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Bioequivalence of Metformin in Ertugliflozin/Metformin Fixed-Dose Combination Tablets to Canadian-Sourced Metformin Coadministered With Ertugliflozin Under Fasted and Fed States

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Abstract

A fixed-dose combination (FDC) product of a selective sodium-glucose cotransporter 2 inhibitor ertugliflozin and immediate-release metformin is approved for type 2 diabetes mellitus in the United States, European Union countries, Canada, and other countries. Two studies were conducted to assess the bioequivalence of metformin in the ertugliflozin/metformin FDC tablets to the corresponding doses of Canadian-sourced metformin (Glucophage) coadministered with ertugliflozin. Both studies were phase 1 randomized, open-label, 2-period, single-dose crossover studies (n = 32) in which healthy subjects received an ertugliflozin/metformin FDC tablet (2.5/500 mg or 7.5/850 mg) and the respective doses of the individual components (ertugliflozin coadministered with Canadian-sourced metformin) under fasted (n = 18) or fed (n = 14) conditions. Blood samples were collected 72 hours postdose to determine metformin concentrations. The 90% confidence intervals were within the bioequivalence acceptance criteria for the adjusted geometric mean ratios (FDC:coadministered) for metformin area under the plasma concentration-time curve from time zero to time t, where t is the last point with a measurable concentration and peak observed plasma concentration for both dose strengths under fasted and fed conditions. All study medications were well tolerated. Bioequivalence was demonstrated for the metformin component of the ertugliflozin/metformin FDC tablets and the corresponding doses of the Canadian-sourced metformin coadministered with ertugliflozin.

Keywords

bioequivalence, diabetes, fixed-dose combination, metformin, sodium-glucose cotransporter 2 inhibitor

Ertugliflozin is an oral selective inhibitor of sodium-glucose cotransporter 2 (SGLT2) that acts by preventing renal glucose reabsorption, resulting in urinary glucose excretion and thereby reducing plasma glucose and glycated hemoglobin (Hb_{A1c}) levels in patients with type 2 diabetes (T2DM).[1-4] Ertugliflozin is approved in the United States, European Union countries, Canada, and other countries. Phase 3 studies have demonstrated that ertugliflozin—administered either as monotherapy or added to metformin alone or in addition to sitagliptin—provides clinically meaningful glycemic control and reduction in systolic blood pressure and body weight.[5–14]

A single oral dose of ertugliflozin is absorbed with a time to maximum plasma concertation (T_{max}) of 1 hour (fasted) to 2 hours (fed) and a terminal half-life ($t_{\frac{1}{2}}$)

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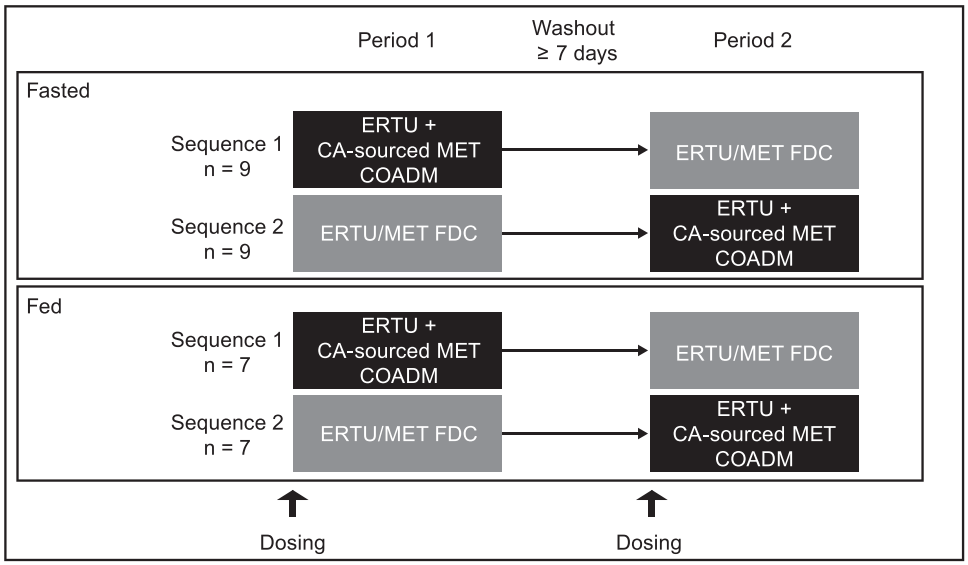

Figure 1. Treatment sequence for each study. CA, Canadian; COADM, coadministered; ERTU, ertugliflozin; FDC, fixed-dose combination; MET metformin.

of 11-17 hours.[1,15] Ertugliflozin demonstrates ~100% absolute bioavailability and a dose-proportional increase in exposure within the tested dose range of 0.5-300 mg[1]; the pharmacokinetics (PK) of ertugliflozin are comparable in healthy people and patients with T2DM.[16] Ertugliflozin is categorized as a Biopharmaceutics Classification System (BCS) class I compound based on high solubility and high permeability characteristics.[17,18] Food has no clinically meaningful effect on ertugliflozin PK, and, therefore, it can be taken without regard to meals.[15] Ertugliflozin also exhibited time-independent PK, and steady-state concentrations were achieved by 4 to 6 days after initiation of once-daily dosing, consistent with its half-life.[19] Ertugliflozin is primarily metabolized via the glucuronidation pathway (86%) to 2 principal pharmacologically inactive glucuronide metabolites, M5a and M5c, which account for ~37% of the dose recovered in urine; oxidation plays a minor role (12%) in the metabolism of ertugliflozin.[20] There is negligible renal excretion of ertugliflozin (~1.5% of the oral dose),[20] and no clinically meaningful effect on ertugliflozin PK was observed in patients with renal impairment[16] or in patients with mild or moderate hepatic impairment.[21] Drug interaction studies assessing ertugliflozin being coadministered with sitagliptin, metformin, glimepiride, or simvastatin did not show any clinically relevant interactions, and, therefore, these drugs can be safely coadministered with ertugliflozin without the need for dose adjustment.[19]

Metformin is the most commonly used first-line treatment for patients with T2DM.[22] Metformin, a biguanide, improves glycemic control by lowering hepatic glucose production as well as glucose absorption and improving insulin-mediated glucose uptake and utilization.[23] Metformin uptake in the liver is mostly mediated by organic cation transporter (OCT) 1 and possibly OCT3.[24] Metformin is excreted by human ortholog multidrug and toxin extrusion (MATE) transporters (MATE1 and MATE2-K).[24] Under fasting conditions, the bioavailability of metformin is ~50% to 60%.[25] It is not highly bound to protein,[26] and following oral administration, the renal system eliminates 90% of the absorbed drug within the first 24 hours, with an elimination half-life of 6.2 hours in plasma and ~17.6 hours in blood.[27]

Combined administration of ertugliflozin and metformin, with their different and complementary mechanisms of action, can provide incremental improvement in glycemic control in patients with T2DM compared with either agent alone.[7] Fixed-dose combinations (FDCs) of ertugliflozin and immediate-release metformin are in use in the United States, European Union countries, Canada, and other countries. Six ertugliflozin/metformin FDC strengths were developed, with tablets containing ertugliflozin/metformin 2.5/500, 2.5/850, 2.5/1000, 7.5/500, 7.5/850, and 7.5/1000 mg. Immediate-release metformin should be given in divided doses and is typically dosed twice daily; therefore, ertugliflozin/metformin FDC containing immediate-release form of metformin is dosed twice daily as well. Consequently, 2.5 and 7.5 mg twice-daily doses of ertugliflozin, which is half the approved once-daily doses, were used for the FDC formulation. To bridge phase 3 efficacy and safety data of ertugliflozin and metformin[7] with the FDC tablet formulation, 4

Table 1. Demographic Characteristics

Characteristic	Metformin 500 mg With Ertugliflozin 2.5 mg			Metformin 850 mg With Ertugliflozin 7.5 mg		
	Fasted (n = 18)	Fed (n = 14)	Total (N = 32)	Fasted (n = 18)	Fed (n = 14)	Total (N = 32)
Sex, n						
Male	8	7	15	11	5	16
Female	10	7	17	7	9	16
Age, years						
Mean (SD)	34.5 (7.2)	33.3 (8.2)	34.0 (7.6)	35.8 (8.0)	34.2 (8.1)	35.1 (7.9)
Range	24-47	20-47	20-47	23-53	25-51	23-53
Race, n						
White	4	0	4	3	1	4
Black	8	11	19	11	11	22
Other	6	3	9	4	2	6
Weight, kg						
Mean (SD)	69.5 (11.6)	73.9 (13.8)	71.4 (12.6)	77.7 (13.3)	72.8 (11.4)	75.5 (12.6)
Range	50.7-90.1	50.6-94.8	50.6-94.8	57.3-99.9	54.9-89.6	54.9-99.9
BMI, kg/m^2						
Mean (SD)	25.1 (3.1)	26.2 (2.8)	25.6 (3.0)	26.7 (2.9)	25.1 (2.9)	26.0 (3.0)
Range	19.4-29.3	21.1-29.6	19.4-29.6	21.0-30.0	20.0-28.9	20.0-30.0

BMI, body mass index; N, number of subjects in the study; n, number of subjects in a cohort; SD, standard deviation.

crossover phase 1 single-dose studies that were randomized and open-label with 2 periods and 2 sequences were conducted in healthy participants in the fasted state and demonstrated the bioequivalence of ertugliflozin and metformin in the ertugliflozin/metformin FDC tablets at doses of 2.5/500, 7.5/850, or 7.5/1000 mg to the corresponding doses of the individual components (United States- or European Union-sourced metformin [Glucophage]) when coadministered with ertugliflozin.[28]

Here we report 2 additional phase 1 randomized, open-label, 2-period, 2-sequence, single-dose crossover studies in healthy participants to assess the bioequivalence of the metformin component in the ertugliflozin/metformin FDC tablets at doses of 2.5/500 or 7.5/850 mg compared with the respective doses of Canadian-sourced metformin (Glucophage)—hereafter, referred to as metformin coadministered with ertugliflozin. As metformin has nonlinear PK with saturable absorption and dose-dependent absolute bioavailability that decreases with increasing dose,[25] the bioequivalence studies were conducted with the lower 2 doses of metformin (500 and 850 mg) in both fed and fasted conditions as per Health Canada guidance.[29] As a 1000-mg strength of the reference metformin product is not available in Canada, a bioequivalence study for the FDC containing 1000 of mg metformin was not conducted. Bioequivalence of the ertugliflozin component was not evaluated in these studies, as bioequivalence of ertugliflozin in the ertugliflozin/metformin FDC has already been established at 2.5- and 7.5-mg doses of ertugliflozin when coadministered with either 500, 850, or 1000 mg metformin.[28] Ertugliflozin also meets requirements for biowaiver as a BCS class I drug. In addition, there are no clinical drug-drug interactions between ertugliflozin and metformin.[19] Therefore, the studies reported here only assess the bioequivalence of the metformin component of the FDC relative to innovator reference metformin product sourced from Canada. The FDC tablets and the coadministered individual tablets were also assessed for safety and tolerability as part of the studies.

Methods

Study Conduct

Two phase 1 randomized, open-label, 2-period, 2-sequence, single-dose crossover studies were conducted in healthy participants (32 subjects enrolled in each study). Both studies were conducted in compliance with the ethical principles of the Declaration of Helsinki and in compliance with all International Conference on Harmonisation Good Clinical Practice guidelines. Signed and dated informed consent was obtained from all subjects. The studies were conducted at the Pfizer Clinical Research Unit in New Haven, Connecticut. The final protocol and informed consent document were reviewed and approved by IntegReview Ethical Review Board, Austin, Texas

Study Design and Treatment

During each study subjects underwent 1 screening visit and 2 study treatment periods. Screening took place in

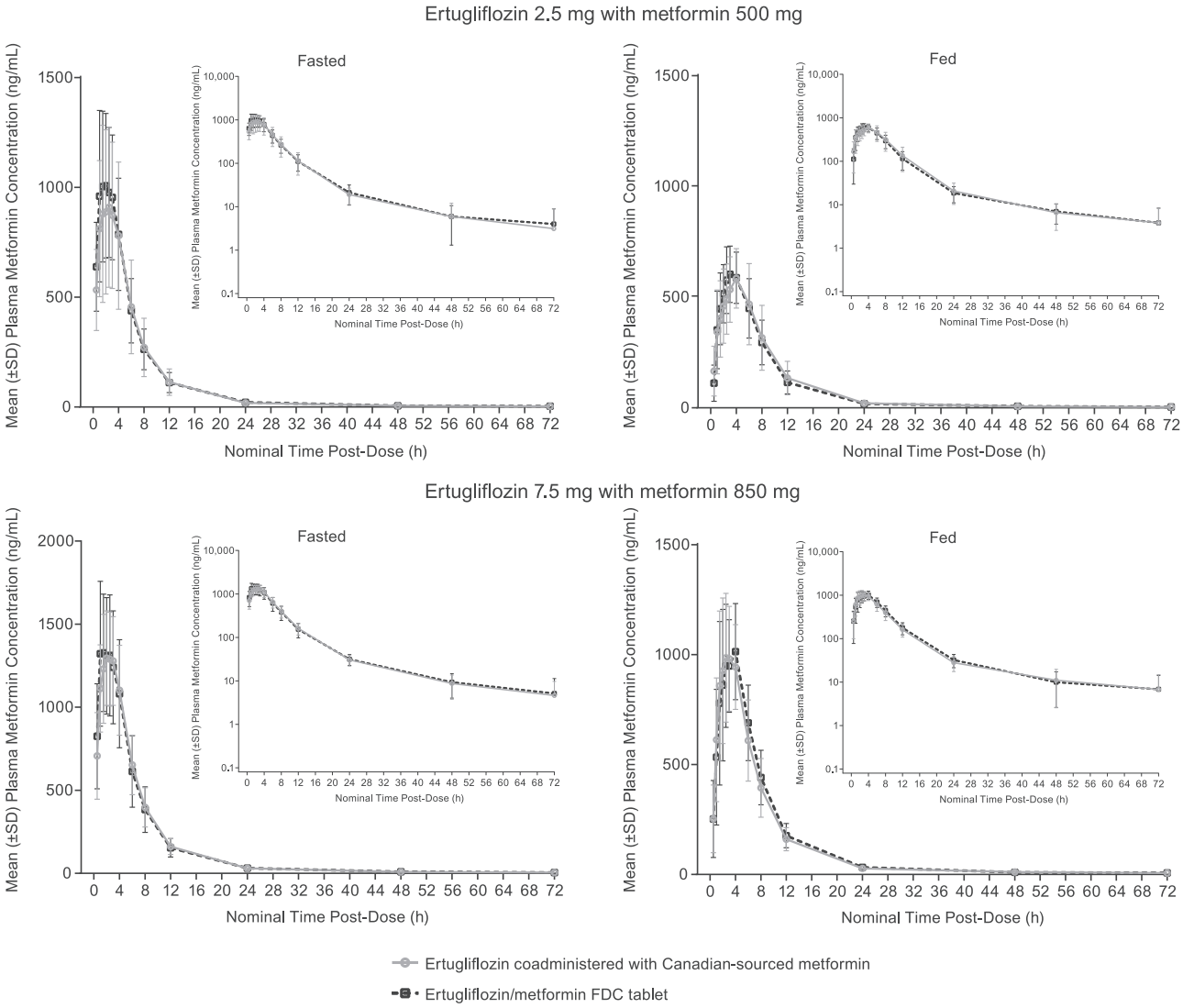

Figure 2. Mean (standard deviation [SD]) plasma metformin concentration-time profiles in linear (principal plot) with semilogarithmic (inset plot) scales following single oral dose of ertugliflozin coadministered with Canadian-sourced metformin (Glucophage) or as a fixed-dose combination (FDC) under fasted or fed conditions. Note: Samples below the lower limit of quantification were set to 0 in the calculation of summary statistics and for pharmacokinetic analysis.

period 1 within 28 days of the first dose of the study medication. All the study participants were admitted to the clinical research unit on day 0 of each period prior to dosing. A single dose of the ertugliflozin/metformin FDC tablet (2.5/500 or 7.5/850 mg) or the respective doses of the individual components (ertugliflozin 2.5 or 7.5 mg coadministered with metformin 500 or 850 mg, respectively) were administered according to 1 of 2 sequences in a crossover design, under fasted or fed conditions as required under Health Canada guidance (Figure 1).[29] A washout period of $\geq$ 7 days separated dosing between consecutive crossover periods. A single tablet of the ertugliflozin/metformin FDC was administered. Similarly, a single tablet of metformin 500- and 850-mg doses and the ertugliflozin 2.5-mg dose were coadministered, whereas the ertugliflozin 7.5-mg dose was administered as one 5-mg and one 2.5-mg tablet.

Fasted subjects (n = 18) received study medication after a minimum 10-hour fast, and food was not allowed for 4 hours postdose. Fed subjects (n = 14) received a standard high-fat, high-calorie breakfast after a minimum 10-hour fast. Participants received study medication ~30 minutes after the start of the breakfast, which was consumed within 25 minutes. Additional food was not permitted for at least 4 hours postdose. All participants were requested to not lie down or drink liquid other than water for the first 4 hours postdose. Water was also not allowed 1 hour predose and 1 hour after administering study medication (except for the liquid consumed with the medica-

Table 2. Descriptive Summary of Plasma Metformin PK Parameter Values Under Fasted or Fed Conditions

	Metformin PK Parameter Summary Statistics[a]			
	Fasted		Fed	
	Metformin 500 mg With Ertugliflozin 2.5 mg		Metformin 500 mg With Ertugliflozin 2.5 mg	
Parameter	FDC	Coadministered	FDC	Coadministered
N, n	18, 14	18, 13	14, 8	14, 9
AUC_{inf}	6945 (27) 7198 ± 2151.6	6904 (31) 7202 ± 2197.6	5259 (24) 5388 ± 1227.8	5085 (29) 5268 ± 1482.4
AUC_{last}	6746 (27) 6993 ± 2059.9	6316 (34) 6653 ± 2222.0	5158 (23) 5284 ± 1192.5	5228 (28) 5409 ± 1434.5
C_{max}	1096 (30) 1144 ± 364.33	1012 (34) 1067 ± 376.06	641.7 (20) 652.6 ± 121.27	632.5 (19) 642.5 ± 118.21
T_{max}	2.00 (1.00-3.02)	2.00 (0.5-4.07)	3.00 (1.00-6.00)	4.00 (1.00-6.02)
$t_{\frac{1}{2}}$	14.21 ± 13.71	8.67 ± 5.069	15.44 ± 11.69	13.06 ± 11.27
	Metformin 850 mg With Ertugliflozin 7.5 mg		Metformin 850 mg With Ertugliflozin 7.5 mg	
	FDC	Coadministered	FDC	Coadministered
N, n	18, 15	18, 15	14, 9	14, 9
AUC_{inf}	9477 (26) 9763 ± 2484.1	9669 (15) 9769 ± 1465.2	8235 (27) 8507 ± 2488.2	8802 (27) 9073 ± 2371.0
AUC_{last}	9340 (26) 9641 ± 2516.2	9446 (18) 9590 ± 1731.8	8357 (21) 8525 ± 1797.9	7898 (23) 8096 ± 1875.0
C_{max}	1453 (28) 1506 ± 425.04	1437 (16) 1455 ± 244.93	1073 (23) 1099 ± 253.14	1088 (24) 1117 ± 262.73
T_{max}	2.00 (1.00-3.02)	2.01 (1.00-4.00)	3.53 (1.03-4.10)	2.52 (1.02-4.03)
$t_{\frac{1}{2}}$	16.69 ± 11.55	16.54 ± 12.33	16.05 ± 11.59	22.03 ± 16.75

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 $t_{\frac{1}{2}}$ and AUC_{inf}; PK, pharmacokinetics; SD, standard deviation; $t_{\frac{1}{2}}$, terminal half-life; T_{max}, time to maximum plasma concentration.

PK parameter units are as follows: AUC_{inf} and AUC_{last}, ng·h/mL; C_{max}, ng/mL; T_{max} and $t_{\frac{1}{2}}$, hours.

[a] Values are geometric mean (geometric %CV) and arithmetic mean ± SD except for $t_{\frac{1}{2}}$, which is only arithmetic mean ± SD, and T_{max} which is median (range).

tion for the fed cohort and water given with the study medication).

Subjects

Healthy subjects (female and male) aged between 18 and 55 years with a body mass index of 18.5-30 kg/m^2 and total body weight > 50 kg were eligible for inclusion. "Healthy" was defined as lack of any clinically relevant abnormalities identified through a detailed medical history/full physical examination, which included monitoring blood pressure and pulse rate, 12-lead electrocardiogram, and clinical laboratory tests. The main exclusion criteria included a positive urine test for drugs of abuse or illicit drug substances; any history within 6 months of screening for alcohol abuse or binge drinking and/or any other illicit drug use or dependence; any clinical signs of a significant malabsorption condition; an estimated glomerular filtration rate < 80 mL/min/1.73 m^2, based on the 4r-variable Modification of Diet in Renal Disease equation[30]; known hypersensitivity or intolerance to any SGLT2 inhibitor or metformin; and pregnant or breastfeeding women.

Pharmacokinetic Assessments

Serial blood samples for PK analysis of metformin were obtained from each subject predose (0 hours) and up to 72 hours postdose in each period. Under fed conditions, predose PK samples were collected prior to consumption of the high-fat breakfast. Plasma samples were analyzed for metformin concentrations at WuXi AppTec (Shanghai, China) using a validated, sensitive, and specific high-performance liquid chromatography-tandem

Table 3. Statistical Summary of Treatment Comparisons Between the Metformin Component of the Ertugliflozin/Metformin FDC Versus Individual Components Administered Under Fasted or Fed Conditions

		Metformin FDC:coadministered GMR (90%CI)[a]	
Treatment Comparison	Condition	AUC_{last}	C_{max}
Ertugliflozin/metformin 2.5/500 mg FDC versus coadministered	Fasted	106.80 (96.17-118.61)	108.27 (95.69-122.50)
	Fed	98.65 (92.79-104.87)	101.46 (97.54-105.52)
Ertugliflozin/metformin 7.5/850 mg FDC versus coadministered	Fasted	98.87 (91.88-106.40)	101.13 (90.58-112.92)
	Fed	105.80 (95.99-116.62)	98.67 (91.50-106.40)

AUC_{last}, area under plasma concentration-time profile from time 0 to time of last quantifiable concentration; C_{max}, maximum observed plasma concentration; CI, confidence interval; C_{max}, maximum observed plasma concentration; FDC, fixed-dose combination; GMR, geometric mean ratio.
[a] Ratios (90%CIs) are expressed as percentages.

mass spectrometry method, as published previously.[19] Calibration standard responses were linear for metformin over the range of 2.00 to 1000 ng/mL using a weighted (1/concentration^2) linear least-squares regression. The lower limit of quantification (LLOQ) for metformin was 2.00 ng/mL. The assay accuracy and precision of analysis runs met acceptance criteria. All the sample reproducibility tests passed the acceptance criteria. Assay precision and accuracy data for metformin concentrations for each study are provided in Table S1.

Safety Assessments

Safety assessments were conducted at screening and throughout the duration of the study. These assessments included adverse events (AEs), blood pressure, pulse rate, physical examination, and clinical laboratory parameters. Subjects were followed up with a phone call 14 ± 3 days after the last dose of study treatment in period 2 was administered to assess for AEs. AEs were classified using the Medical Dictionary for Regulatory Activities (version 19.0) dictionary.

Statistical Analysis

PK parameters were assessed for each subject under fasted or fed conditions using noncompartmental analysis of plasma concentration-time data. These included area under the plasma concentration-time curve (AUC) from time 0 to infinite time (AUC_{inf}), AUC from time 0 to last quantifiable concentration (AUC_{last}, primary end point), maximum observed plasma concentration (C_{max}, primary end point), time for C_{max} (T_{max}), and terminal half-life ($t_{\frac{1}{2}}$). Samples below the LLOQ were set to 0 in the calculation of summary statistics and for PK analysis. Natural log-transformed AUC_{last} and C_{max} values for metformin were calculated for fasted and fed cohorts using a mixed-effects model that included sequence, period, and treatment as fixed effects and subject within sequence as a random effect. Estimates for the adjusted (least-squares) mean differences and 90% confidence intervals (CIs) and estimates of the ratio of adjusted geometric means (test:reference [FDC:coadministered]) and 90%CI for the ratio were obtained using previously described methods.[28] For each FDC strength, the FDC tablet will be considered bioequivalent to coadministration if the 90%CIs for the geometric mean ratios (GMRs) for metformin AUC_{last} and C_{max} fell within 80% and 125%. PK parameters were calculated using electronic noncompartmental analysis (eNCA, version 2.2.4), a Pfizer internally validated software.

A sample size of 16 subjects per study was estimated to provide 91.5% power that the 90%CI for the ratio of the GMR would lie within the acceptance criteria for each of the metformin PK parameters (AUC_{last} and C_{max}) in the fasted state. A sample size of 12 subjects per study was estimated to provide 95.7% power that the 90%CI for the ratio of the GMR would lie within the acceptance region for each of the metformin PK parameters (AUC_{last} and C_{max}) in the fed state. The sample size calculations assumed a true GMR of 1.05 and were based on estimates of within-subject standard deviations (SDs) of 0.1563 and 0.1190 for metformin AUC_{last} in the fasted and fed states, respectively. These estimates were obtained from past crossover studies conducted by Pfizer Inc and/or Merck & Co., Inc., Kenilworth, New Jersey.

Results

Study Subjects

A total of 32 subjects (18 in the fasted condition and 14 in the fed condition) were enrolled in each study; all participants completed the study and were included in both the PK and safety analyses. The demographic

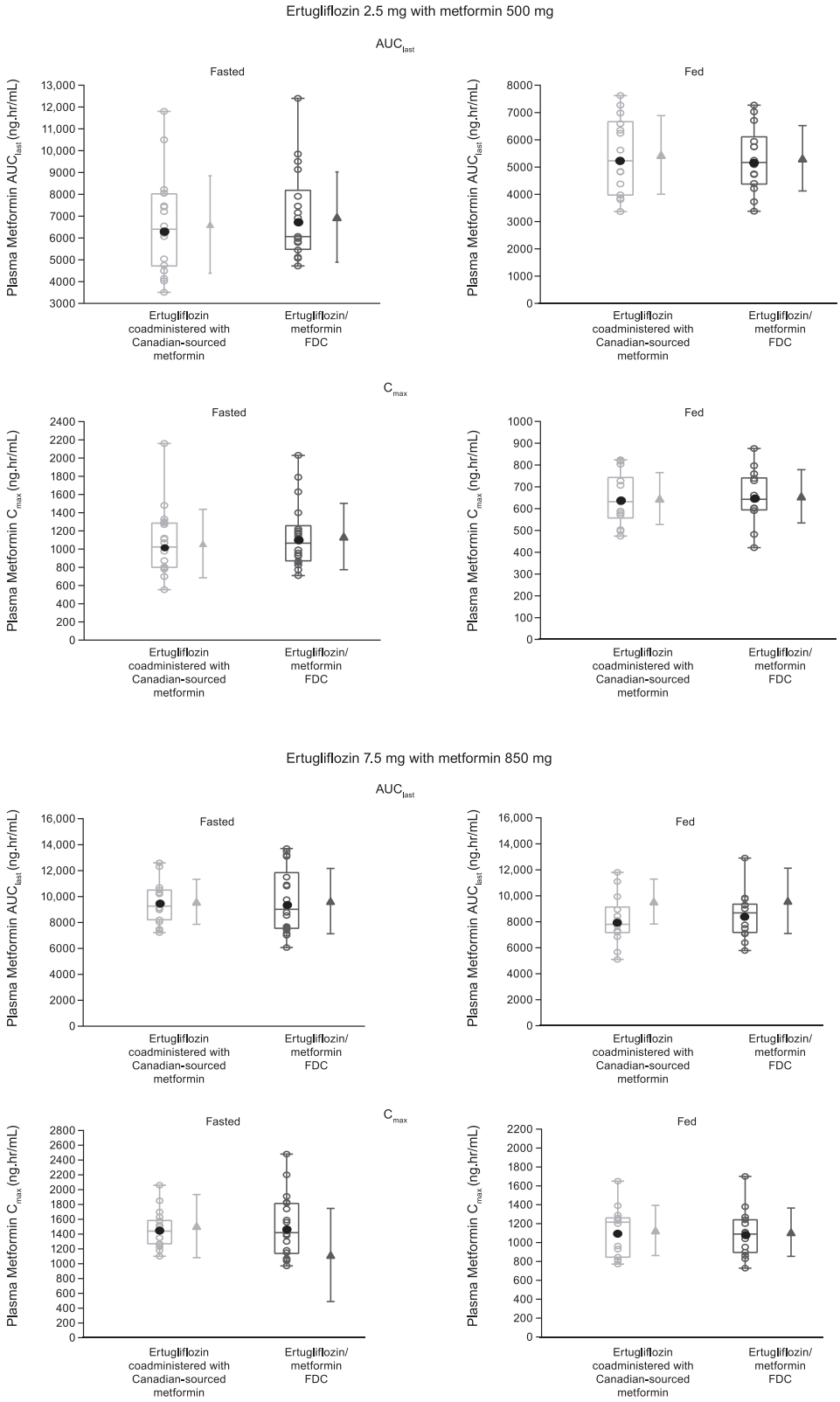

Figure 3. Individual values and geometric and arithmetic means of plasma metformin AUC_{last} and C_{max} following a single oral dose of ertugliflozin coadministered with Canadian-sourced metformin (Glucophage) or as a fixed-dose combination (FDC) under fasted or fed conditions. Open circles identify individual subject data, and closed circles identify geometric means. Offset closed triangles identify arithmetic mean (with standard deviation). Box plots provide medians and 25% and 75% quartiles, with whiskers extended to the minimum/maximum values. AUC_{last}, AUC from time 0 to last quantifiable concentration; C_{max}, maximum observed plasma concentration.

and baseline characteristics of the study populations are shown in Table 1. In each study, the majority of subjects were black (59%-69%). In general, the baseline demographics and characteristics were well balanced between the fasted and fed cohorts within each study.

Pharmacokinetic Assessments

Mean plasma concentration-time profiles for metformin were nearly superimposable following administration of the FDC formulations and coadministration of the respective individual components under fasted or fed conditions (Figure 2). A descriptive summary of plasma metformin PK parameter values is provided in Table 2. The arithmetic and geometric means for metformin AUC_{inf}, AUC_{last}, and C_{max} were similar between the FDC and the corresponding coadministered tablets for each of the dose combinations studied under either fasted or fed conditions. For each treatment (FDC and coadministered tablets), metformin median T_{max} was 2 hours under fasted conditions and ranged from 2.5 to 4 hours under fed conditions. Similarly, metformin mean $t_{\frac{1}{2}}$ ranged from 8.7 to 16.7 hours under fasted conditions and from 13.1 to 22 hours under fed conditions across the 2 studies.

Treatment comparisons for the ertugliflozin/metformin FDCs and coadministration of individual components are summarized in Table 3. The GMRs (90%CIs) (test:reference [FDC:coadministered]) of metformin AUC_{last} and C_{max} for both dose strengths under fasted or fed conditions fell within the bioequivalence acceptance criteria (80%-125%), indicating lack of any meaningful differences in the metformin component of the ertugliflozin/metformin FDC tablets with metformin (500 or 850 mg) coadministered with ertugliflozin (2.5 or 7.5 mg) in either study. Individual values and geometric means of metformin AUC_{last} and C_{max} for both dose strengths under fasted or fed conditions are shown in Figure 3.

Safety

There were no reports of deaths, serious AEs, severe AEs, temporary or permanent discontinuations, or dose reductions because of AEs following administration of a single oral dose of ertugliflozin and metformin as an FDC or when coadministered as individual components. Incidence of treatment-emergent AEs was similar when treatment was administered as the FDC tablet and when coadministered as individual components. Gastrointestinal (GI) events and headache were the most commonly reported AEs. A total of 7 subjects assigned to an FDC reported GI events (1 in ertugliflozin/metformin 2.5/500 mg fed, 2 in ertugliflozin/metformin 2.5/500 mg fasted, 3 in ertugliflozin/metformin 7.5/850 mg fed, 1 in ertugliflozin/metformin 7.5/850 mg fasted), and 14 subjects with concomitant administration (1 in ertugliflozin/metformin 2.5/500 mg fed, 3 in ertugliflozin/metformin 2.5/500 mg fasted, 7 in ertugliflozin/metformin 7.5/850 mg fed, 3 in ertugliflozin/metformin 7.5/850 mg fasted). Headache was reported by a total of 4 subjects assigned to FDC (2 in ertugliflozin/metformin 2.5/500 mg fed, 2 in ertugliflozin/metformin 7.5/850 mg fed) and 2 subjects with concomitant administration (2 in ertugliflozin/metformin 2.5/500 mg fed). Most reported AEs were of mild intensity, except for 6 events of moderate intensity. Five of these moderate AEs were reported by subjects assigned to an FDC: headache (1 in ertugliflozin/metformin 2.5/500 mg fasted, 2 in ertugliflozin/metformin 7.5/850 mg fed), constipation (1 in ertugliflozin/metformin 7.5/850 mg fed), and nausea (1 in ertugliflozin/metformin 2.5/500 mg fasted). There were no clinically significant laboratory abnormalities or changes in blood pressure or pulse rate.

Discussion

The main purpose of the 2 studies reported here was to demonstrate the bioequivalence of the metformin component in ertugliflozin/metformin FDC tablets (2.5/500 or 7.5/850 mg) to metformin 500 or 850 mg coadministered with 2.5 or 7.5 mg ertugliflozin, respectively, under fasted and fed conditions to support the registration of the FDC tablets in Canada.

Bioequivalence of both the 500- and 850-mg doses of metformin in the FDC to the respective doses of metformin was demonstrated under both fasted and fed conditions, as the 90%CIs of the GMRs of AUC_{last} and C_{max} for metformin fell within the acceptable range of 80%-125%. In addition, multimedia dissolution tests showed that both FDC tablets (2.5/500 or 7.5/850 mg) dissolved rapidly, showing > 85% release in 15 minutes.[28] Therefore, both strengths of the ertugliflozin/metformin FDC tablets (2.5/500 and 7.5/850 mg) can be considered bioequivalent to the respective strengths of ertugliflozin and metformin when coadministered.

Metformin exhibits nonlinear PK following single-dose administration because of saturable absorption,[25] resulting in a less than proportional increase in exposure with increasing dose.[25] Therefore, a single-dose study using the lower 2 doses of metformin (500 and 850 mg) under fasted or fed conditions was chosen for these studies as per Health Canada Guidance[29] to demonstrate the bioequivalence of the metformin component in the FDC tablets to the respective strengths of metformin. A phase 1 study on the effect of food on the ertugliflozin/metformin FDC (7.5/1000 mg)

indicated that food had no clinically relevant impact on the PK of the FDC or the individual components.[15]

Bioequivalence of ertugliflozin and metformin at various strengths of the ertugliflozin/metformin tablet and coadministration of individual components (ertugliflozin coadministered with either US-sourced or EU-sourced Glucophage) was demonstrated in 4 pivotal BE studies.[28] As the reference and test treatments for ertugliflozin in the studies presented here are the same as were used in 4 pivotal studies conducted earlier (in which bioequivalence was demonstrated), blood samples for assessing ertugliflozin were not collected, and bioequivalence of the ertugliflozin component was not evaluated.

The standard dose regimen for ertugliflozin is once-daily dosing; however, as the ertugliflozin/metformin FDC tablet contains an immediate-release formulation of metformin, which is usually dosed twice daily, the recommended dosing of the FDC tablet is also twice daily. A phase 1 PK/PD study evaluating ertugliflozin exposure as assessed by AUC over 24 hours (AUC_{24}) and urine glucose excretion over 24 hours (UGE_{24}) at steady state demonstrated equivalence of AUC_{24} and similarity of UGE_{24} at the same total daily dose of ertugliflozin, regardless of whether ertugliflozin was dosed once daily or twice daily (2.5 mg twice daily vs 5 mg once daily and 7.5 mg twice daily vs 15 mg once daily).[31] These data support administration of ertugliflozin in divided doses twice daily as a component of the ertugliflozin/metformin FDC.

The bioequivalence results from the 2 current phase 1 studies, together with the demonstrated glycemic efficacy of coadministration of ertugliflozin and metformin in the VERTIS MET study,[7] suggest that the FDC formulation of ertugliflozin and metformin will provide an incremental benefit in T2DM patients who are not adequately controlled on metformin monotherapy. The ertugliflozin/metformin FDC formulation might be preferred by many patients owing to the convenience of combination treatment without the need to coadminister 2 separate tablets. In addition, the FDC tablets were generally well tolerated in the 2 studies reported here. The observed gastrointestinal-related AEs may have been because of metformin, as these are some of the commonly observed AEs reported with the use of metformin.[32]

Conclusion

In summary, the studied doses of the metformin component of the ertugliflozin/metformin FDC tablets (ertugliflozin 2.5/metformin 500 mg and ertugliflozin 7.5/metformin 850 mg) are bioequivalent to the respective doses of metformin when coadministered with ertugliflozin under fasted or fed conditions. Ertugliflozin plus metformin either coadministered as the FDC tablet or as individual tablets under fasted or fed conditions was safe and well tolerated in healthy subjects. These results support bridging of PK, pharmacodynamics, safety, and efficacy data gathered through the phase 3 VERTIS MET[7] study, which include ertugliflozin/metformin FDC tablets of various strengths.

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Conflicts of Interest

Vikas Kumar Dawra, Kathleen Pelletier, Kyle Matschke, Haihong Shi, Anne Hickman, and Vaishali Sahasrabudhe are employees of Pfizer Inc., New York, New York, and may own shares/stock options in Pfizer Inc. Susan Zhou is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, and may own stock in Merck & Co., Inc., Kenilworth, New Jersey. Rajesh Krishna was an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, at the time the studies were conducted.

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Data-Sharing Statement

On 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 United States and/or European Union 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 de-identified 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 requesters must enter into a data access agreement with Pfizer.

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Supplemental Information

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