

# Pharmacokinetics and Pharmacodynamics of Ertugliflozin in Healthy Japanese and Western Subjects

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## Abstract

Ertugliflozin, a sodium-glucose cotransporter 2 inhibitor, is approved for treatment of type 2 diabetes. This randomized, double-blind (sponsor-open) study in healthy Japanese subjects and open-label study in Western subjects assessed ertugliflozin pharmacokinetics and pharmacodynamics. Cohort A received 3 ascending single doses of ertugliflozin (1, 5, and 25 mg; n = 6 Japanese, n = 6 Western) or placebo (n = 3 Japanese) under fasted conditions. Cohort B received multiple once-daily doses of ertugliflozin 25 mg (n = 6 Japanese) or placebo (n = 3 Japanese) for 7 days under fed conditions. For Japanese subjects in Cohort A, maximum plasma concentrations ( $C_{max}$ ) were observed 1 to 1.5 hours after dosing, and apparent mean terminal half-life was 12.4 to 13.6 hours. The ratios of the geometric means (Japanese/Western) for ertugliflozin 1-, 5-, and 25-mg single doses were 95.94%, 99.66%, and 90.32%, respectively, for area under the plasma concentration–time curve and 107.59%, 97.47%, and 80.04%, respectively, for  $C_{max}$ . Area under the plasma concentration–time curve and  $C_{max}$  increased in a dose-proportional manner. For Cohort B,  $C_{max}$  was observed 2.5 hours after dosing (days 1 and 7), and steady state was reached by day 4. The 24-hour urinary glucose excretion was dose dependent. Ertugliflozin was generally well tolerated. There were no meaningful differences in exposure, urinary glucose excretion, and safety between Japanese and Western subjects.

## Keywords

ertugliflozin, Japanese, PD, PK, SGLT2 inhibitor, type 2 diabetes

Sodium-glucose cotransporter 2 inhibitors lower plasma glucose levels through reducing renal glucose reabsorption and lowering the renal threshold for glucose excretion, thereby increasing urinary glucose excretion (UGE).<sup>1</sup> Ertugliflozin is a selective inhibitor of sodium-glucose cotransporter 2<sup>2,3</sup> that has been evaluated in phase 3 trials for the treatment of type 2 diabetes mellitus (T2DM) in adults.<sup>4–11</sup> Results from these studies demonstrated that ertugliflozin provided clinically meaningful improvements in glycemic control, as well as reductions in body weight and blood pressure, leading to the approval of ertugliflozin at doses of 5 and 15 mg to improve glycemic control in adults with T2DM as an adjunct to diet and exercise.

Absorption of ertugliflozin following oral administration is rapid; maximum plasma concentration ( $C_{max}$ ) under fasted conditions is reached ~1 hour after dosing.<sup>12</sup> Ertugliflozin exposure increases dose dependently over 0.5 to 300 mg, and there is no clinically meaningful effect on pharmacokinetics (PK) when administered with or without food.<sup>12,13</sup> The PK of

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[Correction added on 5 February 2021, after first online publication: the word “ $C_{trough}$ ” is added to the sentence “The following PK parameters were calculated ... and observed accumulation ratio (Rac).” and the order of the author’s name is updated in reference 14.]

ertugliflozin has been shown to be comparable across populations with T2DM, healthy, and obese study participants.<sup>12</sup> Additionally, a population PK analysis of ertugliflozin indicated that race does not have a clinically relevant effect on the PK of ertugliflozin.<sup>14</sup> A phase 1 drug-drug interaction study demonstrated that ertugliflozin exposure (AUC) decreased by 39% following coadministration with rifampin.<sup>15</sup> Further assessment of the drug interaction potential of ertugliflozin showed that concomitant administration of metformin, sitagliptin, glimepiride, or simvastatin did not have clinically meaningful effects on the PK of ertugliflozin or the coadministered medications.<sup>16</sup> Renal impairment studies have predicted a  $\leq 70\%$  increase in ertugliflozin exposure in patients with T2DM and mild, moderate, or severe renal impairment relative to subjects with normal renal function.<sup>17</sup> Additionally, in subjects with moderate hepatic impairment, a decrease in area under the plasma concentration–time curve (AUC; 13%) relative to subjects with normal hepatic function was observed.<sup>18</sup> Based on ertugliflozin PK findings, these studies indicate that there is no meaningful difference in PK between healthy subjects and T2DM patients<sup>12</sup> and that ertugliflozin can be administered without regard to food<sup>13</sup> or race,<sup>14</sup> and dose adjustment of ertugliflozin is not required for coadministration with commonly prescribed drugs,<sup>15,16</sup> or in patients with renal impairment<sup>17</sup> or with mild-to-moderate hepatic impairment.<sup>18</sup>

Ertugliflozin is mainly cleared via metabolism, with the major metabolic pathway being glucuronidation (86%)<sup>3</sup> catalyzed by the uridine diphosphate-glucuronosyltransferase (UGT) enzymes isoforms UGT1A9 and UGT2B7.<sup>2</sup> Oxidative metabolism plays a minor role in the clearance of ertugliflozin (12%), with cytochrome P450 (CYP) 3A4 being the predominant enzyme isoform, together with contributions from CYP2C8 and CYP3A5. Urinary excretion of unchanged drug accounts for 1.5% of the administered dose.<sup>3</sup> In vitro binding studies showed that ertugliflozin is extensively bound to plasma proteins (93.6%).<sup>2</sup>

A pharmacodynamic (PD) study of single oral escalating doses of ertugliflozin in healthy subjects under fasted conditions and multiple oral escalating doses of ertugliflozin in otherwise healthy overweight/obese subjects under fed conditions led to dose-dependent increases in cumulative 24-hour UGE (UGE<sub>24</sub>) values.<sup>19</sup>

This phase 1 study was the first clinical study for ertugliflozin in Japanese subjects in the global development program. The primary objective was to investigate the safety, tolerability, PK, and PD (as measured by UGE) of ertugliflozin in healthy Japanese subjects following single and multiple oral doses of ertugliflozin administered as a tablet. Healthy Western subjects were also included in the single-dose part of this study. Di-

rect comparison of PK and PD of ertugliflozin between Japanese and Western subjects was included to investigate ethnic sensitivity. While the ethnic sensitivity of ertugliflozin could have been explored in a between-study comparison of PK and PD, using individual data from different clinical studies assessing the exposure-response relationship in Japanese and non-Japanese subjects, the direct comparison of PK and PD of ertugliflozin between Japanese and Western subjects presented here reduced the influence of external factors such as differences in study sites, conduction timing, and assay procedures.

## Materials and Methods

### Study Design

This was a randomized, phase 1, double-blind (sponsor-open), parallel-cohort, ascending single-dose (in 1 day) and multiple-dose (with 1 dose level) study in healthy Japanese subjects, and an open-label, ascending single-dose study in healthy Western subjects. The study consisted of 2 cohorts. In Cohort A, healthy Japanese and Western subjects received 3 ascending single doses (1, 5, and 25 mg) of ertugliflozin (n = 6 Japanese subjects, n = 6 Western subjects) or matching placebo (n = 3 Japanese subjects) through 3 dosing periods. In Cohort B, Japanese subjects received once-daily doses of ertugliflozin 25 mg (n = 6) or matching placebo (n = 3) for 7 days. For both cohorts, subjects were screened within 28 days of the first dose of study medication. Japanese subjects were blinded to the study treatment and randomized 2:1 to ertugliflozin or placebo. Western subjects were unblinded and received ertugliflozin. As this was an exploratory study, sample size was selected to minimize first exposure of a new drug to an ethnic population and meet the requirement to provide adequate safety and tolerability information at each dose level.

In Cohort A, eligible subjects were admitted to the study center on day 0 of period 1. Subjects were required to remain in the center for at least 72 hours after dosing and thereafter could discharge from or stay in the center; if discharged, subjects were required to return to the unit on day 0 of each study period. Study medication was dosed on day 1 of each period under fasted conditions, with a washout period of at least 7 days between doses. Subjects were discharged from the study center after PK sampling 72 hours after dosing in period 3. Subjects returned to the study center 7 to 10 days after the last dose for a follow-up visit.

Cohort B was started after completion of Cohort A. In Cohort B, subjects were admitted to the study center on day 0 and were required to remain in the center until the morning of day 10, for a total of 10 overnight days. Study medication was administered within

5 minutes after a light breakfast ( $\approx$  650 calories; mean (range) fat content 38% [29%-50%]). Subjects were discharged from the center after PK sampling 72 hours after the last dose. Subjects returned to the study center 7 to 10 days after the last dose for a follow-up visit.

The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and in compliance with International Conference on Harmonisation Good Clinical Practice guidelines. The study was 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. Investigators were required to inform the Ethical Review Board of the study's progress and occurrence of any serious and/or unexpected adverse events (AEs). All subjects signed an informed consent document before participating in the study.

### Subjects

Detailed inclusion and exclusion criteria for Japanese and Western subjects can be found in the Supplemental Information. Briefly, subjects were healthy men and women of non-childbearing potential, 18 to 55 years of age, a total body weight  $>50$  kg (110 lb), and a body mass index of 17.5 to 30.5 kg/m<sup>2</sup>. Asian or Polynesian subjects were excluded from the Western subject groups. Japanese subjects were required to have 4 Japanese grandparents who were born in Japan. Japanese subjects were enrolled, and mean body weight and body weight range was determined. Western subjects were enrolled later and selected to ensure the mean body weight and body weight range of the Western subjects were similar (within  $\pm 10\%$ ) to those of Japanese subjects.

### Assessments

Blood samples (3 mL) were collected to ensure at least 1.5 mL of plasma was available for PK analysis. For each treatment period in Cohort A, blood samples were collected at 0 hours (predose), and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours after dosing. In Cohort B, blood samples were collected on day 1 at 0 hours and 0.5, 1, 2, 3, 4, 6, 8, and 12 hours after dosing; on days 2, 4, 5, and 6 at 0 hours; and on day 7 at 0 hours and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours after dosing.

Plasma samples were analyzed for ertugliflozin concentrations at Tandem Labs (West Trenton, New Jersey) using a validated high-performance liquid chromatography (HPLC)-tandem mass spectrometric method. Ertugliflozin was extracted from human plasma (100  $\mu$ L) by liquid/liquid extraction using d5-PF-04971729, an isotopically labeled ertugliflozin, as the internal standard. The extracted sample was injected into a high-performance liquid chromatography column, Fortis C18 (Fortis Technologies, Los Ange-

les, California),  $50 \times 2.1$  mm, 5  $\mu$ m with gradient mobile phase containing 0.1% formic acid in water and methanol/acetonitrile solution (1:1, v/v). Detection was performed by API 5000 (SCIEX, Framingham, Massachusetts) in the positive ion mode. The multiple reaction monitoring ion transition was  $m/z$  437 $\rightarrow$ 329 for ertugliflozin and  $m/z$  442 $\rightarrow$ 334 for the internal standard. The lower limit of quantitation of the assay was 0.500 ng/mL, and the calibration range was 0.500 to 250 ng/mL. Those samples with concentrations above the upper limits of quantification were adequately diluted into calibration range. The precision of the assay was no more than 10.0% and 8.7% for the intraday and interday variability, respectively. The intraday and interday accuracy (error) was  $-11.3\%$  to 6.7% and  $-3.1\%$  to 2.3%.

Actual sample collection times were used for the PK analysis. The following PK parameters were calculated for each subject in Cohort A:  $C_{\max}$ , time to  $C_{\max}$  ( $t_{\max}$ ), terminal half-life ( $t_{1/2}$ ), AUC from time zero to the time of the last quantifiable concentration ( $AUC_{\text{last}}$ ), AUC from time zero extrapolated to infinity time ( $AUC_{\text{inf}}$ ), and apparent clearance (CL/F). The following PK parameters were calculated for each subject in Cohort B:  $C_{\max}$ ;  $t_{\max}$ ;  $t_{1/2}$ ; AUC from time 0 to time tau ( $\tau$ ), the dosing interval, where tau = 24 hours (the dosing interval) and ss = steady state ( $AUC_{\tau, \text{Day}1}$  and  $AUC_{\tau, \text{ss}}$ ); predose concentration ( $C_{\text{trough}}$ ), CL/F, and observed accumulation ratio ( $R_{\text{ac}}$ ). Samples below the lower limit of quantitation (0.500 ng/mL for ertugliflozin) were set to 0 for analysis.

Urine samples were collected for PD analysis to assess UGE. Water could be consumed without restriction beginning 1 hour after dosing. In Cohort A, samples were collected on day 1 of each period, and during intervals of 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, and 48 to 72 hours after dosing, with forced voids at the beginning and end of each interval. In Cohort B, samples were collected on day 1 and day 7, and during intervals of 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours after dosing, with forced voids at the beginning and end of each interval. Urine samples were assayed for glucose concentrations using a quantitative diagnostic-use-only assay by VITROS GLU Slides and the VITROS Chemistry Products Calibrator Kit 1 on VITROS Chemistry Systems (Ortho Clinical Diagnostics, Raritan, New Jersey) at the College of American Pathologists/Clinical Laboratory Improvement Amendments (CAP/CLIA) certified Pfizer Clinical Research Unit (New Haven, Connecticut). The assay had a dynamic range of 20 to 650 mg/dL.

Ertugliflozin safety and tolerability were assessed by AE monitoring, clinical safety laboratory measurements (hematology, chemistry, and urinalysis), physical examination and vital signs (blood pressure and pulse

**Table 1.** Demographic Characteristics in Cohort A (Single Dosing) and Cohort B (Multiple Dosing)

	Cohort A			Cohort B	
	Ertugliflozin Japanese (n = 6)	Placebo Japanese (n = 3)	Ertugliflozin Western (n = 6)	Ertugliflozin Japanese (n = 6)	Placebo Japanese (n = 3)
Sex, n					
Male	6	3	6	4	3
Female	0	0	0	2	0
Age, y					
Mean (SD)	35.7 (6.4)	35.0 (10.4)	34.7 (6.2)	42.7 (10.9)	41.0 (6.2)
Range	27-45	28-47	27-46	31-54	36-48
Race, n					
White	0	0	1	0	0
Black	0	0	5	0	0
Asian	6	3	0	6	3
Weight, kg					
Mean (SD)	65.0 (8.9)	64.1 (6.5)	66.3 (3.6)	68.4 (14.3)	67.9 (11.3)
Range	55.8-80.4	58.8-71.4	60.1-70.0	50.9-87.1	57.9-80.2
BMI, kg/m <sup>2</sup>					
Mean (SD)	21.6 (2.5)	21.4 (2.2)	23.8 (2.3)	23.9 (2.9)	22.9 (3.8)
Range	17.7-25.5	20.0-23.9	20.4-26.2	20.9-28.3	20.5-27.3

BMI, body mass index; SD, standard deviation.

rate), and 12-lead electrocardiogram (ECG). AEs were summarized per the Medical Dictionary for Regulatory Activities version 13.1.

### Statistical Analysis

The PK concentration analysis set was defined as all enrolled subjects who received  $\geq 1$  dose of ertugliflozin and in whom  $\geq 1$  concentration value was reported. The PK parameter analysis set included subjects who received  $\geq 1$  dose of ertugliflozin and in whom  $\geq 1$  of the PK parameters of interest was calculated. PK parameters were calculated for each subject in Cohort A and Cohort B, as applicable, using noncompartmental analysis of concentration-time data (electronic noncompartmental analysis version 2.2.2). PK parameters were summarized descriptively by dose and population (Japanese or Western) for Cohort A and by dosing day for Cohort B. Natural log-transformed  $AUC_{inf}$ ,  $AUC_{last}$ , and  $C_{max}$  were analyzed using a mixed-effect model with dose, population, and interaction term of dose by population as fixed effects, subject within population as a random effect, and natural log-transformed body weight as a covariate. The adjusted mean difference among populations (Japanese-Western) and corresponding 90% confidence intervals (CIs) were estimated for each dose level. The adjusted mean differences and corresponding 90% CIs were exponentiated to provide estimates of the ratio of adjusted

geometric means (Japanese/Western) and 90% CIs for the ratio.

Cumulative UGE over 24 hours ( $UGE_{24}$ ) was calculated for each subject and was summarized by dose and population for Cohort A and by dosing day for Cohort B, using descriptive statistics. In addition, 24-hour inhibition (%) of glucose reabsorption, calculated using the equation  $UGE_{24}/(\text{estimated glomerular filtration rate [mL/min]} \times \text{fasting glucose concentration [mg} \bullet \text{h/dL]}) \times 0.0144$ , was summarized for each cohort.

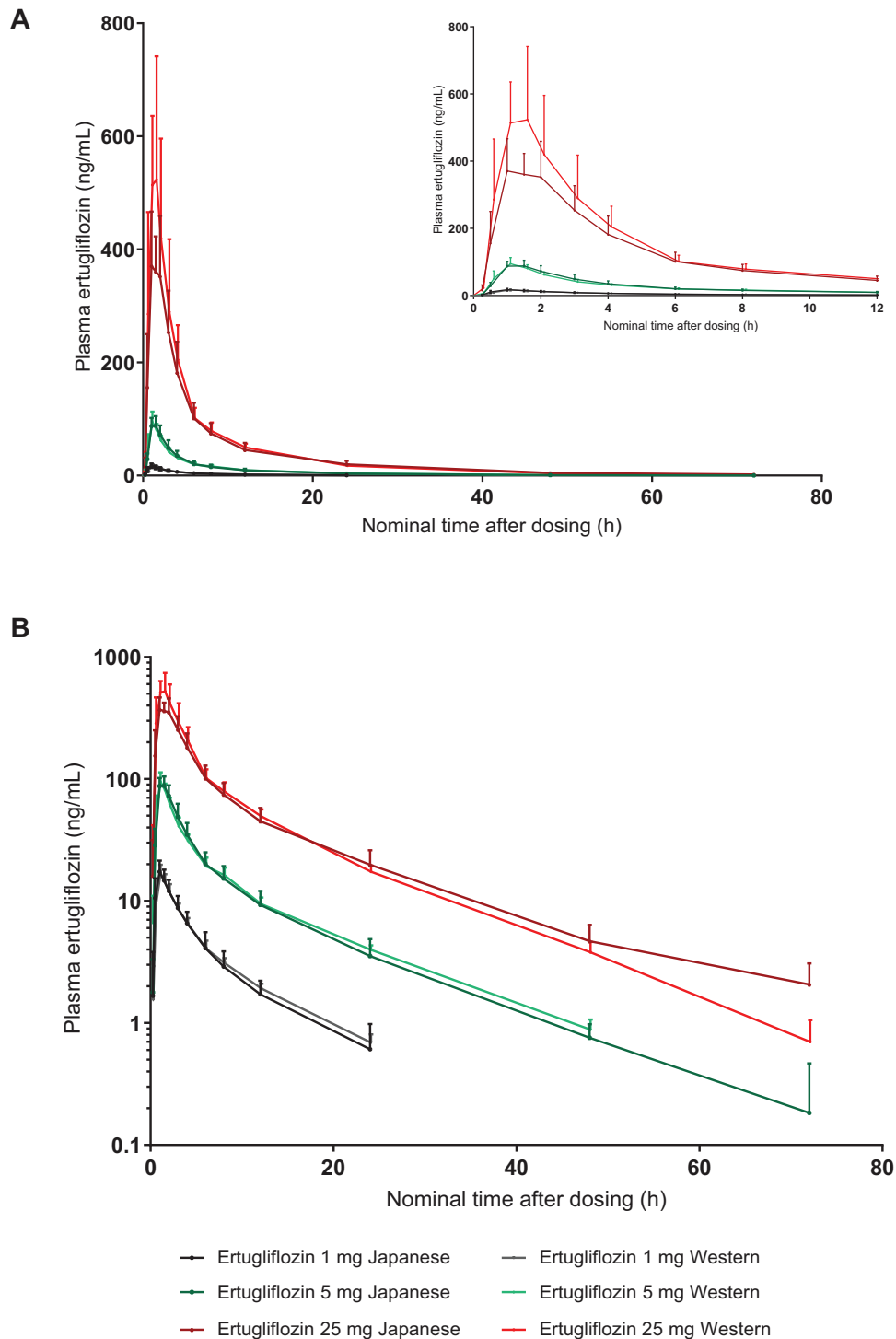
## Results

### Subject Demographics

Fifteen subjects were allocated to Cohort A, and 9 subjects were allocated to Cohort B. All 24 subjects completed the study and were included in the analysis. All subjects in Cohort A were men (9 Japanese and 6 Western); there were no major differences in demographic characteristics other than race between Japanese and Western subjects (Table 1). All subjects in Cohort B were Japanese (7 men and 2 women); there were no major differences in demographic characteristics other than sex between the placebo and ertugliflozin treatment groups (Table 1).

### Pharmacokinetics

In Cohort A, the mean ertugliflozin concentration-time profiles following a single ascending oral dose of 1, 5, and 25 mg of ertugliflozin under fasted conditions were similar in Japanese and Western subjects (Figure 1).



**Figure 1.** Mean (standard deviation) plasma ertugliflozin concentration-time profile in Cohort A in (A) linear (principal plot) with the 0- to 12-hour interval on an expanded time scale (inset plot) and (B) semilogarithmic scales. Summary statistics were calculated by setting concentration values below the lower limit of quantification (0.500 ng/mL) to 0.

Absorption of ertugliflozin was rapid, with median  $t_{\max}$  of 1 to 1.5 hours after dosing in the Japanese and Western populations and across all dose groups (Table 2). The distributions of individual dose-normalized  $C_{\max}$  and  $AUC_{\text{last}}$  overlapped

across the doses and populations, and the geometric means of these values were generally similar (Figure 2A and B). After  $C_{\max}$ , ertugliflozin concentrations declined in a biphasic manner over time with a  $t_{1/2}$  of 12.4 to 13.6 hours in Japanese and 10.7 hours

**Table 2.** Summary of Ertugliflozin PK Parameters in Healthy Japanese and Western Subjects Following Single Oral Doses in Cohort A

Parameter <sup>a</sup>	1 mg		5 mg		25 mg	
	Japanese (n = 6)	Western (n = 6)	Japanese (n = 6)	Western (n = 6)	Japanese (n = 6)	Western (n = 6)
AUC <sub>inf</sub> , ng • h/mL	NC	NC	476 (22) 486 ± 107	481 (10) 483 ± 46	2402 (22) 2448 ± 537	2638 (23) 2692 ± 613
AUC <sub>last</sub> , ng • h/mL	77.6 (25) 79.5 ± 19.8	80.9 (11) 81.2 ± 8.53	466 (23) 476 ± 108	467 (10) 469 ± 47.5	2364 (22) 2412 ± 537	2618 (23) 2673 ± 619
C <sub>max</sub> , ng/mL	17.9 (18) 18.1 ± 3.24	16.6 (18) 16.8 ± 2.99	91.6 (17) 92.8 ± 15.5	93.9 (19) 95.3 ± 17.8	429 (11) 432 ± 48.9	536 (34) 562 ± 188
t <sub>max</sub> , h	1.00 (0.500-2.00)	1.00 (1.00-1.00)	1.50 (1.00-1.50)	1.00 (1.00-1.50)	1.25 (1.00-2.00)	1.00 (1.00-1.50)
t <sub>1/2</sub> , h	NC	NC	12.4 (40)	10.7 (12)	13.6 (20)	10.7 (8)
CL/F, mL/min	NC	NC	175 (20) 178 ± 36.3	173 (9) 174 ± 16.2	174 (20) 177 ± 36.1	158 (20) 161 ± 32.7

AUC, area under the plasma concentration–time curve; AUC<sub>inf</sub>, AUC from time 0 extrapolated to infinite time; AUC<sub>last</sub>, AUC from time 0 to the time of last measurable concentration; CL/F, apparent clearance; C<sub>max</sub>, maximum observed plasma concentration; CV, coefficient of variation; NC, not calculated; t<sub>1/2</sub>, terminal half-life; t<sub>max</sub>, time to C<sub>max</sub>.

<sup>a</sup>Values are geometric mean (geometric %CV) and arithmetic mean ± SD for all except median (range) for t<sub>max</sub> and arithmetic mean (%CV) for t<sub>1/2</sub>.

**Table 3.** Statistical Summary of Ertugliflozin Exposure Comparison Between Healthy Japanese and Western Subjects in Cohort A

Dose	Parameter	Adjusted Geometric Means		Ratio of Adjusted Geometric Means, %	90%CI for Ratio
		Japanese	Western		
1 mg	C <sub>max</sub> , ng/mL	17.9	16.6	107.59	87.61-132.11
	AUC <sub>last</sub> , ng • h/mL	77.6	80.9	95.94	78.76-116.87
5 mg	C <sub>max</sub> , ng/mL	91.6	93.9	97.47	79.38-119.69
	AUC <sub>last</sub> , ng • h/mL	466	467	99.66	81.81, 121.40
	AUC <sub>inf</sub> , ng • h/mL	476	481	98.94	81.17-120.61
25 mg	C <sub>max</sub> , ng/mL	429	536	80.04	65.18-98.28
	AUC <sub>last</sub> , ng • h/mL	2365	2618	90.32	74.14-110.02
	AUC <sub>inf</sub> , ng • h/mL	2402	2638	91.05	74.70-110.99

AUC, area under the plasma concentration–time curve; AUC<sub>inf</sub>, AUC from time 0 extrapolated to infinite time; AUC<sub>last</sub>, AUC from time 0 to the time of last measurable concentration; CI, confidence interval; C<sub>max</sub>, maximum observed plasma concentration.

Mixed-effect model with dose, populations, and interaction term of dose by population as fixed effects, subject within population as random effect.

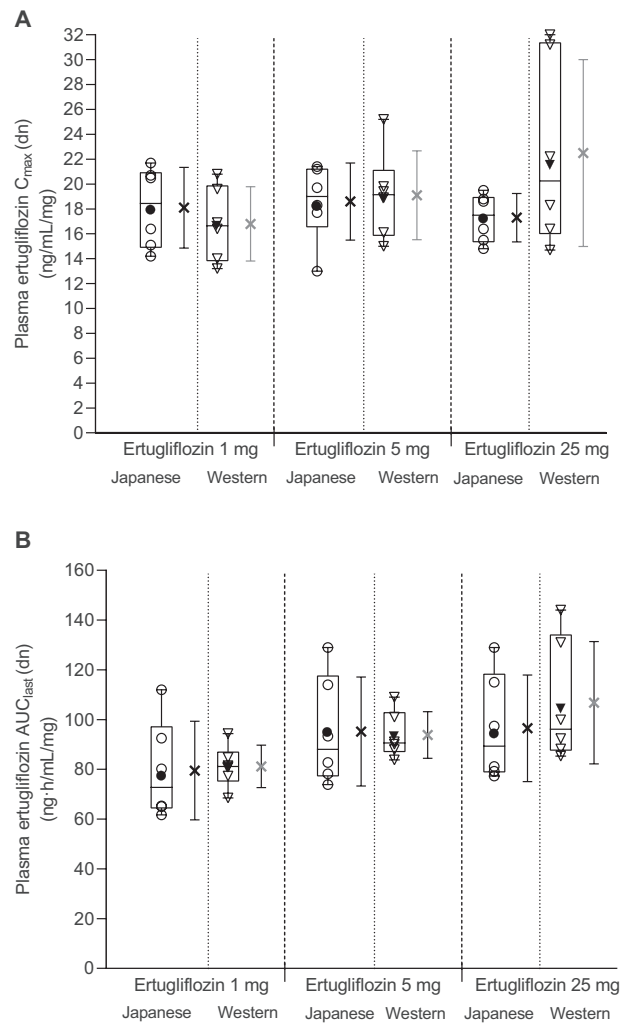
in Western subjects. AUC<sub>last</sub> and C<sub>max</sub> generally increased in a dose-proportional manner in both populations (Figure 2A and B; Table 2). The ratios of the adjusted geometric means (Japanese/Western subjects) for ertugliflozin 1-, 5-, and 25-mg single doses were 95.94%, 99.66%, and 90.32%, respectively, for AUC<sub>last</sub> and 107.59%, 97.47%, and 80.04%, respectively, for C<sub>max</sub> (Table 3).

In Cohort B, following multiple oral doses of ertugliflozin in Japanese subjects under fed conditions, median t<sub>max</sub> was 2.5 hours after dosing on both days 1 and 7 (Table 4). After C<sub>max</sub> was reached, ertugliflozin

concentrations declined in a biphasic manner over time, with t<sub>1/2</sub> of 9.91 hours on day 7 (Figure 3); steady state appeared to have been reached by day 4 based on visual observation of similar median trough concentrations from day 4 to day 8 (data not shown). The geometric mean R<sub>ac</sub> was 1.11 (Table 4).

### Pharmacodynamics

In Cohort A, the UGE<sub>24</sub> following single ertugliflozin 1-, 5-, and 25-mg doses was dose dependent (Figure 4A). Mean UGE<sub>24</sub> values obtained after single-dose administration in Japanese subjects were slightly



**Figure 2.** Individual, geometric, and arithmetic mean plasma ertugliflozin dose-normalized (A)  $C_{max}$  and (B)  $AUC_{inf}$  values by dose and population in Cohort A. Open circles and triangles identify individual subject data; closed circles and triangles identify geometric means. Offset crosses 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 the time of last measurable concentration;  $C_{max}$ , maximum observed plasma concentration; dn, dose-normalized.

higher than those in Western subjects; however, the individual  $UGE_{24}$  values in Japanese subjects overlapped with those in Western subjects at equivalent doses. In Cohort B, mean  $UGE_{24}$  following ertugliflozin 25 mg daily dosing in Japanese subjects was similar on day 7 (72.2 g) compared with day 1 (63.3 g) (Figure 4B).

In Cohort A, the 24-hour inhibition of glucose reabsorption following single ertugliflozin 1-, 5-, and 25-mg doses was dose dependent, with a similar extent of inhibition of glucose absorption occurring in Western subjects compared with Japanese subjects (Fig-

**Table 4.** Summary of Ertugliflozin PK Parameters in Healthy Japanese Subjects Following Multiple Oral Doses in Cohort B

Parameter <sup>a</sup>	Ertugliflozin 25 mg Daily (n = 6)
<b>Day 1</b>	
$AUC_{\tau, Day 1}$ , ng·h/mL	1973 (19) 2003 ± 390
$C_{max}$ , ng/mL	365 (15) 368 ± 55.7
$t_{max}$ , h	2.50 (0.500-4.00)
<b>Day 7</b>	
$AUC_{\tau, ss}$ , ng·h/mL	2191 (25) 2247 ± 565
$C_{max}$ , ng/mL	368 (23) 377 ± 84.8
$C_{trough}$ , ng/mL	22.3 (45) 24.3 ± 11.0
$t_{max}$ , h	2.50 (1.05-4.00)
$t_{1/2}$ , h	9.91 (35)
$R_{ac}$	1.11 (10) 1.12 ± 0.113
CL/F, mL/min	190 (23) 194 ± 43.7

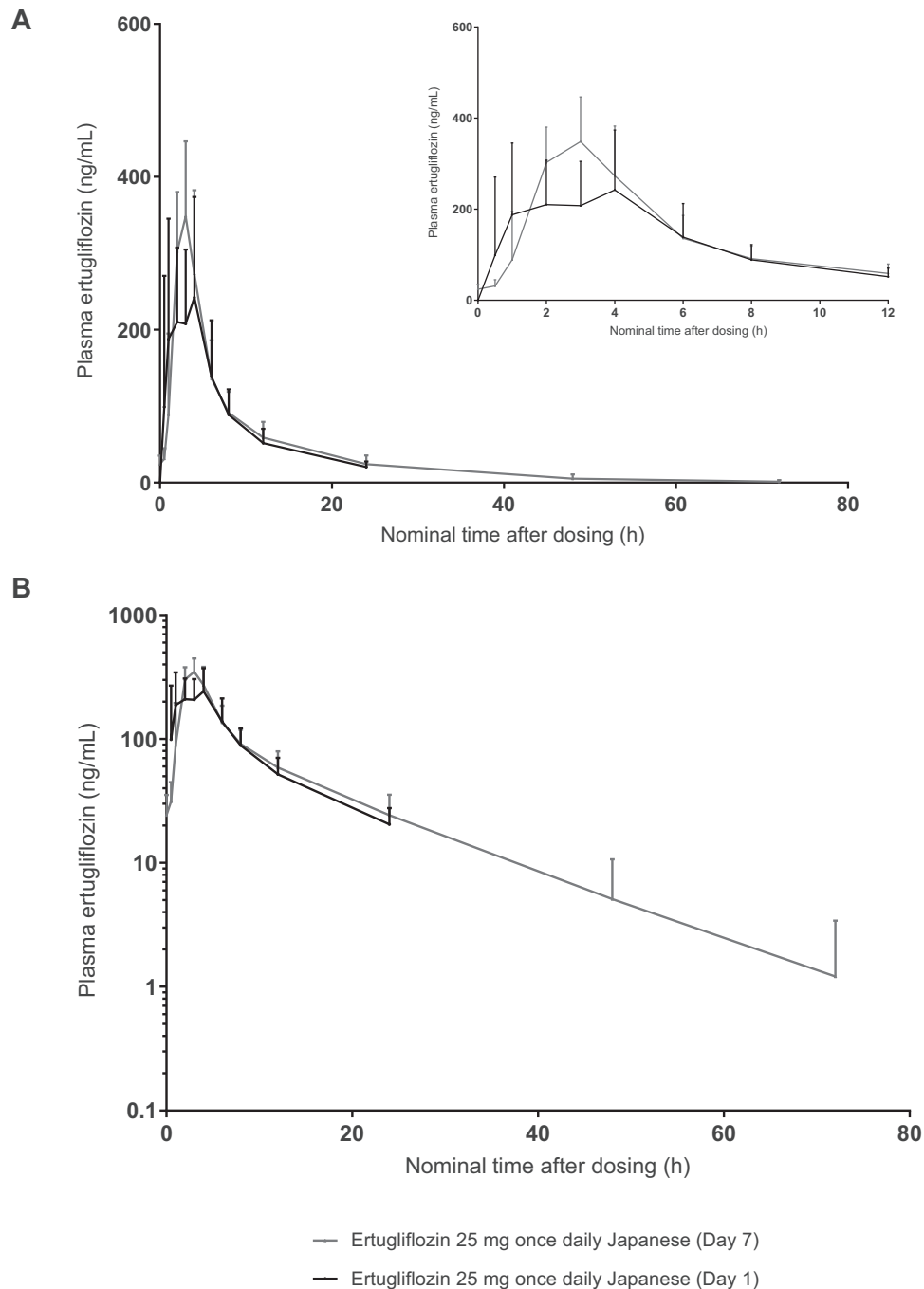
AUC, area under the plasma concentration–time curve;  $AUC_{\tau, Day 1}$ , AUC from time 0 to  $\tau$  on day 1;  $AUC_{\tau, ss}$ , AUC from time 0 to  $\tau$  at steady-state; CL/F, apparent clearance;  $C_{max}$ , maximum observed plasma concentration;  $C_{trough}$ , predose concentration; CV, coefficient of variation;  $R_{ac}$ , observed accumulation ratio;  $\tau$ , dosing interval;  $t_{1/2}$ , terminal half-life;  $t_{max}$ , time to  $C_{max}$ .

<sup>a</sup>Values are geometric mean (geometric %CV) and arithmetic mean ± SD for all except median (range) for  $t_{max}$  and arithmetic mean (%CV) for  $t_{1/2}$ .

ure 5A). For Japanese subjects in Cohort A, the 24-hour inhibition of glucose reabsorption was 19.8%, 37.8%, and 41.8% in the 1-, 5-, and 25-mg treatment groups, respectively. For Western subjects in Cohort A, the 24-hour inhibition of glucose reabsorption was 21.6%, 39.8%, and 44.9% in the 1-, 5-, and 25-mg treatment groups, respectively. In Cohort B, the 24-hour inhibition of glucose reabsorption following ertugliflozin 25-mg daily dosing in Japanese subjects was similar on day 7 (53.4%) compared with day 1 (44.9%) (Figure 5B).

### Safety

Overall, 22 AEs were reported, 15 of which were considered treatment-related (13 in Cohort A and 2 in Cohort B; Table S1). Most AEs were mild in intensity. Fatigue was the most common AE in Cohort A, reported in 5 Western subjects (n = 2 for ertugliflozin 1 mg; n = 2 for ertugliflozin 5 mg; and n = 1 for ertugliflozin 25 mg). In all cases, fatigue was considered treatment related. All other AEs were single occurrences. In Cohort B, single occurrences of diarrhea, application site irritation, and otitis externa were reported by Japanese subjects while on ertugliflozin



**Figure 3.** Mean (standard deviation) plasma ertugliflozin concentration-time profile in Cohort B in (A) linear (principal plot) with the 0- to 12-hour interval on an expanded time scale (inset plot) and (B) semilogarithmic scales. Summary statistics were calculated by setting concentration values below the lower limit of quantification (0.500 ng/mL) to 0.

25 mg. A single occurrence of macular rash was reported in 1 Japanese subject while receiving placebo. Diarrhea and otitis externa were considered related to treatment.

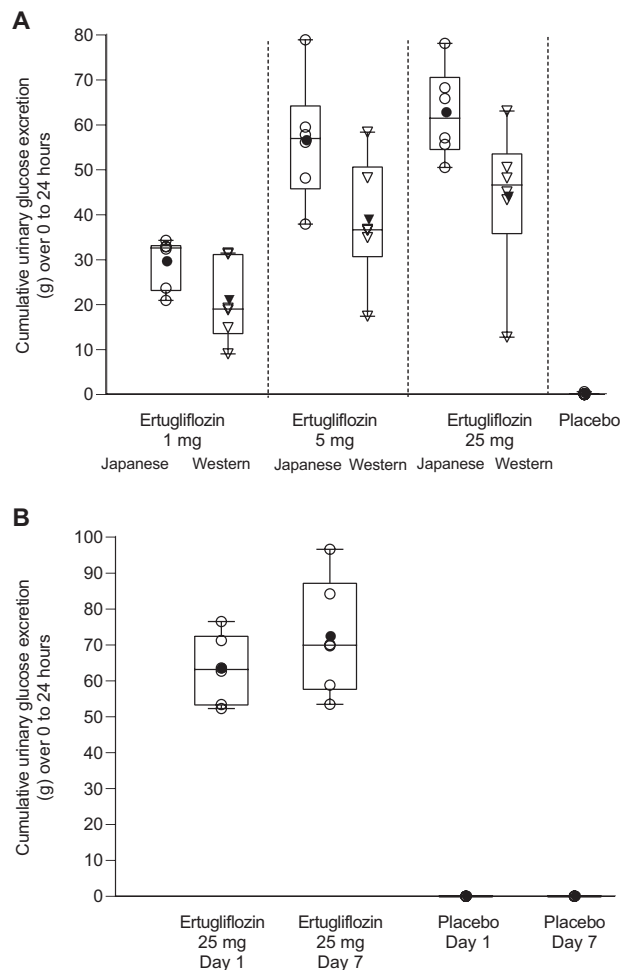
No deaths, serious or severe AEs, or dose reductions or discontinuations due to AEs were reported. No laboratory abnormalities or ECGs of clinical significance or clinically meaningful changes from baseline in vital signs were observed. No relationship was observed

between incidence or severity of AEs, laboratory abnormalities, vital sign changes, or ECG changes and population (Japanese or Western).

## Discussion

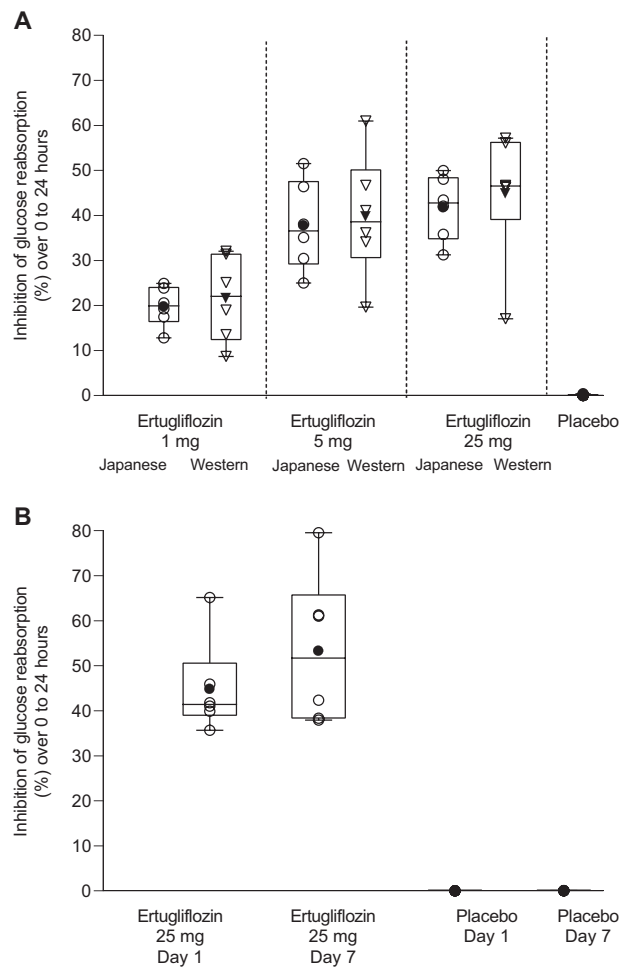
This randomized, phase 1, double-blind (sponsor-open), parallel-cohort study and open-label study evaluated the PK and PD of ertugliflozin in healthy





**Figure 4.** Individual and arithmetic mean  $UGE_{24}$  by (A) treatment (ertugliflozin 1, 5, and 25 mg or placebo) and population (healthy Japanese and Western subjects) in Cohort A and by (B) treatment (ertugliflozin 25 mg or placebo) and dosing day (day 1 and 7) in healthy Japanese subjects in Cohort B. Open circles and triangles identify individual subject data; closed circles and triangles identify arithmetic means. Box plots provide medians, and 25% and 75% quartiles with whiskers extended to the minimum/maximum values.  $UGE_{24}$ , cumulative urinary glucose excretion over 24 hours.

Japanese and Western subjects. Absorption of ertugliflozin was rapid, with median  $t_{max}$  of 1.00 to 1.50 hours under fasted conditions, which was delayed to 2.50 hours under fed conditions. Exposure of ertugliflozin ( $C_{max}$  and  $AUC_{last}$ ) increased with dose in an approximately dose-proportional manner, and apparent  $t_{1/2}$  of ertugliflozin was 9.91 to 13.6 hours following single- and multiple-dose administration. Following multiple-dose administration, steady-state appears to have been reached by day 4 based on visual observation of trough concentrations from day 4 to day 8. The  $R_{ac}$  of 1.11 is consistent with estimated half-life and indicates minimal accumulation of



**Figure 5.** A total of 24-hour inhibition of glucose reabsorption by (A) treatment (ertugliflozin 1, 5, and 25 mg or placebo) and population (healthy Japanese and Western subjects) in Cohort A and by (B) treatment (ertugliflozin 25 mg or placebo) and dosing day (days 1 and 7) in healthy Japanese subjects in Cohort B. Open circles and triangles identify individual subject data; closed circles and triangles identify arithmetic means. Box plots provide medians, and 25% and 75% quartiles with whiskers extended to the minimum/maximum values. A total of 24-hour inhibition (%) of glucose reabsorption was calculated using the equation  $UGE_{24}/(\text{estimated glomerular filtration rate [mL/min]} \times \text{fasting glucose concentration [mg}\cdot\text{h/dL]}) \times 0.0144$ .

ertugliflozin. No meaningful differences were observed in ertugliflozin exposure between Japanese and Western subjects across the 3 doses of ertugliflozin assessed.

The amount of glucose excreted in the urine ( $UGE_{24}$ ) following single ertugliflozin 1-, 5-, and 25-mg doses was dose dependent. The amount of glucose excreted in the urine following ertugliflozin 25-mg once-daily dosing on day 7 was similar compared with day 1.  $UGE_{24}$  for subjects in the placebo group in both cohorts was negligible. The range of  $UGE_{24}$  values and inhibition of renal glucose reabsorption generally

overlapped between Japanese and Western subjects at equivalent doses, suggesting no meaningful differences in the PD between the 2 populations.

The PK and PD results in this study are consistent with previous phase 1 studies of ertugliflozin conducted in Western subjects.<sup>12</sup> The results of the current PK analysis in Japanese subjects are also similar to those observed in a study evaluating the PK, safety, and tolerability of ertugliflozin 5 and 15 mg in healthy Chinese adults.<sup>20</sup> Additionally, in the study of Chinese subjects, the  $R_{ac}$  was  $\approx 1.3$  and 1.2 for ertugliflozin 5 and 15 mg, respectively, which is similar to the  $R_{ac}$  of 1.2 to 1.4 observed in single- and multiple-dose studies of ertugliflozin conducted in healthy Western subjects.<sup>12</sup> Findings from a population PK analysis of ertugliflozin have also indicated that race does not have a clinically relevant effect on the PK of ertugliflozin.<sup>14</sup> The PK of ertugliflozin was also similar in healthy subjects and patients with T2DM,<sup>17</sup> indicating no meaningful differences would be expected between Japanese healthy subjects and Japanese patients with T2DM. Furthermore, results from a longer-term phase 3 study in Asian patients with T2DM demonstrated that ertugliflozin improved glycemic control and reduced body weight and systolic blood pressure in Asian patients with T2DM inadequately controlled on metformin monotherapy.<sup>11</sup> Taken together, the comparable efficacy and safety across the ertugliflozin phase 3 studies in varied populations and the PK and PD findings from the phase 1 studies including Japanese subjects suggest no clinically meaningful PK or PD differences, and no dose modification of ertugliflozin is required based on race.

As UGT1A9 and UGT2B7 are the primary enzymes involved in ertugliflozin glucuronidation,<sup>2</sup> the presence of race-specific polymorphisms in the genes encoding these enzymes could potentially affect UGT activity and ultimately affect the metabolism of ertugliflozin. However, the effects of the allelic variants of UGT1A9 were demonstrated to be within  $\pm 10\%$  of the wild type in a pooled analysis of AUC values from 20 phase 1 studies suggesting these polymorphisms are not clinically relevant.<sup>21</sup> Furthermore, no UGT2B7 polymorphisms have been reported to have a clinically meaningful impact on the PK of ertugliflozin.<sup>22</sup> The low fraction of elimination attributed to CYP3A4, CYP3A5, and CYP2C8 makes it unlikely that any differences would arise from polymorphism of these enzymes. Consequently, race-specific genetic polymorphisms in enzymes that metabolize ertugliflozin are unlikely to have a clinically meaningful impact on the PK, further supporting the results of this study.

Interestingly, in this study of healthy Japanese and Western subjects, the majority of the Western subjects (5 of the 6 subjects) were Black. Given the lack of a

clinically relevant effect of race in a population PK analysis of ertugliflozin and that race-specific genetic polymorphisms in UGT1A9 and UGT2B7 are unlikely to affect ertugliflozin PK parameters, the high proportion of Black subjects in this study is unlikely to impact the comparison of PK and PD parameters between Japanese and Western subjects.

Ertugliflozin at single doses of 1, 5, and 25 mg, as well as 25 mg once daily for 7 days, was found to be safe and well tolerated in this study. There were no deaths, serious or severe AEs, and most reported AEs were mild in severity, and there were no meaningful differences between Japanese and Western subjects with respect to safety. No specific tolerability issues were identified with ertugliflozin dosing in healthy Japanese subjects, and there were no treatment discontinuations due to AEs in this study.

## Conclusions

In healthy Japanese subjects, exposure of ertugliflozin following single-dose (1, 5, and 25 mg) administration increased in a dose-proportional manner. Absorption was rapid, and accumulation after multiple-dose (25 mg daily) administration was minimal. Single oral doses of ertugliflozin in healthy Japanese and healthy Western subjects induced glycosuria; UGE<sub>24</sub> was dose dependent. Little difference was observed for UGE on day 1 and day 7 following multiple daily dosing. The PK and PD findings from this phase 1 study of Japanese and Western subjects suggest no clinically meaningful PK or PD differences, and no dose modification of ertugliflozin is required based on race. Ertugliflozin was generally well tolerated after single- and multiple-dose administration in Japanese subjects. There were no meaningful differences in ertugliflozin exposure, UGE, and safety between healthy Japanese and Western subjects.

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## Conflicts of Interest

Y.L. and Y.Y. are employees of Pfizer Research and Development, Japan. G.N. is an employee of Pfizer Inc., Cambridge, Massachusetts. D.J.F. and V.S. are employees of Pfizer Inc., Groton, Connecticut. All authors may own shares/stock options in Pfizer Inc.

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## Data Accessibility Statement

Upon request, and subject to certain criteria, conditions, and exceptions (see <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the 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 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.

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### Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.