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Effect of Food on the Pharmacokinetics of Ertugliflozin and Its Fixed-Dose Combinations Ertugliflozin/Sitagliptin and Ertugliflozin/Metformin

Vaishali Sahasrabudhe[1], Daryl J. Fediuk[1], Kyle Matschke[2], Haihong Shi[1], Yali Liang[1,*], Anne Hickman[1], Almasa Bass[3,*], Steven G. Terra[4], Susan Zhou[5], Rajesh Krishna[5], and Vikas K. Dawra[1,*]

Abstract

Ertugliflozin, an inhibitor of sodium-glucose cotransporter 2, is approved in the United States and European Union for the treatment of type 2 diabetes in adults, both as monotherapy and as part of fixed-dose combination (FDC) therapies with either sitagliptin or immediate-release metformin. The effect of a standard, high-fat breakfast on the pharmacokinetics of the highest strengths of ertugliflozin monotherapy (15 mg), ertugliflozin/sitagliptin FDC (15-/100-mg), and ertugliflozin/metformin FDC (7.5-/1000-mg) tablets was evaluated. In 3 separate open-label, 2-period, 2-sequence, single-dose, crossover studies, 14 healthy subjects per study were randomized to receive either ertugliflozin monotherapy or FDC tablets comprising ertugliflozin and sitagliptin or ertugliflozin and metformin under fasted and fed (or vice versa) conditions. Food did not meaningfully affect the pharmacokinetics of ertugliflozin, sitagliptin, or metformin. For FDCs, the effect of food was consistent with that described for individual components. All treatments were well tolerated. Ertugliflozin and ertugliflozin/sitagliptin FDC tablets can be administered without regard to meals. As metformin is administered with meals because of its gastrointestinal side effects, the ertugliflozin/metformin FDC should also be administered with meals.

Keywords

diabetes, ertugliflozin, pharmacokinetics, SGLT2 inhibitor

Inhibitors of sodium-glucose cotransporter 2 (SGLT2) offer physicians a new treatment option for type 2 diabetes mellitus (T2DM). Glucose in the blood is filtered through the glomerulus and is subsequently reabsorbed via SGLT2 and SGLT1. SGLT2 is responsible for reabsorption of the majority of glucose (90%) in the kidney.[1] SGLT2 inhibitors have been shown to reduce renal glucose reabsorption and lower the renal threshold for glucose excretion, thereby increasing urinary glucose excretion and reducing plasma glucose and hemoglobin A1C (Hb_{A1c}) independently of pancreatic β-cell function.[2,3]

Ertugliflozin is a selective SGLT2 inhibitor approved in the United States (US) and European Union (EU) at doses of 5 and 15 mg for the treatment of T2DM in adults; its selectivity is 2000-fold higher for SGLT2 than for SGLT1.[4] Phase 2 and 3 studies have shown that ertugliflozin reduces Hb_{A1c}, body weight, and blood pressure.[5–9] It is expected that in clinical practice, ertugliflozin will be used in combination with the dipeptidyl peptidase 4 (DPP-4) inhibitor sitagliptin[10] or with the biguanide antihyperglycemic agent metformin,[11] both of which are indicated for the treatment of T2DM. Sitagliptin inhibits DPP-4, which leads to increases in active incretin hormones, glucagon-like peptide (GLP)-1, and glucose-dependent

[1]Pfizer Inc., Groton, CT, USA
[2]Pfizer Inc., Collegeville, PA, USA
[3]Pfizer Inc., Durham, NC, USA
[4]Pfizer Inc., Andover, MA, USA
[5]Merck & Co., Inc., Kenilworth, NJ, USA

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Corresponding Author:
Vaishali Sahasrabudhe, PhD, Pfizer Inc., 445 Eastern Point Road, Groton, CT 06340, USA
(e-mail: Vaishali.Sahasrabudhe@pfizer.com)

*At the time the study was conducted.

insulinotropic polypeptide (GIP). GLP and GIP are released by enteroendocrine cells in response to food and result in enhanced glucose-dependent insulin secretion from pancreatic β-cells. In addition, GLP-1 suppresses glucagon release from pancreatic α-cells and slows gastric emptying. These mechanisms work to lower both fasting and postprandial glucose concentrations. Metformin reduces glucose production by the liver and absorption in the intestine, improving insulin sensitivity due to increased peripheral glucose uptake and utilization. Combining ertugliflozin with other antihyperglycemic agents that have different and complementary mechanisms of action results in improved glycemic control.[7,8,12,13] As such, fixed-dose combination (FDC) formulations of ertugliflozin/sitagliptin and ertugliflozin/metformin have been developed and are approved in the US and the EU.

Ertugliflozin is a Biopharmaceutical Classification System (BCS) class I drug having high solubility and high permeability. The absolute oral bioavailability of ertugliflozin is 100%.[14] Results of phase 1 studies have shown that ertugliflozin is rapidly absorbed following oral administration, with median time to maximum observed plasma concentration (T_{max}) achieved at 0.5–1.5 hours postdose under fasted conditions. Exposure of ertugliflozin is dose proportional over the dose range of 0.5 to 300 mg, and terminal elimination half-life ($t_{1/2}$) is in the range of 11 to 17 hours.[15] Ertugliflozin is metabolized mainly by uridine diphosphate–glucuronosyltransferase (UGT) isozymes UGT1A9 and UGT2B7, with minor contributions from cytochrome P450 isozymes.[16]

Given that ingestion of a meal may result in changes to the physiology of the gastrointestinal tract or impact the release of drug from the dosage form, which can in turn affect drug bioavailability,[17] understanding the effect of food on bioavailability is particularly important in clinical development. Three phase 1 open-label, randomized, 2-period, single-dose, crossover studies were conducted in healthy subjects to assess the effect of a standard high-fat breakfast on the pharmacokinetics of ertugliflozin and the 2 FDC formulations. These studies also assessed the safety and tolerability of ertugliflozin under fasted and fed conditions when administered as monotherapy and as ertugliflozin/sitagliptin and ertugliflozin/metformin FDCs.

Methods

Ethical Conduct of the Study

The final protocol and informed consent documentation for each of the 3 studies were reviewed and approved by the Comite d'Ethique Hospitalo-Facultaire Erasme-ULB Institutional Review Board (Brussels, Belgium), and all subjects provided signed and dated informed consent. All studies were compliant with the ethical principles of the Declaration of Helsinki and all International Conference on Harmonization Good Clinical Practice guidelines.

Selection of Dose and Meal Conditions

The highest dose of ertugliflozin (15 mg) was selected as the most appropriate for the assessment of food effect in accordance with the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidances.[17,18] Similarly, 100 mg is the maximum daily dose of sitagliptin used in clinical practice,[10] and 1000 mg twice daily is a commonly used dose of metformin in clinical practice.[11] As such, ertugliflozin 15 mg/sitagliptin 100 mg and ertugliflozin 7.5 mg/metformin 1000 mg were the highest strengths developed for the FDC tablets and were used for the assessment of food effect. As the ertugliflozin/metformin FDC contains an immediate-release formulation of metformin that requires twice-daily dosing, the dose strength containing 7.5-mg ertugliflozin was used for evaluation of food effect for this FDC. Consumption of a high-fat meal was included in these studies in keeping with the guidelines from the US FDA and the EMA,[17,18] which recommend using meal components that have the greatest chance of affecting gastrointestinal physiology so that systemic drug availability is maximally affected. Hence, subjects were given a standard high-fat, high-calorie (approximately 800- to 1000-calorie) breakfast, with approximately 50% of the total caloric content as fat.

Study Design

All 3 studies were open-label, 2-period, 2-sequence, single-dose, crossover studies conducted at the Pfizer Clinical Research Unit in Brussels, Belgium. Each study consisted of a screening visit and 2 treatment periods, with screening occurring within 4 weeks of the first dose of study treatment. Eligible subjects were admitted to the Clinical Research Unit on day 0. Each subject received ertugliflozin 15 mg, ertugliflozin 15-mg/sitagliptin 100-mg FDC, or ertugliflozin 7.5-mg/metformin 1000-mg FDC tablets under fasted and fed conditions in a crossover design. During the fasted phase, subjects received study medication after an overnight fast of $\geq$10 hours, and no additional food was allowed for 4 hours postdose. During the fed phase, subjects fasted overnight for $\geq$10 hours and then received a standard high-fat, high-calorie breakfast, as described above. The entire breakfast was to be consumed within 25 minutes, and no additional food was allowed for 4 hours postdosing of study medication, which was administered approximately 30 minutes after beginning the breakfast. Subjects were requested to refrain from lying down or drinking beverages other than water for the first 4 hours postdose. Dosing in

each period was separated by a washout period of ≥5 days for the ertugliflozin monotherapy study and ≥7 days for FDC studies.

Subjects

Healthy male and female subjects aged 18–55 years with a body mass index (BMI) 17.5–30.5 kg/m^2 and a total body weight >50 kg were eligible for enrollment. Female subjects of childbearing potential were also eligible for enrollment, provided they agreed to use accepted methods of contraception. The main exclusion criteria were: positive urine screen for drugs of abuse or recreation; history of alcohol abuse or binge drinking, and/or any other illicit drug use or dependence within 6 months of screening; clinically significant malabsorption condition; known hypersensitivity, intolerance, or contraindication to any SGLT2 inhibitor, DPP-4 inhibitor, or metformin or to any of the foods provided; and/or use of prescription or nonprescription drugs, vitamins, and dietary supplements within 7 days or 5 half-lives (whichever was longer) prior to the first dose of the study medication.

Pharmacokinetic Evaluations

Serial blood samples (4 mL for monotherapy study, 6 mL for FDC studies) for pharmacokinetic analysis were collected from each subject predose (0 hours) and up to 72 hours postdose in each treatment period. Samples were centrifuged at approximately 1700*g* for 10 minutes at 4°C and then stored at −20°C within 1 hour of collection. Plasma samples were analyzed for ertugliflozin and metformin concentrations at WuXi AppTec (Shanghai, China) and for sitagliptin concentrations at inVentiv Health Clinique (Quebec City, Quebec, Canada) using validated high-performance liquid chromatography (HPLC)–tandem mass spectrometry methods. The method for bioanalysis of ertugliflozin has been described previously.[19] Sitagliptin was extracted from 100 µL 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 µm (2.1 × 50 mm) using a mobile phase of acetonitrile/water (80/20, v/v) containing 10 mM ammonium acetate (NH_4Ac; pH 4.7). Detection was performed by Sciex API 4000 in the positive ion mode. The multiple reaction monitoring ion transition was m/z 408→235 for sitagliptin and m/z 412→239 for the internal standard. Metformin was extracted from 50 µL of human plasma by protein precipitation with acetonitrile and metformin-d6 as the internal standard. The supernatant was diluted with 10 mM NH_4Ac in acetonitrile containing 0.5% formic acid. The extracted sample was injected into an HPLC column (Waters Atlantis HILIC Silica 5 µm [2.1 × 50 mm]), with a gradient mobile phase containing 0.5% formic acid and 10 mM NH_4Ac 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→71 for metformin and m/z 136→77 for the internal standard. The calibration curves were linear over the range of 0.500 to 500 ng/mL for ertugliflozin, 1.0 to 1000 ng/mL for sitagliptin, and 2.0 to 1000 ng/mL for metformin.

Data Analysis

Summary statistics for plasma concentrations were calculated by setting concentration values below the lower limit of quantification to zero. The following pharmacokinetic parameters were calculated for each subject and treatment using noncompartmental analysis of plasma concentration-time data using an internally validated software system, electronic non-compartmental analysis (eNCA, version 2.2.4): area under the plasma concentration-time curve (AUC) from time zero extrapolated to infinite time (AUC_{inf}); AUC from time zero to the time of the last quantifiable concentration (AUC_{last}); maximum observed plasma concentration (C_{max}); T_{max}; and $t_{1/2}$. The pharmacokinetic concentration population was defined as all treated subjects who had ≥1 concentration measurement. The pharmacokinetic parameter analysis population was defined as all subjects randomized and treated who had measurements for ≥1 pharmacokinetic parameter in ≥1 treatment period. Natural log-transformed AUC_{inf} and C_{max} measurements were analyzed using a mixed-effects model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect. The adjusted (least-squares) mean differences and 90% confidence intervals (CIs) were exponentiated to provide estimates of the ratio of adjusted geometric means (test:reference [fed:fasted]) and 90% CIs for the ratio. If an individual subject had a known biased estimate of a pharmacokinetic parameter (for example, because of an unexpected event such as vomiting before all the compound was adequately absorbed in the body), the subject was not included in the calculation of summary statistics or statistical analyses.

Safety Evaluations

All subjects who received ≥1 dose of study medication were included in the safety analysis. The safety and tolerability of ertugliflozin when administered under fasted and fed conditions as monotherapy and as ertugliflozin/sitagliptin and ertugliflozin/metformin FDCs were assessed via adverse event (AE) monitoring, physical examination, blood pressure and pulse rate, and measurement of clinical laboratory parameters, which were performed from screening and throughout the duration of study participation. Subjects received a follow-up phone call 14 ± 3 days after administration

Table 1. Baseline Characteristics

	Ertugliflozin 15 mg n = 14	Ertugliflozin 15-mg/ Sitagliptin 100-mg FDC n = 14	Ertugliflozin 7.5-mg/ Metformin 1000-mg FDC n = 14
Sex, n			
Male	10	11	10
Female	4	3	4
Age, years			
Mean (SD)	38.8 (9.0)	35.6 (10.3)	36.1 (9.3)
Range	25–53	20–54	20–52
Race, n			
White	12	11	13
Black	1	2	0
Other	1	1	1
Weight, kg			
Mean (SD)	75.9 (9.3)	81.2 (11.3)	72.5 (11.2)
Range	62.9–95.0	59.5–98.4	55.3–94.7
BMI, kg/m^2			
Mean (SD)	24.9 (2.1)	26.7 (2.7)	23.9 (2.5)
Range	22.2–29.2	20.3–29.6	19.3–28.6

FDC, fixed-dose combination; n, number of subjects in specified category; SD, standard deviation.

of the last dose of study medication in period 2 to assess for AEs. AEs were coded using the Medical Dictionary for Regulatory Activities (version 18.0 or 18.1).

Results

Study Population

Fourteen subjects in each study were assigned to and received study treatments (Table 1). All subjects in the ertugliflozin and ertugliflozin/sitagliptin FDC studies completed the respective studies and were included in pharmacokinetic and safety analyses. In the ertugliflozin/metformin FDC food-effect study, 13 of 14 subjects completed both the fed and fasted treatment periods. One subject withdrew after administration of ertugliflozin/metformin FDC under fasted conditions without proceeding to the fed treatment period because the subject was no longer willing to participate in the study. Subjects were predominantly white men; there were 10 men in both the ertugliflozin and ertugliflozin/metformin FDC studies and 11 men in the ertugliflozin/sitagliptin FDC study. Across the 3 studies, the mean age range of the subjects was 35.6–38.8 years, and the mean BMI was 23.9–26.7 kg/m^2 (Table 1).

Pharmacokinetics

Mean (standard deviation [SD]) plasma ertugliflozin concentration-time profiles following a single oral dose of the ertugliflozin 15-mg tablet in the fasted and fed states are shown in Figure 1. Mean (SD) plasma ertugliflozin and sitagliptin concentration-time profiles following a single oral dose of the ertugliflozin/sitagliptin FDC tablet in the fasted and fed states are shown in Figure 2. Mean (SD) plasma ertugliflozin and metformin concentration-time profiles following a single oral dose of the ertugliflozin/metformin FDC tablet in the fasted and fed states are shown in Figure 3.

Ertugliflozin was rapidly absorbed when administered alone or as part of the ertugliflozin/metformin or ertugliflozin/sitagliptin FDC tablet, with median T_{max} occurring 1.0–1.5 hours postdose under fasted conditions and 2.0–2.5 hours postdose under fed conditions (Table 2). After administration of the FDC formulations, median T_{max} for metformin was 2.3 hours (fasted) and 4.0 hours (fed), and for sitagliptin it was 3.0 hours (fasted) and 1.8 hours (fed); see Table 2. The $t_{1/2}$ values were similar in fasted and fed states for ertugliflozin as monotherapy or in the FDC formulations and for sitagliptin and metformin as part of an FDC (Table 2).

The AUC_{inf} was similar in the fasted and fed states for ertugliflozin, sitagliptin, and metformin (Table 3). Although not predefined as a criterion, the 90% CI of the adjusted geometric mean ratio (GMR; fed:fasted) for AUC_{inf} was within the bioequivalence limits of 80%–125% for ertugliflozin (as monotherapy or as part of an FDC) and for metformin and sitagliptin (as part of an FDC); see Table 3. Based on the adjusted GMRs (fed:fasted), compared with the fasted state, the C_{max} for ertugliflozin in the fed state was decreased by 29% when administered as monotherapy, by 30% when administered as the ertugliflozin/sitagliptin FDC, and by 41% when administered as the ertugliflozin/metformin FDC (Table 3). Similarly, the C_{max} of metformin was decreased by 29% in the fed state compared with the fasted state (Table 3). For sitagliptin, the 90% CI of the adjusted GMR (fed:fasted) for C_{max} when administered as the ertugliflozin/sitagliptin FDC tablet was within the bioequivalence limits of 80%–125% (Table 3).

Safety

A summary of AEs for all 3 studies is presented in Supplemental Table S1. No deaths, serious AEs, severe AEs, or temporary or permanent discontinuations due to AEs were reported. Across all 3 studies, the majority of treatment-emergent AEs (39 of 46 [85%]) were mild in intensity. The most commonly reported AEs were nervous system disorders (headache) for ertugliflozin monotherapy and gastrointestinal disorders for the FDC tablets. Most of these AEs occurred in ≤1 subject; only abdominal pain (ertugliflozin/metformin FDC, fed, n = 3), acne (ertugliflozin/metformin FDC, fed, n = 2), and headache (ertugliflozin monotherapy, fasted, n = 3) were reported in ≥2 subjects. There were

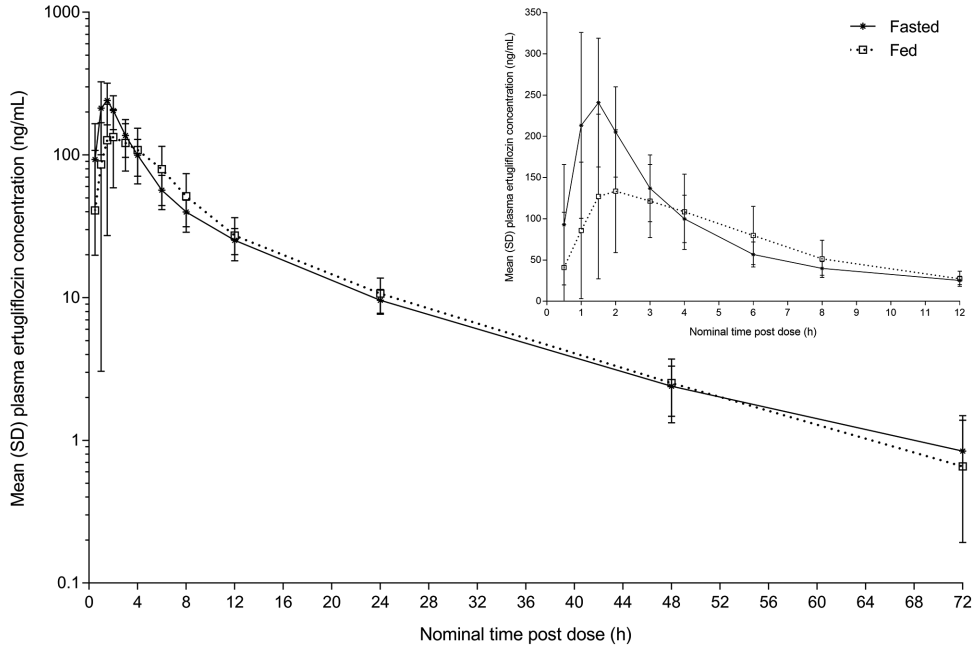

Figure 1. Mean (SD) plasma ertugliflozin concentration-time profile after administration of ertugliflozin 15-mg tablet. The main graph shows concentration over 72 hours postdose plotted on a semilog scale; the inset graph shows concentration over the first 12 hours plotted on a linear scale. Summary statistics were calculated by setting concentration values below the lower limit of quantification to zero. Data for 1 subject were excluded from analysis under fasted conditions because of the occurrence of vomiting within 2 × median T_{max} for the treatment. Data for 1 subject were excluded from analysis under fed conditions because of protocol deviation (subject was administered ertugliflozin at 47 minutes [instead of 30 minutes] after the start of breakfast). SD, standard deviation; T_{max}, time to maximum observed plasma concentration.

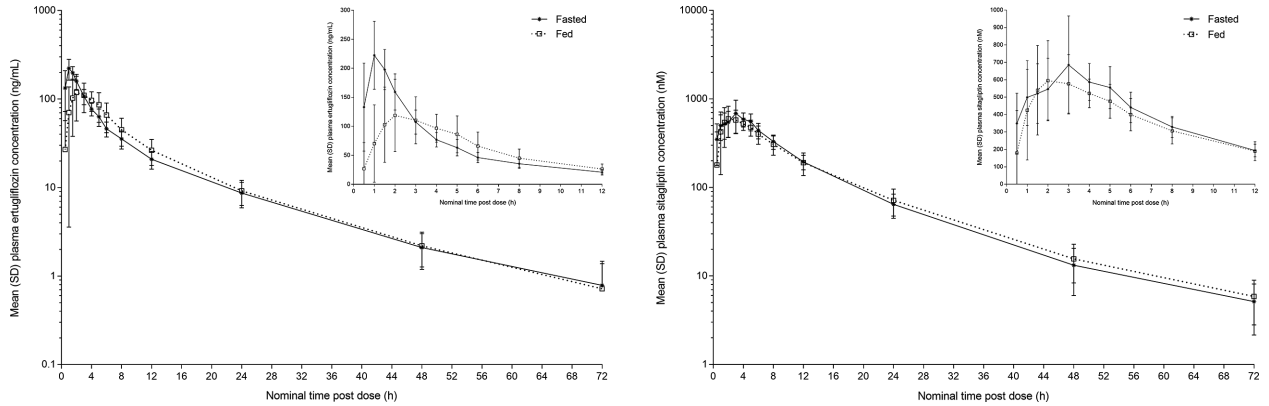

Figure 2. Mean (SD) plasma ertugliflozin (left) and sitagliptin (right) concentration-time profiles after administration of ertugliflozin 15-mg/sitagliptin 100-mg FDC tablet. Main graphs show concentration over 72 hours postdose plotted on a semilog scale; inset graphs show concentration over the first 12 hours plotted on a linear scale. Summary statistics were calculated by setting concentration values below the lower limit of quantification to zero. A sitagliptin concentration of 1.00 ng/mL is equivalent to 2.46 nM. FDC, fixed-dose combination; SD, standard deviation.

no abnormal laboratory findings or changes in blood pressure or pulse rate of clinical significance.

Discussion

Ertugliflozin, an SGLT2 inhibitor, is approved in the US and EU for the treatment of T2DM in adults for use as monotherapy, in combination with other antihyperglycemic agents, and as part of FDCs with sitagliptin or immediate-release metformin. Three separate studies were conducted to evaluate the effect of a standard high-fat breakfast on the pharmacokinetics of ertugliflozin monotherapy, the ertugliflozin/sitagliptin FDC tablet, and the ertugliflozin/metformin FDC tablet. Pharmacokinetic data from these studies suggest that administration of ertugliflozin monotherapy, ertugliflozin/sitagliptin

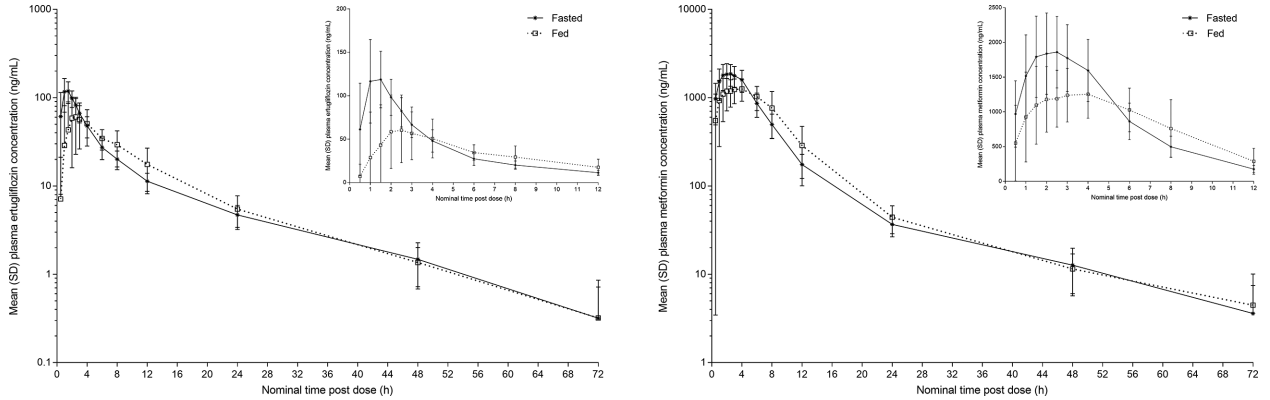

Figure 3. Mean (SD) plasma ertugliflozin (left) and metformin (right) concentration-time profiles after administration of ertugliflozin 7.5-mg/metformin 1000-mg FDC tablet. Main graphs show concentration over 72 hours postdose plotted on a semilog scale; inset graphs show concentration over the first 12 hours plotted on a linear scale. Summary statistics were calculated by setting concentration values below the lower limit of quantification to zero. One subject withdrew following administration of the ertugliflozin/metformin FDC tablet under fasted conditions without proceeding to the fed treatment period. FDC, fixed-dose combination; SD, standard deviation.

FDC tablets, and ertugliflozin/metformin FDC tablets with a high-fat meal had no meaningful effect on the AUC_{inf} of ertugliflozin, sitagliptin, or metformin. When ertugliflozin was administered in the fed state, compared with administration in the fasted state, median T_{max} was delayed by 1 hour in all 3 studies, and C_{max} was reduced by 29%–41%. The delayed T_{max} and decreased C_{max}, without affecting total exposure and half-life, are likely due to delayed gastric emptying following a high-fat meal and are consistent with the BCS class I properties (high solubility and high permeability) of ertugliflozin. Moreover, the effect of food on ertugliflozin C_{max} and T_{max} is not considered clinically relevant, as ertugliflozin efficacy is driven by total exposure (AUC) rather than peak concentration (C_{max}). In a study that compared twice- and once-daily dosing of ertugliflozin in healthy subjects at total daily doses of 5 and 15 mg, there was no meaningful difference in 24-hour urinary glucose excretion (a pharmacodynamic marker of SGLT2 inhibition) or AUC_{24} values for the 2 doses, although, as anticipated, C_{max} values were lower for twice-daily dosing compared with once-daily dosing when given the same total daily dose (data on file and reference[20]). Furthermore, in phase 3 studies, T2DM patients were instructed to take the study medication at approximately the same time of day in the morning without regard to meals. Results from these studies showed a significant improvement in Hb_{A1c}, body weight, and blood pressure after 26 weeks of ertugliflozin treatment.[5–9] Oral doses of ertugliflozin as high as 300 mg (single dose), 100 mg once daily (up to 14 days), and 25 mg once daily (up to 12 weeks) were not associated with any safety concerns in early phase 1 and 2 studies, and a maximum tolerated dose has not been identified. The safety and tolerability of ertugliflozin have also been demonstrated in phase 3 studies comprising subjects representative of the spectrum of patients with T2DM, including a wide array of background medications. Overall, ertugliflozin was well tolerated at both the 5- and 15-mg doses, which demonstrated generally similar safety profiles. The above findings are consistent with the understanding that total exposure is generally more clinically relevant than peak exposure for chronically administered drugs. Based on the lack of a clinically meaningful effect of food on ertugliflozin pharmacokinetics, ertugliflozin can be administered with or without regard to meals. This is also supported by a population pharmacokinetics analysis of phase 1, 2, and 3 studies with ertugliflozin that showed that food has no clinically relevant effect on the pharmacokinetics of ertugliflozin.[21]

The effect of food on the pharmacokinetics of sitagliptin in the ertugliflozin/sitagliptin FDC tablets was consistent with the previously reported effect for sitagliptin administered as monotherapy.[22] In the previously published data, the fed:fasted GMRs (90% CIs) for AUC_{inf} and C_{max} of sitagliptin were 103% (97%–111%) and 94% (86%–103%), respectively, and the GMRs were contained within the bioequivalence bounds of 80% to 125%;[22] as such, sitagliptin tablets can be administered without regard to food. In the current analysis, food also had no effect on the AUC_{inf} or C_{max} of sitagliptin when administered as an ertugliflozin/sitagliptin FDC tablet. Based on the lack of a clinically meaningful effect of food on the pharmacokinetics of the ertugliflozin/sitagliptin FDC tablet, this FDC tablet may be administered without regard to meals.

Results from a study conducted to assess the effect of food on metformin pharmacokinetics revealed

Table 2. Descriptive Summary of Plasma Pharmacokinetic Parameter Values in the Fasted and Fed States

Parameter[a]	Fasted	Fed
Ertugliflozin 15-mg tablet[b,c]		
N, n	13, 13	13, 13
AUC_{inf}	1326 (21)	1240 (17)
	1352 ± 274.9	1257 ± 217.8
AUC_{last}	1308 (21)	1220 (17)
	1334 ± 273.0	1237 ± 218.0
C_{max}	271.1 (24)	194.9 (20)
	278.0 ± 61.5	198.4 ± 39.1
T_{max}	1.0 (1.0–3.0)	2.0 (1.0–6.0)
$t_{1/2}$	11.5 ± 2.6	11.0 ± 2.0
Ertugliflozin 15-mg/sitagliptin 100-mg FDC tablet		
Ertugliflozin 15 mg		
N, n	14, 14	14, 14
AUC_{inf}	1171 (18)	1108 (20)
	1189 ± 219.8	1129 ± 221.1
AUC_{last}	1150 (18)	1090 (20)
	1168 ± 216.5	1111 ± 219.1
C_{max}	223.0 (22)	157.1 (24)
	228.1 ± 50.7	161.4 ± 39.4
T_{max}	1.0 (1.0–1.7)	2.0 (1.0–5.0)
$t_{1/2}$	12.9 ± 3.5	11.6 ± 2.3
Sitagliptin 100 mg		
N, n	14, 14	14, 14
AUC_{inf}	7.4 (16)	7.1 (16)
	7.4 ± 1.3	7.2 ± 1.3
AUC_{last}	7.3 (16)	7.0 (16)
	7.4 ± 1.3	7.1 ± 1.2
C_{max}	750.7 (29)	721.3 (16)
	780.5 ± 235.9	729.3 ± 108.7
T_{max}	3.0 (0.5–5.0)	1.8 (0.5–5.0)
$t_{1/2}$	11.5 ± 1.4	12.1 ± 1.6
Ertugliflozin 7.5-mg/metformin 1000-mg FDC tablet[d]		
Ertugliflozin 7.5 mg		
N, n	14, 14	13, 13
AUC_{inf}	654.8 (24)	602.3 (26)
	673.4 ± 173.5	621.2 ± 167.6
AUC_{last}	639.5 (25)	587.4 (26)
	658.4 ± 173.0	606.3 ± 165.8
C_{max}	126.5 (27)	75.3 (44)
	130.7 ± 35.6	82.3 ± 40.7
T_{max}	1.5 (1.0–2.5)	2.50 (1.0–8.0)
$t_{1/2}$	12.1 ± 2.6	11.2 ± 4.5
Metformin 1000 mg		
N, n	14, 14	13, 12
AUC_{inf}	12 530 (26)	11 550 (29)
	12 890 ± 2936	12 000 ± 3720
AUC_{last}	12 420 (26)	11 760 (29)
	12 770 ± 2892	12 230 ± 3707
C_{max}	2040 (31)	1461 (32)
	2118 ± 547.6	1521 ± 417.1
T_{max}	2.3 (1.0–4.0)	4.0 (0.5–8.0)
$t_{1/2}$	12.3 ± 5.8	11.8 ± 3.8

AUC_{inf}, area under plasma concentration-time profile from time 0 extrapolated to infinity; AUC_{last}, area under plasma concentration-time profile from time 0 to time of last quantifiable concentration; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; FDC, fixed-dose combination; N, number of subjects in the treatment group and contributing to the summary statistics; n, number of subjects with reportable $t_{1/2}$ and AUC_{inf}; $t_{1/2}$, terminal half-life; T_{max}, time to maximum observed plasma concentration.

Pharmacokinetic parameter units are as follows: AUC_{inf} and AUC_{last} for ertugliflozin and metformin (ng·h/mL); AUC_{inf} and AUC_{last} for sitagliptin (μM·h); C_{max} for ertugliflozin and metformin (ng/mL); C_{max} for sitagliptin (nM); T_{max} and $t_{1/2}$ (h). A sitagliptin concentration of 1.00 ng/mL is equivalent to 2.46 nM.

[a]Values for AUC_{inf}, AUC_{last}, and C_{max} are geometric mean (geometric %CV) and arithmetic mean ± standard deviation; for T_{max} are median (range); and for $t_{1/2}$ are arithmetic mean ± standard deviation.

[b]Data for 1 subject excluded from analysis under fasted conditions because of the occurrence of vomiting within 2 × median T_{max} for the treatment.

[c]Data for 1 subject excluded from analysis under fed conditions because of protocol deviation (subject was administered ertugliflozin at 47 minutes [instead of 30 minutes] after the start of breakfast).

[d]One subject withdrew following administration of the ertugliflozin/metformin FDC tablet under fasted conditions without proceeding to the fed treatment period.

that at a dose of 850 mg, food slightly delays and also decreases the extent of absorption, as evidenced by an approximately 35-minute increase in T_{max}, 25% lower AUC, and 40% lower mean C_{max} in the fed versus fasted state.[23] In the ertugliflozin/metformin FDC study presented here, metformin T_{max} was delayed by 1.7 hours and C_{max} was reduced by approximately 29% in the fed versus fasted state, but there was no effect on AUC. As such, the observed effect of food on the AUC_{inf} and C_{max} of metformin when administered as the ertugliflozin/metformin FDC tablet was slightly less than that reported for metformin when administered alone.[23] The magnitude of the decrease in C_{max} for ertugliflozin and metformin when administered as an ertugliflozin/metformin FDC tablet in the fed versus fasted state is not considered clinically relevant; however, the ertugliflozin/metformin FDC tablet should be given with meals to reduce the gastrointestinal side effects associated with metformin.[11]

Conclusions

In summary, ertugliflozin and ertugliflozin/sitagliptin FDC tablets can be administered without regard to food with no meaningful effect on the pharmacokinetics of ertugliflozin and sitagliptin. Taking the dosing recommendation of metformin into consideration, ertugliflozin/metformin FDC should be given twice daily with meals to reduce the gastrointestinal side

Table 3. Statistical Summary of Treatment Comparisons

Formulation	Analyte	Fed:Fasted GMR (90% CI)	
		AUC_{inf}	C_{max}
Ertugliflozin 15-mg tablet	Ertugliflozin	91.7 (88.0–95.4)	70.7 (61.7–80.9)
Ertugliflozin 15-mg/sitagliptin 100-mg FDC tablet	Ertugliflozin	94.6 (91.6–97.8)	70.5 (63.3–78.4)
	Sitagliptin	96.6 (94.0–99.4)	96.1 (82.4–112.1)
Ertugliflozin 7.5-mg/metformin 1000-mg FDC tablet	Ertugliflozin	93.8 (90.1–97.7)	59.4 (51.1–69.1)
	Metformin	92.8 (85.1–101.3)	70.7 (63.6–78.5)

AUC_{inf}, area under plasma concentration-time profile from time 0 extrapolated to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; FDC, fixed-dose combination; GMR, geometric mean ratio.

effects from metformin. All study medications were well tolerated in both the fasted and fed states.

Declaration of Conflicting Interests

V.S., D.J.F., K.M., H.S., A.H., and S.G.T. are employees of Pfizer Inc. and have shares/stock options in Pfizer Inc. Y.L., A.B., and V.K.D. were employees of Pfizer Inc. at the time the study was conducted. S.Z. and R.K. are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, USA and have shares/stock options in the company.

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Data-Sharing Statement

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

References

1. Lee YJ, Lee YJ, Han HJ. Regulatory mechanisms of Na(+)/glucose cotransporters in renal proximal tubule cells. *Kidney Int Suppl*. 2007;(106):S27–S35.
2. Abdul-Ghani MA, Norton L, DeFronzo RA. Renal sodium-glucose cotransporter inhibition in the management of type 2 diabetes mellitus. *Am J Physiol Renal Physiol*. 2015;309(11):F889–F900.
3. Scheen AJ. Metformin should not be contraindicated in patients with type 2 diabetes and mild to moderate renal impairment. *Evid Based Med*. 2015;20(3):115.
4. Mascitti V, Maurer TS, Robinson RP, et al. Discovery of a clinical candidate from the structurally unique dioxa-bicyclo[3.2.1]octane class of sodium-dependent glucose cotransporter 2 inhibitors. *J Med Chem*. 2011;54(8):2952–2960.
5. Amin NB, Wang X, Jain SM, Lee DS, Nucci G, Rusnak JM. Dose-ranging efficacy and safety study of ertugliflozin, a sodium-glucose co-transporter 2 inhibitor, in patients with type 2 diabetes on a background of metformin. *Diabetes Obes Metab*. 2015;17(6):591–598.
6. Amin NB, Wang X, Mitchell JR, Lee DS, Nucci G, Rusnak JM. Blood pressure-lowering effect of the sodium glucose co-transporter-2 inhibitor ertugliflozin, assessed via ambulatory blood pressure monitoring in patients with type 2 diabetes and hypertension. *Diabetes Obes Metab*. 2015;17(8):805–808.
7. Pratley RE, Eldor R, Raji A, et al. Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with type 2 diabetes mellitus inadequately controlled with metformin: the VERTIS FACTORIAL randomized trial. *Diabetes Obes Metab*. 2018;20(5):1111–1120.
8. Dagogo-Jack S, Liu J, Eldor R, et al. Efficacy and safety of the addition of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sitagliptin: the VERTIS SITA2 placebo-controlled randomized study. *Diabetes Obes Metab*. 2018;20(3):530–540.
9. Terra SG, Focht K, Davies M, et al. Phase III, efficacy and safety study of ertugliflozin monotherapy in

people with type 2 diabetes mellitus inadequately controlled with diet and exercise alone. *Diabetes Obes Metab*. 2017;19(5):721–728.
10. Scott LJ. Sitagliptin: A review in type 2 diabetes. *Drugs*. 2017;77(2):209–224.
11. Sanchez-Rangel E, Inzucchi SE. Metformin: clinical use in type 2 diabetes. *Diabetologia*. 2017;60(9):1586–1593.
12. Miller S, Krumins T, Zhou H, et al. Ertugliflozin and sitagliptin co-initiation in patients with type 2 diabetes: the VERTIS SITA randomized study. *Diabetes Ther*. 2018;9(1):253–268.
13. Rosenstock J, Frias J, Pall D, et al. Effect of ertugliflozin on glucose control, body weight, blood pressure and bone density in type 2 diabetes mellitus inadequately controlled on metformin monotherapy (VERTIS MET). *Diabetes Obes Metab*. 2018;20(3):520–529.
14. Raje S, Callegari E, Sahasrabudhe V, et al. Determination of absolute oral bioavailability and fraction absorbed of ertugliflozin using a novel microtracer approach. *Clin Transl Sci*. 2018;11(4):405–411.
15. Kalgutkar AS, Tugnait M, Zhu T, et al. Preclinical species and human disposition of PF-04971729, a selective inhibitor of the sodium-dependent glucose cotransporter 2 and clinical candidate for the treatment of type 2 diabetes mellitus. *Drug Metab Dispos*. 2011;39(9):1609–1619.
16. Miao Z, Nucci G, Amin N, et al. Pharmacokinetics, metabolism, and excretion of the antidiabetic agent ertugliflozin (PF-04971729) in healthy male subjects. *Drug Metab Dispos*. 2013;41(2):445–456.
17. US Department of Health and Human Services, Food and Drug Administration. Guidance for industry: food-effect bioavailability and fed bioequivalence studies. 2002; https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070241.pdf. Accessed July 11, 2018.
18. European Medicines Agency, Committee for Human Medicinal Products (CHMP). Guideline on the investigation of drug interactions. 2012; https://www.ema.europa.eu/documents/scientific-guideline/guideline-investigation-drug-interactions_en.pdf. Accessed July 11, 2018.
19. Sahasrabudhe V, Saur D, Matschke K, et al. A phase 1, randomized, placebo- and active-controlled crossover study to determine the effect of single-dose ertugliflozin on QTc interval in healthy volunteers. *Clin Pharmacol Drug Dev*. 2018;7(5):513–523.
20. Kumar V, Liang Y, Matschke K, et al. A PK/PD study comparing twice-daily to once-daily dosing of ertugliflozin in healthy subjects. *Clin Pharmacol Ther*. 2017;101(S1):S71.
21. Fediuk DJ, Sweeney K, Zhou S, Kumar V, Sahasrabudhe V. Population pharmacokinetic model for ertugliflozin in healthy subjects with type 2 diabetes mellitus. *American Conference on Pharmacometrics (ACoP8) October 15-18, 2017; Fort Lauderdale, FL*; http://www.go-acop.org/assets/Legacy_ACOPs/ACOP8/Abstracts/M-035.pdf. Accessed July 11, 2018.
22. Bergman A, Ebel D, Liu F, et al. Absolute bioavailability of sitagliptin, an oral dipeptidyl peptidase-4 inhibitor, in healthy volunteers. *Biopharm Drug Dispos*. 2007;28(6):315–322.
23. Sambol NC, Brookes LG, Chiang J, et al. Food intake and dosage level, but not tablet vs solution dosage form, affect the absorption of metformin HCl in man. *Br J Clin Pharmacol*. 1996;42(4):510–512.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.