

# Assessment of the Drug Interaction Potential of Ertugliflozin With Sitagliptin, Metformin, Glimepiride, or Simvastatin in Healthy Subjects

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## Abstract

Ertugliflozin, a sodium-glucose cotransporter 2 inhibitor for the treatment of adults with type 2 diabetes mellitus, is expected to be coadministered with sitagliptin, metformin, glimepiride, and/or simvastatin. Four separate open-label, randomized, single-dose, crossover studies were conducted in healthy adults to assess the potential pharmacokinetic interactions between ertugliflozin 15 mg and sitagliptin 100 mg ( $n = 12$ ), metformin 1000 mg ( $n = 18$ ), glimepiride 1 mg ( $n = 18$ ), or simvastatin 40 mg ( $n = 18$ ). Noncompartmental pharmacokinetic parameters derived from plasma concentration–time data were analyzed using mixed-effects models to assess interactions. Coadministration of sitagliptin, metformin, glimepiride, or simvastatin with ertugliflozin had no effect on area under the plasma concentration–time profile from time 0 to infinity ( $AUC_{inf}$ ) or maximum observed plasma concentration ( $C_{max}$ ) of ertugliflozin (per standard bioequivalence boundaries, 80% to 125%). Similarly, ertugliflozin did not have any impact on  $AUC_{inf}$  or  $C_{max}$  of sitagliptin, metformin, or glimepiride.  $AUC_{inf}$  for simvastatin (24%) and simvastatin acid (30%) increased slightly after coadministration with ertugliflozin and was not considered clinically relevant. All treatments were well tolerated. The lack of clinically meaningful pharmacokinetic interactions demonstrates that ertugliflozin can be coadministered safely with sitagliptin, metformin, glimepiride, or simvastatin without any need for dose adjustment.

## Keywords

diabetes, drug-drug interaction, ertugliflozin, glimepiride, metformin, pharmacokinetics, SGLT2i, simvastatin, sitagliptin

Ertugliflozin is a selective sodium-glucose cotransporter 2 (SGLT2) inhibitor<sup>1,2</sup> that reduces plasma glucose and glycated hemoglobin by increasing urinary glucose excretion.<sup>3,4</sup> Ertugliflozin, at once-daily doses of 5 and 15 mg, has been recently approved in the United States (US) and European Union (EU) for the treatment of adults with type 2 diabetes mellitus (T2DM). Phase 3 studies have shown that ertugliflozin significantly improves glycemic control, decreases body weight and blood pressure, and is well tolerated.<sup>5–7</sup> The pharmacokinetics (PK) of ertugliflozin are similar in healthy subjects and patients with T2DM. It is absorbed rapidly after oral administration (time to maximum plasma concentration [ $T_{max}$ ] 1 hour postdose), and terminal phase half-life ( $t_{1/2}$ ) ranges from 11 to 17 hours.<sup>1,2</sup> Additionally, the absolute bioavailability of ertugliflozin is approximately 100%,<sup>8</sup> its exposure increases proportionally with increasing dose over the range of 0.5 to 300 mg,

and its administration with food does not have a clinically meaningful effect on PK.<sup>9</sup> The PK of ertugliflozin are time independent and, consistent with the half-life, steady-state concentrations are achieved

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by 4 to 6 days after initiating once-daily dosing. Ertugliflozin is highly bound to plasma proteins (93.6%). The primary clearance mechanism of ertugliflozin is metabolism. Glucuronidation is the major metabolic pathway (86%), with minor contributions from oxidative metabolism (12%). Renal excretion of unchanged ertugliflozin accounts for 1.5% of the administered dose.

Ertugliflozin is likely to be used in combination with a number of other antihyperglycemic agents including sitagliptin, metformin, and glimepiride. Many T2DM patients also have concomitant dyslipidemia and are likely to be treated with statins, such as simvastatin, in combination with ertugliflozin. Ertugliflozin-sitagliptin and ertugliflozin-metformin fixed-dose combination tablets have been approved for use in the US and EU for the treatment of adult patients with T2DM.

Sitagliptin is an oral antihyperglycemic agent from the dipeptidyl peptidase-4 (DPP-4) inhibitor class, which acts by inhibiting the degradation of incretins, including glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide.<sup>10</sup> Urinary excretion of unchanged drug via glomerular filtration and renal secretion by organic anion transporter-3 (OAT-3), organic anion transporting polypeptide 4C1 (OATP4C1), and multidrug-resistance P-glycoprotein are the major routes of elimination of sitagliptin, with metabolism playing only a minor role.<sup>11</sup> Sitagliptin undergoes limited oxidative metabolism, predominantly by cytochrome P450 (CYP) 3A4 with minor contribution from CYP2C8.<sup>12</sup>

Metformin is a biguanide antihyperglycemic agent that improves glycemic control by decreasing hepatic glucose production, decreasing glucose absorption, and increasing insulin-mediated glucose uptake.<sup>13-15</sup> Metformin is transported by the organic cation transporters OCT1 and OCT2. The uptake of metformin in the liver, which is the primary target of metformin, is mediated primarily by OCT1. Studies in healthy volunteers suggest that human multidrug and toxin extrusion 1 (MATE1) and MATE2-K also contribute to the renal excretion of metformin.<sup>13</sup>

Glimepiride is an orally active blood glucose-lowering agent from the sulfonylurea class, the action of which is dependent on stimulating the release of insulin from pancreatic beta cells by blocking adenosine triphosphate-dependent potassium channels on the beta cell membrane. Glimepiride is extensively metabolized in the liver, mainly by CYP2C9.<sup>16</sup>

Simvastatin is a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor that is hydrolyzed to the active metabolite simvastatin acid. Both simvastatin and simvastatin acid are metabolized by CYP3A4.<sup>17</sup>

Ertugliflozin is metabolized mainly by uridine diphosphate glucuronosyltransferase (UGT) isoen-

zyme 1A9 and UGT2B7 to 2 pharmacologically inactive glucuronide metabolites.<sup>2</sup> CYP3A4 is the predominant CYP enzyme involved in the minor oxidative metabolism of ertugliflozin with some contributions by CYP2C8 and CYP3A5. At clinically relevant concentrations, ertugliflozin is a substrate for the P-glycoprotein and breast cancer resistance protein efflux transporters; however, no clinically relevant interaction is expected with inhibitors of these transporters based on the oral bioavailability of ertugliflozin of approximately 100%, and dose-proportional increases in exposure over the dose range of 0.5 mg to 300 mg. Ertugliflozin is not a substrate for OATP1B1, OATP1B3, OATP2B1, OCT1, OAT1, OAT3, and OCT2 uptake transporters.

Based on *in vitro* studies, ertugliflozin and its glucuronide metabolites are not inhibitors or inducers of CYP isozymes or transporters (including OATP1B1); therefore, it is not anticipated to alter the PK of coadministered drugs, sitagliptin, metformin, glimepiride, or simvastatin. Ertugliflozin is a weak inhibitor of OAT3 and OCT2 transporters, but the unbound clinical maximum observed plasma concentration ( $C_{max}$ )/half maximal inhibitory concentration is  $< 0.1$ ; thus, ertugliflozin is not anticipated to alter the PK of coadministered sitagliptin (substrate of OAT3) or metformin (substrate of OCT2).

There is no evidence and/or data in the literature that sitagliptin, metformin, glimepiride, or simvastatin (or simvastatin acid) either induce or inhibit UGT1A9 or UGT2B7 at clinically relevant plasma levels.<sup>18</sup> Therefore, these coadministered drugs are not anticipated to alter the PK of ertugliflozin.

Four drug-drug interaction (DDI) studies were conducted in healthy volunteers to quantify the effect of the coadministered drugs on the PK of ertugliflozin, and vice versa, following oral administration of a single dose of ertugliflozin 15 mg coadministered with a single dose of either sitagliptin 100 mg, metformin 1000 mg, glimepiride 1 mg, or simvastatin 40 mg. The secondary objective of all 4 studies was to evaluate the safety and tolerability of single doses of ertugliflozin 15 mg and the coadministered drugs.

## Methods

All 4 phase I, open-label, randomized, 3-period, 6-sequence, single oral dose, crossover DDI studies were conducted at the Pfizer Clinical Research Unit in Brussels, Belgium, in compliance with the ethical principles of the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice guidelines. The final protocols and informed consent documentation of all 4 DDI studies were reviewed and approved by

the independent ethics committee (Comité d'Ethique Hospitalo-Facultaire Erasme-ULB, Brussels, Belgium) at the investigational center participating in each study.

### Key Eligibility Criteria

Healthy male and/or female subjects aged 18 to 55 years inclusive, with a body mass index of 17.5 to 30.5 kg/m<sup>2</sup> and total body weight >50 kg, who had provided a signed, dated informed consent form and were willing and able to comply with the study plan, were eligible for inclusion in this study. Subjects with the following were excluded: positive urine screen for drugs, either due to abuse or recreational use; history of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of screening; known hypersensitivity or intolerance to any SGLT2 inhibitor, sitagliptin (or any other DPP-4 inhibitor), metformin, glimepiride (or any other sulfonylurea or sulfonamide), or simvastatin (or any other 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor) in respective trials. For the sitagliptin study, subjects with a calculated creatinine clearance of <80 mL/min based on the Cockcroft-Gault formula<sup>19</sup> were excluded. Similarly, for the metformin, glimepiride, and simvastatin studies, subjects with an estimated glomerular filtration rate of <90 mL/min/1.73 m<sup>2</sup> based on the 4-variable Modification of Diet in Renal Disease equation<sup>20</sup> were excluded. Subjects were not permitted to eat or drink grapefruit or grapefruit-related citrus fruits (eg, Seville oranges, pomelos) from 7 days prior to the first dose of study medication until collection of the final PK blood sample in period 3.

### Study Design and Treatment

Each study consisted of a screening visit and 3 study-treatment periods: (1) ertugliflozin 15 mg; (2) sitagliptin 100 mg/metformin 1000 mg/glimepiride 1 mg/simvastatin 40 mg; (3) ertugliflozin 15 mg + sitagliptin 100 mg/metformin 1000 mg/glimepiride 1 mg/simvastatin 40 mg. Screening occurred within 28 days of the first dose of study medication in period 1. In each study, eligible subjects admitted to the clinical research unit on day 0 were randomized to 1 of 6 treatment sequences and received their assigned treatment in the morning of day 1 of each treatment period after an overnight fast of at least 8 hours. In the coadministered period, subjects received the single-dose oral treatments within 5 minutes of each other, with ertugliflozin administered first. Dosing in consecutive crossover periods was separated by a washout period of at least 5 days. To minimize the risk of hypoglycemia with glimepiride, all study treatments in the ertugliflozin-glimepiride study were administered with approximately 240 mL of a 20% glucose solution, followed by

approximately 60 mL of 20% glucose solution administered approximately every 15 minutes until approximately 4 hours after the dose in each period. Subjects were discharged from the clinical research unit after collection of the 24-hour PK sample in each period and returned to the clinical research unit in an outpatient setting for collection of the 48- and 72-hour PK samples. Sample sizes of 12 subjects for the sitagliptin study and 18 subjects for each of the metformin, glimepiride, and simvastatin studies provided 90% confidence intervals (CIs) for the difference between treatments of  $\pm 0.1832$  and  $\pm 0.2222$  at most, on the natural logarithm scale for area under the plasma concentration–time profile from time 0 extrapolated to infinite time ( $AUC_{inf}$ ) and  $C_{max}$ , respectively, with 80% coverage probability. Within-subject variability estimates were obtained from the weighted average of previous crossover studies.

### Assessments

Serial blood samples for PK analyses were collected from each subject at the following times in each treatment period:

*Ertugliflozin-sitagliptin study:* predose (0 hour) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours postdose

*Ertugliflozin-metformin study:* predose (0 hour) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 48, and 72 hours postdose

*Ertugliflozin-glimepiride and ertugliflozin-simvastatin studies:* predose (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, and 72 hours postdose

Plasma samples were analyzed for ertugliflozin, metformin, glimepiride, simvastatin, and simvastatin acid concentrations at WuXi AppTec (Shanghai, China), and for sitagliptin concentrations by inVentiv Health Clinique (Quebec, Canada) using validated, sensitive, and specific high-performance liquid chromatography–tandem mass spectrometry methods. The method for bioanalysis of ertugliflozin has been described previously.<sup>21</sup>

Sitagliptin was extracted from 100  $\mu$ L of human plasma by protein precipitation with acetonitrile and sitagliptin-d4 as the internal standard. The extracted sample was injected into a Waters Atlantis HILIC Silica column 3  $\mu$ m (2.1 mm  $\times$  50 mm) (Waters Corporation, Milford, Massachusetts) using a mobile phase of acetonitrile/water (80/20, v/v) containing 10 mM NH<sub>4</sub>Ac (pH 4.7). Detection was performed by Sciex API 4000 (SCIEX, Framingham, Massachusetts) in the positive ion mode. The multiple reaction monitoring ion transition was m/z 408  $\rightarrow$  235 for sitagliptin and m/z 412  $\rightarrow$  239 for the internal standard. The calibration curve was linear over the range of 1.0 to 1000 ng/mL.

Metformin was extracted from 50  $\mu\text{L}$  of human plasma by protein precipitation with acetonitrile and metformin-d6 as the internal standard. The supernatant was diluted with 10 mM  $\text{NH}_4\text{Ac}$  in acetonitrile containing 0.5% formic acid. The extracted sample was injected into a high-performance liquid chromatography column (Waters Atlantis HILIC Silica 5  $\mu\text{m}$  [2.1 mm  $\times$  50 mm]), with gradient mobile phase containing 0.5% formic acid and 10 mM  $\text{NH}_4\text{Ac}$  in water, and 0.5% formic acid in acetonitrile. Detection was performed by Sciex API 4000 in the positive ion mode. The multiple reaction monitoring ion transition was  $m/z$  130  $\rightarrow$  71 for metformin and  $m/z$  136  $\rightarrow$  77 for the internal standard. The calibration curve was linear over the range of 2.0 to 1000 ng/mL.

Glimepiride was extracted from 50  $\mu\text{L}$  of human plasma using a solid-phase extraction 96-well plate with methanol and water, and glimepiride-d5 as the internal standard. The extracted sample was injected into a Luna C18(2), 5  $\mu\text{m}$  (2.0 mm  $\times$  50 mm) high-performance liquid chromatography column (Phenomenex, Inc., Torrance, California) with gradient mobile phase containing 0.1% formic acid in water and 0.1% formic acid in acetonitrile. Detection was performed by Sciex API 4000 in the positive ion mode. The multiple reaction monitoring ion transition was  $m/z$  491  $\rightarrow$  352 for glimepiride and  $m/z$  496  $\rightarrow$  357 for the internal standard. The calibration curve was linear over the range of 0.1 to 200 ng/mL.

Simvastatin and simvastatin acid were extracted from 200  $\mu\text{L}$  of human plasma using a solid-phase extraction C18 96-well plate with  $\text{NH}_4\text{Ac}$  and acetonitrile, and simvastatin-d6 and simvastatin acid-d6 as the internal standards, respectively. The extracted sample was injected into a Waters Atlantis dc18, 3  $\mu\text{m}$  (2.1 mm  $\times$  100 mm) column with gradient mobile phase containing ammonium hydroxide and acetonitrile. Detection was performed by Sciex API 5000 (SCIEX) in the positive ion mode for simvastatin and negative mode for simvastatin acid. The multiple reaction monitoring ion transition was  $m/z$  420  $\rightarrow$  199 for simvastatin,  $m/z$  425  $\rightarrow$  199 for simvastatin-d6,  $m/z$  435  $\rightarrow$  319 for simvastatin acid, and  $m/z$  441  $\rightarrow$  319 for simvastatin acid-d6. The calibration curve was linear over the range of 0.05 to 50.0 ng/mL for simvastatin and 0.05 to 10.0 ng/mL for simvastatin acid.

Safety assessments were conducted from screening and throughout the duration of study participation. Subjects also received a follow-up phone call  $14 \pm 3$  days after administration of the last dose of study medication in period 3 to assess for adverse events (AEs). In the glimepiride study, additional fingerstick blood glucose measurements were conducted to monitor for hypoglycemia at predose (0 hour), and at 2, 4, 7, 12 and 24 hours postdose.

## Data Analysis

PK parameters were calculated for each subject for each treatment using noncompartmental analysis of plasma concentration–time data via an in-house validated software system. Plasma concentrations that were below the lower limit of quantification were set to 0 for analysis. Natural log-transformed  $\text{AUC}_{\text{inf}}$ , area under the plasma concentration–time profile from time 0 to time of the last quantifiable concentration ( $\text{AUC}_{\text{last}}$ ), and  $C_{\text{max}}$  were analyzed using separate mixed-effects models with sequence, period, and treatment as fixed effects, and subject within sequence as a random effect. The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios.

## Results

### Subjects

A total of 12 subjects were enrolled in the sitagliptin study, and 18 subjects were enrolled in each of the metformin, glimepiride, and simvastatin studies (each subject participated in 1 study only). The majority of subjects enrolled were male, white, and non-Hispanic. The age and body mass index of the subjects ranged from 19 to 55 years and 19.3 to 30.4  $\text{kg}/\text{m}^2$ , respectively (Table 1). All subjects completed their respective study and were included in the analyses.

### PK Results

*Effect of Coadministered Drugs on the PK of Ertugliflozin.* PK parameters of ertugliflozin with and without the coadministered drugs are summarized in Table 2. Following oral administration of a single dose of ertugliflozin 15 mg alone, or in combination with either a single dose of oral sitagliptin 100 mg, metformin 1000 mg, glimepiride 1 mg, or simvastatin 40 mg, mean plasma ertugliflozin concentration–time profiles were nearly superimposable (Figure 1). While not prospectively specified, the 90% CIs for the geometric mean ratios of ertugliflozin  $\text{AUC}_{\text{inf}}$  and  $C_{\text{max}}$  were within the equivalence bounds of 80% to 125%, indicating that coadministration of ertugliflozin with sitagliptin, metformin, glimepiride, or simvastatin had no clinically meaningful effect on the PK of ertugliflozin (Table 3 and Figure 2).

$T_{\text{max}}$  and  $t_{1/2}$  values of ertugliflozin when administered alone or with coadministered drugs were also similar. Plasma concentrations of ertugliflozin increased rapidly with median  $T_{\text{max}}$  ranging from 1.0 to 3.0 hours when administered alone versus 0.5 to 3.0 hours when coadministered with sitagliptin, metformin, glimepiride, or simvastatin. The mean  $t_{1/2}$  of ertugliflozin administered alone ranged from 10.63 to

**Table 1.** Subject Demographic Characteristics

Characteristic	Sitagliptin Study (N = 12)	Metformin Study (N = 18)	Glimepiride Study (N = 18)	Simvastatin Study (N = 18)
Gender, n				
Male	5	10	10	10
Female	7	8	8	8
Age, n				
18–44 y	9	14	15	16
45–64 y	3	4	3	2
Mean (SD), y	34.7 (10.5)	37.6 (9.8)	32.6 (10.1)	31.3 (9)
Range, y	25–53	24–55	19–50	19–51
Race, n				
White	12	18	16	15
Black	0	0	2	2
Other	0	0	0	1
Ethnicity, n				
Hispanic/Latino	1	0	1	0
Non-Hispanic/Latino	11	18	17	18
Weight, kg				
Mean (SD)	70.6 (13.1)	76.1 (11.3)	72.2 (14.4)	73.2 (12.8)
Range	55.1–104.3	54.1–99.5	50.6–107.7	57.1–95.3
BMI, kg/m <sup>2</sup>				
Mean (SD)	23.4 (2.5)	24.6 (3.0)	24.4 (3.1)	24.4 (3.0)
Range	19.3–28.0	20.9–30.3	19.3–30.4	19.6–28.9

BMI, body mass index; n, number of subjects; SD, standard deviation.

12.63 hours compared with 11.27 to 14.17 hours when coadministered with other drugs (Table 2).

**Effect of Ertugliflozin on the PK of Coadministered Drugs.** Following oral administration of sitagliptin 100 mg alone or metformin 1000 mg alone or either drug in combination with ertugliflozin 15 mg, mean plasma sitagliptin and metformin concentration–time profiles were nearly superimposable between treatments (Figure 1), and  $AUC_{inf}$ ,  $C_{max}$ , and  $AUC_{last}$  values were equivalent between treatments in both ertugliflozin-sitagliptin and ertugliflozin-metformin studies. While not prospectively specified, the 90% CIs for the geometric ratios of sitagliptin and metformin  $AUC_{inf}$  and  $C_{max}$  were within the equivalence bounds of 80% to 125%, indicating that coadministration of ertugliflozin with sitagliptin and metformin did not have any meaningful impact on sitagliptin or metformin PK (Table 3).

Following oral administration of glimepiride 1 mg alone or with ertugliflozin 15 mg, mean plasma glimepiride concentration–time profiles were similar (Figure 1). One subject in the study, who received ertugliflozin 15 mg, vomited within 2 times the median ertugliflozin  $T_{max}$  after administration; 2 subjects, who received ertugliflozin 15 mg and glimepiride 1 mg, vomited within 2 times the median ertugliflozin or glimepiride  $T_{max}$  after administration; therefore, as per the statistical analysis plan, data from these 3 subjects for the affected treatments were excluded from the PK

analysis. The 90% CI for the geometric mean ratios of glimepiride  $AUC_{inf}$  fell within the equivalence bounds of 80% to 125%. The 90% CI for the geometric mean ratio of  $C_{max}$  for glimepiride was wider (71.1%, 133.5%; Table 3). For most subjects, 2 peaks were observed in the plasma glimepiride concentration–time profile, which resulted in a wide range of  $T_{max}$  (1.0–12.0 h) and an intrasubject variability of 53.5% for  $C_{max}$ .

Following oral administration of simvastatin 40 mg alone or with ertugliflozin 15 mg, mean plasma simvastatin and simvastatin acid concentration–time profiles were similar (Figure 1). Geometric mean  $AUC_{inf}$  and  $C_{max}$  ratios for simvastatin were increased slightly (24% and 19%, respectively) when simvastatin was coadministered with ertugliflozin than when administered alone. Geometric mean ratios of  $AUC_{inf}$  and  $C_{max}$  for simvastatin acid also increased in the presence of ertugliflozin by 30% and 16%, respectively (Table 3). The  $T_{max}$  and  $t_{1/2}$  of simvastatin and simvastatin acid were comparable between the 2 treatments (Table 2).

### Safety Results

A single dose of ertugliflozin 15 mg was well tolerated when administered alone or in combination with sitagliptin, metformin, glimepiride, or simvastatin in healthy subjects. Treatment with coadministered drugs was also well tolerated in all studies. No deaths, serious/severe AEs, or discontinuations due

**Table 2.** Descriptive Summary of Plasma Ertugliflozin, Sitagliptin, Metformin, Glimepiride, and Simvastatin (and Simvastatin Acid) Pharmacokinetic Parameter Values

Ertugliflozin-Sitagliptin Study					
	Ertugliflozin Pharmacokinetic Summary <sup>a</sup> by Treatment		Sitagliptin Pharmacokinetic Summary <sup>a</sup> by Treatment		
	Ertugliflozin 15 mg (N = 12)	Ertugliflozin 15 mg + Sitagliptin 100 mg (N = 12)	Sitagliptin 100 mg (N = 12)	Ertugliflozin 15 mg + Sitagliptin 100 mg (N = 12)	
n	12	12	n	12	12
AUC <sub>inf</sub> , ng • h/mL	1456 (380.55)	1485 (364.31)	AUC <sub>inf</sub> , μM • h <sup>b</sup>	7.018 (1.484)	7.130 (1.493)
AUC <sub>last</sub> , ng • h/mL	1428 (379.51)	1450 (353.16)	AUC <sub>last</sub> , μM • h <sup>b</sup>	6.953 (1.501)	7.049 (1.511)
C <sub>max</sub> , ng/mL	270.3 (66.67)	266.0 (67.23)	C <sub>max</sub> , nM <sup>b</sup>	814.3 (213.64)	825.9 (195.29)
T <sub>max</sub> , h	1.00 (1.00–3.00)	1.00 (0.50–2.10)	T <sub>max</sub> , h	2.00 (1.00–4.00)	3.00 (1.00–6.00)
t <sub>1/2</sub> , h	12.63 ± 5.15	14.17 ± 4.55	t <sub>1/2</sub> , h	11.00 ± 2.89	11.79 ± 2.98

Ertugliflozin-Metformin Study				
	Ertugliflozin Pharmacokinetic Summary <sup>a</sup> by Treatment		Metformin Pharmacokinetic Summary <sup>a</sup> by Treatment	
	Ertugliflozin 15 mg (N = 18)	Ertugliflozin 15 mg + Metformin 1000 mg (N = 18)	Metformin 1000 mg (N = 18)	Ertugliflozin 15 mg + Metformin 1000 mg (N = 18)
n	17	17	13	13
AUC <sub>inf</sub> , ng • h/mL	1401 (356.05)	1424 (340.33)	13 170 (3172.9)	12 640 (3167.2)
AUC <sub>last</sub> , ng • h/mL	1382 (339.78)	1399 (323.71)	12 940 (3161.5)	12 560 (2739.0)
C <sub>max</sub> , ng/mL	279.1 (60.68)	269.3 (50.71)	2041 (473.72)	1890 (468.89)
T <sub>max</sub> , h	1.02 (1.00–2.00)	1.29 (1.00–3.00)	2.00 (0.50–4.00)	2.00 (1.00–3.00)
t <sub>1/2</sub> , h	11.79 ± 2.34	13.48 ± 4.65	10.23 ± 2.39	14.47 ± 6.94

Ertugliflozin-Glimepiride Study				
	Ertugliflozin Pharmacokinetic Summary <sup>a</sup> by Treatment		Glimepiride Pharmacokinetic Summary <sup>a</sup> by Treatment	
	Ertugliflozin 15 mg (N = 18)	Ertugliflozin 15 mg + Glimepiride 1 mg (N = 18)	Glimepiride 1 mg (N = 18)	Ertugliflozin 15 mg + Glimepiride 1 mg (N = 18)
N, n	17 <sup>c</sup> , 17	16 <sup>d</sup> , 16	18, 13	16 <sup>c</sup> , 11
AUC <sub>inf</sub> , ng • h/mL	1247 (257.88)	1294 (249.90)	249.3 (213.55)	296.7 (306.9)
AUC <sub>last</sub> , ng • h/mL	1232 (256.73)	1278 (247.81)	217.5 (185.36)	283.9 (245.9)
C <sub>max</sub> , ng/mL	145.8 (24.41)	146.7 (27.01)	34.35 (19.90)	33.47 (15.79)
T <sub>max</sub> , h	2.0 (1.5–3.0)	2.0 (1.5–3.0)	3.00 (1.00–12.0)	4.00 (1.50–12.0)
t <sub>1/2</sub> , h	10.63 ± 2.44	11.27 ± 3.28	5.89 ± 2.79	6.68 ± 4.02

continue

to AEs were reported. The most commonly reported AEs were gastrointestinal disorders in the metformin and glimepiride studies, and headache in the simvastatin study. Treatment-emergent AEs occurring in ≥2 subjects in any treatment group for each study are summarized in Table S1.

## Discussion

Ertugliflozin has been recently approved in the US and EU for the treatment of adults with T2DM, and has been shown to improve glycemic control and reduce body weight and systolic blood pressure in patients with inadequate glycemic control.<sup>5,7</sup> It is likely

Table 2. Continued

Ertugliflozin–Simvastatin Study						
	Ertugliflozin Pharmacokinetic Summary <sup>a</sup> by Treatment		Simvastatin Pharmacokinetic Summary <sup>a</sup> by Treatment		Simvastatin Acid Pharmacokinetic Summary <sup>a</sup> by Treatment	
	Ertugliflozin 15 mg (N = 18)	Ertugliflozin 15 mg + Simvastatin 40 mg (N = 18)	Simvastatin 40 mg (N = 18)	Ertugliflozin 15 mg + Simvastatin 40 mg (N = 18)	Simvastatin 40 mg (N = 18)	Ertugliflozin 15 mg + Simvastatin 40 mg (N = 18)
n	18	18	12	18	16	14
AUC <sub>inf</sub> , ng • h/mL	1407 (313.51)	1446 (337.63)	43.78 (19.23)	59.49 (42.03)	31.44 (23.13)	46.97 (29.13)
AUC <sub>last</sub> , ng • h/mL	1384 (311.06)	1419 (329.16)	43.85 (29.11)	57.52 (41.32)	30.94 (22.46)	40.63 (28.31)
C <sub>max</sub> , ng/mL	273.2 (58.49)	289.8 (69.03)	9.283 (5.67)	12.01 (9.26)	2.605 (2.62)	3.079 (2.843)
T <sub>max</sub> , h	1.5 (1.0–2.5)	1.0 (1.0–2.0)	1.00 (0.50–12.0)	1.25 (0.50–12.00)	4.00 (1.50–12.0)	4.00 (2.50–8.00)
t <sub>1/2</sub> , h	12.34 ± 3.07	12.58 ± 3.98	5.88 ± 1.96	7.44 ± 2.72	8.44 ± 6.00	8.60 ± 2.91

AUC<sub>inf</sub>, area under the plasma concentration–time profile from time 0 extrapolated to infinite time; AUC<sub>last</sub>, area under the plasma concentration–time profile from time 0 to time of the last quantifiable concentration; C<sub>max</sub>, maximum observed plasma concentration; N, number of subjects contributing to summary statistics; n, number of subjects with reportable t<sub>1/2</sub> and AUC<sub>inf</sub>; t<sub>1/2</sub>, terminal half-life; T<sub>max</sub>, time for maximum observed plasma concentration.

<sup>a</sup>Arithmetic mean (standard deviation) for all except median (range) for T<sub>max</sub>.

<sup>b</sup>Sitagliptin concentration of 1.00 ng/mL is equivalent to 2.46 nM.

<sup>c</sup>One subject from ertugliflozin 15 mg treatment vomited within 2 times the median ertugliflozin T<sub>max</sub>; therefore, the pharmacokinetic data from this subject was excluded.

<sup>d</sup>Two subjects from ertugliflozin 15 mg + glimepiride 1 mg treatment vomited within/close to 2 times the median ertugliflozin T<sub>max</sub> and within 2 times the median glimepiride T<sub>max</sub>; therefore, the pharmacokinetic data from these 2 subjects were excluded.

to be used in combination with a number of other antihyperglycemic and lipid-lowering agents (eg, statins) for comorbidities associated with diabetes. The efficacy of ertugliflozin in combination with sitagliptin and metformin was assessed in 3 and 4 phase III studies, respectively.<sup>5,7,22,23</sup> Coadministration of ertugliflozin with sitagliptin 100 mg provided greater glycemic control compared with each individual dose of ertugliflozin and sitagliptin with inadequate control on either metformin or diet and exercise.<sup>5</sup> Similar to these results, on a background of metformin, ertugliflozin at 5- and 15-mg doses provided sustained glycemic control over 52 weeks.<sup>23</sup> Ertugliflozin as an add-on to metformin, and metformin and sitagliptin, also provided clinically meaningful body weight and systolic blood pressure reductions.<sup>5,7,22</sup>

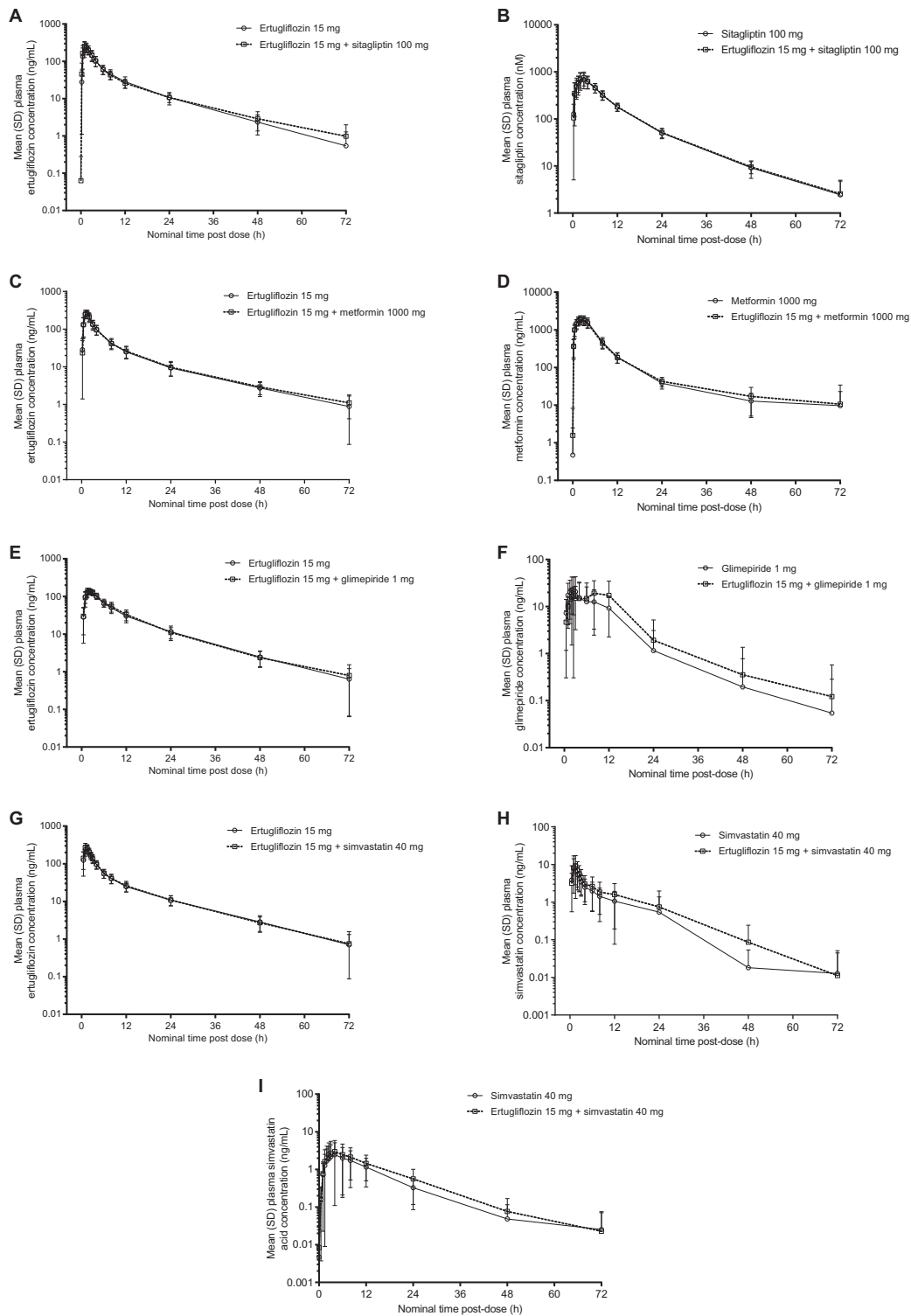
Due to the linear and time-independent PK of ertugliflozin, single-dose PK are predictive of multiple-dose PK of ertugliflozin. There is minimal accumulation observed after repeated ertugliflozin dosing and, based on in vitro data, drug interaction between ertugliflozin and concomitant medications is not expected. Therefore, the single-dose study design used was considered to be adequate for determining the drug interaction with co-administered drugs. Ertugliflozin 15 mg was used in these studies as it is the highest dose evaluated in the phase 3 development program. Across all 4 DDI studies presented here, the plasma concentrations of ertugliflozin observed were

as expected and similar to other studies using a single ertugliflozin 15-mg dose.<sup>8,24,25</sup>

Glucuronidation (UGT1A9 and UGT2B7) is the major elimination pathway of ertugliflozin, with only minor contributions from oxidative metabolism (CYP3A4/5, CYP2C8) and renal excretion.<sup>2</sup> Although ertugliflozin is a substrate of P-glycoprotein and breast cancer resistance protein, no clinically relevant interaction is expected with inhibitors of these transporters based on ertugliflozin's oral bioavailability of approximately 100%.<sup>8</sup> As expected, no differences were observed in ertugliflozin PK when coadministered with a single dose of sitagliptin (100 mg), metformin (1000 mg), glimepiride (1 mg), or simvastatin (40 mg), compared with a single dose of ertugliflozin (15 mg) alone. The geometric mean ratios of AUC<sub>inf</sub> and C<sub>max</sub> for ertugliflozin fell within the accepted equivalence limits (80% to 125% in all 4 studies), suggesting that there was no meaningful impact of these commonly coadministered drugs on ertugliflozin PK.

No differences were observed in sitagliptin or metformin PK when coadministered with ertugliflozin, compared with administration of single doses alone, as the 90% CIs for the geometric mean ratios for AUC<sub>inf</sub> and C<sub>max</sub> for sitagliptin and metformin were within the accepted equivalence limits of 80% to 125%.

In the ertugliflozin-glimepiride DDI study, ertugliflozin had no meaningful impact on the PK of glimepiride as median plasma glimepiride



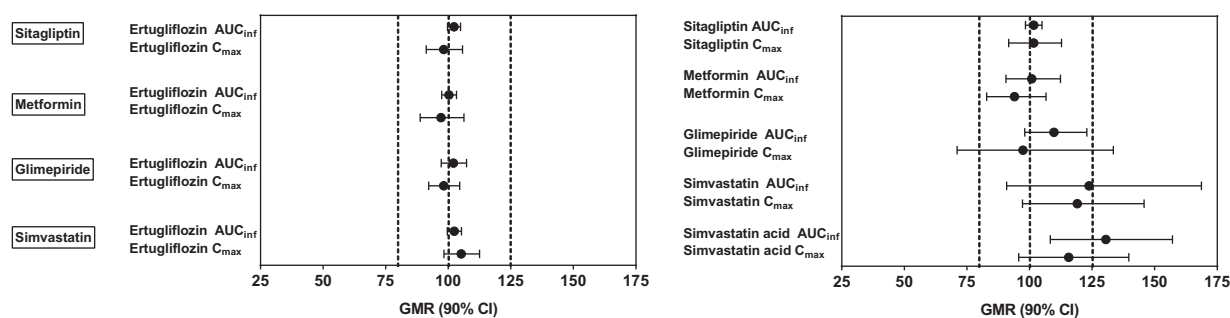
**Figure I.** Mean ( $\pm$  standard deviation) plasma concentration–time profiles for (A) ertugliflozin alone and in combination with sitagliptin; (B) sitagliptin alone and in combination with ertugliflozin; (C) ertugliflozin alone and in combination with metformin; (D) metformin alone and in combination with ertugliflozin; (E) ertugliflozin alone and in combination with glimepiride; (F) glimepiride alone and in combination with ertugliflozin; (G) ertugliflozin alone and in combination with simvastatin; and (H) simvastatin and (I) simvastatin acid after administration of simvastatin alone and in combination with ertugliflozin. Summary statistics were calculated by setting concentration values below the lower limit of quantification to zero. SD, standard deviation.



**Table 3.** Statistical Summary of Treatment Comparisons for Ertugliflozin, Sitagliptin, Metformin, Glimepiride, and Simvastatin

Analyte	Test	Reference	GMR (90% CI)	
			AUC <sub>inf</sub>	C <sub>max</sub>
<b>Ertugliflozin-Sitagliptin Study</b>				
Ertugliflozin	Ertugliflozin + Sitagliptin	Ertugliflozin	102.3 (99.7, 104.9)	98.2 (91.2, 105.7)
Sitagliptin	Ertugliflozin + Sitagliptin	Sitagliptin	101.7 (98.4, 105.0)	101.7 (91.7, 112.8)
<b>Ertugliflozin-Metformin Study</b>				
Ertugliflozin	Ertugliflozin + Metformin	Ertugliflozin	100.3 (97.4, 103.3)	97.1 (88.8, 106.3)
Metformin	Ertugliflozin + Metformin	Metformin	100.9 (90.6, 112.4)	94.0 (82.9, 106.6)
<b>Ertugliflozin-Glimepiride Study</b>				
Ertugliflozin	Ertugliflozin + Glimepiride	Ertugliflozin	102.1 (97.2, 107.3)	98.2 (92.2, 104.6)
Glimepiride	Ertugliflozin + Glimepiride	Glimepiride	109.8 (98.1, 122.9)	97.4 (71.1, 133.5)
<b>Ertugliflozin-Simvastatin Study</b>				
Ertugliflozin	Ertugliflozin + Simvastatin	Ertugliflozin	102.4 (99.6, 105.3)	105.2 (98.3, 112.5)
Simvastatin	Ertugliflozin + Simvastatin	Simvastatin	123.8 (90.9, 168.7)	119.1 (97.2, 145.8)
Simvastatin Acid	Ertugliflozin + Simvastatin	Simvastatin	130.5 (108.3, 157.1)	115.7 (95.7, 139.7)

AUC<sub>inf</sub>, area under the plasma concentration–time profile from time 0 extrapolated to infinite time; CI, confidence interval; C<sub>max</sub>, maximum observed plasma concentration; GMR, geometric mean ratio.



**Figure 2.** Forest plot of statistical summary of treatment comparisons for ertugliflozin, sitagliptin, metformin, glimepiride, and simvastatin. AUC<sub>inf</sub>, area under the plasma concentration–time profile from time 0 extrapolated to infinite time; CI, confidence interval; C<sub>max</sub>, maximum observed plasma concentration; GMR, geometric mean ratio; the vertical dashed lines are 80%, 100%, and 125%.

concentration–time profiles with or without ertugliflozin were similar. The 90% CI for the geometric mean ratio for glimepiride AUC<sub>inf</sub>, with or without ertugliflozin, also fell within the equivalence limit of 80% to 125%. The majority of subjects had 2 peaks in the plasma glimepiride concentration–time profile, resulting in high variability in T<sub>max</sub>. Similarly, C<sub>max</sub> values for glimepiride in both treatment arms were also variable; this high variability and occurrence of 2 peaks was likely due to the administration of the 20% glucose solution until approximately 4 hours after the dose in each period. Due to the high variability, the 90% CI for the geometric mean ratio for C<sub>max</sub> fell outside the equivalence limits (90% CI, 71.1, 133.5). However, the geometric mean ratio for glimepiride C<sub>max</sub> was 97.4%, indicating no clinically meaningful differences in glimepiride PK when coadministered

with ertugliflozin compared with administration of glimepiride alone. A similar PK profile for glimepiride with 2 peaks was observed in a study conducted to assess the interaction between dapagliflozin (another SGLT2 inhibitor) and glimepiride, in which a glucose solution was also administered.<sup>26</sup>

Coadministration of ertugliflozin 15 mg and simvastatin 40 mg slightly increased simvastatin AUC<sub>inf</sub> and C<sub>max</sub> by 24% and 19%, respectively, and increased simvastatin acid AUC<sub>inf</sub> and C<sub>max</sub> by 30% and 16%, respectively; the upper limits of the 90% CIs for the geometric mean ratios were outside the equivalence limits. Other SGLT2 inhibitors such as canagliflozin, dapagliflozin, and empagliflozin have also been evaluated for their interaction with simvastatin. Like ertugliflozin, both canagliflozin and dapagliflozin slightly increased the AUC of simvastatin and simvastatin acid

by 12% to 19% and 18% to 30%, respectively.<sup>27</sup> Empagliflozin had no effect on the  $AUC_{inf}$  and  $C_{max}$  of simvastatin and simvastatin acid.<sup>28</sup> Ertugliflozin and its 2 major glucuronide metabolites have been evaluated extensively in vitro for their potential to inhibit or induce the drug-metabolizing enzyme (CYP3A4) or transporters (OATP) involved in the disposition of simvastatin. These in vitro studies have shown that neither ertugliflozin nor the glucuronide metabolites are inhibitors or inducers of CYP3A4 or OATP. As such, the mechanism for the small increases in simvastatin and its active metabolite's exposure by ertugliflozin are not known. However, these changes in simvastatin and simvastatin acid exposure are not considered clinically relevant, as these modest increases are not expected to alter the active 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitory activity of simvastatin.

Overall, in vitro data indicate that clinically meaningful drug interactions via ertugliflozin-mediated inhibition or induction of CYP/UGT isozymes and transporters with concomitant medications that are substrates of OAT3 (sitagliptin), OCT2 (metformin), CYP isozymes (glimepiride, statins), and OATP1B1 (statins) are not anticipated. The observed lack of interaction between ertugliflozin and sitagliptin, metformin, glimepiride, and simvastatin was consistent with that predicted by the known metabolism of each drug as well as in vitro inhibition data.

The results of the ertugliflozin DDI studies with concomitant medications presented here are consistent with those reported for other SGLT2 inhibitors. Canagliflozin is metabolized by UGT1A9 and UGT2B4 and did not exhibit clinically relevant DDIs when administered with metformin or simvastatin.<sup>29</sup> Dapagliflozin is also metabolized mainly in the liver and kidneys by UGT1A9,<sup>28</sup> and a lack of clinically meaningful DDI was reported when dapagliflozin was coadministered with either sitagliptin, metformin, glimepiride, or simvastatin.<sup>26,27</sup> Similarly, no relevant DDIs were observed when empagliflozin was coadministered with simvastatin,<sup>30</sup> metformin,<sup>31</sup> or sitagliptin.<sup>32</sup>

In summary, the lack of PK interactions demonstrates that ertugliflozin can be administered with sitagliptin, metformin, simvastatin, or glimepiride without any need for dose adjustments. However, when ertugliflozin is coadministered with sulfonylureas, the sulfonylurea dose may need to be reduced to decrease the risk of hypoglycemia.

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## Declaration of Conflicting Interests

H.S., Y.L., A.H., D.S., S.G.T., and V.S. are employees of Pfizer Inc. V.K.D. and C.A. were employees of Pfizer Inc. at the time of study conduct. S.Z. and R.K. are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey. D.L.C. was an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, at the time of study conduct.

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### **Supporting Information**

Additional Supporting Information may be found in the online version of this article at the publisher's website.