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

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Abstract
A fixed-dose combination (FDC) of ertugliflozin, a selective sodium-glucose cotransporter 2 inhibitor, and immediate-release metformin is approved for the treatment of type 2 diabetes mellitus in the United States and European Union. Four open-label, randomized, 2-period, single-dose, crossover studies were conducted under fasted conditions in healthy subjects to demonstrate bioequivalence of the ertugliflozin/metformin FDC tablets and coadministration of the individual components at respective strengths. In each study, 32 or 34 subjects received an ertugliflozin/metformin FDC tablet (2.5 mg/500 mg, 7.5 mg/850 mg, or 7.5 mg/1000 mg) and the respective doses of individual components (ertugliflozin with US- or EU-sourced metformin [Glucophage]). Plasma samples for ertugliflozin and metformin concentrations were collected for 72 hours in each period. For both ertugliflozin and metformin, the 90% confidence intervals for the adjusted geometric mean ratio (FDC : coadministration) for area under the plasma concentration–time profile from time zero extrapolated to infinity and maximum observed plasma concentration were within acceptance criteria for bioequivalence. The majority of adverse events were mild in intensity. The studies demonstrated that each strength of FDC tablet is bioequivalent to respective doses of coadministered individual components, supporting that safety and efficacy can be bridged to the individual components used in phase 3 studies evaluating ertugliflozin in combination with metformin.

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

The global health and economic burden of diabetes is significant. In the United States, 23.1 million people are currently diagnosed with diabetes, with type 2 diabetes (T2DM) accounting for 90% to 95% of cases.¹ It is estimated that 693 million adults globally will have diabetes by 2045.²

Treatment options for patients with T2DM include sodium-glucose cotransporter 2 inhibitors, which reduce plasma glucose and glycated hemoglobin (A1C) by reducing renal glucose reabsorption and lowering the renal threshold for glucose excretion, thus increasing urinary glucose excretion.³,⁴

The oral selective sodium-glucose cotransporter 2 inhibitor, ertugliflozin, is rapidly absorbed, with median time to peak plasma concentration (tmax) occurring at ~1 hour postdose under fasted
conditions and ~2 hours postdose in the fed state. Terminal half-life (t1/2) ranges from 11 to 17 hours across the dose range of 0.5 mg to 300 mg, with maximum observed plasma concentration (Cmax) and area under the plasma concentration–time profile from time 0 extrapolated to infinity (AUCinf) increasing in a dose-proportional manner over the range of 0.5 to 300 mg. Absolute bioavailability of ertugliflozin is ~100%. Metabolism of ertugliflozin is mainly via glucuronidation (uridine diphosphate glucuronosyltransferase isozymes 1A9 and 2B7) and to a lesser extent oxidative metabolism (cytochrome P450 [CYP] isozymes 3A4 and 3A5). The 8 metabolites and unchanged ertugliflozin (35.3%) are excreted via feces (40.9%) and urine (50.2%). 8 Ertugliflozin has no clinically meaningful pharmacokinetic interactions with sitagliptin, metformin, glimepiride, simvastatin, or rifampin. Coadministration of ertugliflozin and metformin in phase 3 trials,12,13,19–21 and ertugliflozin FDC will be dosed BID. Therefore, 2.5 mg and 7.5 mg BID doses of ertugliflozin (half that of the QD doses) were selected for the FDC formulation and are expected to be well tolerated in healthy subjects.

In order to bridge the phase 3 efficacy and safety data12 with the FDC tablet formulation, 4 phase 1, single-dose, open-label, randomized, 2-period, crossover bioequivalence studies were conducted. Two studies compared ertugliflozin/metformin FDC at the highest and lowest strengths of both components (ertugliflozin 7.5 mg/metformin 1000 mg and ertugliflozin 2.5 mg/metformin 500 mg) with respective strengths of metformin (US-sourced Glucophage) coadministered with ertugliflozin. Two further studies compared ertugliflozin/metformin FDC at the higher strength of ertugliflozin (ertugliflozin 7.5 mg/metformin 1000 mg and ertugliflozin 7.5 mg/metformin 850 mg) with the respective strengths of metformin (EU-sourced Glucophage) coadministered with ertugliflozin. The choice of the reference compound (US- versus EU-sourced Glucophage) as well as the FDC dose strengths to be studied were dependent on agreements with the US Food and Drug Administration and European Medicines Agency.

The primary objective of these studies was to demonstrate bioequivalence of the ertugliflozin/metformin FDC tablets vs coadministration of the individual components at 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, single-dose, open-label, randomized, 2-period, crossover bioequivalence studies were conducted in healthy subjects, with 32 subjects to be enrolled per study. 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. All participants provided signed and dated informed consent. The studies were conducted at 2 Pfizer Clinical Research Units (New Haven, Connecticut, for studies using US-sourced metformin; or Brussels, Belgium, for studies using EU-sourced metformin). For each study, the final protocol and informed consent documentation were reviewed and approved by the Independent Ethics Committee at the research unit (Comité’ d’Ethique Hospitalo-Facultaire Erasme-ULB, Brussels, Belgium; and IntegReview Ethical Review Board, Austin, Texas).

Each study consisted of a screening visit and 2 study periods; screening occurred within 28 days of the first dose of study medication in period 1. Eligible subjects were admitted to the clinical research unit on day 0 of each treatment period. Subjects received a single dose of assigned study medication as FDC or coadministered tablets (ertugliflozin 7.5 mg + metformin [US] 1000 mg, ertugliflozin 2.5 mg + metformin [US] 500 mg, ertugliflozin 7.5 mg + metformin [EU] 1000 mg, or ertugliflozin 7.5 mg + metformin [EU] 850 mg) on the morning of day 1 after an overnight fast of ≥10 hours. Ertugliflozin/metformin FDC was administered as a single tablet. For coadministration, metformin 1000 mg, 850 mg, and 500 mg doses and ertugliflozin 2.5 mg were administered as single tablets, whereas the ertugliflozin 7.5 mg dose was administered as one 5-mg and one 2.5-mg tablet. Treatments were administered at approximately the same time of day in each period. Subjects who received coadministered tablets in period 1 were crossed over to FDC at the equivalent dose in period 2 and vice versa. Dosing in each period was separated by a washout period of at least 7 days.

In order to standardize conditions on PK sampling days, all subjects were required to refrain from lying down, eating, and drinking beverages other than water during the first 4 hours after dosing. Water was withheld for 1 hour predose and 1 hour after the administration of the study medication, except for the 240 mL given with the dose.

Subjects
Eligible subjects were healthy male or female adults aged 18 to 55 years at the time of screening, with a body mass index of 17.5–30.5 kg/m² and total body weight >50 kg (110 lb). Healthy was defined as no clinically relevant abnormalities identified by a detailed medical history and full physical examination, including blood pressure and pulse rate measurement, 12-lead electrocardiogram, and clinical laboratory tests.

Exclusion criteria included: evidence or history of clinically significant hematologic, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease; any clinically significant malabsorption condition; 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; estimated glomerular filtration rate <80 mL/min/1.73 m² based on the 4-variable Modification of Diet in Renal Disease equation; serum supine blood pressure ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic); known hypersensitivity or intolerance to any sodium-glucose cotransporter 2 inhibitor or metformin; and pregnant or breastfeeding females.

Pharmacokinetic Sample Assessments
Serial blood samples were collected to provide plasma for PK analysis at the following time points in each period: predose (0 hours) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours after administration.

Plasma samples were analyzed for ertugliflozin and metformin concentrations using validated, sensitive, and specific high-performance liquid chromatography–tandem mass spectrometry methodology (WuXi AppTec, Shanghai, China). Calibration standard responses were linear for ertugliflozin and metformin over the range of 0.500 to 500 ng/mL and 2.00 to 1000 ng/mL, respectively, using a weighted (1/concentration”) linear least squares regression. The lower limit of quantification (LLOQ) was 0.500 ng/mL for ertugliflozin and 2.00 ng/mL for metformin. Between-day assay precision and accuracy data for ertugliflozin and metformin plasma concentrations for each study are shown in Table S1. Detailed methodology for the ertugliflozin and metformin assay procedures have been previously published.

The following plasma ertugliflozin and metformin PK parameters were calculated for each subject for each treatment using noncompartmental analysis of plasma concentration–time data: Cmax, tmax, area under the plasma concentration–time profile from time 0 to the time of the last quantifiable concentration (AUClast), AUCinf, and t1/2. Samples below the LLOQ were set to zero for analysis. PK parameter values were calculated using a Pfizer-validated software system, electronic noncompartmental analysis (eNCA, version 2.2.4).

Safety Assessments
Adverse event (AE) monitoring, physical examination, blood pressure, pulse rate, and measurement of clinical laboratory parameters were performed at 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. Medical Dictionary for Regulatory Activities version 18.1 coding was applied.
Table 1. Baseline Demographics

|                          | Ertugliflozin | Ertugliflozin | Ertugliflozin | Ertugliflozin |
|--------------------------|---------------|---------------|---------------|---------------|
|                          | 7.5 mg + Metformin | 2.5 mg + Metformin | 7.5 mg + Metformin | 7.5 mg + Metformin |
|                          | 1000 mg (US)    | 500 mg (US)   | 1000 mg (EU)   | 850 mg (EU)    |
|                          | (N = 32)        | (N = 32)      | (N = 34)       | (N = 34)       |
| Sex, n Male/Female       | 26/6           | 29/3          | 21/13          | 20/14          |
| Age, y Mean (SD)         | 37.0 (9.6)     | 33.2 (7.9)    | 34.1 (9.3)     | 37.1 (8.6)     |
| Range                    | 21-55          | 18-47         | 19-50          | 23-54          |
| Race                     |                |               |               |               |
| White                    | 7              | 5             | 28             | 31             |
| Black                    | 17             | 20            | 3              | 3              |
| Asian                    | 1              | 1             | 0              | 0              |
| Other                    | 7              | 6             | 3              | 0              |
| Ethnicity                |                |               |               |               |
| Hispanic/Latino          | 8              | 8             | 1              | 2              |
| Not Hispanic/Latino      | 24             | 24            | 33             | 32             |
| Weight, kg Mean (SD)     | 78.7 (11.7)    | 79.7 (11.0)   | 72.9 (16.6)    | 72.6 (11.9)    |
| Range                    | 53.7-98.3      | 50.1-95.3     | 50.7-110.6     | 54.4-99.6      |
| BMI, kg/m² Mean (SD)     | 25.8 (3.2)     | 26.1 (3.4)    | 24.2 (3.5)     | 24.1 (3.1)     |
| Range                    | 19.2-30.4      | 18.2-30.5     | 18.4-29.8      | 18.1-30.4      |

BMI: body mass index; SD, standard deviation.

Statistical Analysis
The PK concentration population was defined as all subjects treated who had at least 1 concentration measurement. The PK parameter analysis population was defined as all subjects treated who had at least 1 of the PK parameters of interest.

Natural log-transformed AUC_{inf}, AUC_{last}, and C_{max} of ertugliflozin and metformin were analyzed using a mixed-effects model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted (least squares) mean differences (test/reference) and corresponding 90% confidence intervals (CIs) were obtained from the model. The adjusted mean differences and 90%CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (test/reference) and 90%CIs for the ratios. For each FDC strength, the FDC tablet was to be declared bioequivalent to coadministration if the 90%CIs for the geometric mean ratios (GMRs) for ertugliflozin and metformin AUC_{inf} and C_{max} were within 80% and 125%.

A sample size of 32 subjects (16 subjects per sequence) per study was estimated to provide 99% power that the 90%CIs for GMRs would lie within the acceptance region for each of the ertugliflozin PK parameters (AUC_{inf} and C_{max}) and metformin PK parameters (AUC_{inf} and C_{max}). Therefore, each study provided at least 96% overall power to meet bioequivalence criteria for ertugliflozin and metformin AUC_{inf} and C_{max}. The sample size calculations assumed a true GMR of 1.05 and were based on estimates of within-subject standard deviations of 0.0956 and 0.1519 for ertugliflozin AUC_{inf} and C_{max}, respectively, and 0.1337 and 0.1698 for metformin AUC_{inf} and C_{max}, respectively, obtained from previous crossover studies conducted by Pfizer and/or Merck. Subjects who dropped out were replaced at the discretion of the sponsor to ensure 32 evaluable subjects, and replacements had the same treatment sequence as the subjects they replaced.

Results
Study Subjects
Subject demographics and baseline characteristics are shown in Table 1. In each study, 32 subjects were randomized to receive treatment. Four subjects discontinued because they were no longer willing to participate for personal reasons and were replaced: 2 subjects from the ertugliflozin 7.5 mg + EU-sourced metformin 1000 mg study and 2 subjects from the ertugliflozin 7.5 mg + EU-sourced metformin 850 mg study. All other subjects received assigned treatments and completed the study. Across the 4 studies, a higher proportion of subjects were male (58%–91%) than female. In the 2 studies assessing the bioequivalence using US-sourced metformin, the majority of subjects were black (53%–62%), while in the remaining 2 studies assessing the bioequivalence of FDC with EU-sourced metformin, the majority of subjects were white (82%–91%).

Pharmacokinetic Assessments
Following a single oral administration of the ertugliflozin/metformin FDC tablet or coadministration as individual tablets under fasted conditions, the mean plasma ertugliflozin and metformin...
Concentration–time profiles were nearly superimposable for all doses evaluated in the 4 studies (Figures 1 and 2). PK parameters are summarized descriptively in Table 2. The arithmetic as well as geometric means for ertugliflozin and metformin C_{\text{max}}, AUC_{\text{inf}}, and AUC_{\text{last}} were similar between the FDC and respective coadministered tablets, for all doses studied. For each treatment (FDC and coadministered tablets), ertugliflozin median t_{\text{max}} occurred at ~1 hour postdose, indicating rapid oral absorption. Mean ertugliflozin terminal phase t_{1/2} ranged from 7.1 to 11.2 hours across the 4 studies and was similar between the FDC and coadministered treatments in each study. For metformin, median t_{\text{max}} ranged from 2 to 3 hours, but overall was similar between FDC and coadministered treatments at each dose studied. Across the 4 studies, metformin mean t_{1/2} ranged from 11.9 to 16.4 hours.

A statistical summary of treatment comparisons for ertugliflozin/metformin FDCs and coadministration of individual components is presented in Table 3, with individual subject ratios for PK parameters shown in Figure 3 (ertugliflozin) and Figure 4 (metformin). For each ertugliflozin and metformin dosing strength, the 90% CIs of the AUC_{\text{inf}}, AUC_{\text{last}}, and C_{\text{max}} GMRs (FDC vs coadministration) for plasma ertugliflozin or metformin fell within the acceptance range for bioequivalence (80% to 125%), indicating that there were no meaningful differences in C_{\text{max}}, AUC_{\text{inf}}, or AUC_{\text{last}} between the FDC and coadministered treatments in any of the studies.
Figure 2. Mean ± SD plasma metformin concentration–time profiles following a single oral dose of ertugliflozin/metformin FDC or coadministration as individual tablets under fasted conditions. Linear (principal plots) and semilogarithmic (inset plots) scales are shown. Values below the lower limit of quantification (2.00 ng/mL) were set to 0 ng/mL for analysis. FDC, fixed-dose combination; SD, standard deviation.

Safety Assessments
There were no deaths, serious AEs, severe AEs, or temporary or permanent discontinuations due to treatment-emergent AEs following a single oral dose of ertugliflozin and metformin when administered as a FDC or when coadministered. The most commonly reported AEs across the 4 studies were gastrointestinal events and headache. Gastrointestinal events were reported by a total of 26 subjects assigned to FDC (range 3–9 across the 4 studies, the lowest being ertugliflozin/metformin 2.5 mg/500 mg and the highest 7.5 mg/1000 mg), and 34 subjects with concomitant administration (range, 6–16 across the 4 studies, the highest being ertugliflozin 7.5 mg + metformin 850 mg and n = 6 in each of the other 3 studies). Headache was reported by a total of 12 subjects assigned to FDC (range, 2–6 across the 4 studies) and 8 subjects with concomitant administration (range, 1–4 across the 4 studies). The majority of AEs were mild in intensity, with the exception of 11 events in 9 subjects, which were moderate. Of these moderate events, 9 events occurred in 7 subjects assigned to ertugliflozin/metformin 7.5 mg/850 mg FDC or 7.5 mg/1000 mg FDC, and the remaining 2 events were in 2 subjects receiving those doses as concomitant administration. There were no clinically significant laboratory abnormalities or changes in blood pressure or pulse rate.

Discussion
Coadministration of ertugliflozin and either US-sourced or EU-sourced metformin tablets was bridged to ertugliflozin/metformin FDC tablets by a combination of bioequivalence study data and in vitro dissolution data. The primary objective of the 4 bioequivalence studies presented here was to demonstrate
Table 2. Descriptive Summary$^a$ of Ertugliflozin and Metformin Pharmacokinetic Parameter Values

| Parameter             | Ertugliflozin 7.5 mg + Metformin 1000 mg (US) | Ertugliflozin 2.5 mg + Metformin 500 mg (US) | Ertugliflozin 7.5 mg + Metformin 1000 mg (EU) | Ertugliflozin 7.5 mg + Metformin 850 mg (EU) |
|-----------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
|                       | FDC Coadministration                          | FDC Coadministration                          | FDC Coadministration                          | FDC Coadministration                          |
| Nb                    | 32                                            | 32                                            | 33                                            | 33                                            |
| AUC$_{inf}$,ng $\cdot$ h/mL | 676.8 (195.8)                                | 677.8 (190.7)                                | 181.7 (43.1)                                  | 185.3 (45.4)                                  |
| AUC$_{last}$,ng $\cdot$ h/mL | 663.3 (194.3)                                | 662.3 (191.0)                                | 169.7 (40.4)                                  | 172.9 (44.2)                                  |
| C$_{max}$,ng/mL       | 127.5 (31.0)                                  | 123.0 (29.9)                                 | 35.83 (8.38)                                  | 35.84 (8.57)                                  |
| t$_{max}$,h           | 1.03 (1.00,3.00)                              | 1.00 (0.50,0.20)                             | 1.00 (1.00,2.00)                              | 1.00 (0.50,3.00)                              |
| t$_{1/2}$,h           | 11.00 (2.70)                                  | 11.19 (3.28)                                 | 7.117 (1.34)                                  | 7.728 (1.86)                                  |
| AUC$_{inf}$,ng $\cdot$ h/mL | 11 510 (2670.1)                              | 11 920 (2817.7)                              | 7200 (1868.1)                                 | 6920 (1371.6)                                 |
| AUC$_{last}$,ng $\cdot$ h/mL | 11 190 (2589.1)                              | 11 490 (2960.2)                              | 7050 (1804.7)                                 | 6918 (1293.3)                                 |
| C$_{max}$,ng/mL       | 1697 (414.2)                                  | 1725 (474.3)                                 | 1070 (287.4)                                  | 1035 (208.3)                                  |
| t$_{max}$,h           | 2.01 (1.00,4.10)                              | 1.98 (0.51,3.98)                             | 2.00 (1.00,4.02)                              | 1.98 (0.48,4.10)                              |
| t$_{1/2}$,h           | 16.20 (11.65)                                 | 16.42 (12.51)                                | 13.65 (8.29)                                  | 14.08 (7.78)                                  |

$^{a}$Arithmetic mean (standard deviation) for all except median (range) for t$_{max}$.

Bioequivalence of the 3 strengths of ertugliflozin/metformin FDC tablets and the individual components at 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. Bioequivalence was demonstrated as the 90% CIs for the GMRs for AUC$_{inf}$ and C$_{max}$ for ertugliflozin as well as for metformin fell within acceptance criteria for bioequivalence (80%-125%). Two pivotal bioequivalence studies conducted using the highest (ertugliflozin 7.5 mg/metformin 1000 mg) and lowest
Table 3. Statistical Summary of Treatment Comparisons for Plasma Ertugliflozin and Metformin Pharmacokinetic Parameters

| Dose                                | Analyte              | AUC<sub>inf</sub> | Geometric Mean Ratio<sup>a,b</sup> (90%CI) | Intrasubject Variability (%)<sup>c</sup> | C<sub>max</sub> | Geometric Mean Ratio<sup>a,b</sup> (90%CI) | Intrasubject Variability (%)<sup>c</sup> |
|-------------------------------------|----------------------|-------------------|------------------------------------------|------------------------------------------|----------------|------------------------------------------|------------------------------------------|
| Ertugliflozin 7.5 mg + metformin 1000 mg (US) | Ertugliflozin       | 99.64             | (97.04-102.30)                           | 6.22                                      | 103.50        | (97.85-109.47)                           | 13.3                                      |
|                                     | Metformin            | 97.14             | (89.98-104.87)                           | 15.8                                     | 99.20         | (92.06-106.90)                           | 17.8                                      |
| Ertugliflozin 2.5 mg + metformin 500 mg (US) | Ertugliflozin       | 98.26             | (96.62-99.94)                            | 3.99                                     | 100.22        | (94.76-106.00)                           | 13.27                                     |
|                                     | Metformin            | 103.24            | (96.16-110.83)                           | 14.95                                    | 101.49        | (93.83-109.76)                           | 18.64                                     |
| Ertugliflozin 7.5 mg + metformin 1000 mg (EU) | Ertugliflozin       | 98.28             | (95.72-100.91)                           | 6.23                                     | 98.99         | (93.84-104.42)                           | 12.66                                     |
|                                     | Metformin            | 103.76            | (96.43-111.65)                           | 16.67                                    | 110.08        | (100.31-120.79)                          | 22.33                                     |
| Ertugliflozin 7.5 mg + metformin 850 mg (EU) | Ertugliflozin       | 100.67            | (97.59-103.84)                           | 7.09                                     | 97.21         | (92.98-101.64)                           | 10.56                                     |
|                                     | Metformin            | 104.96            | (99.83-110.36)                           | 9.52                                     | 98.30         | (93.04-103.87)                           | 13.07                                     |

AUC<sub>inf</sub>, area under plasma concentration–time profile; AUC<sub>inf</sub>, AUC from time 0 extrapolated to infinite time; CI, confidence interval; C<sub>max</sub>, maximum observed plasma concentration; FDC, fixed-dose combination.

<sup>a</sup>Geometric mean ratios: test/reference (FDC/coadministration) of adjusted means and 90% CIs expressed as percentages.

<sup>b</sup>The sample sizes for the geometric mean ratios are shown in Table 2.

<sup>c</sup>Based on mixed-effects model.

Ertugliflozin (7.5 mg/metformin 500 mg) strengths of ertugliflozin/metformin FDC tablets, demonstrated bioequivalence to the respective doses of ertugliflozin and US-sourced metformin coadministered as individual components. In addition, all ertugliflozin/metformin tablet strengths (7.5 mg/1000 mg, 7.5 mg/500 mg, 2.5 mg/1000 mg, and 2.5 mg/500 mg) dissolved rapidly (>85% release in 15 minutes) in a multimedia dissolution test. Thus, 4 strengths of ertugliflozin/metformin FDC tablets (7.5 mg/1000 mg, 7.5 mg/500 mg, 2.5 mg/1000 mg, and 2.5 mg/500 mg) are considered bioequivalent to respective strengths of ertugliflozin and US-sourced metformin coadministered.

Two other pivotal bioequivalence studies performed using 7.5 mg/850 mg and 7.5 mg/1000 mg ertugliflozin/metformin FDC tablets, demonstrated bioequivalence to 7.5 mg ertugliflozin when coadministered with either 850 mg or 1000 mg US-sourced metformin as individual components, respectively. In addition, all ertugliflozin/metformin tablet strengths (7.5 mg/1000 mg, 7.5 mg/850 mg, 2.5 mg/1000 mg, and 2.5 mg/850 mg) dissolved rapidly (>85% release in 15 minutes) in a multimedia dissolution test. Thus, 4 strengths of ertugliflozin/metformin tablets (7.5 mg/1000 mg, 7.5 mg/850 mg, 2.5 mg/1000 mg, and 2.5 mg/850 mg) are also considered bioequivalent to respective strengths of ertugliflozin and EU-sourced metformin coadministered.

A single-dose regimen under fasted conditions was selected to demonstrate bioequivalence of ertugliflozin and metformin in FDC tablets to the individual components coadministered together as this was considered more sensitive than fed or multiple-dose regimens for assessment of the release of the drug substance from the drug product into the systemic circulation, consistent with US Food and Drug Administration guidance. A recent food effect study of ertugliflozin/metformin FDC has also shown that food did not meaningfully affect the PK of ertugliflozin or metformin when ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet was administered with a high-calorie, high-fat meal.

The BID dosing requirement of the FDC is in contrast to the established QD dosing regimen of ertugliflozin. A phase 1 study demonstrated equivalent exposure (steady-state AUC<sub>24</sub>) and similar steady state urinary glucose excretion for BID and QD administration of ertugliflozin at the same total daily dose (2.5 mg BID vs 5 mg QD and 7.5 mg BID vs 15 mg QD), which supports the BID administration of ertugliflozin as a component in ertugliflozin/metformin FDC.

Given the favorable phase 3 efficacy of ertugliflozin in the VERTIS MET study and the bioequivalence
shown in these 4 phase 1 studies, the FDC formulation of ertugliflozin and metformin is expected to be efficacious in patients with T2DM. The FDC tablets were well tolerated in the 4 studies reported here, supporting the safety profile of ertugliflozin in the VERTIS MET study. Although sample sizes were small and direct comparisons between studies are not possible, there was no evidence of a dose-dependent safety signal from the current FDC data. Gastrointestinal events may have been caused by metformin, as these are the most common AEs reported after metformin administration. For patients with T2DM who are inadequately controlled on metformin alone, the addition of ertugliflozin is well tolerated and provides effective glycemic control and a reduction in body weight and blood pressure. The ertugliflozin/metformin FDC formulation provides a convenient mode of administration for combination therapy for patients initiating ertugliflozin on a metformin background and for patients switching from coadministration of ertugliflozin and metformin to the FDC.

Conclusions
The studied doses of the FDC tablets (ertugliflozin 7.5 mg/metformin 1000 mg, ertugliflozin 7.5 mg/metformin 850 mg, and ertugliflozin 2.5 mg/metformin 500 mg) are bioequivalent to the corresponding doses of ertugliflozin and metformin when coadministered. These clinical data, along with the in vitro multimedia dissolution data, support the bridging of PK, pharmacodynamic, safety, and efficacy data obtained in the phase 3 VERTIS MET study to the various strengths of the ertugliflozin/metformin FDC tablets.
Figure 4. Ratios of metformin pharmacokinetic parameters following ertugliflozin/metformin fixed-dose combination (test) vs coadministration (reference), for area under plasma concentration–time profile from time 0 extrapolated to infinite time (AUC_{inf}) and maximum observed plasma concentration (C_{max}). Open circles depict individual subject ratios and gray triangles the geometric mean (with 90% confidence interval [CI]).

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Declaration of Conflicting Interests

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

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Data Sharing

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
United States and/or European Union or (2) in programs that have been terminated (i.e., 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. Centers for Disease Control and Prevention. National diabetes statistics report, 2017. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Published 2017. Accessed January 22, 2019.
2. International Diabetes Federation. IDF Diabetes Atlas, 8th edn. Brussels Belgium: International Diabetes Federation. http://diabetesatlas.org/resources/2017-atlas.html. Published 2017. Accessed January 22, 2019.
3. 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):F889-900.
4. Scheen AJ. Pharmacokinetics, pharmacodynamics and clinical use of SGLT2 inhibitors in patients with type 2 diabetes mellitus and chronic kidney disease. *Clin Pharmacokinet*. 2015;54(7):691-708.
5. Sahasrabudhe V, Fediuk DJ, Matschke K, et al. Effect of food on the pharmacokinetics of ertugliflozin and its fixed-dose combinations ertugliflozin/sitagliptin and ertugliflozin/metformin [published online ahead of print November 14, 2018]. *Clin Pharmacol Drug Dev*. https://doi.org/10.1002/cpdd.629
6. Kalugtak AR, 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.
7. Raje S, Callegari E, Sahasrabudhe V, et al. Novel application of the two period microtracer approach to determine absolute oral bioavailability and fraction absorbed of ertugliflozin. *Clin Transl Sci*. 2018;11(4):405-411.
8. 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.
9. Dawra VK, Cutler D, Zhou S, et al. Assessment of the drug interaction potential of ertugliflozin with sitagliptin, metformin, glimepiride, or simvastatin in healthy subjects. *Clin Pharmacol Drug Dev*. 2019;8(3):314-325.
10. Dawra VK, Sahasrabudhe V, Liang Y, et al. Effect of rifampin on the pharmacokinetics of ertugliflozin in healthy subjects. *Clin Ther*. 2018;40(9):1538-1547.
11. 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.
12. Rosenstock J, Frias J, Páll 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.
13. 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.
14. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. *Diabetologia*. 2017;60(9):1577-1585.
15. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2018. *Diabetes Care*. 2018;41(suppl 1):S73-S85.
16. Wildasin EM, Skaar DJ, Kirchain WR, Hulse M. Metformin, a promising oral antihyperglycemic for the treatment of noninsulin-dependent diabetes mellitus. *Pharmacotherapy*. 1997;17(1):62-73.
17. Tucker GT, Casey C, Phillips PJ, Connor H, Ward JD, Woods HF. Metformin kinet in healthy subjects and in patients with diabetes mellitus. *Br J Clin Pharmacol*. 1981;12(2):235-246.
18. Davidson MB, Peters AL. An overview of metformin in the treatment of type 2 diabetes mellitus. *Am J Med*. 1997;102(1):99-110.
19. Gallo S, Charbonnel B, Goldman A, et al. Long-term efficacy and safety of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy: 104-week VERTIS MET trial [published online ahead of print January 7, 2019]. *Diabetes Obes Metab*. https://doi.org/10.1111/dom.13631
20. Hollander P, Liu J, Hill J, et al. Ertugliflozin compared with glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin: The VERTIS SU randomized study. *Diabetes Ther*. 2018;9(1):193-207.
21. 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.
22. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in
renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006;145(4):247-254.

23. 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.

24. U.S. Food and Drug Administration. Guidance for Industry. Bioavailability and bioequivalence studies submitted in NDAs or INDS—general considerations. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM389370.pdf. Published 2014. Accessed May 28, 2019.

25. Dawra KV, Liang Y, Shi H, et al. A PK/PD study comparing twice-daily to once-daily dosing regimens of ertugliflozin in healthy subjects. *Int J Clin Pharm Ther.* 2019;57(4):207-216.

26. Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med.* 1997;103(6):491-497.

Supporting Information

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