Population Pharmacokinetic Model for Ertugliflozin in Healthy Subjects and Patients With Type 2 Diabetes Mellitus

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Abstract

Ertugliflozin is a selective sodium-glucose cotransporter 2 inhibitor approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). A population pharmacokinetic (popPK) model was developed to characterize the pharmacokinetics (PK) of ertugliflozin and quantify the influence of intrinsic (eg, body weight, age, sex, race, estimated glomerular filtration rate [eGFR], T2DM) and extrinsic (eg, food) covariates on the PK parameters of ertugliflozin. The analysis was conducted using data from 15 clinical studies (phases 1-3) enrolling healthy subjects and patients with T2DM, which included 13,691 PK observations from 2276 subjects and was performed using nonlinear mixed-effects modeling. 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 and in patients with T2DM. Apparent clearance increased with increasing body weight and eGFR, was slightly lower in patients with T2DM and females, and was slightly higher in Asians. Apparent central volume of distribution increased with increasing body weight and was higher in females and Asians. Administration of ertugliflozin with food decreased the absorption rate constant (k_a) and relative bioavailability (F1) compared with fasted. When ertugliflozin was administered without regard to food, estimates of k_a and F1 were similar to those for administration with food. The popPK model successfully characterized ertugliflozin exposure in healthy subjects and patients with T2DM. None of the covariates evaluated had a clinically relevant effect on ertugliflozin PK.

Ertugliflozin is an oral selective sodium-glucose co-transporter 2 (SGLT2) inhibitor[1,2] approved for the treatment of adult patients with type 2 diabetes mellitus (T2DM). Ertugliflozin inhibits SGLT2, reduces renal reabsorption of filtered glucose, and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion. Phase 1 studies conducted in healthy subjects have shown that ertugliflozin is rapidly absorbed following oral administration,[2] with maximal plasma concentration (C_{max}) occurring after approximately 1 hour when administered in the fasted state and approximately 2 hours postdose in the fed state.[3] Based on noncompartmental analyses, the exposure of ertugliflozin increases in a dose-proportional manner over a dose range of 0.5-300 mg, and the terminal elimination half-life ($t_{\frac{1}{2}}$) ranges from 11 to 17 hours.[1] The absolute bioavailability of ertugliflozin is approximately 100%,[4] and administration with food does not have a clinically meaningful effect on ertugliflozin pharmacokinetics (PK).[5] Ertugliflozin does not exhibit

time-dependent PK, and, consistent with the half-life, steady-state concentrations are achieved by 4 to 6 days after initiating once-daily dosing.[6] Ertugliflozin is highly bound to plasma proteins (93.6%).[1] The primary clearance mechanism of ertugliflozin is metabolism:

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glucuronidation is the major metabolic pathway (86%), with minor contributions from oxidative metabolism (12%).[2] Renal excretion of ertugliflozin is minimal (approximately 1.5% of the administered dose). No clinically meaningful PK interactions were seen when ertugliflozin was coadministered with sitagliptin, metformin, glimepiride, or simvastatin,[6] demonstrating that ertugliflozin can be coadministered safely with these agents without any need for dose adjustment.

The PK of ertugliflozin is similar in healthy subjects and in patients with T2DM.[5,7] A phase 1 study in subjects with mild, moderate, and severe renal impairment showed that, based on PK, no dose adjustments of ertugliflozin are necessary in patients with renal impairment,[5] but hemoglobin A_{1c} lowering for SGLT2 inhibitors has been documented to be diminished in patients with moderate or severe renal impairment.[8] Similarly, a phase 1 study in subjects with moderate hepatic impairment showed that no dose adjustments of ertugliflozin are necessary in patients with T2DM and mild to moderate hepatic impairment.[7] In phase 3 studies, ertugliflozin reduced hemoglobin A_{1c}, fasting plasma glucose, body weight, and blood pressure in patients with T2DM.[9–12]

The aim of this current analysis was to develop a population pharmacokinetic (popPK) model, based on PK data from healthy subjects and patients with T2DM and to characterize the factors that contribute to variability in ertugliflozin PK parameters.

Methods

Clinical Studies and Data Collection
All studies were conducted in accordance with principles of Good Clinical Practice and were approved by the appropriate institutional review boards and regulatory agencies. Informed consent was obtained from individuals in each study. Data used for the analysis were obtained from 15 clinical studies: 9 phase 1 studies in healthy subjects and patients with T2DM, 2 phase 2 studies with sparse PK sampling in patients with T2DM, and 4 phase 3 studies with sparse PK sampling in patients with T2DM (Table S1). The study design, study population, and timing of collection of blood samples varied among the 15 clinical studies.

Ertugliflozin Analytical Assay
Plasma samples to determine ertugliflozin concentration were taken according to the PK sampling scheme for each protocol (Table S2) and analyzed using a previously reported, validated high-performance liquid chromatography-tandem mass spectrometric method.[13] The lower limit of quantification of the assay used for samples included in this popPK model was 0.5 ng/mL for 14 of the studies and 0.1 ng/mL for 1 study.

Data for Analysis
The final model data file for the analysis contained 13 691 ertugliflozin concentration records from 2276 subjects. The popPK data file included subject identification, dosing information, time of sample collection, ertugliflozin concentrations, and baseline demographic and laboratory data (including body weight, age, estimated glomerular filtration rate [eGFR], sex, race, patient status, and food status). Because drug-drug interaction studies demonstrated that there was no impact of glycemic rescue medication (ie, glimepiride and metformin) on the PK of ertugliflozin,[6] PK data post–glycemic rescue therapy were not excluded. As the number of plasma concentrations reported as below the limit of quantification (BLQ) was small (848 observation records; 5% of total records), BLQ concentrations were removed from the analysis data set. As stated in Beal et al,[14] when the frequency of BLQ observations is small, removing the BLQ observations will serve about as well or better than any other such method.

Modeling Strategy and Software
Log-transformed plasma concentration-time data were analyzed using nonlinear mixed-effects modeling (NONMEM) methodology as implemented by the software program NONMEM version 7.3 (ICON plc, Gaithersburg, Maryland) within an internally validated Pfizer analysis platform (ePharmacology version 4.4) and tested internally. NONMEM was used to estimate the population parameters, mean and interindividual variance (IIV), and to identify potential covariates that explain IIV in the parameters. The first-order conditional estimation with interaction method was used for all model runs. Postprocessing of NONMEM output to generate goodness-of-fit plots was performed using R software (version 3.0.2 or higher). Visual predictive checks and bootstraps (n = 1035) were conducted using Perl-speaks-NONMEM (PsN 4.2.0 or higher). Xpose (version 4.4) was used for the plotting of simulation results.

PopPK Model
Model Development. Previous studies demonstrated that ertugliflozin was rapidly absorbed and plasma ertugliflozin concentrations decreased in a biphasic manner following oral administration.[3] Therefore, ertugliflozin PK parameters after single and multiple dosing were described using a 2-compartment model with first-order absorption and a lag time and first-order elimination. IIV in the PK parameters was modeled assuming a log-normal parameter distribution (see Supplementary Appendix for details), and the estimate of IIV was calculated as percent coefficient of variation (% CV) for base and final models. Separate residual variance parameters were incorporated for

phase 1 and phase 2/3 data as measurement error is often larger in sparsely sampled outpatient studies. The effect of baseline body weight was included on apparent clearance (CL/F), apparent central volume of distribution (V_c/F), apparent peripheral volume of distribution (V_p/F), and apparent intercompartmental clearance (Q/F). These effects were modeled using an allometric relationship, with the exponent fixed to 0.75 and 1.0 for apparent clearance and volume, respectively.

Covariate Evaluation. Because bioavailability and fraction absorbed were approximately 100% following oral administration of ertugliflozin under fasted conditions[4] and food slightly decreased ertugliflozin area under the plasma concentration-time curve (AUC),[15] the effect of food on absorption (k_a) and bioavailability (F1) was tested in the base model development. In the phase 2 studies, ertugliflozin was administered with the morning meal. In the phase 3 studies, food status was not documented and per-protocol ertugliflozin could be administered without regard to food. A covariate modeling approach using the full model estimation (FME) procedure was implemented for this popPK analysis to assess the effect of various (demographic or physiological) covariates on ertugliflozin PK parameters. Covariate-parameter relationships were identified based on clinical judgment, physiologic relevance, and mechanistic plausibility; then the full model was constructed with care to avoid inclusion of colinear covariates. For example, age and eGFR were, as expected, negatively correlated (correlation coefficient, −0.531), so eGFR was included and age excluded as a covariate on CL/F. In addition, because the glycemic efficacy of SGLT2 inhibitors is dependent on the amount of glucose filtered through the kidney, eGFR was the more relevant covariate.[5] The eGFR values were calculated using the 4-variable Modification of Diet in Renal Disease equation.[16] Hyperfiltration, especially early on in the disease course of T2DM, can result in eGFR values that are difficult to reconcile with physiology,[17] so eGFR values exceeding 120 mL/min/1.73 m^2 were set to 120 mL/min/1.73 m^2. Other covariates screened and added to the base model included body weight, eGFR, sex, race, patient status (T2DM) on CL/F; body weight, age, sex, race on V_c/F; and food effect on k_a and on F1. By using the FME procedure, all covariates were estimated simultaneously to establish the final model. The parameterization of the continuous and categorical covariates is described in the Supplementary Appendix.

Model Evaluation. The base and final models were evaluated using goodness-of-fit criteria: reduction in minimum objective function value (OFV), visual inspection of diagnostic plots, plausibility of parameter estimates and their relative standard errors (RSEs) values, change in the objective function relative to the change in the number of parameters, and changes in both interindividual and residual variability. Nonparametric bootstrapping and visual predictive checks were performed to provide parameter uncertainty and evaluate the adequacy and stability of the final model and parameter estimates, respectively. For the nonparametric bootstrapping procedure, a minimum of 1000 simulated data sets were generated. Population parameters for each data set were subsequently estimated using the final model and parameter uncertainty was expressed as 95% confidence interval (CI) for the estimate. Observed concentrations as the dependent variable (DV) versus population- or individual-predicted concentrations (PRED or IPRED, respectively) were plotted for model diagnostics. In addition, conditional weighted residuals (CWRES) were plotted against the predicted concentrations and time after last dose. Shrinkage in CL/F was explored to evaluate the validity of using post hoc individual PK parameter estimates for subsequent exposure-response analyses.[18] Model stability was tested through the evaluation of the condition number. When evaluating the base and final models, concentration records identified as outliers—defined as extreme values of a weighted residual (ie, weighted differences between observed and predicted values)—were examined as part of the entire concentration-time profile for that individual, and their influence on estimates of key fixed-effect PK parameters such as CL/F or V_c/F were evaluated.[19] Outliers were excluded from the analysis if the parameter estimates differed by >20%.

Results

Baseline Demographic Covariates for Analysis
The data set included a broad range of baseline characteristics: age of 18 to 87 years, body weight of 42.6 to 197 kg, and 56.5% male (Table 1). Most subjects were white (71.8%). Overall, 91.6% of subjects had T2DM (8.4% healthy). Baseline eGFR was 6.8-196 mL/min/m^2. Approximately 44% of subjects had normal renal function (eGFR ≥90 mL/min/1.73 m^2), approximately 41% had mild renal impairment (eGFR ≥60 to <90 mL/min/1.73 m^2), 14% moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2), and 1% severe renal impairment (eGFR <30 mL/min/1.73 m^2).

Ertugliflozin PopPK Analysis
Base Model Results. Visual examination of plasma ertugliflozin concentrations after single and multiple oral administration showed that ertugliflozin is rapidly absorbed and eliminated in a biphasic manner,[3] which suggested adequacy of the 2-compartment model to describe ertugliflozin with linear PK. Table S3 presents the key base model building steps. IIV was initially

Table 1. Summary of Baseline Demographic Covariates for Analysis

Covariate	Statistic	Total
Baseline BWT (kg)	n	2276
	Mean (SD)	86.9 (19.7)
	Median (min, max)	84.8 (42.6, 197.0)
Age (y)	n	2276
	Mean (SD)	55.7 (11.6)
	Median (min, max)	57.0 (18.0, 87.0)
Baseline eGFR, mL/min/1.73 m^2	n	2276
	Mean (SD)	85.9 (24.3)
	Median (min, max)	86.6 (6.8, 196.0)
Sex		
Male	n (%)	1287 (56.5)
Female	n (%)	989 (43.5)
Race		
White	n (%)	1634 (71.8)
Black	n (%)	199 (8.74)
Asian	n (%)	315 (13.8)
Other	n (%)	128 (5.62)
Patient status		
Healthy	n (%)	192 (8.4)
T2DM	n (%)	2084 (91.6)
Food status[a]		
Fasted	n (%)	275 (11.2)
Fed	n (%)	473 (19.3)
Without regard to food	n (%)	1697 (69.4)

BWT, body weight; eGFR, estimated glomerular filtration rate; n, number of subjects; SD, standard deviation; T2DM, type 2 diabetes mellitus.
[a] Subjects in some phase 1 studies may have been captured as fasted or fed in different periods of the same study. Therefore, the total number of subjects for food status exceeds 2276.

included on the mean PK parameters of CL/F, V_c/F, V_p/F, Q/F, and k_a. However, this resulted in a very large estimate of IIV on V_c/F because of the large variability of C_{max} from the phase 3 data. Exploration of the base model diagnostic plots revealed a systematic trend in the DV versus population predictions (PRED) plots for the 5- and 15-mg dose strengths (data not shown). For the data points depicting a vertical trend along the *y* axis, the model predictions (PRED) were in accordance with expected predose concentrations; however, the observed concentrations (DV) in the analysis data file were unusually high and appeared to be postdose concentrations. For the data points depicting a horizontal trend along the *x* axis, model predictions (PRED) were in accordance with expected postdose concentrations; however, the observed concentrations (DV) in the analysis data set were unusually low and appeared to be predose concentrations. These data points were retained in the full model and their impact evaluated in a sensitivity analysis by reestimating the full model with and without these data points (see below, in the

Final Model Results section). Table 2 presents the parameter estimates for the final base model. The diagnostic plots of the final base model indicated that the model provided adequate fit to the ertugliflozin concentration-time data (Figure S1). In summary, the final base model was a 2-compartment PK model with lag time, first-order absorption, and first-order elimination from the central compartment. The effect of food was included on k_a and F1. The effect of weight was included as a fixed allometric exponent on CL/F, V_c/F, V_p/F, and Q/F. Estimation of these allometric exponents during base model development reduced the OFV (Table S3), but the magnitude of the associated relative standard errors (RSEs) did not justify this approach.

Final Model Results. After adding all covariate parameters, the final model converged with a successful covariance ($COV) step. The final form of the equation for individual *i* is given in the Supplementary Appendix and describes the incorporation of covariate effects into the final model. Continuous covariates included baseline body weight, age, and baseline eGFR. Categorical covariates included patient status, sex, race, and food.

Twenty-four observations identified as outliers were excluded from the final model because of their disproportionately large influence on V_c/F. Sensitivity analysis suggested that observations in the base model results depicting a vertical and horizontal systematic trend in the DV-versus-PRED plots for the 5- and 15-mg dose strengths were not influential in the final model and so were retained in the final analysis.

Final Model Evaluation. Diagnostic plots (Figure 1) and visual predictive checks (Figure 2) illustrated final model appropriateness. The diagnostic plots of mean PRED or IPRED versus DV (Figure 1) indicate central tendency to the identity line ($Y = X$), and no major bias was observed. Plots of CWRES versus PRED and time after the last dose (Time) did not show any systematic trend with regard to PRED or Time, indicating that the final model described the data reasonably well (Figure 1). A comparison of the final diagnostic plots (Figure 1) to similar base model plots (Figure S1) demonstrated no obvious covariate trends. In the visual predictive checks, the median values and corresponding 95%CIs (2.5 and 97.5 percentile points) for simulated and observed dose-normalized ertugliflozin plasma concentrations were similar (Figure 2A,B); the observed median (solid red line) was generally contained within the 95%CI of the simulated median data (semitransparent red area), which indicated that the model adequately described the central tendency of the ertugliflozin concentration-time profile. Additional visual predictive checks stratified by study and dose also demonstrated adequacy of fit across the different study designs (data not shown).

Table 2. Parameter Estimates and Nonparametric Bootstrap Median (95%CI) for the Base and Final Models

Parameter (Unit)	Final Base Model			Final Model		
	Estimate	RSE (%)	Median (95%CI)	Estimate	RSE (%)	Median (95%CI)
CL/F (L/h)	11.1	2.37	11.1 (10.6-11.6)	12.0	2.18	12.0 (11.5-12.5)
Effect of body weight	0.750 FIX	–	–	0.750 FIX	–	–
Effect of eGFR				0.455	7.47	0.453 (0.382-0.523)
Effect of T2DM patient status				0.904	2.96	0.906 (0.850-0.958)
Effect of female sex				0.962	1.87	0.963 (0.927-0.998)
Effect of Black race				0.985	2.69	0.985 (0.935-1.04)
Effect of Asian race				1.08	2.68	1.08 (1.02-1.14)
Effect of other race				0.992	3.40	0.992 (0.928-1.06)
V_c/F (L)	7.29	14.1	7.40 (5.56-9.20)	6.54	13.2	6.60 (5.17-8.48)
Effect of body weight	1.00 FIX	–	–	1.00 FIX	–	–
Effect of age				−0.243	−95.5	−0.229 (−0.678 to 0.223)
Effect of female sex				1.36	13.6	1.36 (1.05-1.79)
Effect of Black race				0.917	17.7	0.931 (0.649-1.30)
Effect of Asian race				2.12	21.7	2.13 (1.40-3.18)
Effect of other race				1.15	17.0	1.15 (0.803-1.60)
V_p/F (L)	115	6.41	115 (105-133)	107	2.65	107 (102-113)
Effect of body weight	1.00 FIX	–	–	1.00 FIX	–	–
Q/F (L/h)	6.55	14.8	6.70 (4.78-8.00)	7.77	5.73	7.84 (7.00-8.67)
Effect of body weight	0.750 FIX	–	–	0.750 FIX	–	–
k_a (h^{-1})	0.286	10.3	0.289 (0.231-0.334)	0.329	4.80	0.331 (0.303-0.364)
Effect of food	0.713	5.54	0.712 (0.653-0.783)	0.726	4.59	0.726 (0.670-0.783)
Effect of without regard to food	0.619	4.77	0.620 (0.563-0.681)	0.663	5.29	0.663 (0.596-0.744)
Lag time (h)	0.232	1.87	0.232 (0.222-0.239)	0.228	1.94	0.228 (0.218-0.235)
Relative bioavailability (F1)	1.00 FIX	–	–	1.00 FIX	–	–
Effect of food	0.125	24.8	0.120 (0.0630-0.181)	0.0683	34.7	0.0685 (0.0217-0.110)
Effect of without regard to food	−0.027	−128	−0.0304 (−0.0996 to 0.0353)	0.0809	40.2	0.0809 (0.0136-0.151)
ω^2 (CL/F)	0.142	8.38	0.141 (0.121-0.167)	0.102	9.53	0.101 (0.0831-0.120)
Phase 1 residual error	0.471	5.50	0.467 (0.427-0.510)	0.387	2.95	0.385 (0.366-0.405)
Phase 2/3 residual error	0.833	1.90	0.832 (0.801-0.865)	0.836	1.84	0.836 (0.808-0.864)

CI, confidence interval; CL/F, apparent clearance; eGFR, estimated glomerular filtration rate; F1, relative bioavailability; k_a, absorption rate constant; Q/F, apparent intercompartmental clearance; RSE, relative standard error; T2DM, type 2 diabetes mellitus; V_c/F, apparent central volume of distribution; V_p/F, apparent peripheral volume of distribution; ω^2, interindividual variance.
Point estimates and RSEs of the estimates were estimated using NONMEM; medians and 95%CIs of the estimates were obtained from nonparametric bootstrap estimates (n = 1035, 8 runs with minimization terminated and 22 runs with estimates near a boundary were skipped when calculating the bootstrap results). The effect of body weight was included as a fixed allometric exponent on CL/F, V_c/F, V_p/F, and Q/F indicated by FIX in the table.

Parameter Estimate Results. The parameter estimates for CL/F, V_c/F, V_pF, Q/F, k_a, and F1 for the final model are summarized in Table 2. The condition number for the final model was 141, indicating a stable model, supported by the overall precision of parameter estimates. The shrinkage for CL/F was 28.7%. Except for the effect of age on V_c/F and the effect of administering ertugliflozin with food on F1, all fixed-effect parameters were estimated with reasonable precision (RSE <25%; Table 2). IIV for CL/F (expressed as % CV) was reduced from the base model (38%) to the final model (32%) with the inclusion of the covariate effects. Residual error estimates were 38.7% and 83.6% for the phase 1 and phase 3 studies, respectively. Covariate effects on CL/F, area under the curve for a dosing interval at steady state (AUC_τ), and V_c/F at
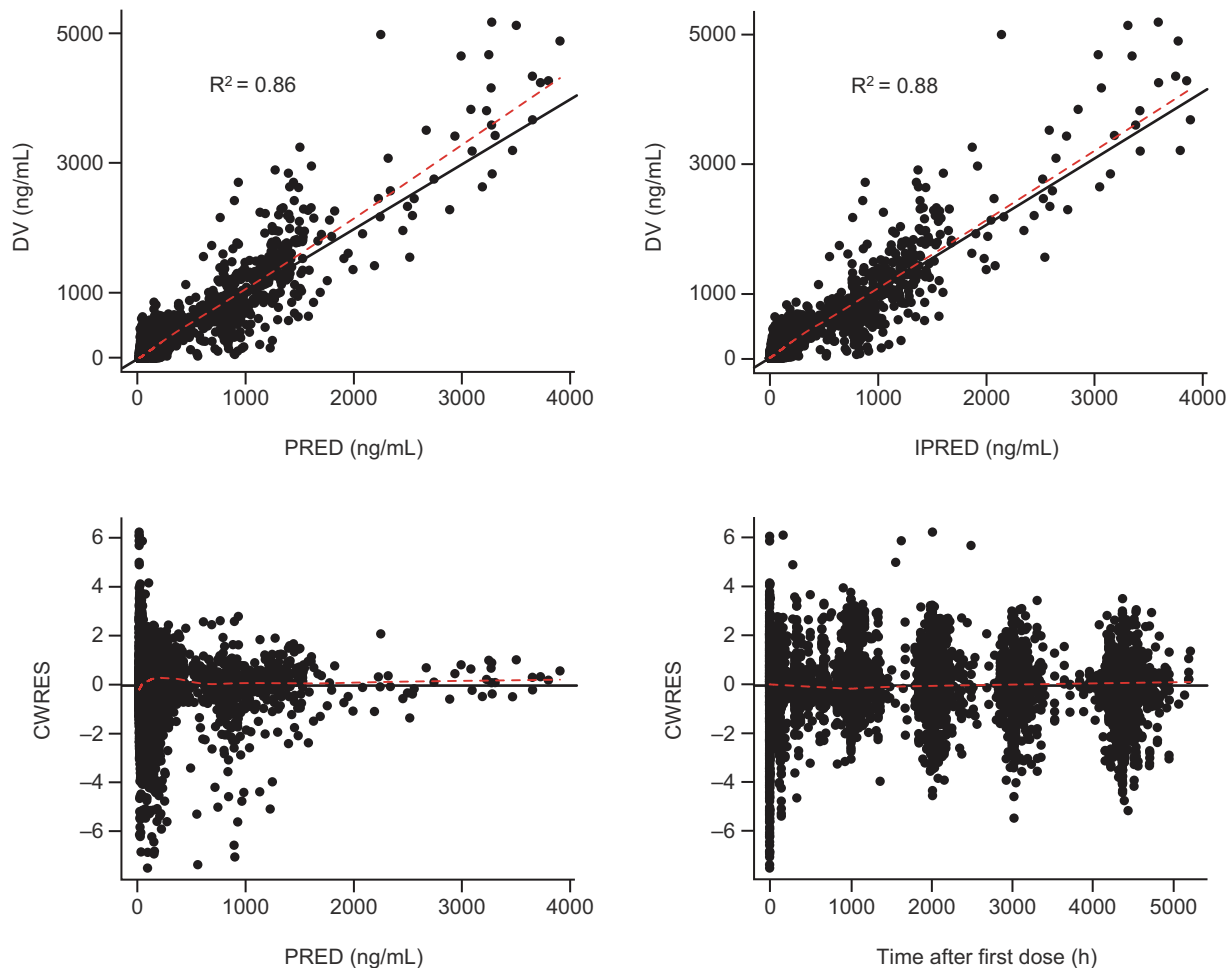
Figure 1. Final model diagnostic plots. The solid line in the DV versus PRED/IPRED plots represents the line of unity ($y = x$). The solid line in the CWRES-versus-PRED/TIME plots represents the horizontal line ($y = 0$). The dashed line represents a smooth regression line. CWRES, conditional weighted residual; DV, dependent variable; IPRED, individual-predicted concentration; PRED, population-predicted concentration.

steady state were compared with the reference subject (a 65-year-old healthy white man with a baseline body weight of 85 kg, eGFR of 90 mL/min/1.73 m^2, and taking ertugliflozin in the fasted state) and are illustrated in Figure 3A-C. CL/F increased with increasing eGFR up to 120 mL/min/1.73 m^2. The magnitude of the effect of patient status, sex, and race on CL/F was significant but small; CL/F decreased by 10% and 4% in patients with T2DM and in those who were female, respectively, and increased by 8% in Asians (Table 2, Figure 3A). IIV on CL/F expressed as % CV was 32%. AUC$_\tau$ increased with decreasing eGFR; for example, exposure would be 20% and 37% greater in subjects with an eGFR of 60 and 45 mL/min/1.73 m^2, respectively, relative to the reference eGFR of 90 mL/min/1.73 m^2 (Figure 3B). In addition, the magnitude of the effect of patient status, sex, and race on AUC$_\tau$ was significant but small; AUC$_\tau$ increased by 11% and 4% in patients with T2DM and female patients, respectively, and decreased

by 7% in Asians. V$_c$/F increased by 36% and 112% in women and Asians, respectively (Table 2, Figure 3C). An allometric model described the effect of baseline body weight on CL/F, V$_c$/F, V$_p$/F, and Q/F over the range of 59.5-123 kg (corresponding to the 5th and 95th percentiles of the observed body weights), relative to the reference (data not shown): CL/F fixed effect increased from 9.18 to 15.8 L/h (<32% change relative to reference), AUC$_\tau$ changed by <31%, V$_c$/F increased from 4.58 to 9.46 L (<45% change relative to reference), V$_p$/F increased from 75 to 155 L (<45% change relative to reference), and Q/F increased from 5.95 to 10.3 L/h (<32% change relative to the reference). Administration of ertugliflozin with food and without regard to food decreased k$_a$ by approximately 27% and 34%, respectively, and decreased F1 by approximately 7% and 8%, respectively (Table 2).

Based on the final model, the mean elimination half-life (% CV) of ertugliflozin was 15.3 hours
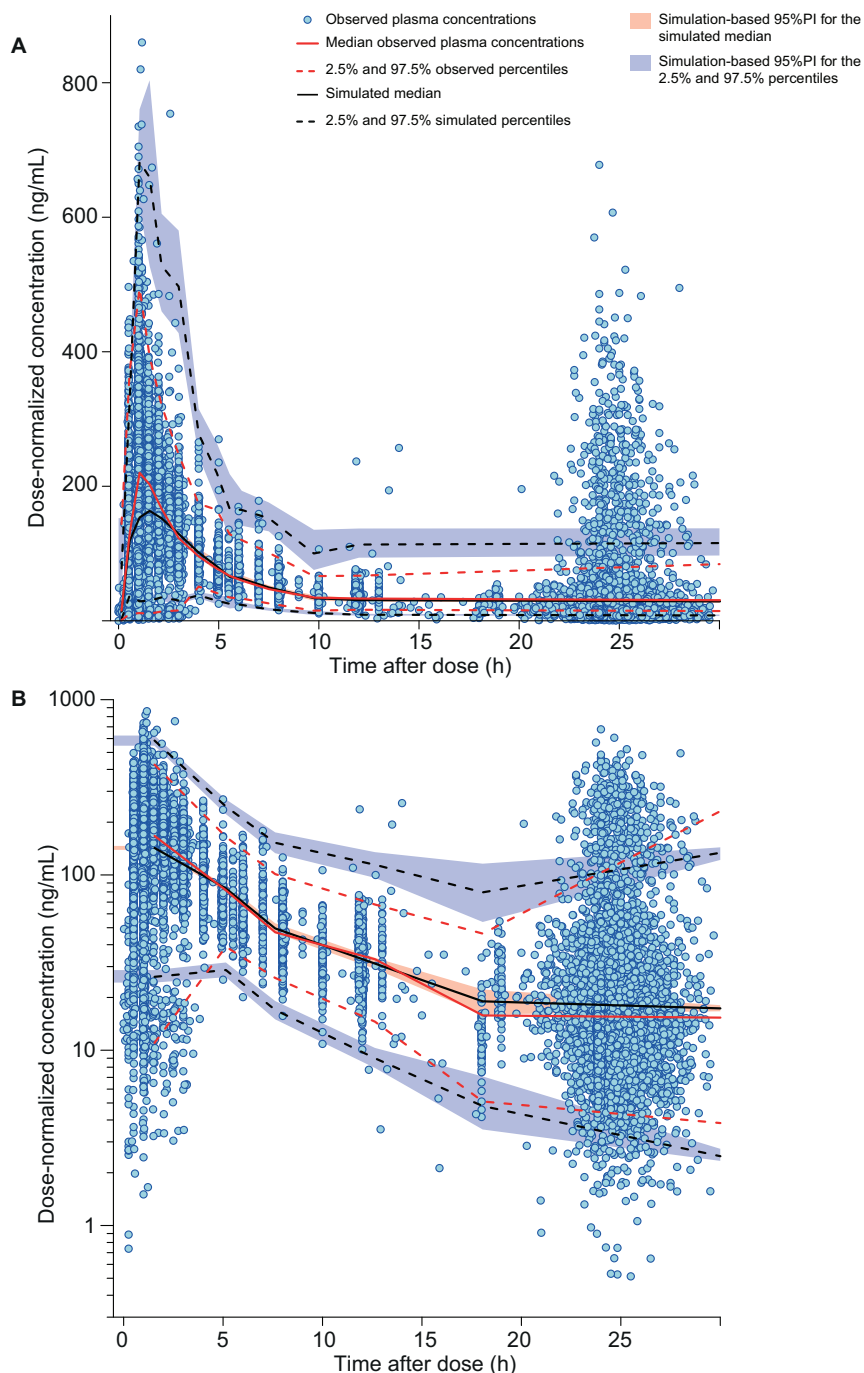
Figure 2. Visual predictive check. (A) Linear scale. (B) Log scale. PI, prediction interval.

(7.89) for healthy subjects and 16.6 hours (15.5) for patients with T2DM and normal renal function (eGFR $\geq$90 mL/min/1.73 m^2).

Discussion

This popPK analysis of ertugliflozin included a large data set of 15 clinical studies involving 192 healthy subjects and 2084 patients with T2DM. The PK of ertugliflozin was adequately described with a 2-compartment model with lag time, first-order absorption, and first-order elimination.

In the final model, covariates that were predictive of ertugliflozin CL/F included baseline body weight, baseline eGFR, T2DM status, sex, and Asian race. Covariate effects on CL/F were translated to the effect on AUC$_\tau$. The findings from a phase 1 drug-drug interaction study demonstrated that ertugliflozin exposure
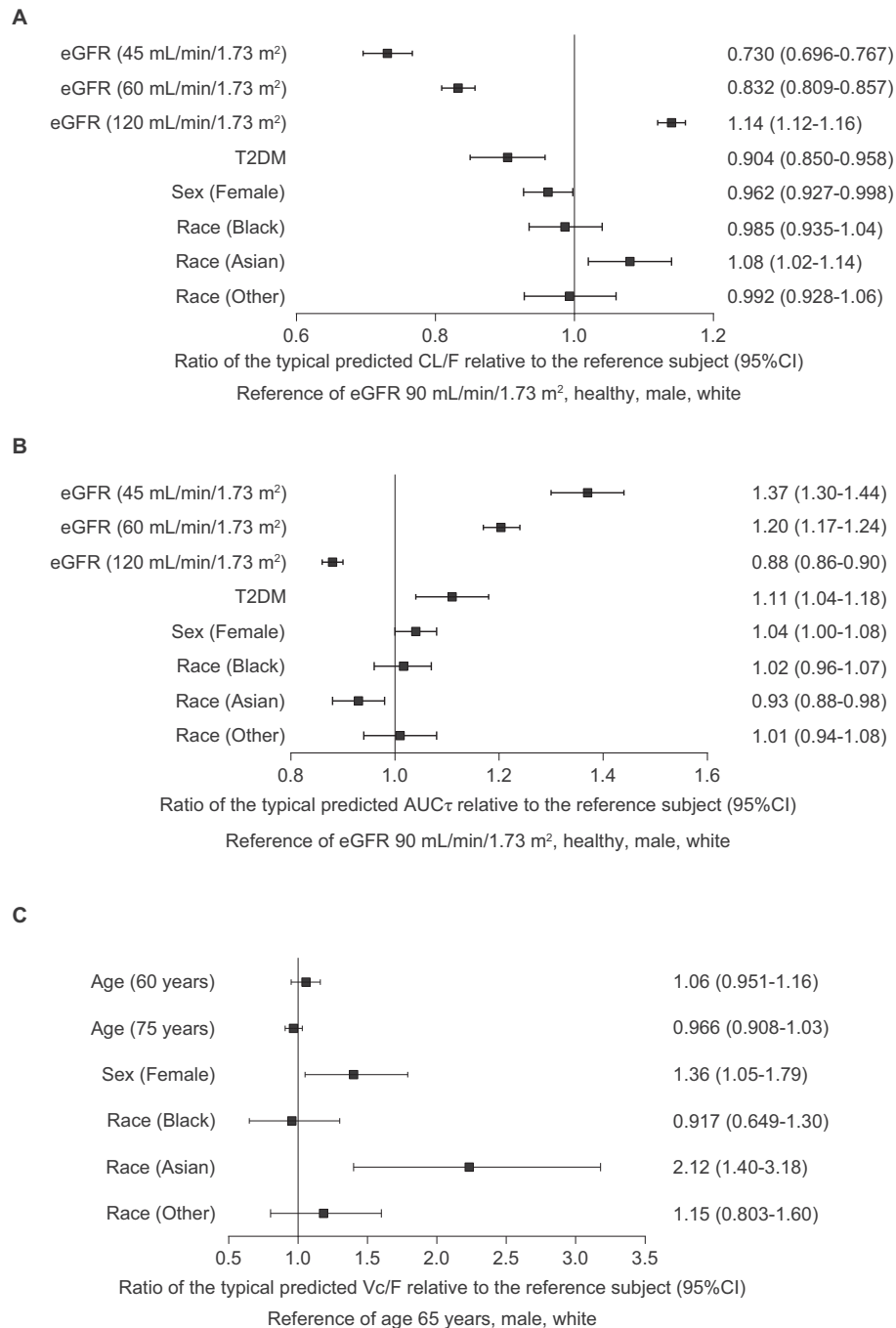
A

B

C

Figure 3. Covariate effects on (A) apparent clearance, (B) area under the concentration-time curve for a dosing interval at steady state, and (C) central volume of distribution (95%CI). Solid squares represent the ratio of the typical predicted CL/F, AUCτ, or V$_c$/F relative to the reference subject. Thus, a value of 1 (1.0) represents unity or a null covariate effect. The error bars represent the 95%CI of the ratio. AUC$_\tau$, area under the curve for dosing interval at steady state; CI, confidence interval; CL/F, apparent clearance; eGFR, estimated glomerular filtration rate; T2DM, type 2 diabetes mellitus; V$_c$/F, apparent central volume.

(AUC) was decreased by 39% following coadministration with rifampin.[20] Based on the ertugliflozin dose-versus-hemoglobin A$_{1c}$ response model, the 5- and 15-mg dose strengths following coadministration with rifampin were predicted to maintain clinically meaningful glycemic efficacy despite the reduced ertugliflozin exposure experienced.[20] Furthermore, oral doses of ertugliflozin as high as 300 mg (single dose), 100 mg once daily (up to 14 days), and 25 mg once daily (up to 12 weeks) were not associated with any safety concerns in the early phase 1 and phase 2 studies, and a maximum tolerated dose has not been identified.[3,21]

The ertugliflozin doses used in those studies cover the extremes of individual exposures for the ertugliflozin therapeutic doses of 5 and 15 mg. Therefore, for baseline body weight in this popPK analysis, a change in AUC_τ by a maximum of $\pm31\%$ relative to the reference subject was not anticipated to be clinically relevant. Similarly, as the magnitude of the effect of patient status, sex, or race on AUC_τ was small ($<11\%$), this was not expected to be clinically relevant. The greater exposure of ertugliflozin (as determined by AUC_τ) with decreasing eGFR demonstrated by this popPK analysis is consistent with findings from a phase 1 study of subjects with T2DM and renal impairment.[5] In that study, the higher ertugliflozin exposure observed in patients with T2DM and mild, moderate, and severe renal impairment compared with that in subjects with normal renal function was not anticipated to be clinically meaningful, and, based on PK, no dose adjustments of ertugliflozin are recommended.

In the final model, baseline body weight, female sex, and Asian race were determined to be predictive of ertugliflozin V_c/F. Increases in V_c/F would result in a decrease in C_{max} but would not be expected to impact AUC. In addition, as efficacy of ertugliflozin is driven by AUC,[22] the changes in V_c/F would not impact efficacy. Overall, none of the covariates included in the final model were clinically significant predictors of V_c/F, and no dose adjustments of ertugliflozin are recommended.

The magnitude of the decrease in k_a and F1 for ertugliflozin when administered with food or without regard to food, relative to the fasted state, is consistent with findings from a phase 1 food-effect study in healthy subjects showing that ertugliflozin C_{max} in the fed state was decreased by 29%, median time to maximum plasma concentration was delayed by 1 hour, and total exposure (AUC from time zero extrapolated to infinite time [AUC_{inf}]) was decreased slightly by approximately 8%.[15] Because ertugliflozin efficacy is dependent on total exposure (AUC) and not peak concentration (C_{max}),[22] the effect of food on ertugliflozin PK in that study was not clinically meaningful. Therefore, the decreases in k_a and F1 in this popPK analysis were not anticipated to be clinically relevant, and ertugliflozin may be administered without regard to meals.

Residual variability was lower in the phase 1 studies than in the phase 2/3 studies. This was expected as measurement error is often larger in sparsely sampled outpatient studies with nonwitnessed dosing relative to phase 1 studies in patients with T2DM or in healthy volunteers with intensive PK sampling, with the predose sample therefore not accurately reflecting a trough concentration. In this analysis, the shrinkage in CL/F was explored to evaluate the validity of using post hoc individual PK parameter estimates for subse-

quent exposure-response analyses. In the final model, the shrinkage for CL/F was 28.7%. Therefore, caution was exercised in the interpretation of the post hoc individual estimates of CL/F. In population analyses, when data are sparse and less informative, as is the case with phase 2/3 studies, there can be a tendency for individual PK parameter estimates to move (or shrink) toward the population mean.[18] The pooling of densely sampled phase 1 data with large amounts of sparsely sampled phase 2/3 data may have led to slightly higher shrinkage in the random effect on CL/F. Because other diagnostics such as the visual predictive check and CWRES plots showed adequacy of the model, estimation of the parameters was unlikely to be affected by the slightly higher shrinkage.[18]

In this popPK analysis, the FME procedure was used to evaluate the effect of demographic and physiological covariates on ertugliflozin PK parameters for the final model. This was appropriate, as it only required a single run and enabled direct assessment of all covariate relationships of interest, in which all covariates were added to the base model and estimated simultaneously to establish the final model. Other options for covariate evaluation, such as stepwise covariate modeling, were also considered.[23] Because the FME procedure affords the ability to make inferences about covariate effects, even when that particular effect may be nonsignificant, this was the preferred approach for covariate selection.[24]

During model development, several absorption models were explored to characterize the concentration-time profile for ertugliflozin in the absorption phase. A lag time with first-order absorption was used to describe the absorption profile. A transit compartment model, describing absorption as a multistep process represented by several presystemic compartments,[25] and a mixed zero- and first-order absorption model, with or without a lag time, were also attempted.[26] Predictive performance of all absorption models was evaluated using visual predictive checks that demonstrated minor differences between tested models. In addition, comparison of all absorption models revealed that model run times were considerably reduced compared with the other absorption models when including a lag time with only first-order absorption. Based on all these assessments, the model with lag time and first-order absorption was chosen as an adequate model to characterize the ertugliflozin absorption profile.

During base structural model development, an unusually high IIV on V_c/F was observed along with unusually high predose and/or low postdose concentration from phase 2 and phase 3 studies in the diagnostic plots. The high IIV on V_c/F rendered the model unstable and resulted in minimization failures. Therefore, several reduced variance-covariance matrix omega (Ω) structures were evaluated to obtain a stable and

parsimonious covariance structure.[27] Furthermore, it was suspected that patient noncompliance and/or misspecification of dosing or relative PK collection times for the unusually high predose and/or low postdose concentration values contributed to the observed systematic trend in the diagnostic plots. Refinement of the Ω structure continued until model performance was adequate using the sparsely sampled data. Including IIV only on CL/F produced a stable model that adequately described the variability despite the unusually high predose and low postdose concentrations. In addition, because the measure of exposure relevant for efficacy is average concentration at steady state (C_{av}), allowing IIV on CL/F still provided flexibility on CL/F, which is the main parameter that impacts C_{av}.

Conclusions

The popPK model successfully characterized ertugliflozin exposure in healthy subjects and patients with T2DM. None of the covariate effects evaluated in this analysis have a clinically relevant effect on the PK of ertugliflozin.

Data Accessibility

On request and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States and/or European Union or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The 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 requesters must enter into a data access agreement with Pfizer.

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Supplemental Information

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