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Meta-Analysis of Noncompartmental Pharmacokinetic Parameters of Ertugliflozin to Evaluate Dose Proportionality and *UGT1A9* Polymorphism Effect on Exposure

Jean-Claude Marshall, PhD[1], Yali Liang, MS[1], Vaishali Sahasrabudhe, PhD[1], Thomas Tensfeldt, MS[1], Daryl J. Fediuk, PhD[1], Susan Zhou, PhD[2], Rajesh Krishna, PhD[2], Vikas Kumar Dawra, PhD[3], Linda S. Wood, MS[1], and Kevin Sweeney, PhD[1]

Abstract

Ertugliflozin, a sodium-glucose cotransporter 2 inhibitor, is primarily metabolized via glucuronidation by the uridine 5′-diphospho-glucuronosyltransferase (UGT) isoform UGT1A9. This noncompartmental meta-analysis of ertugliflozin pharmacokinetics evaluated the relationship between ertugliflozin exposure and dose, and the effect of *UGT1A9* genotype on ertugliflozin exposure. Pharmacokinetic data from 25 phase 1 studies were pooled. Structural models for dose proportionality described the relationship between ertugliflozin area under the plasma concentration-time curve (AUC) or maximum observed plasma concentration (C_{max}) and dose. A structural model for the *UGT1A9* genotype described the relationship between ertugliflozin AUC and dose, with genotype information on 3 *UGT1A9* polymorphisms (*UGT1A9-2152*, *UGT1A9*3*, *UGT1A9*1b*) evaluated as covariates from the full model. Ertugliflozin AUC and C_{max} increased in a dose-proportional manner over the dose range of 0.5-300 mg, and population-predicted AUC and C_{max} values for the 5- and 15-mg ertugliflozin tablets administered in the fasted state demonstrated good agreement with the observed data. The largest change in ertugliflozin AUC was in subjects carrying the *UGT1A9*3* heterozygous variant, with population-predicted AUC (90% confidence interval) values of 485 ng·h/mL (458 to 510 ng·h/mL) and 1560 ng·h/mL (1480 to 1630 ng·h/mL) for ertugliflozin 5 and 15 mg, respectively, compared with 436 ng·h/mL (418 to 455 ng·h/mL) and 1410 ng·h/mL (1350 to 1480 ng·h/mL), respectively, in wild-type subjects. Overall, the mean effects of the selected *UGT1A9* variants on ertugliflozin AUC were within ±10% of the wild type. *UGT1A9* genotype did not have any clinically meaningful effects on ertugliflozin exposure in healthy subjects. No ertugliflozin dose adjustment would be required in patients with the *UGT1A9* variants assessed in this study.

Ertugliflozin is a selective inhibitor of sodium-glucose cotransporter 2 approved in the United States,[1] Europe,[2] and other countries as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). It is recommended for use as monotherapy or in combination with other diabetes therapies at single daily doses of 5 and 15 mg.[1,2]

The pharmacokinetics (PK) of ertugliflozin have been well characterized across a number of different study populations.[3] Oral absorption of ertugliflozin is rapid, with a median time to maximum plasma concentrations (T_{max}) of 1.0 hour (single doses; fasted) to 2.0 hours (multiple doses; fed) postdose.[4] Ertugliflozin has a mean terminal-phase half-life ($t_{1/2}$) of ∼10 to 17 hours.[4] No clinically meaningful effect on ertugliflozin exposure is observed following administration with food[5] or following concomitant administration with commonly coprescribed drugs such as metformin, sitagliptin, glimepiride, or simvastatin,[6] and no adjustment of ertugliflozin dose is required in patients with renal impairment[7] or mild to moderate hepatic impairment[8] based on ertugliflozin

[1]Pfizer Inc., Groton, Connecticut, USA
[2]Merck & Co., Inc., Kenilworth, New Jersey, USA
[3]Pfizer Inc., New York, New York, USA

Corresponding Author:
Kevin Sweeney, PhD, Pfizer Inc., 445 Eastern Point Road, Groton, CT 06340
Email: kevin.sweeney@pfizer.com

Authors Jean-Claude Marshall and Yali Liang contributed equally to this work.

Yali Liang: affiliation at the time the study was conducted; current address: Bristol-Myers Squibb, Lawrenceville, New Jersey, USA.

Rajesh Krishna: affiliation at the time the study was conducted; current address: Certara USA Inc., Parsippany, New Jersey, USA; ORCID identifier: 0000-0002-3127-9732.

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PK. A mass-balance study in humans revealed that ~35% of the administered dose is recovered in urine and feces as unchanged ertugliflozin.[9] O-glucuronidation is the major biotransformation pathway for ertugliflozin, with 2 pharmacologically inactive glucuronide metabolites—ertugliflozin-2-O-β-glucuronide and ertugliflozin-3-O-β-glucuronide—representing the primary metabolites of ertugliflozin in plasma.[9,10] In vitro metabolism studies have shown that formation of these metabolites is catalyzed primarily by the uridine 5′-diphospho-glucuronosyltransferase (UGT) enzyme isoform UGT1A9 (81%); the UGT2B7 and UGT2B4 isoforms play a minor role in ertugliflozin glucuronidation (19%).[9–11]

Sequence variation in *UGT* genes has been shown to affect enzyme expression and activity levels, with the potential to profoundly affect target drug exposures.[12] As such, current regulatory guidance recommends that for drugs in which the primary biotransformation pathway is governed by an enzyme that is genetically polymorphic, the effect of this variation on the PK of the active substance is assessed.[13,14] Three *UGT1A9* variants were chosen for this analysis based on their allelic frequency across different racial groups and the potential for a clinical effect on drug disposition.[12] The *UGT1A9*-2152(C>T) single-nucleotide polymorphism (SNP), occurring in the *UGT1A9* promoter with a minor allele frequency (MAF) in whites of 0.06, results in increased UGT1A9 expression and higher rates of substrate glucuronidation.[12,15] The *UGT1A9*3* 98(T>C) nonsynonymous SNP has a minor allele frequency in whites of 0.02-0.04 and encodes an $M^{33}T$ substitution that leads to reduced enzyme activity for certain substrates.[12,16] The *UGT1A9*1b*-118(dT)$_{9>10}$ allele, which results from a 1-bp insertion in the *UGT1A9* promoter and leads to increased UGT1A9 expression and higher substrate clearance, has a minor allele frequency in whites of ~0.4.[12,17]

As the allelic frequency of *UGT1A9* variants is generally low, a pooled analysis of ertugliflozin exposure values from phase 1 trials was prospectively planned to assess the impact of *UGT1A9* genotype on ertugliflozin PK. In addition, although the dose proportionality of ertugliflozin exposure when administered as a solution or suspension was evaluated in the first-in-human studies,[1–4] dose proportionality of ertugliflozin tablets was not formally assessed in a dedicated clinical study during phase 1 development. Instead, a model-based approach was taken to evaluate dose proportionality of ertugliflozin using data from the phase 1 development program (including solution, suspension, and tablet formulations, and fasted or fed conditions) to support the conclusion of dose-proportional increases in ertugliflozin exposure in the product label. Hence, the objectives of this analysis of pooled data from

25 ertugliflozin phase 1 studies were (1) to assess the dose proportionality of ertugliflozin area under the plasma concentration-time curve (AUC) and maximum observed plasma concentration (C_{max}) across various ertugliflozin doses, regimens, and formulations, and (2) to evaluate the impact of *UGT1A9* genotype on ertugliflozin AUC in sufficient numbers of participants to allow a meaningful analysis across *UGT1A9* variants that have relatively low minor allele frequencys in global populations.

Methods

Ethical Conduct of the Studies
The final protocols and informed consent documentation for the studies included in this analysis were reviewed and approved by an institutional review board. A list of study sites and locations is provided in Table S1. All subjects provided signed and dated informed consent. All studies were compliant with the ethical principles of the Declaration of Helsinki and all International Conference on Harmonisation Good Clinical Practice guidelines.

Genotyping
K_2-ethylenediaminetetraacetic acid blood samples were taken prior to dosing for each subject and frozen until time of analysis. DNA was extracted from whole-blood samples using a QIAsymphony DNA Mini Kit (Qiagen, Germantown, Maryland), quantified by NanoDrop spectroscopy (Thermo Fisher Scientific, Waltham, Massachusetts), and normalized to a concentration of 8 ng/μL.

DNA samples from the study participants were genotyped for 3 *UGT1A9* polymorphisms (2 SNPs and 1 insertion-deletion mutation), chosen for analysis based on their population frequency and their potential for a clinical effect on drug disposition.[12,15–18] None of these polymorphisms represent complete loss of function of the UGT1A9 isozyme, and, as such, they do not constitute a traditional poor metabolizer status, as found with the cytochrome P450 (CYP) 2D6 isozyme.[19] The 2 SNPs were *UGT1A9*-2152(C>T) (rs17868320) and *UGT1A9*3* 98(T>C) (rs72551330), and the insertion-deletion mutation was *UGT1A9*1b*-118(dT)$_{9>10}$ (rs3832043; previously referred to as *UGT1A9*22*). The specified *UGT1A9* polymorphisms were assessed by polymerase chain reaction (PCR). Commercially available TaqMan assays were used to genotype the 2 *UGT1A9* SNPs, rs17868320 (C__34418857_10) and rs72551330 (C__64627083_10), which were analyzed using a QuantStudio 12K Flex Real-Time PCR system (Applied Biosystems, Thermo Fisher Scientific, Waltham, Massachusetts). The insertion-deletion mutation, rs3832043, was detected by amplifying a

region around the base insertion (forward primer, ACTTAACATTGCAGCACAGG; reverse primer, 6FAM-CAGAGAACTGCAGCTGAGAGCA) and sizing the fragment using an Applied Biosystems 3730xl DNA Analyzer (Thermo Fisher Scientific, Waltham, Massachusetts).

Data Sources

Study Selection and Data Sets. PK data from 25 phase 1 studies of ertugliflozin were included in this pooled analysis (Table S1). Selected studies were phase 1 studies with dense PK sampling and appropriate informed consent for DNA sampling to allow a pharmacogenomic analysis. Studies consisted of single- and multiple-dose regimens of ertugliflozin as well as crossover study designs that evaluated the effects of dose regimen, formulation, food, and concomitant medications on the PK of ertugliflozin across a range of study populations.

The pooled data set included subject identification, dosing information, and the reported PK parameters. Two analytical data sets (1 for AUC values and 1 for C_{max} values) were created from the pooled data set. Both the AUC and C_{max} data sets were used in the dose-proportionality analysis; only the AUC data set was used in the *UGT1A9* genotype analysis. Of the 25 studies in the data set, data from 17 studies contributed to the dose-proportionality analysis and data from 20 studies contributed to the *UGT1A9* genotype analysis (Table S1).

Data Inclusion Criteria for the Dose-Proportionality and UGT1A9 *Genotype Analyses.* All AUC and C_{max} data reported using noncompartmental analysis methods were included in the dose-proportionality and *UGT1A9* genotype analyses. For bioequivalence, drug-drug interaction (DDI) and twice-daily versus once-daily regimen studies, only PK parameters from the reference treatment arms were included (see Table S1). For single-dose studies, AUC from time zero extrapolated to infinite time (AUC_{inf}) and C_{max} were included. For multiple-dose studies, AUC from time zero to time tau, the dosing interval, where tau is 24 hours (AUC_{tau}) at steady state and C_{max} following the first dose (day 1 data, if available) were included. For the food-effect study on the commercial ertugliflozin tablet, PK parameters from the fasted arm were included. For the renal or hepatic impairment studies, only PK parameters from the healthy subjects with normal renal or hepatic function were included.

Data Exclusion Criteria for the Dose-Proportionality and UGT1A9 *Genotype Analyses.* Data excluded from statistical analyses because of vomiting or protocol devia-

tions in the original studies were also excluded from the current analyses.

Specific Data Inclusion/Exclusion Criteria for the Dose-Proportionality Analysis. For the dose-proportionality analysis only, PK parameters from studies with fasted oral administration of ertugliflozin or administration of ertugliflozin with a light meal in healthy subjects in the absence of other drugs were included. Bioequivalence studies evaluating fixed-dose combinations of ertugliflozin and metformin or ertugliflozin and sitagliptin versus coadministration of individual components were excluded.

Specific Data Inclusion/Exclusion Criteria for the UGT1A9 *Genotype Analysis.* For the *UGT1A9* genotype analysis only, AUC values from studies with fasted oral administration of ertugliflozin tablets in healthy subjects in which *UGT1A9* genotype data were collected were included; studies with no *UGT1A9* genotype data available were excluded. PK parameters from the reference arms of bioequivalence studies evaluating fixed-dose combinations of ertugliflozin and metformin or ertugliflozin and sitagliptin were included because clinical drug-drug interaction studies have shown that there are no meaningful differences in ertugliflozin PK between coadministration of ertugliflozin with metformin or sitagliptin versus ertugliflozin alone.[6]

Model Development for the Dose-Proportionality Analysis

Structural Model. The data sets were used to develop regression models that described the relationships between dose and exposure parameters (AUC or C_{max}). The models were constructed using AUC or C_{max} as the dependent variable and dose as the independent variable. The model structures are shown below:

$$AUC = INT + SLP \times DOSE$$

$$C_{max} = SLP \times DOSE$$

where DOSE is the ertugliflozin dose in milligrams, SLP (slope) is the increase of AUC or C_{max} per milligram increase in dose, and INT (intercept) is the AUC or C_{max} at a dose of zero. The requirement for an intercept was assessed using a likelihood ratio test (based on differences in the NONMEM objective function values, ΔOFV) between the model with and without an intercept to determine the significance. The test was performed at a significance of $\alpha = 0.05$, and the intercept was included in the structural model if the *P* value was less than α ($\Delta OFV > 3.841$). An intercept was included in the AUC model for fitting purposes ($\Delta OFV > 3.841$) but was not included in the C_{max}

model (ΔOFV < 3.841). Power models were tested during structural model development. However, the power model did not provide appropriate fitting to the AUC data with increase of OFV (ΔOFV, 41). The C_{max} power model seemed to have a good fit to the data, but the estimate of 95% confidence interval (CI) of the power parameter included 1 after covariates were added to the model, which further supported that the linear model is more appropriate for the data.

Random-Effects Model. The equations shown below provided the structure for random effects on slope and base model parameterization:

$$SLP_i = \theta_{Slope} \times e^{\eta 1,i}$$

$$AUC_{ij} = INT + SLP_i \times DOSE_{ij}$$

$$C_{max\,ij} = SLP_i \times DOSE_{ij}$$

where i indexes subjects and j indexes dose for each ith subject, SLP_i represents the individual model-predicted slope, θ_{Slope} is the mean value of the slope, and $\eta1,i$ denotes the interindividual error around the slope, accounting for the ith subject's deviation from the mean value having zero mean and variance ω^2.

The residual variability was modeled using an additive residual error model shown below:

$$AUC(or\ C_{max})_{ij} = AUC(or\ C_{max})(t_{ij}) + \varepsilon_{ij}$$

where $AUC(or\ C_{max})_{ij}$ is the observed AUC or C_{max} of the ith subject at the jth dose, $AUC(or\ C_{max})(t_{ij})$ represents the model-predicted AUC or C_{max}, and ε_{ij} denotes the normally distributed intraindividual (residual) error assumed to have a mean of zero and variance σ^2.

Full Model. The full models for AUC and C_{max} were generated by the addition of the covariates of interest to the base model multiplicatively as a factor. The covariates of interest for the dose-proportionality analysis were formulation (tablet as reference) and food status (light meal versus fasted).

The method of addition of covariates onto the slope parameter is shown below:

$$TVSLP = \theta_{Slope} \times \theta_{Susp,slope}^{FLG1} \times \theta_{Solu,slope}^{FLG2} \times \theta_{Food,slope}^{Food}$$

where TVSLP is the typical individual (mean) value of slope with covariates, and θ_{Slope} is the population central tendency of slope with the tablet formulation and the fasted state. The theta for each covariate describes the fold change in θ_{Slope} when the formulation is a suspension or solution ($\theta_{Susp,slope}$ and $\theta_{Solu,slope}$, respectively) or when the drug is administered with a light meal ($\theta_{Food,slope}$). FLG1, FLG2, and Food are all indicator variables. FLG1 and FLG2 are the flags for formulation, and values were derived based on the FORM (formulation) variable in the data set, which was coded as 2, 3, and 4 for tablet, suspension, and solution, respectively. When FORM = 2 (tablet), then FLG1 = 0 and FLG2 = 0; when FORM = 3 (suspension), then FLG1 = 1 and FLG2 = 0; when FORM = 4 (solution), then FLG1 = 0 and FLG2 = 1. Food was coded as 0 and 1 for fasted and fed (light meal) states, respectively.

The full model approach was implemented for model building; no stepwise inclusion or exclusion of covariates for model building was performed. Rather, all covariates were retained in the full model regardless of significance. The purpose of the covariate analysis was not to identify the covariate effect size, but to account for confounding covariate effects and better understand dose proportionality. If a linear model was successfully fitted to the AUC or C_{max} versus dose data, then dose proportionality could be concluded for AUC or C_{max}.

Model Development for the *UGT1A9* Genotype Analysis

The same methods from the dose-proportionality analysis were used to develop the structural model for the *UGT1A9* genotype analysis. Briefly, the relationship between AUC and dose was described with a structural model, and then the covariates of interest were added to the base model to develop the full model.

The covariates of interest for the *UGT1A9* genotype analysis consisted of 3 allelic variants of *UGT1A9*: (1) *UGT1A9*-2152(C>T) — rs17868320 — abbreviated as RS20 in the model, with the wild type of rs17868320 coded as "C/C" and the heterozygous variant coded as "C/T"; (2) *UGT1A9*3* 98(T>C) — rs72551330 — abbreviated as RS30 in the model, with the wild type of rs72551330 coded as "T/T" and the heterozygous variant coded as "T/C"; and (3) *UGT1A9*1b*−118(dT)$_{9>10}$ — rs3832043 — abbreviated as RS43 in the model, with the wild type of rs3832043 coded as "9/9," the heterozygous variant coded as "9/10," and the homozygous variant coded as "10/10."

The covariate model development focused on *UGT1A9* genotype only because all data were from fasted subjects who received the tablet formulation. The 3 allelic variants were included in the model as categorical variables. As the slope is the determinant of the change in exposure as a function of dose, covariates were included on the slope parameter. The method of addition of covariates onto the slope parameter is shown below:

$$TVSLP = \theta_{Slope} \times \theta_{RS43Hom,slope}^{RS43} \times \theta_{RS43Het,slope}^{RS43}$$
$$\times \theta_{RS20,slope}^{RS20} \times \theta_{RS30,slope}^{RS30}$$

where TVSLP is the typical individual (mean) value of slope with covariates and θ_{Slope} is the population central tendency of slope in *UGT1A9* wild-type subjects. The theta of each covariate describes the fold change in θ_{Slope} for each type of *UGT1A9* variant carriers: $\theta_{RS43Hom,slope}$ and $\theta_{RS43Het,slope}$ for the *UGT1A9*1b* homozygous and heterozygous variants, respectively; $\theta_{RS20,slope}$ for the *UGT1A9-2152* heterozygous variant; and $\theta_{RS30,slope}$ for the *UGT1A9*3* heterozygous variant. There were no homozygous *UGT1A9-2152* or *UGT1A9*3* variants in the data set. In the final data set, [RS]20 (*UGT1A9-2152*) and [RS]30 (*UGT1A9*3*) were coded as 0 and 1 for wild-type and heterozygous variants, respectively; and [RS]43 (*UGT1A9*1b*) was coded as 0, 1, and 2 for wild-type, homozygous, and heterozygous variants, respectively.

All 3 variants (4 covariates) were added to the model simultaneously, so the effect of each variant against the "true" wild type (the wild type for all 3 alleles) could be defined. The full model was used for all inferences regarding variance in drug exposure attributable to the covariates. The effects of the *UGT1A9* genotype on the ertugliflozin AUC were estimated by the covariate effect as a fold change relative to the AUC of wild-type subjects.

Assessment of Model Adequacy (Goodness of Fit)

Goodness of fit was evaluated using change in the log likelihood, visual inspection of diagnostic plots, precision of the parameter estimates, and impact on between-subject variability or residual variability. At both the base- and full-model stages, diagnostic plots were examined to assess model adequacy, possible lack of fit, or violation of assumptions. Plots of AUC and C_{max} versus dose and population-predicted and individual-predicted versus dose were evaluated for base- and full-model appropriateness. Furthermore, observed versus predicted and observed versus individual-predicted values were evaluated for concordance with the line of unity. Similarly, plots of residuals versus predicted values were evaluated for randomness around the zero line.

Assessment of Model Predictive Performance (Evaluation)

The full model was used in bootstrap analysis (stratified by protocol) with 1000 replications to evaluate parameter uncertainty. The resultant parameter estimates for slope and intercept (for AUC model only) from the bootstrap analysis were used to derive AUC and C_{max} with 95%CI at ertugliflozin doses of 5 and 15 mg. The 5th and 95th percentiles of the predicted exposure data were then quantified to determine the predicted mean AUC and C_{max} following administration of a 5- or 15-mg oral dose. The results were displayed graphically and overlaid with the observed data to allow for a visual predictive check of the model fit for the dose-proportionality analysis. The predicted mean AUC at 5- and 15-mg doses of ertugliflozin for different *UGT1A9* genotypes was then evaluated. For simulated parameters, 90%CIs were reported.

Modeling Software

Modeling was performed in the Pfizer repository ePharmacology (version 4.4.1) using the software program NONMEM (version 7.3; ICON plc, Gaithersburg, Maryland). All analyses were conducted using the first-order conditional estimation method with interaction. Preanalysis and postprocessing diagnostic plots and summary statistics were generated using R software (version 3.0.2 or higher; https://www.r-statistics.com/).

Results

Dose-Proportionality Analysis

Observed Data. For the dose-proportionality analysis, 344 records from 309 subjects and 307 records from 260 subjects were used in the analysis for AUC and C_{max}, respectively. The number of records by dose for the fasted-versus-fed and formulation covariates is shown in Table 1. The doses contained within the dose-proportionality data set ranged from 0.5 to 300 mg, with the largest number of records obtained following administration of a 15-mg dose, which is the highest approved dose for ertugliflozin. The majority of subjects received the tablet formulation administered under fasted conditions.

Across the ertugliflozin dose range included in the data set, exposure data ranged from 37.3 to 32 600 ng·h/mL for AUC and 6.1 to 5160 ng/mL for C_{max}. Ertugliflozin dose-normalized AUC and C_{max} values demonstrated an approximately linear relationship between observed AUC and dose and between observed C_{max} and dose (Figure 1).

Modeled Data. For the dose-proportionality base models, linear models relating AUC to ertugliflozin dose and C_{max} to ertugliflozin dose were fitted and displayed a positive linear relationship between dose and AUC and between dose and C_{max}. The parameter estimates from the base model fits for AUC and C_{max} are shown in Table 2.

The covariates of formulation and food status (light meal) were added into the base models to develop full models for dose proportionality, and a positive linear relationship between dose and predicted AUC and C_{max} was again observed. Population-predicted, individual-predicted, and observed values for AUC and C_{max} fits using the full model are shown in Figure 2, including the model fit for the lower ertugliflozin dose range of 0.5 to

Table 1. Number of Records by Formulation, Fed Status, Regimen, and Ertugliflozin Dose in the Dose-Proportionality Analysis

	Ertugliflozin Dose (mg)										
Covariate	0.5	1	2.5	5	10	15	25	30	100	300	Total
Food											
Fed (light meal)	0	8	0	8	0	0	14	0	8	0	38
Fasted	8	0/12[a]	8	34/12[a]	20	155/128[a]	18	8	48	7	306/269[a]
Formulation											
Tablet	0	0/12[a]	0	34/12[a]	12	155/128[a]	18	0	40	0	259/222[a]
Suspension	0	0	0	8	8	0	14	8	16	7	61
Solution	8	8	8	0	0	0	0	0	0	0	24
Regimen											
Single dose[b]	8	0	8	12	20	127	18	8	48	7	256
Steady state[b]	0	8	0	30	0	28	14	0	8	0	88
Total	8	8/20[a]	8	42/20[a]	20	155/128[a]	32	8	56	7	344/307[a]

AUC, area under the plasma concentration-time curve; C_{max} maximum observed plasma concentration.

[a]Values are for the AUC data set/C_{max} data set.

[b]Single-dose and steady-state values are for the AUC data set only. All C_{max} data were obtained after administration of the first dose.
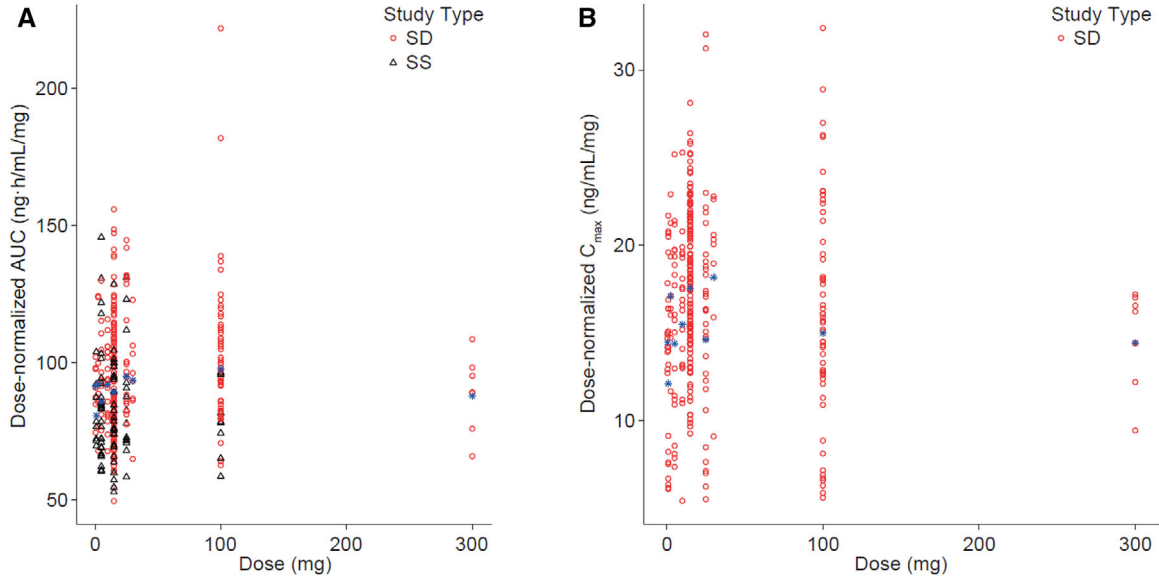

Figure 1. Observed ertugliflozin dose-normalized (A) AUC and (B) C_{max} values by dose from the dose-proportionality analysis. Red circles represent dose-normalized AUC_{inf} or dose-normalized C_{max} following a single dose; black triangles represent dose-normalized AUC_{tau} at steady state; geometric mean values for each dose group are represented by blue asterisks. AUC, area under the plasma concentration-time curve; AUC_{inf}, AUC from time zero extrapolated to infinite time; AUC_{tau}, AUC from time zero to time tau, the dosing interval, for which tau is 24 hours; C_{max}, maximum observed plasma concentration; SD, single dose; SS, steady state.

15 mg. The parameter estimates from the full models for AUC and C_{max} and the 95%CIs generated from a nonparametric bootstrap utilized for model performance qualification are shown in Table 2. Administration of ertugliflozin as a suspension formulation did not have a significant effect on ertugliflozin AUC or C_{max} relative to administration as a tablet. When administered as a solution, ertugliflozin AUC was higher by 16% (95%CI, 2%-31%), but C_{max} was lower by 18% (95%CI, 5%-28%) versus the tablet form. AUC and C_{max} were lower by 10% (95%CI, 1%-19%) and by 46% (95%CI, 39%-54%),

respectively, when ertugliflozin was administered with a light meal relative to fasting administration (Table 2).

The predicted mean (90%CI) AUC values following administration of the 5- and 15-mg tablet doses in the fasted state were 437 ng·h/mL (422-451 ng·h/mL) and 1380 ng·h/mL (1350-1410 ng·h/mL), respectively. For C_{max}, these values were 88.7 ng/mL (86.0-91.4 ng/mL) and 266 ng/mL (258-274 ng/mL), respectively. The density plots of the predicted mean AUC overlaid with the mean observed AUC and the predicted mean C_{max} overlaid with the mean observed C_{max} are shown in

Table 2. Base- and Full-Model Parameter Values and Precision Estimates for AUC and C_{max} as a Function of Dose From the Dose-Proportionality Analysis

	Base Model	Full Model	
	Estimate (RSE, %[a])	Estimate (RSE, %[a])	95%CI[b]
AUC[c]			
Slope (ng·h/mL/mg)	93.2 (1.50)	94.1 (1.76)	91.1-97.4
Intercept (ng·h/mL)	−26.5 (28.8)	−33.7 (33.2)	−57.3 to −11.6
Suspension	—	1.04 (3.44)	0.976-1.11
Solution	—	1.16 (6.35)	1.02-1.31
Food (light meal)	—	0.896 (4.98)	0.813-0.985
C_{max}[d]			
Slope (ng/mL/mg)	16.2 (2.20)	17.7 (1.92)	17.1-18.4
Suspension	—	0.897 (4.77)	0.830-0.978
Solution	—	0.821 (7.08)	0.719-0.946
Food (light meal)	—	0.539 (8.09)	0.462-0.613

AUC, area under the plasma concentration-time curve; CI, confidence interval; C_{max}, maximum observed plasma concentration; RSE, relative standard error.
[a] Percent relative standard error was calculated as ($100 \times$ standard error/estimate).
[b] 95%CIs were generated from bootstrap.
[c] AUC residual error was 44.9 ng·h/mL for the base model and 44.5 ng·h/mL for the full model (square root sigma values).
[d] C_{max} residual error was 25.2 ng/mL for the base model and 24.5 ng/mL for the full model (square root sigma values).

Table 3. Number of Subjects by *UGT1A9* Genotype and Ertugliflozin Dose in the *UGT1A9* Genotype Analysis

	Ertugliflozin Dose (mg)					
Genotype	2.5	5	7.5	15	100	Total
WT for all SNPs	7	14	24	51	4	100
UGT1A9-2152_het	1	5	4	6	0	16
*UGT1A9*3_het*	0	2	1	15	13	31
*UGT1A9*1b_hom*	10	10	17	33	0	70
*UGT1A9*1b_het*	12	26	47	62	0	147
*UGT1A9-2152_het, UGT1A9*1b_het*	2	1	2	5	0	10
*UGT1A9*3_het, UGT1A9*1b_het*	0	0	2	15	16	33
*UGT1A9*3_het, UGT1A9*1b_hom*	0	0	0	3	0	3
*UGT1A9-2152_het, UGT1A9*3_het*	0	0	0	0	6	6
*UGT1A9-2152_het, UGT1A9*3_het, UGT1A9*1b_het*	0	0	0	0	1	1
Total	32	58	97	190	40	417

het, heterozygous; hom, homozygous; SNPs, single-nucleotide polymorphisms; WT, wild type.

Figure S1 and demonstrated good agreement between the predicted and observed data. The observed mean C_{max} at 5 mg fell at the boundary of the predicted range of mean C_{max} values. This could be because of the very small number of subjects (n = 12) in the 5-mg dose group for the observed data.

UGT1A9 Genotype Analysis

Observed Data. For the *UGT1A9* genotype analysis, 417 subjects (1 record per subject) were included in the analysis for AUC. The number of subjects by dose for the *UGT1A9* genotype covariates is shown in Table 3. The doses contained within the *UGT1A9* genotype data set ranged from 2.5 to 100 mg, with the largest number of records obtained following administration of a 15-mg dose. The majority of subjects in this data set were carriers of *UGT1A9*1b* allelic variants (Table 3).

Across the ertugliflozin dose range included in the data set, exposure data ranged from 115 to 22 200 ng·h/mL for AUC. Ertugliflozin dose-normalized AUC values are shown in Figure 3A; dose-normalized AUC values by *UGT1A9* genotype are shown in Figure 3B. An approximate linear relationship between observed AUC and dose was observed when AUC values were plotted by ertugliflozin dose (Figure 3A).

Modeled Data. For the *UGT1A9* genotype base model, a linear model relating AUC to ertugliflozin dose was successfully fitted to the observed data. The parameter estimates from the base model for AUC are shown in Table 4.

The covariates of the 3 allelic variants of *UGT1A9* were added into the base model to develop the full model for *UGT1A9* genotype, and a positive linear
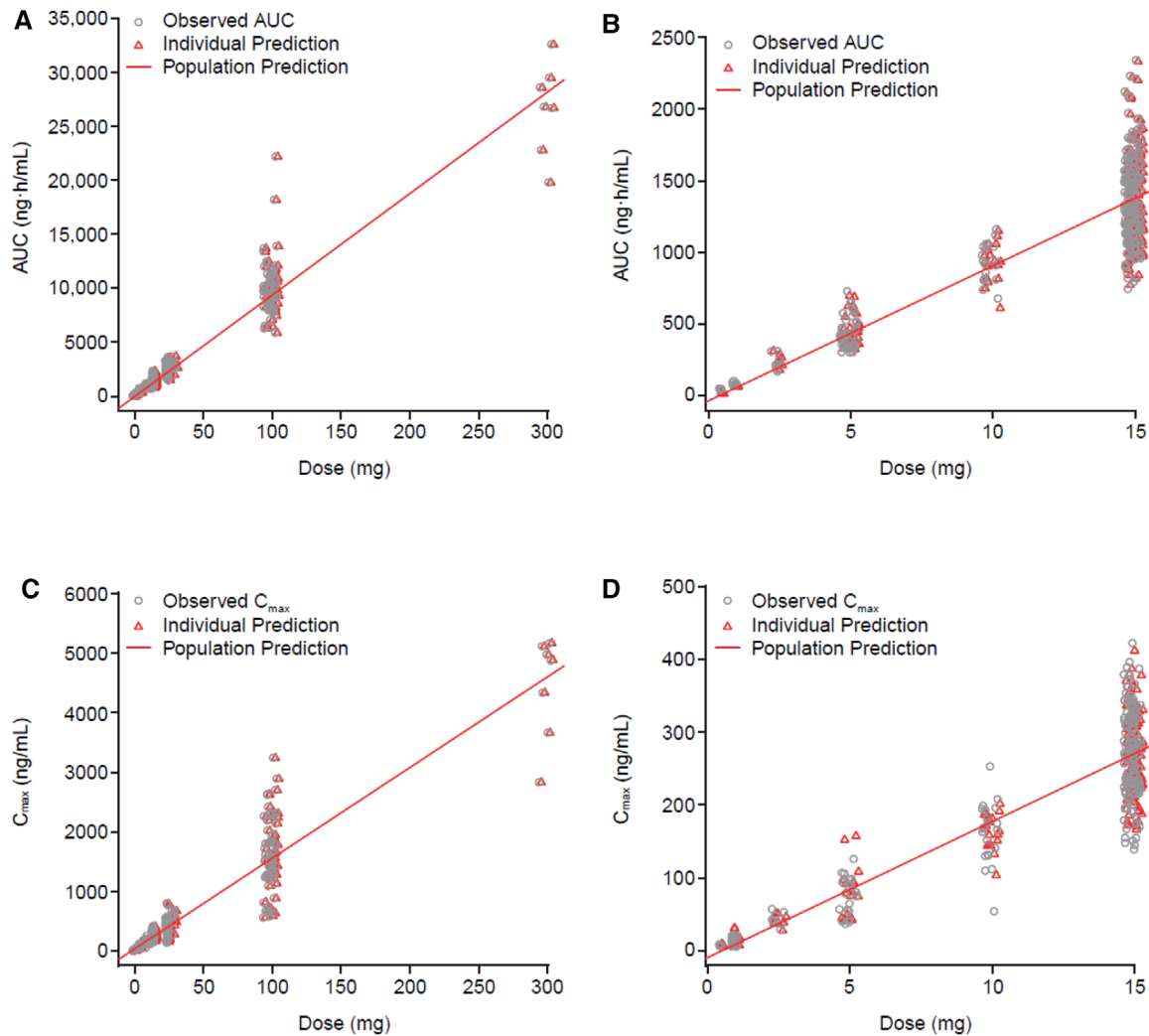
Figure 2. Population-predicted, individual-predicted, and observed ertugliflozin (A, B) AUC and (C, D) C_{max} values by dose from the full model in the dose-proportionality analysis. Results are shown across the full dose range (A, C) and across the 0.5- to 15-mg dose range (B, D). AUC, area under the plasma concentration-time curve; C_{max}, maximum observed plasma concentration.

relationship between dose and predicted AUC was observed. Population-predicted and -observed values for the AUC fit using the full model are shown in Figure S2. The parameter estimates from the full model for AUC and the 95%CIs generated from a nonparametric bootstrap utilized for model performance qualification are provided in Table 4. Based on the final parameter estimates, the *UGT1A9-2152* heterozygous variant did not have a significant effect on ertugliflozin AUC (the 95%CI included 1). The *UGT1A9*3* heterozygous variant increased ertugliflozin AUC by 10% (95%CI, 3%-17%). The *UGT1A9*1b* heterozygous variant decreased ertugliflozin AUC by 6% (95%CI, 1%-11%), whereas homozygosity for *UGT1A9*1b* did not have a significant effect on ertugliflozin AUC (the 95%CI included 1). The fold change of ertugliflozin AUC for each *UGT1A9* variant relative to the wild-type variant is shown in Figure 4.

The predicted mean (90%CI) AUC values for the different *UGT1A9* genotypes following administration of ertugliflozin 5- and 15-mg tablets in the fasted state were derived using the full model and are shown in Table S2. The largest change in ertugliflozin AUC was with the *UGT1A9*3* heterozygous variant: the mean (90%CI) AUC values following administration of the 5- and 15-mg doses were 485 ng·h/mL (458-510 ng·h/mL) and 1560 ng·h/mL (1480-1630 ng·h/mL), respectively, compared with mean (90%CI) AUC values in *UGT1A9* wild-type subjects of 436 ng·h/mL (418-455 ng·h/mL) and 1410 ng·h/mL (1350-1480 ng·h/mL), respectively.

For multiple variants, the combined effect on ertugliflozin AUC was determined by multiplication of the effect from each individual variant. The maximum combined effect from the genotypes observed in the study participants would be for subjects carrying both *UGT1A9-2152* heterozygous and *UGT1A9*1b*
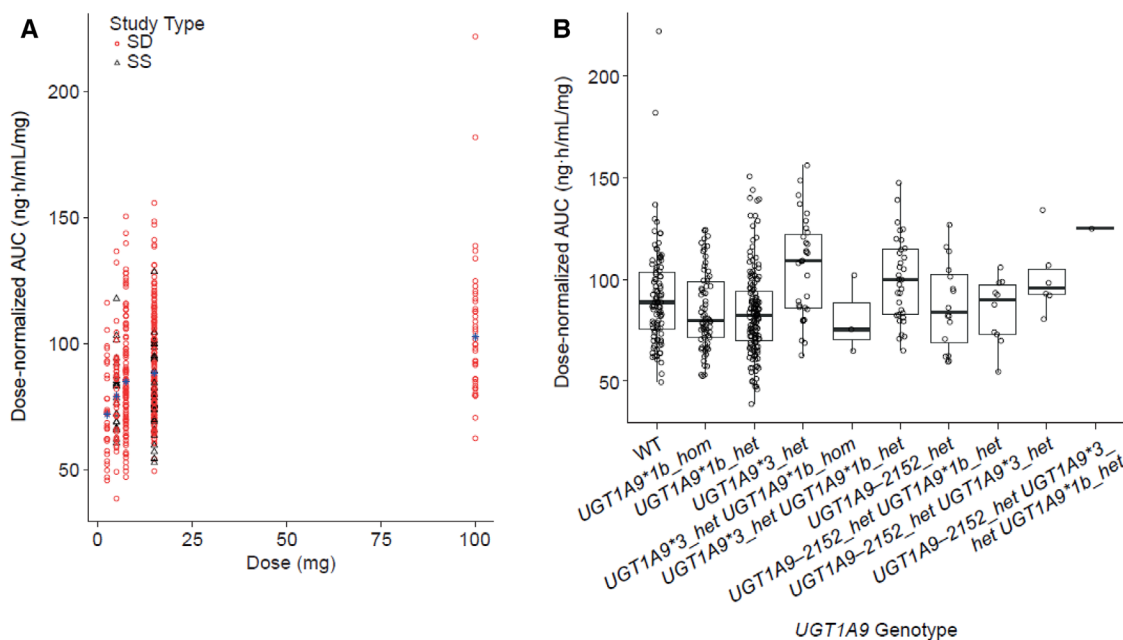
Figure 3. Observed ertugliflozin dose-normalized AUC values by (A) dose and (B) *UGT1A9* genotype from the *UGT1A9* genotype analysis. (A) Red circles represent dose-normalized AUC_{inf} following a single dose; black triangles represent dose-normalized AUC_{tau} at steady state; geometric means for each dose group are represented by blue asterisks. (B) Open circles represent individual subject dose-normalized AUC values. Box plot provides median and 25%/75% quartiles with whiskers to the last point within $1.5\times$ interquartile range. AUC, area under the plasma concentration-time curve; AUC_{inf}, AUC from time zero extrapolated to infinite time; AUC_{tau}, AUC from time zero to time tau, the dosing interval, for which tau is 24 hours; het, heterozygous; hom, homozygous; SD, single dose; SS, steady state; WT, wild type.

Table 4. Base- and Full-Model Parameter Values and Precision Estimates for AUC as a Function of Dose From the *UGT1A9* Genotype Analysis

	Base Model	Full Model	
	Estimate (RSE, %[a])	Estimate (RSE, %[a])	95%CI[b]
Slope (ng·h/mL/mg)	96.7 (1.89)	97.1 (3.25)	91.8-104
Intercept (ng·h/mL)	−63.9 (16.3)	−50.1 (22.8)	−72.9 to −30.6
UGT1A9–2152_het	—	0.988 (3.72)	0.914-1.05
*UGT1A9*3_het*	—	1.10 (3.35)	1.03-1.17
*UGT1A9*1b_hom*	—	0.945 (3.53)	0.879-1.01
*UGT1A9*1b_het*	—	0.938 (2.89)	0.887-0.987

CI, confidence interval; het, heterozygous; hom, homozygous; RSE, relative standard error.
[a] Percent relative standard error was calculated as (100 × standard error/estimate).
[b] 95%CIs were generated from bootstrap.
Residual error was 0.244 ng·h/mL for the base model and 0.238 ng·h/mL for the full model (square root sigma values).

heterozygous variants. The combined effect of this genotype ($0.988 \times 0.938 = 0.927$) corresponds to a 7.3% decrease in ertugliflozin AUC compared with subjects carrying wild-type *UGT1A9*.

Although some of the covariates were statistically significant, the magnitude of the effect of the allelic variants on ertugliflozin AUC were within ±10% of the wild type and were not considered clinically relevant (discussed below).

Discussion

This noncompartmental meta-analysis of ertugliflozin PK parameters from 25 phase 1 studies evaluated the

relationship between ertugliflozin exposure (AUC and C_{max}) and dose and the effect of *UGT1A9* genotype on ertugliflozin exposure (AUC). The outcomes of this analysis provided confirmation of a linear dose-exposure relationship between ertugliflozin AUC and C_{max} and the 5- and 15-mg tablet formulation. Most importantly, because of the numbers of subjects and data in the analysis, precise estimates of *UGT1A9* genotype impact on exposure were generated, affording the ability to indicate that there was no significance of the *UGT1A9* variants assessed on ertugliflozin exposure. If a small study exploring the impact of genotype on the dose-exposure relationship had been conducted, the ability to tease out the effect of genotype on exposure would have been diminished because of
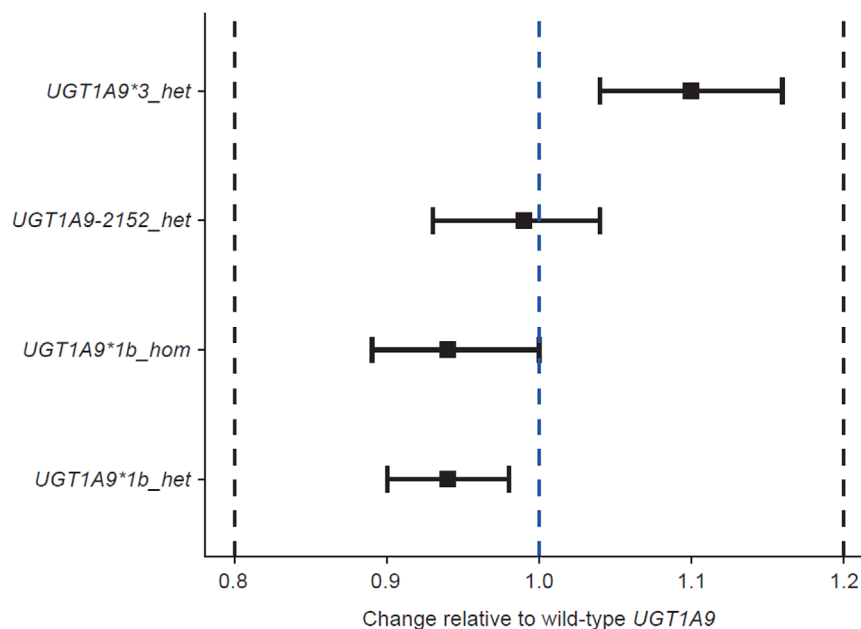
Figure 4. *UGT1A9* polymorphic effects on ertugliflozin AUC from the *UGT1A9* genotype analysis. The 90th percentiles of the bootstrap confidence intervals for AUC are provided. Effects are reported relative to the wild-type subjects in the analysis. A value of 1 represents no change relative to the wild type. AUC, area under the plasma concentration-time curve.

the relatively low allelic frequency of *UGT1A9* variants in the general population.

Within the data set of subjects with ertugliflozin AUC values and *UGT1A9* genotype information, 100 subjects were wild type for all 3 *UGT1A9* allelic variants examined, 33 subjects carried heterozygous variants of *UGT1A9-2152*, 74 subjects carried heterozygous variants of *UGT1A9*3*, and 264 subjects carried homozygous or heterozygous variants of *UGT1A9*1b* (Table 3). The relative proportions of subjects carrying each allelic variant within this data set are generally consistent with the known population frequencies of these variants,[12,15–17] with the majority of subjects carrying the common allelic variant *UGT1A9*1b* (minor allele frequency of 40% to 60%).[12,17]

Dose proportionality of ertugliflozin exposure was assessed via a meta-analysis of ertugliflozin AUC and C_{max} parameters across phase 1 studies to evaluate the relationship between ertugliflozin exposure and dose in healthy subjects. This analysis established that ertugliflozin AUC and C_{max} values increased in a dose-proportional manner across an ertugliflozin dose range of 0.5 to 300 mg. The effect on AUC and C_{max} values when ertugliflozin was administered with a light meal relative to fasting administration was consistent with the results of the clinical study examining the effect of food on ertugliflozin PK,[5] where administration of the ertugliflozin 15-mg commercial tablet with a high-fat meal resulted in no meaningful effect on ertugliflozin AUC. The effect of food on ertugliflozin C_{max} is not considered clinically relevant, as ertugliflozin efficacy

is driven by total exposure (AUC) rather than peak concentration.[20]

The AUC data from these trials in healthy subjects were also used to conduct a pooled analysis evaluating the impact of the *UGT1A9* genotype on ertugliflozin exposure. UGT-mediated glucuronidation is an important biotransformation pathway in humans and facilitates the inactivation and excretion of a number of therapeutic drug targets.[18] Indeed, the primary clearance pathway for ertugliflozin is metabolism, with glucuronidation accounting for nearly 90% of ertugliflozin biotransformation, primarily mediated by the UGT1A9 isoform.[9,10] Polymorphic variation in the *UGT* gene family has the potential to affect UGT enzyme expression and activity levels, and ultimately target drug exposures, which may require compensatory modifications of drug dosages.[12] Allelic variations that result in decreased glucuronidation activity or enzyme expression may lead to lower target drug clearance, necessitating the use of a reduced dose. Conversely, variants that result in increased enzyme activity or expression may lead to accelerated drug clearance, requiring administration of an increased dose. The Pharmacogenomics Knowledgebase[21] lists nearly 90 reported associations between ∼40 separate *UGT1A9* variants (SNPs or haplotypes) and a drug phenotype, with around half these associations classified as significant. However, functional evidence of an effect on UGT enzyme activity or expression with the potential to affect drug metabolism exists for only a handful of these variants (reviewed in reference [12])

and appears to be compound specific. For example, the immunosuppressant mycophenolic acid (MPA) is metabolized by several enzymes, including UGT1A9, with the major metabolic pathway being glucuronidation. A systematic meta-analysis indicated that heterozygous white carriers of the *UGT1A9*3* variant (associated with lower clearance of MPA) might benefit from receiving only about 70% of the average dose, whereas carriers of *UGT1A9-2152* (associated with higher clearance of MPA) may need higher than average doses.[12] This current analysis found that the mean effects on ertugliflozin AUC of *UGT1A9* polymorphic variation, as represented by the 3 *UGT1A9* variants assessed in this study, were within ±10% of the wild-type variant. Based on the dose-linear PK of ertugliflozin (this study and references [3] and [4]) and the dose-safety relationships observed in phase 1-3 clinical studies,[3,4,22–24] combined with dose-response modeling of clinical efficacy using phase 2/3 data,[25] no adjustments in ertugliflozin posology are proposed for any extrinsic or intrinsic factors that were found to contribute to observed or predicted changes in ertugliflozin exposure.[1,2] This included an assessment of potential DDIs, in which coadministration of the UGT and CYP inducer rifampin resulted in about a 39% reduction in ertugliflozin AUC,[26] and physiologically based PK modeling demonstrated that coadministration of the UGT inhibitor mefenamic acid increased ertugliflozin AUC by ~1.5-fold.[27] In the context of changes to ertugliflozin exposure of these magnitudes, the observed effects on ertugliflozin AUC of the *UGT1A9* polymorphisms assessed in this study (within ±10%) will not have a clinically meaningful effect on ertugliflozin exposure, and no adjustments of the approved doses are required for patients carrying these *UGT1A9* variants.

A meta-analysis of pooled data from several phase 1 clinical studies was used in this analysis, which offers a number of advantages over a small, dedicated clinical study. Pooling data from several studies and conducting a meta-analysis using this larger data set increases the statistical power of the analysis to detect if there is any impact on drug exposure because of the presence of specific enzyme variants. As the frequency of *UGT* variants is generally low, a dedicated clinical study would require the screening of a large number of individuals to find those few carriers of the specific variants. Often, dedicated genotyping clinical studies are relatively small and therefore lack the statistical power to detect the impact of genotype on drug exposure. In addition, there is no reported evidence of the UGT phenotype being impacted by T2DM or any other disease state; hence, the results of this meta-analysis of pooled data from healthy subjects is applicable to T2DM patients.

Although a population PK analysis using ertugliflozin concentration-versus-time data could have been used for these analyses, the preferred approach was to not make any assumptions regarding ertugliflozin disposition but rather perform a meta-analysis of noncompartmentally derived PK parameters. Therefore, this meta-analysis was performed on individual subject AUC and C_{max} values, precluding the parameterization of a population PK model, which would have required a number of additional binary covariates to accommodate the many patient populations and study design features with what, most likely, would have generated imprecise parameter estimation.

Conclusions

This meta-analysis of healthy subjects from phase 1 trials showed that ertugliflozin AUC and C_{max} increased in a dose-proportional manner over the ertugliflozin dose range of 0.5 to 300 mg. No dose adjustments are required for patients with the *UGT1A9* allelic variations examined in this study.

Conflicts of Interest

Funding

Data Availability Statement

On request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual anonymized participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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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.