonlin® software. Maximum concentration of serum glucose and plasma insulin at steady-state ($G_{max,ss}$, $E_{max,ss}$) were directly derived from observed data. Area under the serum glucose and plasma insulin concentration-time curve during a dosing interval at steady-state ($AUGC_{\tau,\sigma\varsigma}$, $AUEC_{\tau,\sigma\varsigma}$) were calculated by the linear trapezoidal method.

Plasma concentrations of insulin were analyzed with immunoradiometric assay (IRMA) method (gamma counter: Dream Gamma-10, Shin Jin, Republic of Korea). Serum concentrations of glucose were analyzed with glucose hexokinase assay method (automatic chemical analyzer: TBA-FX8, Toshiba, Japan).

Safety assessment

Safety and tolerability were assessed through vital sign, physical examination, clinical laboratory test, 12-lead electrocardiogram (ECG) and adverse event (AE) monitoring. All AEs occurred during the study were recorded, coded using MedDRA® (Version 19.0), and evaluated by investigators.

Statistical analysis

Descriptive statistics were used to summarized demographic characteristics, pharmacokinetic and pharmacodynamic parameters. To assess pharmacokinetic interaction between evogliptin and pioglitazone, geometric mean ratios (GMR) and 90% confidence intervals (CI) of log-transformed pharmacokinetic parameters ($C_{max,ss}$, $AUC_{\tau,\sigma\varsigma}$) of EVO+PIO and EVO or PIO alone were calculated using linear mixed effect model which assumed treatment, period and sequence as fixed effect.

RESULTS

Demographics

A total of 36 healthy male subjects were enrolled in the study. Age, height, weight and BMI were 33.0 ± 6.0 years (mean ± standard deviation), 173.7 ± 5.3 cm, 68.8 ± 7.7 kg and 22.8 ± 2.0 kg/m^2, respectively. The baseline demographic characteristics were similar across sequence groups. During the study, one subject discontinued before drug administration due to non-treatment emergent adverse event, and one subject withdrew consent in the first period of the study. Therefore, 35 subjects who received study drug at least once were included in safety assessment, and 34 subjects who completed the whole study were included in pharmacokinetic and pharmacodynamic assessment.

Pharmacokinetics

Pharmacokinetic profiles of evogliptin and pioglitazone after EVO+PIO were similar with those after evogliptin or pioglitazone alone, respectively. The mean plasma concentration-time profiles of evogliptin with its metabolites (M6, M7) after EVO and EVO+PIO, and pioglitazone with its metabolites (M3, M4) after PIO and EVO+PIO were comparable (Figure 2 and Supplementary figure 1).

GMR (90% CI) of EVO+PIO to EVO and for $C_{max,ss}$ and $AUC_{\tau,\sigma\varsigma}$ of evogliptin were 1.01 (0.97 – 1.05) and 1.01 (0.98 - 1.04), contained within conventional bioequivalence range[17] of 0.80 – 1.25 (Table 1). The corresponding values of EVO+PIO to PIO and its 90% CI for $C_{max,ss}$ and $AUC_{\tau,\sigma\varsigma}$ of pioglitazone were 1.07 (0.99 – 1.17) and 1.08 (0.99 – 1.17), contained within conventional bioequivalence range as well (Table 2).

Pharmacodynamics

Reduction of serum glucose level during OGTT for EVO+PIO was greater than PIO and similar to EVO (Figure 3). The $G_{max,ss}$ and $AUGC_{\tau,\sigma\varsigma}$ for EVO+PIO compared to baseline also showed similar trend (Table 3). On the other hand, reduction of plasma insulin level during OGTT for all treatments were similar (Figure 3), as well as the $E_{max,ss}$ and $AUEC_{\tau,\sigma\varsigma}$ (Table 3).

Safety

A total of 35 subjects received study drug at least once, and 10 of them reported 20 AEs. Among reported AEs, 12 AEs were evaluated as drug-related by the investigators (Table 4). A total of 13 AEs, 3 AEs and 4 AEs were reported after EVO, PIO, and EVO+PIO, respectively. All AEs were spontaneously recovered during the study period, except for one case of lip blister which was recovering during to follow-up period. No serious AEs or clinically significant findings in vital signs, physical examinations, clinical laboratory tests and ECGs were reported.

DISCUSSION

According to *in vitro* studies, evogliptin does not induce nor inhibit CYP enzymes, while its metabolism is primarily mediated by CYP3A4 to form metabolites with unknown activity (M7 and M8).[10, 18] On the other hand, pioglitazone is extensively metabolized, mainly by CYP2C8, CYP3A4 and CYP2C9 to form active metabolites (M3 and M4).[13, 14] No clinically significant CYP enzyme induction nor inhibition by pioglitazone has been identified*in vivo.* [13, 14] Since the elimination pathways of evogliptin and pioglitazone shows little possibility to affect each other, pharmacokinetic interaction of the two drug is unlikely to occur, as the result of current study suggests.

For pioglitazone, total pioglitazone (pioglitazone, M3 and M4) concentration were also similar between treatment groups. GMR (90% CI) of EVO+PIO to PIO for $C_{max,ss}$ and $AUC_{\tau,\sigma\varsigma}$ were 106.95 (102.16 – 111.97) and 106.38 (101.76 – 111.22), respectively, and contained within conventional limits of bioequivalence.

Changes of glucose and insulin level during OGTT were measured as pharmacodynamic parameters at baseline and each treatment period. Reduction of glucose level after combination therapy compared to baseline, expressed as maximum concentrations ($G_{max,ss}$, $E_{max,ss}$) and area under-curves ($AUGC_{\tau,\sigma\varsigma}$, $AUEC_{\tau,\sigma\varsigma}$), was not superior compared to administration of each drug alone. Since combination of other DPP-4s (alogliptin, vildagliptin and linagliptin) with pioglitazone have led to greater efficacy (HbA1C reduction) than each medication alone in T2DM patients, a greater reduction of glucose level was expected.[19-21] The discrepancy could be attributable to the study design which includes healthy subjects with unimpaired glucose tolerance. To verify pharmacodynamic interaction and clinical implication of combination of evogliptin and pioglitazone, further study with larger sample size of T2DM patients can be considered.

Despite insulinotropic effect of DPP-4 inhibitor, postprandial insulin level at all three treatment periods were lower than baseline. Similar insulin profiles were obtained from previous studies which administered evogliptin and other drugs of same class including sitagliptin to healthy subjects.[8] In case of sitagliptin, insulinotropic effect was observed in DM patients after administration of the same dose that did not produce significant change of insulin level in healthy subjects.[22, 23] Therefore, these pharmacodynamic results in healthy volunteers should not be used alone to determine the efficacy of evogliptin.

CONCLUSION

In conclusion, concomitant administration of evogliptin and pioglitazone showed similar glucose lowering effets with those of evogliptin alone and no clinically significant pharmacokinetic interactions. Safe and tolerability of concomitant administration was comparable to administration of each drug alone.

ACKNOWLEDGEMENTS

This study was sponsored by Dong-A ST Co., Ltd., Seoul, Republic of Korea.

CONFLICT OF INTEREST

The authors have no competing interests to declare.

REFERENCES

1. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018;41(12):2669-701.

2. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nature Reviews Endocrinology. 2018;14(2):88-98.

3. Brown JB, Nichols GA, Perry A. The burden of treatment failure in type 2 diabetes. Diabetes Care. 2004;27(7):1535-40.

4. Qaseem A, Barry MJ, Humphrey LL, Forciea MA, Clinical Guidelines Committee of the American College of P. Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians. Ann Intern Med. 2017;166(4):279-90.

5. Thornberry NA, Gallwitz B. Mechanism of action of inhibitors of dipeptidyl-peptidase-4 (DPP-4). Best Practice & Research Clinical Endocrinology & Metabolism. 2009;23(4):479-86.

6. Nauck MA, Meier JJ. Incretin hormones: Their role in health and disease. Diabetes, Obesity and Metabolism. 2018;20(S1):5-21.

7. McCormack PL. Evogliptin: First Global Approval. Drugs. 2015;75(17):2045-9.

8. Gu N, Park MK, Kim T-E, Bahng MY, Lim KS, Cho S-H, et al. Multiple-dose pharmacokinetics and pharmacodynamics of evogliptin (DA-1229), a novel dipeptidyl peptidase IV inhibitor, in healthy volunteers. Drug design, development and therapy. 2014;8:1709.

9. Jeong HU, Kim JH, Lee DY, Shim HJ, Lee HS. In Vitro Metabolic Pathways of the New Anti-Diabetic Drug Evogliptin in Human Liver Preparations. Molecules. 2015;20(12):21802-15.

10. Oh ES, Choi C, Kim CO, Kim KH, Kim YN, Kim SJ, et al. Effects of clarithromycin on the pharmacokinetics of evogliptin in healthy volunteers. J Clin Pharm Ther. 2017;42(6):689-94.

11. MFDS approval of a new, domestically-developed, oral antihyperglycaemic agent [media release]: Ministry of Food and Drug Safety; 2015 [Available from:*https://www.mfds.go.kr/brd/m_99/view.do?seq=28999*.

12. Hanefeld M. Pharmacokinetics and clinical efficacy of pioglitazone. Int J Clin Pract Suppl. 2001(121):19-25.

13. America TP. ACTOS package insert. 2011.

14. Kajosaari LI, Jaakkola T, Neuvonen PJ, Backman JT. Pioglitazone, an in vitro inhibitor of CYP2C8 and CYP3A4, does not increase the plasma concentrations of the CYP2C8 and CYP3A4 substrate repaglinide. Eur J Clin Pharmacol. 2006;62(3):217-23.

15. Mikhail N. Combination therapy with DPP-4 inhibitors and pioglitazone in type 2 diabetes: theoretical consideration and therapeutic potential. Vascular health and risk management. 2008;4(6):1221-7.

16. Sripalakit P, Maphanta S, Neamhom P, Saraphanchotiwitthaya A, Polnok S, Yokubol D. Comparative study on the bioequivalence of two formulations of pioglitazone tablet in healthy Thai male volunteers. Drug development and industrial pharmacy. 2007;33(12):1362-8.

17. Food U, Administration D. Clinical drug interaction studies—study design, data analysis, and clinical implications guidance for industry. FDA<*https://www* fda gov/downloads/drugs/guidances/ucm292362 pdf. 2017.

18. 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.

19. Rosenstock J, Inzucchi SE, Seufert J, Fleck PR, Wilson CA, Mekki Q. Initial combination therapy with alogliptin and pioglitazone in drug-naive patients with type 2 diabetes. Diabetes Care. 2010;33(11):2406-8.

20. Rosenstock J, Kim SW, Baron MA, Camisasca RP, Cressier F, Couturier A, et al. Efficacy and tolerability of initial combination therapy with vildagliptin and pioglitazone compared with component monotherapy in patients with type 2 diabetes. Diabetes, obesity & metabolism. 2007;9(2):175-85.

21. Bajaj M, Gilman R, Patel S, Kempthorne-Rawson J, Lewis-D'Agostino D, Woerle HJ. Linagliptin improved glycaemic control without weight gain or hypoglycaemia in patients with type 2 diabetes inadequately controlled by a combination of metformin and pioglitazone: a 24-week randomized, double-blind study. Diabet Med. 2014;31(12):1505-14.

22. Herman GA ZP, Dietrich B, et al. The DP-IV inhibitor MK-043 enhances active GLP-1 and reduces glucose following an OGTT in type 2 diabetics. Diabetes. 2004;52(A82).

23. Herman GA, Stevens C, Van Dyck K, Bergman A, Yi B, De Smet M, et al. Pharmacokinetics and pharmacodynamics of sitagliptin, an inhibitor of dipeptidyl peptidase IV, in healthy subjects: results from two randomized, double-blind, placebo-controlled studies with single oral doses. Clinical Pharmacology & Therapeutics. 2005;78(6):675-88.

FIGURE LEGENDS

Figure 1. Study design. Abbreviation: PK, pharmacokinetics; OGTT, oral glucose tolerance test; EVO, evogliptin 5 mg once daily; PIO, pioglitazone 30 mg once daily; EVO+PIO: evogliptin 5 mg + pioglitazone 30 mg once daily.

Figure 2. Mean plasma evogliptin and pioglitazone concentration-time profiles at steady-state after EVO, PIO, and EVO+PIO. Error bars represent standard deviations. (a) evogliptin, linear scale, (b) evogliptin, semi-log scale, (c) pioglitazone, linear scale, (d) pioglitazone, semi-log scale.

Figure 3. Mean (a) Δ serum glucose and (b) Δ plasma insulin level-time profiles at steady-state after EVO, PIO, and EVO+PIO. Error bars represent standard deviations.

Supplementary figure 1. Mean plasma (a) evogliptin M7, (b) M8 and pioglitazone (c) M3, (d) M4 concentration-time profiles at steady-state after EVO, PIO or EVO+PIO. Error bars represent standard deviations.

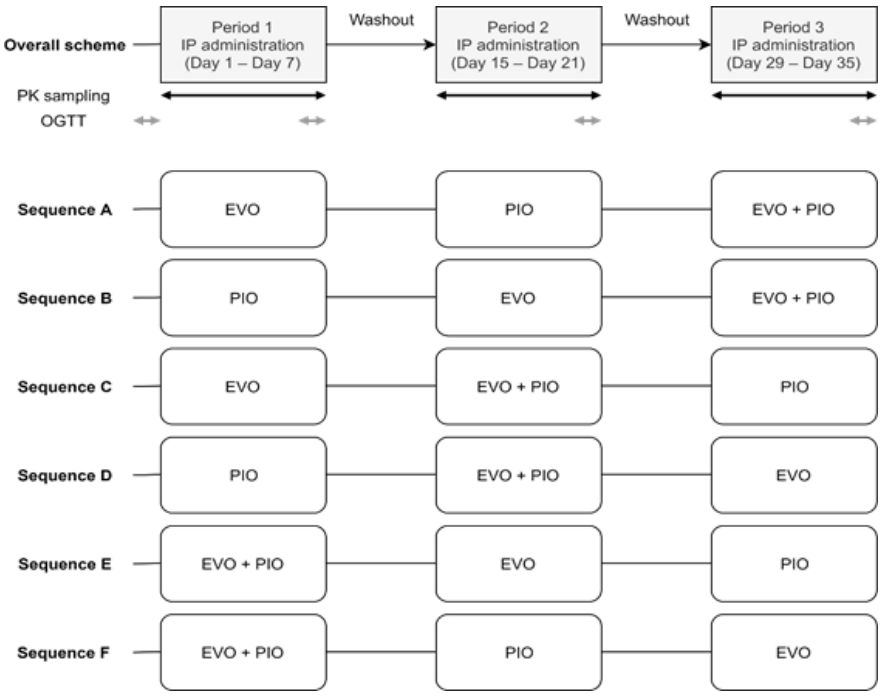
WORD COUNT:

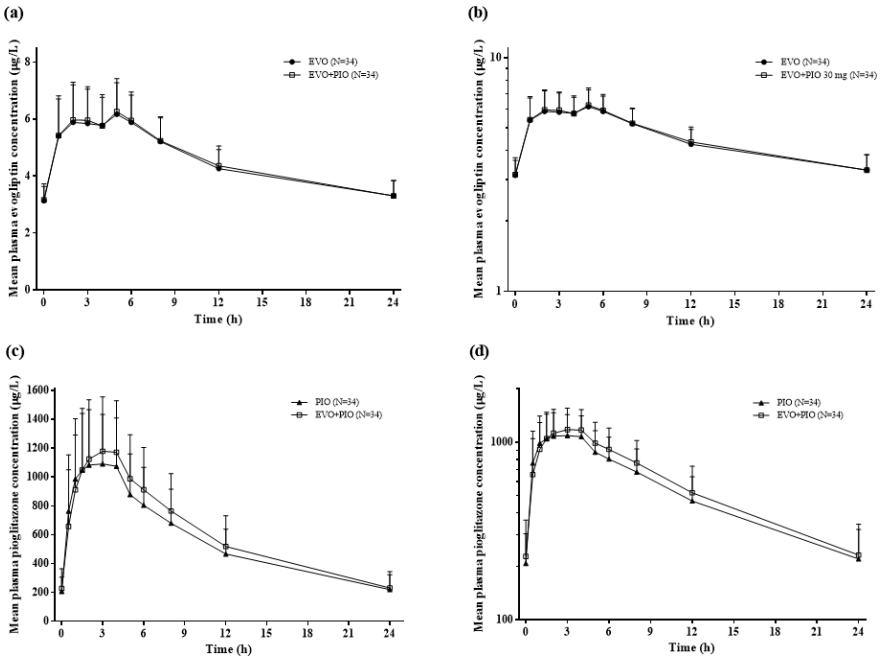
Body of the manuscript: 2539

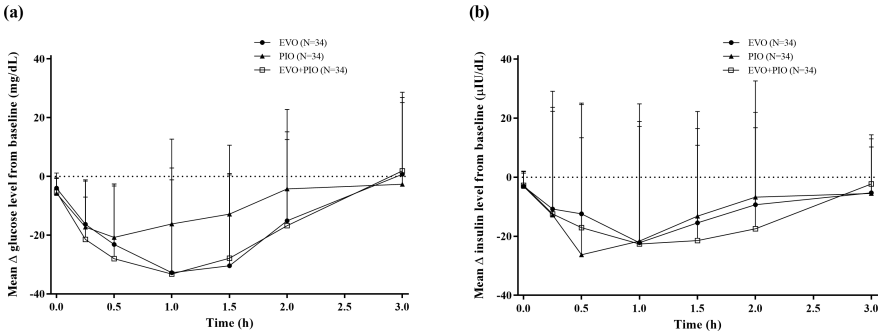
Figures: 3

Tables: 4

References: 23







Hosted file

[DA1229_DIP_I]journal_final_200612_table1.docx available at https://authorea.com/users/333068/articles/459335-pharmacokinetic-pharmacodynamic-interaction-between-evogliptin-and-pioglitazone-in-healthy-male-subjects

Hosted file

[DA1229_DIP_I]journal_final_200612_table2.docx available at https://authorea.com/users/333068/articles/459335-pharmacokinetic-pharmacodynamic-interaction-between-evogliptin-and-pioglitazone-in-healthy-male-subjects

Hosted file

[DA1229_DIP_I]journal_final_200612_table3.docx available at https://authorea.com/users/333068/articles/459335-pharmacokinetic-pharmacodynamic-interaction-between-evogliptin-and-pioglitazone-in-healthy-male-subjects

Hosted file

[DA1229_DIP_I]journal_final_200612_table4.docx available at https://authorea.com/users/333068/articles/459335-pharmacokinetic-pharmacodynamic-interaction-between-evogliptin-and-pioglitazone-in-healthy-male-subjects