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Population Pharmacokinetic Analyses of Ertugliflozin in Select Ethnic Populations

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Abstract

Ertugliflozin, a sodium-glucose cotransporter 2 inhibitor, is approved for treatment of type 2 diabetes. Two population pharmacokinetic (PK) analyses were conducted, using data from up to 17 phase 1 to 3 studies, to characterize ertugliflozin PK parameters in select ethnic subgroups: (1) East/Southeast (E/SE) Asian vs non-E/SE Asian subjects; (2) Asian subjects from mainland China vs Asian subjects from the rest of the world and non-Asian subjects. A 2-compartment model with first-order absorption, lag time, and first-order elimination was fitted to the observed data. For the E/SE Asian vs non-E/SE Asian analysis (13 692 PK observations from 2276 subjects), E/SE Asian subjects exhibited a 17% increase in apparent clearance (CL/F) and 148% increase in apparent central volume of distribution (Vc/F) vs non-E/SE Asian subjects. However, individual post hoc CL/F values were similar between groups when body weight differences were considered. For the second analysis (16 018 PK observations from 2620 subjects), compared with non-Asian subjects, CL/F was similar while Vc/F increased by 44% in Asian subjects from mainland China and both CL/F and Vc/F increased in Asian subjects from the rest of the world (8% and 115%, respectively) vs non-Asian subjects. Increases in Vc/F would decrease the ertugliflozin maximum concentration but would not impact area under the concentration-time curve. Therefore, the differences in CL/F (area under the concentration-time curve) and Vc/F were not considered clinically relevant or likely to result in meaningful ethnic differences in the PK of ertugliflozin.

Keywords

diabetes, ertugliflozin, population pharmacokinetics, sodium-glucose cotransporter 2 inhibitor

The International Diabetes Federation Western Pacific Region includes 39 countries and territories such as China, Republic of Korea, Taiwan, and other East Asian nations.[1] International Diabetes Federation estimates for this region indicate that the prevalence of diabetes in adults (aged 20-79 years) is expected to increase from 9.5% (159 million people) in 2017 to an estimated 10.3% (183 million people) by 2045.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors lower plasma glucose levels by reducing renal glucose reabsorption and lowering the renal threshold for glucose excretion, thereby increasing urinary glucose excretion.[2] Ertugliflozin is an SGLT2 inhibitor[3,4] that has been evaluated for the treatment of adults with type 2 diabetes mellitus (T2DM) in the phase 3 VERTIS (e**V**aluation of **ERT**ugliflozin e**I**fficacy and **S**afety) clinical trial program.[5–11] The results led to the approval of ertugliflozin as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, including in China, Hong Kong, Korea, Taiwan, and several other East Asian countries.

Pharmacokinetic (PK) studies have shown rapid oral absorption of ertugliflozin[4] and an absolute bioavailability of ≈ 100%.[12,13] The increase in exposure is dose proportional from 0.5 to 300 mg, and the terminal

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elimination half-life is typically 11 to 17 hours after oral administration.[3,13] Food intake does not meaningfully affect the PK of ertugliflozin, and tablets can be taken without regard to meals.[13,14] Ertugliflozin reached peak plasma concentration (C_{max}) after ≈1 hour and at ≈2 hours after dosing in the fasted and fed states, respectively.[13,15] Ertugliflozin PK is not time dependent, with steady state being achieved 4 to 6 days after once-daily dosing has started.[13,16] The PK of ertugliflozin is similar in healthy subjects and patients with T2DM.[13,17] Furthermore, PK studies have shown that the dose of ertugliflozin does not need to be adjusted when used concomitantly with drugs that are commonly prescribed.[13,18] Similarly, dose adjustments are not required in patients with renal impairment[17] or with mild-to-moderate hepatic impairment.[13,19]

A number of studies have explored the effect of ethnicity on ertugliflozin PK. In a phase 1 study conducted in healthy Chinese subjects, exposure (C_{max}, area under the concentration-time curve [AUC] from time 0 extrapolated to infinite time, and AUC for a dosing interval at steady state [$AUC_{\tau,ss}$]) of ertugliflozin increased in a dose-proportional manner following single- and multiple-dose administration.[20] The apparent terminal elimination half-life of ertugliflozin ranged from ≈9.5 to 11.9 hours, and the accumulation ratio (based on the AUC) of ertugliflozin exposure after multiple-dose administration was ≈1.3 and 1.2 for ertugliflozin 5 and 15 mg, respectively. Comparison of observed PK parameters with non-Asian subjects indicated that there were no clinically meaningful ethnic differences, and no dose modification of ertugliflozin is required on the basis of ethnicity or body weight. Ertugliflozin was generally well tolerated when administered as single and multiple oral doses of 5 mg and 15 mg in healthy Chinese subjects. In addition, a phase 1 study evaluating the PK and pharmacodynamics of single 1-, 5-, and 25-mg doses of ertugliflozin in Japanese and Western subjects showed no meaningful differences in exposure (C_{max} and AUC) or urinary glucose excretion between Japanese and Western subjects.[21]

To support the initial global filing of ertugliflozin, a population pharmacokinetic (popPK) analysis was conducted to quantify the influence of intrinsic and extrinsic covariates including body weight, age, sex, estimated glomerular filtration rate (eGFR), T2DM, and food on ertugliflozin PK parameters.[22] A 2-compartment popPK model with first-order absorption and a lag time and first-order elimination described the plasma concentration–time profile of ertugliflozin after single and multiple dosing in healthy subjects as well as in patients with T2DM. None of the covariates evaluated in the popPK model had a clinically relevant effect on ertugliflozin PK. The effect of race on both apparent clearance (CL/F) and apparent central volume of distribution (Vc/F) was explored (with White race as the reference). The effect of Black race or other ethnicity on CL/F and Vc/F was not significant; however, the effect of Asian descent was shown to be significant, but the differences were not considered clinically meaningful. A post hoc analysis exploring the potential impact of ethnicity in ertugliflozin clinical studies demonstrated clinically meaningful reductions in glycemic (glycated hemoglobin, fasting plasma glucose) and metabolic (body weight, blood pressure) end points in patients with T2DM from East/Southeast (E/SE) Asian countries.[23] The objective of the present study was to expand on the original popPK analysis and further evaluate potential ethnic differences in the PK of ertugliflozin to support the registration of ertugliflozin in China and E/SE Asian countries including Hong Kong, Republic of Korea, Malaysia, Philippines, Taiwan, and Thailand.

Methods

Clinical Studies and Data Collection

Studies included in this analysis followed the principles of Good Clinical Practice and approval from the appropriate institutional review boards and regulatory agencies was obtained. Individuals in each study provided informed consent. The analysis included data from up to 17 clinical studies: 10 phase 1 studies in healthy subjects and patients with T2DM; 2 phase 2 studies in patients with T2DM; and 5 phase 3 studies in patients with T2DM. There were differences in study design, study population, and timing of sample collection among the 17 clinical studies. Of these studies, 15 contributed to and are summarized in the previously published popPK analysis[22]; details of the additional 2 studies are listed in Table S1.

Ertugliflozin Analytical Assay

Plasma ertugliflozin concentration was determined as outlined in the sampling scheme for each study included in the previously published popPK analysis with details of the additional 2 studies listed in Table S2. Samples were analyzed using a high-performance liquid chromatography–tandem mass spectrometric method, as previously reported.[24] Plasma concentrations below the lower limit of quantification (0.5 ng/mL for 16 of the studies and 0.1 ng/mL for 1 study) were removed from the analysis data set.

Data for Analysis

Two popPK analyses were conducted independently: (1) In the first analysis, subjects were categorized into E/SE Asian vs non-E/SE Asian subjects to support the registration of ertugliflozin in E/SE Asian countries excluding mainland China (as the mainland China study

was ongoing and data were not available at the time of analysis); and (2) in the second analysis, subjects were categorized into 3 ethnic populations—Asian subjects from mainland China vs Asian subjects from the rest of the world and non-Asian subjects, to support the registration of ertugliflozin in China.

Data Set 1: E/SE Asian Subjects Versus Non-E/SE Asian Subjects. The final model data file for the analysis contained 13 692 PK observations from 2276 subjects. The data set for this popPK analysis was the same data set used in the previously published popPK analysis.[22] This current analysis categorized ethnicity into 2 mutually exclusive groups: E/SE Asian (N = 154) or non-E/SE Asian (N = 2122). Subjects were categorized as E/SE Asian if 1 of the following applied: Japanese subjects from a PK/pharmacodynamic phase 1 study,[21] subjects from phase 2/3 studies whose ethnicity was Asian (based on self-reporting) and who were enrolled at sites located in Hong Kong, Republic of Korea, Malaysia, Philippines, Taiwan, and Thailand. Asian subjects enrolled at US or European sites were categorized as non-E/SE Asian.

Data Set 2: Asian Subjects From Mainland China Versus Asian Subjects From the Rest of the World vs Non-Asian Subjects. The final model data file for the analysis contained 16 018 PK observations from 2620 subjects. The new, larger data set for this popPK analysis is updated from the previously published data set[22] with the inclusion of 2 additional studies: a phase 1 single- and multiple-dose PK study in healthy Chinese subjects[20] and a phase 3 study in Asian patients with T2DM.[8] These 2 studies (see Table S1) were not included in the previously published popPK analysis because the data were not available at the time of the original analysis.[22] For this analysis, ethnicity was categorized into 3 mutually exclusive groups: Asian subjects from mainland China (N = 277), Asian subjects from the rest of the world (N = 382), and non-Asian subjects (N = 1961).

Modeling Strategy and Software

The nonlinear mixed-effects modeling methodology used in this analysis has been described previously.[22]

Population PK Models

Model Development and Covariate Evaluation. Both popPK models were developed from the 2-compartment model with first-order absorption with lag time and first-order elimination as described in the previously published popPK analysis.[22] Covariates, including eGFR, sex, ethnicity, and patient status (healthy/T2DM) on CL/F, and age, sex, and ethnicity on Vc/F, were incorporated into the updated final model using the full model estimation procedure. Bootstrap analysis was implemented to generate the 95% confidence interval (CI) for the final popPK model parameters. Using post hoc individual CL/F estimates from the updated final model, boxplots were generated to compare the CL/F of the E/SE Asian subjects vs non-E/SE Asian subjects and of Asian subjects from mainland China vs Asian subjects from the rest of the world and non-Asian subjects.

Data Set 1: Analysis of E/SE Asian Subjects Versus Non-E/SE Asian Subjects. Covariates were normalized to the typical individual (a 65-year-old, healthy, non-E/SE Asian man with a baseline body weight of 85 kg, baseline eGFR of 90 mL/min/1.73 m^2, administered ertugliflozin in the fasted state) and incorporated into the final model. Continuous covariates included baseline body weight, age, and eGFR (values exceeding 120 mL/min/1.73 m^2 were fixed to 120 mL/min/1.73 m^2). Categorical covariates included ethnicity, which was parameterized as a fractional change and categorized to create covariate indicator variables that equaled 1 for E/SE Asian subjects and 0 for non-E/SE Asian subjects.

Data Set 2: Analysis of Asian Subjects From Mainland China Versus Asian Subjects From the Rest of the World and Non-Asian Subjects. Covariates were normalized to the typical individual (a 65-year-old, healthy, non-Asian man with a baseline body weight of 85 kg, baseline eGFR of 90 mL/min/1.73 m^2, administered ertugliflozin in the fasted state) and incorporated into the final model. Continuous covariates included baseline body weight, age, and eGFR (with values exceeding 120 mL/min/1.73 m^2 fixed to 120 mL/min/1.73 m^2). Categorical covariates included ethnicity, which was categorized into 3 mutually exclusive groups: Asian subjects from mainland China, Asian subjects from the rest of the world, and non-Asian subjects.

Results

Baseline Demographic Covariates for Analysis

The baseline demographic covariates for data set 1 (E/SE Asian vs non-E/SE Asian subjects) have been published previously[22] (included in Table 1 for comparison). Of the total number of subjects contributing to data set 1, there were 154 (6.8%) E/SE Asian subjects and 2122 (93.2%) non-E/SE Asian subjects. The baseline demographic covariates for data set 2 (Asian subjects from mainland China vs Asian subjects from the rest of the world and non-Asian subjects) are shown in Table 1. Of the total number of subjects contributing to data set 2, there were 277 (10.6%) Asian subjects from mainland China, 382 (14.6%) Asian subjects from the rest of the world, and 1961 non-Asian (74.8%) subjects. Baseline demographic covariates were generally similar between ethnic subgroups within each data set, with

Table 1. Summary of Baseline Demographic Covariates for Analysis

		Dataset 1: E/SE Asian vs non-E/SE Asian Subjects			Dataset 2: Asian Subjects From Mainland China vs Asian Subjects From the ROW and Non-Asian Subjects			
	Statistic	Total	E/SE Asian Subjects	Non-E/SE Asian Subjects	Total	Asian Subjects From Mainland China	Asian Subjects From the ROW	Non-Asian Subjects
Baseline BWT, kg	N	2276	154	2122	2620	277	382	1961
	Mean (SD)	86.9 (19.7)	69.7 (14.6)	88.2 (19.4)	84.7 (19.6)	70.5 (10.7)	72.8 (15.4)	89.1 (19.4)
	Median (min, max)	84.8 (42.6, 197)	68.4 (42.6, 126)	86.0 (43.4, 197)	82.4 (42.6, 197)	69.9 (47.1, 103)	70.4 (42.6, 139)	87.0 (43.4, 197)
Age, y	N	2276	154	2122	2620	277	382	1961
	Mean (SD)	55.7 (11.6)	54.1 (10.4)	55.8 (11.7)	55.6 (11.5)	54.5 (11.0)	54.9 (10.1)	55.8 (11.8)
	Median (min, max)	57.0 (18.0, 87.0)	55.0 (24.0, 81.0)	57.0 (18.0, 87.0)	57.0 (18.0, 87.0)	56.0 (22.0, 80.0)	55.0 (24.0, 87.0)	57.0 (18.0, 87.0)
Baseline eGFR, mL/min/1.73 m^2	N	2276	154	2122	2620	277	382	1961
	Mean (SD)	85.9 (24.3)	85.3 (25.3)	85.9 (24.3)	87.8 (24.4)	103 (20.9)	87.4 (21.9)	85.7 (24.6)
	Median (min, max)	86.6 (6.80, 196)	86.6 (28.0, 178)	86.6 (6.80, 196)	88.0 (6.80, 196)	101 (56.0, 185)	87.2 (28.0, 178)	86.2 (6.80, 196)
Sex								
Male	n (%)	1287 (56.5)	79.0 (51.3)	208 (56.9)	1482 (56.6)	158 (57.0)	226 (59.2)	1098 (56.0)
Female	n (%)	989 (43.5)	75.0 (48.7)	914 (43.1)	1138 (43.4)	119 (43.0)	156 (40.8)	863 (44.0)
Patient status								
Healthy	n (%)	192 (8.44)	12.0 (7.79)	180 (8.48)	208 (7.94)	16 (5.78)	15 (3.93)	177 (9.03)
T2DM	n (%)	2084 (91.6)	142 (92.2)	1942 (91.5)	2412 (92.1)	261 (94.2)	367 (96.1)	1784 (91.0)

BWT, body weight; eGFR, estimated glomerular filtration rate; E/SE, East/Southeast; ROW, rest of the world; SD, standard deviation; T2DM, type 2 diabetes mellitus.

Table 2. Parameter Estimates and Bootstrap Median (95%CI) for the Final Model: Data Set 1 (E/SE Asian vs Non-E/SE Asian Subjects) and Data Set 2 (Asian Subjects From Mainland China vs Asian Subjects From ROW and Non-Asian Subjects)

	Data Set 1: E/SE Asian Versus Non-E/SE Asian Subjects		Data Set 2: Asian Subjects From Mainland China vs Asian Subjects From the ROW and Non-Asian Subjects	
Parameter, Unit	Estimate	Median (95%CI)	Estimate	Median (95%CI)
CL/F, L/h	11.9	11.9 (11.5 to 12.2)	11.8	11.7 (11.4 to 12.1)
Effect of body weight	0.750 (fixed)	…	0.750 (fixed)	…
Effect of eGFR	0.458	0.457 (0.393 to 0.522)	0.449	0.451 (0.385 to 0.514)
Effect of T2DM patient status	0.921	0.922 (0.870 to 0.972)	0.856	0.859 (0.801 to 0.920)
Effect of female sex	0.960	0.960 (0.926 to 0.996)	0.970	0.969 (0.939 to 1.00)
Effect of E/SE Asian ethnicity	1.17	1.17 (1.11 to 1.24)	…	…
Effect of Asian from mainland China	…	…	1.04	1.04 (0.991 to 1.08)
Effect of Asian from ROW	…	…	1.08	1.09 (1.03 to 1.14)
V_c/F, L	6.51	6.58 (5.05 to 8.20)	5.23	5.23 (3.40 to 7.44)
Effect of body weight	1.00 (fixed)	…	1.00 (fixed)	…
Effect of age	−0.192	−0.185 (−0.548 to 0.146)	−0.603	−0.614 (−0.991 to −0.241)
Effect of female sex	1.46	1.45 (1.12 to 1.86)	1.66	1.66 (1.25 to 2.15)
Effect of E/SE Asian ethnicity	2.48	2.45 (1.65 to 3.82)	…	…
Effect of Asian from mainland China	…	…	1.44	1.45 (1.08 to 1.97)
Effect of Asian from ROW	…	…	2.15	2.14 (1.53 to 2.99)
V_p/F, L	107	107 (102 to 113)	113	112 (104 to 130)
Effect of body weight	1.00 (fixed)	…	1.00 (fixed)	…
Q/F, L/h	7.76	7.79 (6.99 to 8.64)	7.17	7.34 (4.84 to 8.81)
Effect of body weight	0.750 (fixed)	…	0.750 (fixed)	…
k_a, h^{-1}	0.329	0.329 (0.302 to 0.364)	0.323	0.328 (0.245 to 0.394)
Effect of food	0.725	0.727 (0.668 to 0.782)	0.639	0.641 (0.580 to 0.705)
Effect of without regard to food	0.654	0.656 (0.591 to 0.729)	0.796	0.793 (0.701 to 0.915)
Lag time (ALAG1), h	0.226	0.227 (0.217 to 0.234)	0.227	0.228 (0.219 to 0.235)
Relative bioavailability (F1)	1.00 (fixed)	…	1.00 (fixed)	…
Effect of food	0.0702	0.0696 (0.0271 to 0.111)	0.157	0.154 (0.102 to 0.204)
Effect of without regard to food	0.0681	0.0693 (0.00771 to 0.136)	0.148	0.145 (0.0495 to 0.241)
$\omega 2_{CL/F}$	0.101	0.101 (0.0805 to 0.121)	0.0999	0.0989 (0.0834 to 0.116)
Phase 1 residual error	0.389	0.386 (0.367 to 0.406)	0.486	0.482 (0.444 to 0.523)
Phase 2/3 residual error	0.837	0.837 (0.806 to 0.866)	0.831	0.831 (0.803 to 0.859)

ALAG1, lag time; CI, confidence interval; CL/F, apparent clearance; eGFR, estimated glomerular filtration rate; E/SE, East/Southeast; F1, relative bioavailability; k_a, absorption rate constant; Q/F, apparent intercompartmental clearance; T2DM, type 2 diabetes mellitus; V_c/F, apparent central volume of distribution; V_p/F, apparent volume of distribution.

Point estimates were estimated using nonlinear mixed-effects modeling. Median and 95%CI of the estimates were obtained from nonparametric bootstrap estimates (data set 1: N = 1100, 13 runs with minimization terminated and 53 runs with estimates near a boundary were skipped when calculating the bootstrap results; data set 2: N = 1100, 11 runs with minimization terminated were skipped when calculating the bootstrap results).

the exception of mean body weight, which was lower in E/SE Asian vs non-E/SE Asian subjects in data set 1 (69.7 and 88.2 kg, respectively) and in Asian subjects from mainland China and Asian subjects from the rest of the world vs non-Asian subjects in data set 2 (70.5, 72.8, and 89.1 kg, respectively).

Ertugliflozin PopPK Analysis
E/SE Asian Versus Non-E/SE Asian Subjects

The parameter estimates for CL/F, Vc/F, apparent volume of distribution, apparent intercompartmental clearance, absorption rate constant, and relative bioavailability for the final model are summarized in Table 2. Residual error estimates were 38.9% for the phase 1 studies and 83.7% for the phase 2/3 studies. CL/F increased by 17% in E/SE Asian subjects compared with the typical non-E/SE Asian subject. The magnitude of the effect of E/SE Asian ethnicity on CL/F was significant based on the CI from the bootstrap (median, 1.17 [95%CI, 1.11-1.24]; Table 2) but this was not anticipated to be clinically meaningful. This magnitude of effect of E/SE Asian ethnicity translates to $AUC_{\tau,ss}$ of 0.855 (95%CI, 0.806-0.901). The final model individual post hoc CL/F values (median [95%CI]), calculated based on the final model equations (Table S3), for E/SE Asian and non-E/SE Asians groups were 10.4 L/h (5.94-18.2) and 10.7 L/h (5.28-19.2), respectively (Figure 1). Interindividual variation (IIV)

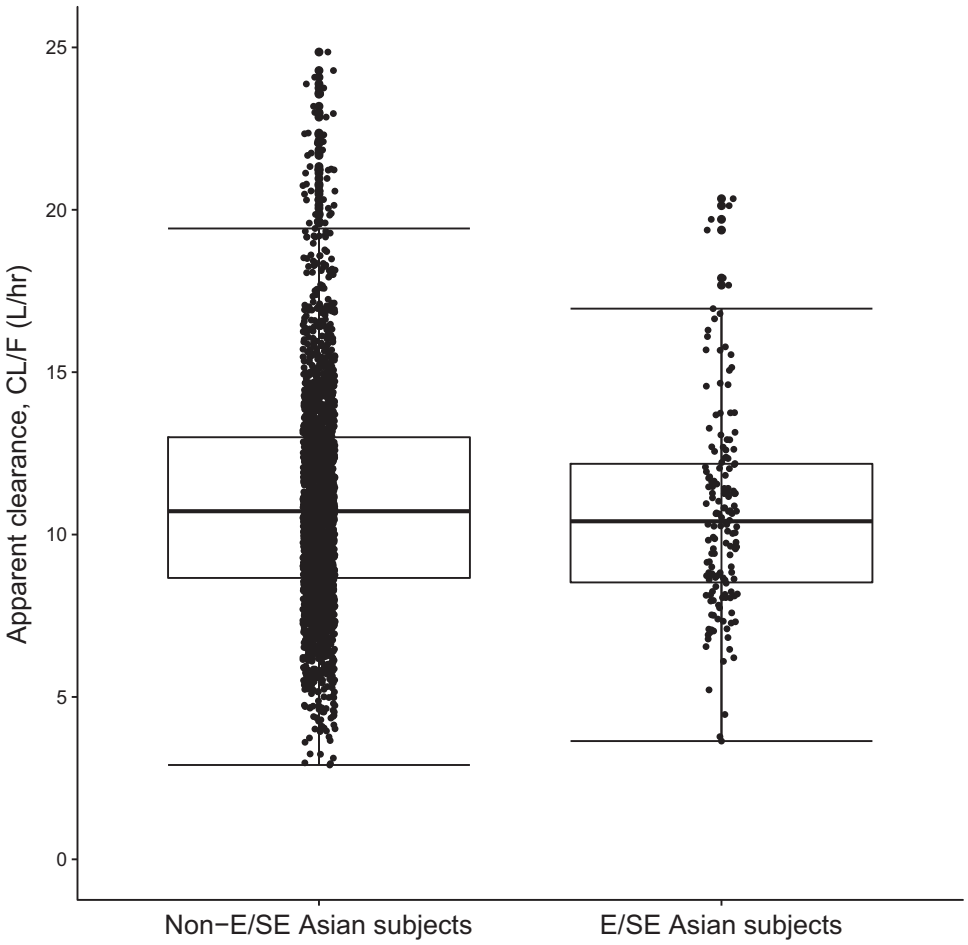

Figure 1. Final model individual post hoc apparent clearance (CL/F) for E/SE Asian and non-E/SE Asian subjects. Boxes provide median and 25th and 75th percentiles, and the lower/upper whiskers extend to 1.5× the interquartile range. Data points beyond the end of the whiskers are outliers. CL/F, individual post hoc apparent clearance; E/SE, East/Southeast.

on CL/F expressed as a coefficient of variation was 31.8%. V_C/F increased by 148% in E/SE Asian subjects compared with the typical non-E/SE Asian subject. The magnitude of the effect of E/SE Asian ethnicity on Vc/F was significant based on the CI from the bootstrap (median, 2.45 [95%CI, 1.65-3.82]) relative to the typical non-E/SE Asian subject (Table 2).

Asian Subjects From Mainland China Versus Asian Subjects From the Rest of the World and Non-Asian Subjects

The parameter estimates for CL/F, Vc/F, apparent volume of distribution, apparent intercompartmental clearance, absorption rate constant, and relative bioavailability for the final model are summarized in Table 2. Residual error estimates expressed as a coefficient of variation were 48.6% for the phase 1 studies and 83.1% for the phase 2/3 studies. CL/F increased by 4% in Asian subjects from mainland China and by 8% in Asian subjects from the rest of the world compared with the typical non-Asian subject. The magnitude of the effect on CL/F was nonsignificant based on the CI from the bootstrap for Asian subjects from mainland China on CL/F (median, 1.04 [95%CI, 0.991-1.08]; Table 2) but significant for Asian subjects from the rest of the world (median, 1.09 [95%CI, 1.03-1.14]; Table 2). The magnitude of effect of Asian ethnicity from mainland China and Asian ethnicity from the rest of the world translate to an $AUC_{\tau,ss}$ of 0.962 (95%CI, 0.926-1.01) and 0.917 (95%CI, 0.877-0.971), respectively. The final model individual post hoc CL/F values (median [95% CI]), calculated on the basis of the final model equations (Table S3), were generally consistent among Asian subjects from mainland China, Asian subjects from the rest of the world, and non-Asian subjects: 9.42 (6.05-14.5), 9.51 (4.47-15.5), and 10.1 L/h (4.97-17.7), respectively (Figure 2). IIV on CL/F expressed as a coefficient of variation was 31.6%. Vc/F increased by 44% in Asian subjects from mainland

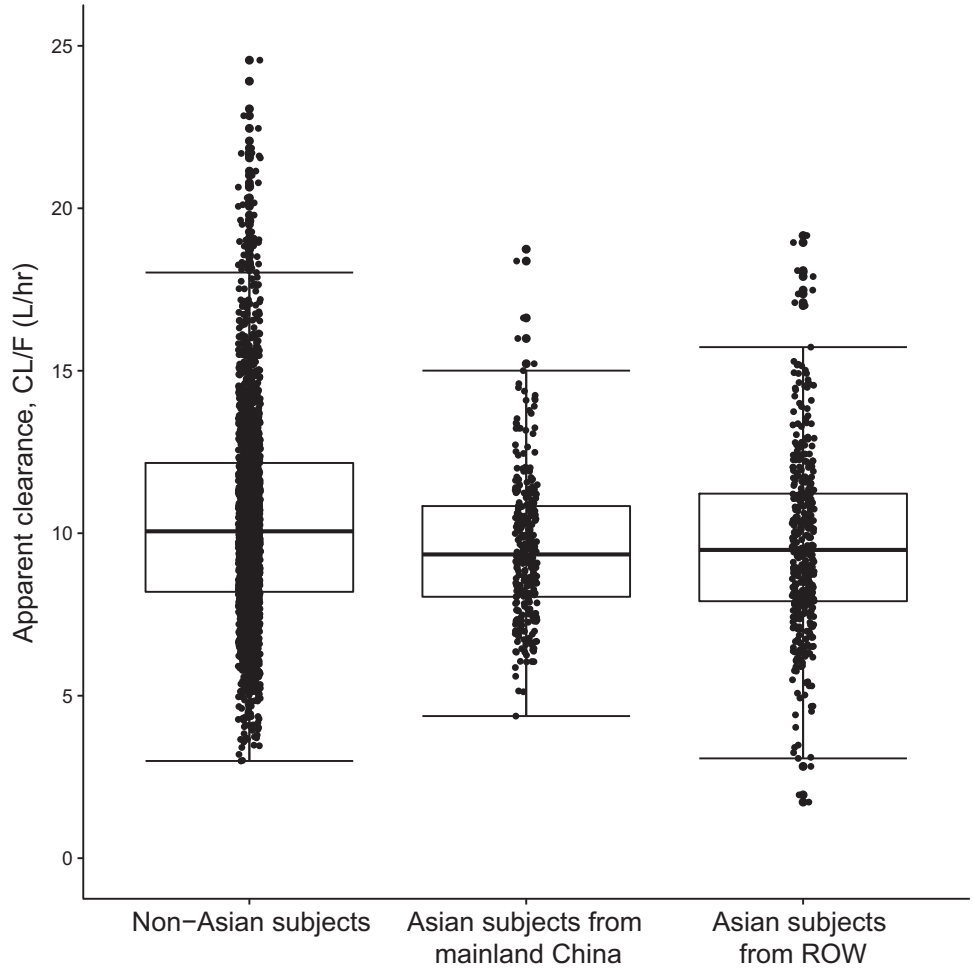

Figure 2. Final model individual post hoc apparent clearance (CL/F) for non-Asian subjects, Asian subjects from mainland China, and Asian subjects from the rest of the world. Boxes provide median and 25th and 75th percentiles, and the lower/upper whiskers extend to 1.5× the interquartile range. Data points beyond the end of the whiskers are outliers. CL/F, individual post hoc apparent clearance; ROW, rest of the world.

China and 115% in Asian subjects from the rest of the world compared with the typical non-Asian subject. The magnitude of these effects on Vc/F was significant based on the CI from the bootstrap for Asian subjects from mainland China on Vc/F (median, 1.45 [95%CI, 1.08-1.97]) and for Asian subjects from the rest of the world (median, 2.14 [95%CI, 1.53-2.99]; Table 2).

Discussion

The 2 popPK analyses of ertugliflozin reported here included a large data set of up to 17 clinical studies involving 208 healthy subjects and 2412 patients with T2DM. Parameter estimates for these current analyses were similar to those reported in the previously published popPK report.[22] CL/F was estimated to be 11.9 L/h for the typical individual in the analysis of E/SE Asian subjects vs non-E/SE Asian subjects and 11.8 L/h for the typical individual in the analysis of Asian subjects from mainland China vs Asian subjects from the rest of the world and non-Asian subjects. E/SE Asian ethnicity represented a 17% increase in CL/F, which translates to a 15% decrease in area under the concentration-time curve for a dosing interval at steady state. From the phase 1 clinical pharmacology studies, the maximum observed decrease in ertugliflozin exposure was 39% following rifampin coadministration.[13] Based on the ertugliflozin dose vs glycated hemoglobin response model, the ertugliflozin 5-mg dose following coadministration with rifampin was predicted to maintain clinically meaningful glycemic efficacy. Therefore, a change in $AUC_{\tau,ss}$ that is <39% relative to the reference subject is not clinically relevant. Furthermore, while the effect of E/SE Asian ethnicity on CL/F was significant based on the CI from the bootstrap, individual post hoc CL/F values were similar between E/SE Asian and non-E/SE Asian groups when differences in body weight were taken into account (geometric mean of 69.7 kg for

E/SE Asian subjects and 88.2 kg for non-E/SE Asian subjects). This difference in mean body weight and corresponding body mass index (BMI) for E/SE Asian and non-E/SE Asian subjects has been shown previously in a pooled analysis of ertugliflozin phase 3 studies where the mean body weight was 67.5 to 69.8 and 89.0 to 90.8 kg, respectively, for E/SE Asians and non-E/SE Asians, and BMI was 26.1 to 26.9 and 32.0 to 32.4 kg/m^2, respectively, for E/SE Asians and non-E/SE Asians across treatment groups.[23] Other reports have also noted a lower BMI in Asian populations compared with Western populations, although the increased risk of T2DM starts at a lower BMI in Asian compared with Western patients.[25,26] The mean baseline BMI in E/SE Asian subjects in this current analysis is similar to studies of other SGLT2 inhibitors in Asian and E/SE Asian populations (25.5-26.0 kg/m^2).[27,28] The distribution of final model post hoc CL/F values was generally consistent among Asian subjects from mainland China, Asian subjects from the rest of the world, and non-Asian subjects. Together, these findings suggest that there is no clinically meaningful difference in ertugliflozin exposure levels ($AUC_{\tau,ss}$) between ethnic subgroups (ie, between E/SE Asian subjects and non-E/SE Asian subjects and between Asian subjects from mainland China, Asian subjects from the rest of the world, and non-Asian subjects) and no dose modification of ertugliflozin is required on the basis of race/ethnicity.

Vc/F was estimated to be 6.51 L for the typical individual in the analysis of E/SE Asian subjects vs non-E/SE Asian subjects and 5.23 L for the typical individual in the analysis of Asian subjects from mainland China vs Asian subjects from the rest of the world and non-Asian subjects. The magnitude of the increase in Vc/F in the analyses of E/SE Asian subjects (vs non-E/SE Asian) and of Asian subjects from mainland China and Asian subjects from the rest of the world (vs non-Asian subjects) was significant. Increases in Vc/F would result in a decrease in C_{max} but would not be expected to impact ertugliflozin overall exposure, as determined by $AUC_{\tau,ss}$. Additionally, as glycemic efficacy of ertugliflozin is driven by $AUC_{\tau,ss}$,[13,14] these changes in Vc/F were not considered clinically relevant nor likely to result in meaningful differences in the PK and efficacy of ertugliflozin between ethnic subgroups (ie, between E/SE Asian subjects and non-E/SE Asian subjects and between Asian subjects from mainland China, Asian subjects from the rest of the world, and non-Asian subjects). Hence, no dose modification of ertugliflozin is required on the basis of race/ethnicity.

PK bridging studies are typically required by Asian regulatory agencies to extrapolate foreign clinical data for the development of new therapeutic agents. It is acknowledged that ethnic differences among populations can potentially cause differences in the safety and/or efficacy of a medicine. However, the characteristics and effects of many medicines are comparable across ethnic populations.[29] The findings of the 2 separate popPK analyses presented here support both the previously published popPK analysis[22] and phase 1 studies that suggested no clinically meaningful ethnic differences in ertugliflozin PK, and no dose modification of ertugliflozin is required on the basis of race/ethnicity.[20,21] The popPK findings reported here for E/SE Asian subjects vs non-E/SE Asian subjects and for Asian subjects from mainland China vs Asian subjects from the rest of the world and non-Asian subjects are also supported by the results from phase 3 clinical studies. A post hoc analysis of 3 phase 3 clinical studies demonstrated that treatment with ertugliflozin was associated with clinically meaningful reductions in glycated hemoglobin, fasting plasma glucose, body weight, and systolic blood pressure, and was generally well tolerated in patients with T2DM from E/SE Asian countries.[23] Also, 2 further pooled analyses of the efficacy and safety of ertugliflozin across racial subgroups[30] and Hispanic patients[31] from the ertugliflozin phase 3 program demonstrated that treatment with ertugliflozin improved glycated hemoglobin, body weight, and systolic blood pressure across all racial/ethnic subgroups evaluated. The comparable efficacy and safety across the ertugliflozin phase 3 studies in varied populations, together with the PK findings from the phase 1 studies and the results of the popPK analyses suggest no clinically meaningful PK differences based on race/ethnicity.

Ertugliflozin is primarily metabolized via glucuronidation by the uridine 5′-diphosphoglucuronosyltransferase (UGT) isoforms UGT1A9 and UGT2B7.[3,13] Race-specific polymorphisms in the genes encoding these enzymes could potentially affect UGT activity and ultimately affect the metabolism of ertugliflozin. However, a noncompartmental meta-analysis of ertugliflozin PK evaluated the effect of UGT1A9 genotype on ertugliflozin exposure; allelic variants of UGT1A9 were within ±10% of the wild type, suggesting that such polymorphisms are not clinically relevant.[19] Also, UGT2B7 polymorphisms have not been associated with a clinically meaningful impact on the PK of ertugliflozin.[32] It is therefore unlikely that race-specific polymorphisms in UGT1A9 and UGT2B7 will have a clinically meaningful impact on the PK, and no ertugliflozin dose adjustment would be required in patients with the UGT1A9 variants.

One limitation of the 2 popPK analyses reported here is the limited number of observations of the ethnic subgroups in each data set: in data set 1, 6.8% of subjects were E/SE Asian compared with 93.2% non-E/SE Asian subjects; in data set 2, 10.6% of subjects were Asian from mainland China, 14.6% were Asian from

the rest of the world, compared with 74.9% non-Asian subjects.

Conclusions

The popPK model successfully characterized ertugliflozin exposure in E/SE Asian and non-E/SE Asian subjects as well as Asian subjects from mainland China, Asian subjects from the rest of the world, and non-Asian subjects. Differences between ethnic subgroups were not considered clinically relevant and were not expected to result in meaningful differences in ertugliflozin exposure ($AUC_{\tau,ss}$). The increases in Vc/F obtained in the popPK analyses would result in a decrease in ertugliflozin maximum concentration but would not impact $AUC_{\tau,ss}$. As glycemic efficacy of ertugliflozin is driven by $AUC_{\tau,ss}$,[14] these changes in Vc/F were not considered clinically relevant, nor likely to result in meaningful ethnic differences in the PK and efficacy of ertugliflozin. Therefore, no dose modification of ertugliflozin is required on the basis of race/ethnicity.

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Conflicts of Interest

D.J.F., V.S., V.K.D., and K.S. are employees of Pfizer Inc., New York, NY, USA and may own shares/stock options in Pfizer Inc. S.Z. is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and may own stock in Merck & Co., Inc., Kenilworth, NJ, USA.

Data Sharing Statement

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