Clinical Pharmacology in Drug Development
2019, 8(7) 884–894

DOI: 10.1002/cpdd.722

Bioequivalence of Ertugliflozin/Sitagliptin Fixed-Dose Combination Tablets and Coadministration of Respective Strengths of Individual Components

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Abstract

A fixed-dose combination (FDC) tablet of ertugliflozin, a selective inhibitor of sodium-glucose cotransporter 2, and sitagliptin, a dipeptidyl peptidase-4 inhibitor, was developed for the treatment of patients with type 2 diabetes mellitus. Four studies were conducted under fasted conditions to demonstrate bioequivalence of ertugliflozin/sitagliptin FDC tablets and individual components at respective strengths when coadministered in healthy subjects. All studies had open-label, randomized, 2-period, 2-sequence, single-dose crossover designs. In each study 18 or 19 subjects were enrolled and received an ertugliflozin/sitagliptin FDC tablet (5 mg/50 mg, 5 mg/100 mg, 15 mg/50 mg, or 15 mg/100 mg) and corresponding strengths of ertugliflozin and sitagliptin coadministered as individual components. For both ertugliflozin and sitagliptin, the 90%CIs for the ratio (FDC:coadministration) of geometric means for area under the plasma concentration-time profile from time 0 extrapolated to infinite time, and maximum observed plasma concentration, were within acceptance criteria for bioequivalence (80% to 125%). All adverse events were mild in intensity. The 4 studies demonstrated that each strength of FDC tablet is bioequivalent to the respective dose of coadministered individual components. This indicates that the known efficacy and tolerability of ertugliflozin and sitagliptin when coadministered can be translated to the use of a FDC formulation.

Keywords

bioequivalence, ertugliflozin, fixed-dose combination, sitagliptin

Diabetes mellitus is a highly prevalent disease with significant global health and economic burden that is projected to affect 642 million people worldwide by the year 2040.[1] Type 2 diabetes mellitus (T2DM) accounts for about 90% to 95% of all cases of diabetes mellitus in the United States.[2]

Ertugliflozin (PF-04971729, MK-8835) is a selective inhibitor of the sodium-glucose cotransporter 2 (SGLT2) for the treatment of adult patients with T2DM.[3] SGLT2 inhibitors reduce renal glucose reabsorption and lower the renal threshold for glucose excretion, thereby increasing urinary glucose excretion and reducing plasma glucose and glycated hemoglobin (A_{1c}).[4,5] Oral absorption of ertugliflozin is rapid, with median time to maximum plasma concentration (T_{max}) occurring at ~1 hour postdose in the fasted state and at ~2 hours postdose in the fed state.[6] The area under the plasma concentration-time curve (AUC) for

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Submitted for publication 31 August 2018; accepted 3 June 2019.

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ertugliflozin increases in a dose-proportional manner over the dose range of 0.5 to 300 mg.[7]

Absolute bioavailability of ertugliflozin is ~100%.[8] The terminal-phase half-life ($t_{½}$) is in the range of 11 to 17 hours.[7] After oral administration of a radioactive ertugliflozin dose, excretion of radioactivity in urine and feces accounted for 50.2% and 40.9% of the dose, respectively.[9] Renal excretion is not a major clearance pathway for ertugliflozin, as unmetabolized ertugliflozin accounts for only 1.5% of the administered dose recovered in urine.[9,10] The major biotransformation pathway for ertugliflozin is glucuronidation, catalyzed primarily by uridine diphosphate glucuronosyltransferase (UGT) isozyme UGT1A9 with minor contributions from UGT2B7.[7,9] The 3-O-β glucuronide (M5c) and 2-O-β glucuronide (M5a) (referred to as M4c and M4a in Miao et al) are considered the primary circulating metabolites of ertugliflozin; both metabolites are pharmacologically inactive.[9] Oxidative metabolism accounts for a minor metabolic pathway and is principally catalyzed by cytochrome P450 (CYP) isozymes CYP3A4 and CYP3A5.[9] Intrinsic factors including age, body weight, gender, race, UGT1A9 polymorphism, renal impairment, and mild or moderate hepatic impairment do not have clinically meaningful effects on the pharmacokinetics (PK) of ertugliflozin.[10–13] In vitro, ertugliflozin and its glucuronide metabolites do not inhibit or induce CYP enzymes or transporters.[14] Concomitant administration of UGT inhibitors and rifampin (a UGT and CYP inducer) does not have a clinically meaningful effect on the PK of ertugliflozin.[15,16] Ertugliflozin has no clinically meaningful PK interactions with commonly coadministered drugs such as sitagliptin, metformin, glimepiride, or simvastatin.[14] Overall, the potential for ertugliflozin to be a victim or perpetrator of clinically meaningful drug interactions is low.

Sitagliptin is a selective dipeptidyl peptidase-4 (DPP-4) inhibitor indicated for the treatment of patients with T2DM that has been shown to lower both fasting and postprandial glucose concentrations.[17] The improvements in glycemic control associated with sitagliptin are mediated by increases in active incretin hormones, glucagon-like peptide-1, and glucose-dependent insulinotropic polypeptide.[18,19] In healthy subjects AUC for sitagliptin increases in an approximately dose-dependent manner.[20] Sitagliptin is rapidly absorbed, with a median T_{max} between 1 and 4 hours and an apparent $t_{½}$ ranging from 8 to 14 hours.[20,21] Absolute bioavailability of sitagliptin is 87%, and it is excreted mostly unmetabolized in urine (87%) and feces (13%).[22,23] The oxidative metabolism of sitagliptin is primarily catalyzed by CYP3A4, with a minor contribution from CYP2C8.[23] Active tubular secretion appears to be involved in the renal elimination of sitagliptin, as its renal clearance is approximately 388 mL/min.[20] Consistent with its primarily renal elimination, renal function is the most significant factor impacting sitagliptin PK.[24] However, mild renal insufficiency (ie, creatinine clearance $\geq$50 mL/min and $<$80 mL/min) does not have a clinically meaningful impact on sitagliptin PKs; therefore, no dosage alteration is necessary.[24]

In phase 1 clinical pharmacology studies, sitagliptin was not found to meaningfully alter the PK of metformin, simvastatin, warfarin, oral contraceptives, rosiglitazone, or glyburide; these studies provide in vivo evidence for a low propensity of sitagliptin for perpetrating drug interactions with substrates of human organic cation transporter, CYP3A4, CYP2C8, and CYP2C9.[25–31] Multiple doses of sitagliptin slightly increased plasma immunoreactive digoxin concentrations; however, these increases are not considered likely to be clinically meaningful.[32] In a population PK analysis of phase 1 and phase 2b studies, 83 concomitantly administered medications were screened for potential effects on sitagliptin PK; none of the evaluated medications was found to meaningfully alter sitagliptin plasma concentrations.[33]

Both ertugliflozin and sitagliptin are class 1 drugs under the Biopharmaceutical Classification System.[34] The combination of these 2 antihyperglycemic agents, which have different but complementary mechanisms of action and favorable safety profiles, results in a more robust antihyperglycemic effect compared with administration of either agent alone.[35] This approach is presumed to have clinical benefits in patients with T2DM inadequately controlled with metformin monotherapy or would provide an alternative treatment regimen for patients who cannot tolerate metformin.

A phase 1 single-dose study demonstrated that no PK interactions were observed when ertugliflozin and sitagliptin were coadministered.[14] Phase 3 studies have shown that ertugliflozin alone or when added to metformin and sitagliptin reduces A_{1c}, body weight, and blood pressure (BP) in patients with T2DM.[35–40] In these studies the combination of ertugliflozin and sitagliptin was superior to the individual components or placebo in reducing A_{1c} and superior to sitagliptin alone in reducing systolic BP and body weight and was generally well tolerated.[35,36]

In order to bridge the efficacy and safety data from the phase 3 trials of ertugliflozin and sitagliptin coadministration to the fixed-dose combination (FDC) tablet, bioequivalence studies were required. Four studies were conducted. The selected fixed doses (ertugliflozin 5 mg + sitagliptin 50 mg, ertugliflozin 5 mg + sitagliptin 100 mg, ertugliflozin 15 mg + sitagliptin 50 mg, and ertugliflozin 15 mg + sitagliptin 100 mg) were chosen on the basis of the approved daily

dose of sitagliptin 100 mg as the highest indicated dose for patients with normal renal function and 50 mg for patients with T2DM and moderate renal insufficiency.[24] Ertugliflozin doses of 5 mg and 15 mg were selected as these were the ertugliflozin doses evaluated in phase 3 studies.[36–40]

The primary objective of these current studies was to demonstrate bioequivalence of the 4 strengths of ertugliflozin/sitagliptin FDC tablets to coadministration of the individual components at the respective strengths, under fasting conditions, in healthy subjects. The secondary objective was to evaluate the safety and tolerability of the FDC tablets and the coadministered individual tablets.

Methods

Study Design

Four phase 1, open-label, randomized, 2-period, single-dose crossover studies were conducted in healthy subjects. All 4 studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki, and in compliance with all International Conference on Harmonisation Good Clinical Practice Guidelines. The studies were conducted at a single site (Pfizer Clinical Research Unit, New Haven, Connecticut), and the final protocol and informed consent documentation were reviewed and approved by the Institutional Review Board at the clinical research unit. All participants provided signed and dated informed consent.

Each study consisted of a screening visit and 2 study treatment periods. Eligible subjects were admitted to the clinical research unit on day 0 of each treatment period and received a single dose of assigned treatment (FDC or coadministered tablets: ertugliflozin 5 mg + sitagliptin 50 mg, ertugliflozin 5 mg + sitagliptin 100 mg, ertugliflozin 15 mg + sitagliptin 50 mg, or ertugliflozin 15 mg + sitagliptin 100 mg) on day 1 after an overnight fast of at least 10 hours. Coadministered treatments were administered as tablets within 5 minutes of each other, and ertugliflozin was administered first. Subjects who received FDC tablets in period 1 were crossed over to coadministration in period 2, and vice versa. Dosing in consecutive crossover periods was separated by a washout period of at least 7 days.

In order to standardize the conditions on PK sampling days, all subjects were required to refrain from lying down, eating, or drinking beverages other than water during the first 4 hours after dosing. Water was withheld for 1 hour predose and 1 hour after treatment administration, except for the 240 mL administered with the study treatments. Ertugliflozin/sitagliptin FDC was administered as a single-dose tablet. When coadministered, sitagliptin 50-mg and 100-mg doses and ertugliflozin 5-mg doses were administered as single tablets, whereas the ertugliflozin 15-mg dose was administered as 1 × 10-mg and 1 × 5-mg tablet (in accordance with administration in phase 3 trials). Treatments were administered at approximately the same time of day in each period.

Subjects

The main inclusion criteria for the studies were healthy men or women, aged 18-55 years inclusive, with a body mass index of 17.5-30.5 kg/m^2 and total body weight >50 kg. Healthy participants were defined as having no clinically relevant abnormalities, as identified by a detailed medical history and full physical examination, including BP and pulse rate measurements, 12-lead electrocardiogram, and clinical laboratory tests.

The main exclusion criteria for the studies 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, calculated creatinine clearance <80 mL/min, known hypersensitivity or intolerance to any SGLT2 or DPP-4 inhibitor, and/or pregnant or breastfeeding women.

Assessments

Bioanalysis. Serial blood samples to obtain plasma for PK analysis were collected from each subject at predose (0 hours) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours postdose in each period. Plasma samples were analyzed for ertugliflozin (WuXi AppTec, Shanghai, China) and sitagliptin (inVentiv Health Clinique, Quebec City, Quebec, Canada) concentrations using validated, sensitive, and specific high-performance liquid chromatography–tandem mass spectrometry methodology. Calibration standard responses, using a weighted (1/concentration^2) linear least-squares regression, were linear for ertugliflozin and sitagliptin over the range of 0.500-500 ng/mL and 1.00-1000 ng/mL (2.46-2460 nM), respectively. The lower limit of quantification was 0.500 ng/mL for ertugliflozin and 1.00 ng/mL (2.46 nM) for sitagliptin. Matrix effects including hemolyzed and hyperlipidemic plasma, carryover, and selectivity using blank matrix or blank matrix with internal standard were tested during method validations. The methods were specific and selective to the analytes. There was no significant matrix effect or carryover for either assay. At least 10% of obtained samples were selected for reanalysis for each study. All reanalyzed sample results were less than ±15% different from the original value for both analytes.

Detailed methodology for the ertugliflozin assay procedure has been previously published.[41] Sitagliptin

was extracted from 100 μL human plasma by protein precipitation with acetonitrile.[42] Sitagliptin-d_4 was the labeled internal standard. The extracted sample was injected onto a Waters Atlantis HILIC Silica column 3 μm (2.1 mm × 50 mm) (Waters Corporation, Milford, Massachusetts). The mobile phase was acetonitrile/water (80/20, v/v) containing 10 mM NH_4Ac (pH 4.7), and 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→235 and m/z 412→239 for sitagliptin and sitagliptin-d_4, respectively. Between-day assay precision and accuracy data for ertugliflozin and sitagliptin plasma concentrations for each study are shown in Supplementary Table 1.

Pharmacokinetics. The following PK parameters were calculated for each subject for each treatment using standard noncompartmental analysis of plasma concentration-time data: peak concentration (C_{max}), time to C_{max} (T_{max}), AUC from time 0 extrapolated to infinite time (AUC_{inf}), AUC from time 0 to the time of the last quantifiable concentration (AUC_{last}), and $t_{½}$. Samples below the lower limit of quantification were set to 0 for analysis. PK parameter values were calculated using a Pfizer-validated software system, electronic noncompartmental analysis, version 2.2.4.

Safety. The safety and tolerability of ertugliflozin and sitagliptin were assessed via adverse event (AE) monitoring, physical examination, BP, 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 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 18.1.

Statistical Analysis

The primary end points in each study were AUC and C_{max} of ertugliflozin and sitagliptin. Natural log–transformed AUC_{inf}, AUC_{last}, and C_{max} values for ertugliflozin and sitagliptin 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 mean differences and 90%CIs were exponentiated to provide estimates of the ratio of adjusted geometric means (Test:Reference [FDC:coadministered]) and 90%CIs for the ratios. For each strength, the FDC tablet was considered to be bioequivalent to coadministered ertugliflozin and sitagliptin if the 90%CIs for the geometric mean ratios (GMRs) for sitagliptin AUC_{inf} and C_{max}, and ertugliflozin AUC_{inf} and C_{max} were within 80% to 125%. A sample size of 18 subjects (9 subjects per sequence) was estimated to provide 99.0%, 95.3%, 99.0%, and 96.9% power that the 90% (CIs) for GMRs would lie within the acceptance range for bioequivalence (80% to 125%) for ertugliflozin AUC_{inf}, ertugliflozin C_{max}, sitagliptin AUC_{inf}, and sitagliptin C_{max}, respectively, which resulted in 90.5% overall power for each study. The study protocol prespecified that subjects who dropped out or who were considered to be nonevaluable with respect to either of the primary PK end points would be replaced to ensure at least 18 evaluable subjects. It was also prespecified that if a subject vomited at or before 2 × median T_{max} (ie, before complete treatment absorption), parameter values would not be included in the calculation of summary statistics or statistical analyses for that treatment.

Results

Subject Demographics

Subject demographics and baseline characteristics are presented in Table 1. In each study 18 or 19 subjects were randomized and assigned to receive treatment. Across all studies, a higher proportion of subjects were male (79% to 94%) than female, and the majority were black (47% to 61%). Two subjects in the ertugliflozin 5 mg/sitagliptin 50 mg study were discontinued: 1 subject was lost to follow-up, and 1 was withdrawn due to behavioral reasons of violating clinical research unit rules. Both subjects received both treatments and were analyzed for PK and safety. One subject in the ertugliflozin 15 mg/sitagliptin 50 mg study was discontinued after completion of period 1 because the investigator became aware that the subject did not meet the inclusion criteria; the subject had received treatment with an investigational product in another clinical trial within 30 days preceding the first dose of study medication in this study. Therefore, PK samples from this subject were not analyzed for ertugliflozin or sitagliptin concentrations, but the data were included in the safety analysis. All other subjects received treatments and completed the study.

PK Results

Following single oral administration of each ertugliflozin/sitagliptin FDC tablet or coadministration as individual tablets under fasted conditions, the median plasma concentration-time profiles for ertugliflozin and sitagliptin were almost superimposable (Figures 1 and 2). For both ertugliflozin and sitagliptin, C_{max}, T_{max}, AUC_{inf}, and $t_{½}$ values were similar for each of the FDC formulations and the coadministration of their respective individual components (Table 2). For each treatment (FDC and coadministered tablets), plasma concentrations of ertugliflozin peaked at ~1 hour postdose, indicating rapid oral absorption. Ertugliflozin mean terminal phase $t_{½}$ ranged from 11.2

Table 1. Baseline Demographics

	Ertugliflozin 5 mg + Sitagliptin 50 mg n=19	Ertugliflozin 5 mg + Sitagliptin 100 mg n=18	Ertugliflozin 15 mg + Sitagliptin 50 mg n=19	Ertugliflozin 15 mg + Sitagliptin 100 mg n=18
Sex, n				
Male	15	17	15	15
Female	4	1	4	3
Age, y				
Mean (SD)	37.0 (8.6)	35.3 (7.9)	37.8 (8.5)	38.2 (10.5)
Range	22-51	19-51	25-54	23-53
Race, n				
White	4	3	3	2
Black	9	11	10	11
Other	6	4	6	5
Ethnicity, n				
Hispanic/Latino	5	3	6	5
Non-Hispanic/Latino	14	15	13	13
Weight, kg				
Mean (SD)	78.0 (10.4)	81.6 (8.8)	80.9 (10.6)	85.2 (11.8)
Range	60.7-101.1	63.5-98.8	57.3-100.1	56.1-99.4
BMI, kg/m^2				
Mean (SD)	25.9 (2.5)	26.2 (2.3)	26.0 (2.9)	27.3 (2.5)
Range	21.5-30.2	22.5-30.5	19.9-30.0	21.7-30.4

BMI indicates body mass index; n, number of subjects in specified category; SD, standard deviation.

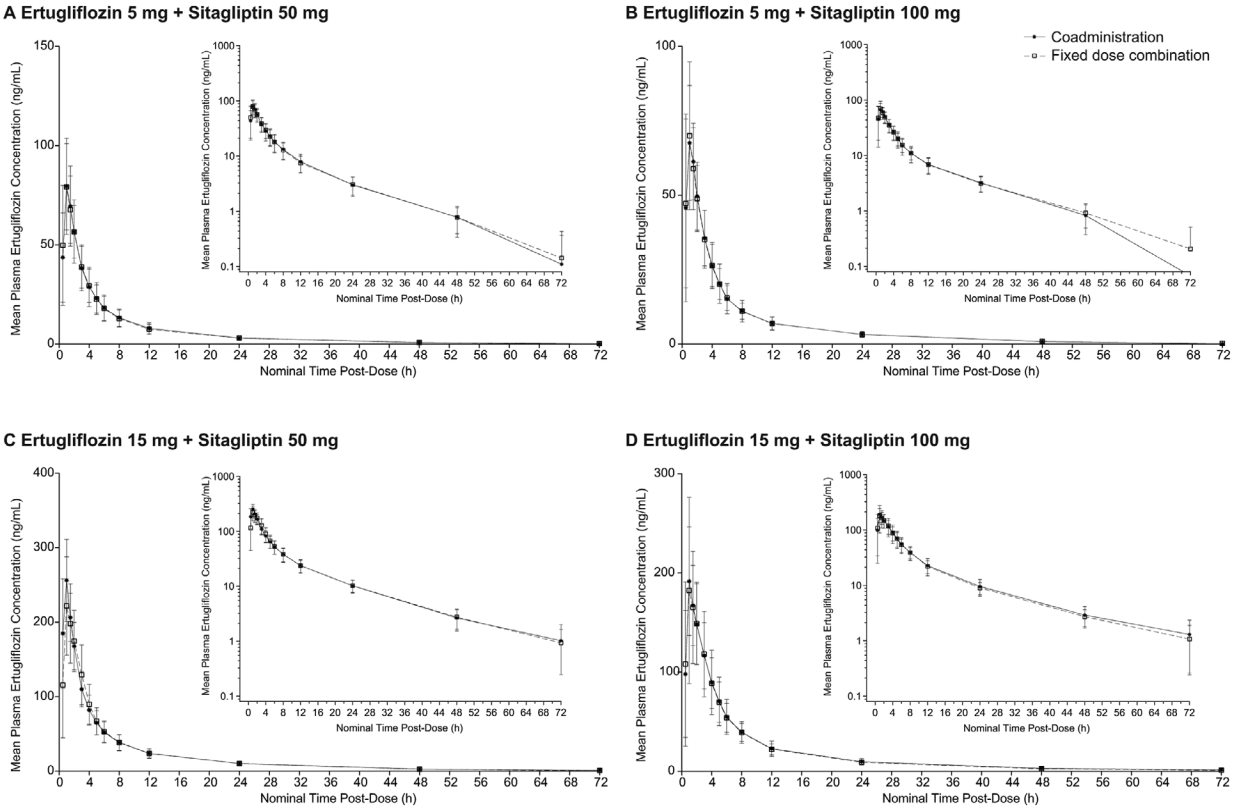

Figure 1. Mean ± SD plasma ertugliflozin concentration-time profiles. Following single oral dose of 4 different FDC formulations and their respective individual components. Linear (principal plots) and semilogarithmic (inset plots) scales are shown. Summary statistics were calculated by setting concentration values below the lower limit of quantification (0.500 ng/mL) to 0. Key to symbols: open squares/dashed line, FDC of ertugliflozin and sitagliptin; circles/solid line, coadministration of respective individual components. FDC indicates fixed dose combination; SD, standard deviation.

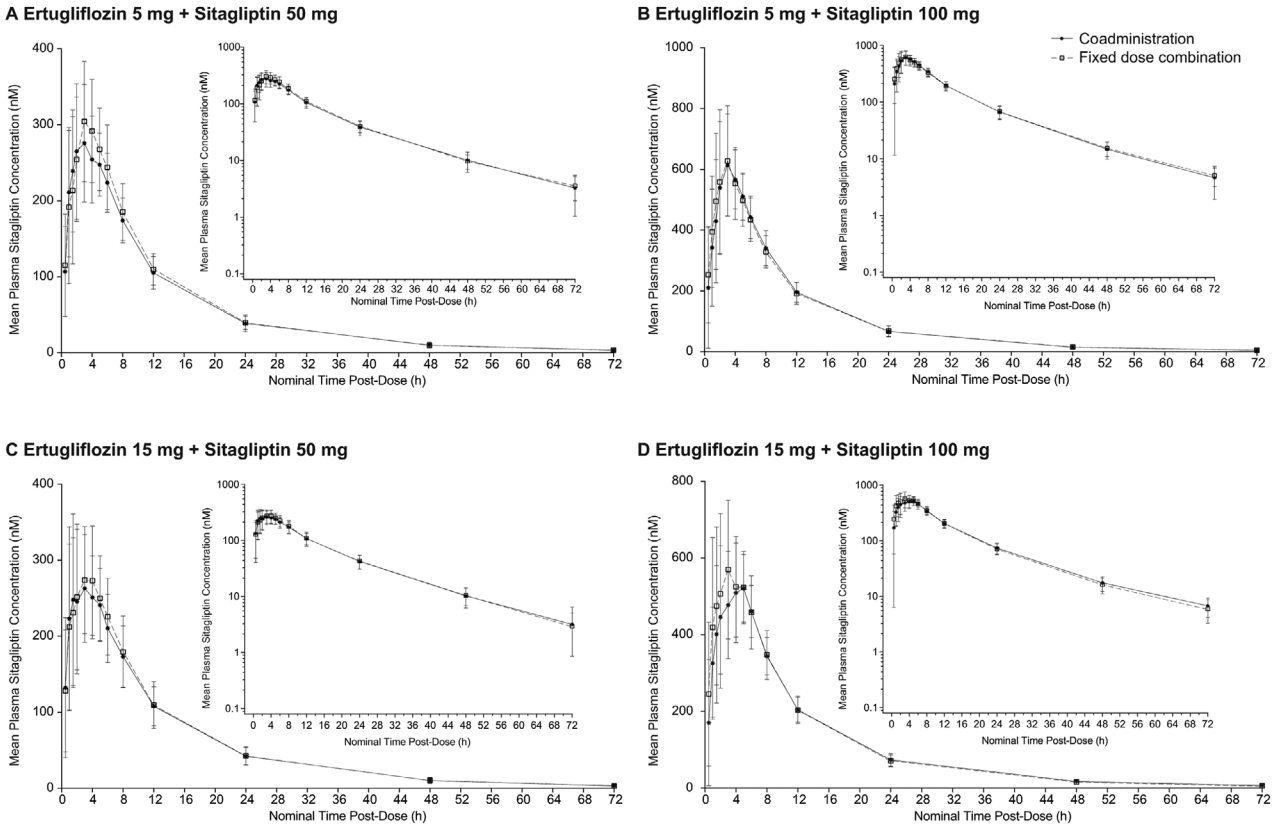

Figure 2. Mean ± SD plasma sitagliptin concentration-time profiles. Following single oral dose of 4 different FDC formulations and their respective individual components. Linear (principal plots) and semilogarithmic (inset plots) scales are shown. Summary statistics have been calculated by setting concentration values below the lower limit of quantification (1.00 ng/mL [2.46 nM]) to 0. Data in ertugliflozin 5 mg + sitagliptin 100 mg coadministered treatments for 1 subject were excluded due to occurrence of vomiting within 2 × median sitagliptin T_{max} for the treatment. Key to symbols: open squares/dashed line, FDC of ertugliflozin and sitagliptin; circles/solid line, coadministration of respective individual components. FDC indicates fixed dose combination; SD, standard deviation; T_{max}, time to maximum observed plasma concentration.

to 13.8 hours across the 4 studies and was comparable between FDC and coadministered treatments in each study. For sitagliptin, median T_{max} ranged from 2.2 to 4.0 hours but was generally similar between FDC and coadministered treatments in each study. Across the 4 studies, sitagliptin mean $t_{½}$ ranged from 11.2 to 12.5 hours.

A statistical summary of treatment comparisons for ertugliflozin/sitagliptin FDCs and coadministration of individual components is presented in Table 3. For each ertugliflozin/sitagliptin strength, the 90%CIs of the AUC_{inf}, AUC_{last}, and C_{max} GMRs (FDC versus coadministration) for plasma ertugliflozin or sitagliptin fell within the acceptance range for bioequivalence (80% to 125%), indicating that there were no meaningful differences in C_{max}, AUC_{inf}, or AUC_{last} between the FDC and coadministered treatments in any of the studies.

Safety

There were no deaths, serious AEs, severe AEs, or temporary or permanent discontinuations due to AEs following a single oral dose of ertugliflozin and sitagliptin, either when administered as a FDC or when coadministered as individual components. All AEs were mild in intensity. There were no abnormal laboratory findings or changes in BP or pulse rate.

Discussion

The primary objective of the studies described here was to demonstrate bioequivalence of 4 strengths of ertugliflozin/sitagliptin FDC tablets and the individual components at respective strengths when coadministered as a single dose under fasting conditions. Secondary objectives were to evaluate the safety and tolerability of the FDC and coadministered treatments. A single-dose study under fasted conditions was selected for this analysis as this was considered more sensitive than fed or multiple-dose studies for assessment of the release of the drug substance from the drug product into systemic circulation, which is consistent with the Food and Drug Administration/European

Table 2. Descriptive Summary[a] of Ertugliflozin and Sitagliptin PK Parameter Values

PK Parameter Summary Statistics[a]					
Ertugliflozin			Sitagliptin[b]		
Parameter	Ertugliflozin 5 mg + Sitagliptin 50 mg FDC	Ertugliflozin 5 mg + Sitagliptin 50 mg Coadministration[c]	Parameter	Ertugliflozin 5 mg + Sitagliptin 50 mg FDC	Ertugliflozin 5 mg + Sitagliptin 50 mg Coadministration[c]
N, n[d]	19, 19	19, 18	N, n[d]	19, 19	19, 18
AUC_{inf}, ng·h/mL	424.8 (112.8)	428.8 (120.2)	AUC_{inf}, μM·h	3.978 (0.713)	3.837 (0.662)
AUC_{last}, ng·h/mL	411.4 (112.5)	415.1 (119.3)	AUC_{last}, μM·h	3.919 (0.700)	3.769 (0.651)
C_{max}, ng/mL	82.07 (19.99)	82.32 (21.53)	C_{max}, nM	329.9 (83.57)	307.3 (68.24)
T_{max}, h	1.00 (0.50-2.02)	1.00 (0.50-2.00)	T_{max}, h	3.00 (1.00-6.00)	3.00 (1.00-6.02)
$t_{½}$, h	12.05 ± 4.293	11.16 ± 3.181	$t_{½}$, h	11.93 ± 1.319	11.56 ± 1.908
Parameter	Ertugliflozin 5 mg + Sitagliptin 100 mg FDC	Ertugliflozin 5 mg + Sitagliptin 100 mg Coadministration	Parameter	Ertugliflozin 5 mg + Sitagliptin 100 mg FDC	Ertugliflozin 5 mg + Sitagliptin 100 mg Coadministration[e]
N, n	18, 18	18, 18	N, n	18, 18	18, 17
AUC_{inf}, ng·h/mL	394.7 (76.38)	390.2 (79.81)	AUC_{inf}, μM·h	7.228 (1.170)	7.162 (1.125)
AUC_{last}, ng·h/mL	380.2 (77.78)	372.9 (79.24)	AUC_{last}, μM·h	7.153 (1.158)	7.087 (1.103)
C_{max}, ng/mL	75.45 (17.92)	73.00 (17.10)	C_{max}, nM	704.5 (206.9)	680.6 (178.2)
T_{max}, h	1.01 (0.50-3.00)	1.01 (0.50-4.00)	T_{max}, h	3.00 (1.00-4.08)	2.98 (0.48-5.00)
$t_{½}$, h	12.99 ± 3.534	11.84 ± 2.595	$t_{½}$, h	11.56 ± 0.917	11.18 ± 1.189
Parameter	Ertugliflozin 15 mg + Sitagliptin 50 mg FDC	Ertugliflozin 15 mg + Sitagliptin 50 mg Coadministration	Parameter	Ertugliflozin 15 mg + Sitagliptin 50 mg FDC	Ertugliflozin 15 mg + Sitagliptin 50 mg Coadministration
N, n	18, 18	18, 18	N, n	18, 18	18, 18
AUC_{inf}, ng·h/mL	1309 (277.8)	1328 (276.5)	AUC_{inf}, μM·h	3.953 (0.904)	3.867 (0.812)
AUC_{last}, ng·h/mL	1285 (275.6)	1303 (271.8)	AUC_{last}, μM·h	3.881 (0.901)	3.784 (0.802)
C_{max}, ng/mL	237.9 (45.13)	259.5 (49.29)	C_{max}, nM	313.9 (87.17)	307.3 (93.90)
T_{max}, h	1.00 (1.00-3.03)	1.00 (0.50-1.50)	T_{max}, h	3.00 (1.00-5.00)	2.24 (0.98-5.05)
$t_{½}$, h	12.80 ± 2.476	12.60 ± 3.091	$t_{½}$, h	11.68 ± 1.771	11.70 ± 1.941

(*Continued*)

Medicines Agency guidelines on the investigation of bioequivalence.[43,44] Because both agents are Biopharmaceutical Classification System class 1 compounds, a clinically meaningful food effect on exposure is unlikely due to their high solubility and permeability.[45] Indeed, a recent study has shown that ertugliflozin 15 mg and sitagliptin 100 mg FDC tablets can be administered without regard to meals.[6]

Bioequivalence was demonstrated for the 4 assessed strengths of ertugliflozin/sitagliptin FDC tablet and the individual components: for both ertugliflozin and sitagliptin, the 90%CIs for the ratios (FDC/coadministration) of geometric means for AUC_{inf} and C_{max} were within the acceptance criteria for bioequivalence (80% to 125%). Although caution should be taken when drawing conclusions regarding the general clinical applicability of data from single-dose studies in healthy volunteers, all treatment combinations of ertugliflozin and sitagliptin (FDC or when coadministered) were well tolerated: no serious AEs, severe AEs, or temporary or permanent discontinuations due to AEs were observed in any of the 4 single-dose studies.

The efficacy of the combination of ertugliflozin and sitagliptin coadministered as individual agents in patients with T2DM has been reported in 3 double-blind, placebo-controlled, randomized phase 3 trials.[35,36,38] In the VERTIS SITA2 study, ertugliflozin 5 mg or 15 mg was administered as an add-on therapy in patients receiving treatment with stable metformin ≥1500 mg and sitagliptin 100 mg.[38] In the VERTIS SITA and VERTIS FACTORIAL studies, ertugliflozin 5 mg or 15 mg coadministered with sitagliptin 100 mg was evaluated versus placebo, or their individual components at corresponding doses.[35,36] In each of these studies the coadministration of ertugliflozin and sitagliptin significantly reduced A_{1c}, fasting plasma glucose, body weight, and systolic

Table 2. Continued

Parameter	Ertugliflozin 15 mg + Sitagliptin 100 mg FDC	Ertugliflozin 15 mg + Sitagliptin 100 mg Coadministration	Parameter	Ertugliflozin 15 mg + Sitagliptin 100 mg FDC	Ertugliflozin 15 mg + Sitagliptin 100 mg Coadministration
N, n	18, 18	18, 17[f]	N, n	18, 18	18, 17[f]
AUC_{inf}, ng·h/mL	1216 (278.1)	1271 (300.6)	AUC_{inf}, μM·h	7.418 (1.114)	7.301 (0.986)
$AUC_{last,}$ ng·h/mL	1190 (273.3)	1216 (301.9)	AUC_{last}, μM·h	7.316 (1.103)	7.122 (0.996)
C_{max}, ng/mL	212.5 (68.03)	203.3 (46.06)	C_{max}, nM	675.9 (147.8)	590.6 (123.0)
$T_{max,}$ h	1.01 (0.50-4.00)	1.01 (0.50-5.00)	T_{max}, h	3.00 (0.50-6.02)	3.98 (1.98-5.00)
$t_{½}$, h	13.38 ± 3.050	13.84 ± 2.734	$t_{½}$, h	12.16 ± 2.025	12.53 ± 1.285

AUC indicates area under plasma concentration-time profile; AUC_{extrap}%, percentage of AUC_{inf} obtained by forward extrapolation; AUC_{inf}, AUC from time 0 extrapolated to infinite time; $AUC_{last,}$ AUC from time 0 to time of last quantifiable concentration; C_{max}, maximum observed plasma concentration; FDC, fixed dose combination; h, hour; N, number of subjects in the treatment group and contributing to the descriptive summary statistics; n, number of subjects with reportable $t_{½}$ and AUC_{inf}; PK, pharmacokinetics; SD, standard deviation; $t_{½}$, terminal half-life; T_{max}, time of maximum plasma concentration.

[a]Values are arithmetic mean (SD) for all except T_{max}, which is median (range).

[b]Before the calculation of PK parameters, sitagliptin plasma concentration values in ng/mL were converted to nM as follows: concentration (nM) = concentration (ng/mL) × 1000 / MW, where MW is the molecular weight of sitagliptin anhydrous free base (407.321).

[c]One subject discontinued coadministration of ertugliflozin 5 mg + sitagliptin 50 mg after the 6-hour PK sample was collected; therefore, ertugliflozin and sitagliptin AUC_{inf}, AUC_{last}, and $t_{½}$ were not calculated for this subject.

[d]Number of subjects with reportable $t_{½}$, AUC_{last}, and AUC_{inf}.

[e]Sitagliptin data for ertugliflozin 5 mg + sitagliptin 100 mg coadministration treatment for 1 subject were excluded due to occurrence of vomiting within twice the median sitagliptin T_{max} for the treatment. Ertugliflozin data for this subject were included because vomiting occurred >2 times the median ertugliflozin T_{max}.

[f]AUC_{inf} and $t_{½}$ were not reportable for 1 subject for ertugliflozin and sitagliptin because the terminal phases of the PK profiles were not well characterized. A well-characterized terminal phase was defined as a phase with at least 3 data points, $r^2 \geq 0.9$ (where r^2 is a goodness-of-fit statistic for the log-linear regression), and $AUC_{extrap}\% \leq 20$.

Table 3. Statistical Summary of Treatment Comparisons for Plasma Ertugliflozin and Sitagliptin PK Parameters

Parameter	Ertugliflozin 5 mg + Sitagliptin 50 mg	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 50 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg
Ertugliflozin geometric mean ratio[a] (90%CI)				
AUC_{inf}, ng·h/mL	101.61 (97.98-105.37)	101.23 (97.15-105.49)	98.40 (95.37-101.52)	98.25 (95.07-101.54)
AUC_{last}, ng·h/mL	101.69 (97.81-105.73)	102.01 (97.89-106.32)	98.47 (95.49-101.54)	98.18 (95.17-101.30)
C_{max}, ng/mL	99.80 (91.21-109.20)	103.17 (93.76-113.52)	91.74 (84.65-99.43)	102.13 (92.32-112.99)
Sitagliptin geometric mean ratio[a,b] (90%CI)				
AUC_{inf}, μM·h	104.34 (101.21-107.57)	99.80 (98.12-101.51)	101.89 (99.73-104.10)	102.40 (99.51-105.38)
AUC_{last}, μM·h	104.63 (101.43-107.93)	99.77 (98.05-101.52)	102.20 (99.92-104.53)	102.60 (99.78-105.50)
C_{max}, nM	106.60 (99.32-114.40)	99.76 (93.63-106.28)	103.02 (94.37-112.46)	114.14 (108.35-120.24)

AUC indicates area under plasma concentration-time profile; AUC_{inf}, AUC from time 0 extrapolated to infinite time; AUC_{last}, AUC from time 0 to time of the last quantifiable concentration; CI, confidence interval; C_{max}, maximum observed plasma concentration; FDC, fixed dose combination; h, hour; PK, pharmacokinetics.

[a]Geometric mean ratios are test/reference (FDC:coadministration) of adjusted means and 90%CI expressed as percentages.

[b]Before the calculation of PK parameters, sitagliptin plasma concentration values in ng/mL were converted to nM as follows: concentration (nM) = concentration (ng/mL) × 1000 / MW, where MW is the molecular weight of sitagliptin anhydrous free base (407.321).

BP compared with placebo or individual components, and the treatment was well tolerated. Given the favorable efficacy profile demonstrated in the VERTIS SITA, VERTIS SITA2, and VERTIS FACTORIAL studies and the bioequivalence shown in the current analysis, it can be concluded that the FDC formulation of ertugliflozin and sitagliptin would be efficacious in patients with T2DM.

Conclusions

It is expected that in future clinical practice, sitagliptin will be used in combination with ertugliflozin for the treatment of patients with T2DM. By demonstrating bioequivalence, these studies indicate that the favorable efficacy and tolerability of ertugliflozin and sitagliptin coadministered as individual agents that have been demonstrated in phase 3 trials can be translated to the

use of a FDC formulation. The provision of a FDC tablet of combination ertugliflozin plus sitagliptin is likely to benefit patients by increasing treatment adherence, thereby supporting effective glycemic control.

Disclosures

These studies were sponsored by Pfizer Inc, New York, NY and Merck Sharp & Dohme Corp, a subsidiary of Merck & Co Inc, Kenilworth, NJ (MSD). Vaishali Sahasrabudhe, Daryl J. Fediuk, Kyle Matschke, Kathleen B. Pelletier, Hua Wei, Haihong Shi, Anne Hickman, and Steven G. Terra are employees of Pfizer Inc and have shares/stock options in Pfizer Inc. Yali Liang and Almasa Bass were employees of Pfizer Inc at the time of study conduct. Susan Zhou and Rajesh Krishna are employees of MSD, who may own stock in Merck & Co, Inc, Kenilworth, NJ. Medical writing support was provided by Katy Beck, PhD, and Beth Elam, PhD, of Engage Scientific Solutions (Horsham, UK) and was funded by Pfizer Inc and MSD.

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 the 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 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.

Declaration of Conflicting Interests

Vaishali Sahasrabudhe, Daryl J. Fediuk, Kyle Matschke, Kathleen B. Pelletier, Hua Wei, Haihong Shi, Yali Liang, Anne Hickman, and Steven G. Terra are employees of Pfizer Inc and have shares/stock options in Pfizer Inc. Almasa Bass was an employee of Pfizer Inc at the time of study conduct. Susan Zhou and Rajesh Krishna are employees of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ, who may own stock in the Company.

Funding and Support

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Supporting Information

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