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ORIGINAL ARTICLE

Saxagliptin, a potent, selective inhibitor of DPP-4, does not alter the pharmacokinetics of three oral antidiabetic drugs (metformin, glyburide or pioglitazone) in healthy subjects

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Aim: To evaluate the pharmacokinetic interactions of the potent, selective, dipeptidyl peptidase-4 inhibitor, saxagliptin, in combination with metformin, glyburide or pioglitazone.

Methods: To assess the effect of co-administration of saxagliptin with oral antidiabetic drugs (OADs) on the pharmacokinetics and tolerability of saxagliptin, 5-hydroxy saxagliptin, metformin, glyburide, pioglitazone and hydroxy-pioglitazone, analyses of variance were performed on maximum (peak) plasma drug concentration (C_{max}), area under the plasma concentration–time curve from time zero to infinity (AUC_{∞}) [saxagliptin + metformin (study 1) and saxagliptin + glyburide (study 2)] and area under the concentration–time curve from time 0 to time t (AUC_{τ}) [saxagliptin + pioglitazone (study 3)] for each analyte in the respective studies. Studies 1 and 2 were open-label, randomized, three-period, three-treatment, crossover studies, and study 3 was an open-label, non-randomized, sequential study in healthy subjects.

Results: Co-administration of saxagliptin with metformin, glyburide or pioglitazone did not result in clinically meaningful alterations in the pharmacokinetics of saxagliptin or its metabolite, 5-hydroxy saxagliptin. Following co-administration of saxagliptin, there were no clinically meaningful alterations in the pharmacokinetics of metformin, glyburide, pioglitazone or hydroxy-pioglitazone. Saxagliptin was generally safe and well tolerated when administered alone or in combination with metformin, glyburide or pioglitazone.

Conclusions: Saxagliptin can be co-administered with metformin, glyburide or pioglitazone without a need for dose adjustment of either saxagliptin or these OADs.

Keywords: diabetes mellitus, drug–drug interaction, glyburide, metformin, pharmacokinetics, pharmacology, pioglitazone, saxagliptin, type 2 diabetes

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Introduction

Saxagliptin (Onglyza™, Bristol-Myers Squibb, Princeton, NJ, USA, AstraZeneca, Wilmington, DE, USA) [1] is a potent, selective dipeptidyl peptidase-4 (DPP-4) inhibitor, specifically designed for extended inhibition of the DPP-4 enzyme, an enzyme that selectively cleaves dipeptides from various peptides. Substrates include a key insulinotropic hormone glucagon-like peptide-1 (GLP-1), converting it from the intact and active form to an inactive form. Thus, DPP-4 is responsible for the short half-life of intact GLP-1 *in vivo* [2]. Inhibitors of DPP-4 increase levels of endogenous intact GLP-1 and potentiate its physiological actions, augmenting postprandial insulin secretion and improving the glycaemic profile in patients with type 2 diabetes mellitus (T2DM) [3]. Because they stimulate insulin secretion in a glucose-dependent manner, DPP-4 inhibitors present lower risks of hypoglycaemia and may not lead to weight gain [4,5].

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The inhibition of DPP-4 activity is becoming an increasingly recognized mode for the treatment of T2DM and has been studied in both monotherapy and combination therapy [6]. Clinical data indicate that treatment with DPP-4 inhibitors, in combination with sulphonylureas, such as glimepiride or glyburide, results in significantly improved glycaemic control compared with glimepiride or glyburide alone or glimepiride in combination with metformin treatment [7,8]. When studied in combination with thiazolidinediones, such as pioglitazone, DPP-4 inhibitors showed increased glycaemic control, low risk of hypoglycaemia and a similar tolerability profile compared with monotherapy [9–12]. Thus, saxagliptin is likely to be co-administered with other oral antidiabetic drugs (OADs) in the treatment of T2DM.

On the basis of the known pharmacokinetic properties of saxagliptin, metformin, glyburide and pioglitazone, no clinically meaningful metabolic or transporter-based drug–drug interaction is expected to occur when saxagliptin is co-administered with one of these OADs. However, pharmacokinetic drug–drug interaction studies of saxagliptin with metformin, glyburide or pioglitazone would provide valuable

information for prescribers as to whether each modifies the disposition of the other. Three such studies are described here. A saxagliptin dose of 100 mg was employed in study 1 (CV181017, metformin), and 10 mg was employed in study 2 [CV181026, the sulphonylurea (glyburide)] and study 3 [CV181028, the thiazolidinedione (pioglitazone)]. The selected doses of saxagliptin were the highest in the clinical development programme at the time when these studies were conducted. The usual clinical dose of saxagliptin is 5 mg administered once daily (o.d.) in patients with T2DM and normal renal function, and 2.5 mg o.d. in patients with T2DM and moderate or severe renal impairment or end-stage renal disease [1]. Metformin 1000 mg, glyburide 5 mg and pioglitazone 45 mg doses were employed in studies 1, 2 and 3, respectively. Metformin 1000 mg is the highest starting daily dose of metformin [13], pioglitazone 45 mg is the highest recommended daily dose of pioglitazone [14] and glyburide 5 mg is the highest recommended starting dose for drug-naïve patients [15].

Methods

Study Designs and Subjects

Healthy subjects [men or women not of child-bearing potential (i.e. postmenopausal or surgically sterile)], age 18 to 45 years, with body mass index (BMI) of 18–30 kg/m^2, inclusive (study 1), and 18–35 kg/m^2, inclusive (studies 2 and 3), were eligible. Medical history was disclosed, and physical examination, ECG and clinical laboratory determinations (including routine haematological, biochemical and urine tests) were conducted to determine eligibility for enrollment.

Exclusion criteria included history of significant drug allergies, previous exposure to saxagliptin or allergies to other DPP-4 inhibitors, use of prescription medications or over-the-counter (OTC) acid controllers within 4 weeks prior to enrollment and use of any other drugs, including OTC medications and herbal preparations, within 1 week (study 1) or 2 weeks (studies 2 and 3) prior to enrollment. Patients with evidence of organ dysfunction or any clinically significant deviations from normal in physical examinations, vital signs, ECG or clinical laboratory determinations were also excluded.

In study 1, the protocol, protocol amendments and informed consents were approved by the Heartland Institutional Review Board (IRB). In studies 2 and 3, the protocol, protocol amendments and informed consents were approved by the New England IRB. Written informed consents were obtained from all study participants prior to study enrollment.

Vital signs were measured at screening, during each treatment period and prior to discharge from the study. Routine clinical laboratory determinations were made at screening, prior to treatment with any study medications and prior to discharge. Safety monitoring for serious and non-serious adverse events was conducted during each period of study drug administration. Study drugs were administered after an 8–10-h overnight fast, with a 4-h fast post-dosing on pharmacokinetic sampling days.

Studies 1 and 2. Studies 1 and 2 were open-label, randomized, three-period, three-treatment (A, B or C), crossover studies in healthy subjects. On study day 1 of period 1, eligible subjects [n = 16 (study 1); n = 30 (study 2)] were randomized to one of the six possible treatment sequences (ABC, ACB, BAC, BCA, CAB and CBA). A 2-day washout period was employed between treatment periods after which subjects were crossed over to receive the next treatment specified in their treatment sequence. The 2-day washout period was considered sufficient based on the plasma terminal phase half-life of saxagliptin (2.5 h), its metabolite, 5-hydroxy-saxagliptin (3.5 h) [1], metformin (~7 h) [13] or glyburide (~10 h) [15].

In study 1, each subject was administered one of the three possible treatments: single oral dose of saxagliptin 100 mg administered alone (Treatment A), single oral dose of metformin 1000 mg administered alone (Treatment B) or a single oral dose of saxagliptin 100 mg co-administered with a single oral dose of metformin 1000 mg (Treatment C).

In study 2, each subject was administered one of the three possible treatments: single oral dose of saxagliptin 10 mg administered alone (Treatment A), single oral dose of glyburide 5 mg administered alone (Treatment B) or a single oral dose of saxagliptin 10 mg co-administered with a single oral dose of glyburide 5 mg (Treatment C). To prevent hypoglycaemia during glyburide administration (Treatments B and C), subjects took the study medications with 240 ml of 20% unflavoured glucose solution in water. Thereafter, subjects were administered 60 ml of 20% glucose solution every 15 min for 4 h.

Study 3. Study 3 was an open-label, non-randomized, sequential study in healthy subjects. All subjects (n = 30) were administered oral doses of saxagliptin 10 mg o.d. on days 1–3 (Treatment A), oral doses of pioglitazone 45 mg o.d. on days 4–8 (Treatment B) and oral doses of saxagliptin 10 mg o.d. in conjunction with pioglitazone 45 mg on days 9–13 (Treatment C). There was no washout between treatments in study 3. Because of the longer half-life of the pharmacologically active metabolite of pioglitazone, hydroxy-pioglitazone (~28 h) relative to pioglitazone (~8 h) [14], a multiple dose regimen was used during Treatment B in order to ensure that steady state was achieved for both pioglitazone and hydroxy-pioglitazone.

Pharmacokinetic Sampling

To characterize the plasma concentration–time profiles of saxagliptin, 5-hydroxy saxagliptin (studies 1, 2 and 3), metformin (study 1), glyburide (study 2) and pioglitazone and its pharmacologically active metabolite, hydroxy-pioglitazone (study 3), serial blood samples were collected at specified times in each study.

Serial blood samples for pharmacokinetic analysis were collected pre-dose and at 0.25 (studies 2 and 3 only), 0.5, 0.75 (study 1 only), 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 36 and 48 h after dosing during each treatment period. In study 3, trough blood samples for plasma concentrations of saxagliptin and 5-hydroxy saxagliptin were collected on days 2 and 3, and on days 6, 7 and 8 for pioglitazone and hydroxy-pioglitazone.

Plasma Assays

Validated liquid chromatography tandem mass spectrometry (LC–MS/MS) methods were used for all the analytes. All assays were considered specific and selective and they satisfied the usual criteria of accuracy and precision; samples were analysed within their known period of stability. Plasma samples for the quantification of saxagliptin and 5-hydroxy saxagliptin were analysed at Tandem Labs, West Trenton, NJ, USA. In study 1, the standard curve ranged from 5 to 1000 ng/ml for saxagliptin and 10 to 2000 ng/ml for 5-hydroxy saxagliptin, and in studies 2 and 3, the ranges were from 1 to 100 ng/ml for saxagliptin and 2 to 200 ng/ml for 5-hydroxy saxagliptin. Plasma samples for the quantification of metformin in study 1 were analysed at PPD, Richmond, VA, USA, and the standard curve ranged from 10 to 5000 ng/ml. Plasma samples for the quantification of glyburide in study 2 were analysed at Anapharm, Inc., Quebec, Canada, and the standard curve ranged from 2.0 to 300.6 ng/ml. Plasma samples for the quantification of pioglitazone and hydroxy-pioglitazone were analysed at Anapharm, Inc., Quebec, Canada, and the standard curves ranged from 10.2 to 4079.2 ng/ml for pioglitazone and 9.9 to 1981.6 ng/ml for hydroxy-pioglitazone.

Assessments

To assess the effect of co-administration of saxagliptin with the oral antidiabetics on the pharmacokinetics of saxagliptin, 5-hydroxy saxagliptin, metformin, glyburide, pioglitazone and hydroxy-pioglitazone, analyses of variance (ANOVA) were performed on maximum (peak) plasma drug concentration (C_{max}), area under the plasma concentration–time curve from time zero to infinity (AUC_{∞}) (studies 1 and 2) and area under the concentration–time curve (AUC_{τ}) (study 3) for each analyte in the respective studies. Factors in the ANOVA for studies 1 and 2 were sequence, subject within sequence, period and treatment; in study 3 they were subject and treatment.

Point estimates and 90% confidence intervals (CIs) for treatment differences on the log scale were exponentiated to obtain point estimates and 90% CIs for the ratios of geometric means on the original scale of measurement. Lack of effect of the OADs on the pharmacokinetics of saxagliptin was to be concluded if the 90% CIs for the combination treatment to saxagliptin alone ratios for the respective studies of the population geometric mean values of both C_{max} and AUC_{∞} (studies 1 and 2), and C_{max} and AUC_{τ} (study 3) of saxagliptin were contained within 0.80 and 1.25. Lack of an effect of saxagliptin on the pharmacokinetics of metformin, glyburide or pioglitazone was to be concluded if the 90% CIs for the combination treatment to the oral antidiabetic alone ratios of population geometric mean values of both C_{max} and AUC_{∞} of metformin and glyburide, and the C_{max} and AUC_{τ} values of pioglitazone were contained within 0.80 and 1.25.

Results

Subject Demographics

Study 1. Eighteen male subjects were randomized and dosed. Two (11%) subjects withdrew consent and were discontinued from the study. Fifteen (83%) subjects were white/Caucasian, two (11%) subjects were black/African American and one (6%) subject was classified as other. Age ranged from 19 to 42 years (mean 27 years). Weight ranged from 57.4 to 116.9 kg (mean 81.0 kg) and BMI from 20.3 to 29.0 kg/m^2 (mean 25.0 kg/m^2).

Study 2. Thirty male subjects were randomized, dosed and completed the study. Nineteen (63%) subjects were black/African American, nine (30%) subjects were white/Caucasian, one (3%) subject was Asian and one (3%) subject was classified as other. Age ranged from 21 to 45 years (mean 31 years). Weight ranged from 51.3 to 112.4 kg (mean 77.8 kg) and BMI from 19.3 to 30.2 kg/m^2 (mean 25.4 kg/m^2).

Study 3. Thirty male subjects were dosed and completed the study. Two (7%) subjects were discontinued from the study early after receiving at least one treatment. Fifteen (50%) subjects were white/Caucasian, twelve (43%) subjects were black/African American and two (7%) subjects were Asian. Age ranged from 22 to 42 years (mean 30 years). Weight ranged from 59.4 to 111.6 kg (mean 78.0 kg) and BMI from 19.3 to 32.2 kg/m^2 (mean 25.3 kg/m^2).

Safety and Tolerability

There were no deaths or serious adverse events reported in any of these studies. All of the reported adverse events resolved prior to discharge from the studies.

Study 1. Twenty-four adverse events were reported. The most common adverse events reported in subjects administered saxagliptin alone or with metformin were headache in six (33%) subjects, chills and upper respiratory tract infection with influenza-like illness in two (11.1%) subjects and chlamydial urethritis, streptococcal tonsillitis and ecchymosis each reported in one (5.6%) subject.

Study 2. Thirty-nine adverse events were reported in 17 (56.7%) subjects. Asthenia was the most frequently reported adverse event, with one subject reporting this adverse event in the saxagliptin alone treatment group, three subjects in the glyburide alone treatment group and three subjects in the saxagliptin with glyburide treatment group. Hypoglycaemia was the second most frequently reported adverse event, with one subject experiencing this event during treatment with glyburide alone and three subjects during concomitant administration of saxagliptin with glyburide. Hypoglycaemia was not reported in any subjects receiving saxagliptin alone. All events of hypoglycaemia were associated with glyburide treatment.

Study 3. One subject discontinued because of dizziness and one subject withdrew consent because of family emergency. Headache was the most common adverse event, with six adverse events reported by four subjects. Two subjects had three adverse events when receiving saxagliptin alone (dizziness, headache and phlebitis), two subjects had two adverse events while receiving pioglitazone alone (blurred vision and headache) and one subject had one adverse event (nervousness) during co-administration of saxagliptin and pioglitazone.

Table 1. Summary statistics and statistical analyses of the pharmacokinetic parameters of SAXA, 5-hydroxy SAXA and MET for SAXA 100 mg, or MET 1000 mg, administered alone or during co-administration.

	SAXA (n = 16)			5-hydroxy SAXA (n = 16)			MET (n = 16)		
Pharmacokinetic parameter	SAXA alone (Treatment A)	SAXA with MET (Treatment C)	Point estimate (90% CI) (Treatment C/A)	SAXA alone (Treatment A)	SAXA with MET (Treatment C)	Point estimate (90% CI) (Treatment C/A)	MET alone (Treatment B)	MET with SAXA (Treatment C)	Point estimate (90% CI) (Treatment C/B)
C_{max} (ng/ml) geometric mean (% CV)	640 (21)	493 (27)	0.79 (0.71, 0.87)	866 (40)	767 (39)	0.88 (0.82, 0.94)	1615 (17)	1766 (24)	1.09 (1.01, 1.19)
AUC_{∞} (ng•h/ml) geometric mean (% CV)	2048 (23)	1989 (21)	0.98 (0.93, 1.04)	5128 (31)	5066 (33)	0.99 (0.96, 1.02)	10 022 (13)	12 014 (16)	1.20 (1.16, 1.24)
AUC_{τ} (ng•h/ml) geometric mean (% CV)	2007 (24)	1947 (21)	0.98 (0.92, 1.04)	5022 (32)	4952 (33)	0.99 (0.95, 1.02)	9862 (13)	11 868 (16)	1.20 (1.17, 1.24)
t_{max} (h) median (min, max)	0.75 (0.50, 1.50)	0.75 (0.50, 3.00)	N/A	1.50 (1.00, 4.00)	2.00 (1.00, 4.00)	N/A	2.00 (1.00, 4.00)	3.00 (0.75, 4.00)	N/A
$t_{1/2}$ (h) mean (s.d.)	2.65 (0.52)	2.88 (0.50)	N/A	3.76 (0.60)	4.28 (0.88)	N/A	7.00 (4.34)	6.24 (3.44)	N/A

AUC_{∞}, area under the plasma concentration–time curve from time zero to infinity; AUC_{τ}, area under the concentration–time curve from time 0 to time t; C_{max}, maximum (peak) plasma drug concentration; CI, confidence interval; CV, coefficient of variation; max, maximum; MET, metformin; min, minimum; N/A, not applicable; SAXA, saxagliptin; s.d., standard deviation; $t_{1/2}$, elimination half-life; t_{max}, time to reach maximum (peak) plasma concentration following drug administration.

Pharmacokinetics

Study 1. Mean ± standard deviation (s.d.) plasma concentration–time profiles for saxagliptin, 5-hydroxy saxagliptin and metformin are presented in Figure 1a–c, respectively. Summary statistics and statistical analyses of the pharmacokinetic parameters for saxagliptin, 5-hydroxy saxagliptin and metformin are presented in Table 1.

Effect of metformin on the pharmacokinetics of saxagliptin and 5-hydroxy saxagliptin. When saxagliptin 100 mg was co-administered with metformin 1000 mg, the geometric means for C_{max} and AUC_{∞} of saxagliptin were 21 and 2% lower, respectively, and the means for 5-hydroxy saxagliptin decreased by 12 and 1%, respectively, relative to those observed following administration of saxagliptin 100 mg alone. The 90% CI for the ratios of the population geometric means, with and without metformin, were within the no-effect interval (0.80, 1.25) for AUC_{∞} (0.93, 1.04) of saxagliptin and were within the pre-specified no-effect intervals for both C_{max} and AUC_{∞} of 5-hydroxy saxagliptin. The mean and the lower bound of the 90% CI violated the no-effect criteria for C_{max} of saxagliptin. Carryover, sequence and period effects were not statistically significant for any of the above analyses.

Effect of saxagliptin on the pharmacokinetics of metformin. When metformin 1000 mg was co-administered with saxagliptin 100 mg, the geometric means for C_{max} and AUC_{∞} of metformin were 9 and 20% higher, respectively, relative to those observed following administration of metformin 1000 mg alone. The 90% CI for the ratios of the population geometric means, with and without saxagliptin, was within the no-effect interval (0.80, 1.25) for C_{max} (1.01, 1.19) and AUC_{∞} (1.16, 1.24) of metformin. Carryover and sequence effects were not statistically significant in any of the above analyses. Although statistically significant period effects were detected in the analysis of AUC_{∞} of metformin, these did not affect the treatment comparisons and were therefore not investigated further.

Study 2. Mean ± s.d. plasma concentration–time profiles for saxagliptin, 5-hydroxy saxagliptin and glyburide are presented in Figure 2a–c, respectively. Summary statistics and statistical analyses of the pharmacokinetic parameters for saxagliptin, 5-hydroxy saxagliptin and glyburide are presented in Table 2.

Effect of glyburide on the pharmacokinetics of saxagliptin and 5-hydroxy saxagliptin. Compared with saxagliptin 10 mg administered alone, when saxagliptin 10 mg was co-administered with glyburide 5 mg, the geometric mean for the C_{max} of saxagliptin was 8% higher and the geometric mean for the AUC_{∞} of saxagliptin was 2% lower, with no meaningful differences observed in these parameters for 5-hydroxy saxagliptin. The 90% CIs for the ratios of population geometric means, with and without glyburide, were within the no-effect interval (0.80, 1.25) for both C_{max} (1.02, 1.14) and AUC_{∞} (0.95, 1.01) of saxagliptin. Carryover effect was not statistically significant in any of the analyses. Although statistically significant sequence and period effects were detected in the analysis of AUC_{∞} of saxagliptin, these did not affect the treatment comparisons and were not investigated further.

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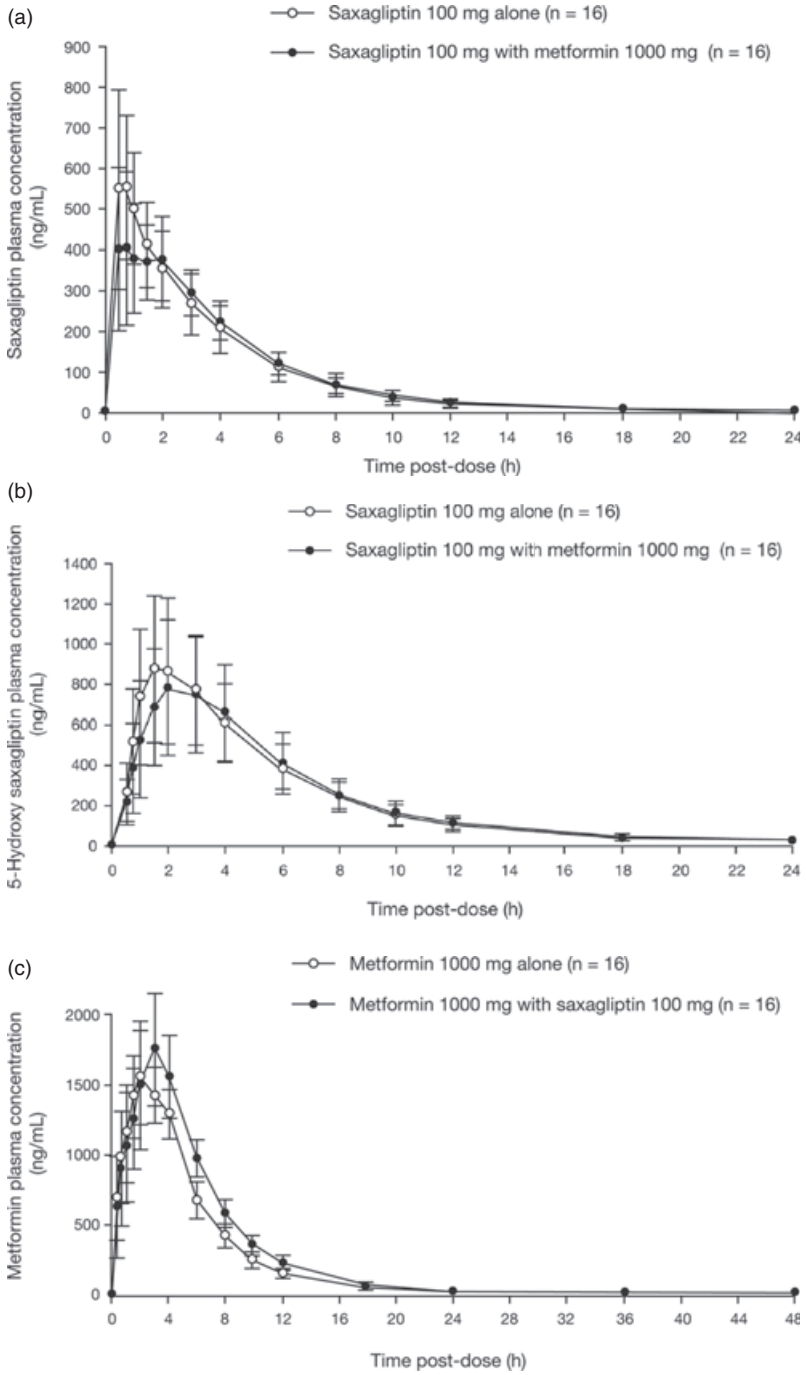

Figure 1. Plot of mean ± standard deviation plasma concentration–time profiles of (a) saxagliptin, (b) 5-hydroxy saxagliptin for saxagliptin 100 mg administered alone or in conjunction with metformin 1000 mg and (c) metformin for metformin 1000 mg administered alone or in conjunction with saxagliptin 100 mg.

Effect of saxagliptin on the pharmacokinetics of glyburide. When glyburide 5 mg was co-administered with saxagliptin 10 mg, the geometric means for the C_{max} and AUC_{∞} of glyburide were 16 and 6% higher, respectively, relative to those observed following administration of glyburide 5 mg alone. The 90% CI for the ratio of population geometric means, with and without saxagliptin, was within the no-effect interval (0.80, 1.25) for the AUC_{∞} (1.00, 1.13) of glyburide. However, the 90% CI for the ratio of population geometric means, with and without saxagliptin, extended slightly above the no-effect interval (0.80, 1.25) for the C_{max} (1.06, 1.28) of glyburide. None of the carry-over, sequence or period effects were statistically significant in any of the analyses.

Study 3. Mean ± s.d. plasma concentration–time profiles for saxagliptin, 5-hydroxy saxagliptin, pioglitazone and

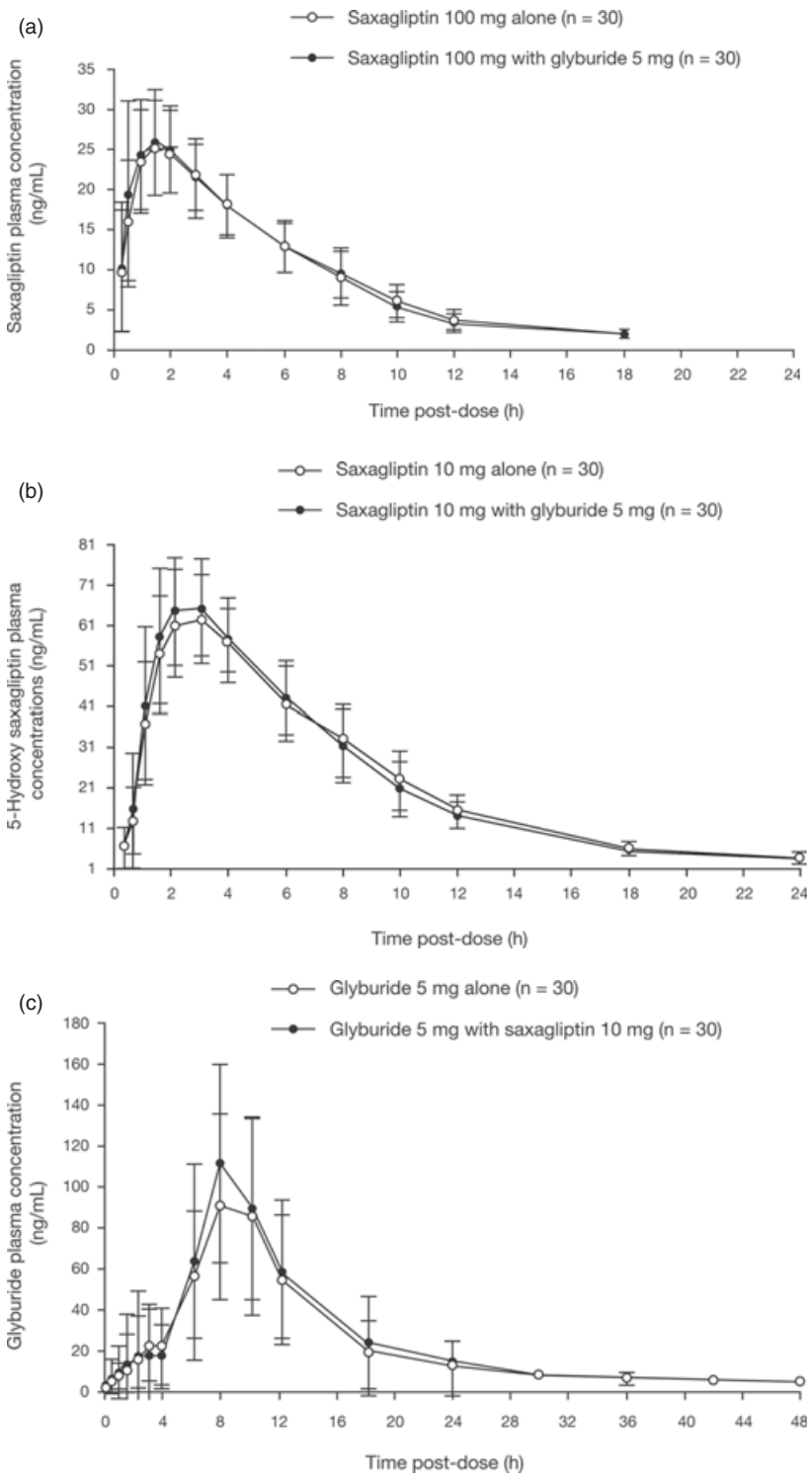

Figure 2. Plot of mean ± standard deviation plasma concentration–time profiles of (a) saxagliptin, (b) 5-hydroxy saxagliptin for saxagliptin 10 mg administered alone or in conjunction with glyburide 5 mg and (c) glyburide for glyburide 5 mg administered alone or in conjunction with saxagliptin 10 mg.

hydroxy-pioglitazone are presented in Figure 3a–d, respectively. Summary statistics and statistical analyses of the pharmacokinetic parameters for saxagliptin and 5-hydroxy saxagliptin are presented in Table 3a and those for pioglitazone and hydroxy-pioglitazone are presented in Table 3b. The saxagliptin plasma concentration of one subject was unusually low during the saxagliptin-alone treatment (C_{max}, 4.16 ng/ml and AUC_{τ}, 28.22 ng·h/ml), suggesting the possibility of a dosing error.

Table 2. Summary statistics and statistical analyses of the pharmacokinetic parameters of SAXA, 5-hydroxy SAXA and GLY for 10 mg SAXA, or 5 mg GLY, administered alone or during co-administration.

	SAXA (n = 30)			5-hydroxy SAXA (n = 30)			GLY (n = 30)		
Pharmacokinetic parameter	SAXA alone (Treatment A)	SAXA with GLY (Treatment C)	Point estimate (90% CI) (Treatment C/A)	SAXA alone (Treatment A)	SAXA with GLY (Treatment C)	Point estimate (90% CI) (Treatment C/A)	GLY alone (Treatment B)	GLY with SAXA (Treatment C)	Point estimate (90% CI) (Treatment C/B)
C_{max} (ng/ml) geometric mean (% CV)	26 (22)	28 (28)	1.08 (1.02, 1.14)	62 (19)	65 (20)	N/C	103 (37)	120 (31)	1.16 (1.06, 1.28)
AUC_{∞} (ng•h/ml) geometric mean (% CV)	169 (21)	165 (22)	0.98 (0.95, 1.01)	488 (21)	488 (21)	N/C	881 (36)	933 (44)	1.06 (1.00, 1.13)
AUC_{τ} (ng•h/ml) geometric mean (% CV)	160 (22)	156 (23)	N/A	471 (22)	472 (21)	N/A	847 (38)	910 (45)	N/A
t_{max} (h) median (min, max)	1.50 (0.50, 3.00)	1.50 (0.50, 2.00)	N/A	3.00 (1.50, 4.00)	3.00 (1.00, 4.00)	N/A	8.00 (3.00, 18.00)	8.00 (2.00, 18.00)	N/A
$t_{1/2}$ (h) mean (s.d.)	2.87 (0.55)	2.63 (0.37)	N/A	3.55 (0.47)	3.43 (0.42)	N/A	7.76 (5.57)	4.84 (2.94)	N/A

AUC_{∞}, area under the plasma concentration–time curve from time zero to infinity; AUC_{τ}, area under the concentration–time curve from time 0 to time t; C_{max}, maximum (peak) plasma drug concentration; CI, confidence interval; CV, coefficient of variation; GLY, glyburide; max, maximum; min, minimum; N/A, not applicable; N/C, not calculated; SAXA, saxagliptin; s.d., standard deviation; $t_{1/2}$, elimination half-life; t_{max}, time to reach maximum (peak) plasma concentration following drug administration.

This subject was excluded from the pharmacokinetic data analysis for saxagliptin, but pioglitazone data are included in the summary data.

Effect of pioglitazone on the pharmacokinetics of saxagliptin and 5-hydroxy saxagliptin. Compared with 10 mg saxagliptin administered alone, the geometric means for both C_{max} and AUC_{τ} of saxagliptin were 11% higher when 10 mg saxagliptin was co-administered with 45 mg pioglitazone. The 90% CIs for the ratios of population geometric means, with and without pioglitazone, were within the 0.80–1.25 no-effect interval for both C_{max} (1.03, 1.20) and AUC_{τ} (1.06, 1.16) of saxagliptin. As shown in Table 3a, the values of C_{max} and AUC_{τ} for 5-hydroxy saxagliptin were similar in the presence or absence of pioglitazone.

Effect of saxagliptin on the pharmacokinetics of pioglitazone and hydroxy-pioglitazone. Compared with pioglitazone 45 mg administered alone, when saxagliptin 10 mg was co-administered with pioglitazone 45 mg, the geometric means for C_{max} and AUC_{τ} of pioglitazone were 14 and 8% higher, respectively, relative to those observed following administration of 45 mg pioglitazone alone. The 90% CI for the ratio of population geometric means, with and without saxagliptin, was within the no-effect interval (0.80, 1.25) for AUC_{τ} (0.99, 1.17) of pioglitazone. However, the 90% CI for the ratio of population geometric means, with and without saxagliptin, extended slightly above the no-effect interval for C_{max} (1.03, 1.27) of pioglitazone. As shown in Table 3b, the values of C_{max} and AUC_{τ} for hydroxy-pioglitazone were similar in the presence or absence of saxagliptin.

Discussion

The results of three separate pharmacokinetic, two-way drug–drug interaction studies of saxagliptin co-administered with metformin, glyburide or pioglitazone indicate that none of these OADs cause a clinically meaningful alteration in the pharmacokinetics of saxagliptin or its pharmacologically active major metabolite, 5-hydroxy saxagliptin. Likewise, saxagliptin does not cause a clinically meaningful alteration in the pharmacokinetics of metformin, glyburide or pioglitazone when they are co-administered with saxagliptin.

Saxagliptin is metabolized by CYP3A4/3A5 enzymes to a pharmacologically active major metabolite, 5-hydroxy saxagliptin. During *in vitro* DPP-4 inhibition experiments, 5-hydroxy saxagliptin is observed to be twofold less potent than saxagliptin; however, its overall pharmacological contribution during saxagliptin treatment is not known. Approximately 23.5 and 35.8% of an orally administered dose of saxagliptin is excreted in urine as saxagliptin and 5-hydroxy saxagliptin, respectively [16]. Metformin is predominantly excreted in the unchanged form in urine, does not appear to undergo hepatic metabolism (no metabolites have been identified in humans), and is not excreted in bile [17]. No *in vitro* or clinical evidence has been reported to date indicating that metformin alters the activity of CYP3A4/3A5. Saxagliptin [16], 5-hydroxy saxagliptin [18] and metformin [17] are not known to be inducers or inhibitors of CYP3A-mediated metabolism. There

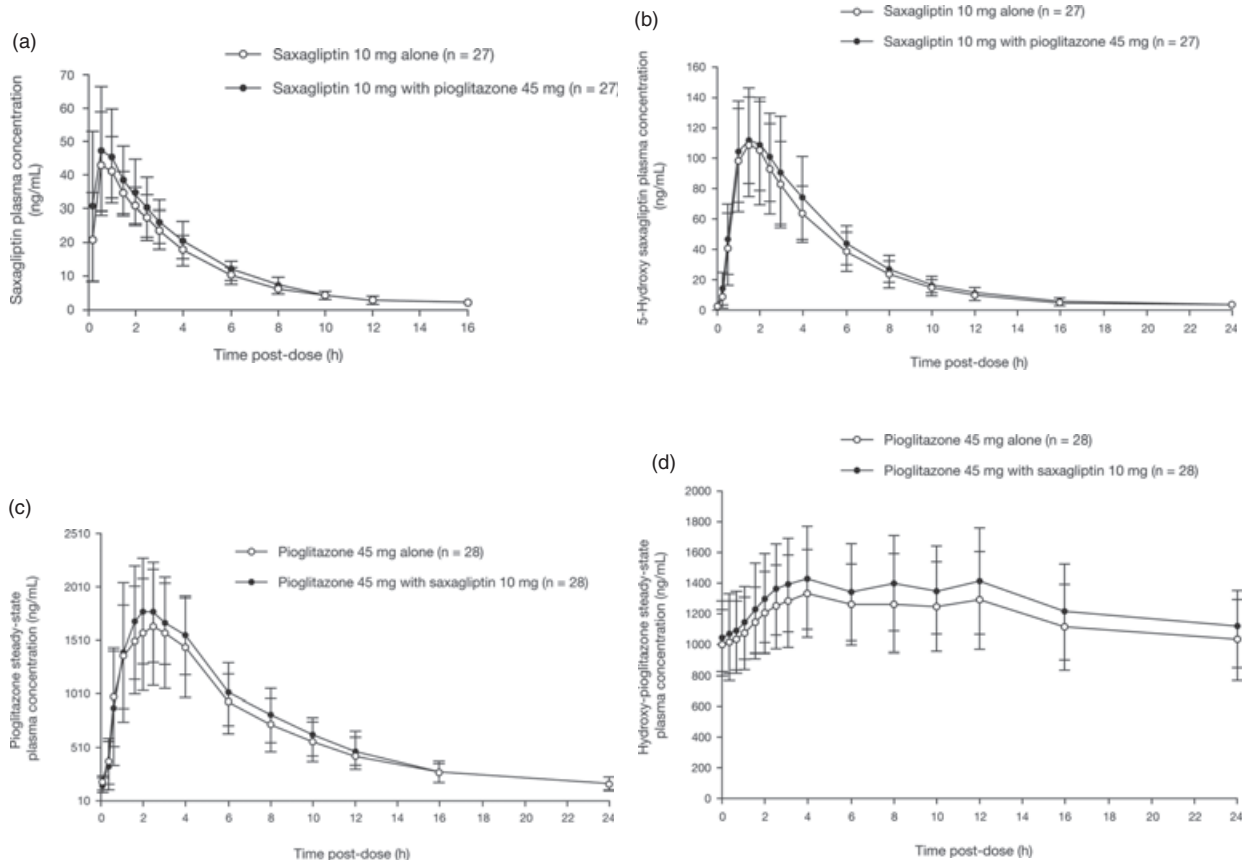

Figure 3. Plot of mean ± standard deviation plasma concentration–time profiles of (a) saxagliptin, (b) 5-hydroxy saxagliptin for saxagliptin 10 mg administered alone or in conjunction with pioglitazone 45 mg and (c) pioglitazone and (d) hydroxy-pioglitazone for pioglitazone 45 mg administered alone or in conjunction with saxagliptin 10 mg.

is evidence from *in vitro* studies to show that metformin is a substrate for organic cation transport protein-1 (OCT-1) and -2 (OCT-2) in the liver and kidney [19]. *In vitro*, neither saxagliptin nor 5-hydroxy saxagliptin has been shown to be a substrate for OCT-1 or OCT-2 [18].

Compared with saxagliptin administered alone, when 100 mg saxagliptin and 1000 mg metformin were co-administered, the C_{max} of saxagliptin was 21% lower, whereas the AUC_{τ} and AUC_{∞} remained unchanged. Although the 90% CI for the ratios of the population geometric means of the C_{max} of saxagliptin fell below the 0.80 lower bound, suggesting an effect of metformin on the rate of saxagliptin absorption, the lack of an effect on AUC of saxagliptin indicates that metformin did not alter the extent to which saxagliptin was absorbed. In contrast to its plasma terminal phase half-life, saxagliptin has a long pharmacodynamic (plasma DPP-4 inhibition) half-life (~26 h) [1], due, at least in part, to a slow off-rate from the DPP-4 enzyme. The pharmacological effect of saxagliptin is primarily driven by the plasma AUC, and thus, the effect of metformin on the C_{max} of saxagliptin was considered small and unlikely to be of any clinical consequence. On the basis of the lack of a meaningful pharmacokinetic drug–drug interaction between saxagliptin and metformin, and the good tolerability when these agents are co-administered [20], saxagliptin can be administered in conjunction with metformin without the need for dose adjustment or dose separation in patients with T2DM. It can also be inferred that neither saxagliptin nor 5-hydroxy saxagliptin alters the activity of OCT-1 or OCT-2.

Glyburide is primarily metabolized by CYP2C9 to hydroxylated metabolites that are inactive and are excreted in urine (50%) and in feces (50%) via bile [21]. Glyburide has also been shown *in vitro* to inhibit the activity of CYP2C9 with a weak inhibition of CYP3A4 [22]. Neither saxagliptin [16,18] nor 5-hydroxy saxagliptin [16,18] has been observed *in vitro* to inhibit or induce the activity of CYP2C9. Thus, the likelihood of a pharmacokinetic drug–drug interaction between these OADs when they are co-administered is low.

When saxagliptin 10 mg was co-administered with glyburide 5 mg, there were only small changes in the C_{max} and AUC_{∞} of saxagliptin and 5-hydroxy saxagliptin, showing a lack of effect of glyburide on the pharmacokinetics of saxagliptin and 5-hydroxy saxagliptin. When glyburide was co-administered with saxagliptin, the C_{max} of glyburide was 16% higher and the 90% CI for the ratios of the population geometric means extended only slightly above the 1.25 upper bound for concluding absence of effect. The small increase in the C_{max} of glyburide and the lack of an effect of saxagliptin on the AUC_{∞} of glyburide show the lack of a clinically meaningful pharmacokinetic interaction between saxagliptin and glyburide.

Table 3a. Summary statistics and statistical analyses of the pharmacokinetic parameters of SAXA and 5-hydroxy SAXA for 10 mg SAXA, administered alone or in conjunction with 45 mg pioglitazone.

	SAXA (n = 27)			5-hydroxy SAXA (n = 27)		
Pharmacokinetic parameters	SAXA alone (Treatment A)	SAXA with pioglitazone (Treatment C)	Point estimate (90% CI) (Treatment C/A)	SAXA alone (Treatment A)	SAXA with pioglitazone (Treatment C)	Point estimate (90% CI) (Treatment C/A)
C_{max} (ng/ml) geometric mean (% CV)	46 (24)	51 (29)	1.11 (1.03, 1.20)	119 (25)	120 (28)	N/C
AUC_τ (ng•h/ml) geometric mean (% CV)	176 (19)	196 (21)	1.11 (1.06, 1.16)	588 (23)	628 (28)	N/C
t_{max} (h) median (min, max)	0.50 (0.50, 1.00)	1.00 (0.50, 2.50)	N/A	1.50 (1.00, 3.00)	1.50 (1.00, 3.00)	N/A

AUC_τ, area under the concentration–time curve from time 0 to time t; C_{max}, maximum (peak) plasma drug concentration; CI, confidence interval; CV, coefficient of variation; max, maximum; min, minimum; N/A, not applicable; N/C, not calculated; SAXA, saxagliptin; t_{max}, time to reach maximum (peak) plasma concentration following drug administration.

Table 3b. Summary statistics and statistical analyses of the pharmacokinetic parameters of pioglitazone and hydroxy-pioglitazone for 45 mg pioglitazone, administered alone or in conjunction with 10 mg SAXA.

	Pioglitazone (n = 28)			Hydroxy-pioglitazone (n = 28)		
Pharmacokinetic parameters	Pioglitazone alone (Treatment B)	Pioglitazone with SAXA (Treatment C)	Point estimate (90% CI) (Treatment C/B)	Pioglitazone alone (Treatment B)	Pioglitazone with SAXA (Treatment C)	Point estimate (90% CI) (Treatment C/B)
C_{max} (ng/ml) geometric mean (% CV)	1672 (32)	1911 (25)	1.14 (1.03, 1.27)	1390 (24)	1536 (24)	N/C
AUC_τ (ng•h/ml) geometric mean (% CV)	14 018 (28)	15 068 (24)	1.08 (0.99, 1.17)	28 102 (23)	30 568 (22)	N/C
t_{max} (h) median (min, max)	2.00 (0.50, 4.00)	2.00 (1.00, 4.00)	N/A	4.00 (1.50, 12.00)	6.00 (1.50, 12.00)	N/A

AUC_τ, area under the concentration–time curve from time 0 to time t; C_{max}, maximum (peak) plasma drug concentration; CI, confidence interval; CV, coefficient of variation; max, maximum; min, minimum; N/A, not applicable; N/C, not calculated; SAXA, saxagliptin; t_{max}, time to reach maximum (peak) plasma concentration following drug administration.

Hypoglycaemia is a recognized adverse event associated with sulphonylurea therapy; thus consideration of the risk for hypoglycaemia is warranted when treating with a sulphonylurea—either alone or in combination with other OADs [23]. In this study, a higher incidence of hypoglycaemia was observed when saxagliptin and glyburide were co-administered; however, there were no incidences of hypoglycaemia when saxagliptin was administered alone and all of the observed cases of hypoglycaemia were associated with glyburide treatment. Hypoglycaemia was not unexpected as both saxagliptin and glyburide have a complementary mechanism of action of increasing insulin secretion. Further, a recent randomized placebo-controlled, 24-week trial examining the efficacy and safety of saxagliptin (dose of 2.5, 5 or 10 mg administered o.d.) added to submaximal-dose sulphonylurea therapy, compared with uptitration of glyburide monotherapy, in patients with T2DM and inadequate glycaemic control with submaximal-dose sulphonylurea therapy alone showed no statistically significant difference in hypoglycaemia incidence between saxagliptin treatment groups vs. the uptitrated glyburide group [8]. Taken together, it is reasonable to assume that no dosage adjustment of either agent would be necessary when co-administered. It can also be concluded that neither saxagliptin nor 5-hydroxy saxagliptin meaningfully alters the activity of CYP2C9.

Pioglitazone undergoes extensive hepatic metabolism by CYP2C8 and to a lesser extent by CYP3A4 [24,25]. The hydroxy and keto metabolites of pioglitazone have been shown to be pharmacologically active in diabetic animal models [26]. Although pioglitazone is a weak inhibitor of CYP2C8 and CYP3A4 *in vitro*, there is no *in vivo* or clinical evidence to suggest that it alters the disposition of CYP2C8 and CYP3A4 substrates [27–29]. As neither saxagliptin nor 5-hydroxy saxagliptin is known to alter the activity of CYP2C8 [18], the potential for observing a pharmacokinetic drug–drug interaction between saxagliptin and pioglitazone is low. There were 11% higher C_{max} and AUC_τ values for saxagliptin when saxagliptin 10 mg was co-administered with pioglitazone 45 mg administered to steady state, and the 90% CIs for the ratios of the population geometric means of C_{max} and AUC_τ of saxagliptin and 5-hydroxy saxagliptin satisfied the pre-specified criteria to conclude no effect. The C_{max} and AUC_τ of pioglitazone were 14 and 8%, higher, respectively, when saxagliptin was co-administered with pioglitazone. For the C_{max} of pioglitazone, the 90% CI for the ratios of the population geometric means extended only slightly above the 1.25 upper bound to conclude no effect. There were no changes in the pharmacokinetic parameters of hydroxy-pioglitazone. The small increase in the C_{max} of pioglitazone and the lack of effect of saxagliptin on the AUC_τ of pioglitazone show the lack of a clinically meaningful pharmacokinetic interaction between saxagliptin and pioglitazone. Saxagliptin co-administered with pioglitazone was well tolerated, further indicating that no dosage adjustment of either agent would be necessary when co-administered

to patients with T2DM. It can also be inferred that neither saxagliptin nor 5-hydroxy saxagliptin meaningfully alters the activity of CYP2C8.

The studies presented here showed a lack of meaningful pharmacokinetic interactions between saxagliptin and any of these (metformin, glyburide or pioglitazone) co-administered OADs. Saxagliptin can, thus, be co-administered with these OADs without a need for dose adjustment of either saxagliptin or the OADs.

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Conflict of Interest

D. W. B., D. K., N. V., B. K., M. H. D. and E. B. designed the study. M. H. D. and E. B. conducted the study and collected the data. C. G. P., D. B., B. K., L. L., D. K., N. V., M. H. D. and E. B. performed the analyses and wrote the manuscript.

All authors were employees of Bristol-Myers Squibb Company, Princeton, NJ, USA at the time the study was conducted. None of the authors are fellows of the American College of Clinical Pharmacology. D. K. was an employee of Bristol-Myers Squibb until October of 2006 and was an employee of Icon Development Solutions until July of 2007, and is now retired and does not have any conflict of interests to disclose. N. V. is currently an employee of Advinus Therapeutics and does not have any conflict of interests to disclose. E. B. is currently an employee of Centocor Research and Development, Inc., and does not have any conflict of interests to disclose. M. H. D. is currently an employee of Pfizer Inc., and does not have any conflict of interests to disclose. C. G. P., B. K., L. L. and D. W. B. are currently employees of Bristol-Myers Squibb.

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