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REVIEW

End-to-end application of model-informed drug development for ertugliflozin, a novel sodium-glucose cotransporter 2 inhibitor

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Abstract

Model-informed drug development (MIDD) is critical in all stages of the drug-development process and almost all regulatory submissions for new agents incorporate some form of modeling and simulation. This review describes the MIDD approaches used in the end-to-end development of ertugliflozin, a sodium-glucose cotransporter 2 inhibitor approved for the treatment of adults with type 2 diabetes mellitus. Approaches included (1) quantitative systems pharmacology modeling to predict dose–response relationships, (2) dose–response modeling and model-based meta-analysis for dose selection and efficacy comparisons, (3) population pharmacokinetics (PKs) modeling to characterize PKs and quantify population variability in PK parameters, (4) regression modeling to evaluate ertugliflozin dose-proportionality and the impact of uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A9 genotype on ertugliflozin PKs, and (5) physiologically-based PK modeling to assess the risk of UGT-mediated drug–drug interactions. These end-to-end MIDD approaches for ertugliflozin facilitated decision making, resulted in time/cost savings, and supported registration and labeling.

INTRODUCTION

The term model-informed drug development, or MIDD, is used to describe the application of various quantitative models that leverage an understanding of physiology, disease processes, and pharmacology to facilitate the decision-making process during drug development. MIDD has utility in all stages of the drug-development process, and improves the delivery of new therapies by: increasing confidence in decision making; improving efficiency; reducing late-stage attrition; reducing development time; reducing the number of studies required or study sample size; and lowering development costs.[1–4] Drug regulatory authorities in the United States and the European Union consider modeling and simulation as key enablers of efficient and effective drug development[5–7]; as such, MIDD has also been used to support the approval and

*At the time the studies described in this article were conducted.

labeling decisions for a number of drugs,[1,4–7] including ertugliflozin.[1] Ertugliflozin is a selective inhibitor of sodium-glucose cotransporter 2 (SGLT2) approved for use in the United States,[8] Europe,[9] and other countries as an adjunct to diet and exercise to control blood glucose levels in adults with type 2 diabetes mellitus (T2DM). Ertugliflozin is also approved as fixed-dose combination therapies with metformin[10,11] and with the dipeptidyl peptidase-4 (DPP4) inhibitor sitagliptin.[12,13]

Inhibition of SGLT2 blocks the re-absorption of glucose in the kidneys, leading to increased urinary glucose excretion (UGE) and, in patients with hyperglycemia, reduced levels of glycated hemoglobin (HbA_{1c}) in the plasma.[14,15] As such, both HbA_{1c} and the pharmacodynamic (PD) marker UGE are considered as effective markers for the assessment of clinical efficacy of this drug class. In phase III trials of ertugliflozin monotherapy or combination therapy with other antihyperglycemic agents,[16–23] clinically meaningful reductions in HbA_{1c}, systolic blood pressure, and body weight were observed in patients with T2DM. Ertugliflozin also displayed a favorable safety and tolerability profile that was consistent with other members of the SGLT2 inhibitor drug class.[24]

The primary route of clearance for ertugliflozin is glucuronidation via the uridine 5'-diphospho-glucuronosyltransferase (UGT) isoforms UGT1A9 and, to a lesser extent, UGT2B4 and UGT2B7.[25–27] Ertugliflozin undergoes minimal oxidative metabolism by cytochrome P450 (CYP) isoforms.[25,26] Absorption of ertugliflozin is rapid, with time to peak plasma concentrations (T_{max}) occurring 2 h postdose in the fed state, and 1 h postdose in the fasted state.[28] The half-life of ertugliflozin is 11–18 h, and a dose-proportional increase in exposure is observed over the ertugliflozin dose range 0.5–300 mg.[28] Ertugliflozin can be administered without regard to food, and drug–drug interaction (DDI) studies showed that there are no clinically meaningful effects on ertugliflozin pharmacokinetics (PKs) when co-administered with metformin, sitagliptin, glimepiride, simvastatin, or rifampin.[28]

In this review, we describe the MIDD approaches that were applied during the end-to-end development of ertugliflozin to characterize the PKs (dose proportionality and the impact of *UGT1A9* genotype on PK), PDs (measured as 24-h UGE [UGE_{24}]), efficacy (HbA_{1c} levels), and DDI potential (via UGT enzyme inhibition) of ertugliflozin, and how these modeling approaches, including the use of all available SGLT2 inhibitor data through quantitative systems pharmacology (QSP) modeling and model-based meta-analysis (MBMA), facilitated the drug development and registration process.

QUANTITATIVE SYSTEMS PHARMACOLOGY MODELING

Systems pharmacology refers to the quantitative assessment of the dynamic relationships between a drug (or drugs) and a biological system to better understand the behavior of the system overall, rather than the behavior of the individual components within that system.[29] The Metabolism PhysioLab platform (Entelos, Inc.)[30] is a mathematical model of human T2DM pathophysiology consisting of several hundred ordinary differential and algebraic equations. The model is based on an extensive survey of published literature and represents the major physiological systems involved in the regulation of nutrient intake, utilization, storage, and disposal in health and disease. Using this platform,[30] a QSP model of SGLT2 inhibition was developed[1,31,32] to provide a framework to improve the quality and speed of decision making during the clinical development of ertugliflozin (e.g., clinical trial design, dose selection, and dosing regimens). This QSP model integrated information on the physiological mechanism of action of SGLT2 inhibitors, including early clinical development data published for dapagliflozin[33–36] (another SGLT2 inhibitor now approved for treatment of diabetes and in the same class as ertugliflozin), and ertugliflozin PK/PD data as they became available from phase I studies.[28,37] The model[1,31,32] described the relationship between SGLT2 inhibition and UGE, establishing a mechanistic link between UGE_{24} in healthy subjects and the improvements in glycemic control and body weight that were observed over the longer-term (up to 12 weeks) in patients with T2DM.

The development of the model was based on data from published single- and multiple-dose studies assessing the PK and UGE of dapagliflozin in healthy subjects and in patients with T2DM,[33,34] and the model was validated by comparison to efficacy results from a 12-week dapagliflozin study.[35] As ertugliflozin PK and UGE data became available from a phase I single-dose study,[28,37] the predicted population PK parameters for ertugliflozin were included in the model, and maximum effect (E_{max}) and drug potency (drug concentration producing 50% of the maximum effect [EC_{50}]) were adjusted in "real time" to match the observed exposure–response data (UGE_{24} and time course of UGE) obtained from both single- and multiple-dose phase I studies of ertugliflozin.[28,37] Ertugliflozin doses, fasted/fed dosing regimens, and calorie intake were implemented to match the clinical protocol.[1,31,32]

Using this final QSP model, predictions for the dose–response relationship for HbA_{1c} in patients with T2DM after 12 weeks of ertugliflozin treatment were generated (Figure 1).[1] These predictions were based on a virtual population of patients with T2DM with a mean baseline HbA_{1c} of 8.0% and a mean baseline body weight of 94 kg; additionally, estimated glomerular filtration rate (eGFR) and other renal glucose-handling parameters were varied to ensure consistency with the reported variability in UGE from competitor SGLT2 inhibitor clinical trials.[34,35] These data informed ertugliflozin dose selection for a 12-week dose-ranging phase II trial.[38] In turn, data from this 12-week ertugliflozin study[38] were subsequently used to validate the efficacy projections from the QSP model (Figure 1).[1]

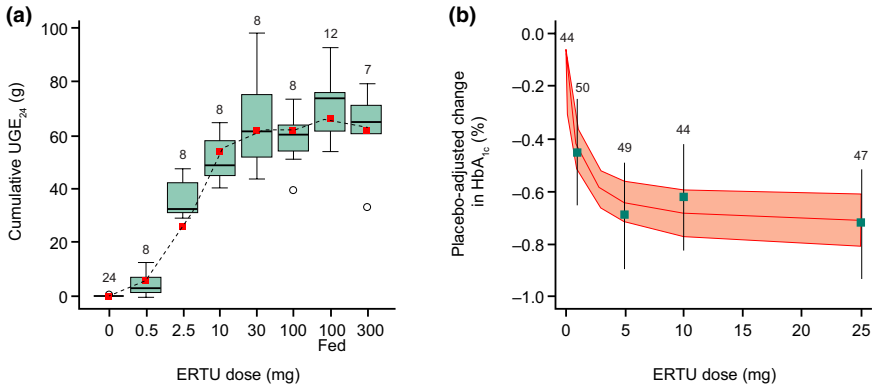

FIGURE 1 Quantitative systems pharmacology model prediction. Model-predicted effect of ertugliflozin on (a) cumulative UGE_{24} in healthy subjects (red symbols; superimposed on observed data represented by the blue box plots with open circles indicating outliers in the data) and (b) placebo-adjusted change in HbA_{1c} at 12 weeks in patients with T2DM (red line with shaded red area showing the 90% CI of the prediction; superimposed on observed data represented by the blue symbols with observed 80% CI). Values shown above each data point are for the number of subjects in each dose group contributing to the observed data. HbA_{1c}, glycated hemoglobin; CI, confidence interval; ERTU, ertugliflozin; T2DM, type 2 diabetes mellitus; UGE_{24}, 24-hour urinary glucose excretion. Figure from ref. 1 (© 2013 American Society for Clinical Pharmacology and Therapeutics. Published by John Wiley & Sons)

The QSP model described above was critical in expediting the phase I and II clinical explorations for ertugliflozin[1] as it enabled the design of efficient phase II studies with increased confidence in dose selection. This modeling approach also allowed the successful prediction of changes in body weight and circulating hormones (such as insulin) following treatment with ertugliflozin, and simulation of the efficacy (UGE and HbA_{1c}) of different ertugliflozin dosing regimens and combination therapies, including in patients with renal impairment. Most notably, the QSP model was used alongside the dose–response modeling described below to corroborate the selection of ertugliflozin doses for phase III studies, highlighting how multiple modeling techniques can work together to achieve well-informed decisions.

DOSE–RESPONSE MODELING

Dose–response, or exposure–response, modeling is a mathematical approach that links dose/drug concentration or an exposure metric to the intensity of the observed response to characterize the dose–concentration–effect of a drug.[39] During the clinical development of ertugliflozin, dose–response modeling was used to quantitatively assess the relationship between ertugliflozin dose and HbA_{1c} response, as well as ertugliflozin dose and UGE response, to inform dose selection for later-phase trials and to determine whether the evaluated covariates had a significant impact on response in patients with T2DM. The dose versus HbA_{1c} response model also allowed an evaluation of the impact on dose–response of co-administration with rifampin, a UGT and CYP inducer known to decrease ertugliflozin exposure. Finally, MBMA incorporating published clinical trial data from other SGLT2 inhibitors allowed an indirect comparison of HbA_{1c}-lowering efficacy across the drug class.

Phase III dose selection using phase II data

In phase I and phase II studies, single oral doses of ertugliflozin up to 300 mg, and multiple oral doses of ertugliflozin up to 100 mg once daily for 14 days or up to 25 mg once daily for up to 12 weeks, were safe and well-tolerated.[28,37,38,40] As such, the key driver for phase III dose selection[41] was the dose–response relationships for change from baseline in HbA_{1c} at week 12 in patients with T2DM from a 12-week phase II dose-ranging study of ertugliflozin.[38] The relationship between HbA_{1c} change from baseline at week 12 versus dose was described by an empirical E_{max} model that included time as a continuous variable.[41] Dose selection was also supported by dose–response modeling of UGE_{24} data (fitted by an E_{max} model) from a 4-week phase II ambulatory blood pressure study of ertugliflozin in patients with T2DM.[40]

Model-predicted responses for HbA_{1c} and UGE_{24} at ertugliflozin doses of 5 mg and 15 mg are presented in Table 1.[41] At 5-mg and 15-mg doses, the model-predicted responses were >80% and >90%, respectively, of the maximum response. Thus, both the 5-mg and 15-mg doses were expected to provide clinically meaningful efficacy, with the 15-mg dose providing incremental HbA_{1c} lowering and UGE compared with the 5-mg dose, and with adequate safety margins relative to the highest exposures tested in the early-phase studies.

These dose–response modeling results supported the selection of ertugliflozin 5-mg and 15-mg once-daily doses for the phase III program and, together with the QSP modeling

TABLE 1 Model-predicted placebo-adjusted change from baseline response for key end points based on phase II and phase II/III study data

	Phase II study data		Phase II/III study data
	HbA_{1c}	UGE_{24}	HbA_{1c}
ED_{50}	1.03 mg (80% CI: not reported)[a]	0.752 mg (95% CI: 0.299 to 1.58)	1.30 mg (95% CI: 0.070 to 2.64)
E_{max}	−0.77% (80% CI: −0.95 to −0.59)	71.5 g (95% CI: 57.9 to 87.3)	−0.745% (95% CI: −0.899 to −0.624)
Treatment			
Ertugliflozin 5 mg	−0.64% (80% CI: −0.81 to −0.47)	62.5 g (90% CI: 54.9 to 69.7)	−0.617% (95% CI: −0.753 to −0.491)
Ertugliflozin 15 mg	−0.72% (80% CI: −0.89 to −0.56)	68.9 g (90% CI: 58.9 to 78.7)	−0.698% (95% CI: −0.821 to −0.596)

Note: Baseline HbA_{1c} was normalized to 8%.

Abbreviations: HbA_{1c}, glycated hemoglobin; CI, confidence interval; ED_{50}, dose producing 50% of the maximal effect; E_{max}, maximum effect; UGE_{24}, 24-h urinary glucose excretion.

[a]The CI for the ED_{50} value from the dose versus HbA_{1c} model was not estimated precisely due to limited data at the inflection of the dose–response relationship, and is therefore not reported. However, the ED_{50} point estimate is consistent with the ED_{50} estimate from the dose versus UGE model and the dose versus HbA_{1c} model based on phase II and phase III study data.

described above, ensured a thorough assessment of the benefit/risk profile for the ertugliflozin doses selected for the late-stage development program.

Dose versus HbA_{1c} response analysis using phase II/III data

The results of the initial dose–response analysis using only phase II ertugliflozin data were consistent with the results of a subsequent longitudinal dose–response model[41] for HbA_{1c} based on ertugliflozin data from one phase II study[38] and four phase III studies (VERTIS RENAL, VERTIS FACTORIAL, VERTIS MONO, and VERTIS MET).[19,23,42,43] A total of 10,109 observations from 2185 subjects were included in the final model. A longitudinal exposure–response model was also fitted to the HbA_{1c} data; however, this did not provide any additional predictive performance benefit over the dose–response model.

The final longitudinal dose–response model included two first-order rate constant parameters describing the temporal profiles of HbA_{1c}: one for the placebo data and a second for the ertugliflozin data. A point estimate placebo parameter characterized the placebo response, with E_{max} and dose producing 50% of the maximum effect (ED_{50}) parameters characterizing the ertugliflozin response. The ED_{50} and E_{max} values were 1.30 mg (95% confidence interval [CI]: 0.070 to 2.64) and −0.745% (95% CI: −0.899 to −0.624), respectively (Table 1). Covariates included baseline HbA_{1c} (normalized to 8.0%) on placebo response, and baseline HbA_{1c} (normalized to 8.0%), eGFR (normalized to 90 ml/min/1.73 m^2), diabetes disease duration (normalized to 8 years), and background treatment other than metformin on E_{max}. Baseline body weight (normalized to 85 kg) and age (normalized to 65 years) were included on ED_{50}. The estimated effect of baseline body weight on ED_{50} was not significant (the 95% CI included the null-effect value); diet and exercise alone as a background treatment on E_{max} was also not significant. All other covariates were significant. Higher baseline HbA_{1c} and eGFR were associated with a higher E_{max}, and longer diabetes disease duration was associated with a lower E_{max}. Therefore, any estimate of E_{max} would need to account for these three influential covariates. Although age was found to be a significant predictor of ED_{50}, the effect of age on ED_{50} was not well-estimated; therefore, any predictions incorporating age should be interpreted with caution.

Based on the final model parameter estimates, the 5-mg and 15-mg doses of ertugliflozin elicited HbA_{1c} responses (−0.617% and −0.698%, respectively) that were >80% and >90%, respectively, of the model-estimated E_{max} (−0.745%), consistent with the results from the dose–response model using phase II data (see Table 1). Observed and final model-predicted mean HbA_{1c} responses versus ertugliflozin dose by study at week 26 for the final longitudinal dose–response model are shown in Figure 2.[44] For a representative patient with T2DM (age: 57.3 years; weight: 85 kg; baseline HbA_{1c}: 8.1%; eGFR: 88.9 ml/min/1.73 m^2; disease duration: 7.5 years; and background treatment: metformin), the model-predicted mean placebo-adjusted change from baseline HbA_{1c} for the ertugliflozin 5-mg and 15-mg doses at week 26 was −0.674% (95% CI: −0.805 to −0.565) and −0.735% (95% CI: −0.869 to −0.626), respectively.

Dose versus HbA_{1c} response analysis following rifampin co-administration

The phase II/III dose–response model[41] described above was used to evaluate the impact of reduced ertugliflozin exposure following co-administration with rifampin, a UGT and CYP

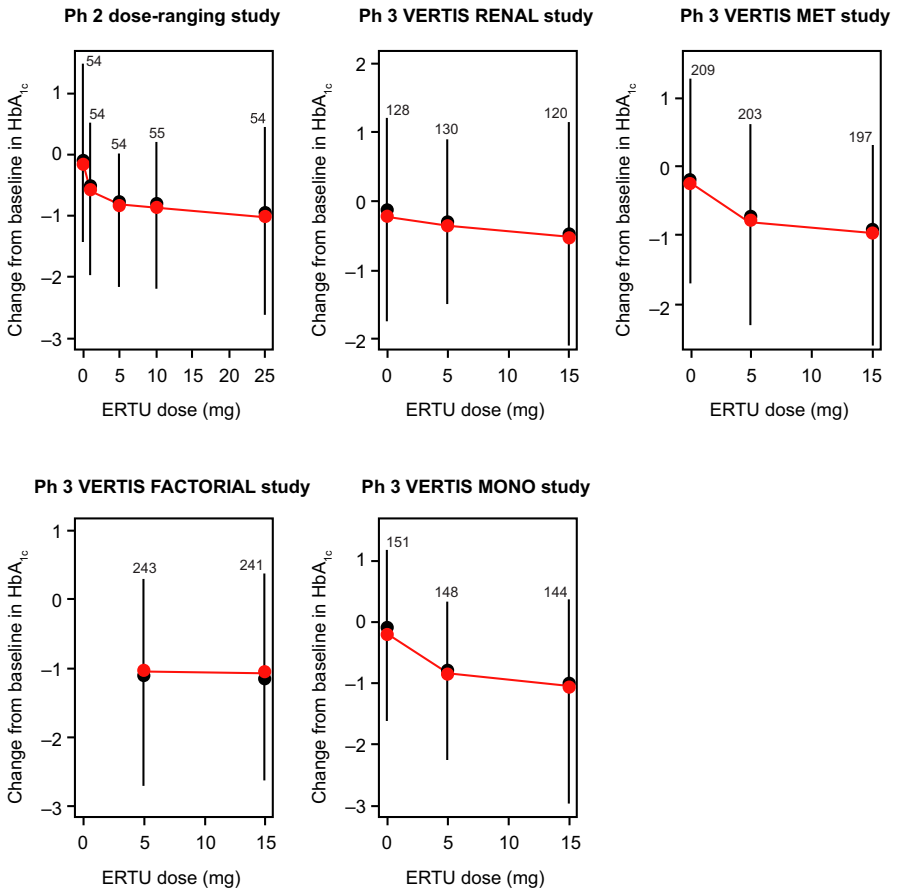

FIGURE 2 Observed and final model-predicted mean HbA_{1c} response versus ertugliflozin dose by study at week 26. Mean observed (black circles) and estimated (red circles) HbA_{1c} change from baseline (%). Vertical black lines represent associated 5th and 95th quantiles of observed individual patient data for each dose in the respective studies. Values shown above each data point are for the number of subjects in each dose group contributing to the observed data. Estimated HbA_{1c} was generated as the difference between each subject's individual prediction of HbA_{1c} and baseline HbA_{1c}. ERTU, ertugliflozin; HbA_{1c}, glycated hemoglobin; Ph, phase. Figure from data on file and also available from ref. 44

inducer that decreased ertugliflozin exposure by 39% in a phase I clinical study.[28,45]

As ertugliflozin exposure increases in a dose-proportional manner and PK variability was low, the decrease in exposure with rifampin co-administration (assuming a similar decrease in ertugliflozin exposure in patients with T2DM as was observed in healthy volunteers in the phase I study) was included within the model as a decrease in dose with associated uncertainty. Using representative patient demographics, the model-predicted mean placebo-adjusted change from baseline HbA_{1c} for the ertugliflozin 5-mg and 15-mg doses following rifampin co-administration was −0.625% (95% CI: −0.783 to −0.482) and −0.713% (95% CI: −0.841 to −0.604), respectively. Based on the results, the 5-mg ertugliflozin dose following co-administration with rifampin was predicted to maintain clinically meaningful glycemic efficacy. This supports ertugliflozin dosing recommendations for co-administration with inducers of UGT and CYP enzymes without any dose adjustment.[8,9]

Dose versus HbA_{1c} response analysis using MBMA

MBMA was conducted alongside other MIDD approaches during the clinical development of ertugliflozin, and incorporated all publicly available data on SGLT2 inhibitors to allow an assessment of comparative efficacy across the SGLT2 inhibitor class.

One such MBMA[46] utilized summary-level data from the Quantify Diabetes Clinical Database (version 2017-04-04; Certara USA Inc.) that included published, randomized placebo- and active-controlled trials of ≤54 weeks' duration evaluating the safety and efficacy of antihyperglycemic agents in patients with T2DM. Of the 496 randomized controlled trials in the database, 94 studies representing >30,000 patients with T2DM were with SGLT2 inhibitors, including canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, remogliflozin, sotagliflozin, or tofogliflozin. This MBMA allowed an indirect comparison of SGLT2 inhibitor efficacy across trials by quantifying the

time course of dose versus HbA_{1c} response of the included SGLT2 inhibitors. Overall, ertugliflozin 5-mg and 15-mg doses demonstrated similar or numerically greater HbA_{1c} lowering compared with therapeutic doses of other SGLT2 inhibitors, with predicted HbA_{1c} responses (95% CI) of −0.70% (−0.77 to −0.62) and −0.79% (−0.86 to −0.70), respectively, at 26 weeks for a patient on background oral antidiabetic treatment and with baseline HbA_{1c} of 8.0% and an eGFR of 90 ml/min/1.73 m^2.

POPULATION PHARMACOKINETICS MODELING

Population PKs (PopPK) analyses aim to characterize the PK properties of a drug and to quantify sources of variability in drug concentrations among individuals by estimating the impact of intrinsic and extrinsic factors that may affect the PKs.[47] Therefore, the results of PopPK analyses are often included in drug labels, typically supporting dosing recommendations for special populations (e.g., renal/hepatic impairment, pediatrics, elderly, etc.) as well as the clinical relevance of drug–drug interactions. In the case of ertugliflozin, PopPK modeling was used successfully in assessing the clinical relevance of patient demographic and clinical characteristics on ertugliflozin PKs to support product registration and inform the product label. A PopPK model was developed[48] using nonlinear mixed-effects modeling to describe ertugliflozin disposition, characterize the effects of intrinsic and extrinsic factors on ertugliflozin exposure, and quantify the population variability in ertugliflozin PK parameters. Data from nine phase I, two phase II, and four phase III ertugliflozin studies contributed to the final PopPK data file, which contained 13,691 PK observations from 2276 subjects.

A two-compartment model with first-order absorption with lag time, and first-order elimination, described the plasma concentration–time profile of ertugliflozin after single and multiple doses. The PopPK model was used to determine the effect of several covariates (body weight, age, sex, race, eGFR, T2DM, and food) on the PK parameters of ertugliflozin. Covariate effects on apparent clearance (CL/F)—translated to the effect on area under the concentration–time

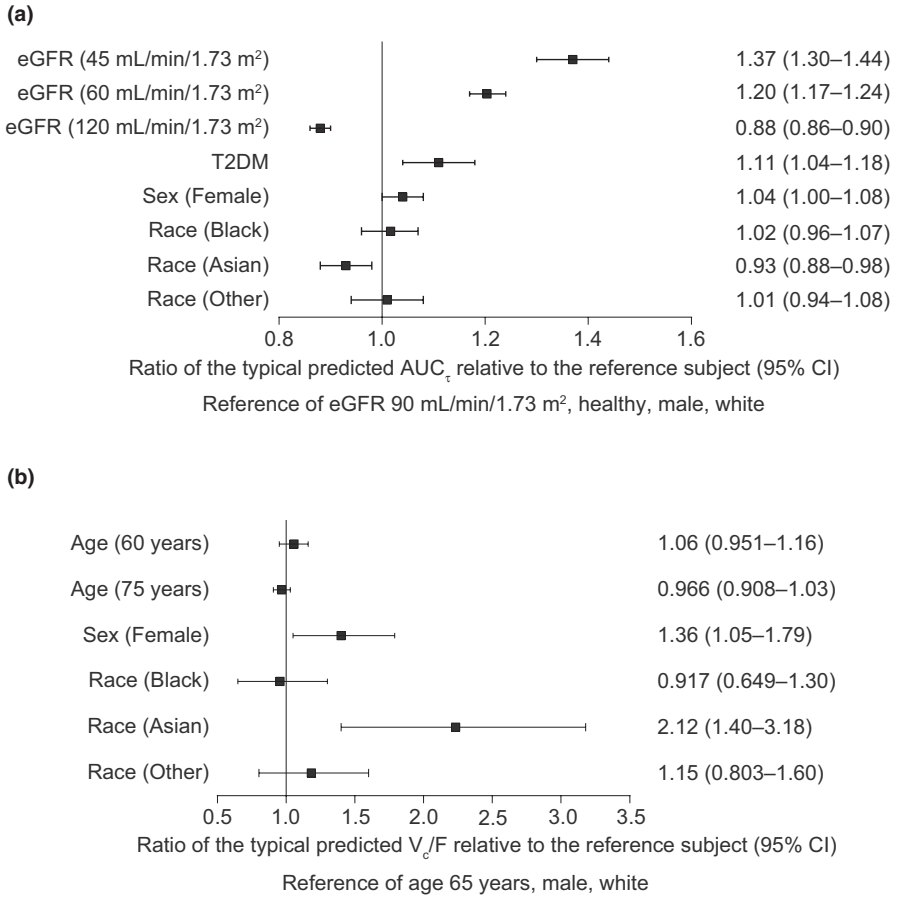

FIGURE 3 Covariate effects on (a) AUC_τ and (b) V_c/F in the PopPK model. Solid squares represent the ratio of the typical predicted AUC_τ or V_c/F relative to the reference subject; a value of 1 represents unity or a null covariate effect. Horizontal lines represent the 95% CI. AUC_τ, area under the concentration–time curve for dosing interval at steady state; CI, confidence interval; eGFR, estimated glomerular filtration rate; PopPK, population pharmacokinetics; T2DM, type 2 diabetes mellitus; V_c/F, apparent central volume of distribution. Figure reproduced from ref. 48 (published under CC BY-NC-ND 4.0)

curve (AUC) for a dosing interval at steady-state (AUC_τ)—and apparent central volume of distribution (V_c/F) at steady-state were compared to the reference subject: a 65-year-old, healthy, White male with a baseline body weight of 85 kg, eGFR of 90 ml/min/1.73 m^2, and taking ertugliflozin in the fasted state.

In the model, CL/F increased with increasing eGFR up to 120 ml/min/1.73 m^2. CL/F was slightly lower in patients with T2DM and in women, and slightly higher in Asian subjects. Covariate effects on CL/F were translated to an effect on AUC_τ. The AUC_τ decreased with increasing baseline body weight and eGFR, was slightly higher in patients with T2DM, and slightly lower in Asian subjects (Figure 3a). Early phase I and phase II studies of ertugliflozin found that single oral doses of up to 300 mg, and multiple oral doses of up to 100 mg once daily for 14 days or up to 25 mg once daily for up to 12 weeks, were not associated with any safety concerns and a maximum tolerated dose of ertugliflozin was not identified.[28,37,38,40] Conversely, based on the phase I clinical pharmacology studies,[28] the maximum expected decrease in ertugliflozin exposure due to extrinsic or intrinsic factors was 39%, which was observed following rifampin co-administration.[28,45] However, the phase II/III dose–response model described above[41] demonstrated that the lower (5-mg) dose of ertugliflozin was predicted to maintain clinically meaningful glycemic efficacy following co-administration with rifampin. As such, increases or decreases in exposure of the magnitudes obtained following PopPK modeling were not considered clinically relevant. Regarding the impact of renal function on ertugliflozin PKs/PDs, consistent with the mechanism of action for SGLT2 inhibitors, a decrease in UGE was observed with declining renal function despite increased ertugliflozin exposures.[49] It is well-recognized that HbA_{1c} lowering for SGLT2 inhibitors is diminished in patients with moderate or severe renal impairment.[50,51] Indeed, eGFR was found to be a significant predictor of HbA_{1c} response in the longitudinal dose–response model incorporating ertugliflozin phase II/III data (described above). Therefore, dose adjustments based on matching exposures are not appropriate for the SGLT2 inhibitor class. However, although dose adjustments for ertugliflozin are not required in patients with renal impairment based on PKs, initiation of ertugliflozin is not currently recommended in patients with an eGFR of 30 to <60 ml/min/1.73 m^2.[8,9]

V_c/F increased with increasing body weight and was higher in women and Asian subjects (Figure 3b). Increases in V_c/F would result in a decrease in maximum plasma concentration (C_{max}). However, the results of a phase I PK/PD study comparing twice-daily versus once-daily dosing of ertugliflozin total daily doses of 5 and 15 mg[52] found no meaningful differences in UGE_{24} or AUC over 24 h (AUC_{24}) between the two dose regimens despite C_{max} values being lower for twice-daily versus once-daily dosing (as would be expected), indicating that ertugliflozin efficacy is driven by AUC rather than C_{max}. Hence, the increases in V_c/F observed in the PopPK model were not considered clinically relevant.

Administration of ertugliflozin with food decreased the absorption rate constant (k_a) by 27% and relative bioavailability (F1) by 7% relative to the fasted state; similar estimates of k_a and F1 were observed when ertugliflozin was administered without regard to food relative to the fasted state (34% and 8%, respectively). These findings were consistent with the results of a phase I food-effect study in healthy subjects where ertugliflozin AUC from time zero extrapolated to infinite time (AUC_{inf}) was similar in the fed versus fasted state despite decreases in C_{max} when ertugliflozin was administered with food.[53] Given the dependence of ertugliflozin efficacy on AUC rather than C_{max},[52] the effect of food on ertugliflozin PK was not considered to be clinically meaningful.

To further explore the effect of Asian descent on ertugliflozin PK parameters, two additional PopPK analyses were conducted in selected ethnic subgroups: (1) East/South-East (E/SE) Asian versus non-E/SE Asian subjects; and (2) Asian subjects from mainland China versus Asian subjects from the rest of the world (ROW) versus non-Asian subjects.[54] As observed in the overall PopPK model, increases in CL/F and V_c/F were observed in E/SE Asian subjects compared with non-E/SE Asian subjects, and in Asian subjects from mainland China and Asian subjects from the ROW compared with non-Asian subjects. As noted above for the overall model results, increases in V_c/F would result in a decrease in ertugliflozin C_{max}; however, the magnitude of the increases in CL/F would not substantially impact ertugliflozin AUC, which is the driver of ertugliflozin efficacy. As such, the differences in CL/F and V_c/F were considered unlikely to result in meaningful differences in ertugliflozin PKs among the Asian ethnic subgroups assessed in these analyses. The results of these additional PopPK models were used to support the registration of ertugliflozin in China and E/SE Asian countries.

Overall, none of the covariates assessed in the PopPK models had a clinically relevant effect on the PKs of ertugliflozin, and the results of these analyses were used to support product registration and labeling recommendations that ertugliflozin can be administered without regard to food, age, body weight, gender, and race.[8,9]

REGRESSION MODELING

Regression analysis is a statistical technique widely used to investigate the dependence of a variable on one or more independent variables and to estimate the value of the dependent variable in terms of fixed values of the independent variable(s).[55] Regression modeling was used to evaluate the dose proportionality of ertugliflozin to determine whether the increase in ertugliflozin exposure is linear with increasing

dose, indicating constant clearance over the dose range, as well as the impact of *UGT1A9* polymorphism on the ertugliflozin AUC versus dose relationship.

Dose-proportionality analysis

Dose proportionality in ertugliflozin systemic exposure was assessed as part of a linear mixed-effects analysis[56] of AUC and C_{max} pooled datasets (derived using noncompartmental methods) from 17 phase I studies with ertugliflozin doses of 0.5–300 mg. A total of 344 records from 309 subjects and 307 records from 260 subjects were used in the analysis for AUC and C_{max}, respectively.

Linear regression models were constructed using AUC or C_{max} as the dependent variable, and dose as the independent variable. Full models for AUC and C_{max} were produced by the addition of formulation (tablet as reference) and food status (light meal vs. fasted) as covariates to the base model. The observed AUC and C_{max} values and the model predictions from this analysis, including the model fit for the lower dose range of 0 to 15 mg, are shown in Figure 4. The dose–AUC relationship and dose–C_{max} relationship were adequately described by a linear model fit to the data. The population-predicted mean (90% CI) AUC values following administration of the 5-mg and 15-mg doses in the fasted state were 437 (422 and 451) ng.h/ml and 1380 (1350 and 1410) ng.h/ml, respectively. For C_{max}, these values were 88.7 (86.0 and 91.4) ng/ml and 266 (258 and 274) ng/ml, respectively.

Based on the final parameter estimates, it was concluded that ertugliflozin AUC and C_{max} increase in a dose-proportional manner over the dose range of 0.5 to 300 mg, and there were no clinically relevant effects of formulation or food on ertugliflozin AUC or C_{max}. This dose-proportionality analysis corroborated the results obtained from individual clinical studies[28,37,53] and the PopPK model[48] described above, and was used to support ertugliflozin product registration. Moreover, the model structure provided a framework for an assessment of the impact of *UGT1A9* genotype on ertugliflozin exposure, as described below.

UGT1A9 genotype analysis

Ertugliflozin clearance is mediated primarily via metabolism, with glucuronidation playing the major role in ertugliflozin biotransformation. The principal enzyme involved in the glucuronidation of ertugliflozin is the UGT isoform UGT1A9.[25,26] As the prevalence of *UGT1A9* genetic variants is low, data from 20 phase I studies were pooled and an analysis of AUC values was conducted to evaluate the impact

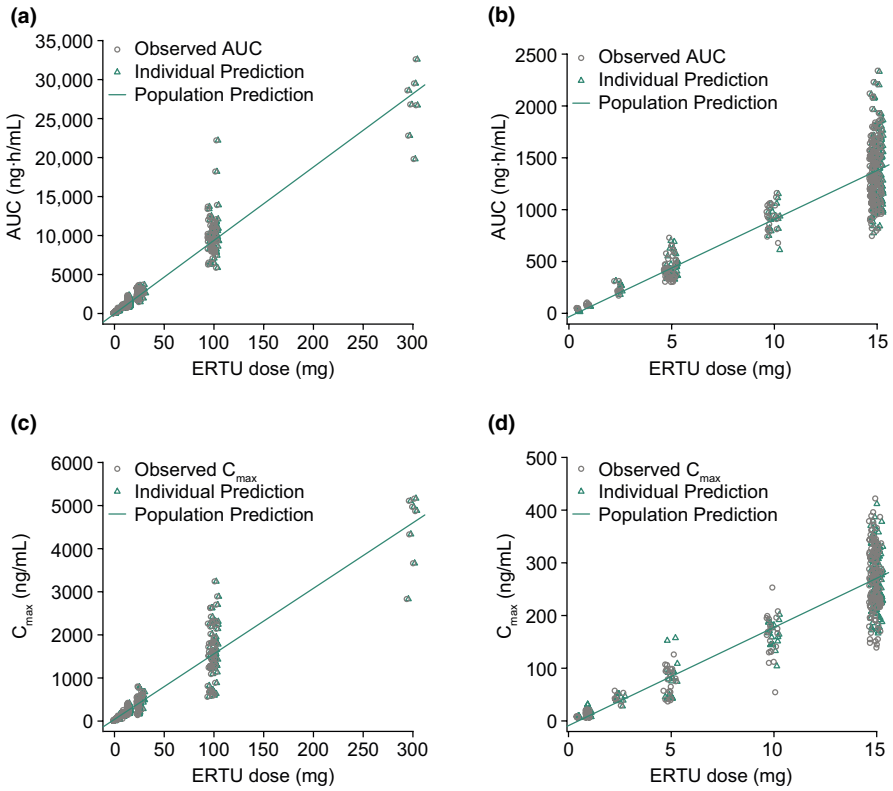

FIGURE 4 Ertugliflozin AUC (a) full dose range; (b) 0–15 mg dose range and C_{max} (c) full dose range; (d) 0–15 mg dose range versus dose. AUC, area under the concentration–time curve; C_{max}, maximum observed concentration; ERTU, ertugliflozin. Figure from ref. 56 (published under CC BY-NC-ND 4.0)

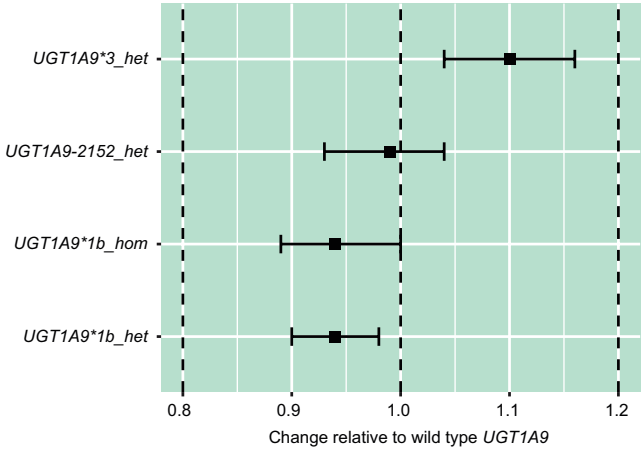

FIGURE 5 *UGT1A9* genotype effects on ertugliflozin AUC. The 90th percentiles of the bootstrap confidence intervals for AUC are provided. Effects are reported relative to the wild-type UGT1A9 subjects in the analysis. A value of 1 represents no change. AUC, area under the concentration–time curve; het, heterozygous variant; hom, homozygous variant; *UGT1A9*, uridine 5'-diphosphoglucuronosyltransferase 1A9. Figure from ref. 56 (published under CC BY-NC-ND 4.0)

of *UGT1A9* genotype on the overall exposure of ertugliflozin.[56] A total of 417 subjects (one record per subject) were included in the analysis.

Using the model structure from the AUC dose-proportionality analysis described above, the final model was developed by the addition of the three *UGT1A9* polymorphic alleles as covariates: *UGT1A9* −2152(C>T), *UGT1A9*3* 98(T>C), and *UGT1A9*1b* $-118(dT)_{9>10}$ (previously referred to as *UGT1A9*22*). These alleles were chosen due to their relatively high allelic frequency across populations and the potential for a clinical effect on drug disposition.[57] Within the dataset, 100 subjects were wild type for the three *UGT1A9* variants; 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*. The *UGT1A9–2152* heterozygous variant and the *UGT1A9*1b* homozygous variant did not have a statistically significant impact on ertugliflozin AUC, as the 95% CI included 1. The *UGT1A9*3* heterozygous variant increased ertugliflozin AUC by 10%, whereas the *UGT1A9*1b* heterozygous variant decreased ertugliflozin AUC by 6%. The fold change of ertugliflozin AUC for each *UGT1A9* variant relative to the wild-type variant is shown in Figure 5.

Overall, the mean effects of *UGT1A9* allelic variants on ertugliflozin AUC were within ± 10% of wild-type *UGT1A9* and were not considered clinically relevant.[56] Current regulatory guidance recommends an assessment of the effect of pharmacogenetics on PKs for drugs where the primary biotransformation pathway is governed by a genetically polymorphic enzyme or transporter.[58,59] The use of a pooled, meta-analysis approach relating ertugliflozin AUC and *UGT1A9* genotype data fulfilled this requirement without the need for a dedicated clinical pharmacogenetic study, which would not be feasible given the low prevalence of *UGT1A9* variants in the general population.

PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELING

Physiologically-based pharmacokinetic (PBPK) modeling utilizes a mathematical model to simulate the PKs of a drug over time by considering the absorption, distribution, metabolism, and excretion (ADME) properties of a drug and the inter-relation between the physiological and chemical determinants of the disposition of the drug.[60] PBPK modeling supports the complexity required to evaluate mechanistic questions that require an in-depth understanding of human physiology and can be used to support decisions related to conduct of clinical pharmacology studies and support dosing recommendations in product labeling. As glucuronidation by UGT1A9 is the primary route of metabolism for ertugliflozin,[25,26] it was important to assess the potential for DDIs between ertugliflozin and UGT enzyme inhibitors. Previously, clinical DDI studies have shown that UGT inhibitors typically elicit less than twofold increases in substrate drug exposures.[61] Indeed, a clinical study found that co-administration of an SGLT2 inhibitor (dapagliflozin) and the UGT inhibitor mefenamic acid (MFA) resulted in a weak DDI, with an AUC ratio (AUC of dapagliflozin co-administered with MFA:AUC of dapagliflozin alone) of 1.51 and C_{max} ratio (C_{max} of dapagliflozin co-administered with MFA:C_{max} of dapagliflozin alone) of 1.13.[62] Therefore, the sponsor decided to assess UGT-mediated DDI for ertugliflozin in humans by PBPK modeling using the Simcyp platform (version 15, release 1; Certara USA Inc.) and MFA as the UGT inhibitor.[63] The use of the PBPK model supported the registration and labeling of ertugliflozin, without the need for a dedicated clinical study to assess the potential for UGT-mediated DDIs.

As dapagliflozin has similar ADME properties and is metabolized by the same UGT enzymes as ertugliflozin,[36] the results from dapagliflozin–MFA co-administration study[62] were used in conjunction with published clinical and in vitro data for MFA in a "top-down" approach to develop and verify a PBPK model for MFA. A common "middle-out" approach, where clinical PK and human ADME results were combined with in vitro data, was used in the development and verification of PBPK models for ertugliflozin and dapagliflozin. For the ertugliflozin PBPK model, ertugliflozin PK parameters following intravenous administration were used as input parameters into Simcyp. The simulations captured the biphasic distribution kinetics of ertugliflozin. Subsequently,

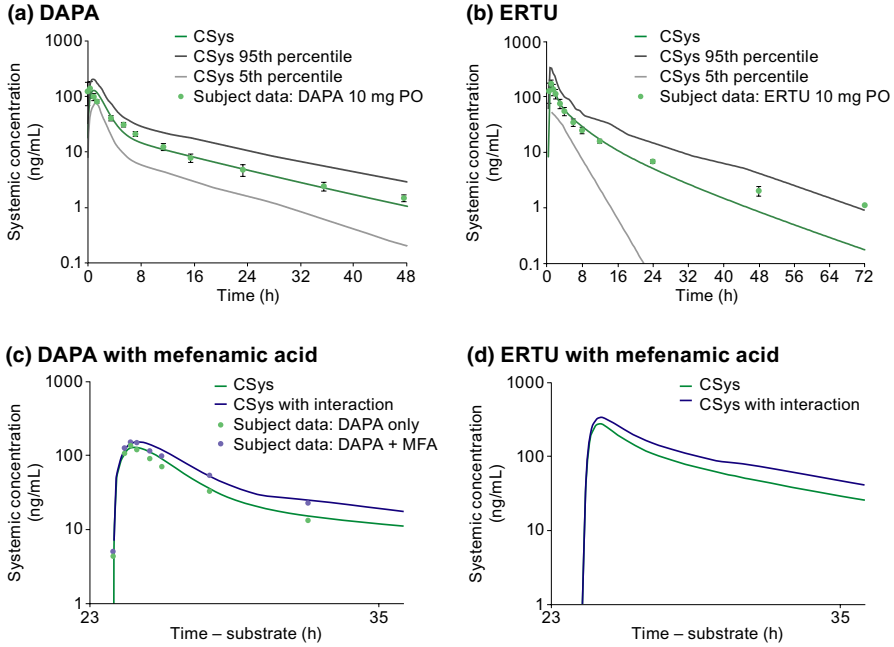

FIGURE 6 Clinically observed and PBPK model-predicted plasma concentrations of ertugliflozin and dapagliflozin in the presence or absence of MFA. (a) dapagliflozin 10 mg, (b) ertugliflozin 10 mg, (c) dapagliflozin 10 mg following MFA administration, and (d) ertugliflozin 15 mg following MFA administration. Observed (green or purple circles) and predicted (green or purple lines) plasma concentrations were expressed as mean, with 5th and 95th percentiles shown (gray lines), in the control treatment (green) and following coadministration with MFA (purple). Where available, standard deviation around the observed means is also shown (black whiskers). CSys, systemic concentration; DAPA, dapagliflozin; ERTU, ertugliflozin; MFA, mefenamic acid; PBPK, physiologically-based pharmacokinetic; PO, oral. Figure reproduced from ref. 63 (published under CC BY-NC-ND 4.0)

absorption and elimination model parameters were incorporated into the ertugliflozin PBPK model, which was verified with results from oral single-dose (0.5–300 mg) and multiple-dose (5 and 15 mg) phase I PK studies.[28,37]

The verified MFA and ertugliflozin PBPK models were then used to simulate the co-administration of MFA (500-mg loading dose then 250 mg every 6 h for 4 days) and ertugliflozin (15-mg single dose on day 2) to assess the impact of the UGT inhibitor on the PKs of ertugliflozin (Figure 6). Similar to the dapagliflozin clinical DDI results with MFA, the simulation predicted a weak DDI between ertugliflozin and MFA, with an AUC ratio of 1.51 (95% CI: 1.48–1.54) and C_{max} ratio of 1.19 (95% CI: 1.17–1.20); this DDI was not considered clinically relevant.[63]

The ertugliflozin PBPK model-based DDI results were included in the ertugliflozin regulatory submission and the results incorporated into the DDI section of the label[8] without the need for a clinical DDI study with a UGT inhibitor.

DISCUSSION

This review details the end-to-end application of MIDD throughout the early- and late-stage clinical development of a single drug. A previous review[1] described the evolution of MIDD and provided a series of examples to illustrate the role of MIDD approaches in accelerating and optimizing development strategies across a number of different compounds at various stages of the drug-development process, including ertugliflozin. This current review focuses on how MIDD was used throughout the drug-development continuum for ertugliflozin: from a real-time, model-based approach during early clinical development to guide dose selection and design of longer-term studies, through to the further development and refinement of PK, PD, and PBPK models during late-stage development to support the successful regulatory filing and labeling of this novel SGLT2 inhibitor for the treatment of T2DM in adults.[8,9] Moreover, this review highlights how the use of multiple MIDD approaches allowed for the corroboration of individual model outputs at various stages of development.

By integrating information on the mechanism of action of SGLT2 inhibition with early-phase PK/PD and glycemic efficacy data from trials of a competitor SGLT2 inhibitor, QSP modeling[1,31,32] was used to establish a mechanistic link between UGE_{24} in healthy subjects and improvements in HbA_{1c} in patients with T2DM. Through the addition of early phase I PK/PD data for ertugliflozin, the final QSP model predicted the dose–response relationship for HbA_{1c} in patients with T2DM and informed ertugliflozin dose selection for the 12-week dose-ranging phase II study.[38] HbA_{1c} and UGE_{24} data from phase II studies[38,40] were

subsequently used to fit E_{max} dose–response models[41] to inform ertugliflozin dose selection for phase III trials. Dose–response modeling of ertugliflozin was further refined using phase II/III data, where a longitudinal dose–response model was fitted to the data for the primary evaluation of the HbA_{1c}-lowering effect of ertugliflozin.[41] Overall, these dose–response models demonstrated that the 5-mg and 15-mg doses of ertugliflozin elicited HbA_{1c} responses that were >80% and >90%, respectively, of the model-estimated maximum response, thus establishing the clinically meaningful efficacy of these doses, with incremental HbA_{1c} lowering with the 15-mg dose over the 5-mg dose. These dose–response modeling results were supported and corroborated by MBMA using the totality of available data on SGLT2 inhibitors to allow an indirect comparison of efficacy across the SGLT2 inhibitor class.[46] This MBMA approach demonstrated that ertugliflozin 5-mg and 15-mg doses show similar or numerically greater HbA_{1c} lowering to approved doses of other SGLT2 inhibitors.[46]

Data from initial phase I clinical studies demonstrated that ertugliflozin exposure is dose proportional over the range of 0.5–300 mg.[28] This was corroborated by the results of regression modeling using a linear mixed-effects analysis, which found that ertugliflozin AUC and C_{max} increased in a dose-proportional manner over the same dose range.[56] Based on phase I clinical pharmacology studies[28] and the PopPK analysis,[48] the maximum expected decrease in ertugliflozin exposure due to extrinsic or intrinsic factors was 39%, which was observed following rifampin co-administration.[28,45] However, in the phase II/III dose–response model,[41] the lower (5-mg) dose of ertugliflozin was predicted to maintain clinically meaningful glycemic efficacy following co-administration with rifampin. Therefore, dose adjustment is not required when ertugliflozin is co-administered with a UGT and CYP inducer, such as rifampin.[8,9] Furthermore, the results of the PopPK analysis[48] demonstrated that ertugliflozin can also be administered without regard to food, age, body weight, gender, and race.[8,9] An increase in ertugliflozin exposure of ~1.5-fold following concomitant administration of the higher (15-mg) dose of ertugliflozin with the UGT inhibitor MFA was predicted by PBPK modeling.[63] As ertugliflozin exposure increases in a dose-proportional manner, and as oral doses of ertugliflozin as high as 300 mg as a single dose, up to 100 mg once daily for 14 days, and up to 25 mg once daily for up to 12 weeks have not been associated with any safety concerns in early phase I and II studies (i.e., exposures that are up to 20-fold higher relative to the exposure for the 15-mg dose),[28,37,38,40] no dosing adjustments are proposed when ertugliflozin is co-administered with a UGT inhibitor.[8,9] In phase III studies,[16–23] both 5-mg and 15-mg doses of ertugliflozin provided significant and clinically meaningful glycemic efficacy alone or in combination with other antihyperglycemic agents through up to 104 weeks, and were safe and well-tolerated.[24] Thus, the approved ertugliflozin doses[8,9] of 5 mg or 15 mg once daily are based on the totality of the efficacy and safety data from clinical studies and are robustly supported by the application of various quantitative models to inform the dosing recommendations.

An important aspect of the MIDD approaches described in this review was the utilization of published data from other SGLT2 inhibitors alongside existing ertugliflozin data, which was key to the successful use of QSP modeling, PBPK modeling, and MBMA during the clinical development of ertugliflozin.[41] The QSP model[1,31,32] was developed by integrating information on the general mechanism of action of SGLT2 inhibitors, as well as published early-phase PK/PD data for dapagliflozin, which shares similar ADME properties to ertugliflozin. The published DDI data of dapagliflozin with MFA also underpinned the PBPK modeling[63] approach used to assess the potential for a DDI following co-administration of ertugliflozin with the UGT enzyme inhibitor MFA. Finally, published summary-level data from 94 trials of SGLT2 inhibitors contributed to the development of an MBMA[46] to examine the comparative effectiveness of ertugliflozin in the wider SGLT2 inhibitor landscape. These examples demonstrate how MIDD approaches can enable researchers to leverage the totality of data pooled from different candidates across a drug class.[64,65]

The use of MIDD during the drug development and approval process is increasing as the benefits of this approach become ever more apparent.[66–70] MIDD has the potential to streamline the development of new therapies by improving overall efficiency through increased confidence in decision making, a reduction in the attrition of drugs in late-phase drug development, and the minimization of the requirement for (or size of) clinical studies, which can translate to significant time and cost savings for pharmaceutical organizations.[1–4] The numerous regulatory applications of MIDD also support approval and labeling decisions during the registration of new agents.[1,4–7] In the case of ertugliflozin, MIDD expedited the clinical development of the drug by facilitating a comprehensive pharmacological characterization with cost and time savings prior to regulatory approval of ertugliflozin in 2017–2018. For example, QSP modeling enabled the completion of ertugliflozin phase I and II clinical explorations within ~15 months by negating the need for a phase IIa dose-ranging study in patients with T2DM.[1] Furthermore, pooled regression analyses and PBPK modeling negated the need for dedicated clinical trials to examine the impact of *UGT1A9* genotype on ertugliflozin PKs and the potential for UGT-mediated DDIs, respectively.[56,63] However, an important consideration in the successful adoption and realization

of the maximum benefits of MIDD approaches is the need for them to be integrated early and throughout the development lifecycle of a drug.[6,71]

Both the US Food and Drug Administration (FDA) and the European Medicines Agency support the implementation of good practice and consistent standards governing the use of MIDD strategies during the development and regulatory review of new therapies.[3,72,73] Recent publications by the FDA underline this supportive outlook, encouraging the incorporation of MIDD into rational drug development and for best practices to be established and shared.[6,70,74] However, the continued use of MIDD depends on the acceptance of the techniques by all those involved in bringing a new drug to patients, including decision makers in regulatory agencies as well as the pharmaceutical industry, medical experts, physicians, and payers.[75] This includes the ability to rely on alternative technical expertise and to overcome perceptions that modeled data are less robust than data from clinical trials.[76] During the development of ertugliflozin, each MIDD approach was developed in a collaborative and supportive manner whereby clinical, clinical pharmacology, pharmacometrics, statistics, QSP, biology, and regulatory colleagues aligned on the principles of MIDD to develop a comprehensive analysis plan, with communication and feedback a key component throughout the model-development process.

In conclusion, the clinical development of ertugliflozin employed a range of end-to-end MIDD approaches that facilitated decision making, saved resources, and supported the successful registration and labeling of this novel SGLT2 inhibitor for the treatment of T2DM in adults.

CONFLICTS OF INTEREST

D.J.F., G.N., V.K.D., E.C., C.J.M., K.S., and V.S. are employees of Pfizer Inc. and may own shares/stock options in Pfizer Inc. Y.L. was an employee of Pfizer Inc. at the time the studies described in this review were conducted. 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.

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