CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	209803
Link to EDR	\\Cdsesub1\evsprod\NDA209803\209803.enx
Submission Date	19 Dec 2016
Submission Type	505 (b)(1)
Brand Name	Steglatro
Generic Name	Ertugliflozin
Dosage Form and Strength	Tablet; 5 mg and 15 mg
Route of Administration	Oral
Proposed Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant	Merck Sharp & Dohme Corp
Associated IND	IND 106447
OCP Review Team	*Suryanarayana Sista, PhD; Lian Ma, PhD; Yaning Wang, PhD; Manoj Khurana, PhD*
OCP Final Signatory	*Chandrahas Sahajwalla, PhD*

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1. EXECUTIVE SUMMARY

This is an original NDA submitted by Merck Sharp & Dohme Corporation on 19 December 2016, seeking marketing approval for Ertugliflozin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Currently 3 other approved therapies in this class (Canagliflozin, Dapagliflozin and Empagliflozin) are available in the US for this indication. Ertugliflozin is an oral, selective inhibitor of sodium glucose co-transporter-2 (SGLT2) which inhibits renal glucose reabsorption and results in urinary glucose excretion (UGE) and reductions in plasma glucose and hemoglobin A1c (HbA1c) in patients with type 2 diabetes mellitus (T2DM). *In vitro*, ertugliflozin has been shown to be a highly selective SGLT2 inhibitor with greater than 2000x selectivity for SGLT2 (50% inhibitory concentration [IC_{50}] = 0.877 nM) compared to SGLT1 (IC_{50} = 1960 nM). Ertugliflozin is included in the drug product as a co-crystal with L-pyroglutamic acid (L-PGA), known as ertugliflozin L-PGA.

The proposed dosing regimen is to start with a dose of ertugliflozin 5 mg once daily, taken in the morning, with or without food. In patients tolerating ertugliflozin 5 mg once daily, the dose may be increased to 15 mg once daily if additional glycemic control is needed. Ertugliflozin is proposed to be marketed under the tradename Steglatro, and will be available in 5 mg and 15 mg strengths as oral tablets.

The efficacy and safety of ertugliflozin in T2DM patients was supported by data from 4 Phase 3 studies (P001/1016, P007/1017, P005/1019, P003/1022) conducted in T2DM patients. A total of 24 studies (19 Phase 1, 2 Phase 2, and 4 Phase 3) conducted in healthy subjects and in T2 DM patients, assessed the pharmacokinetics (PK) and pharmacodynamics (PD) of ertugliflozin. The proposed 5 mg and 15 mg commercial tablets are made from [redacted] (b) (4) and use the same composition as the Phase 3 formulation [redacted] (b) (4). The pink and red film coating used for the 5 mg and 15 mg commercial tablets are the same as the white film coating used in Phase 3 tablets except for the addition of iron oxide [redacted] (b) (4). The commercial tablets were scientifically bridged to the formulation used in Phase 3 studies in a dedicated bridging study (P023/1037).

From a clinical pharmacology perspective, the proposed dosing regimen of ertugliflozin 5 mg once daily, followed by an increase to 15 mg once daily if additional glycemic control is needed, is appropriate. The PK and PD of ertugliflozin in T2DM patients were evaluated in pivotal Phase 3 studies. The PK in T2DM patients were comparable to that in healthy subjects. Ertugliflozin steady state exposure was equivalent when administered as 2.5 mg BID vs. 5 mg QD and as 7.5 mg BID vs. 15 mg QD. In addition, UGE during a 24-hour interval at steady state was similar when administered as 2.5 mg BID vs. 5 mg QD and as 7.5 mg BID vs. 15 mg QD. This information facilitated to develop fixed-dose combination (FDC) products in combination with Metformin and with Sitagliptin. Along with the current NDA, two separate NDAs for the FDCs, ertugliflozin/sitagliptin FDC tablets ([redacted] (b) (4) 5 mg/100 mg, [redacted] (b) (4) 15 mg/100 mg) (NDA 209805), ertugliflozin/metformin FDC tablets (2.5mg/500mg, 2.5mg/1000mg, 7.5mg/500mg, 7.5mg/1000mg) (NDA 209806) for the treatment of type 2 diabetes mellitus (T2DM) as adjunct to diet and exercise therapy, were submitted. Please see Clinical Pharmacology reviews by Dr. Lei He in DARRTS for NDAs 209805 and 209806.

The Clinical Pharmacology review of NDA 209803 focused on the dose selection for Phase 3 studies, and confirming the PK/PD results from dose-response and population pharmacokinetics (PopPK) analyses of ertugliflozin.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 209803 and found it acceptable to support approval of Ertugliflozin in the T2DM population. Key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	The reduction in HbA1c from baseline at week 26 in pivotal Phase 3 studies provides primary evidence of effectiveness. The PK and PD (UGE) of ertugliflozin in healthy volunteers and T2DM patients provide supportive evidence for effectiveness.
General dosing instructions	From a Clinical Pharmacology perspective, the proposed treatment regimen of starting ertugliflozin at a dose of 5 mg once daily, followed by an increase to 15 mg once daily if additional glycemic control is needed, is acceptable.
Dosing in patient subgroups	No separate dosing/dosing regimen is recommended in any patient subgroups due to intrinsic (e.g., age and body weight) and extrinsic factors. Ertugliflozin is not recommended for use in patients with eGFR <60 mL/min/1.73m^2, or in patients with severe hepatic impairment.
Bridge between the "to-be-marketed" and clinical trial formulations	A dedicated bridging study (P023/1037) provided evidence that the "to-be-marketed" (commercial image) formulation and the formulation used in Phase 3 efficacy trials are bioequivalent.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Ertugliflozin is an oral, selective inhibitor of sodium glucose co-transporter-2 (SGLT2) which inhibits renal glucose reabsorption and results in urinary glucose excretion (UGE) and reductions in plasma glucose and hemoglobin A1c (HbA1c) in patients with type 2 diabetes mellitus (T2DM). *In vitro*, ertugliflozin has been shown to be a highly selective SGLT2 inhibitor with greater than 2000x selectivity for SGLT2 (50% inhibitory concentration [IC_{50}] = 0.877 nM) compared to SGLT1 (IC_{50} = 1960 nM).

The following is a summary of the clinical pharmacokinetics of ertugliflozin:

Absorption:	• Following single-dose oral administration of 5 mg and 15 mg of ertugliflozin, under fasted conditions, time to peak plasma concentrations (T_{max}) of ertugliflozin occur at 1 hour postdose. • A dose-proportional increase in plasma ertugliflozin C_{max} and AUC was observed following single doses from 0.5 mg to 300 mg and following multiple doses from 1 mg to 100 mg. • The absolute oral bioavailability of ertugliflozin following administration of a 15 mg dose is approximately 100%. • Ertugliflozin C_{max} is reduced by 29% and T_{max} prolonged by 1 hour following administration of ertugliflozin with a high-fat and high-calorie meal compared to the fasted state, however AUC was unaffected.
Distribution:	• The mean steady-state volume of distribution of ertugliflozin is approximately 86 L following an intravenous dose. • Plasma protein binding of ertugliflozin is independent of ertugliflozin plasma concentrations, and is approximately 94%. In patients with renal or hepatic impairment, plasma protein binding is not meaningfully altered. The blood-to-plasma concentration ratio of ertugliflozin is 0.66.
Elimination:	• The mean systemic plasma ertugliflozin clearance following an intravenous microdose of 100 µg dose was 11.2 L/hr. Based on PopPK analysis, the mean elimination half-life in T2DM patients with normal renal function was estimated to be approximately 16.6 hours. • Approximately 41% and 50% of the drug-related radioactivity was eliminated in feces and urine, respectively, following administration of an oral [^{14}C]-ertugliflozin solution to healthy subjects. Only 1.5% of the administered dose was excreted as unchanged ertugliflozin in urine and approximately 34% as unchanged ertugliflozin in feces, which may likely be due to biliary excretion of glucuronide metabolites and subsequent hydrolysis to parent.
Metabolism:	• The primary clearance mechanism for ertugliflozin is by metabolism. The major metabolic pathway for ertugliflozin is UGT1A9 and UGT2B7-mediated O-glucuronidation (86%) to two glucuronides that are pharmacologically inactive at clinically relevant concentrations. There is minimal CYP-mediated oxidative metabolism of ertugliflozin (12%).

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed starting dose of Steglatro is 5 mg once daily, taken in the morning, with or without food. In patients tolerating Steglatro 5 mg once daily, the dose may be increased to 15 mg once daily if additional glycemic control is needed.

In patients with volume depletion, correcting this condition prior to initiation of Steglatro is recommended.

A longitudinal dose-response model was fitted to the data for the primary evaluation of HbA1c lowering effect of ertugliflozin. Since exposures of ertugliflozin increased in a dose-proportional manner and PK variability of ertugliflozin was low, dose was considered to be a good surrogate for ertugliflozin exposure. A longitudinal exposure-response model was therefore also fitted to the HbA1c data. The longitudinal exposure-response model did not provide any additional predictive performance benefit over the dose-response model. Therefore, the dose-response model was considered the final model for evaluation of HbA1c lowering effect of ertugliflozin. Based on the final model parameter estimates, the 5 mg and 15 mg doses elicited HbA1c responses (-0.617% and -0.698%, respectively) that were >80% and >90% of the model-estimated E_{max} (-0.745%) and consistent with the results on the dose-response model using data from Phase 2 studies.

The proposed dosing regimen is supported by a dose-response analysis. For further details, see section Section 4.3.2.

2.2.1.1 QD Dosing vs. BID Dosing

The equivalence of ertugliflozin exposure at steady-state (AUC_{24}) following daily dosing of 5 mg QD vs. 2.5 mg BID, and following 15 mg QD vs. 7.5 mg BID were evaluated in Study P035/1051. To demonstrate bioequivalence, the 90% CI for the ratio (BID/QD) of geometric means for AUC_{24} would have to be within the 80% - 125% limits. This study also evaluated the similarity of PD effect (UGE_{24}) following 5 mg QD vs. 2.5 mg BID, and following 15 mg QD vs. 7.5 mg BID dosing. To demonstrate bioequivalence, the the 90% CI for the ratio (BID/QD) of geometric means for UGE_{24} would have to be within 70% - 143% limits.

For the 5 mg QD vs. 2.5 mg BID comparison, the 90% CI for the ratio of geometric means for AUC_{24} was 98.76% - 102.83%, and for the 15 mg QD vs. 7.5 mg BID comparison, the 90% CI for the ratio of geometric means for AUC_{24} was 97.08% - 102.45%, demonstrating PK bioequivalence for the two regimens for both strengths of ertugliflozin.

For the 5 mg QD vs. 2.5 mg BID comparison, the 90% CI for the ratio of geometric means for UGE_{24} was 102.96% - 117.87%, and for the 15 mg QD vs. 7.5 mg BID comparison, the 90% CI for the ratio of geometric means for UGE_{24} was 97.69% - 108.12%, demonstrating PK bioequivalence for the two regimens for both strengths of ertugliflozin.

Results from this study provided support for the development of ertugliflozin FDC products with sitagliptin and metformin, respectively (NDAs 209805 and 209806, respectively).

2.2.2 Therapeutic individualization

No therapeutic individualization of ertugliflozin is recommended. Prior to initiating ertugliflozin therapy, assessing renal function is recommended. Initiation of or use of ertugliflozin is not recommended in patients with an eGFR less than 60 mL/min/1.73 m^2.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts be included in the final package insert:

Label Section	Recommendation
HIGHLIGHTS **DOSAGE AND ADMINISTRATION** **CONTRAINDICATIONS**	• Assess renal function before initiating TRADEMARK. Initiation of TRADEMARK is not recommended in patients with an eGFR less than 60 mL/min/1.73 m² (2.2). • Delete following sentence: [redacted (b) (4)] • Severe renal impairment (eGFR <30 mL/min/1.73 m²), end-stage renal disease, or dialysis (4)
2.2 Patients with Renal Impairment	• Initiation of TRADEMARK is not recommended in patients with an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m² [see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]. • Delete [redacted (b) (4)] • Use of TRADEMARK is not recommended in patients with eGFR persistently between 30 and less than 60 mL/min/1.73 m².
12.2 Pharmacodynamics	Cardiac Electrophysiology • The effect of TRADEMARK on QTc interval was evaluated in a Phase 1 randomized, placebo- and positive-controlled 3-period crossover study in 42 healthy subjects. At 6.7-times the therapeutic exposures with maximum recommended dose, TRADEMARK does not prolong QTc to any clinically relevant extent.
12.3 Pharmacokinetics **Special Population** **Renal Impairment**	• In a Phase 1 clinical pharmacology study in patients with type 2 diabetes and mild, moderate, or severe renal impairment (as determined by eGFR), following a single-dose administration of 15 mg TRADEMARK, the mean increases in AUC of ertugliflozin were 1.6, 1.7 and 1.6-fold, respectively, for mild, moderate and severe renally impaired patients, compared to subjects with normal renal function. These increases in ertugliflozin AUC are not considered clinically relevant. There were no clinically meaningful differences in the ertugliflozin C_{max} values among the different renal function groups. The 24-hour urinary glucose excretion declined with increasing severity of renal impairment [see Warnings and Precautions (5.3)]. The plasma protein binding of ertugliflozin was unaffected in patients with renal impairment.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The clinical development program for ertugliflozin comprised of 24 studies: 19 Phase 1 studies, 2 Phase 2 studies, and 4 Phase 3 studies. A total of 3751 subjects participated in these clinical studies, including healthy volunteers (n = 395) and T2DM patients (n=3356). These studies provide information supporting proof-of-concept as well as the definitive efficacy and safety of Steglatro in the target population for the treatment of diabetes.

The regulatory history regarding these communications is summarized below:

Dates	Meeting Type	Key Communication Points
12/17/2012	EOP2	**Dose Selection for P3 studies:** Agency pointed out that the 10 mg daily dose does not appear to provide any additional benefit over the 5 mg daily dose for reduction in baseline HbA1c **Formulation:** Recommendation to use the 'to-be-marketed' formulation in pivotal trials **Renal Impairment Study:** Recommendation to first complete the Phase 1 clinical pharmacology study in patients with renal impairment and use the data from this study, such as pharmacodynamic data, to inform and support the clinical evaluation of efficacy and safety for ertugliflozin in patients with varying degrees of renal dysfunction. **Clinical Pharmacology Plan:** Agreement that based on the results summarized in briefing package, the proposed clinical pharmacology program seems adequate. Sponsor was advised that, with respect to DDI, however, they should provide detailed assessment for cases where they do not plan to conduct *in vivo* studies because DDI is not anticipated (if any), following the decision trees from the recent FDA guidance on evaluation of DDI (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf). Sponsor was advised that the potential of *in vivo* chiral conversion of ertugliflozin needed to be addressed before NDA submission. The Sponsor was asked to evaluate the impact of ertugliflozin on renal function by performing analysis such as baseline eGFR vs. change in eGFR and longitudinal change in eGFR for data from Phase 2 and Phase 3 trials representing different treatment durations and treatment arms.
08/26/2013	Advice/Information Request	Final agreed upon Initial Pediatric Study Plan (iPSP)
09/10/2013	EOP2 Follow-up	Discussion of 5mg and 15 mg as acceptable doses for P3 trials Discussion of dedicated study in subjects with T2DM and Stage 3 CKD, together with the pooled analysis of the data of subjects with Stage 3 CKD from the entire Phase 3 program
12/07/2015	Email communication	Acceptance of legacy data format for Phase 1 and Phase 2 trials
04/15/2016	Written Communication	Acceptance of "Steglatro" as the proprietary name for ertugliflozin
09/06/2016	Pre-NDA Meeting	Clarification on requirements for submitting PopPK data and SymCYP data files

3.2 General Pharmacological and Pharmacokinetic Characteristics

Ertugliflozin L-PGA is a white to off-white powder. The solubility of ertugliflozin (using ertugliflozin L-PGA as source of ertugliflozin) in unbuffered water at pH 5.5, simulated gastric fluid with no enzymes (SGN) at pH 1.2, and phosphate buffered saline (PBS) at pH 6.5 was found to be 0.76, 0.74 and 0.64 mg/mL, respectively. Ertugliflozin immediate release tablets are to be made avaialble at 5 mg and 15 mg strengths. (b) (4). The 5 mg tablet

is to be presented as a triangular, pink film-coated tablet debossed with '701' on one side and plain on the other side. The 15 mg tablet is to be presented as a triangular, red film-coated tablet debossed with '702' on one side and plain on the other side. The drug product is to be packaged in heat induction sealed high density polyethylene (HDPE) bottles with desiccant or in aluminum foil blisters with aluminum foil backing.

3.2.1 Mechanism of Action:

Sodium-glucose co-transporter 2 (SGLT2) expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Ertugliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, ertugliflozin reduces reabsorption of filtered glucose and lowers renal threshold for glucose (RT_G), and thereby increases urinary glucose excretion (UGE) (Figure 1).

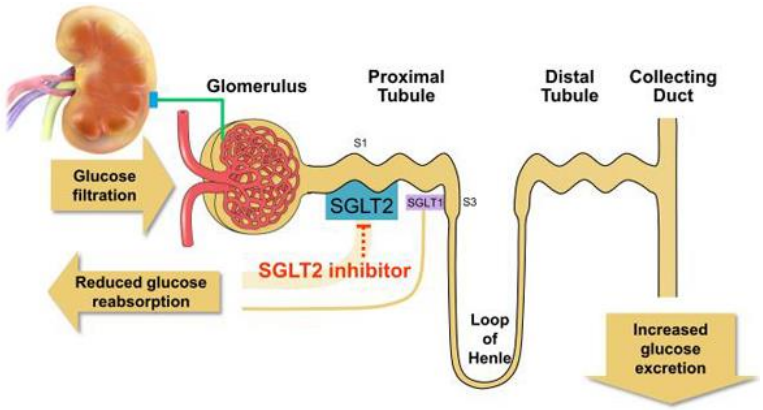


Figure 1 Schematic of the mechanism of Action of Ertugliflozin

3.2.2 Pharmacokinetics:

A total of 24 completed clinical studies conducted in healthy volunteers and T2DM patients assessed the PK and PD of ertugliflozin.

3.2.2.1 Absorption

Following single or multiple dose oral administration of ertugliflozin, absorption of ertugliflozin is independent of dose, with a median T_{max} of approximately 1 hour in the fasted state and approximately 2 hours post dose in the fed state. The oral bioavailability (BA) following administration of a single 15 mg dose of ertugliflozin in healthy volunteers is approximately 100%. A high-fat and high-calorie meal decreased ertugliflozin C_{max} by 29% with a corresponding prolongation of T_{max} by 1 hour, however, there was no change in AUC compared to the fasted state. The observed effect of food on ertugliflozin pharmacokinetics is not considered clinically relevant, and ertugliflozin may be administered without regards to food.

3.2.2.2 Distribution

The mean steady-state volume of distribution of ertugliflozin following IV dosing was estimated to be 85.5 L, indicating moderate extravascular distribution. The *in* vitro plasma protein binding of ertugliflozin was estimated to be 93.6% and was independent of ertugliflozin plasma concentrations. The plasma protein binding in T2DM patients with varying degrees of renal impairment or in subjects with moderate hepatic impairment was not meaningfully altered. The mean unbound ertugliflozin fraction ranged from

0.034-0.041 in these groups of patients. At a nominal concentration of 1 µg/mL (2.3 µM), ertugliflozin distributed preferentially into plasma over red blood cells, with a blood-to-plasma concentration ratio of 0.66.

3.2.2.3 Metabolism

Metabolism is the primary clearance mechanism for ertugliflozin. UGT1A9 and UGT2B7-mediated O-glucuronidation were the major metabolic pathway for ertugliflozin, accounting for 86% of the metabolism to two glucuronides (3-O-ß glucuronide, or M5c and 2-O-ß glucuronide or M5a) that are pharmacologically inactive at clinically relevant concentrations. CYP-mediated (oxidative) metabolism of ertugliflozin is minimal (12%). For these minor oxidative pathways, CYP3A4 is the predominant enzyme involved in the metabolism of ertugliflozin to hydroxy ertugliflozin (M1 and M3) and desethyl ertugliflozin (M2), with minor contributions from CYP2C8 and CYP3A5. The proposed metabolic pathway of Ertugliflozin is shown in Figure 2 below:

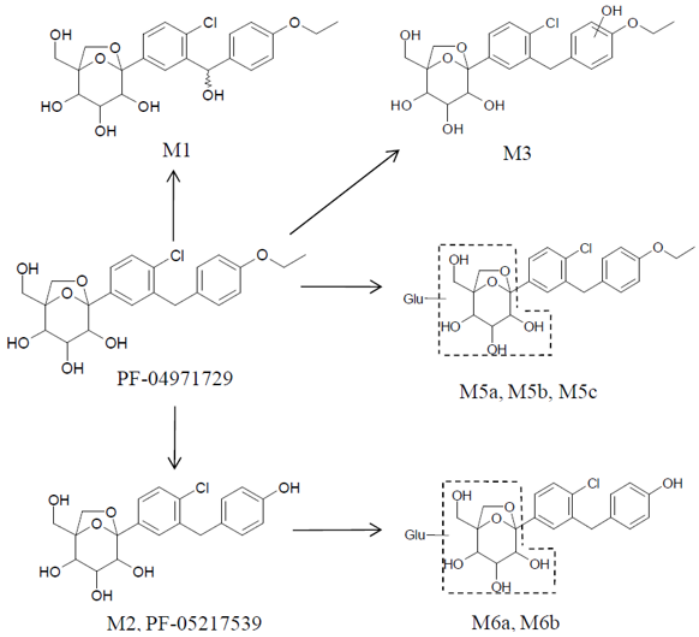


Figure 2 Proposed Metabolic Pathway for Ertugliflozin

3.2.2.4 Elimination

Following an intravenous microdose of 100 µg and an oral dose of 15 mg, the mean systemic plasma clearance was 11.2 L/hr and 10.7 L/h, respectively. Based on PopPK analysis, the mean elimination half-life in T2DM patients with normal renal function was estimated to be 16.6 hours, and 15.3 hours for healthy subjects. Following administration of an oral [^{14}C]-ertugliflozin solution to healthy subjects, approximately 40.9% and 50.2% of the drug-related radioactivity was eliminated in feces and urine, respectively. About 1.5% of the administered dose was excreted as unchanged ertugliflozin in urine and 33.8% as unchanged ertugliflozin in feces, likely due to biliary excretion of glucuronide metabolites and subsequent hydrolysis to parent. Renal clearance values for ertugliflozin ranged from 1.6 to 2.2 mL/min in healthy and T2DM subjects with normal renal function.

Through evaluation of pooled human plasma samples obtained from 24 subjects at steady state after administration of ertugliflozin 15 mg qd x 6 days, chiral inversion of ertugliflozin was not observed.

3.2.2.5 Drug-drug Interactions

Key results from in vitro studies:
In vitro studies showed that ertugliflozin and ertugliflozin glucuronides did not inhibit CYP450 isoenzymes 1A2, 2C9, 2C19, 2C8, 2B6, 2D6, or 3A4, and did not induce CYPs 1A2, 2B6, or 3A4. Ertugliflozin was not a time-dependent inhibitor of CYP3A *in vitro*. Ertugliflozin did not inhibit UGT1A6, 1A9, or 2B7 *in vitro* and was a weak inhibitor (IC50 >39 μM) of UGT1A1 and 1A4. Ertugliflozin glucuronides did not inhibit UGT1A1, 1A4, 1A6, 1A9, or 2B7 *in vitro*. Ertugliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters and is not a substrate of organic anion transporters (OAT1, OAT3), organic cation transporters (OCT1, OCT2), or organic anion transporting polypeptides (OATP1B1, OATP1B3).

Key results from in vivo studies:
When ertugliflozin was co-administered with metformin, sitagliptin, glimepiride, or simvastatin, as compared to ertugliflozin alone, there were no meaningful PK differences (Figure 3). However, concomitant administration of multiple doses of rifampin 600 mg qd reduced the AUC_{inf} and C_{max} of ertugliflozin by 39% and 15%, respectively. Dose - HbA1c response analysis that the 5 mg ertugliflozin dose following co-administration with rifampin is predicted to maintain clinically meaningful glycemic efficacy (predicted response of -0.625% at week 26 when rifampin was coadministered with ertugliflozin, versus -0.674% when ertugliflozin was administered alone). Dose adjustment is not recommended when ertugliflozin is co-administered with a UGT and CYP inducer like rifampin. The recommended labeling indicates that in subjects tolerating ertugliflozin 5 mg, the dose can be increased to 15 mg if additional glycemic control is required. These general dosing instructions apply to concomitant use of UGT and CYP inducer such as rifampin.

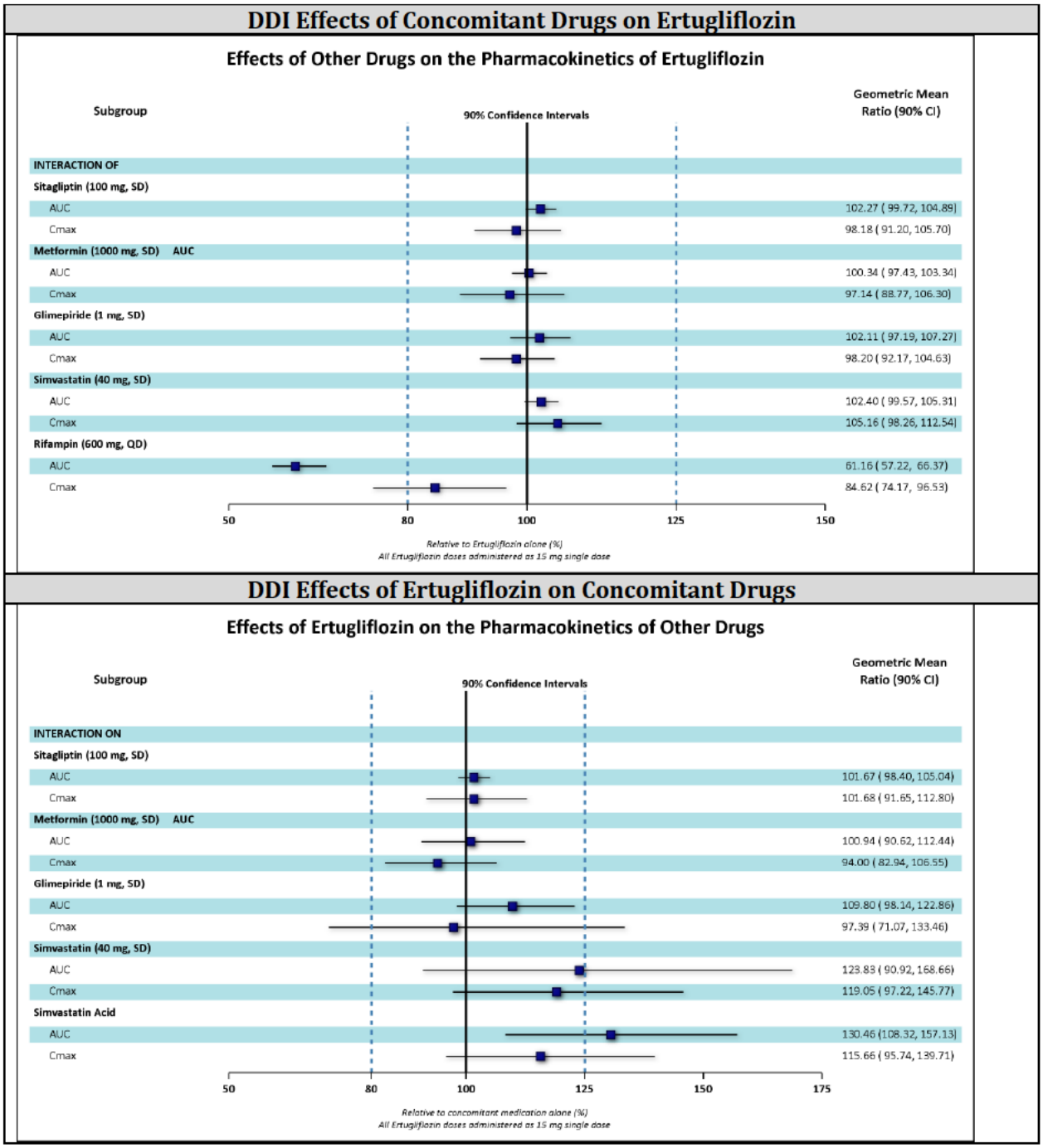


Figure 3 Drug-Drug Interactions Between Ertugliflozin and Concomitant Medications

Physiologically-based PK (PBPK) modeling of ertugliflozin co-administered with an UGT inhibitor mefenamic acid predicted a ≤1.51-fold increase in ertugliflozin AUC and C_{max}, which is not considered clinically relevant.

3.2.2.6 Special Populations

3.2.2.6.1 Renal Impairment

In T2DM patients with mild, moderate, or severe renal impairment, following a single-dose administration of ertugliflozin 15 mg, the mean increases in AUC of ertugliflozin were 1.6, 1.7 and 1.6-fold for mild, moderate and severe renally impaired patients, respectively, compared to subjects with normal renal function. These increases in ertugliflozin AUC are not considered clinically relevant. There were no clinically meaningful differences in the ertugliflozin C_{max} values among the different renal function groups. Mean half-life estimates for ertugliflozin were slightly longer in subjects with renal impairment compared to those with normal renal function for both T2DM and healthy subjects. Apparent oral clearance (CL/F) and CLr decreased with decreasing renal function for all renal impairment groups.The 24-hour urinary glucose excretion declined with increasing severity of renal impairment (See Figure 17). The plasma protein binding of ertugliflozin was unaffected in patients with renal impairment.

3.2.2.6.2 Hepatic Impairment

Exposure of ertugliflozin was not increased in moderate hepatic impairment. The AUC of ertugliflozin decreased by approximately 13%, and C_{max} decreased by approximately 21% compared to subjects with normal hepatic function. This decrease in ertugliflozin exposure is not considered clinically meaningful. Ertugliflozin was not studied in patients with severe hepatic impairment. The plasma protein binding of ertugliflozin was unaffected in patients with moderate hepatic impairment.

3.2.2.6.3 Pediatric

Ertugliflozin has not been studies in pediatric patients.

3.2.2.6.4 Effects of Age, Body Weight, Gender, Ethnicity and Race

PopPK analysis did not identify age, body weight, gender, ethnicity and race to have any clinically clinically relevant impact on the pharmacokinetics of ertugliflozin.

3.2.3 Pharmacodynamics:

3.2.3.1 Urinary Glucose Excretion (UGE) in Healthy Subjects

In healthy subjects, following single and multiple dose ertugliflozin administration, there was a dose related increase in UGE up to 25 mg. The 24-hour UGE values appeared to plateau at doses ≥25 mg. Similar 24-hour UGE values were observed on Day and at steady-state. UGE between Japanese and Western healthy subjects were similar, indicating no differences due to ethnicity. No meaningful differences in UGE were found between bid and corresponding qd doses (UGE values of 58.58 g, 57.63 g, 57.09 g, and 52.46 g for the 7.5 mg bid, 15 mg qd, 2.5 mg bid, and 5 mg qd doses, respectively).

3.2.3.2 UGE in T2DM Patients

At a dose of 15 mg ertugliflozin, higher median change from baseline in 24-hour UGE was observed in T2DM subjects with normal renal function (68.1 g) compared to healthy subjects (45.8 g). Data from a Phase 2 dose-ranging was used to fit an E_{max} model to the observed 24-hour UGE data as a function of administered dose (Figure 4). A maximal baseline-adjusted 24-hour UGE response of 71.5 (95% CI:57.9, 87.3) g and an ED_{50} of 0.752 (95% CI: 0.299, 1.58) mg was estimated from the model. The predicted mean 24-hour UGE following administration of ertugliflozin 5 mg and 15 mg doses for 28 days were 62.5 (90% CI: 54.9, 69.7) and 68.9 (90% CI:58.9, 78.7) g. Dose-response modeling indicated that ertugliflozin 5 mg and 15 mg result in near maximal UGE, with the 15 mg dose providing only incrementally greater UGE relative to the 5 mg dose.

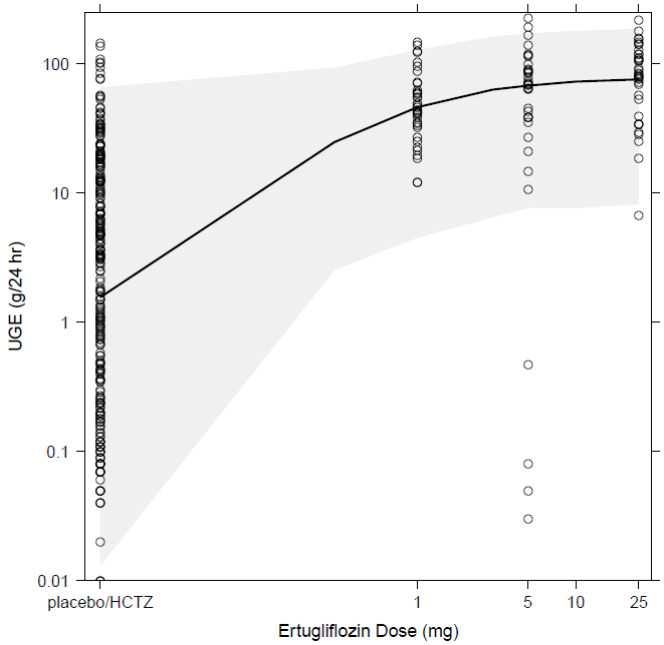


Figure 4 UGE versus Ertugliflozin Dose in T2DM Subjects

(Source: eCTD for NDA 209803, Module 5.3.5.3, CSR for Report ASR-EQDD-B152a-DP3-253, Figure 1, Page 8)

Similar to the finding in healthy subjects, no meaningful differences were found in UGE for bid vs the corresponding qd doses (69.45 g, 70.43 g, 78.29 g, and 80.54 g, for the 1 mg bid, 2 mg qd, 2 mg bid, and 4 mg qd ertugliflozin doses, respectively).

Compared to the median UGE value in T2DM subjects with normal renal function, administration of ertugliflozin 15 mg to T2DM subjects with mild and moderate renal impairment resulted in UGE that was approximately 53% to 69% of normal in subjects with mild renal impairment, and 42% to 48% of normal in subjects with moderate renal impairment. Based on a regression model, the mean 24-hour UGE for a T2DM subject with a BSA-normalized eGFR of 52.5 mL/min/1.73m^{2,} the UGE was predicted to be 29.5 g.

3.2.4 QT Prolongation:

No significant QTc prolongation effect of ertugliflozin 100 mg was detected in a dedicated TQT study. The largest upper bound of the 2-sided 90% CI for the mean difference between ertugliflozin 100 mg and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated, indicating that assay sensitivity was established. (Figure 5). For full details, please refer to the review by Dr. Moh Jee Ng in DARRTS.

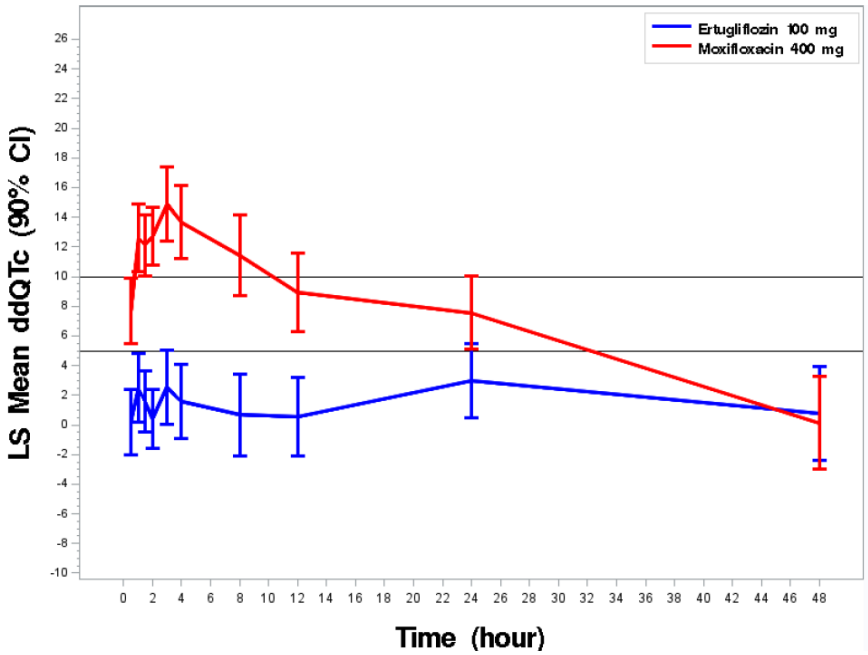


Figure 5 Plot of Estimated Mean Differences of QTcF With 90% Confidence Intervals Between Ertugliflozin and Placebo, and Moxifloxacin and Placebo

(Source: TQT Study Review by Dr. Ng, Document ID 4111621 in DARRTS, Figure 3, Page 14)

3.3 Clinical Pharmacology Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

Yes. Two dosing regimens of ertugliflozin, 5 mg qd and 15 mg qd, evaluated in the Phase 3 program demonstrated clinically meaningful reductions from baseline in HbA1c at week 26 in the general T2DM patient population. In 3 Phase 3 studies conducted in T2DM population comparing ertugliflozin to placebo, significant ($p<0.001$ for all comparisons) and clinically meaningful reductions in HbA1c were observed for both the 5 mg and 15 mg doses of ertugliflozin compared to placebo when administered either as monotherapy or when added to subjects who had inadequate glycemic control on other anti-hyperglycemic agents (AHAs) (Table 1). Placebo-corrected reductions in HbA1c across the studies in the ertugliflozin 5 mg and 15 mg arms ranged from 0.69% to 1.16%.

Durable HbA1c lowering through at least 52 Weeks of treatment was demonstrated by ertugliflozin 5 and 15 mg (Figure 6). Across all studies, the 15 mg dose of ertugliflozin provided a numerically greater reduction in A1C relative to 5 mg.

Table 1 Change from Baseline in A1C(%) at Primary Timepoint by Study Full Analysis Set: Excluding Rescue Approach

	N	Baseline Mean ± SD	LS Mean Change ± SE	LS Mean Difference (95% CI)	p-value
P003/1022 (Week 26) Monotherapy					
Placebo	153	8.1 ± 0.92	0.20 ± 0.089		
Ertugliflozin 5 mg	156	8.2 ± 0.88	-0.79 ± 0.081	-0.99 (-1.22,-0.76)	<0.001
Ertugliflozin 15 mg	151	8.4 ± 1.12	-0.96 ± 0.082	-1.16 (-1.39,-0.93)	<0.001
P007/1017 (Week 26) Add-on to Metformin					
Placebo	209	8.2 ± 0.90	-0.03 ± 0.065		
Ertugliflozin 5 mg	207	8.1 ± 0.89	-0.73 ± 0.062	-0.70 (-0.87,-0.53)	<0.001
Ertugliflozin 15 mg	205	8.1 ± 0.93	-0.91 ± 0.063	-0.88 (-1.05,-0.71)	<0.001
P006/1015 (Week 26) Add-on to Metformin+Sitagliptin					
Placebo	153	8.0 ± 0.93	-0.09 ± 0.070		
Ertugliflozin 5 mg	156	8.1 ± 0.86	-0.78 ± 0.067	-0.69 (-0.87,-0.50)	<0.001
Ertugliflozin 15 mg	153	8.0 ± 0.83	-0.86 ± 0.068	-0.76 (-0.95,-0.58)	<0.001

LS means and p-value are based on the cLDA model for the primary analysis.
(Source: eCTD for NDA 209803, Module 2.5, Clinical Overview, Table 5, Page 32)

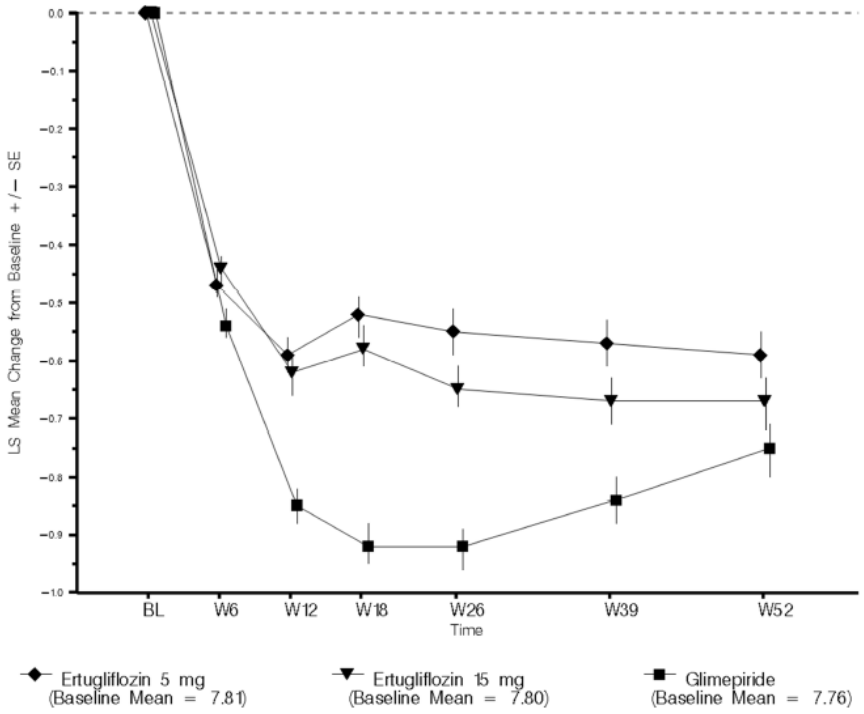
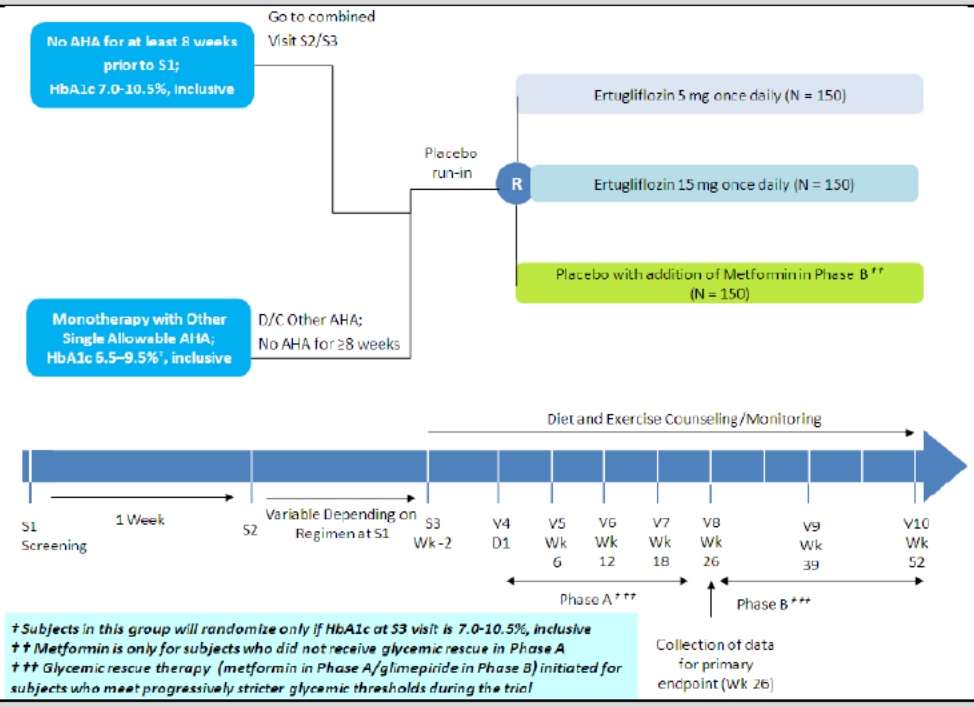


Figure 6 Least Squares Mean Change from Baseline in A1C (%) at Week 52 in Study P002/1013, FAS (constrained longitudinal data analysis); Excluding Rescue Approach

(Source: eCTD for NDA 209803, Module 2.5, Clinical Overview, Figure 3, Page 35)

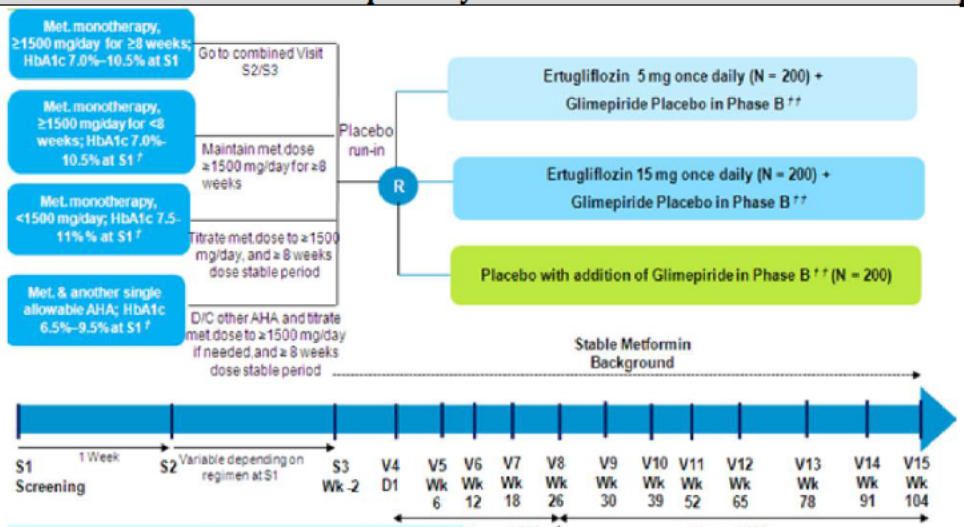
Study schematics for the 3 similarly designed studies (Studies P003/1022, P007/1017, and P006/1015) to assess the efficacy of ertugliflozin when compared with placebo, are shown in Figure 7.

Study P003/1022:	26-Week Multicenter Study with a 26-Week Extension of Ertugliflozin Monotherapy in T2DM and Inadequate Glycemic Control despite Diet and Exercise



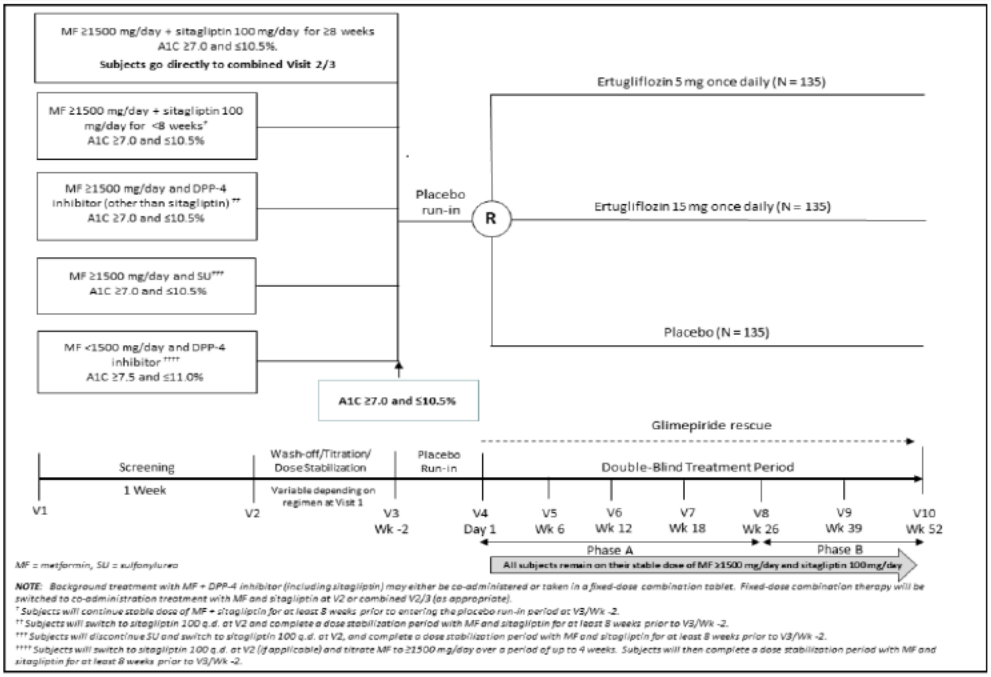
† Subjects in this group will randomize only if HbA1c at S3 visit is 7.0-10.5%, inclusive
†† Metformin is only for subjects who did not receive glycemic rescue in Phase A
††† Glycemic rescue therapy (metformin in Phase A/glimepiride in Phase B) initiated for subjects who meet progressively stricter glycemic thresholds during the trial

Study P007/1017:	26-Week Multicenter Study with a 78-Week Extension of Ertugliflozin in T2DM and Inadequate Glycemic Control on Metformin Monotherapy



† Subjects in these groups will be randomized only if HbA1c at S3 visit is between 7.0-10 .5 % inclusive.
†† Glimepiride/Glimepiride placebo is only for subjects who did not receive glycemic rescue therapy in Phase A.
††† Glycemic rescue therapy (Open Label glimepiride) and basal insulin initiated for subjects meeting progressively stricter glycemic thresholds in Phase A.
Basal insulin also initiated in Phase B for subjects meeting progressively stricter glycemic thresholds.

Study P006/1015: 26-Week Multicenter Study with a 26-Week Extension of Ertugliflozin in T2DM Who Have Inadequate Glycemic Control on Metformin and Sitagliptin



A1C=hemoglobin A_{1c}; DPP-4=dipeptidyl peptidase-4; MF=metformin; N=number of subjects; q.d.=once daily; R=randomization; SU=sulfonylurea; V=visit; Wk=week.

Figure 7 Schematic for Studies P003/1022, P007/1017 and P006/1015

(Source: eCTD for NDA 209803, Module 5.3.5.1, CSR for Study P003/1022, Figure 1, Page 66, CSR for Study P007/1017, Figure 1, Page 76, and CSR for Study P006/1015, Figure 1, Page 67)

Study P003/1022 *(26-Week Multicenter Study with a 26-Week Extension of Ertugliflozin Monotherapy in T2DM and Inadequate Glycemic Control despite Diet and Exercise)*:

Pharmacokinetics:

Trough plasma ertugliflozin concentrations drawn from weeks 6 through 26 showed that steady state was achieved following both 5 mg and 15 mg doses (Figure 8).

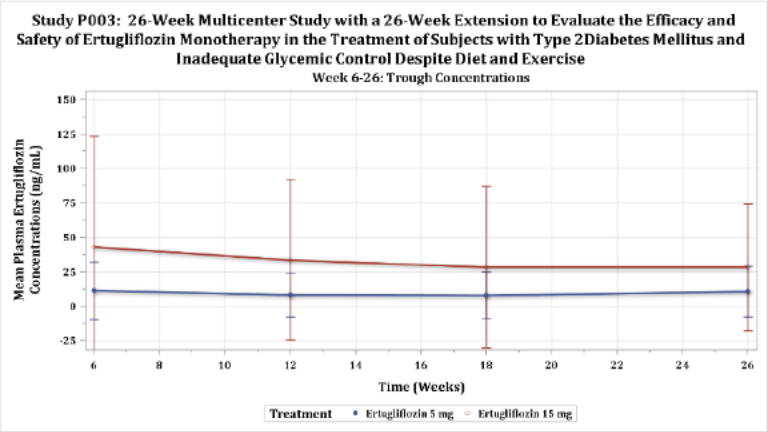


Figure 8 Mean (±SD) Trough Plasma Ertugliflozin Concentrations Following 5 mg and 15 mg Doses

(Source: Reviewer generated plot)

Change From Baseline in HbA1c:
Least Squares mean changes from baseline in HbA1c over time showed that the initial reductions in mean HbA1c at Week 6 were followed by smaller subsequent reductions at each time point through Week 26. Baseline mean HbA1c of 8.11, 8.16 and 8.35 for placebo, ertugliflozin 5 mg and ertugliflozin 15 mg, respectively, was similar among all treatment groups. The point estimate of the reduction in A1C was numerically greater in the ertugliflozin 15 mg group than in the ertugliflozin 5 mg group at each time point (Figure 9). In the placebo group, there was a small increase from baseline in HbA1c throughout the study. Both treatments reached statistical significance (p<0.001 for both treatments) when compared to placebo.

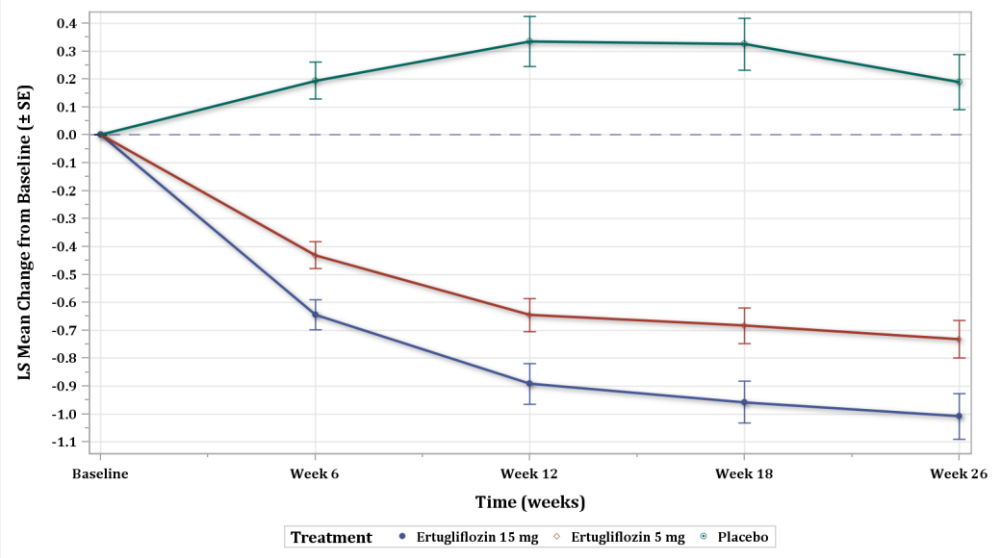


Figure 9 **LS Mean Change From Baseline Over Time for HbA1c (Study P003, Full Analysis Set: Excluding Rescue Approach)**

(Source: Reviewer generated plot)

Study P007/1017 *(26-Week Multicenter Study with a 78-Week Extension of Ertugliflozin in T2DM and Inadequate Glycemic Control on Metformin Monotherapy)***:**

Pharmacokinetics:
Trough plasma ertugliflozin concentrations drawn at weeks 6, 12 and 18 showed that steady state was achieved following both 5 mg and 15 mg doses.

Change From Baseline in HbA1c:
LS mean changes from baseline in HbA1c over time, excluding data after initiation of glycemic rescue therapy showed that large reductions in mean HbA1cHbA1c in the ertugliflozin groups through Week 12 were followed by smaller reductions through Week 26. Baseline mean HbA1c of 8.17, 8.06 and 8.13 for placebo, ertugliflozin 5 mg and ertugliflozin 15 mg, respectively, was similar among all treatment groups. The point estimate of the reduction in HbA1c was numerically greater in the ertugliflozin 15 mg group than in the ertugliflozin 5 mg group at each time point (Figure 10). In the placebo group, there was no clinically meaningful change from baseline in HbA1c throughout the study. Both treatments reached statistical significance (p<0.001 for both treatments) when compared to placebo.

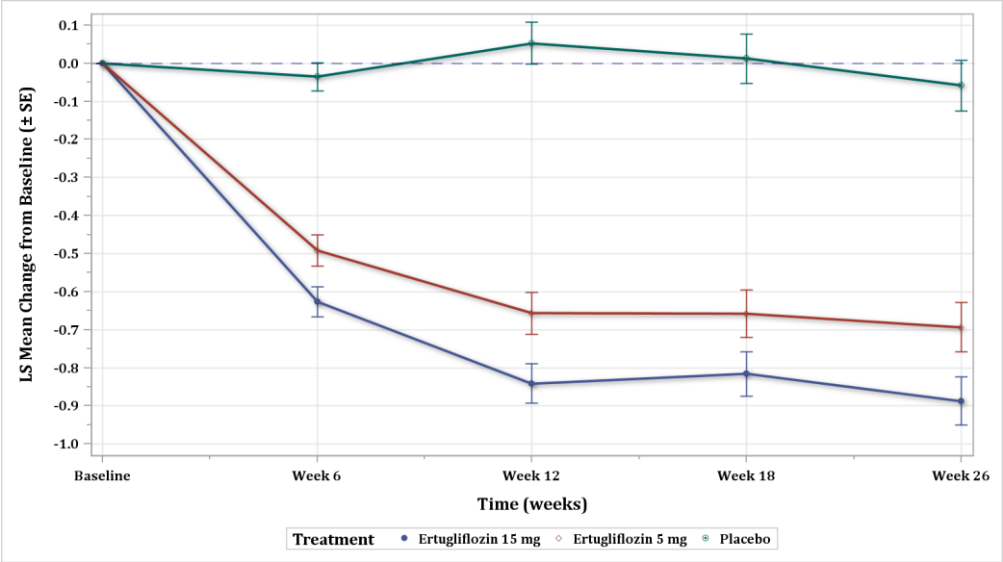


Figure 10 LS Mean Change From Baseline Over Time for HbA1c (Study P007, Full Analysis Set: Excluding Rescue Approach)

(Source: Reviewer generated plot)

Study P006/1015 *(26-Week Multicenter Study with a 26-Week Extension of Ertugliflozin in T2DM Who Have Inadequate Glycemic Control on Metformin and Sitagliptin)***:**

Change From Baseline in HbA1c:

LS mean changes from baseline in HbA1c over time, excluding data after initiation of glycemic rescue therapy, show that in the ertugliflozin groups, reductions from baseline in HbA1c were observed at Week 6 (first scheduled post-randomization assessment) with subsequent further reductions seen at Week 26. Baseline mean HbA1c of 8.03, 8.05 and 8.00 for placebo, ertugliflozin 5 mg and ertugliflozin 15 mg, respectively, was similar among all treatment groups.As was observed in other studies, the reduction in HbA1c was numerically greater in the ertugliflozin 15 mg group than in the ertugliflozin 5 mg group at each time point (Figure 11). In the placebo group, there was essentially no change from baseline in HbA1c through Week 18; thereafter, a small reduction in HbA1c was observed at Week 26.

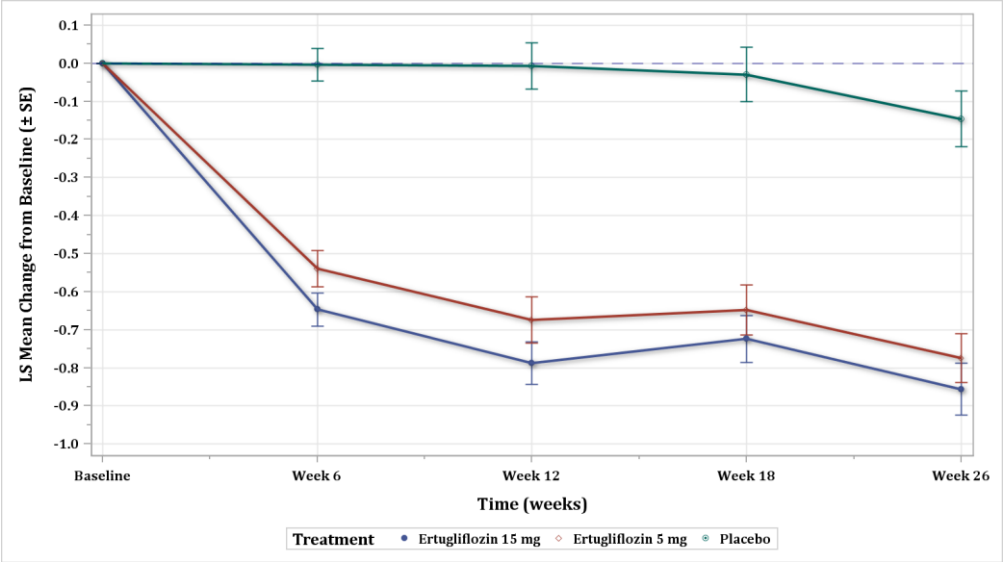


Figure 11 LS Mean Change From Baseline Over Time for HbA1c (Study P006, Full Analysis Set: Excluding Rescue Approach)

(Source: Reviewer generated plot)

Study P001/1016 *(26-Week Multicenter Study with a 26-Week Extension of Ertugliflozin in T2DM Patients with Stage 3 Chronic Kidney Disease Who Have Inadequate Glycemic Control on Background Antihyperglycemic Therapy)*:

Pharmacokinetics:
Trough plasma ertugliflozin concentrations drawn at weeks 6, 12 and 18 showed that steady state was achieved following both 5 mg and 15 mg doses.

Change From Baseline in HbA1c:
LS mean changes from baseline in HbA1c over time, excluding data after initiation of glycemic rescue therapy showed that large reductions in mean HbA1c in the ertugliflozin groups through Week 12 were followed by smaller reductions through Week 26. Baseline mean HbA1c of 8.17, 8.06 and 8.13 for placebo, ertugliflozin 5 mg and ertugliflozin 15 mg, respectively, was similar among all treatment groups. Decreases in HbA1c were seen in both the ertugliflozin 15 mg and 5 mg groups with an apparent nadir at the first measurement (Week 6), followed by stable reductions in HbA1c levels over the remainder of the treatment period. For the placebo group, a modest but progressive decrease was observed through Week 18, with a more notable decrease after Week 18, attenuating the differences between the placebo and ertugliflozin treatment groups at Week 26 (Figure 12).

The safety and efficacy of ertugliflozin have not been established in patients with moderate renal impairment (see clinical review by Dr. Frank Pucino and statistical review by Dr. Alexander Cambon in DARRTS for further details). The glucose-lowering efficacy of ertugliflozin decreased in patients with worsening renal function. Compared to placebo-treated patients, patients with moderate renal impairment treated with ertugliflozin had increased risks for renal impairment, renal-related adverse reactions and volume depletion adverse reactions. Ertugliflozin is contraindicated in patients with severe renal impairment (eGFR below 30 mL/minute/1.73 m^2), end-stage renal disease, or receiving dialysis. Initiation of ertugliflozin in patients with moderate renal impairment (eGFR of 30 to less than 60 mL/minute/1.73 m^2) is not recommended. Use of ertugliflozin in patients whose eGFR later falls persistently between 30 and 60 mL/min/1.73 m^2 is not recommended.

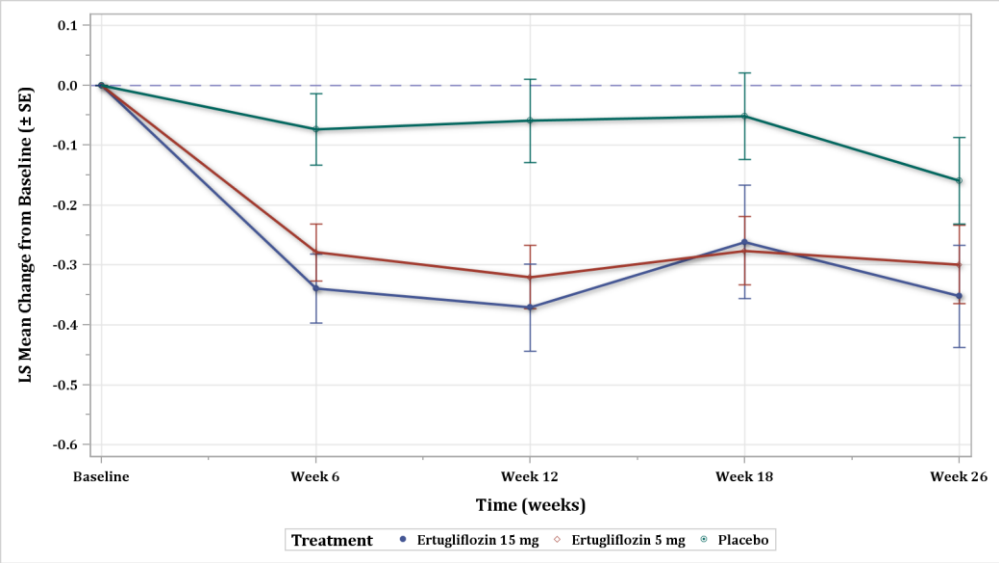


Figure 12 LS Mean Change From Baseline Over Time for HbA1c (Study P001, Full Analysis Set: Excluding Rescue Approach)

(Source: Reviewer generated plot)

3.3.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed general dosing regimen of ertugliflozin 5 mg once daily, taken in the morning, with or without food is appropriate for T2DM patients, based on the assessment of PK, PD, efficacy and safety measurements. In patients tolerating ertugliflozin 5 mg once daily, the dose may be increased to 15 mg once daily if additional glycemic control is needed.

3.3.2.1 Ertugliflozin Dose Selection

Phase 3 Dose Selection

The phase 3 dose selection was primarily based on the dose-response results in HbA1c reduction in T2DM subjects from a 12-week Phase 2 dose-ranging study (Study P016/1006). The summary of the statistical analysis (ANCOVA) of change from baseline in HbA1c at Week 12 (primary efficacy endpoint) is shown in Table 2. The dose-response relationship in change from baseline of HbA1c at Week 12 was described by a maximum effect (E_{max}) model that included dose as a continuous variable (Figure 13).

Table 2: Summary of the Statistical Analysis (ANCOVA) of Change From Baseline in HbA1c at Week 12(Study P016/1006)

	Placebo	Sitagliptin 100 mg QD	Ertugliflozin			
			1 mg QD	5 mg QD	10 mg QD	25 mg QD
Week 12						
N	51	53	54	53	51	50
LSM	-0.11	-0.87	-0.56	-0.80	-0.73	-0.83
80% CI	-0.25, 0.04	-1.01, -0.73	-0.69, -0.42	-0.94, -0.66	-0.87, -0.58	-0.98, -0.69
Difference from placebo						
LSM		-0.76	-0.45	-0.69	-0.62	-0.72
80% CI		-0.97, -0.56	-0.65, -0.25	-0.89, -0.49	-0.82, -0.42	-0.93, -0.52
p-value		0.000	0.002	0.000	0.000	0.000

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; HbA1c=glycosylated hemoglobin A1c; LSM=least squares mean; N=number of subjects; Based on ANCOVA with treatment as fixed effect and baseline as a covariate. Full Analysis Set was based on primary endpoint HbA1c. p-value was one-sided.

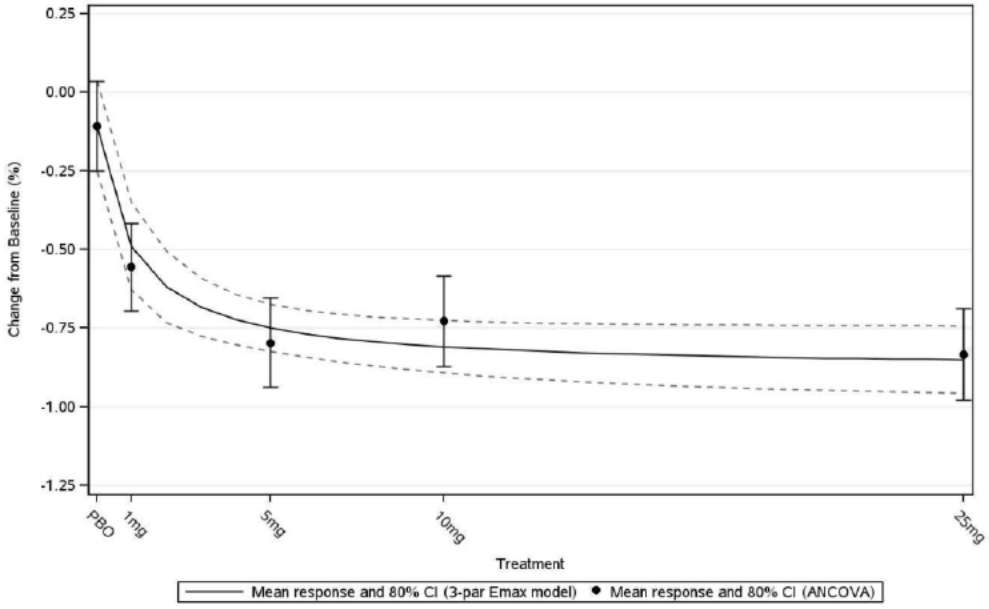


Figure 13 Dose-Response Analysis (3-Parameter E_{max}) of Percent Change From Baseline in HbA1c at Week 12

(Source: Applicant's study report for Study P016/1006, Figure 2)

The phase 3 dose selection was also supported by dose-response relationship of 24-hour UGE, in subjects with T2DM from the 4-week Phase 2 Study P042/1004. See section 3.2.3.2 for details.

Ertugliflozin doses of 5 mg and 15 mg QD were selected for evaluation in the phase 3 studies. Model-predicted responses for key endpoints at ertugliflozin doses of 5 mg and 15 mg are presented in Table 3. At the 5 mg and 15 mg doses, the model-predicted responses were >80% and >90% of the maximum response, respectively.

Table 3 Model-Predicted Placebo-adjusted Change from Baseline Responses for Key Endpoints Based on Phase 2 Studies

Ertugliflozin Dose (mg)	A1C (%) ED_{50}=1.0 mg E_{max}=-0.77%	FPG (mg/dL) ED_{50}=1.1 mg E_{max}=-34.8 mg/dL	Body weight (%) ED_{50}=0.8 mg E_{max}=-2.11%	UGE_{24} (g) ED_{50}=0.75 mg E_{max}=71.5 g
5	-0.64	-28.4	-1.81	62.5
15	-0.72	-32.4	-2.00	68.9

(Source: Applicant's Summary Of Clinical Pharmacology Studies, Table 13)

Therefore, both the 5 mg and 15 mg doses were predicted to provide clinically meaningful efficacy, with the 15 mg dose providing incremental HbA1c lowering compared to the 5 mg dose. Both doses are expected to be safe, because the safety profiles of single oral doses as high as 300 mg, multiple doses of 100 mg QD up to 14 days and 25 mg QD up to 12 weeks were found to be acceptable in the phase 1 and phase 2 studies.

Dose-Response Analyses on HbA1c

The applicant additionally conducted population dose-response analyses on HbA1c based on pooled data from study P016/1006 and four phase 3 studies. The effects of intrinsic (e.g. demographic, baseline HbA1c, renal function), diabetes duration and/or extrinsic (e.g. background treatment, lead-in time) factors were explored. See section 4.3.2 for details.

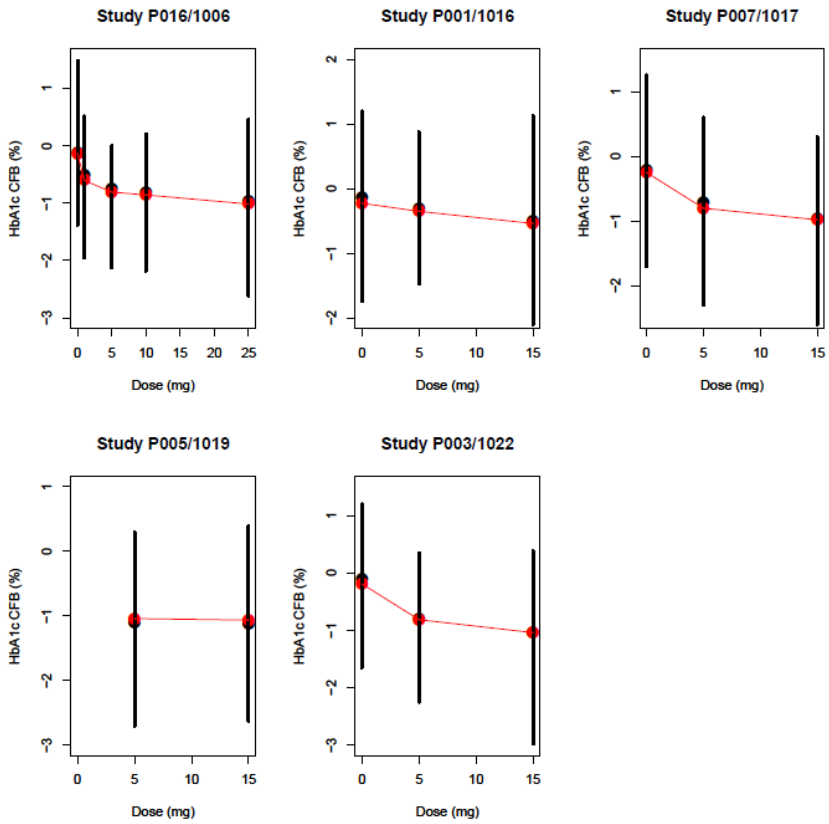
A longitudinal dose-response model was fitted to the data for the primary evaluation of HbA1c lowering effect of ertugliflozin. Based on the final model parameter estimates, the 5 mg and 15 mg doses elicited HbA1c responses (-0.617% and -0.698%, respectively) that were >80% and >90% of the model-estimated Emax (-0.745%) and consistent with the results on the dose-response model using Phase 2 data (Table 3). HbA1c responses for ertugliflozin 5 mg and 15 mg for a representative T2DM patient were predicted based on the final model and are presented in Table 4.

Table 4: Model-Predicted Mean (95% CI) HbA1c Response for Ertugliflozin 5 mg and 15 mg Doses at Week 26 for a Representative T2DM Patient

Response	Mean change from baseline (%) (95% CI)	Mean Placebo-Adjusted change from baseline (%) (95% CI)
Placebo	-0.113 (-0.201, -0.003981)	—
Ertugliflozin 5 mg	-0.788 (-0.855, -0.723)	-0.674 (-0.805, -0.565)
Ertugliflozin 15 mg	-0.849 (-0.905, -0.794)	-0.735 (-0.869, -0.626)

The "representative T2DM patient" for this analysis was defined ased on the demographics of placebo-controlled pool as a 57.3 year old patient, weighing 85 kg, with an eGFR of 88.9 mL/min/1.73 m2, a baseline HbA1c of 8.1%, disease duration of 7.5 years, and on a background treatment of metformin.
(Source: Applicant's Summary Of Clinical Pharmacology Studies, Table 15)

Observed and final model-predicted mean HbA1c response versus ertugliflozin dose by study at week 26 for the longitudinal dose-response final model are shown in Figure 14.



Mean observed (black circle) and estimated (red circle) HbA1c change from baseline (%). Vertical black lines represent associated 5th and 95th quantiles of observed individual patient data for each dose in the respective studies. Estimated HbA1c was generated as the difference between each subject's individual prediction of HbA1c and baseline HbA1c.

Figure 14 Observed and Final Model-Predicted Mean HbA1c Response versus Ertugliflozin Dose by Study at Week 26

(Source: eCTD for NDA 209803, Module 5.3.5.3, CSR for Report PMAR-EQDD-B152a-DP4-407, Figure 3, Page 31)

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

No, based on PopPK analysis, an alternative dose or dosing regimen is not required for subpopulation based on the intrinsic factors such as weight, age, gender, and race. Effect of other intrinsic factors – hepatic impairment, renal impairment, ethnicity and UGT1A9 polymorphism are discussed below.

3.3.3.1 Hepatic Impairment

Total ertugliflozin AUC and C_{max} decreased by approximately 13% and 21%, respectively, in moderate hepatic impairment compared to the normal hepatic function group (Table 5). Approximately 3%-4% of ertugliflozin was unbound in plasma, and there were no meaningful differences in the plasma protein binding of ertugliflozin between the two groups. There was an approximately 4% and 13% decrease in unbound AUC and C_{max}, respectively. This slight decrease in AUC and C_{max} observed in subjects with moderate hepatic impairment was not considered to be clinically relevant. Terminal ertugliflozin $t_{1/2}$ values were similar for the two groups. There was a ~46% higher exposures of the glucuronide metabolite M5c (formed mainly via UGT1A9) in the moderate hepatic group compared to the normal hepatic function group. Metabolite M5a (formed via UGT2B7) exposures followed similar trends as ertugliflozin and was slightly lower in moderate hepatic impairment subjects compared to normal hepatic function

subjects. Ertugliflozin pharmacokinetics were not evaluated in patients with mild hepatic impairment, however, it would be expected that there would be no increase in exposure with mild hepatic impairment.

Table 5 Statistical Summary of Treatment Comparisons for Ertugliflozin Pharmacokinetic Parameters– Moderate Hepatic Impairment Versus Normal Hepatic Function

Parameter (Units)	Adjusted Geometric Means: Moderate Hepatic Impairment (Test)	Adjusted Geometric Means: Normal Hepatic Function (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{inf} (ng•hr/mL)	1430	1636	87.43	(68.11, 112.22)
AUC_{last} (ng•hr/mL)	1413	1618	87.31	(68.01, 112.08)
C_{max} (ng/mL)	251.1	319.0	78.70	(65.74, 94.23)

[a] The ratios (and 90% CIs) are expressed as percentages

(Source: eCTD for NDA 209803, Module 5.3.3.3 CSR for Study P014, Table 12, Page 59)

Distribution and expression of the predominant metabolic pathway UGT1A9 and UGT2B7 in tissues other than the liver, e.g., kidney, probably explains the lack of an increase in ertugliflozin AUC due to moderate hepatic impairment. No dose adjustment is recommended in patients with mild or moderate hepatic impairment. Ertugliflozin PK have not been evaluated in subjects with severe hepatic impairment.

3.3.3.2 Renal Impairment

Ertugliflozin pharmacokinetics were evaluated in a dedicated renal impairment study in mild, moderate and severe renal impairment patients. Ertugliflozin AUC_{inf} was higher in subjects with mild, moderate and severe renal impairment (Figure 15). The mean increases in exposures were less than 2-fold (Figure 16) and are not anticipated to be clinically meaningful. Compared to T2DM subjects with normal renal function, the change from baseline in 24-hour UGE on Day 1 for T2DM subjects with mild, moderate and severe renal impairment decreased with decline in renal function.

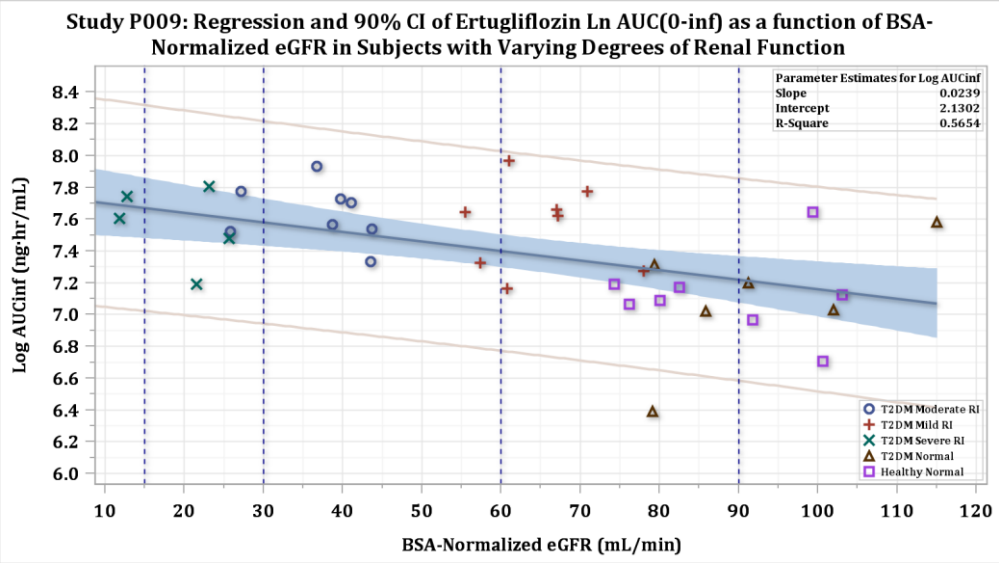


Figure 15 Regression and 90% CI of Ln AUC_{inf} After Oral Administration of Ertugliflozin Versus BSA-Normalized eGFR in Subjects with Varying Degrees of Renal Function

(Source: Reviewer generated plot)

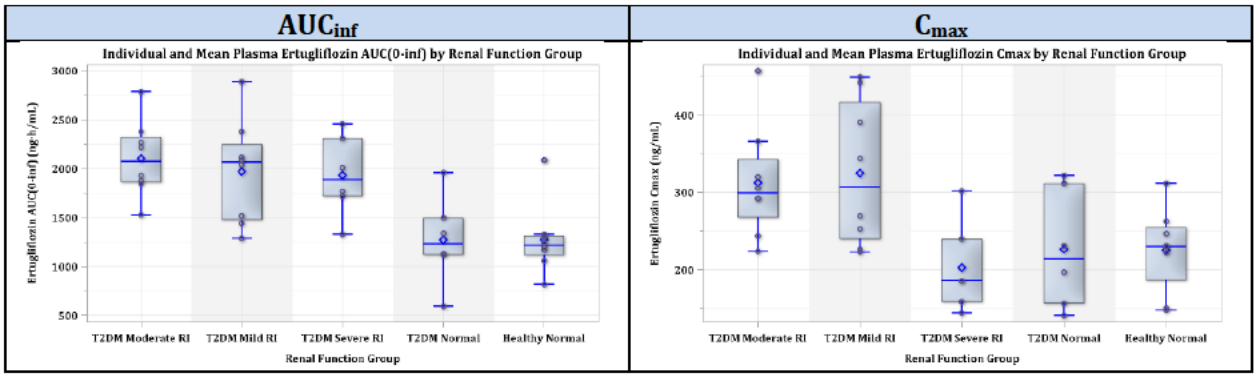


Figure 16 Individual and Geometric Mean Plasma Ertugliflozin AUC_{inf} (Left Panel) and C_{max} (Lower Panel) Values by Renal Function Group

(Source: Reviewer generated plot)

Based on the population PK analysis, ertugliflozin CL/F is reduced with decreasing eGFR. Subjects with an eGFR of 75 mL/min/1.73 m^2 (mild renal impairment) and 45 mL/min/1.73 m^2 (moderate renal impairment) would have 8% and 27% lower CL/F, respectively, relative to a reference subject with an eGFR of 90 mL/min/1.73 m^2. These changes in CL/F translate to an increase in AUC of ~9% and 37%, respectively, and are consistent with the results of the renal impairment study (Table 6). Since the increases in ertugliflozin exposure with renal impairment are ≤1.7-fold, these are not considered clinically relevant and no dosage adjustment is recommended in patients with renal impairment based on PK.

Table 6 Statistical Summary of Treatment Comparisons for Ertugliflozin Pharmacokinetic Parameters

Parameters (Units)	Test[a]	Reference	Adjusted Geometric Mean		Ratio[b] (%)	90% CI (%)
			Test	Reference		
AUC_{inf} (ng•hr/mL)	Healthy normal	T2DM Normal	1236	1199	103.07	(80.32, 132.27)
	Mild	Pooled Normal	1908	1220	156.34	(127.83, 191.23)
	Moderate	Pooled Normal	2075	1220	170.04	(139.02, 207.98)
	Severe	Pooled Normal	1895	1220	155.26	(124.38, 193.80)
AUC_{last} (ng•hr/mL)	Healthy normal	T2DM Normal	1214	1174	103.42	(80.66, 132.61)
	Mild	Pooled Normal	1814	1196	151.63	(124.05, 185.34)
	Moderate	Pooled Normal	2011	1196	168.11	(137.53, 205.49)
	Severe	Pooled Normal	1816	1196	151.80	(121.69, 189.36)
CL/F (mL/min)	Healthy normal	T2DM Normal	202.1	208.8	96.80	(75.41, 124.25)
	Mild	Pooled Normal	130.9	205.0	63.85	(52.19, 78.11)
	Moderate	Pooled Normal	120.4	205.0	58.74	(48.01, 71.86)
	Severe	Pooled Normal	132.0	205.0	64.39	(51.57, 80.40)
C_{max} (ng/mL)	Healthy normal	T2DM Normal	219.3	215.9	101.57	(78.83, 130.87)
	Mild	Pooled Normal	313.1	217.8	143.74	(117.15, 176.37)
	Moderate	Pooled Normal	305.7	217.8	140.37	(114.40, 172.23)
	Severe	Pooled Normal	196.4	217.8	90.18	(71.99, 112.96)
CL_r (mL/min)	Healthy normal	T2DM Normal	1.682	2.092	80.39	(59.41, 108.76)
	Mild	Pooled Normal	0.9872	1.847	53.46	(41.64, 68.63)
	Moderate	Pooled Normal	0.8024	1.847	43.45	(33.85, 55.78)
	Severe	Pooled Normal	0.5360	1.847	29.02	(22.04, 38.21)

[a] Mild, moderate and severe refer to T2DM subjects with corresponding degrees of renal impairment.
[b] The ratios (and 90% CIs) are expressed as percentages
(Source: eCTD for NDA 209803, Module 5.3.3.3 CSR for Study P009, Table 14, Page 79)

Similar to other SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin), a decline in 24-hour UGE was observed with a decrease in renal function despite increased ertugliflozin exposures in subjects with

T2DM (Figure 17). Dose adjustments based on matching exposures are not appropriate for the SGLT2 inhibitor class. Since glycemic efficacy of ertugliflozin depends on the filtered glucose load, ertugliflozin is not recommended for use in patients with eGFR <45 mL/min/1.73m^2.

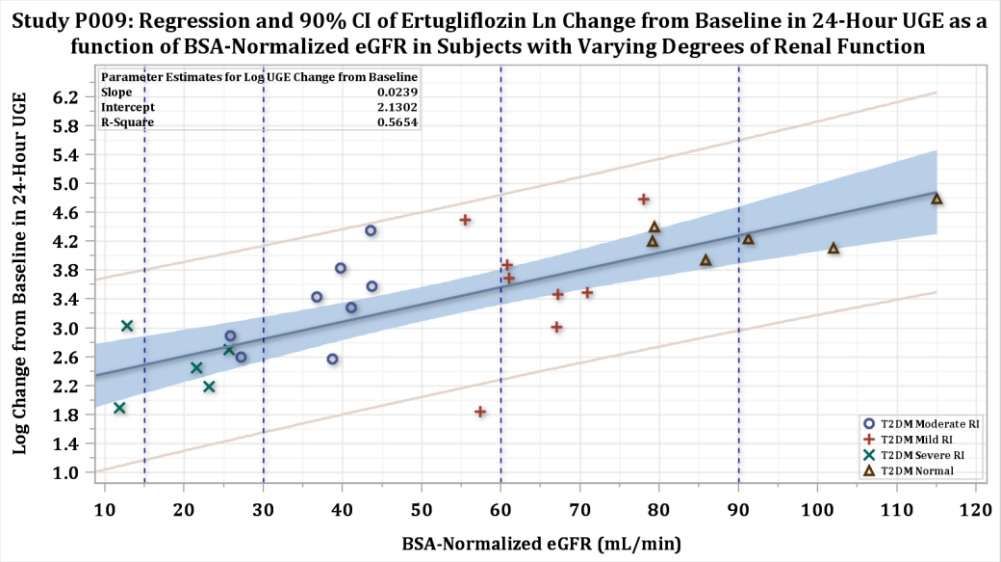


Figure 17 Regression and 90% CI of Ln Change from Baseline in 24-Hour UGE After Oral Administration of Ertugliflozin Versus BSA-Normalized eGFR in Subjects with Varying Degrees of Renal Function

(Source: Reviewer generated plot)

3.3.3.3 Ethnicity

In a study evaluating the PK/PD of ertugliflozin in healthy Japanese and Western subjects, following single dose administration, ertugliflozin C_{max} and AUC_{last} increased with dose in an approximately dose proportional manner in both populations. No meaningful ethnic differences were observed in dose-normalized ertugliflozin C_{max} and AUC_{last} between Japanese and Western healthy subjects through all 3 doses evaluated (Figure 18). The median T_{max} was 1.0 to 1.5 hours under fasting conditions, and 2.5 hours under fed conditions. Following multiple-dose administration, steady-state was reached reached by Day 4. The accumulation ratio of following multiple-dose was 1.11 and the estimated half-life was 9.91 hours.

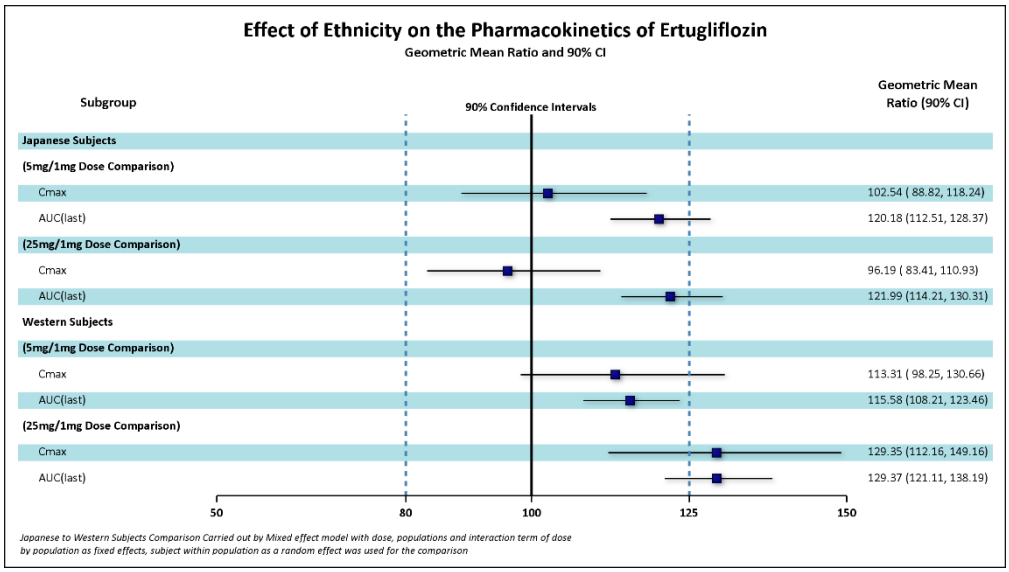


Figure 18 Dose-Normalized Ertugliflozin Exposure Comparison Among Dose Levels by Ethnic Groups

(Source: Reviewer generated plot)

A dose-dependent effect on UGE as well as inhibition of renal glucose reabsorption was observed after administration of ertugliflozin single oral doses to healthy Japanese and Western subjects. There was an overlap of the range of UGE values and inhibition of renal glucose reabsorption between Japanese and Western subjects at equivalent doses suggesting no meaningful ethnic differences in the PD between the 2 populations (Figure 19).

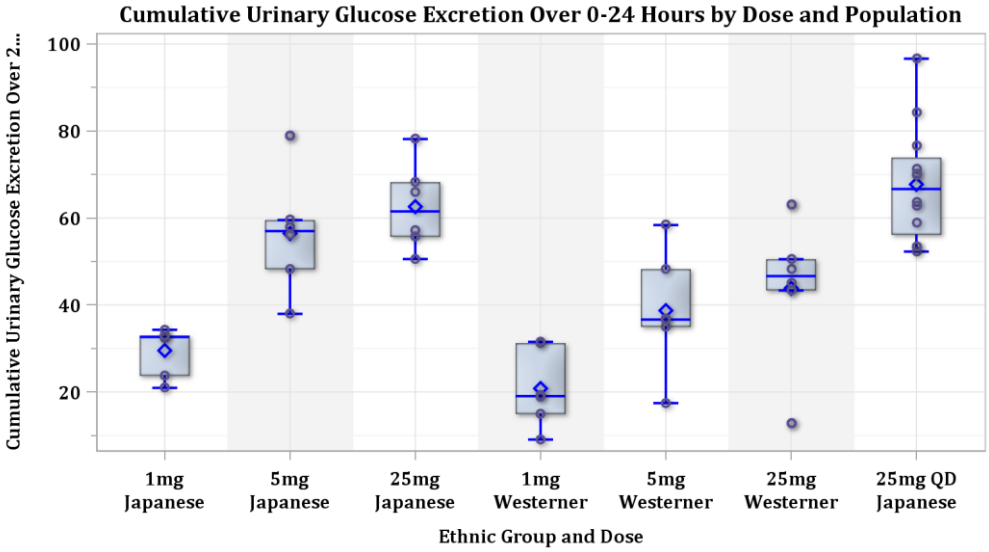


Figure 19 Cumulative Urinary Glucose Excretion Over 0-24 Hours by Dose and Population

(Source: Reviewer generated plot)

3.3.3.4 UGT1A9 polymorphism

Since UGT1A9 is polymorphic, the Sponsor collected genotype data for 3 allelic variants, rs72551330 (UGT1A9*3), rs17868320 (UGT1A9 -2152), and rs3832043 (UGT1A9*22; recently reclassified as UGT1A9 *1b) in 20 Phase 1 studies (11 Phase 1 studies supporting ertugliflozin and 8 BE studies supporting FDC formulations of ertugliflozin with metformin or sitagliptin. A pooled analysis of AUC values from the 20 Phase 1 studies was conducted to evaluate the impact of UGT1A9 genotype on the PK of ertugliflozin. The dataset contained 417 subjects with ertugliflozin AUC values and UGT1A9 genotype information. There were 100 true wild type subjects, 16 heterozygous variants of rs17868320, 31 heterozygous variants of rs72551330, 70 homozygous variants of rs3832043, and 147 heterozygous variants of rs3832043.

The relationship between AUC values (AUC_{inf} after single-dose or AUC_{24} at steady state) and dose was described with the structural model (AUC=Slope*Dose+Intercept) and the 3 UGT1A9 allelic variants were introduced multiplicatively as categorical covariates. The impact of UGT1A9 genotype on ertugliflozin AUC based on the final parameter estimates is shown in Figure 20. Ertugliflozin AUC was not significantly affected by the rs17868320 heterozygous variant or the rs3832043 homozygous variant (95% CI included 1). Ertugliflozin AUC increased by about 10% (95% CI: 3%, 17%) with the rs72551330 heterozygous variant, and decreased by about 6% (95% CI: 1%, 11%) with the rs3832043 heterozygous variant.

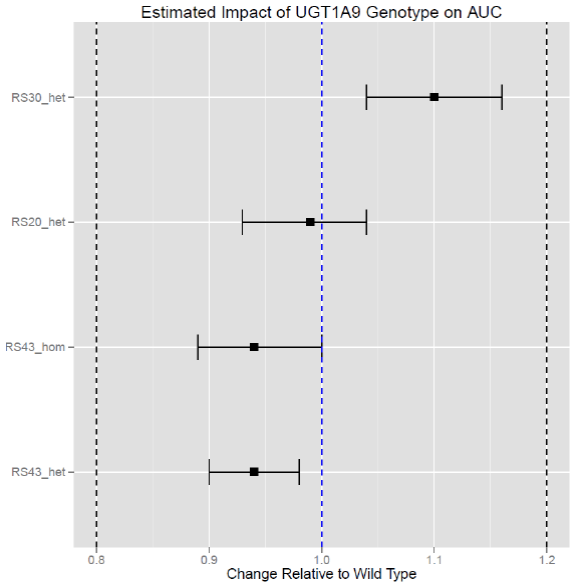


Figure 20 UGT1A9 Genotype Effects on Ertugliflozin AUC

The 90th percentiles of the bootstrap confidence intervals for AUC are provided. Effects are reported relative to the wild type subjects in the analysis. A value of one (1) represents no change. RS30_het = rs72551330 heterozygous variant; RS20_het = rs17868320 heterozygous variant; RS43_hom = rs3832043 homozygous variant; RS43_het = rs3832043 heterozygous variant.
(Source: eCTD for NDA 209803, Module 2.7.2 Summary Of Clinical Pharmacology Studies, Figure 3, Page 67)

Overall, the mean effects of the allelic variants on AUC were within ±10% of the wild type and are not considered clinically relevant.

3.3.4 *Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?*

3.3.4.1 *Food-Drug Interaction*

Compared to fasted conditions, administration of 15 mg ertugliflozin with a high fat meal reduced AUC by about 9%, C_{max} by approximately 29% and delayed median T_{max} by 1 hour (Table 7). There were no meaningful effects on AUC_{inf} (Figure 21). The decrease in ertugliflozin C_{max} with food is not anticipated to be clinically relevant.

Table 7 Statistical Summary of Treatment Comparisons for Plasma Ertugliflozin Pharmacokinetic Parameters Under Fasting and Fed Conditions

Parameter (Units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Ertugliflozin 15 mg Fed (Test)	Ertugliflozin 15 mg Fasted (Reference)		
AUC_{inf} (ng•h/mL)	1210	1320	91.65	(88.01, 95.44)
AUC_{last} (ng•h/mL)	1191	1302	91.51	(87.62, 95.57)
C_{max} (ng/mL)	193.2	273.4	70.65	(61.71, 80.88)

[a] The ratios (and 90% CIs) are expressed as percentages

(Source: eCTD for NDA 209803, Module 5.3.1.1 CSR for Study P024, Table 10, Page 43)

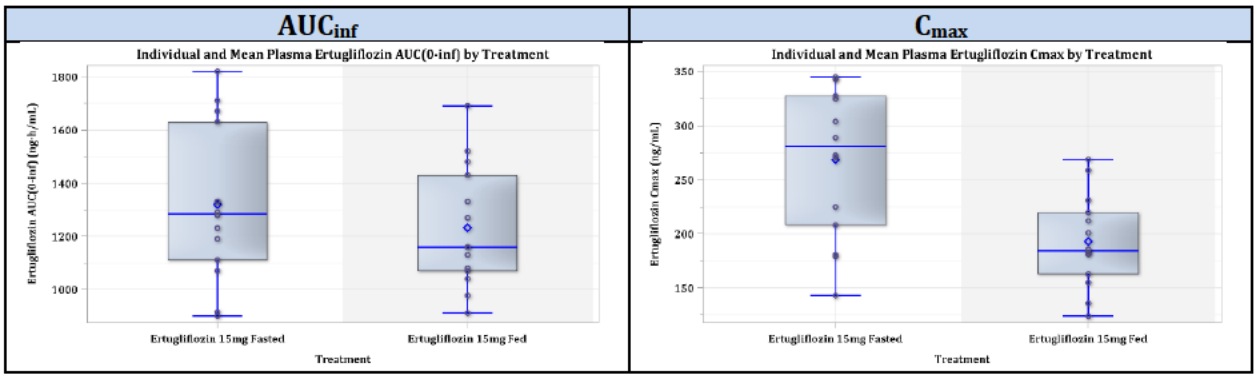


Figure 21 Individual and Geometric Mean Plasma Ertugliflozin AUC_{inf} (Left Panel) and C_{max} (Right Panel) Values by Treatment

(Source: Reviewer generated plot)

Ertugliflozin may be administered without regard to meals.

3.3.4.2 *Drug-Drug Interactions*

Five drug-drug interaction studies were conducted with ertugliflozin, as shown in the table below:

Category	Study Description	Study Number
DDI	Ertugliflozin 15 mg and sitagliptin 100 mg	P022/1033
	Ertugliflozin 15 mg and metformin 1000 mg	P019/1032
	Ertugliflozin 15 mg and glimepiride 1 mg	P032/1044
	Ertugliflozin 15 mg and simvastatin 40 mg	P030/1036
	Ertugliflozin 15 mg and rifampin 600 mg qd x 10 days	P021/1040

3.3.4.2.1 Two-Way Drug-Drug Interaction Between Ertugliflozin 15 mg and Sitagliptin 100 mg

A two-way drug-drug interaction study to evaluate the effect of ertugliflozin on the PK of sitagliptin, and the effect of sitagliptin on the PK of ertugliflozin were evaluated in Study P022.

As shown Table 8, the geometric mean ratios for ertugliflozin AUC_{inf} and C_{max} were 102.27% and 98.18%, respectively, and the corresponding 90% CIs were (99.72%, 104.89%) and (91.20%, 105.70%), indicating that there are no meaningful differences in the PK of ertugliflozin when it is administered with sitagliptin, as compared to oral administration of single dose of ertugliflozin alone (Figure 22).

Table 8 Statistical Summary of Treatment Comparisons for Plasma Ertugliflozin Pharmacokinetic Parameters Following a Single Oral Dose of Ertugliflozin Alone and Co-administered with Sitagliptin

Plasma Ertugliflozin parameter (unit)	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Ertugliflozin 15 mg SD + Sitagliptin 100 mg SD (Test)	Ertugliflozin 15 mg SD (Reference)		
AUC_{inf} (ng·hr/mL)	1445	1413	102.27	(99.72, 104.89)
C_{max} (ng/mL)	258.1	262.9	98.18	(91.20, 105.70)

[a] The ratios (and 90% CIs) are expressed as percentages

(Source: eCTD for NDA 209803, Module 5.3.3.4 CSR for Study P022, Table 11, Page 44)

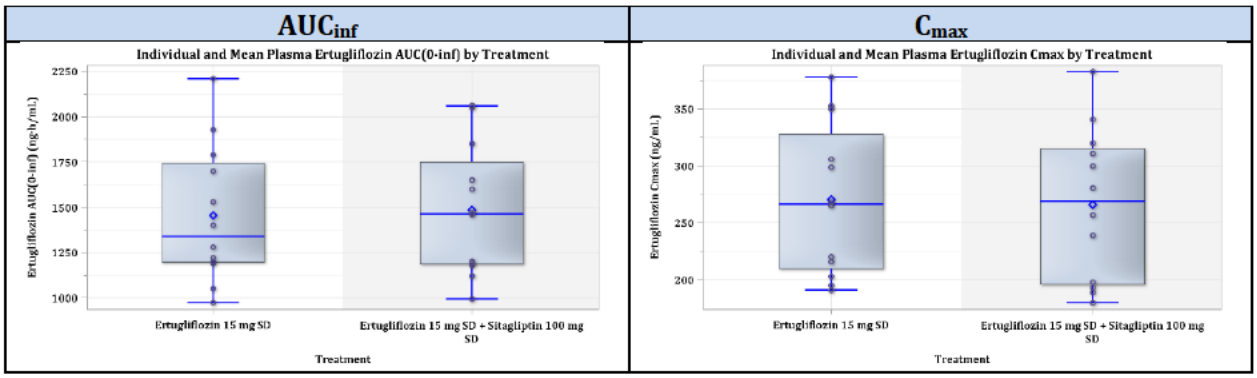


Figure 22 Individual and Geometric Mean Plasma Ertugliflozin AUC_{inf} (Left Panel) and C_{max} (Right Panel) Values Following a Single Oral Dose of Ertugliflozin Alone and Co-administered with Sitagliptin

(Source: Reviewer generated plot)

As shown in Table 9, the geometric mean ratios for sitagliptin AUC_{inf} and C_{max} were 101.67% and 101.68%, respectively, and the corresponding 90% CIs were (98.40%, 105.04%) and (91.65%, 112.80%), indicating that there are no meaningful differences in the PK of sitagliptin when it is administered with ertugliflozin, as compared to oral administration of single dose of sitagliptin alone (Figure 23).

Table 9 Statistical Summary of Treatment Comparisons for Plasma Sitagliptin Pharmacokinetic Parameters Following a Single Oral Dose of Sitagliptin Alone and Co-administered with Ertugliflozin

Plasma Sitagliptin parameter (unit)	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Ertugliflozin 15 mg SD + Sitagliptin 100 mg SD (Test)	Sitagliptin 100 mg SD (Reference)		
AUC_{inf} (uM·hr)	6.997	6.882	101.67	(98.40, 105.04)
C_{max} (nM)	805.3	792.0	101.68	(91.65, 112.80)

[a] The ratios (and 90% CIs) are expressed as percentages

(Source: eCTD for NDA 209803, Module 5.3.3.4 CSR for Study P022, Table 13, Page 49)

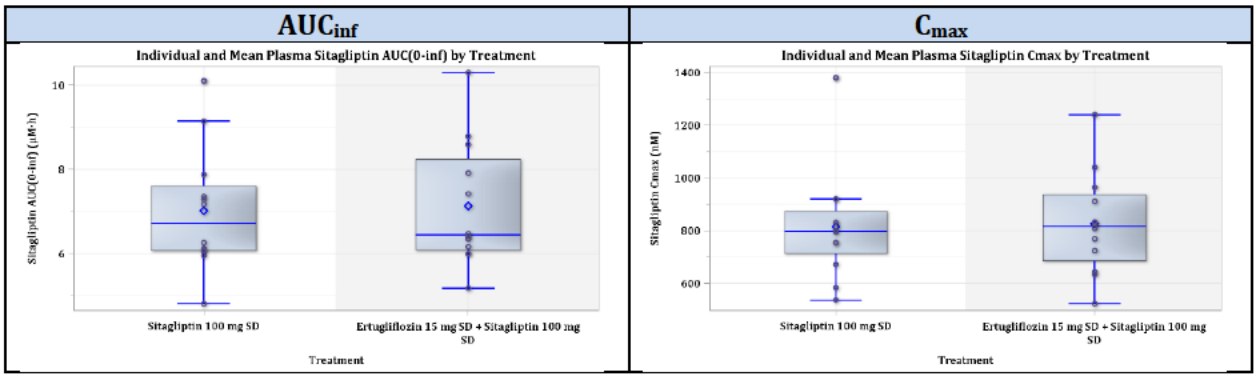


Figure 23 Individual and Geometric Mean Plasma Sitagliptin AUC_{inf} (Left Panel) and C_{max} (Right Panel) Values Following a Single Oral Dose of Sitagliptin Alone and Co-administered with Ertugliflozin

(Source: Reviewer generated plot)

3.3.4.2.2 Two-Way Drug-Drug Interaction Between Ertugliflozin 15 mg and Metformin 1000 mg

A two-way drug-drug interaction study to evaluate the effect of ertugliflozin on the PK of metformin, and the effect of metformin on the PK of ertugliflozin were evaluated in Study P019.

As shown in Table 10, in presence of metformin, the ratios of the adjusted least squares means for ertugliflozin AUC_{inf}, and C_{max} were 100.34% and 97.14%, respectively, and the 90% CIs for the ratios fell entirely within the equivalence limits of (80%, 125%), indicating that there are no clinically meaningful differences in ertugliflozin PK when it is co-administered with metformin, as compared to a single dose of ertugliflozin alone (Figure 24).

Table 10 Statistical Summary of Treatment Comparisons for Plasma Ertugliflozin Pharmacokinetic Parameters Following a Single Oral Dose of Ertugliflozin Alone and Co-administered with Metformin

Parameter (Units)	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Ertugliflozin 15 mg + Metformin 1000 mg (Test)	Ertugliflozin 15 mg (Reference)		
AUC_{inf} (ng.h/mL)	1380	1376	100.34	97.43, 103.34
AUC_{last} (ng.h/mL)	1367	1346	101.52	98.65, 104.48
C_{max} (ng/mL)	264.5	272.3	97.14	88.77, 106.30

[a] The ratios (and 90% CIs) are expressed as percentages

(Source: eCTD for NDA 209803, Module 5.3.3.4 CSR for Study P019, Table 10, Page 43)

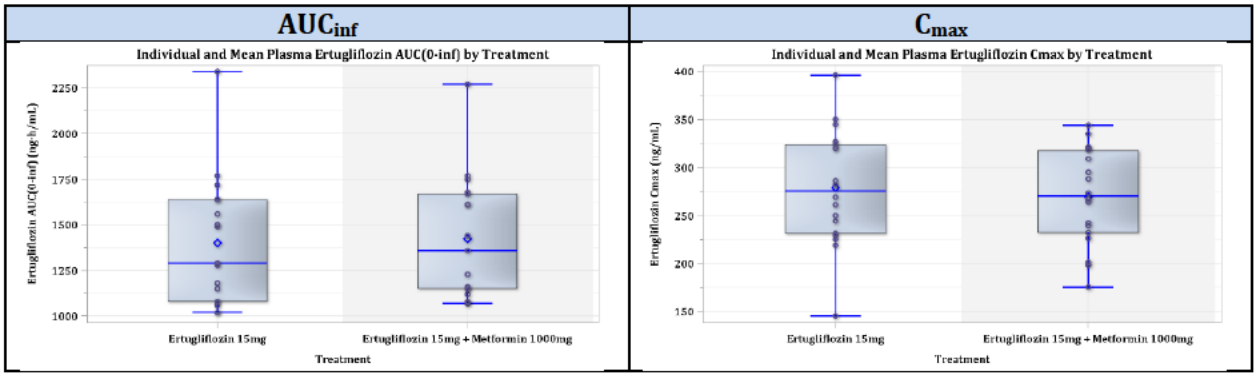


Figure 24 Individual and Geometric Mean Plasma Ertugliflozin AUC_{inf} (Left Panel) and C_{max} (Right Panel) Values Following a Single Oral Dose of Ertugliflozin Alone and Co-administered with Metformin

(Source: Reviewer generated plot)

As shown in Table 11, in presence of ertugliflozin, the ratios of the adjusted least squares means for metformin AUC_{inf} and C_{max} were 100.94% and 94.00%, respectively, and the 90% CIs for the ratios fell entirely within the equivalence limits of (80%, 125%), indicating that there are no clinically meaningful differences in metformin PK when it is co-administered with ertugliflozin, as compared to a single dose of metformin alone (Figure 25).

Table 11 Statistical Summary of Treatment Comparisons for Plasma Sitagliptin Pharmacokinetic Parameters Following a Single Oral Dose of Sitagliptin Alone and Co-administered with Ertugliflozin

Parameter (Units)	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Ertugliflozin 15 mg + Metformin 1000 mg (Test)	Metformin 1000 mg (Reference)		
Data excluded due to vomiting[b]				
AUC_{inf} (ng.h/mL)	12490	12370	100.94	90.62, 112.44
AUC_{last} (ng.h/mL)	12270	12560	97.75	89.46, 106.82
C_{max} (ng/mL)	1835	1952	94.00	82.94, 106.55
All Data Included				
AUC_{inf} (ng.h/mL)	12490	12370	100.94	90.62, 112.44
AUC_{last} (ng.h/mL)	12270	12550	97.81	89.99, 106.31
C_{max} (ng/mL)	1835	1983	92.52	81.99, 104.39

[a] The ratios (and 90% CIs) are expressed as percentages
[b] Metformin 1000 mg treatment data for Subject 10011018 has been excluded due to vomiting. Only AUC_{last} and C_{max} are affected since AUC_{inf} was not reportable for this subject and treatment.
(Source: eCTD for NDA 209803, Module 5.3.3.4 CSR for Study P019, Table 12, Page 48)

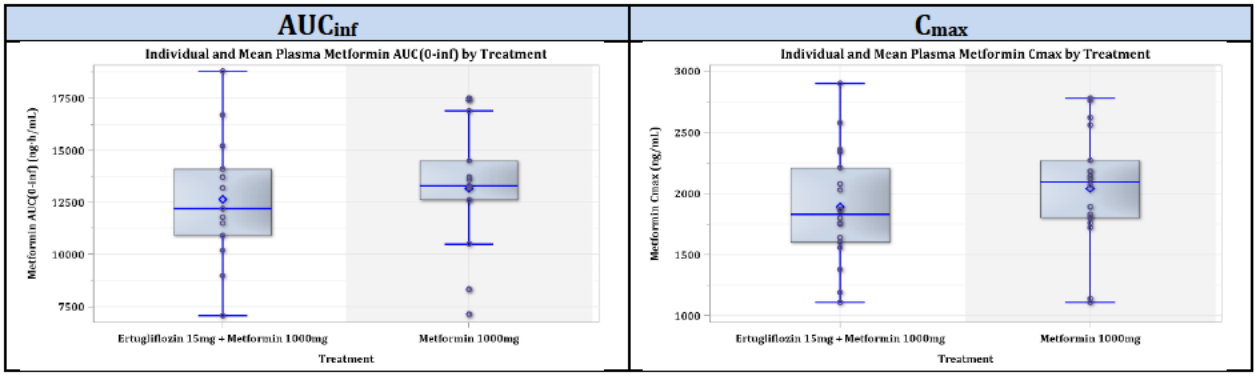


Figure 25 Individual and Geometric Mean Plasma Metformin AUC_{inf} (Left Panel) and C_{max} (Right Panel) Values Following a Single Oral Dose of Metformin Alone and Co-administered with Ertugliflozin

(Source: Reviewer generated plot)

3.3.4.2.3 Two-Way Drug-Drug Interaction Between Ertugliflozin 15 mg and Glimepiride 1 mg

A two-way drug-drug interaction study to evaluate the effect of ertugliflozin on the PK of glimepiride, and the effect of glimepiride on the PK of ertugliflozin were evaluated in Study P032.

As shown in Table 12, co-administration of ertugliflozin with single doses of glimepiride did not affect ertugliflozin AUC_{inf} and C_{max}, as reflected by the ratio of adjusted least squares geometric means (Test/Reference) of 102.11% and 98.20% for AUC_{inf} and C_{max}, respectively. The 90% CI for the ratio of adjusted means was (97.19%, 107.27%) for AUC_{inf} and (92.17%, 104.63%) for C_{max}, indicating that there were no differences in ertugliflozin PK when it was administered with glimepiride as compared to the oral administration of ertugliflozin alone (Figure 26).

Table 12 Statistical Summary of Treatment Comparisons for Plasma Ertugliflozin Pharmacokinetic Parameters Following a Single Oral Dose of Ertugliflozin Alone and Co-administered with Glimepiride

Parameter (units)	Adjusted Geometric Means: Ertugliflozin 15 mg + Glimepiride 1 mg (Test)	Adjusted Geometric Means: Ertugliflozin 15 mg (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{inf} (ng•hr/mL)	1256	1231	102.11	(97.19, 107.27)
C_{max} (ng/mL)	141.5	144.1	98.20	(92.17, 104.63)
AUC_{last} (ng•hr/mL)	1240	1216	101.96	(97.25, 106.90)

[a] The ratios (and 90% CIs) are expressed as percentages

(Source: eCTD for NDA 209803, Module 5.3.3.4 CSR for Study P032, Table 11, Page 48)

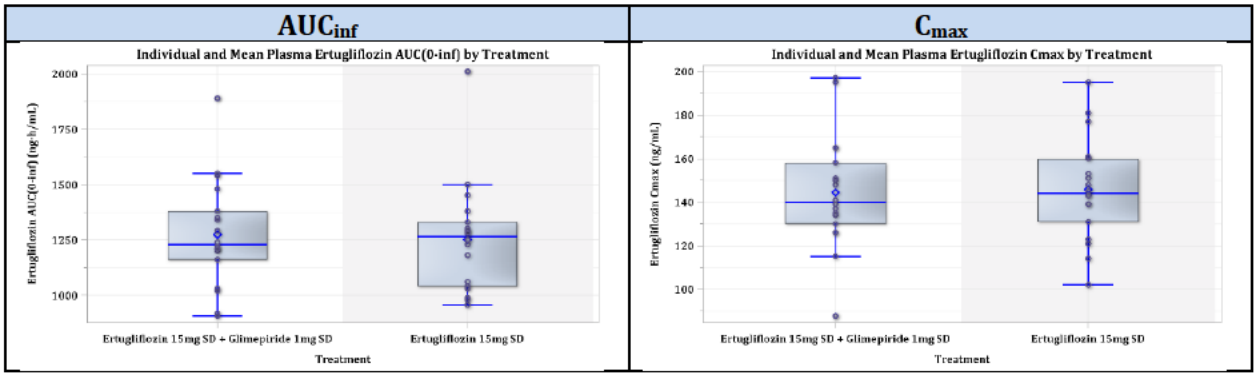


Figure 26 Individual and Geometric Mean Plasma Ertugliflozin AUC_{inf} (Left Panel) and C_{max} (Right Panel) Values Following a Single Oral Dose of Ertugliflozin Alone and Co-administered with Glimepiride

(Source: Reviewer generated plot)

As shown in Table 13, in presence of ertugliflozin, the ratio of the adjusted geometric means (Test/Reference) of glimepiride AUC_{inf}, and C_{max} (90% CI) were 109.80% (98.14%, 122.86%), and 97.39% (71.07%, 133.46%), respectively, relative to glimepiride administered alone. The ratio of the adjusted geometric means for AUC_{inf} and C_{max} indicated that these parameters were comparable for both treatments (Figure 27).

Table 13 Statistical Summary of Treatment Comparisons for Plasma Glimepiride Pharmacokinetic Parameters Following a Single Oral Dose of Glimepiride Alone and Co-administered with Ertugliflozin

Parameter (units)	Adjusted Geometric Means: Ertugliflozin 15 mg + Glimepiride 1 mg (Test)	Adjusted Geometric Means: Glimepiride 1 mg (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{inf} (ng•hr/mL)	217.9	198.5	109.80	(98.14, 122.86)
AUC_{last} (ng•hr/mL)	222.2	174.4	127.40	(108.33, 149.83)
C_{max} (ng/mL)	28.65	29.42	97.39	(71.07, 133.46)

[a] The ratios (and 90% CIs) are expressed as percentages

(Source: eCTD for NDA 209803, Module 5.3.3.4 CSR for Study P032, Table 13, Page 54)

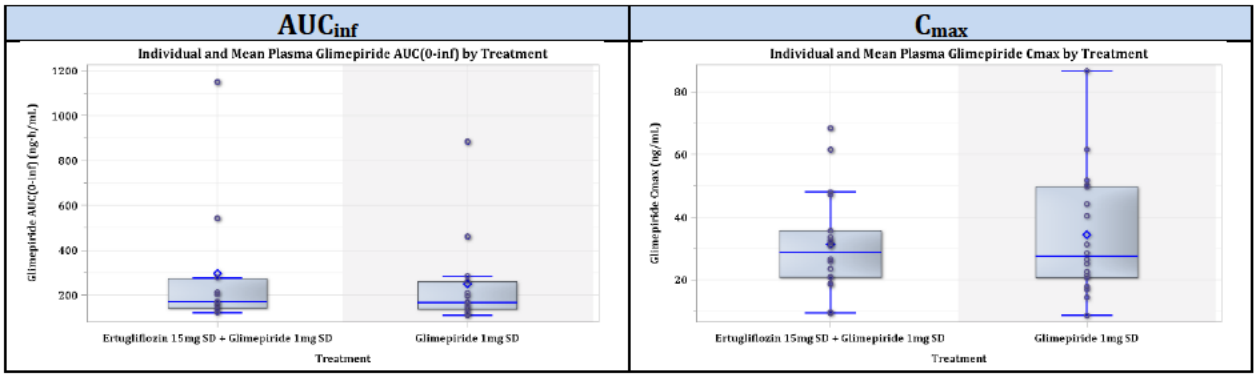


Figure 27 Individual and Geometric Mean Plasma Glimepiride AUC_{inf} (Left Panel) and C_{max} (Right Panel) Values Following a Single Oral Dose of Glimepiride Alone and Co-administered with Ertugliflozin

(Source: Reviewer generated plot)

Collectively, these results indicate that there were no meaningful differences in glimepiride PK when it was administered with ertugliflozin as compared to the oral administration of glimepiride alone. The inter-subject variability for glimepiride exposure was high with %CV values ranging between 66%-78% and 52%-64% for geometric mean AUC_{inf} and C_{max}, respectively.

3.3.4.2.4 Two-Way Drug-Drug Interaction Between Ertugliflozin 15 mg and Simvastatin 40 mg

A two-way drug-drug interaction study to evaluate the effect of ertugliflozin on the PK of simvastatin, and the effect of simvastatin on the PK of ertugliflozin were evaluated in Study P030.

As shown in Table 14, co-administration of ertugliflozin with a single dose of simvastatin did not affect ertugliflozin exposure, as reflected by the ratios of adjusted least squares geometric means (Test/Reference) of 102.40% and 105.16% for AUC_{inf} and C_{max}, respectively. The 90% CIs for the ratios were (99.57%, 105.31%) for AUC_{inf} and (98.26%, 112.54%) for C_{max}, and both fell wholly within the equivalence bounds (80%, 125%) (Figure 28).

Table 14 Statistical Summary of Treatment Comparisons for Plasma Ertugliflozin Pharmacokinetic Parameters Following a Single Oral Dose of Ertugliflozin Alone and Co-administered with Simvastatin

	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
Parameter (units)	Ertugliflozin 15 mg + Simvastatin 40 mg (Test)	Ertugliflozin 15 mg (Reference)		
AUC_{inf} (ng•hr/mL)	1404	1371	102.40	99.57, 105.31
AUC_{last} (ng•hr/mL)	1378	1348	102.26	99.58, 105.01
C_{max} (ng/mL)	280.8	267.0	105.16	98.26, 112.54

[a] The ratios (and 90% CIs) are expressed as percentages

(Source: eCTD for NDA 209803, Module 5.3.3.4 CSR for Study P030, Table 11, Page 46)

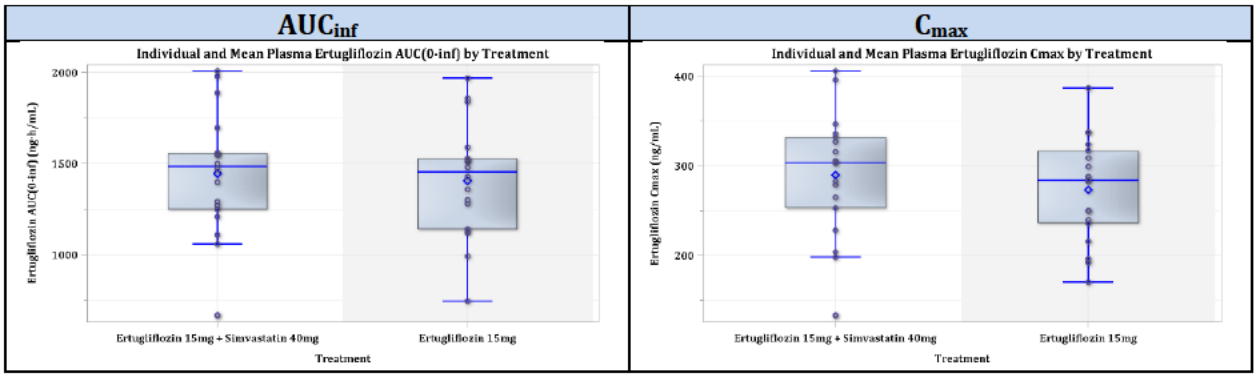


Figure 28 Individual and Geometric Mean Plasma Ertugliflozin AUC_{inf} (Left Panel) and C_{max} (Right Panel) Values Following a Single Oral Dose of Ertugliflozin Alone and Co-administered with Simvastatin

(Source: Reviewer generated plot)

As shown in Table 15, co -administration of simvastatin with a single dose of ertugliflozin increased simvastatin AUC_{inf} by approximately 24% and C_{max} by approximately 19%, as reflected by the ratios of adjusted least squares geometric means (Test/Reference) of 123.83% for AUC_{inf} and 119.05% for C_{max}. The 90% CIs for the ratios were (90.92%, 168.66%) for AUC_{inf} and (97.22%, 145.77%) for C_{max} (Figure 29). The increases in simvastatin AUC_{inf} and C_{max} when co-administered with ertugliflozin are not expected to be clinically relevant.

Table 15 Statistical Summary of Treatment Comparisons for Plasma Simvastatin Pharmacokinetic Parameters Following a Single Oral Dose of Simvastatin Alone and Co-administered with Ertugliflozin

	Adjusted (Least-Squares) Geometric Means			
Parameter (units)	Ertugliflozin 15 mg + Simvastatin 40 mg (Test)	Simvastatin 40 mg (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{inf} (ng•hr/mL)	46.88	37.86	123.83	90.92, 168.66
AUC_{last} (ng•hr/mL)	45.11	36.28	124.32	101.56, 152.17
C_{max} (ng/mL)	9.421	7.914	119.05	97.22, 145.77

[a] The ratios (and 90% CIs) are expressed as percentages

(Source: eCTD for NDA 209803, Module 5.3.3.4 CSR for Study P030, Table 13, Page 51)

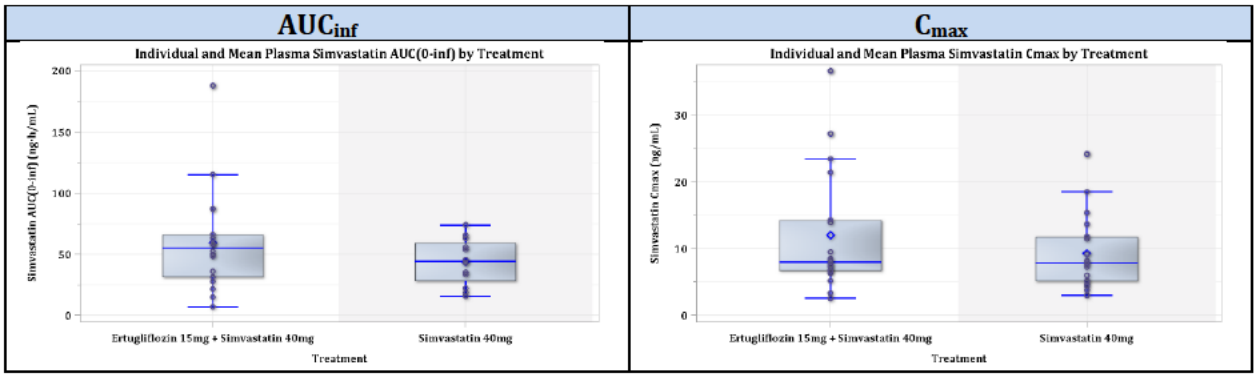


Figure 29 Individual and Geometric Mean Plasma Simvastatin AUC_{inf} (Left Panel) and C_{max} (Right Panel) Values Following a Single Oral Dose of Simvastatin Alone and Co-administered with Ertugliflozin

(Source: Reviewer generated plot)

Co-administration of simvastatin with a single dose of ertugliflozin increased simvastatin acid AUC_{inf} by approximately 30% and C_{max} by approximately 16%, as reflected by the ratios of adjusted least squares geometric means (Test/Reference) of 130.46% for AUC_{inf} and 115.66% for C_{max} (Table 16). The 90% CI for the ratios were (108.32%, 157.13%) for AUC_{inf} and (95.74%, 139.71%) for C_{max} (Figure 30). The increases in simvastatin acid AUC_{inf} and C_{max} are not expected to be clinically relevant.

Table 16 Statistical Summary of Treatment Comparisons for Plasma Simvastatin Acid Pharmacokinetic Parameters Following a Single Oral Dose of Simvastatin Alone and Co-administered with Ertugliflozin

	Adjusted (Least-Squares) Geometric Means			
Parameter (units)	Ertugliflozin 15 mg + Simvastatin 40 mg (Test)	Simvastatin 40 mg (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{inf} (ng•hr/mL)	29.84	22.87	130.46	108.32, 157.13
AUC_{last} (ng•hr/mL)	29.47	23.03	127.99	111.87, 146.44
C_{max} (ng/mL)	2.085	1.803	115.66	95.74, 139.71

[a] The ratios (and 90% CIs) are expressed as percentages

(Source: eCTD for NDA 209803, Module 5.3.3.4 CSR for Study P030, Table 15, Page 56)

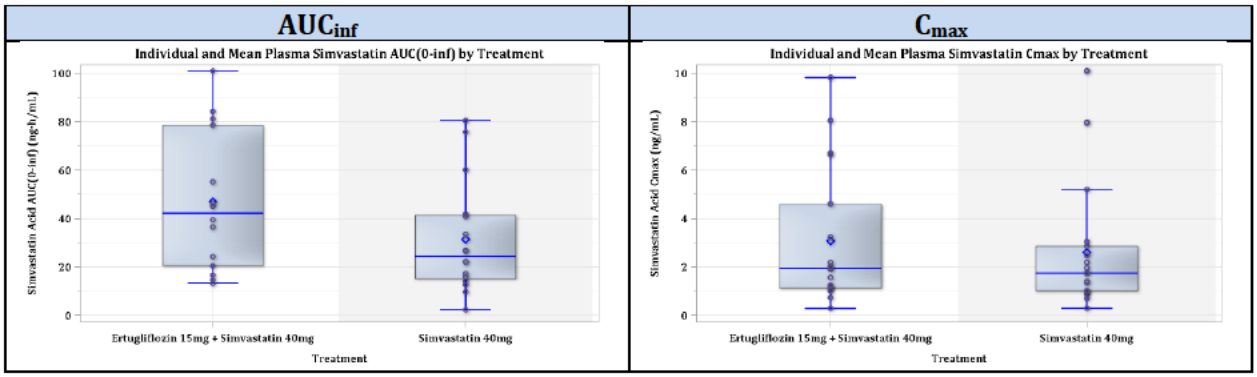


Figure 30 Individual and Geometric Mean Plasma Simvastatin Acid AUC_{inf} (Left Panel) and C_{max} (Right Panel) Values Following a Single Oral Dose of Simvastatin Alone and Co-administered with Ertugliflozin

(Source: Reviewer generated plot)

3.3.4.2.5 Effect of Multiple Dose Rifampin 600 mg on the PK of Ertugliflozin15 mg

A one-way drug-drug interaction study to evaluate the effect of multiple doses of rifampin on the PK of a single-dose of ertugliflozin were evaluated in Study P021.

As shown in Table 17, co-administration of a single-dose of ertugliflozin with multiple-dose rifampin, resulted in reductions in plasma ertugliflozin AUC_{inf} and C_{max} of 39% and 15%, respectively, the ratio of adjusted least squares geometric means (90% CI) for ertugliflozin AUC_{inf} and C_{max} being 61.16% (57.22%, 65.37%) and 84.62% (74.17%, 96.53%), respectively (Figure 31). The median T_{max} of 1 hour, and was unchanged for both treatments.

Table 17 Statistical Summary of Treatment Comparisons for Plasma Ertugliflozin Pharmacokinetic Parameters Following a Single Oral Dose of Ertugliflozin Alone and Co-administered with Simvastatin

Plasma Ertugliflozin parameter (unit)	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Mean[a]	90% CI for Ratio
	Ertugliflozin 15 mg SD (Reference)	Rifampin 600 mg QD + Ertugliflozin 15 mg SD (Test)		
AUC_{inf} (ng•hr/mL)	1370	838.1	61.16	(57.22, 65.37)
C_{max} (ng/mL)	236.1	199.8	84.62	(74.17, 96.53)

[a] The ratios (and 90% CIs) are expressed as percentages

(Source: eCTD for NDA 209803, Module 5.3.3.4 CSR for Study P021, Table 12, Page 41)

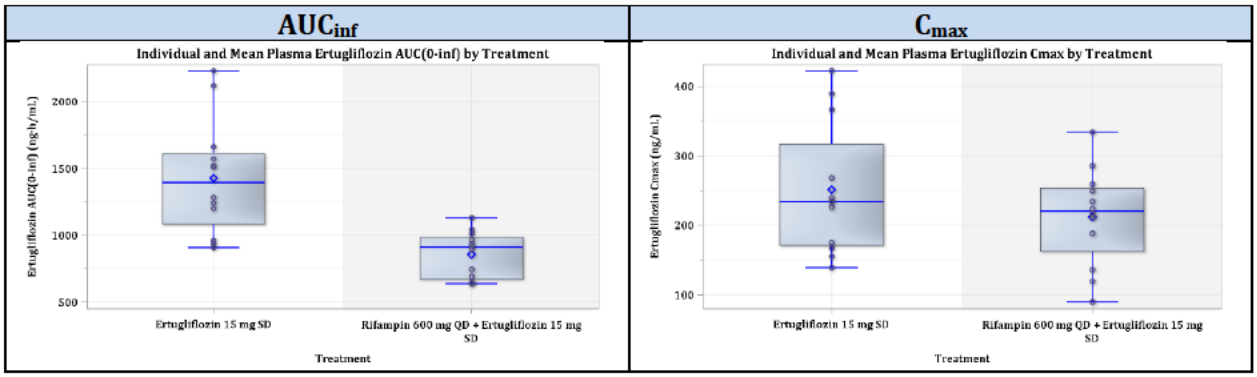


Figure 31 Individual and Geometric Mean Plasma Ertugliflozin AUC_{inf} (Left Panel) and C_{max} (Right Panel) Values Following a Single Oral Dose of Ertugliflozin Alone and Co-administered with Multiple Doses of Rifampin

(Source: Reviewer generated plot)

Mean terminal t½ was 12.3 hours for ertugliflozin administered alone compared to 9.2 hours for ertugliflozin co-administered with rifampin.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

In the Phase 3 trials, the 15 mg dose of ertugliflozin was administered as one 10 mg tablet and one 5 mg tablet (b) (4). Following the development of a 15 mg commercial image (the to-be-marketed formulation), the Sponsor conducted a bioequivalence study (P023/1037) to demonstrate bioequivalence, under fasted conditions, of the 15 mg commercial image tablet of ertugliflozin to the ertugliflozin 15 mg dose used in Phase 3 studies (administered as one 10 mg tablet + one 5 mg tablet) to support the registration of ertugliflozin.

Mean plasma ertugliflozin concentrations following the 15 mg commercial image tablet and ertugliflozin 15 mg dose used in Phase 3 studies (administered as one 10 mg tablet + one 5 mg tablet) is shown in Figure 32. The plasma curves are virtually superimposable.

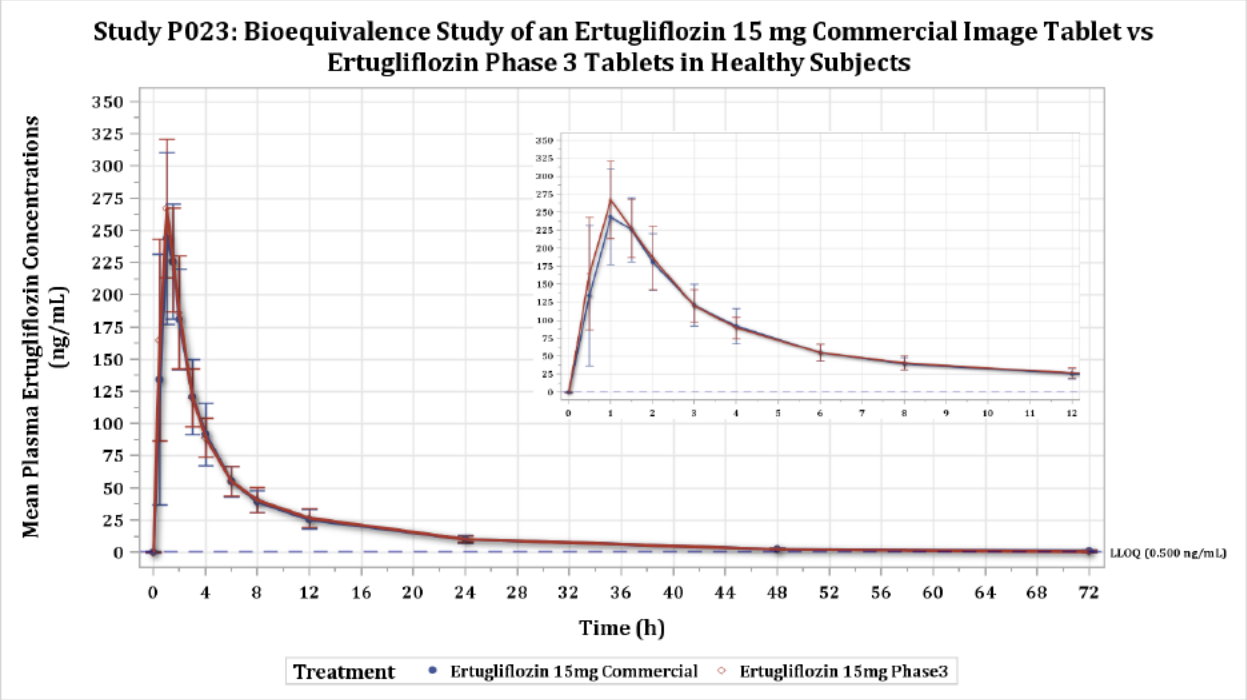


Figure 32 **Mean (±SD) Plasma Ertugliflozin Concentrations Following Administration of 15 mg Phase 3 Formulation and 15 mg Commercial image Formulation (inset shows profile up to 12 hours)**

The geometric mean C_{max}, AUC_{inf} and AUC_{last} were similar. Median T_{max} was 1 hour for both treatments. Results of the statistical comparison show that the 90% CIs for the least squares means ratios fell wholly within the (80%, 125%) acceptance range for bioequivalence (Table 18).

The analysis conducted by this reviewer agreed with the Applicant's findings.

Table 18 **Statistical Summary of Treatment Comparisons for Plasma Ertugliflozin Pharmacokinetic Parameters**

Treatment	PK Parameter	N	Geometric means (C.I.)	Ratio (90% C.I.)
Ertugliflozin 15mg Commercial	$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	16	1334 (1218, 1462)	0.96 (0.93, 1.00)
Ertugliflozin 15mg Phase3	$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	16	1388 (1266, 1520)	
Ertugliflozin 15mg Commercial	$AUC_{(0\text{-}t)}$ (ng.hr/mL)	16	1308 (1194, 1432)	0.96 (0.93, 1.00)
Ertugliflozin 15mg Phase3	$AUC_{(0\text{-}t)}$ (ng.hr/mL)	16	1358 (1239, 1487)	
Ertugliflozin 15mg Commercial	C_{max} (ng/mL)	16	262 (237, 290)	0.96 (0.86, 1.08)
Ertugliflozin 15mg Phase3	C_{max} (ng/mL)	16	272 (246, 302)	
T = Ertugliflozin 15 mg (Commercial) R = Ertugliflozin 15 mg (Phase 3)				

(Source: Analysis performed by Reviewer)

Individual and mean AUC_{inf} and C_{max} plotted by treatment are shown in Figure 33.

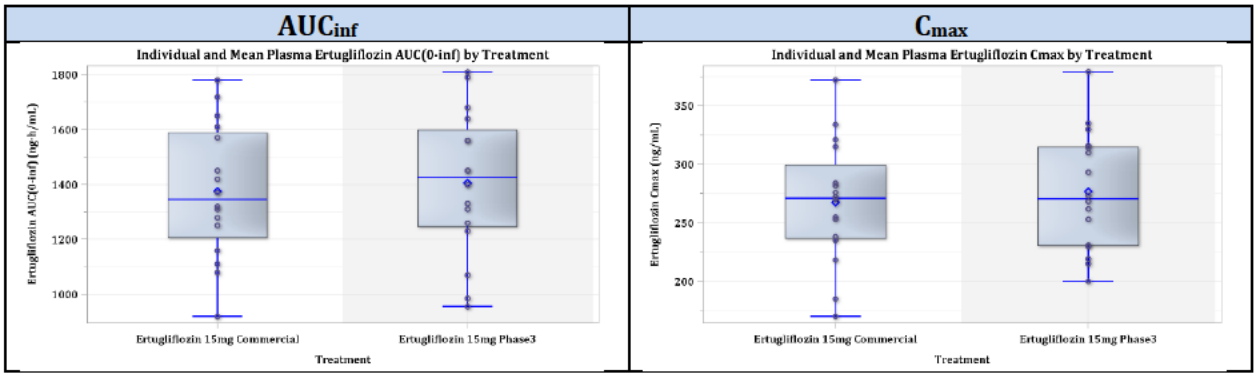


Figure 33 Individual and Geometric Mean Plasma Ertugliflozin AUC_{inf} (Left Panel) and C_{max} (Right Panel) Values Following 15 mg Phase 3 Formulation and 15 mg Commercial image Formulation

The data indicated that ertugliflozin 15 mg commercial image tablet was successfully bridged to the ertugliflozin Phase 3, 15 mg dose (administered as one 10 mg tablet + one 5 mg tablet).

A request to inspect the clinical facility was sent to the Office of Study Integrity and Surveillance (OSIS). In a memo dated 16 February 2017 (see memo from Shila S, Nkah in DARRTS, document ID 4057167), OSIS recommended accepting the study data without an on-site inspection. The rationale for this decision was that OSIS had recently inspected the site, and the inspectional outcome from the inspection was classified as No Action Indicated (NAI).

4. APPENDICES

Tabular Listing of Phase 1 studies Providing Clinical Pharmacology Data

Phase 1 Studies		
Category	**Study Description**	**Study Number**
PK/PD/Safety	Single escalating oral dose, including initial assessment of food effect	P036/1001[a]
	Multiple escalating dose	P037/1002[a]
	[^{14}C]ADME study	P038/1003
	qd vs bid regimen after single day dose in T2DM subjects; 1 mg bid vs 2 mg qd, 2 mg bid vs 4 mg qd	P040/1007[a]
	qd vs bid regimen at steady state in healthy subjects; 2.5 mg bid vs 5 mg qd, 7.5 mg bid vs 15 mg qd	P035/1051[a]
	Thorough QT study	P010/1025
Biopharmaceutics[b]	Absolute BA	P020/1043
	BE between Phase 3 and commercial tablet	P023/1037
	Food effect of commercial tablet	P024/1048
	Relative BA of amorphous form vs cocrystal	P011/1034
	Relative BA of MR vs IR tablets[c]	P039/1005
Special Population	Single escalating dose and multiple dose study in Japanese vs Western subjects	P041/1009[a]
	PK in moderate hepatic impairment	P014/1024
	PK and PD in mild, moderate and severe renal impairment	P009/1023[a]
DDI	Ertugliflozin 15 mg and sitagliptin 100 mg	P022/1033
	Ertugliflozin 15 mg and metformin 1000 mg	P019/1032
	Ertugliflozin 15 mg and glimepiride 1 mg	P032/1044
	Ertugliflozin 15 mg and simvastatin 40 mg	P030/1036
	Ertugliflozin 15 mg and rifampin 600 mg qd x 10 days	P021/1040

In addition, population PK analysis was conducted from data obtained from 9 Phase 1 studies (Studies P036/1001, P037/1002, P040/1007, P041/1009, P009/1023, P010/1025, P024/1048, P035/1051), 2 Phase 2 studies with sparse PK sampling (Studies P042/1004, P016/1006), and 4 Phase 3 studies with sparse PK sampling (Studies P001/1016, P007/1017, P005/1019, P003/1022).

4.1 Appendix - Summary of Bioanalytical Method Validation

4.1.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

Ertugliflozin concentrations in human plasma and human urine were detected by specific and sensitive bioanalytical assays using liquid chromatography with tandem mass spectrometry detection (LC-MS/MS). Several of these methods were also used to simultaneously determine concentrations of ertugliflozin metabolites (glucuronide PF-06685948 [M5a], glucuronide PF-06481944 [M5c], and oxidative metabolite PF-05217539. Validation of a quantitative method for the HPLC and AMS analysis of [^{14}C] ertugliflozin in human plasma (K_2EDTA) was also performed. Assays were validated at (b) (4) and (b) (4) for the LC-MS/MS assays and at (b) (4) for the HPLC and accelerator mass spectrometry (AMS) analysis. All assays were validated in accordance to appropriate regulatory guidances. A summary of each of the method used is presented in Table 4.1.1-1.

Table 4.1.1-1: Summary of Ertugliflozin Validated Analytical Methods

Method Validation Report	Laboratory	Compound	LLOQ (ng/mL)	Linear Range (ng/mL)	Matrix
B1529001	(b) (4)	Ertugliflozin	0.100	0.100-50.0	Plasma
B1529002		Ertugliflozin	0.100	0.100-50.0	Urine
B1529003		Ertugliflozin	0.500	0.500-250	Plasma
		PF-05217539	0.100	0.100-50.0	
B1529004[b]		Ertugliflozin	0.500	0.500-250	Plasma
		PF-05217539	0.100	0.100-50.0	
B1529005		Ertugliflozin	0.500	0.500-500	Plasma
		PF-06685948	0.250	0.250-125	
		PF-06481944	0.500	0.500-250	
B1529006		Ertugliflozin	0.500	0.500-250	Urine
		PF-06685948	1.00	1.00-500	
		PF-06481944	1.00	1.00-500	
B1529007		Ertugliflozin	0.250	0.250-250	Plasma Dialysate
B1529008		Ertugliflozin	0.500	0.500-500	Plasma
B1529101		^{14}C Ertugliflozin	0.0204	0.0204-0.563	Plasma

(Source: eCTD for NDA 209803, Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 5, Page 18)

4.1.2 What was the performance of bioanalytical methods?

The analytical methods were found to be selective, sensitive, precise, and accurate for the determination of ertugliflozin in human plasma andin human urine. The effective analytical ranges were as follows:

The between run precision of the assay, as determined by the percent coefficient of variation were as follows:

Performance details of the assays with the corresponding studies where the assay was utilized, are presented in Table 4.1.2-1.

Table 4.1.2-1: Bioanalytical Methods Summary

Clinical Study	Method	Compounds Analyzed	Matrix	Inter-run Accuracy %RE[a]	Inter-run Precision %CV[a]
P036/1001	B1529001	Ertugliflozin	Plasma	-1.0% to 4.8%	≤9.2%
P036/1001	B1529002	Ertugliflozin	Urine	-17.4% to 0.3%	≤17.1%
P037/1002	B1529003	Ertugliflozin PF-05217539	Plasma	1.5% to 8.5% 0.0% to 5.0%	≤5.1% ≤7.7%
P038/1003[b]	B1529004	Ertugliflozin	Plasma	-6.4% to -0.5%	≤5.5%
P042/1004[b]	B1529004	Ertugliflozin	Plasma	-5.6% to 1.3%	≤5.0%
P039/1005[b]	B1529004	Ertugliflozin	Plasma	-2.0% to 2.0%	≤3.5%
P016/1006[b]	B1529004	Ertugliflozin	Plasma	-1.6% to 2.7%	≤5.1%
P040/1007[b]	B1529004	Ertugliflozin	Plasma	-2.7% to 0.0%	≤8.1%
P041/1009[b]	B1529004	Ertugliflozin	Plasma	-3.2% to 0.7%	≤6.1%
P009/1023	B1529005	Ertugliflozin PF-06685948 (M5a) PF-06481944 (M5c)	Plasma	-2.4% to 3.2% -1.4% to 1.3% 0.5% to 4.0%	≤6.8% ≤7.6% ≤7.2%
P009/1023	B1529006	Ertugliflozin PF-06685948 (M5a) PF-06481944 (M5c)	Urine	-3.5% to 2.0% -4.0% to 3.6% -0.5% to 5.5%	≤9.8% ≤8.0% ≤8.5%
P009/1023	B1529007	Ertugliflozin	Plasma dialysate	-0.8% to 3.7%	≤7.7%
P014/1024	B1529005	Ertugliflozin PF-06685948 (M5a) PF-06481944 (M5c)	Plasma	2.8% to 7.2% 1.3% to 11.5% 0.0% to 5.6%	≤3.8% ≤7.3% ≤5.9%
P014/1024	B1529006	Ertugliflozin PF-06685948 (M5a) PF-06481944 (M5c)	Urine	-3.2% to 0.0% -2.0% to 2.0% -7.5% to 0.8%	≤6.2% ≤4.0% ≤10.4%
P014/1024	B1529007	Ertugliflozin	Plasma dialysate	0.0% to 6.2%	≤3.0%
P010/1025	B1529008	Ertugliflozin	Plasma	-2.5% to 1.6%	≤5.5%
P019/1032	B1529008	Ertugliflozin	Plasma	-4.0% to 2.8%	≤4.4%
P022/1033	B1529008	Ertugliflozin	Plasma	-2.0% to 2.4%	≤5.0%
P011/1034	B1529008	Ertugliflozin	Plasma	-4.3% to 2.4%	≤3.6%
P030/1036	B1529008	Ertugliflozin	Plasma	0.0% to 3.2%	≤3.6%
P023/1037	B1529008	Ertugliflozin	Plasma	-0.8% to 3.6%	≤2.7%
P021/1040	B1529008	Ertugliflozin	Plasma	-1.5% to 2.4%	≤2.9%
P020/1043[c]	B1529008	Ertugliflozin	Plasma	-1.6% to 2.8%	≤4.7%
P020/1043[c]	B1529101	^{14}C Ertugliflozin	Plasma	-12.5% to -4.2%	≤7.4%
P032/1044	B1529008	Ertugliflozin	Plasma	-4.8% to 2.5%	≤4.8%
P024/1048	B1529008	Ertugliflozin	Plasma	-1.6% to 3.2%	≤4.3%
P035/1051	B1529008	Ertugliflozin	Plasma	-1.5% to 2.4%	≤5.2%
P001/1016	B1529008	Ertugliflozin	Plasma	-1.8% to 4.0	≤8.6%
P005/1019	B1529008	Ertugliflozin	Plasma	-4.8% to -0.4%	≤4.8%
P007/1017	B1529008	Ertugliflozin	Plasma	-2.8% to 2.0%	≤10.5%
P003/1022	B1529008	Ertugliflozin	Plasma	-1.5% to 1.6%	≤4.6%

%CV=percent coefficient of variation; %RE=percent relative error; ISR=incurred sample reproducibility; QC=quality control; SOPs=standard operating procedures.

[a] Statistics (%RE and %CV) based on mean assay performance of low, mid-low, mid-high, high and dilution (if applicable) QC samples from all analytical batches meeting acceptance criteria.

[b] Metabolite PF-05217539 was not quantified in this study.

[c] This study also measured the total 14C in urine using accelerator mass spectrometry by (b) (4) following (b) (4) standard operating procedures. No specific method validation performed.

(Source: eCTD for NDA 209803, Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 6, pp 19-20)

The parameters and validation metrics used for the LC-MS/MS assay are presented in Table 4.1.2-2.

Table 4.1.2-2: Parameters and Validation Metrics for LC-MS/MS Assay (No. B1529008)

Assay Conditions	
Sample Storage Temperature	Pooled QC Samples: -20°C
Extraction Method	Protein Precipitation
Detection Method	HPLC-MS/MS
Sample Aliquot Volume	100 µL
Regression Weighting	Linear, $1/conc^2$
Quantification	Peak Area Ratios
Calibration Range	0.500 to 500 ng/mL
ULOQ	500 ng/mL
LLOQ	0.500 ng/mL
Validation (VQC) Sample Concentrations	0.500, 1.25, 12.5, 250, 400, and 2500 (VS-DIL) ng/mL
Assay Performance	
Intra-assay Validation (VQC) Sample Statistics	
Precision (%CV)	<3.3%
Accuracy (%RE)	-5.6% to -1.6%
Recovery	
Mean Analyte Recovery	87.0%
Mean Internal Standard Recovery	84.6%
Selectivity	
Matrix	10 out of 10 Human K_2EDTA Plasma Lots Passed
Ionization Effects	10 out of 10 Normal Human K_2EDTA Plasma Lots Passed 2 out of 2 Hyperlipidemic Human K_2EDTA Plasma lots passed 2 out of 2 Hemolyzed Human K_2EDTA Plasma lots passed 20 out of 20 Patient Population Plasma lots passed
Analyte Carryover	≤4.8%
Internal Standard Carryover	≤0.0%
Batch Size	The maximum batch size investigated within this validation was 176 injections conducted in Run 7
Stability	
Primary Stock Solution	21 hours at room temperature (25°C) 97 days at -20°C Refer to validation Study B1529005 [Ref. 5.3.1.4: 04GRQV]
High Working Solution	25.9 hours at room temperature (25°C) 92 days at -20
Low Working Solution	25.9 hours at room temperature (25°C) 92 days at -20°C
Ambient Matrix Stability	27 hours at 25°C in human K_2EDTA plasma
Frozen Storage Matrix Stability Established at Validation	753 days at -20°C and -70°C
Freeze/Thaw Matrix Stability	5 Cycles at -20°C and -70°C in human K_2EDTA Plasma
Extract Stability	115.5 hours at 4°C in human K_2EDTA plasma
Re-injection Reproducibility Stability	104.1 hours at 4°C in human K_2EDTA plasma
Whole Blood Stability	Stable after 3 hours at room temperature (25°C) followed by centrifugation at both 4°C and ambient conditions

(Source: eCTD for NDA 209803, Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 7, pp 20-21)

A 510K-approved enzymatic assay for urine glucose validated on the Roche Cobas 6000 analyzer was used to measure urine glucose as a PD endpoint in Study P035/1051 (QD *versus* BID dosing of ertugliflozin). Tables 4.1.2-3 and 4.1.2-4 provide the summary of validated analytical method for urinary glucose measurements, and summary of the performance of the urinary glucose method for assay of clinical study samples.

Table 4.1.2-3: Urine Glucose Analytical Methods

Method Validation Report	Laboratory	Analyte	LLOQ (mg/dL)	Range (mg/dL)	Matrix
B1528003	(b) (4)	Glucose	2.00	2.00-717.4	Urine

Abbreviations: LLOQ=lower limit of quantification, (b) (4)
(Source: eCTD for NDA 209803, Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 8, page 22)

Table 4.1.2-4: Urine Glucose Method Used to Support Clinical Study Together with Study Assay Performance

Clinical Study	Method	Analytes Analyzed	Matrix	Inter-run Accuracy %RE[a]	Inter-run Precision %CV[a]
P035/1051	B1528003	Glucose	Urine	-9.0% to -6.7%	≤1.0%

Abbreviations: %CV=percent coefficient of variation; %RE=percent relative error.
[a] Statistics (%RE and %CV) based on mean assay performance of low, mid, and high quality control samples from all analytical batches meeting acceptance criteria.
(Source: eCTD for NDA 209803, Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 9, page 23)

The parameters and validation metrics used for the urine glucose assay are presented in Table 4.1.2-5.

Table 4.1.2-5: Parameters and Validation Metrics for Urine Glucose Assay (No. B1528003)

Assay Conditions	
Sample Storage Temperature	Pooled QC Samples: -20°C
Extraction Method	None
Detection Method	Coupled Enzymatic Assay
Sample Aliquot Volume	2.0 µL per replicate
Regression Weighting	2-point calibration: Factory installed by vendor
Quantification	Absorbance at 340 n.m.
Calibration Range	2.0 to 717.4 mg/dL
ULOQ	717.4 mg/dL
LLOQ	2.0 mg/dL
Validation (VQC) Sample Concentrations	2.0, 5.0, 10.1, 20.6, 54.9, 126.8, 528.3, 686.7, 717.4 and 2,500 (VS-DIL with 4-fold dilution) mg/dL
Assay Performance	
Intra-assay Validation (VQC) Sample Statistics	
Precision (%CV)	≤1.4%
Accuracy (%RE)	-1.1% to 1.4%
Recovery	
Analyte Recovery	99.9 to 104.3%
Selectivity	
Matrix	10 out of 10 Human Urine Lots Passed
Stability	
Primary Stock Solution	NA; vendor supplies lyophilized Calibrator 2 (c.f.a.s.) which can be stored refrigerated for up to 24 hours.
High Working Solution	NA; vendor supplies lyophilized Calibrator 2 (c.f.a.s.) which can be stored refrigerated for up to 24 hours.
Low Working Solution	NA; vendor supplies lyophilized Calibrator 2 (c.f.a.s.) which can be stored refrigerated for up to 24 hours.
Ambient Matrix Stability	24 hours at Room Temperature in human urine
Frozen Storage Matrix Stability Established at Validation	126 days at -20°C and -70°C
Freeze/Thaw Matrix Stability	5 Cycles at -20°C and -70°C in human urine
Refrigerated Storage Matrix Stability	24 hours at 2-8°C in human urine

Abbreviations: %CV=percent coefficient of variation; %RE=percent relative error; c f.a.s=calibrator for automated systems; LLOQ=lower limit of quantification; NA=not applicable; QC=quality control; ULOQ=upper limit of quantification; VQC=validation quality control; VS-DIL=validation sample – dilution QC.
(Source: eCTD for NDA 209803, Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 10, page 23)

4.2 Appendix – Individual Study Review

(Based on sponsor's Summary of Clinical Pharmacology, Summary of Biopharmaceutics and Associated Bioanalytical Methods, and Review of Individual Study Reports)

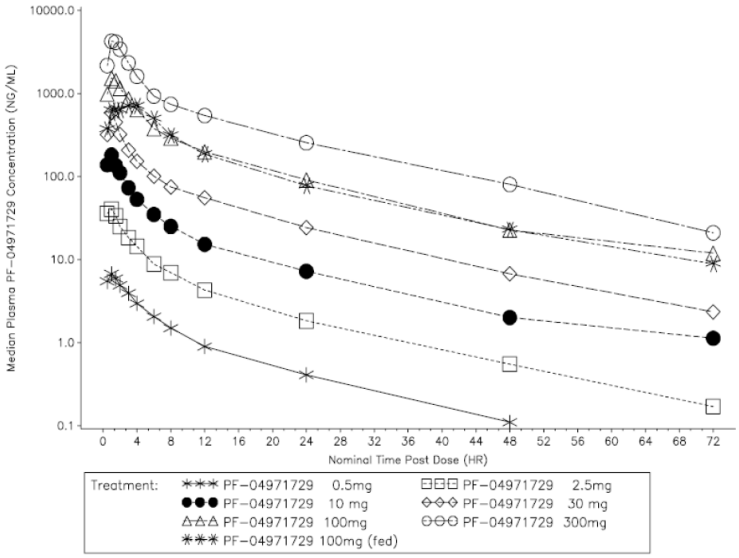
4.2.1 Study P036/1001 - Safety, Tolerability and PK of Single Escalating Oral Doses of Ertugliflozin

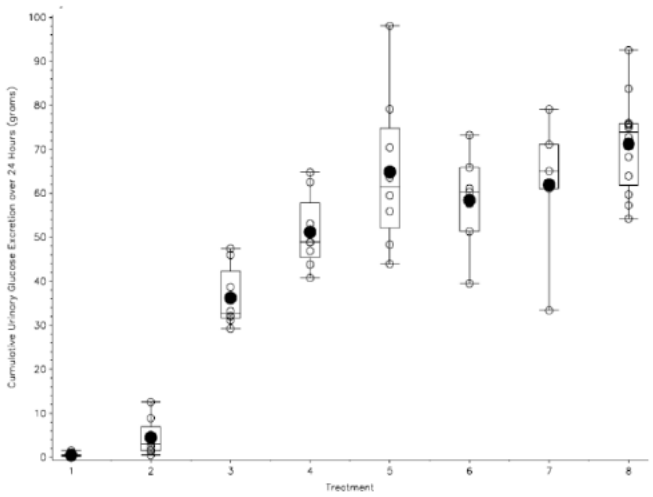
Study:	**P036/1001**
Study Title:	*A Phase 1 Placebo-Controlled Study to Assess the Safety, Tolerability and Pharmacokinetics of PF-04971729 After Administration of Single Escalating Oral Doses Under Fed and Fasted Conditions in Healthy Volunteers*
Objectives:	• To characterize the PK of ertugliflozin following single oral doses in healthy subjects. • To characterize the UGE, renal reabsorption inhibition, and serum glucose profiles resulting from single oral doses of ertugliflozin in healthy subjects. • To estimate the effect of food on ertugliflozin PKparameters.
Study Design:	Investigator- and subject-blinded (sponsor open), randomized, placebo-controlled, ascending single oral dose, 2-cohort, interleaving design, with placebo substitution, crossover study
Study Population:	Population: Healthy male subjects; Mean age (range): 34.5 (20-49) years; n = 24
Results:	See table below

Treatment Route of Administration (ROA) Dose/Dosage Form	Mean PK Parameters[a]					
	AUC_{tau} (ng•hr/mL)	AUC_{inf} (ng•hr/mL)	AUC_{last} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
Treatment: Single-dose, fed ROA: PO Dose/Dosage form: 100 mg ertugliflozin (suspension)	NA	8230 (16)	8010 (16)	824 (33)	3.5 (0.5-6.0)	15.8 (21)
Treatment: Single-dose, fasted ROA: PO Dose/Dosage form:						
0.5 mg ertugliflozin (solution)	NA	45.7 (10)	43.0 (12)	7.23 (11)	1.0 (0.5-1.5)	11.4 (19)
2.5 mg ertugliflozin (solution)	NA	231 (22)	227 (21)	42.8 (21)	1.0 (0.5-1.1)	13.1 (24)
10 mg ertugliflozin (suspension)	NA	909 (15)	880 (16)	182 (22)	1.0 (0.5-1.5)	17.4 (42)
30 mg ertugliflozin (suspension)	NA	2810 (18)	2740 (19)	545 (24)	1.0 (0.5-1.5)	15.2 (33)
100 mg ertugliflozin (suspension)	NA	9610 (16)	9330 (16)	1620 (16)	1.0 (0.5-1.5)	16.2 (36)
300 mg ertugliflozin (suspension)	NA	26400 (16)	25900 (16)	4330 (20)	1.0 (0.5-1.5)	13.8 (18)
Statistical Comparison: Ratio (100 mg Fed/100 mg fasting) (90% CI)[b]						
	NA	81.70 (77.09-86.59)	81.84 (78.30-85.53)	46.37 (38.82-55.39)	NA	NA

Treatment Route of Administration (ROA) Dose/Dosage Form	24-Hour UGE (g)[a]
Placebo	0.4 (0.1-1.5)
Treatment: Single-dose, fed ROA: PO Dose/Dosage form: 100 mg ertugliflozin (suspension)	73.9 (54.3-92.5)
Treatment: Single-dose, fasted ROA: PO Dose/Dosage form:	
0.5 mg ertugliflozin (solution)	3.0 (0.5-12.6)
2.5 mg ertugliflozin (solution)	32.7 (29.2-47.4)
10 mg ertugliflozin (suspension)	48.9 (40.8-64.7)
30 mg ertugliflozin (suspension)	61.5 (44-98.1)
100 mg ertugliflozin (suspension)	60.3 (39.6-73.2)
300 mg ertugliflozin (suspension)	65.1 (33.4-79.1)

Median Plasma PF-04971729 Concentration-Time Profile Following Single Oral Doses (Semi-logarithmic Plot)



	Box and Whisker Plot of UGE Over 0-24 Hours  Source: Figure 14.4.2 Abbreviation: UGE = urinary glucose excretion 1 = placebo, 2 = 0.5 mg PF-04971729, 3 = 2.5 mg PF-04971729, 4 = 10 mg PF-04971729, 5 = 30 mg PF-04971729, 6 = 100 mg PF-04971729, 7 = 300 mg PF-04971729, 8 = 100 mg PF-04971729 (fed) Open circles identify individual subject data. Closed circles identify means. Box plot provides median and 25% and 75% quartiles with whiskers extended to the minimum/maximum values.
Conclusions:	***Pharmacokinetics/Pharmacodynamics:*** Ertugliflozin exposure (plasma AUCinf and Cmax) increased proportionally with increasing dose following PO administration of single-doses (0.5 mg to 300 mg), with renal excretion accounting for a very small fraction of total elimination. Single PO doses of ertugliflozin in healthy subjects induced glucosuria with the amount of glucosuria being dose-dependent. Maximal UGE was observed with single PO doses of ertugliflozin ≥30 mg. The PK characteristics of ertugliflozin together with its PD characteristic of maintaining sustained glucosuria over the 0-24 hour interval supports a once daily dosing regimen. Food extended the Tmax but had little effect on the AUC of ertugliflozin indicating that the drug can be administered with or without food. ***Safety:*** Single PO doses of ertugliflozin up to 300 mg (the maximum dose studied) were found to be safe and well-tolerated in healthy subjects.

Reviewer's Comments:
The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the pharmacokinetic and pharmacodynamic effect (urinary glucose excretion) of ertugliflozin.

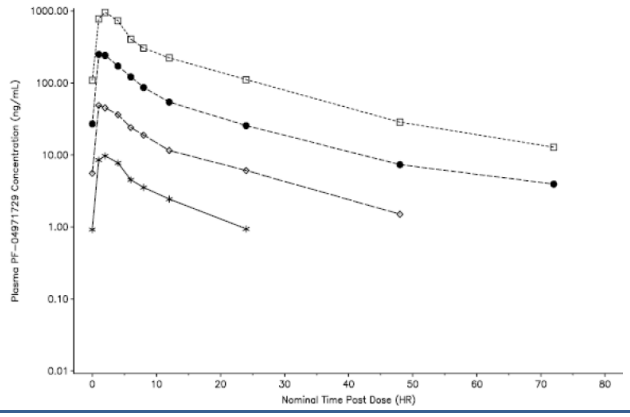
4.2.2 Study P037/1002 - Safety, Tolerability and PK of Repeated Doses of Ertugliflozin

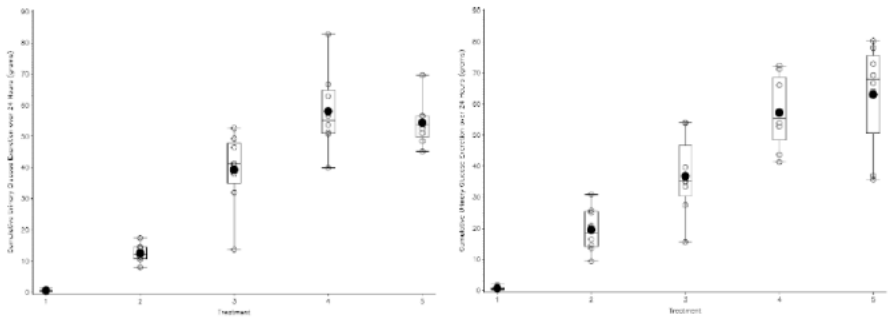
Study:	**P037/1002**
Study Title:	*A Phase 1, Randomized, Placebo-Controlled, Parallel Group, 14 Day Repeated Dose Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of PF- 04971729 in Otherwise Healthy Overweight and Obese Adult Subjects*
Objectives:	• To characterize the PK of ertugliflozin and its metabolite PF-05217539 following single and multiple oral doses in otherwise healthy overweight and obese subjects • To investigate the effect of ertugliflozin on PD parameters after single and multiple oral doses of ertugliflozin in otherwise healthy overweight and obese subjects
Study Design:	Single-center, randomized, double-blind, third-party open (subject and investigator-blinded), parallel-group, placebo-controlled study
Study Population:	Population: Healthy male subjects; Age range: 23-54 years; n = 40
Results:	

Treatment Route of Administration (ROA) Dose/Dosage Form	Mean PK Parameters[a]					
	AUC_{tau} (ng•hr/mL)	AUC_{inf} (ng•hr/mL)	AUC_{last} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
Day 1 PK						
Treatment: Day 1 of multiple dose, light meal ROA: PO Dose/Dosage form:						
1 mg ertugliflozin (solution)	59.46 (12)	NA	NA	7.154 (15)	4.00 (0.983-4.02)	NA
5 mg ertugliflozin (suspension)	361.6 (31)	NA	NA	49.22 (27)	2.00 (1.00-2.00)	NA
25 mg ertugliflozin (suspension)	1681 (26)	NA	NA	195.4 (27)	4.00 (1.00-4.02)	NA
100 mg ertugliflozin (suspension)	5647 (16)	NA	NA	669.2 (15)	4.00 (1.00-4.02)	NA
Multiple-dose PK (Day 14)						
Treatment: Multiple-dose, light meal ROA: PO Dose/Dosage form:						
1 mg ertugliflozin (solution)	80.85 (15)	NA	NA	10.19 (15)	2.00 (1.00-4.00)	NC
5 mg ertugliflozin (suspension)	450.5 (35)	NA	NA	50.83 (28)	1.50 (1.00-4.03)	12.28 (24)
25 mg ertugliflozin (suspension)	2045 (26)	NA	NA	280.8 (28)	2.00 (1.00-2.00)	14.81 (41)
100 mg ertugliflozin (suspension)	7761 (17)	NA	NA	1035 (25)	2.00 (1.00-4.00)	14.13 (14)

Treatment Route of Administration (ROA) Dose/Dosage Form	24-Hour UGE (g)[a]
Day-1	
Placebo	0.41 (0.19-0.90)
Treatment: Single-dose, fed ROA: PO Dose/Dosage form: 1 mg ertugliflozin (solution)	0.21 (0.12-0.38)
5 mg ertugliflozin (suspension)	0.44 (0.19-0.73)
25 mg ertugliflozin (suspension)	0.68 (0.61-1.22)
100 mg ertugliflozin (suspension)	0.41 (0.28-0.63)
Single-dose (Day1)	
Placebo	0.54 (0.25-1.27)
Treatment: Single-dose, fed ROA: PO Dose/Dosage form: 1 mg ertugliflozin (solution)	12.07 (7.98-17.40)
5 mg ertugliflozin (suspension)	41.13 (13.69-52.65)
25 mg ertugliflozin (suspension)	55.14 (39.90-82.79)
100 mg ertugliflozin (suspension)	53.70 (45.15-69.63)
Multiple-dose (Day 14)	
Placebo	0.66 (0.21-1.99)
Treatment: Multiple-dose (Day 14), fed ROA: PO Dose/Dosage form: 1 mg ertugliflozin (solution)	18.70 (9.46-30.95)
5 mg ertugliflozin (suspension)	35.17 (15.60-54.03)
25 mg ertugliflozin (suspension)	55.28 (41.36-72.25)
100 mg ertugliflozin (suspension)	67.97 (35.70-80.27)

Median Plasma PF-04971729 Concentration-Time Profiles Following 14 Days of QD Dosing



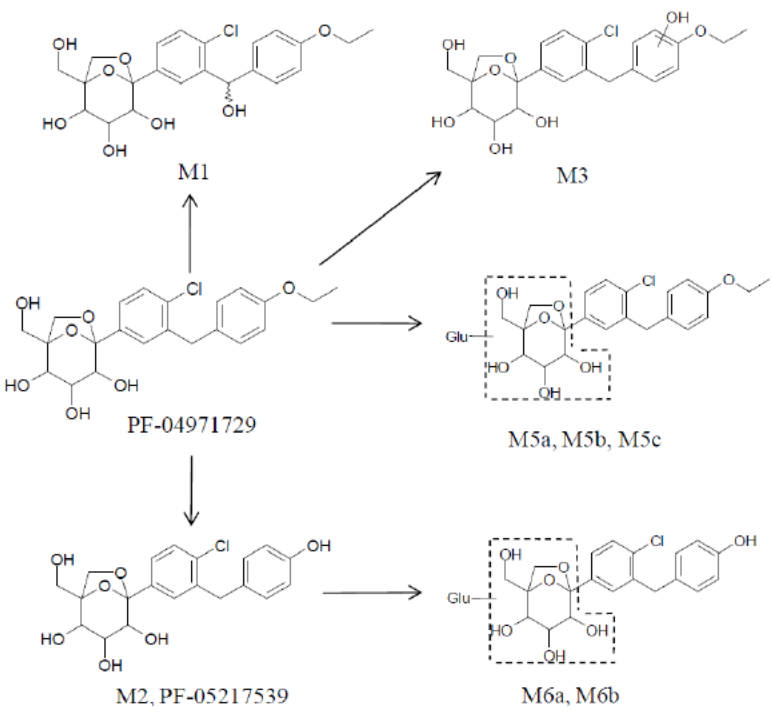
	Cumulative UGE (g) Over 0-24 Hours, Days 1 and 14  Day 1 Day 14 Source: Figure 14.3.1 1 = placebo; 2, 3, 4, and 5 = PF-04971729 1 mg, 5 mg, 25 mg, and 100 mg, respectively Open circles identify individual subject data. Closed circles identify geometric means. Box plot provides median and 25%/75% quartiles with whiskers extended to the minimum/maximum values. Abbreviations: UGE = urinary glucose excretion, g = gram, mg = milligram
Conclusions:	***Pharmacokinetics/Pharmacodynamics:*** Following qd PO doses of 1 to 100 mg ertugliflozin for 14 days, peak and total exposure (Cmax and AUCtau) increased proportionally with increasing dose for both ertugliflozin and its metabolite PF-05217539. Total exposure (AUCtau) for the metabolite was negligible relative to the parent. Single PO doses of ertugliflozin qd for 14 days in healthy subjects induced glycosuria without reducing serum glucose with the amount of glycosuria being dose-dependent and a maximal UGE achieved with ertugliflozin doses of ≥25 mg. Orally administered qd doses of ertugliflozin up to 100 mg to overweight and obese, otherwise healthy subjects had no sustained effect on fluid balance, serum and urinary electrolytes, nor iPTH. ***Safety:*** Orally administered, qd doses of ertugliflozin up to 100 mg (the maximum dose studied) were found to be safe and well-tolerated in overweight and obese, otherwise healthy subjects.

Reviewer's Comments:
The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the pharmacokinetic and pharmacodynamic effect (urinary glucose excretion) of ertugliflozin.

4.2.3 Study P038/1003 - PK Mass Balance, and Metabolism of ^{14}C Ertugliflozin

Study:	**P038/1003**
Study Title:	*An Open Label, Single-Period, Phase 1 Study to Evaluate the Pharmacokinetics, Excretion Balance and Metabolism of [^{14}c] PF-04971729 in Healthy Adult Male Subjects*
Objectives:	• Mass Balance: To characterize the rate and extent of excretion of total radioactivity in urine and feces, following a single oral dose of [14C]PF-04971729 (25 mg/100 microcurie [□Ci] suspension). • Pharmacokinetic (PK) Parameters: To quantify plasma concentrations and PK parameters of PF-04971729 and total radioactivity in plasma following a single oral dose of [^{14}C]PF-04971729 (25 mg/100 µCi suspension). • Metabolic Profiling/Metabolite Identification: To characterize the metabolic profile and identify circulating and excreted metabolites following a single oral dose administration of [^{14}C]PF-04971729 (25 mg/100 µCi suspension). • Safety: To evaluate the safety and tolerability of a single oral dose of [^{14}C]PF-04971729 (25 mg/100 µCi suspension) in healthy volunteers.
Study Design:	Randomized, open-label, single-period, PK study
Study Population:	Population: Healthy male subjects; Mean Age (range): 34.8 (20-55) years; n = 6
Results:	

Treatment Route of Administration (ROA) Dose/Dosage Form	Mean PK Parameters[a]					
	AUC_{tau} (ng•hr/mL)	AUC_{inf} (ng•hr/mL)	AUC_{last} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
	Plasma ertugliflozin PK					
Treatment: single-dose ROA: PO Dose/Dosage form: [^{14}C]ertugliflozin (25 mg/100 µCi suspension)	NA	2802 (21)	2787 (21)	490.2 (14)	1.00 (0.500-1.05)	16.87 (43)
	Plasma radioactivity PK[d]					
	NA	6441 (19)	6223 (19)	734.4 (12)	1.02 (1.00-2.00)	17.25 (61)

	Proposed Metabolic Pathways of PF-04971729 in Healthy Male Human Subjects Following Oral Administration of [^{14}C]PF-04971729 (25 mg; 100 µCi) 
Conclusions:	***Pharmacokinetics/Pharmacodynamics:*** The recovery of administered radioactivity following PO dosing with ertugliflozin was >90%, with approximately 50% recovered in urine and 41% in feces. Elimination of the metabolites was found to be similar to ertugliflozin, which accounted for approximately half of the total radioactivity found in the plasma. Glucuronidation was found to be the major metabolic pathway, with minor contribution from Phase 1 metabolism; renal excretion of unchanged ertugliflozin was negligible. ***Safety:*** A single oral, 25 mg dose of [^{14}C]ertugliflozin appeared to be safe and well-tolerated in healthy, adult male subjects.

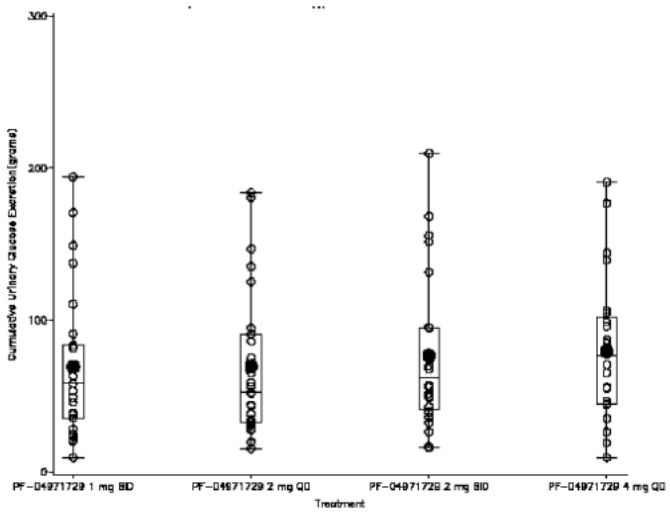
Reviewer's Comments:
The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the pharmacokinetic and metabolic profile of ertugliflozin.

4.2.4 *Study P040/1007 - PK and PD of 2 and 4 mg qd, and 1 mg and 2 mg bid Daily PO Administration of Ertugliflozin in T2DM Patients*

Study:	**P040/1007**
Study Title:	*A Phase 1, Randomized, Double-Blind, Placebo-Controlled, 2-Period, Cross-Over Single Day Evaluation of the Pharmacokinetic-Pharmacodynamic Effect of Once and Twice Daily Oral Administration of PF-04971729 in Patients with Type 2 Diabetes Mellitus*
Objectives:	• To evaluate the PD effects of single day dosing of 2 mg and 4 mg doses of PF-04971729 each administered once and split into twice daily dosing in adults with T2DM. • To characterize the safety and tolerability of single day dosing of 2 mg and 4 mg doses of PF-04971729 each administered once and split into twice daily dosing in adults with T2DM. • To assess the PK of PF-04971729 administered once and split into twice daily dosing in adults with T2DM. • To investigate the relationship between plasma concentrations of PF-04971729 and PD effects in adults with T2DM.
Study Design:	Randomized, double-blind, sponsor-open, 4-arm study
Study Population:	Population: T2DM Patients Age (range): 33-66 years; n = 52
Results:	

Treatment Route of Administration (ROA) Dose/Dosage Form	Mean PK Parameters[a]					
	AUC_{tau} (ng•hr/mL)	AUC_{inf} (ng•hr/mL)	AUC_{last} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
Treatment: qd and bid dosing ROA: PO Dose/Dosage form:						
1 mg bid ertugliflozin Cohort 1	NA	NA	131.8 (26)	19.51 (39)	6.00 (0.50-12.0)	NA
2 mg qd ertugliflozin Cohort 1	NA	NA	132.7 (28)	26.98 (37)	1.00 (0.50-5.50)	NA
2 mg bid ertugliflozin Cohort 2	NA	NA	272 (19)	34.80 (23)	6.00 (0.50-8.00)	NA
4 mg qd ertugliflozin Cohort 2	NA	NA	270.5 (20)	50.83 (25)	1.00 (0.50-6.00)	NA

Treatment Route of Administration (ROA) Dose/Dosage Form	24-Hour UGE (g)[a]
Treatment: single day dosing ROA: PO Dose/Dosage form 1 mg, 2 mg and 4 mg ertugliflozin 1 mg Tablets	
Ertugliflozin 1 mg bid	69.45 (9.08)
Ertugliflozin 2 mg qd	70.43 (9.08)
Ertugliflozin 2 mg bid	78.29 (9.77)
Ertugliflozin 4 mg qd	80.54 (9.81)

	Box and Whisker Plot of Cumulative Urinary Glucose Excretion (g) Ov 0 to 24 Hours  Source: Figure 14.2.1.3 Circles identify individual subject data; dots identify means. Box plots provide median and 25%/75% quartiles, with whiskers extended to the minimum/maximum values. Abbreviations: BID = twice daily, QD = daily
Conclusions:	***Pharmacokinetics/Pharmacodynamics:*** PD effects (UGE, plasma glucose, and C-peptide) were similar for all treatment groups following single day dosing of 2 mg and 4 mg doses of ertugliflozin administered qd or split into bid dosing in adults with T2DM. Bid dosing of ertugliflozin resulted in delayed plasma ertugliflozin T_{max}, lower C_{max}, but similar AUC_{last} relative to qd administration of the same total dose. ***Safety:*** Administration of PO doses of ertugliflozin up to 4 mg was considered to be safe and well-tolerated in adults with a diagnosis of T2DM.

Reviewer's Comments:
The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the pharmacokinetic and pharmacodynamic effect (urinary glucose excretion) of ertugliflozin.

4.2.5 *Study P035/1051 - Steady State PK and PD of 5 and 15 mg qd, and 2.5 and 7.5 mg bid PO Administration of Ertugliflozin in Healthy Subjects*

<table>
<tr><td>Study:</td><td>P035/1051</td></tr>
<tr><td>Study Title:</td><td>An Open-Label, Randomized, 2-Period, Crossover, Steady State Evaluation of the Pharmacokinetics and Pharmacodynamics of Once Daily and Twice Daily Oral Administration of Ertugliflozin in Healthy Subjects</td></tr>
<tr><td>Objectives:</td><td>Cohort C:
To demonstrate equivalence of exposure (AUC24) on Day 6 of ertugliflozin at total daily dosing of 5 mg when administered QD vs. BID in healthy subjects (5 mg QD and 2.5 mg BID)
To demonstrate similar steady state PD effect (UGE0-24) of ertugliflozin at total daily dosing of 5 mg when administered QD vs. BID in healthy subjects (5 mg QD and 2.5 mg BID)
Cohort B:
To demonstrate equivalence of exposure (AUC24) on Day 6 of ertugliflozin at total daily dosing of 15 mg when administered QD vs. BID in healthy subjects (15 mg QD and 7.5 mg BID)
To demonstrate similar steady state PD effect (UGE0-24) of ertugliflozin at total daily dosing of 15 mg when administered QD vs. BID in healthy subjects (15 mg QD and 7.5 mg BID)</td></tr>
<tr><td>Study Design:</td><td>Phase 1, open-label, multiple-dose, randomized, 2-period, 2-way crossover study</td></tr>
<tr><td>Study Population:</td><td>Population: Healthy Subjects
Mean Age (range): 34.4 (20-53) years;
n = 52</td></tr>
<tr><td>Results:</td><td>
<table>
<tr><th>Treatment
Route of Administration (ROA)
Dose/Dosage Form</th><th colspan="6">Mean PK Parameters[a]</th></tr>
<tr><th></th><th>AUC_{tau} (ng•hr/mL)</th><th>AUC_{inf} (ng•hr/mL)</th><th>AUC_{last} (ng•hr/mL)</th><th>C_{max} (ng/mL)</th><th>T_{max} (hr)</th><th>$t_{1/2}$ (hr)</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>2.10)</td><td></td></tr>
<tr><td>Ertugliflozin 5 mg qd cohort C</td><td>AUC_{24}: 397.9 (18)</td><td>NA</td><td>NA</td><td>C_{max} 1: 81.27 (29) C_{max} 2: NA</td><td>T_{max} 1: 1.00 (0.500, 2.05) T_{max} 2: NA</td><td>NA</td></tr>
<tr><td colspan="7">Statistical Comparison: Ratio (bid/qd) (90% CI)</td></tr>
<tr><td>Ertugliflozin 2.5 mg bid vs. ertugliflozin 5 mg qd</td><td colspan="6">AUC_{24}: 100.78 (98.76, 102.83)</td></tr>
<tr><td>Ertugliflozin 7.5 mg bid vs. ertugliflozin 15 mg qd</td><td colspan="6">AUC_{24}: 99.73 (97.08, 102.45)</td></tr>
</table>
<table>
<tr><th>Treatment
Route of Administration (ROA)
Dose/Dosage Form</th><th>24-Hour UGE (g)[a]</th></tr>
</table>
</td></tr>
</table>

Primary Analysis

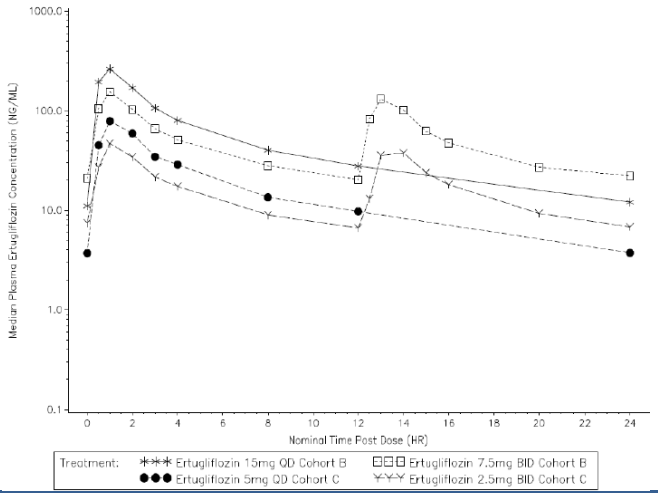
Treatment: multiple-dose
ROA: PO
Dose/Dosage form:

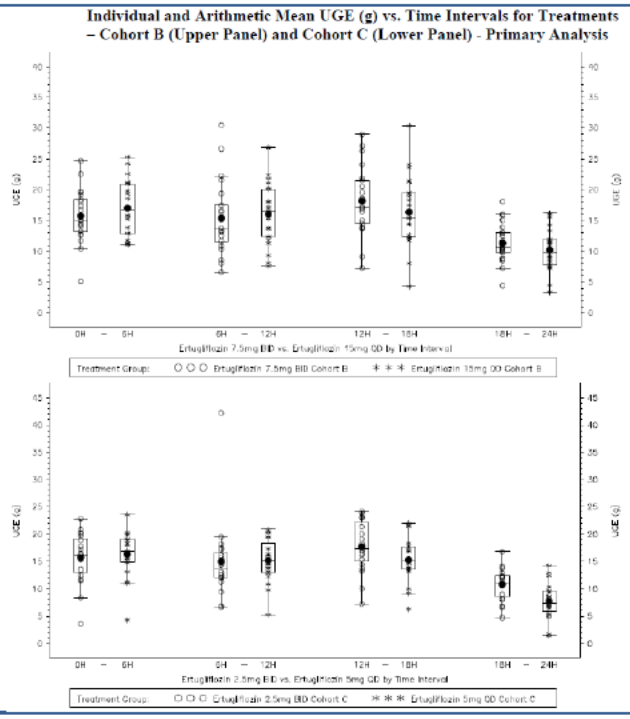
Ertugliflozin 7.5 mg bid	58.58 (28)
Ertugliflozin 15 mg qd	57.63 (28)
Ertugliflozin 2.5 mg bid	57.09 (31)
Ertugliflozin 5 mg qd	52.46 (34)

Primary Analysis

Ertugliflozin 7.5 mg bid vs Ertugliflozin 15 mg qd	102.77 (97.69, 108.12)
Ertugliflozin 2.5 mg bid vs Ertugliflozin 5 mg qd	110.16 (102.96, 117.87)

Median Plasma Ertugliflozin Concentration-Time Profiles on Day 6 Following Multiple QD or BID Oral Doses



	
Conclusions:	***Pharmacokinetics/Pharmacodynamics:*** For ertugliflozin 5 mg total daily dose, the 90% CI for the ratio (bid/qd) of geometric means for AUC_{24} on Day 6 was wholly within the acceptance criteria for equivalence (80%, 125%), indicating that ertugliflozin steady state exposure was equivalent when administered as 2.5 bid vs. 5 mg qd. For ertugliflozin 15 mg total daily dose, the 90% CI for the ratio (bid/qd) of geometric means for AUC_{24} on Day 6 was wholly within the acceptance criteria for equivalence (80%, 125%), indicating that ertugliflozin steady state exposure was equivalent when administered as 7.5 mg bid vs. 15 mg qd. For ertugliflozin 5 mg total daily dose, the 90% CI for UGE_{0-24} on Day 6 was wholly within the protocol pre-specified boundaries of (70%, 143%), indicating that the UGE_{0-24} at steady state was similar when administered as 2.5 mg bid vs 5 mg qd. For ertugliflozin 15 mg total daily dose, the 90% CI for the ratio (bid/qd) of geometric means for UGE_{0-24} on Day 6 was wholly within the protocol pre-specified boundaries of (70%, 143%), indicating that the UGE_{0-24} at steady state was similar when administered as 7.5 mg bid vs. 15 mg qd. ***Safety:*** Daily doses of ertugliflozin 5 mg and 15 mg administered as 2.5 mg bid, 5 mg qd, 7.5 mg bid or 15 mg qd for 6 days were safe and well-tolerated in healthy subjects.

Reviewer's Comments:
The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the pharmacokinetic and pharmacodynamic effect (urinary glucose excretion) of ertugliflozin.

4.2.6 *Study P010/1025 - Definitive QTc Study*

Study:	**P010/1025**
Study Title:	*A Phase 1, Randomized, Double-Blind, Placebo-Controlled, 2-Period, Cross-Over Single Day Evaluation of the Pharmacokinetic-Pharmacodynamic Effect of Once and Twice Daily Oral Administration of PF-04971729 in Patients with Type 2 Diabetes Mellitus*
Objectives:	• To demonstrate a lack of effect of ertugliflozin on the QTc interval relative to time-matched placebo in healthy volunteers
Study Design:	Phase 1, single-dose, randomized, 3-treatment, 6-sequence, 3-period, crossover, placebo- and active-controlled study
Study Population:	Population: Healthy Subjects Mean Age (range): 35.7 (18-54) years n = 42
Results:	

Treatment Route of Administration (ROA) Dose/Dosage Form	Mean PK Parameters[a]					
	AUC_{tau} (ng•hr/mL)	AUC_{inf} (ng•hr/mL)	AUC_{last} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
Ertugliflozin PK						
Treatment: single-dose ROA: PO Dose/Dosage form: 100 mg ertugliflozin tablet	NA	10290 (25)	9932 (24)	1735 (32)	1.50 (0.52-3.00)	11.55 ± 2.47

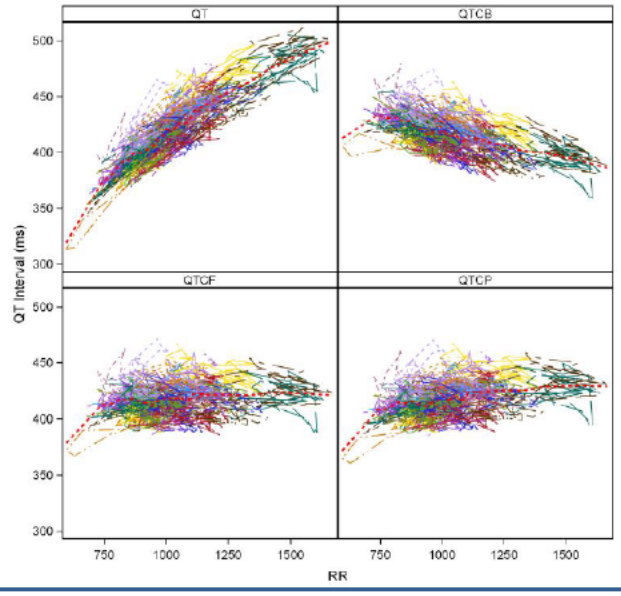
The Point Estimates and the 90% CIs of ΔΔQTcF corresponding to the Largest Upper Bound for Ertugliflozin 100 mg and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Ertugliflozin 100 mg	24	3.0	(0.5, 5.5)
Moxifloxacin 400 mg*	3	14.9	(12.4, 17.4)

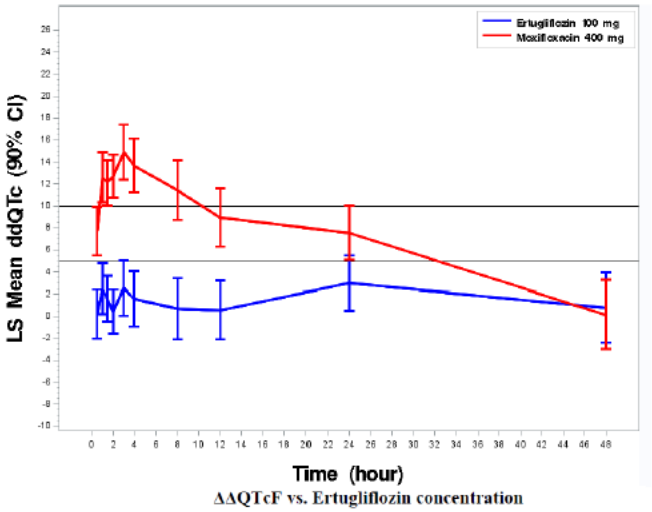
* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 11.5 ms.

The following are plots from FDA's QT-IRT analysis:

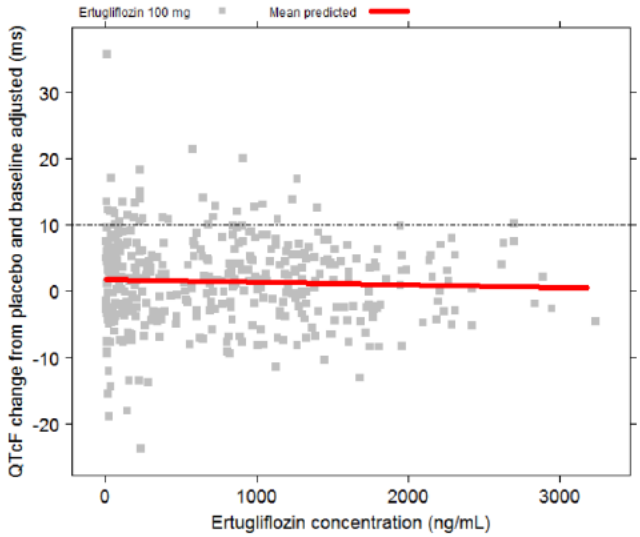
QT, QTcB, QTcF, and QTcP vs. RR (Each Subject's Data Points are Connected with a Line)



Mean and 90% CI ΔΔQTcF Time Profile



ΔΔQTcF vs. Ertugliflozin concentration



Conclusions:

Pharmacokinetics/Pharmacodynamics:

A lack of an effect on QTc interval was demonstrated with a single supratherapeutic PO dose of ertugliflozin 100 mg.

The study was adequately sensitive to assess the effect of ertugliflozin on QTc interval, as the lower bound of the 2-sided 90% CIs for the mean difference in QTcF between moxifloxacin (positive control) and placebo was greater than the predefined cutoff of 5 msec at each pre-specified time point (2, 3, or 4 hours) post dose.

The median ertugliflozin T_{max} was 1.5 hours following a single 100 mg oral dose. Geometric mean C_{max} and AUC_{inf} were 1735 ng/mL and 10,290 ng•hr/mL, respectively, and mean $t_{½}$ was 11.55 hours.

FDA Conclusion:

The ertugliflozin geometric mean C_{max} at the supratherapeutic 100 mg ertugliflozin dose (1735 ng/mL) was ~6.5 times the mean steady-state C_{max} following highest proposed dose of 15 mg qd dose under fasted state (268.2 ng/mL). Amongst the potential worst

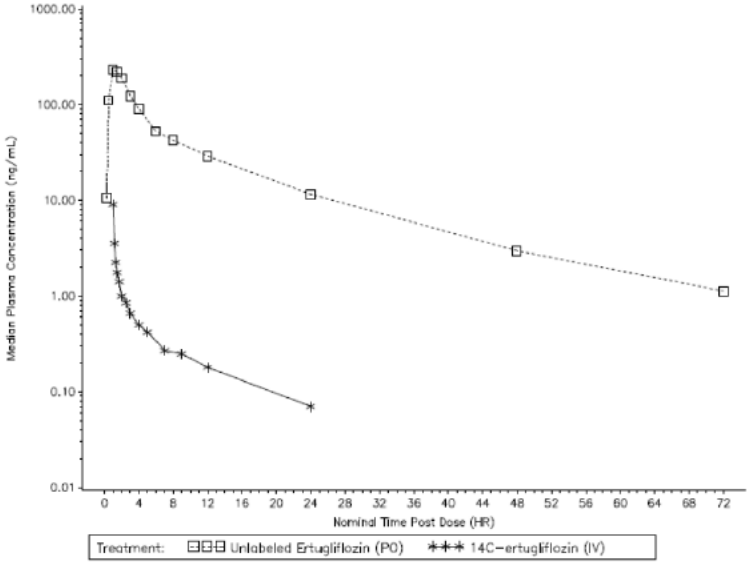
	case scenarios, the subjects with mild, moderate and severe renal impairment had mean increases in AUC_{inf} of ≤1.7-fold, and no clinically meaningful increases in C_{max}. Regarding the interaction with a UGT inhibitor (mefenamic acid), based on PBPK modeling, the predicted ertugliflozin AUC and C_{max} ratio (ertugliflozin + mefenamic acid/ertugliflozin alone) were 1.51 and 1.19, respectively. Thus, the exposures with the supratherapeutic dose of 100 mg adequately cover potential highest clinically relevant exposure scenario due to the effects of intrinsic/extrinsic factors with therapeutic dose. ***Safety:*** A single supratherapeutic PO dose of ertugliflozin 100 mg was safe and well tolerated in the subjects evaluated in this study.

4.2.7 *Study P020/1043 - Absolute BA and Fraction Absorbed of Ertugliflozin Using a ^{14}C Microdose Approach*

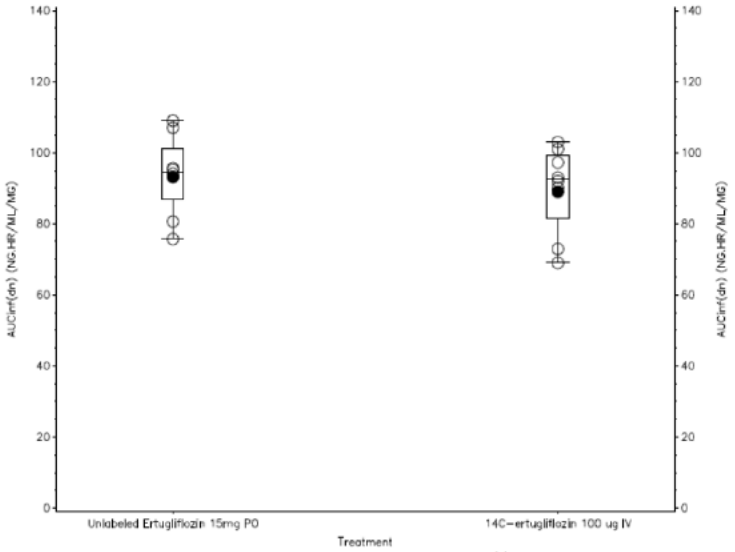
Study:	**P020/1043**
Study Title:	*A Phase 1, Open-Label, Non-Randomized, 2-Period, Fixed Sequence, Study to Assess the Absolute Bioavailability and Fraction Absorbed of Ertugliflozin in Healthy Male Subjects Using a ^{14}C-Microdose Approach*
Objectives:	• To determine the oral absolute bioavailability (F) of ertugliflozin
Study Design:	Open-label, non-randomized, fixed sequence, 2-period, single-dose
Study Population:	Population: Healthy Subjects Age (range): 22-54 years n = 8
Results:	

Treatment Route of Administration (ROA) Dose/Dosage Form	Mean PK Parameters[a]					
	AUC_{tau} (ng•hr/mL)	AUC_{inf} (ng•hr/mL)	AUC_{last} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
Unlabeled ertugliflozin (PO)	NA	1397 (13)	1376 (12)	256.3 (14)	1.00 (1.00, 1.50)	14.04 ±2.17
[^{14}C]ertugliflozin (IV)	NA	8.477 (15)	7.859 (14)	8.514 (32)	0.083 (0.083, 0.100)	8.098±2.248

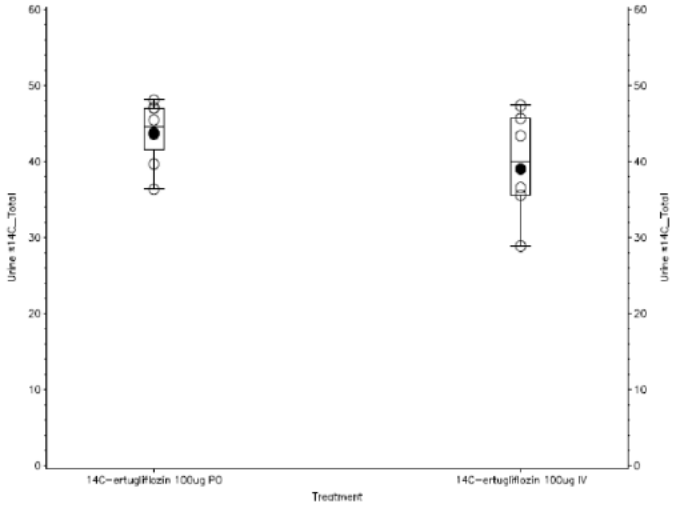
Median Plasma Concentration-Time Profiles for PO (unlabeled) and IV (^{14}C-labeled) Ertugliflozin



Individual and Geometric Mean Dose Normalized AUC_{inf} Values for Unlabeled Ertugliflozin and ^{14}C-Ertugliflozin



Individual and Geometric Mean Urine %^{14}C_Total Values



Conclusions:

Pharmacokinetics/Pharmacodynamics:
Following oral administration of ertugliflozin, estimates of absolute bioavailability and fraction absorbed were approximately 100% (F=105% and F_a=111%), suggesting complete absorption.

Following IV administration, ertugliflozin CL and V_{ss} were 187.2 mL/min and 85.5 L, respectively.

Safety:
Ertugliflozin was safe and well tolerated following simultaneous oral/IV administration.

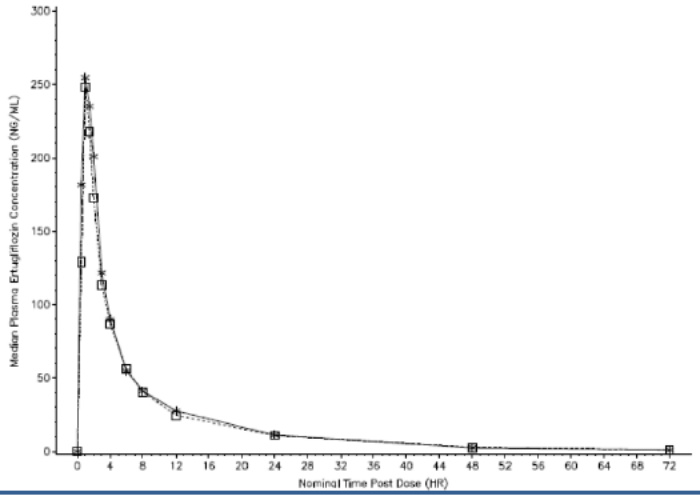
Reviewer's Comments:
The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the absolute bioavailability of ertugliflozin.

4.2.8 Study P023/1037 – Bioequivalence of Phase 3 and Commercial Image Tablets

Study:	**P023/1037**
Study Title:	*A Phase 1, Single Dose, Open-Label, Randomized, Crossover Bioequivalence Study of an Ertugliflozin 15 mg Commercial Image Tablet vs Ertugliflozin Phase 3 Tablets in Healthy Subjects*
Objectives:	• To demonstrate bioequivalence of the ertugliflozin 15 mg commercial image tablet to the ertugliflozin Phase 3, 15 mg dose (administered as one 10 mg tablet + one 5 mg tablet) under fasted conditions.
Study Design:	Pivotal, Phase 1, open-label, randomized, 2-period, 2-sequence single dose crossover study
Study Population:	Population: Healthy Subjects Mean Age (range): 30.8 (23-48) years n = 16
Results:	

Treatment: Dose Dosage Form Route of Administration (ROA)	Mean PK Parameters[a]				
	AUC_{inf} (ng•hr/mL)	AUC_{last} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
Test: Treatment: Single-dose Dosage form: ertugliflozin 15 mg commercial image tablet ROA: PO	1354 (19)	1334 (18)	262.4 (21)	1.00 (0.500-1.50)	12.58 (± 2.53)
Reference: Treatment: Single-dose Dosage form: ertugliflozin 15 mg dose administered as one 10 mg + one 5 mg Phase 3 tablets ROA: PO	1380 (20)	1358 (20)	272.3 (19)	1.00 (0.500-2.00)	12.18 (± 2.53)
Statistical Comparison: Ratio (Test/Reference) (90% CI)[b]					
Test/Reference:	98.07 (95.40, 100.81)	98.24 (95.57, 100.97)	96.34 (86.29, 107.56)	NA	NA

Median Plasma Ertugliflozin Concentration-Time Profiles Following Single Oral Doses



Conclusions:	***Pharmacokinetics/Pharmacodynamics:*** The 90% CIs for the ratios (commercial image tablet/Phase 3 tablets) of adjusted (least squares) geometric means for both AUCinf and Cmax were wholly within the acceptance criteria for bioequivalence (80%, 125%), indicating that the ertugliflozin 15 mg commercial image tablet is bioequivalent to the ertugliflozin Phase 3, 15 mg dose (administered as one 10 mg tablet + one 5 mg tablet).

	Safety: Administration of a single 15 mg dose of ertugliflozin as either the commercial image tablet or the Phase 3, 15 mg dose (administered as one 10 mg tablet + one 5 mg tablet) to healthy subjects was safe and well tolerated.

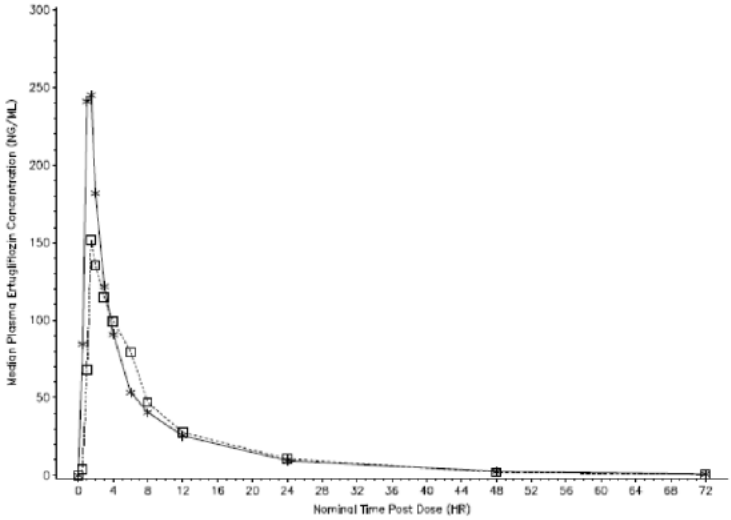
Reviewer's Comments:
The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the pharmacokinetics of ertugliflozin.

4.2.9 *Study P024/1048 - Effect of Food on the PK of Ertugliflozin 15 mg Commercial Image Tablet*

Study:	**P024/1048**
Study Title:	*A Phase 1, Randomized, Open-Label, 2-Sequence, 2-Period Crossover Study to Estimate the Effect of Food on the Pharmacokinetics of an Ertugliflozin Commercial Image Tablet in Healthy Subjects*
Objectives:	• To estimate the effect of food on the PK of ertugliflozin following administration of the ertugliflozin 15 mg commercial image tablet.
Study Design:	Phase 1, open-label, randomized, 2-period, 2-sequence, single-dose, crossover study
Study Population:	Population: Healthy Subjects Mean Age (range): 38.8 (25-53) years n = 14
Results:	See table and figure below
Conclusions:	***Pharmacokinetics/Pharmacodynamics:*** Administration of ertugliflozin 15 mg commercial image tablet with a high-fat meal resulted in no meaningful effect on AUC_{inf}. Food delayed median T_{max} by 1 hour and reduced mean C_{max} by approximately 29% compared to fasted conditions. The decrease in ertugliflozin C_{max} with food is not anticipated to be clinically relevant. Ertugliflozin may be administered without regard to meals.

Treatment Route of Administration (ROA) Dose/Dosage Form	Mean PK Parameters[a]					
	AUC_{tau} (ng•hr/mL)	AUC_{inf} (ng•hr/mL)	AUC_{last} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
Ertugliflozin PK						
Test: Treatment: single-dose Fed ROA: PO Dose/Dosage form: 15 mg ertugliflozin commercial tablets	NA	1240 (17)	1220 (17)	194.9 (20)	2.00 (1.00-6.00)	10.99 ± 1.98
Reference: Treatment: single-dose Fasted ROA: PO Dose/Dosage form: 15 mg ertugliflozin commercial tablets	NA	1326 (21)	1308 (21)	271.1 (24)	1.00 (1.00-3.00)	11.51 ± 2.57
Statistical Comparison: Ratio (Fed/Fasted) (90% CI)[b]						
	NA	91.65 (88.01, 95.44)	91.51 (87.62, 95.57)	70.65 (61.71, 80.88)	NA	NA

Median Plasma Ertugliflozin Concentration-Time Profiles Following Single Oral Doses



	Safety: Administration of the ertugliflozin 15 mg commercial image tablet under fasted and fed conditions was safe and well tolerated.

Reviewer's Comments:
The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the pharmacokinetics and the effect of food on ertugliflozin.

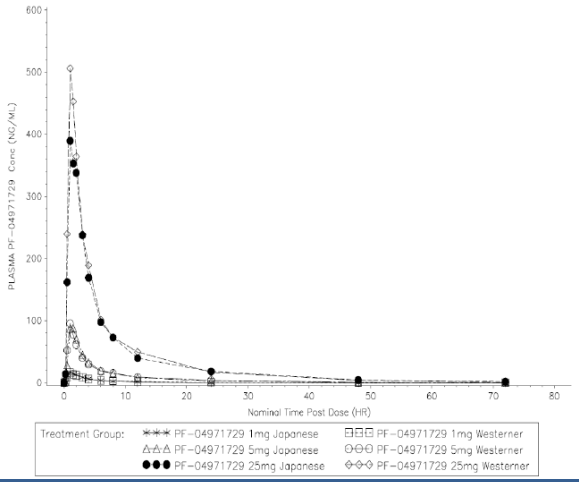
4.2.10 Study – P041/1009 - Safety, Tolerability, PK, and PD of Single Escalating and Multiple Doses of Ertugliflozin in Japanese Subjects

Study:	**P041/1009**
Study Title:	*A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Parallel-Cohort, Single-Dose Escalation and Multiple-Dose Study in Japanese Healthy Subjects, and Open-Label, Single-Dose Escalation Study in Western Healthy Subjects to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of PF-04971729*
Objectives:	• To investigate the safety, tolerability, PK and pharmacodynamics (PD) of single and multiple doses of PF-04971729 in Japanese healthy subjects • To investigate the safety, tolerability, PK and PD of single doses of PF-04971729 in Western healthy subjects. • To compare the PK and PD of single doses of PF-04971729 in Japanese and Western healthy subjects.
Study Design:	Randomized, double-blind (Sponsor open), placebo-controlled, parallel-cohort, single-dose escalation and multiple-dose study in Japanese healthy subjects, and open-label, single-dose escalation study in Western healthy subjects
Study Population:	Population: Healthy Subjects Age (range): 27-54 years n = 18 Japanese subjects (N=12 ertugliflozin and N=6 placebo) and 6 Western subjects (N=6 ertugliflozin)
Results:	

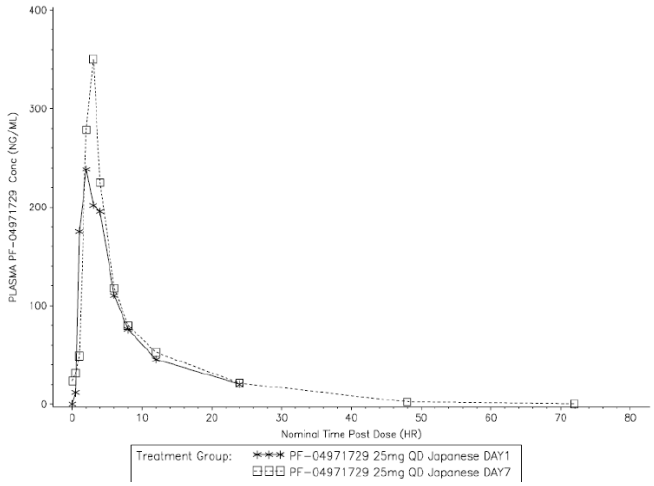
Treatment Route of Administration (ROA) Dose/Dosage Form	Mean PK Parameters[a] AUC_{tau} (ng•hr/mL)	AUC_{inf} (ng•hr/mL)	AUC_{last} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
Statistical Comparison of Single Dose: Ratio (Japanese Subjects/Western Subjects) (90% CI)[b]						
1 mg ertugliflozin	NA	NA	95.94 (78.76, 116.87)	107.59 (87.61, 132.11)	NA	NA
5 mg ertugliflozin	NA	98.94 (81.17, 120.61)	99.66 (81.81, 121.40)	97.47 (79.38, 119.69)	NA	NA
25 mg ertugliflozin	NA	91.05 (74.70, 110.99)	90.32 (74.14, 110.02)	80.04 (65.18, 98.28)	NA	NA
Multiple Dose PK						
Day 1 Treatment: multiple dose ROA: PO Dose/Dosage form: 25 mg qd ertugliflozin tablet	1973 (19)	NA	NA	365 (15)	2.50 (0.500-4.00)	NA
Day 7 Treatment: multiple dose ROA: PO Dose/Dosage form: 25 mg ertugliflozin tablet	2191 (25)	NA	NA	368 (23)	2.50 (1.05-4.00)	9.91 (35)

Treatment Route of Administration (ROA) Dose/Dosage Form	24-Hour UGE (g)[a]
Single-dose	
Placebo	0.1 (0.0-0.2)
Treatment: single-dose ROA: PO Dose/Dosage form: 1 mg ertugliflozin tablet (Japanese subjects)	32.6 (20.9-34.3)
1 mg ertugliflozin tablet (Western subjects)	19.0 (9.0-31.5)
5 mg ertugliflozin tablet (Japanese subjects)	57.0 (37.9-78.9)
5 mg ertugliflozin tablet (Western subjects)	36.6 (17.4-58.4)
25 mg ertugliflozin tablet (Japanese subjects)	61.5 (50.6-78.2)
25 mg ertugliflozin tablet (Western subjects)	46.6 (12.8-63.1)
Multiple Dose	
Day 1 Placebo	0.0 (0.0-0.0)
Day 1 Treatment: multiple dose ROA: PO Dose/Dosage form: 25 mg qd ertugliflozin tablet	63.1 (52.3-76.5)
Day 7 Placebo	0.0 (0.0-0.1)
Day 7 Treatment: multiple dose ROA: PO Dose/Dosage form: 25 mg ertugliflozin tablet	69.9 (53.4-96.6)

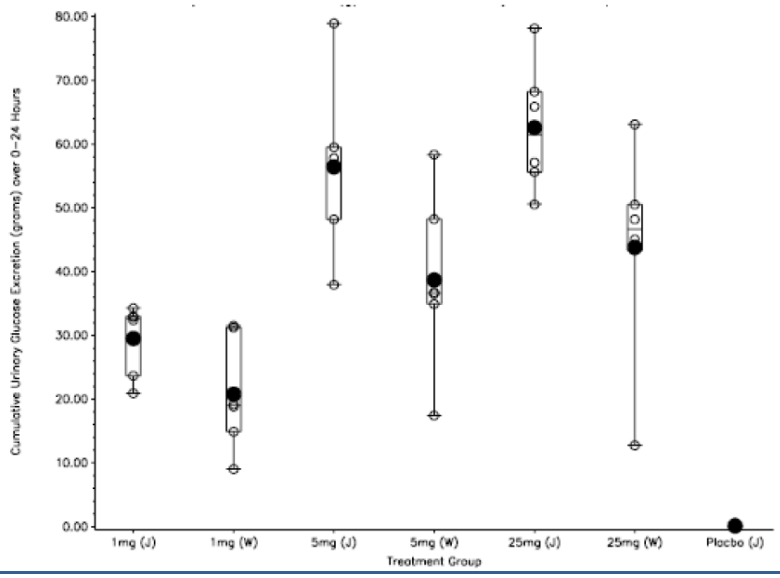
Median PF-04971729 Concentration-Time Profiles in Japanese and Western Healthy Subjects Following Single Oral Doses in Cohort A

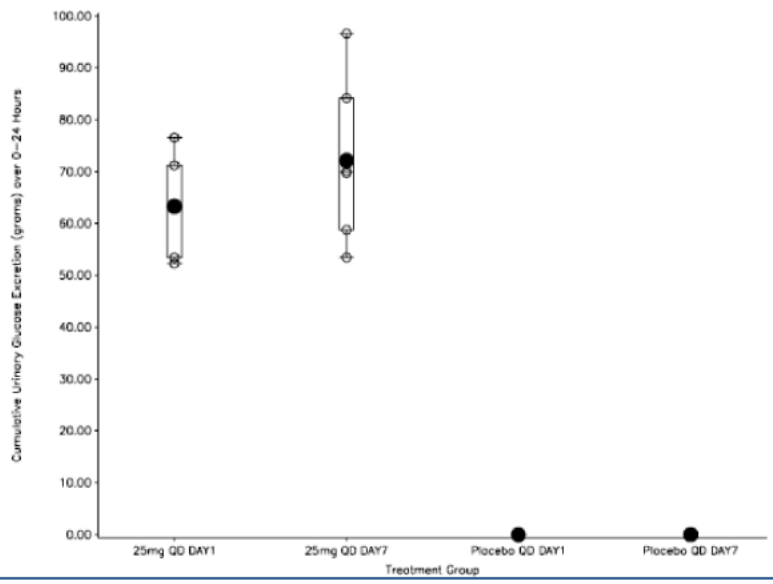


Median PF-04971729 Concentration-Time Profiles Following Multiple Dose Administrations of PF-04971729 on Day 1 and Day 7 in Cohort B



Cumulative Urinary Glucose Excretion Over 0-24 Hours by Dose and Population - Cohort A



	Cumulative Urinary Glucose Excretion Over 0-24 Hours by Dosing Day-Cohort B 
Conclusions:	***Pharmacokinetics/Pharmacodynamics:*** The median T_{max} was 1.00 to 1.50 hours under fasted conditions and was delayed to 2.50 hours under fed conditions. Exposure (C_{max} and AUC_{last}) of ertugliflozin increased with dose in an approximately dose proportional manner in both Japanese and Western healthy subjects following single-dose administration. Apparent $t_{½}$ of ertugliflozin in Japanese and Western healthy subjects was approximately 9.91 to 13.6 hours following single- and multiple-dose administration. The accumulation of ertugliflozin exposure after multiple dose administration was minimal. Single PO doses of ertugliflozin of 1 mg, 5 mg, and 25 mg in healthy Japanese and Western subjects induced glycosuria; the amount of UGE and inhibition of renal glucose reabsorption was dose dependent. In addition, little difference was observed for these parameters between Day 1 and Day 7 following ertugliflozin 25 mg qd dosing. There were no meaningful ethnic differences in ertugliflozin exposure (C_{max} and AUC_{last}) and ertugliflozin-induced UGE between Japanese and Western healthy subjects. ***Safety:*** Ertugliflozin administered orally as single-doses of 1 mg, 5 mg, and 25 mg in healthy Japanese and Western subjects and multiple doses of 25 mg qd in healthy Japanese subjects were safe and well-tolerated with no deaths, serious adverse events, severe adverse events, or discontinuations due to adverse events.

Reviewer's Comments:
The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the pharmacokinetic and pharmacodynamic effect (urinary glucose excretion) of ertugliflozin.

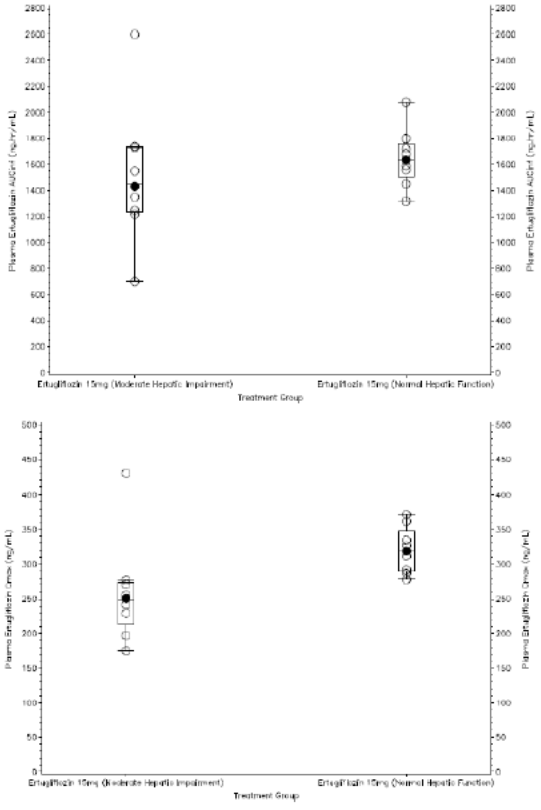
4.2.11 Study P014/1024 - Evaluation of Hepatic Impairment on the PK of Ertugliflozin 15 mg

Study:	**P014/1024**
Study Title:	*A Phase 1, Non-Randomized, Open-Label, Single Dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Ertugliflozin (MK-8835/PF-04971729) in Subjects With Hepatic Impairment and in Healthy Subjects With Normal Hepatic Function*
Objectives:	• To evaluate the effect of moderate hepatic impairment on the PK of ertugliflozin following a single oral dose of ertugliflozin 15 mg
Study Design:	Phase 1 open-label, single-dose, single-treatment, non-randomized study of ertugliflozin in subjects with hepatic impairment and normal healthy subjects matched for gender, age and weight
Study Population:	Population: Healthy Subjects and Hepatic Impaired Patients Age (range): 49-60 years n = 16 (8 normal hepatic function and 8 moderate hepatic impairment)
Results:	

Treatment Route of Administration (ROA) Dose/Dosage Form	Mean PK Parameters[a]					
	AUC_{tau} (ng•hr/mL)	AUC_{inf} (ng•hr/mL)	AUC_{last} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
	Total Ertugliflozin					
Test: Moderate hepatic impairment Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets	NA	1430 (39)	1413 (39)	251.1 (27)	1.25 (0.500-4.00)	14.56 ± 6.54
Reference: Normal hepatic function Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets	NA	1636 (14)	1618 (14)	319.0 (11)	1.00 (1.00-2.00)	13.77 ± 4.51
Statistical Comparison: Ratio (Moderate hepatic impairment/Normal hepatic function) (90% CI)[b]						
	NA	87.43 (68.11, 112.22)	87.31 (68.01, 112.08)	78.70 (65.74, 94.23)	NA	NA
	Unbound Ertugliflozin					
Test: Moderate hepatic impairment Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets	NA	AUC_{inf-u} 53.14	$AUC_{last,u}$ 52.47 (44)	C_{max-u} 9.336 (30)	NA	NA
Reference: Normal hepatic function Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets	NA	AUC_{inf-u} 55.40 (16)	$AUC_{last,u}$ 54.77 (15)	C_{max-u} 10.79 (15)	NA	NA
Statistical Comparison: Ratio (Moderate hepatic impairment/Normal hepatic function) (90% CI)[b]						
	NA	AUC_{inf-u} 95.92 (72.46, 126.97)	$AUC_{last,u}$ 95.81 (72.40, 126.79)	C_{max-u} 86.52 (70.49, 106.20)	NA	NA

PF-06481944 (M5c)						
Test: Moderate hepatic impairment Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets	NA	2636 (41)	2602 (41)	317.1 (35)	2.03 (1.50-4.00)	14.18 ± 6.15
Reference: Normal hepatic function Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets	NA	1807 (31)	1785 (31)	263.9 (32)	2.00 (1.00-3.00)	14.99 ± 6.10
PF-06685948 (M5a)						
Test: Moderate hepatic impairment Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets	NA	384.7 (32)	378.7 (32)	40.64 (35)	2.55 (2.00-6.00)	14.37 ± 6.07
Reference: Normal hepatic function Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets	NA	522.1 (31)	512.5 (32)	62.38 (34)	2.50 (2.00-4.00)	13.43 ± 5.16

Individual and Geometric Mean Plasma Ertugliflozin AUC_{inf} and C_{max} Values by Hepatic Function Group



Upper panel is AUC_{inf} and lower panel is C_{max}.
Dots represent geometric means and open circles represent individual subjects. Box plot provides median and 25%/75% quartiles with whiskers to the last point within 1.5 times interquartile range.

Conclusions:

Pharmacokinetics/Pharmacodynamics:

Based on the total and unbound ertugliflozin exposure, moderate hepatic impairment did not result in an increase in the exposure of ertugliflozin. The slight decrease in C_{max} and AUC observed in subjects with moderate hepatic impairment compared to subjects with normal hepatic function is not anticipated to be clinically relevant.

	Safety: A single PO dose of ertugliflozin 15 mg administered to healthy subjects with normal hepatic function and moderate hepatic impairment was safe and well tolerated.

Reviewer's Comments:
The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the effect of moderate hepatic impairment on the pharmacokinetics of ertugliflozin.

4.2.12 Study P009/1023 - Evaluation of Renal Impairment on the PK and PD of Ertugliflozin 15 mg in Subjects with T2DM

Study:	**P009/1023**
Study Title:	*A Phase 1, Non-Randomized, Open-Label, Single Dose Study to Evaluate the Effect of Renal Impairment on the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Ertugliflozin in Subjects With Type 2 Diabetes Mellitus*
Objectives:	• To evaluate the effect of renal impairment on the PK of ertugliflozin following a single oral dose of 15 mg. • To evaluate the effect of renal impairment on the PD effects of ertugliflozin following a single oral dose of 15 mg. • To evaluate the safety and tolerability of a single oral dose of ertugliflozin 15 mg in T2DM subjects with varying degrees of renal impairment and in healthy subjects with normal renal function.
Study Design:	Phase 1, open-label study of a single oral dose of ertugliflozin 15 mg administered in the fasted state to T2DM subjects with various degrees of renal impairment and to T2DM and healthy subjects with normal renal function
Study Population:	Population: Healthy Subjects and Renal Impaired Patients Age (range): 49-76 years n = 36 (8 healthy normal renal function, 6 T2DM normal renal function, 8 T2DM mild renal impairment, 8 T2DM moderate renal impairment, 6 T2DM severe renal impairment)
Results:	

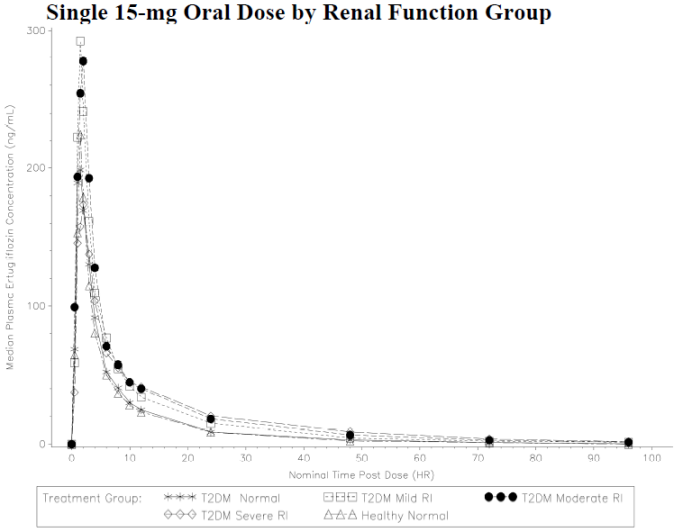
Treatment Route of Administration (ROA) Dose/Dosage Form	Mean PK Parameters[a]					
	AUC_{tau} (ng•hr/mL)	AUC_{inf} (ng•hr/mL)	AUC_{last} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
Ertugliflozin						
Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets						
Healthy normal renal function	NA	1236 (27)	1214 (27)	219.3 (26)	1.00 (1.00-2.00)	17.71 ± 3.53
T2DM normal renal function	NA	1199 (42)	1174 (42)	215.9 (35)	1.00 (1.00-1.50)	14.62 ± 6.37
T2DM mild renal impairment	NA	1908 (28)	1814 (27)	313.1 (30)	1.50 (1.00-2.00)	25.94 ± 13.98
T2DM moderate renal impairment	NA	2075 (19)	2011 (18)	305.7 (23)	1.50 (0.500-2.00)	22.89 ± 7.35
T2DM severe renal impairment	NA	1895 (23)	1816 (23)	196.4 (28)	1.51 (0.500-3.02)	24.17 ± 5.98
PF-06481944 (M5c)						
Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets						
Healthy normal renal function	NA	1113 (32)	1090 (33)	168.6 (34)	2.00 (1.50-3.00)	17.51 ± 5.69
T2DM normal renal function	NA	1559 (21)	1536 (21)	217.8 (18)	2.00 (1.00-3.00)	16.68 ± 9.46
T2DM mild renal	NA	2620	2517	309.0	2.00	22.04 ± 12.15

impairment		(34)	(32)	(30)	(1.50-4.00)	
T2DM moderate renal impairment	NA	3668 (56)	3552 (55)	358.5 (28)	3.00 (1.50-3.00)	23.33 ± 6.15
T2DM severe renal impairment	NA	2742 (41)	2642 (40)	218.6 (33)	3.00 (1.50-4.00)	22.83 ± 5.92
	PF-06685948 (M5a)					
Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets						
Healthy normal renal function	NA	337.6 (27)	329.1 (28)	43.90 (24)	2.00 (2.00-3.00)	15.68 ± 4.66
T2DM normal renal function	NA	383.9 (26)	371.9 (27)	44.44 (22)	2.00 (1.50-3.00)	14.87 ± 7.77
T2DM mild renal impairment	NA	604.1 (39)	579.8 (37)	53.56 (17)	3.00 (2.00-4.03)	21.71 ± 11.26
T2DM moderate renal impairment	NA	950.9 (75)	917.7 (74)	63.10 (42)	4.00 (2.00-4.00)	22.49 ± 5.30
T2DM severe renal impairment	NA	975.0 (53)	922.1 (51)	46.42 (35)	3.51 (3.00-	25.22 ± 10.42

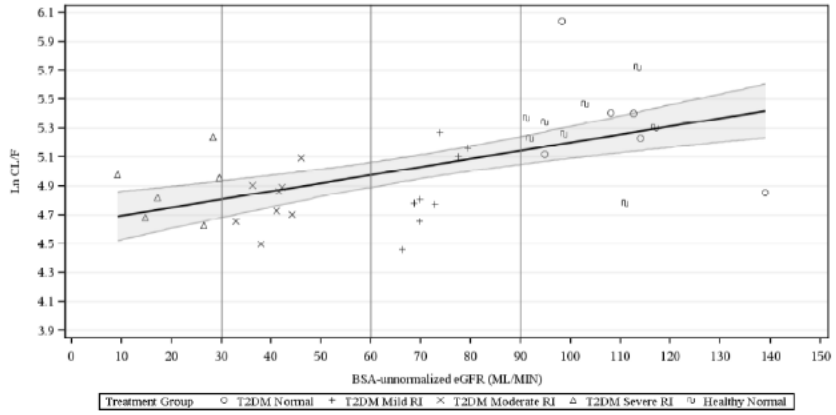
Treatment **Route of Administration (ROA)** **Dose/Dosage Form**	**24-Hour UGE (g)[a]**
Day -2 Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets	
Healthy normal renal function	0.1 (0.0-0.1)
T2DM normal renal function	8.2 (0.1-29.0)
T2DM mild renal impairment	0.1 (0.0-29.0)
T2DM moderate renal impairment	0.2 (0.0-2.7)
T2DM severe renal impairment	2.3 (0.1-8.9)
Day 1 Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets	
Healthy normal renal function	45.8 (27.4-70.0)
T2DM normal renal function	68.1 (51.5-120.5)
T2DM mild renal impairment	36.4 (6.3-119.9)
T2DM moderate renal impairment	28.8 (13.1-77.2)
T2DM severe renal impairment	10.3 (4.9-20.7)

Day 2 Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets	
Healthy normal renal function	31.9 (5.1-50.2)
T2DM normal renal function	64.2 (20.4-101.9)
T2DM mild renal impairment	32.1 (02.-85.6)
T2DM moderate renal impairment	19.6 (7.9-46.1)
T2DM severe renal impairment	15.4 (9.6-20.0)
Day 3 Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets	
Healthy normal renal function	16.9 (4.8-37.2)
T2DM normal renal function	40.6 (6.3-89.7)
T2DM mild renal impairment	23.8 (0.2-79.2)
T2DM moderate renal impairment	11.9 (7.4-42.9)
T2DM severe renal impairment	14.6 (5.3-19.7)
Day 4 Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets	
Healthy normal renal function	7.4 (1.7-18.0)
T2DM normal renal function	24.0 (3.4-59.1)
T2DM mild renal impairment	9.5 (0.0-77.4)
T2DM moderate renal impairment	6.6 (3.7-37.7)
T2DM severe renal impairment	11.5 (4.8-16.2)

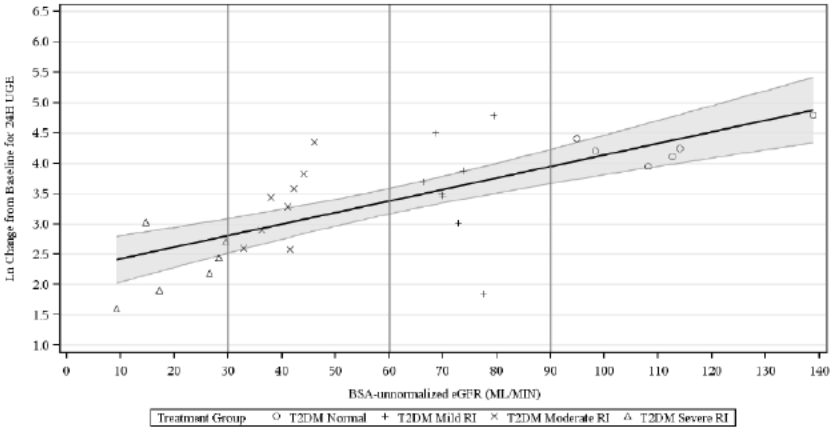
Median Plasma Ertugliflozin Concentration-Time Profiles Following a Single 15-mg Oral Dose by Renal Function Group



Regression and 90% CI of Ln CL/F After Oral Administration of Ertugliflozin Versus BSA-unnormalized eGFR in Subjects with Varying Degrees of Renal Function



Ln Change from Baseline in 24-Hour UGE Versus BSA-Unnormalized eGFR



Conclusions:

Pharmacokinetics/Pharmacodynamics:

Ertugliflozin PK were similar between healthy and T2DM subjects with normal renal function. Systemic exposure (AUCinf) of ertugliflozin was higher in subjects with mild, moderate and severe renal impairment. The mean increases in exposures were less than 2-fold and are not anticipated to be clinically meaningful.

The change from baseline in 24-hour UGE on Day 1 for T2DM subjects with mild, moderate and severe renal impairment decreased with decline in renal function compared to T2DM subjects with normal renal function.

Safety:

A single PO dose of 15 mg ertugliflozin was safe and well-tolerated in the healthy and T2DM subjects with normal renal function, and T2DM subjects with mild, moderate, and severe renal impairment.

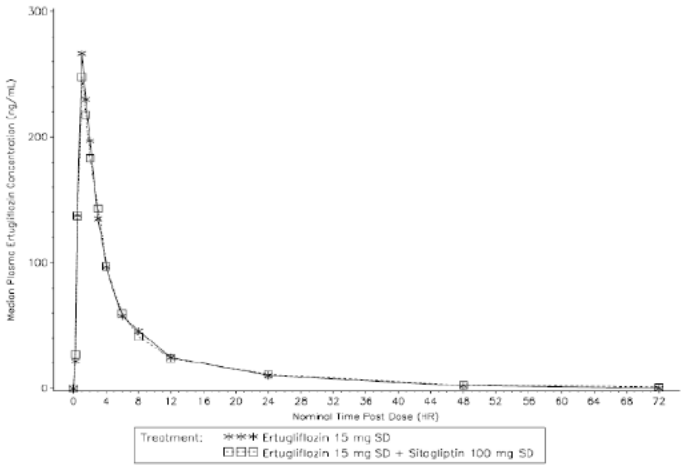
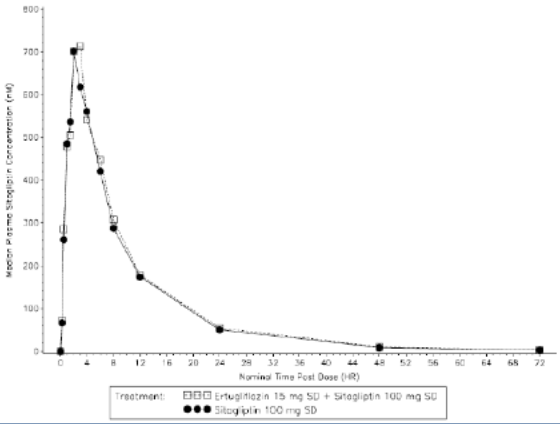
Reviewer's Comments:

The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the effects of renal impairment on the pharmacokinetics of ertugliflozin.

4.2.13 Study P022/1033 - Two-Way DDI between Ertugliflozin 15 mg and Sitagliptin 100 mg

Study:	**P022/1033**
Study Title:	*A Phase 1, Randomized, Open-Label, 3-Period, 6-Sequence Study to Estimate the Pharmacokinetic Interaction between Ertugliflozin and Sitagliptin in Healthy Subjects*
Objectives:	• To estimate the effect of sitagliptin on the PK of ertugliflozin following oral administration of a single dose (SD) of 15 mg ertugliflozin and 100 mg sitagliptin in healthy volunteers. • To estimate the effect of ertugliflozin on the PK of sitagliptin following oral administration of ertugliflozin 15 mg SD and sitagliptin 100 mg SD in healthy volunteers.
Study Design:	Phase 1, open-label, randomized, 3-period, 6-sequence single oral dose crossover DDI study
Study Population:	Population: Healthy Subjects Mean Age (range): 34.7 (25-53) years n = 12
Results:	

Treatment Route of Administration (ROA) Dose/Dosage Form	Mean PK Parameters[a]					
	AUC_{tau} (ng•hr/mL)	AUC_{inf} (ng•hr/mL)	AUC_{last} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
					4.02)	
	Ertugliflozin PK					
Test Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin + 100 mg sitagliptin tablet	NA	1445 (25)	1412 (24)	258.1 (26)	1.00 (0.500-2.10)	14.17 ± 4.55
Reference Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets	NA	1413 (26)	1385 (26)	262.9 (25)	1.00 (1.00-3.00)	12.63 ± 5.15
Statistical Comparison: Ratio (Co-administration ertugliflozin + sitaglipin/Ertugliflozin monotherapy) (90% CI)[b]	NA	102.27 (99.72, 104.89)	NA	98.18 (91.20, 105.70)	NA	NA
	Sitagliptin PK[c]					
Test Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin + 100 mg sitagliptin tablet	NA	6.997 (20)	6.912 (21)	805.3 (24)	3.00 (1.00-6.00)	11.79 ± 2.98
Reference Treatment: single-dose ROA: PO Dose/Dosage form: 100 mg sitagliptin tablets	NA	6.882 (21)	6.814 (21)	792.0 (24)	2.00 (1.00-4.00)	11.00 ± 2.89

	Median Plasma Ertugliflozin Concentration-Time Profiles Following a Single Oral Dose of Ertugliflozin Alone and Co-administered with Sitagliptin  **Median Plasma Sitagliptin Concentration-Time Profiles Following a Single Oral Dose of Sitagliptin Alone and Co-administered with Ertugliflozin** 
Conclusions:	***Pharmacokinetics/Pharmacodynamics:*** For ertugliflozin, the GMRs and corresponding 90% CIs for AUC_{inf} and C_{max} were 102.27% (99.72%, 104.89%) and 98.18% (91.20%, 105.70%), respectively, indicating that there are no meaningful differences in the PK of ertugliflozin when it is administered with sitagliptin, as compared to single PO dose of ertugliflozin alone. For sitagliptin, the GMRs and corresponding 90% CIs for AUC_{inf} and C_{max} were 101.67% (98.40%, 105.04%) and 101.68% (91.65%, 112.80%), respectively, indicating that there are no meaningful differences in the PK of sitagliptin when it was administered with ertugliflozin, as compared to single PO dose of sitagliptin alone. ***Safety:*** Administration of ertugliflozin 15 mg single-dose with sitagliptin 100 mg single-dose was shown to be safe and well tolerated.

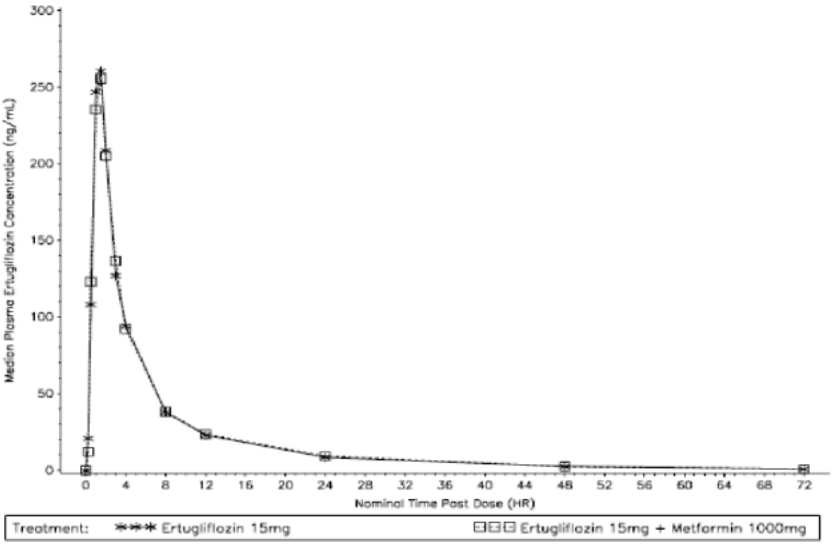
Reviewer's Comments:
The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the drug-drug interaction between ertugliflozin and sitagliptin.

4.2.14 Study P019/1032 - Two-Way DDI between Ertugliflozin 15 mg and Metformin 1000 mg

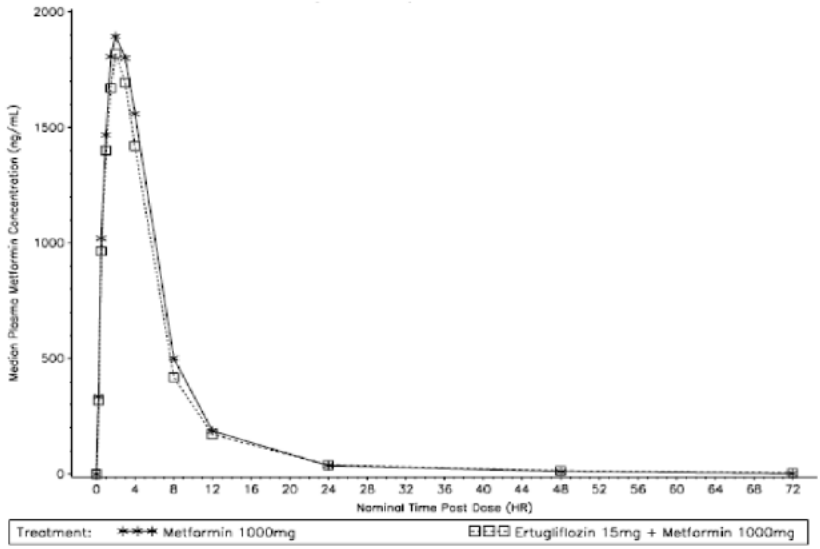
Study:	**P019/1032**
Study Title:	*A Phase 1, Randomized, Open-Label, 3-Period, 6-Sequence Study to Estimate the Pharmacokinetic Interaction Between Ertugliflozin and Metformin in Healthy Subjects*
Objectives:	• To estimate the effect of metformin on the PK of ertugliflozin following oral administration of a single dose of 15 mg ertugliflozin and 1000 mg metformin in healthy volunteers. • To estimate the effect of ertugliflozin on the PK of metformin following oral administration of a single dose of 15 mg ertugliflozin and 1000 mg metformin in healthy volunteers.
Study Design:	Phase 1, open-label, randomized, 3-period, 6-sequence, single-dose, crossover study
Study Population:	Population: Healthy Subjects Mean Age (range): 37.6 (24-55) years n = 18
Results:	

Treatment Route of Administration (ROA) Dose/Dosage Form	Mean PK Parameters[a]					
	AUC_{tau} (ng•hr/mL)	AUC_{inf} (ng•hr/mL)	AUC_{last} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
Ertugliflozin PK						
Test Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin + metformin 1000 mg tablet	NA	1388 (23)	1367 (22)	264.5 (20)	1.29 (1.00-3.00)	13.48 ± 4.65
Reference Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets	NA	1363 (24)	1346 (23)	272.3 (24)	1.02 (1.00-2.00)	11.79 ± 2.34
Statistical Comparison: Ratio (Coadministration ertugliflozin + metformin/Ertugliflozin monotherapy) (90% CI)[b]	NA	100.34 (97.43, 103.34)	101.52 (98.65, 104.48)	97.14 (88.77, 106.30)	NA	NA
Metformin PK						
Test Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin + metformin 1000 mg tablet	NA	12260 (27)	12270 (23)	1835 (26)	2.00 (1.00-3.00)	14.47 ± 6.94
Reference Treatment: single-dose ROA: PO Dose/Dosage form: 1000 mg metformin	NA	12770 (27)	12550 (26)	1983 (26)	2.00 (0.50-4.00)	10.23 ± 2.39
Statistical Comparison: Ratio (Coadministration ertugliflozin + metformin/Metformin monotherapy) (90% CI)[b]	NA	100.94 (90.62, 112.44)	97.75 (89.46, 106.82)	94.00 (82.94, 106.55)	NA	NA

Median Plasma Ertugliflozin Concentration-Time Profiles Following Single 15 mg Oral Dose Alone and With 1000 mg Metformin



Median Plasma Metformin Concentration-Time Profiles Following Single 1000 mg Oral Dose Alone and With 15 mg Ertugliflozin



Conclusions:

Pharmacokinetics/Pharmacodynamics:

For ertugliflozin, the ratios of the adjusted least squares means for AUC_{inf}, and C_{max} were 100.34% and 97.14%, respectively, and the 90% CIs for the ratios fell entirely within the accepted equivalence limits of (80%, 125%), indicating that there are no clinically meaningful differences in ertugliflozin PK when it is co-administered with metformin, as compared to a single-dose of ertugliflozin alone.

For metformin, the ratios of the adjusted least squares means for AUC_{inf} and C_{max} were 100.94% and 94.00%, respectively, and the 90% CIs for the ratios fell entirely within the accepted equivalence limits of (80%, 125%), indicating that there are no clinically meaningful differences in metformin PK when it is co-administered with ertugliflozin, as compared to a single-dose of metformin alone.

	Safety: A single PO dose of ertugliflozin 15 mg, administered alone or in combination with metformin 1000 mg was safe and well tolerated.

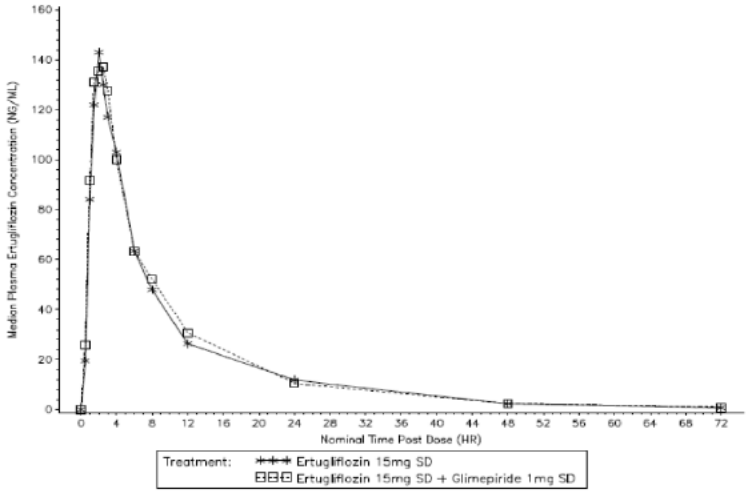
Reviewer's Comments:
The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the drug-drug interaction between ertugliflozin and metformin.

4.2.15 Study P032/1044 - Two-Way DDI between Ertugliflozin 15 mg and Glimepiride 1 mg

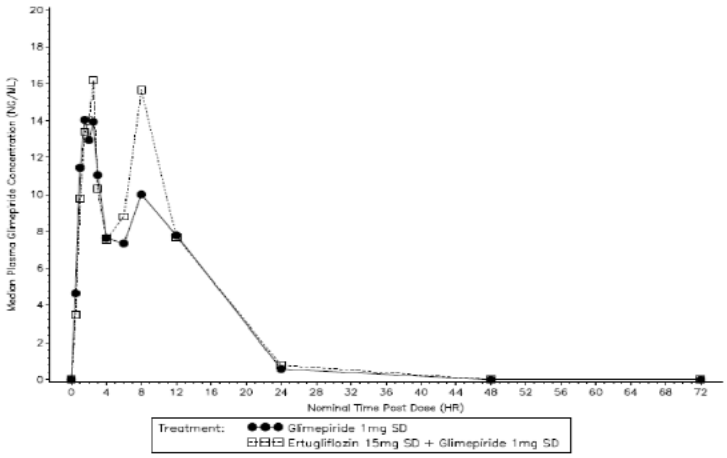
Study:	**P032/1044**
Study Title:	*A Phase 1, Randomized, Open-Label, 3-Period, 6-Sequence Study to Estimate the Pharmacokinetic Interaction Between Ertugliflozin and Glimepiride in Healthy Subjects*
Objectives:	• To estimate the effect of glimepiride on the PK of ertugliflozin following oral administration of single doses of ertugliflozin 15 mg and glimepiride 1 mg in healthy subjects. • To estimate the effect of ertugliflozin on the PK of glimepiride following oral administration of single doses of ertugliflozin 15 mg and glimepiride 1 mg in healthy subjects.
Study Design:	Phase 1, open-label, randomized, 3-period, 6-sequence, single-dose, crossover, DDI study
Study Population:	Population: Healthy Subjects Mean Age (range): 32.6 (19-50) years n = 18
Results:	

Treatment Route of Administration (ROA) Dose/Dosage Form	Mean PK Parameters[a]					
	AUC_{tau} (ng•hr/mL)	AUC_{inf} (ng•hr/mL)	AUC_{last} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
Ertugliflozin PK						
Test: Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin + glimepiride 1 mg tablet	NA	1272 (19)	1256 (19)	144.3 (20)	2.00 (1.50-3.00)	11.27 ± 3.28
Reference: Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets	NA	1225 (19)	1210 (19)	143.8 (17)	2.00 (1.50-3.00)	10.63 ± 2.44
Statistical Comparison: Ratio (Coadministration ertugliflozin + glimepiride/Ertugliflozin monotherapy) (90% CI)[b]	NA	102.11 (97.19, 107.27)	101.96 (97.25, 106.90)	98.20 (92.17, 104.63)	NA	NA
Glimepiride PK						
Test: Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin + glimepiride 1 mg tablet	NA	223.8 (78)	231.7 (64)	30.13 (52)	4.00 (1.50-12.0)	6.677 ± 4.018
Reference: Treatment: single-dose ROA: PO Dose/Dosage form: 1 mg glimepiride tablet	NA	202.3 (66)	174.4 (73)	29.42 (64)	3.00 (1.00-12.0)	5.888 ± 2.793
Statistical Comparison: Ratio (Coadministration ertugliflozin + glimepiride/Glimepiride monotherapy) (90% CI)[c]	NA	109.80 (98.14, 122.86)	127.40 (108.33, 149.83)	97.39 (71.07, 133.46)	NA	NA

Median Plasma Ertugliflozin Concentration-Time Profiles Following a Single Oral Dose of Ertugliflozin Alone and with Glimepiride



Median Plasma Glimepiride Concentration-Time Profiles Following a Single Oral Dose of Glimepiride Alone and with Ertugliflozin



Conclusions:

Pharmacokinetics/Pharmacodynamics:

There are no meaningful differences in ertugliflozin PK when it is administered with glimepiride, as compared to a single-dose of ertugliflozin alone. There are no meaningful differences in glimepiride PK when it is administered with ertugliflozin, as compared to a single-dose of glimepiride alone.

Safety:

Single PO doses of ertugliflozin 15 mg, glimepiride 1 mg, and co-administration of single-doses of ertugliflozin 15 mg and glimepiride 1 mg were found to be safe and well tolerated in healthy subjects in this study.

Reviewer's Comments:

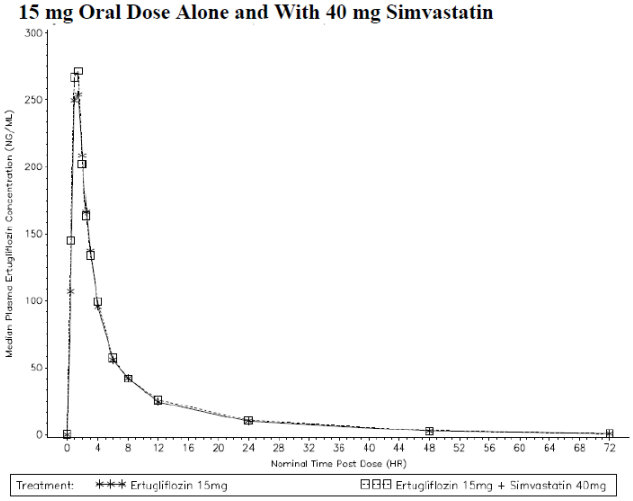
The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the drug-drug interaction between ertugliflozin and glimepiride.

4.2.16 Study P030/1036 - Two-Way DDI between Ertugliflozin 15 mg and Simvastatin 40 mg

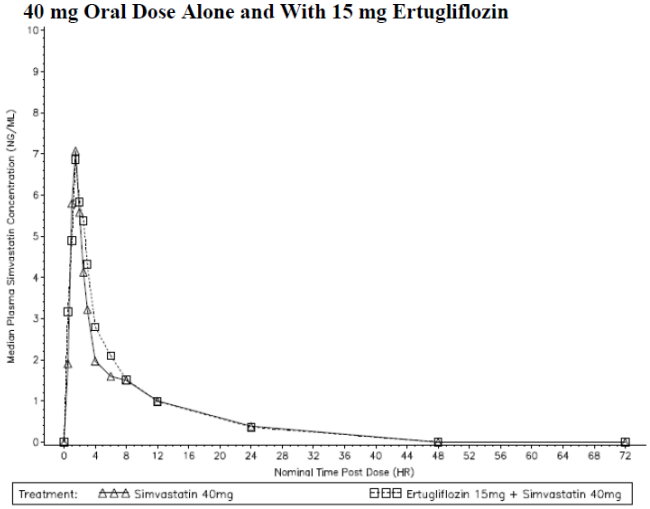
Study:	**P030/1036**
Study Title:	*A Phase 1, Randomized, Open-Label, 3-Period, 6-Sequence Study to Estimate the Pharmacokinetic Interaction Between Ertugliflozin and Simvastatin in Healthy Subjects*
Objectives:	• To estimate the effect of simvastatin on the PK of ertugliflozin following oral administration of a single dose of ertugliflozin 15 mg and simvastatin 40 mg in healthy subjects. • To estimate the effect of ertugliflozin on the PK of simvastatin and simvastatin acid following oral administration of a single dose of ertugliflozin 15 mg and simvastatin 40 mg in healthy subjects.
Study Design:	Phase 1, open-label, randomized, 3-period, 6-sequence, single-dose, crossover, DDI interaction study
Study Population:	Population: Healthy Subjects Mean Age (range): 31.3 (19-51) years n = 18
Results:	

Treatment Route of Administration (ROA) Dose/Dosage Form	Mean PK Parameters[a]					
	AUC_{tau} (ng•hr/mL)	AUC_{inf} (ng•hr/mL)	AUC_{last} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
Ertugliflozin PK						
Test: Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin + simvastatin 40 mg tablet	NA	1404 (27)	1378 (26)	280.8 (28)	1.00 (1.00-2.00)	12.58 ± 3.98
Reference: Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets	NA	1371 (24)	1348 (25)	267.0 (23)	1.50 (1.00-2.50)	12.34 ± 3.07
Statistical Comparison: Ratio (Coadministration ertugliflozin + simvastatin/Ertugliflozin monotherapy) (90% CI)[b]	NA	102.40 (99.57, 105.31)	102.26 (99.58, 105.01)	105.16 (98.26, 112.54)	NA	NA
Simvastatin PK						
Test: Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin + simvastatin 40 mg tablet	NA	46.88 (89)	45.11 (90)	9.421 (81)	1.25 (0.500-12.0)	7.436 ± 2.717
Reference: Treatment: single-dose ROA: PO Dose/Dosage form: 40 mg simvastatin tablets	NA	39.28 (55)	36.28 (72)	7.914 (63)	1.00 (0.500-12.0)	5.883 ± 1.962
Statistical Comparison: Ratio (Coadministration ertugliflozin + simvastatin/Simvastatin monotherapy) (90% CI)[b]	NA	123.83 (90.92, 168.66)	124.32 (101.56, 152.17)	119.05 (97.22, 145.77)	NA	NA
Simvastatin Acid PK						
Test: Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin + simvastatin 40 mg tablet	NA	38.35 (78)	29.47 (125)	2.085 (117)	4.00 (2.50-8.00)	8.603 ± 2.911
Reference: Treatment: single-dose ROA: PO Dose/Dosage form: 40 mg simvastatin tablets	NA	23.49 (107)	23.03 (110)	1.803 (106)	4.00 (1.50-12.0)	8.436 ± 6.001
Statistical Comparison: Ratio (Coadministration ertugliflozin + simvastatin/Simvastatin monotherapy) (90% CI)[b]	NA	130.46 (108.32, 157.13)	127.99 (111.87, 146.44)	115.66 (95.74, 139.71)	NA	NA

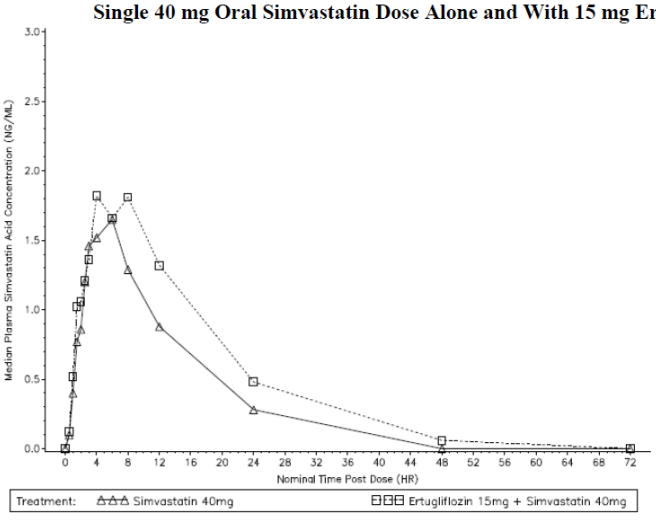
Median Plasma Ertugliflozin Concentration-Time Profiles Following Single 15 mg Oral Dose Alone and With 40 mg Simvastatin



Median Plasma Simvastatin Concentration-Time Profiles Following Single 40 mg Oral Dose Alone and With 15 mg Ertugliflozin



Median Plasma Simvastatin Acid Concentration-Time Profiles Following Single 40 mg Oral Simvastatin Dose Alone and With 15 mg Ertugliflozin



Conclusions:	***Pharmacokinetics/Pharmacodynamics:*** There is no effect of simvastatin on the PK of ertugliflozin following PO administration of a single-dose of ertugliflozin 15 mg and simvastatin 40 mg in healthy subjects. Oral administration of a single-dose of ertugliflozin 15 mg and simvastatin 40 mg in healthy subjects increased simvastatin AUCinf and Cmax by approximately 24% and 19%, respectively, and increased simvastatin acid AUC_{inf} and C_{max} by approximately 30% and 16%, respectively. These increases in simvastatin and simvastatin acid exposures are not expected to be clinically relevant. ***Safety:*** Co-administration of a single-dose of ertugliflozin 15 mg and simvastatin 40 mg was safe and well-tolerated in this study.

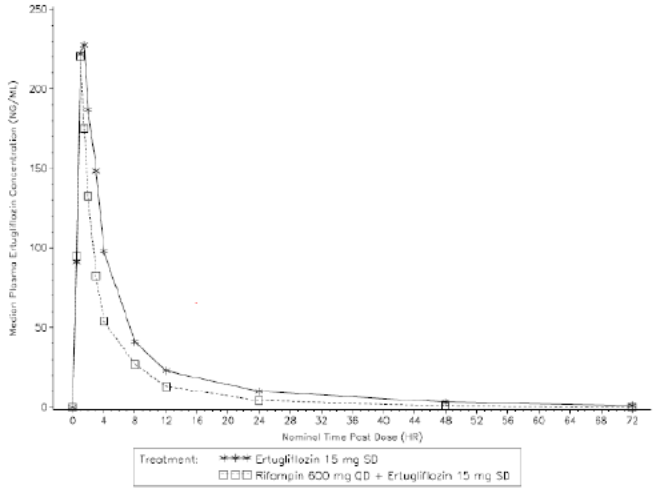
Reviewer's Comments:
The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the drug-drug interaction between ertugliflozin and simvastatin.

4.2.17 Study P021/1040 - Effect of Multiple Dose Rifampin 600 mg on the PK of Ertugliflozin 15 mg

Study:	**P021/1040**
Study Title:	*A Phase 1, Open-Label, 2-Period, Fixed Sequence Study to Estimate the Effect of Rifampin on the Pharmacokinetics of Ertugliflozin in Healthy Volunteers*
Objectives:	• To estimate the effect of rifampin oral administration on the PK of ertugliflozin 15 mg single dose (SD).
Study Design:	Phase 1, open-label, 2-period, fixed-sequence study
Study Population:	Population: Healthy Subjects Mean Age (range): 41.3 (19-54) years n = 12
Results:	

Treatment Route of Administration (ROA) Dose/Dosage Form	Mean PK Parameters[a]					
	AUC_{tau} (ng•hr/mL)	AUC_{inf} (ng•hr/mL)	AUC_{last} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
	Ertugliflozin PK					
Test: Treatment: multiple doses of rifampin 600 mg qd (Days 1-7 and Days 9-10) and single-dose of ertugliflozin ROA: PO Dose/Dosage form: 15 mg ertugliflozin + rifampin 600 mg qd tablet	NA	838.1 (21)	828.5 (22)	199.8 (40)	1.00 (0.50-3.08)	9.2 ± 2.8
Reference: Treatment: single-dose ROA: PO Dose/Dosage form: 15 mg ertugliflozin tablets	NA	1370 (30)	1350 (31)	236.1 (38)	1.00 (1.00-3.00)	12.3 ± 2.9
Statistical Comparison: Ratio (Coadministration ertugliflozin + rifampin/Ertugliflozin monotherapy) (90% CI)[b]						
	NA	61.16 (57.22, 65.37)	NA	84.62 (74.17, 96.53)	NA	NA

Median Plasma Ertugliflozin Concentration-Time Profiles Following a Single Oral Dose of Ertugliflozin Alone and Co-administered with Multiple Dose Rifampin



Conclusions:	***Pharmacokinetics/Pharmacodynamics:*** Co-administration of multiple doses of 600 mg qd rifampin and a single 15 mg ertugliflozin dose decreased ertugliflozin exposure (AUC_{inf}) and peak exposure (C_{max}) by approximately 39% and 15%, respectively, relative to when ertugliflozin was administered alone. ***Safety:*** A single PO dose of ertugliflozin 15 mg, administered in the absence and the presence of multiple-dose rifampin was safe and well tolerated in healthy subjects evaluated in this study.

Reviewer's Comments:
The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The trial reasonably captured the drug-drug interaction between ertugliflozin and rifampin.

4.3 Pharmacometrics Assessment

4.3.1 Applicant's Population PK Analysis

The applicant conducted population PK analysis to:

- Describe the structural pharmacokinetic (PK) model and quantify the population variability in the PK parameters of ertugliflozin.
- Describe the effects of intrinsic and/or extrinsic factors on ertugliflozin exposure.
- Generate individual clearance estimates for patients in Phase 2 and 3 studies that can be used for subsequent exposure-response analyses.

Pharmacokinetic data from 15 clinical studies (nine Phase 1, two Phase 2, and four Phase 3 studies) were included in the analysis. The study design, study population, and timing of blood samples varied among the 15 clinical studies. The study designs are summarized in Table 4.3.1-1. The data file for the final model contained 13691 PK observations from 2276 subjects.

Table 4.3.1-1 Study Design Summary

Protocol # & Study Design	Dosage Regimen & Study Description	Number of Subjects in POPPK Analysis, Subject Type & Food Status	Dose(s) [mg]
MK-8835-036/B1521001: Phase 1, randomized, double-blind, placebo-controlled, two cohort, interleaving design, first-in-human, crossover study	Solution/suspension administered as single ascending dose to evaluate PK, safety & tolerability	24 healthy and fasted/fed (100 mg)	0.5, 2.5, 10, 30, 100, 300
MK-8835-037/B1521002: Phase 1, randomized, double-blind, placebo-controlled, parallel group study	Solution/suspension administered as single & 14-day repeated QD dose to evaluate PK, PD, safety & tolerability	32 healthy and fed	1, 5, 25, 100
MK-8835-038/B1521003: Phase 1, non-randomized, open-label, single group, single-period study	Suspension administered as single radiolabeled dose to evaluate PK, mass balance & metabolism	6 healthy and fasted	25
MK-8835-040/B1521007: Phase 1, randomized, double-blind, placebo-controlled, 2-cohort, 2-period crossover study	Tablet(s) administered as a single dose or split into two doses, administered 5 hours apart, to evaluate PK, PD, safety & tolerability	52 T2DM and fed	2 mg QD or 1 mg BID/ 4 mg QD or 2 mg BID

MK-8835-041/B1521009: Phase 1, randomized, double-blind, placebo-controlled, two cohort, parallel group study	Tablet(s) administered as ascending single & multiple daily dose × 7 days to evaluate PK, PD, safety & tolerability	18 healthy and fasted/fed (25 mg QD × 7 days)	1, 5, 25
MK-8835-009/B1521023: Phase 1, non-randomized, open label, parallel group study	Tablet(s) administered as single dose to evaluate effect of RI on PK, PD, safety & tolerability	36; 8 healthy and fasted, 28 T2DM and fasted	15
MK-8835-010/B1521025: Phase 1, randomized, sponsor open, placebo- & active-controlled, 3-period crossover study	Tablet(s) administered as single dose to evaluate effect on QT interval	40 healthy and fasted	100
MK-8835-024/B1521048: Phase 1, randomized, open-label, 2-period, crossover study	Tablet(s) administered as single dose to evaluate effect of food on PK	14 healthy and fasted/fed	15
MK-8835-035/B1521051: Phase 1, randomized, open-label, 2-period, 2-way crossover study	Tablet(s) administered as a single dose or split into two doses × 6 days to demonstrate bioequivalent PK & similar PD effect	50 healthy and fasted	5 mg QD or 2.5 mg BID/ 15 mg QD or 7.5 mg BID
MK-8835-042/B1521004: Phase 2, randomized, double-blind, double-dummy, placebo- & active-controlled, 5-arm, parallel group study	Tablet(s) administered daily for 4-weeks to evaluate effect on systolic blood pressure	111 T2DM and fed	1, 5, 25
MK-8835-016/B1521006: Phase 2, randomized, double-blind, double-dummy, placebo- & active-controlled, 6-arm, 2-period, parallel group study	Tablet(s) administered daily for 12-weeks to evaluate dose-response of glycemic control	196 T2DM and fed	1, 5, 10, 25
MK-8835-001/B1521016: Phase 3, randomized, double-blind, multicenter, placebo-controlled, parallel group study	Tablet(s) administered once daily for 52 weeks (including a 26-week Phase A and 26-week Phase B) to evaluate safety and efficacy	289 T2DM and without regard to food [a]	5, 15

MK-8835-007/B1521017: Phase 3, randomized, double-blind, multicenter, placebo-controlled study	Tablet(s) administered once daily for 26 weeks to evaluate effect on HbA1c, safety & tolerability followed by 78-week extension	386 T2DM and without regard to food [a]	5, 15
MK-8835-005/B1521019: Phase 3, randomized, double-blind, active-controlled, 5-arm, multicenter, parallel group study	Tablet(s) administered once daily for 52 weeks (including a 26-week Phase A and 26-week Phase B) to evaluate safety and efficacy when combined with sitagliptin	736 T2DM and without regard to food [a]	5, 15
MK-8835-003/B1521022: Phase 3, randomized, double-blind, multicenter, placebo-controlled study	Tablet(s) administered once daily for 26 weeks to evaluate effect on HbA1c, safety & tolerability followed by 26-week extension	286 T2DM and without regard to food [a]	5, 15

[a] Data from Phase A was included; Abbreviations: RI=Renal impairment, PK=Pharmacokinetics, T2DM=Type 2 diabetes mellitus, QD=Once daily, BID=Twice daily, QT=Time interval from Q wave start to T wave end, HbA1c=Glycated hemoglobin;
(Source: Applicant's Population PK report, Table S1)

Table 4.3.1-2 provides summary statistics of the baseline demographic covariates in the analysis dataset. Approximately 44% of subjects had normal renal function (eGFR≥ 90 mL/min/1.73 m^2), 41% had mild renal impairment (60 ≤eGFR < 90 mL/min/1.73 m^2), 14% had moderate renal impairment (30 ≤ eGFR < 60 mL/min/1.73 m^2), and 1% had severe renal impairment (eGFR < 30 mL/min/1.73 m^2).

Table 4.3.1-2 Summary of Baseline Demographic Covariates for Analysis

Covariate	Statistic	Total
Baseline Body Weight (kg)	N	2276
	Mean (SD)	86.9 (19.7)
	Median (min, max)	84.8 (42.6, 197)
Age (year)	N	2276
	Mean (SD)	55.7 (11.6)
	Median (min, max)	57.0 (18.0, 87.0)
Baseline eGFR (mL/min/1.73m^2)	N	2276
	Mean (SD)	85.9 (24.3)
	Median (min, max)	86.6 (6.80, 196)
Sex		
Male	N (%)	1287 (56.5)
Female	N (%)	989 (43.5)
Race		
White	N (%)	1634 (71.8)
Black/African American	N (%)	199 (8.74)
Asian	N (%)	315 (13.8)
Other	N (%)	128 (5.62)
Subject Status		
Healthy	N (%)	192 (8.44)
T2DM	N (%)	2084 (91.6)
Food Status		
Fasted	N (%)	275 (11.2)
Fed	N (%)	473 (19.3)
Without Regard to Food	N (%)	1697 (69.4)

(Source: Applicant's Population PK report, Table 5)

A 2-compartment model with lag time, first-order absorption, and first-order elimination was used to fit the observed data in terms of the following parameters: apparent clearance (CL/F), apparent inter-compartmental clearance (Q/F), apparent central volume of distribution (Vc/F), apparent peripheral volume of distribution (Vp/F), first-order absorption rate constant (ka), and absorption lag time (ALAG1). Interindividual variance was included on CL/F. The effect of baseline body weight was included on CL/F, Vc/F, Vp/F, and Q/F as an allometric relationship, with the exponent fixed to 0.75 and 1.0 for apparent clearances and volumes, respectively. The effect of food (fed and without regard to food) was included on the ka and on relative bioavailability (F1). Separate residual variance parameters were also incorporated for Phase 1 and Phase 2/3 data. Covariate model building used the full model estimation (FME) procedure. The selection of covariates included in the final model was based upon clinical judgment, physiologic relevance and mechanistic plausibility. Additionally, collinearity of covariates was assessed to ensure that no collinear covariates were added to the model. Covariates including estimated glomerular filtration rate (eGFR), gender, race and patient status on CL/F, and age, gender and race on Vc/F were added to the final model. A negative correlation between age and eGFR was observed (ie, as age increases, eGFR decreases), and therefore age was not included as a covariate on CL/F. By using the FME procedure, all covariate effects were estimated simultaneously to establish the final model. Bootstrapping was used to generate 95% confidence intervals (CIs) for the final population PK model parameters.

The reference subject for the population PK analysis was defined as a 65 year-old, healthy, white male in the fasted state with a baseline body weight of 85 kg and an eGFR of 90 mL/min/1.73 m2. The reference subject chosen for this analysis is slightly different from the typical patient in the Phase 3 program (e.g., type 2 diabetic, median age 59 years, median eGFR 83 mL/min, median body weight 86 kg)[Ref. 5.3.5.3: 04J759]. Continuous covariate reference values were set to 85 kg for baseline body weight (based upon the population median of 84.8 kg in the dataset), an age of 65 years (which was the minimum age considered as elderly), and an eGFR of 90 mL/min/1.73 m^2 (based upon the minimum value considered as normal renal function).

Covariate effects on CL/F are illustrated in Figure 4.3.1-1. The 95% CI of the ratio was generated from 1035 non-parametric bootstrapped sets of population parameter values using the final population PK model. Parameter estimates for the final model are presented in Table 4.3.1-3, and diagnostic plots for the overall final model fit are provided in. Figure 4.3.1-2.

Table 4.3.1.3 Parameter Estimates for the Final Model

Parameter (unit)	Estimate	RSE(%)	Median (95% CI)
CL/F (L/hr) (θ_1)	12.0	2.18	12.0 (11.5, 12.5)
Effect of body weight	0.750 FIX	—	—
Effect of eGFR (θ_{13})	0.455	7.47	0.453 (0.382, 0.523)
Effect of $PTST_{T2DM}$ (θ_{14})	0.904	2.96	0.906 (0.850, 0.958)
Effect of sex_{female} (θ_{15})	0.962	1.87	0.963 (0.927, 0.998)
Effect of $race_{black}$ (θ_{16})	0.985	2.69	0.985 (0.935, 1.04)
Effect of $race_{asian}$ (θ_{17})	1.08	2.68	1.08 (1.02, 1.14)
Effect of $race_{other}$ (θ_{18})	0.992	3.40	0.992 (0.928, 1.06)
Vc/F (L) (θ_2)	6.54	13.2	6.60 (5.17, 8.48)
Effect of body weight	1.00 FIX	—	—
Effect of age (θ_{19})	-0.243	-95.5	-0.229 (-0.678, 0.223)
Effect of sex_{female} (θ_{20})	1.36	13.6	1.36 (1.05, 1.79)
Effect of $race_{black}$ (θ_{21})	0.917	17.7	0.931 (0.649, 1.30)
Effect of $race_{asian}$ (θ_{22})	2.12	21.7	2.13 (1.40, 3.18)
Effect of $race_{other}$ (θ_{23})	1.15	17.0	1.15 (0.803, 1.60)
Vp/F (L) (θ_3)	107	2.65	107 (102, 113)
Effect of body weight	1.00 FIX	—	—
Q/F (L/hr) (θ_4)	7.77	5.73	7.84 (7.00, 8.67)
Effect of body weight	0.750 FIX	—	—
k_a (θ_5) (hr^{-1})	0.329	4.80	0.331 (0.303, 0.364)
Effect of food (θ_9)	0.726	4.59	0.726 (0.670, 0.783)
Effect of without regard to food (θ_{10})	0.663	5.29	0.663 (0.596, 0.744)
ALAG1 (hr) (θ_6)	0.228	1.94	0.228 (0.218, 0.235)
F1	1.00 FIX	—	—
Effect of food (θ_{11})	0.0683	34.7	0.0685 (0.0217, 0.110)
Effect of without regard to food (θ_{12})	0.0809	40.2	0.0809 (0.0136, 0.151)
ω^2-CL/F	0.102	9.53	0.101 (0.0831, 0.120)
Phase 1 residual error (θ_7)	0.387	2.95	0.385 (0.366, 0.405)
Phase 2/3 residual error (θ_8)	0.836	1.84	0.836 (0.808, 0.864)

Point estimates and relative standard errors (RSE) of the estimates were estimated using NONMEM; Median and 95% confidence intervals of the estimates were obtained from nonparametric bootstrap estimates (N=1035, 8 runs with minimization terminated and 22 runs with estimates near a boundary were skipped when calculating the bootstrap results); Abbreviations: PTST=Patient type, CI=Confidence interval; Source: ePharmacology Step ID Number: 638370 (final model) and 638381 (bootstrap)

(Source: Applicant's Population PK report, Table 8)

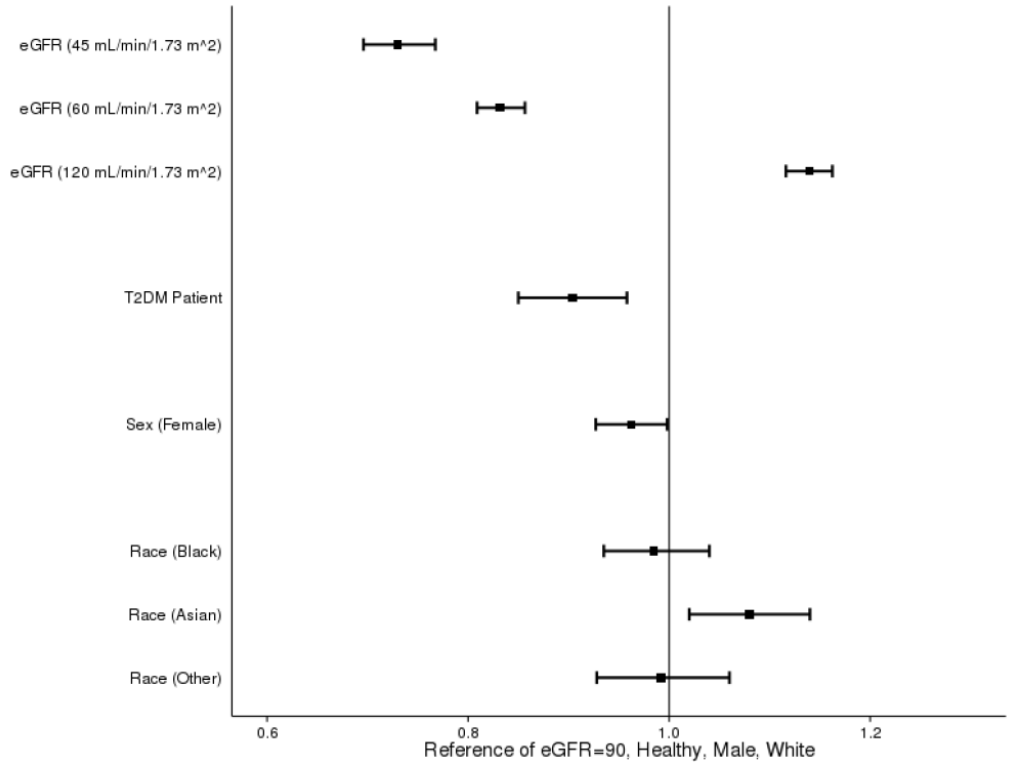


Figure 4.3.1-1 Covariate Effects on Apparent Clearance (95% CI)
(Source: Applicant's Population PK report, Figure 3)

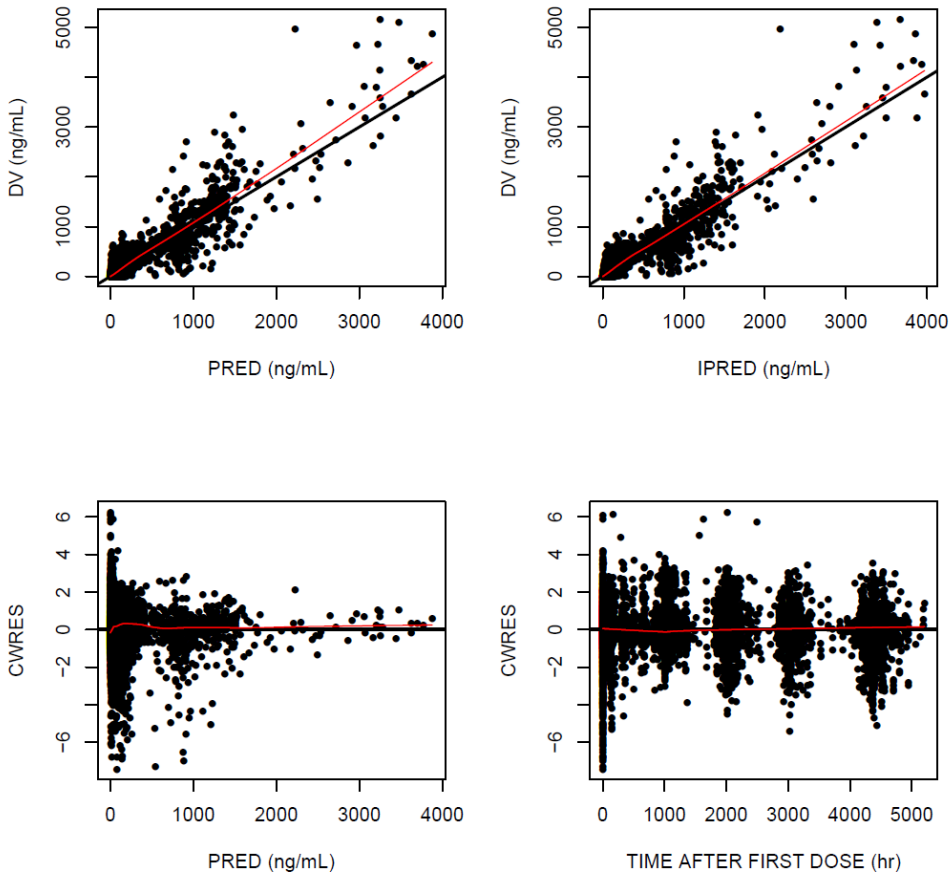


Figure 4.3.1-2 Final Model Diagnostic Plots
(Source: Applicant's Population PK report, Figure 2)

Applicant's Conclusion:

- Ertugliflozin pharmacokinetics were adequately characterized by a 2-compartment model with lag time, first-order absorption, and first-order elimination.
- Apparent clearance was estimated to be 12.0 L/hr for the reference subject: a 65 year-old, healthy, white male with a baseline body weight of 85 kg, an eGFR of 90 mL/min/1.73 m2, and taking ertugliflozin in the fasted state.
- Covariates that were determined to be predictive of ertugliflozin CL/F included baseline body weight, baseline eGFR, T2DM status, female sex, and Asian race. Apparent clearance increased with increasing body weight and eGFR. Furthermore, apparent clearance was slightly lower in T2DM patients (vs healthy subjects) and females, and slightly higher in Asian subjects. These covariate effects are not anticipated to be clinically relevant.
- The shrinkage for CL/F was 28.7% and therefore the post-hoc individual estimates of CL/F should be used with caution.
- Covariates that were determined to be predictive of ertugliflozin Vc/F included baseline body weight, female sex, and Asian race. Apparent central volume of distribution increased with increasing body weight, and was higher in females and Asian subjects. These covariate effects are not anticipated to be clinically relevant.
- Administration of ertugliflozin with food decreased the rate of absorption and relative bioavailabilty of ertugliflozin. When ertugliflozin is administered without regard to food,

estimates of the rate of absorption and relative bioavailability were similar to those for administration with food. These covariate effects are not anticipated to be clinically relevant.

Reviewer's Comments:
The applicant's final PopPK model was able to describe the ertugliflozin plasma concentration versus time data in healthy subjects and T2DM patients reasonably well. The covariate effects identified on CL/F and V/F are not considered to be clinically significant and therefore no dose adjustment is warranted based on these factors. The shrinkage of CL/F (28.7%) exceeded the pre-specified value 25% in analysis plan, the applicant subsequently selected a longitudinal dose-response analysis as the primary analysis to characterize the exposure/dose-response relationship.

4.3.2 Applicant's Dose-Response Analysis

The applicant conducted population dose-response analyses in T2DM subjects to:

- Describe the appropriate structural exposure-response or dose-response model and quantify the population response and variability in glycated hemoglobin (HbA1c) lowering of ertugliflozin.
- Describe the effects of intrinsic (e.g. demographic, baseline HbA1c, renal function), diabetes duration and/or extrinsic (e.g. background treatment, lead-in time) factors on ertugliflozin HbA1c exposure-response.

Data from one phase 2 and four phase 3 studies were included in the exposure (and dose) versus HbA1c response analysis. Details of the study designs are provided in Table 4.3.2-1. As per the analysis plan, data from the ertugliflozin co-administered with sitagliptin treatments in Study P005/1019 and the sitagliptin treatment in Studies P016/1006 and P005/1019 were excluded from the efficacy analysis. All observed cases were included in the dataset. For subjects that received glycemic rescue prior to Week 26 in any study, the observations post rescue initiation were excluded from the dose-response analysis. Additionally, subjects identified as metformin users during the conduct of Study P001/1016 were also excluded from this analysis. The final model-ready dataset included 10109 records from 2185 subjects. The baseline demographics of the population included in the analysis are summarized in Table 4.3.2-2.

Table 4.3.2-1 Study Design Summary

Protocol # & Study Design	Dosage Regimen & Study Description: A1C Observation Times	Total # of Study Population Administered Ertugliflozin	Ertugliflozin Dose(s) (mg, QD)
MK-8835-016/B1521006: Phase 2, randomized, double-blind, double-dummy, placebo- & active-controlled, 6-arm, 2-period, parallel group study.	Tablet(s) administered daily for 12-weeks to evaluate dose-response of glycemic control: Week 0, 2, 4, 8 and 12.	217 T2DM with inadequate glycemic control on stable doses of metformin for glycemic control	1, 5, 10, 25

MK-8835-001/B1521016: Phase 3, randomized, double-blind, multicenter, placebo-controlled, parallel group study.	Tablet(s) administered once daily for 26 weeks (Phase A) to evaluate safety and efficacy followed by 26-week extension: Week 0, 6, 12, 18 and 26.	250 T2DM with inadequate glycemic control on background anti-hyperglycemic therapy (variable anti-hyperglycemic agents) & Stage 3 chronic kidney disease	5, 15
MK-8835-007/B1521017: Phase 3, randomized, double-blind, multicenter, placebo-controlled study.	Tablet(s) administered once daily for 26 weeks (Phase A) to evaluate effect on A1C, safety & tolerability followed by 78-week extension: Week 0, 6, 12, 18 and 26.	400 T2DM with inadequate glycemic control on metformin monotherapy & 41% of total study population are post-menopausal women	5, 15
MK-8835-005/B1521019: Phase 3, randomized, double-blind, active-controlled, 5-arm, multicenter, parallel group study. Only the 5 mg and 15 mg ertugliflozin arms will be included.	Tablet(s) administered once daily for 26 weeks (Phase A) to evaluate safety and efficacy when combined with sitagliptin, followed by 26-week extension: Week 0, 6, 12, 18 and 26.	484 T2DM with inadequate glycemic control on metformin monotherapy	5, 15
MK-8835-003/B1521022: Phase 3, randomized, double-blind, multicenter, placebo-controlled study.	Tablet(s) administered once daily for 26 weeks (Phase A) to evaluate effect on A1C, safety & tolerability followed by 26-week extension: Week 0, 6, 12, 18 and 26.	292 T2DM with inadequate glycemic control despite diet & exercise background	5, 15

(Source: Applicant's Dose-response analysis report, Table S1)

Table 4.3.2-2. Summary of Baseline Demographics for the Ertugliflozin Dose vs HbA1c Response Dataset

Demographic	N	Mean	Median	Range
Baseline A1C (%)	2185	8.23	8.00	5.40 to 12.5
Baseline eGFR (mL/min/1.73 m^2)	2185	82.4	83.0	22.0 to 196
eGFR≥90 (normal renal function)	824	107	103	90.0 to 196
eGFR≥60 and <90 (mild RI)	943	76.8	78.0	60.0 to 89.7
eGFR≥30 and <60 (moderate RI)	409	47.1	48.8	30.0 to 59.0
eGFR≥45 and <60 (stage 3A CKD)	272	51.6	51.0	45.0 to 59.0
Baseline Body Weight (kg)	2185	88.0	85.6	42.6 to 208
Age (year)	2185	57.9	59.0	21.0 to 87.0
T2DM Disease Duration (year)	2185	8.09	6.40	0.00 to 46.4

(Source: Applicant's Summary of Clinical Pharmacology, Table 14)

The analysis of HbA1c versus time data explored ertugliflozin efficacy as a function of average steady-state concentration (Cav) (exposure-response) and dose (dose-response). The decision to implement HbA1c modeling as a function of dose was based on an assessment of Empirical Bayes prediction of the inter-individual random effect (h) shrinkage on apparent clearance (CL/F) from the population PK analysis. Since shrinkage of CL/F exceeded the pre-specified 25% as stated in analysis plan (28.7%), the decision was made to implement a longitudinal dose-response analysis. A longitudinal exposure-response model was also fitted to the observed HbA1c data, but did not provide any additional predictive performance benefit over the dose-response model.

The final dose-response model included two first order rate constant parameters describing the temporal profiles of HbA1c for placebo and ertugliflozin data respectively, a point estimate for placebo response, maximum effect (Emax) and dose at half maximum effect (ED50) characterizing ertugliflozin response, and an estimated baseline HbA1c. Two inter-individual variance parameters were included in the final model, one each associated with the baseline HbA1c (multiplicative exponential) and placebo (additive) parameters, and an additive residual variance parameter. Covariate inclusion in the final model was implemented through the full model estimation (FME) approach, relying on clinical judgment, physiologic relevance and mechanistic plausibility to determine which covariates should be included with the various efficacy parameters. The final model included baseline HbA1c, baseline eGFR, duration of diabetes and anti-hyperglycemic background treatment on Emax, and age and baseline body weight on ED50. Finally, bootstrap analysis was used to predict ertugliflozin 5 and 15 mg HbA1c responses for a representative patient defined by values of demographics for subjects included in the pooled analysis of the Ertugliflozin Summary of Clinical Efficacy and a Stage 3a chronic kidney disease (CKD) patient.

The final forms of placebo, E_{max} and ED_{50} in the final model were as follows:

$$PBO = \theta_2 \cdot \left(\frac{E0}{8}\right)^{\theta_{14}}$$

$$E_{max} = \theta_4 \cdot \left(\frac{E0}{8}\right)^{\theta_6} \cdot \left(\frac{eGFR}{90}\right)^{\theta_8} \cdot (1 + \{PDUR - 8\} \cdot \theta_{11}) \cdot (\theta_{12})^{other} \cdot (\theta_{13})^{diet}$$

$$ED50 = \theta_5 \cdot \left(\frac{AGE}{65}\right)^{\theta_9} \cdot \left(\frac{WT}{85}\right)^{\theta_{10}}$$

In these equations, θ_2 represents placebo, $\theta 14$ the scalar describing the effect of baseline HbA1c on PBO, θ_4 represents E_{max}, θ_6 the scalar describing the effect of baseline HbA1c on E_{max}, θ_8 the scalar describing the effect of eGFR on E_{max}, θ_{11} the scalar describing the effect of diabetes duration on E_{max}, θ_{12} the scalar describing the effect of other background antidiabetic treatment on E_{max} (not metformin or diet and exercise alone), θ_{13} the scalar describing the effect of a background of diet and exercise alone on E_{max}, θ_5 represents ED_{50}, θ_9 the scalar describing the effect of baseline age on ED_{50}, and θ_{10} the scalar describing the effect of baseline weight on ED_{50}.

Basic goodness of fit diagnostics plots for the longitudinal dose-response final model are depicted in Figure 4.3.2.1.

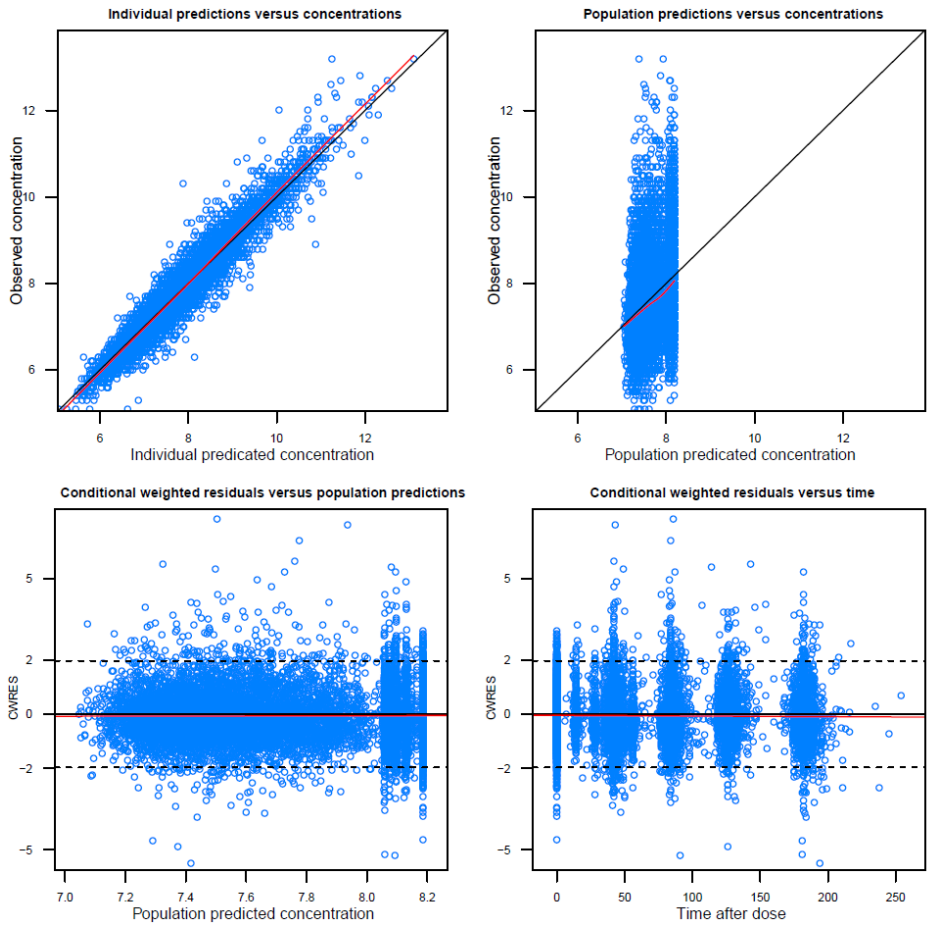


Figure 4.3.2-1 Final Model Diagnostic Plots

Final model parameter estimates and bootstrap 95% confidence intervals are presented in Table 4.3.2-3. Based on the 95% confidence interval results, the estimated effect of baseline weight on ED_{50} and a background of diet and exercise alone were not significant. All other covariates were significant.

Table 4.3.2-3 Final model parameter estimates and bootstrap 95% confidence intervals

Parameter	Estimate (%RSE)	Lower 95% Bound	Upper 95% Bound
$k_{day.PBO}$ (day^{-1})	0.0113 (11.9)	0.00879	0.0146
$k_{day.Ertu}$ (day^{-1})	0.0353 (12.4)	0.0269	0.0433
PBO (%)	-0.135 (42.1)	-0.223	-0.00412
E0 (%)	8.19 (0.260)	8.14	8.23
E_{max} (%)	-0.745 (8.81)	-0.899	-0.624
ED_{50} (mg)	1.30 (45.0)	0.0699	2.64
E0 ~ E_{max}	1.47 (28.9)	0.772	2.45
E0 ~ PBO	3.41 (8.84)	2.82	3.93
eGFR ~ E_{max}	0.368 (38.6)	0.104	0.658
Age ~ ED_{50}	3.25 (40.9)	0.648	16.7
WT ~ ED_{50}	0.417 (444)	-11.0	6.37
PDUR ~ E_{max}	-0.0265 (21.2)	-0.0373	-0.0161
Other ~ E_{max}	0.729 (16.9)	0.511	0.999
Diet ~ E_{max}	0.882 (7.37)	0.750	1.01
ω^2_{PBO}	0.545 (11.5)	0.434	0.705
ω^2_{E0}	0.013 (3.34)	0.012	0.014
σ^2	0.115 (4.03)	0.106	0.124

(Source: Applicant's Dose-response analysis report, Table 6)

Table 4.3.2-4 presents ertugliflozin placebo-adjusted CFB HbA1c responses for a representative T2DM patient at week 26, identified from the pooled efficacy analysis. Differences between the dose-response model-estimated and the pooled analysis mean responses are likely related to the differences in the studies that were included in dataset for these respective analyses, as well as the uncertainty in the estimate of ED_{50} and associated covariates in the dose-response analysis. Additionally, the dose-response model is a longitudinal model characterizing the time-course of the HbA1c response, while the pooled analysis focused only on the Week 26 response.

The impact of reduced ertugliflozin exposure with rifampin co-administration was evaluated using the dose-response model. The decrease in exposure with rifampin co-administration was included within the model as a decrease in dose (with associated uncertainty). Using representative patient demographics, the model-predicted mean (95% CI) placebo-adjusted CFB HbA1c responses for 5 mg and 15 mg doses of ertugliflozin co-administered with rifampin were 0.625% (0.783%, -0.482%) and -0.713% (0.841%, 0.604%), respectively.

Table 4.3.2-4. Predicted Mean Ertugliflozin Change from Baseline and Placebo-Adjusted Change from Baseline HbA1c Response [95% Confidence Intervals] for the Representative Patient atWeek 26

Response	Mean CFB [95% CI]	Mean Placebo-Adjusted CFB [95% CI]
Placebo Response (%)	-0.113 [-0.201, -0.00398]	...
5 mg Response (%)	-0.788 [-0.855, -0.723]	-0.674 [-0.805, -0.565]
15 mg Response (%)	-0.849 [-0.905, -0.794]	-0.735 [-0.869, -0.626]
5/15 mg Difference (%)	-0.0611 [-0.134, -0.000960]	-0.0611 [-0.134, -0.000960]
5 mg Response, Effect of Rifampin (%)	-0.739 [-0.846, -0.633]	-0.625 [-0.783, -0.482]
15 mg Response, Effect of Rifampin (%)	-0.826 [-0.875, -0.772]	-0.713 [-0.841, -0.604]

(Source: Applicant's Dose-response analysis report, Table 7)

Table 4.3.2-5 presents model predicted ertugliflozin mean placebo-adjusted CFB HbA1c responses for individuals with varying degrees of renal function. These predictions were generated using values of eGFR set to the mid-point of the range in each specific renal function group. Additionally, renal function group-specific values for the other influential covariates on E_{max} were used in these predictions, including baseline HbA1c and diabetes duration, since all three of these covariates have a significant impact on HbA1c response. Covariates associated with ED_{50}, age and weight, were set to 65 years and 85 kg, respectively, due to the uncertainty in these covariate estimates.

Table 4.3.2-5 Predicted Effect of Renal Function on Mean Ertugliflozin Placebo-Adjusted Change from Baseline HbA1c Response at Week 26

Group	Estimate	Lower 95% Bound	Upper 95% Bound
5 mg Normal Renal Function: eGFR of 105 mL/min/1.73 m^2, baseline A1C 8.34%, diabetes duration 6.51 years (%)	-0.725	-0.902	-0.559
15 mg Normal Renal Function: eGFR of 105 mL/min/1.73 m^2, baseline A1C 8.34%, diabetes duration 6.51 years (%)	-0.820	-0.982	-0.693
5 mg Mild Renal Impairment: eGFR of 75 mL/min/1.73 m^2, baseline A1C 8.19%, diabetes duration 7.03 years (%)	-0.614	-0.767	-0.482
15 mg Mild Renal Impairment: eGFR of 75 mL/min/1.73 m^2, baseline A1C 8.19%, diabetes duration 7.03 years (%)	-0.695	-0.839	-0.577

5 mg Moderate Renal Impairment: eGFR of 45 mL/min/1.73 m^2, baseline A1C 8.12%, diabetes duration 13.6 years (%)	-0.420	-0.573	-0.300
15 mg Moderate Renal Impairment: eGFR of 45 mL/min/1.73 m^2, baseline A1C 8.12%, diabetes duration 13.6 years (%)	-0.476	-0.652	-0.343
5 mg Stage 3a CKD: eGFR of 52.5 mL/min/1.73 m^2, baseline A1C 8.10%, diabetes duration 12.4 years (%)	-0.458	-0.603	-0.339
15 mg Stage 3a CKD: eGFR of 52.5 mL/min/1.73 m^2, baseline A1C 8.10%, diabetes duration 12.4 years (%)	-0.518	-0.681	-0.393

(Source: Applicant's Dose-response analysis report, Table 8)

Applicant's conclusion for the ertugliflozin dose-response analysis for HbA1c response:

- The HbA1c efficacy data were adequately described by a longitudinal E_{max} dose-response model.
- The covariates baseline HbA1c, baseline eGFR and diabetes duration had an influential impact on E_{max}, and baseline age had a influential impact on ED_{50}. Other background treatment on E_{max} was significant, but was confounded by study (MK-8835-001/B1521016). E_{max} increased with increasing baseline HbA1c and eGFR, and decreased with increasing disease duration. While age was significant predictor of ED_{50}, it was not well estimated and variable. Diet and exercise alone as a background treatment on E_{max} and baseline weight on ED_{50} were not significant.
- The mean placebo-adjusted CFB HbA1c responses for the ertugliflozin 5 mg and 15 mg doses were >80% and >90% of E_{max}, respectively.
- A representative T2DM patient mean placebo-adjusted CFB HbA1c responses for the ertugliflozin 5 mg and 15 mg doses at week 26 were -0.674% and -0.735%, respectively.
- A representative T2DM patient mean placebo-adjusted CFB HbA1c responses for the ertugliflozin 5 mg and 15 mg doses with concomitant use of rifampin at week 26 were -0.625% and -0.713%, respectively.
- The final model adequately described the effect of renal function over the range of eGFR observed in the five studies contributing data to the analysis. The ertugliflozin 5 mg and 15 mg predicted mean placebo-adjusted CFB HbA1c responses in Stage 3a CKD were -0.458% and -0.518%, respectively.

4.4 Applicant's Physiological-based Pharmacokinetic (PBPK) Modeling Assessment

The applicant conducted a PBPK modeling based analysis to assess the risk of a uridine diphosphateglucuronosyltransferase (UGT)-mediated drug-drug interaction (DDI) for ertugliflozin in humans with mefenamic acid as the UGT inhibitor, using Simcyp® PBPK software (v 15, release 1).

4.4.1 Background

The Sponsor assessed the DDI potential for ertugliflozin and its 2 primary circulating glucuronide metabolites, M5c and M5a, on selected CYP and UGT enzymes and drug transporters. M5c and M5a are pharmacologically inactive at clinically relevant concentrations, however, they are present at ~50% and ~25% of circulating ertugliflozin concentrations after oral administration of [^{14C}]ertugliflozin. Hence, the potential for M5c and M5a mediated DDI was evaluated *in vitro*. Assessment of CYP, UGT, P-gp, and BCRP DDI risk in the gastrointestinal (GI) tract was not conducted, since M5c and M5a are metabolites and not administered orally.

The major elimination pathway of ertugliflozin is glucuronidation (86%), with minor contributions from oxidative metabolism (12%) and renal excretion (2%). At clinically relevant concentrations, ertugliflozin was a substrate for the P-gp and BCRP efflux transporters, but not the OATP1B1, OATP1B3, OATP2B1, OCT1, OAT1, OAT3, and OCT2 uptake transporters.

The minor contribution of oxidative metabolism indicates that inhibitors or inducers of CYP isozymes are not expected to impact ertugliflozin exposure significantly. Since oral BA of ertugliflozin is ~100%, and dose-proportional increases in exposure are observed over the dose range of 0.5 mg to 300 mg, no clinically relevant interaction is expected with inhibitors of P-gp and BCRP transporters though ertugliflozin is a substrate for P-gp and BCRP.

Overall, the potential for ertugliflozin to be a victim of clinically meaningful drug interactions is low. Only inhibition/induction of UGT would be considered to have a potential effect on the exposure of ertugliflozin.

Citing little evidence in the literature for clinically relevant interactions with inhibitors of UGT enzymes, the Sponsor did not conduct a clinical drug interaction study with a UGT inhibitor. Instead, the risk of a UGT-mediated DDI for ertugliflozin in humans was assessed using Simcyp PBPK modeling with mefenamic acid as the UGT inhibitor.

Mefenamic acid is a known UGT inhibitor. In a clinical drug interaction study, co-administration of mefenamic acid with dapagliflozin, a UGT substrate, resulted in a dapagliflozin AUC_R of 1.51 and C_{maxR} of 1.13. Dapagliflozin, an SGLT2 inhibitor, is in the same chemical class as ertugliflozin with comparable physicochemical and ADME properties. Dapagliflozin is also mainly metabolized by UGT1A9/UGT2B7 to a similar extent as ertugliflozin. Using published clinical data for ertugliflozin, dapagliflozin and mefenamic acid, and utilizing the clinical DDI results for dapagliflozin and mefenamic acid , the Sponsor attempted to develop and verify PBPK models for all 3 compounds. Mefenamic acid and ertugliflozin PBPK models were then used to simulate the PK profile of ertugliflozin when coadministered with mefenamic acid.

4.4.2 Methods

The models and simulation results described here were performed using the population-based simulator Simcyp (version 15.1).

Table 4.4.2-1 summarizes ertugliflozin parameters used in the PBPK model. Simulations were performed in a virtual population library of healthy volunteers supplied by Simcyp (Sim-Healthy Volunteers). Table 4.4.2-2 lists the trial designs used in PBPK simulations in the submitted report.

Table 4.4.2-1: Simcyp Input Parameters for Ertugliflozin

Parameter	Value	Method	Reference
Compound	PF-04971729	-	-
Molecular Weight	436	-	17
LogP	2.5	-	17
pKa	Neutral	-	-
B/P ratio	0.66	Experimental	17
$f_{u,gut}$	0.064	Assumed	-
$f_{u,plasma}$	0.064	Experimental	17
F_a	1	Clinical Data	4
K_a (h^{-1})	1.2	Simcyp® estimate using sensitivity analysis and parameter estimate	-
T_{lag} (h)	0.5	Simcyp® estimate using sensitivity analysis and parameter estimate	-
Caco-2 (10^{-6} cm/s)	4.1	Experimental	5
Q_{gut} (L/h)	5.62	Predicted in Simcyp®	-
V_{ss} (L/kg)	1.23	Clinical Data	4
V_{sac} (L/kg)	1.12	Simcyp® parameter estimate	-
k_{in} (h^{-1})	3.34	Simcyp® parameter estimate	
k_{out} (h^{-1})	0.56	Simcyp® parameter estimate	
CL_{iv} (L/h)	11.2	Clinical data	4
CL_r(L/h)	0.1	Clinical data	7
CL_{int} (CYP) ($\mu L \cdot min^{-1} \cdot pmol^{-1}$)	3A4=0.041 3A5=0.006 2C8=0.011	CL_{int} retrospectively predicted based on CL_{iv} (11.2 L/h) and CL_r (0.1 L/h); CYP f_m=0.12, CYP3A4 (86%) CYP3A5 (10%) CYP2C8 (4%)	9
CL_{int} (UGT) ($\mu L \cdot min^{-1} \cdot mg^{-1}$)	35 (UGT1A9); 8 (UGT2B7)	Predicted based on contribution of UGT1A9 (81%) and UGT2B7 (19%)	8

B/P ratio = Blood to plasma ratio; CLint = Intrinsic clearance; CLiv = Intravenous clearance; CLr = Renal clearance; CYP = Cytochrome P450 enzyme; Fa = Fraction of dose absorbed from the gut; fu,gut = Fraction unbound in the gut; fu,plasma = Fraction unbound in plasma; Ka = Absorption rate constant; kin = First order rate constant in; kout = first order rate constant out; LogP = Partition coefficient; Peff = Permeability coefficient; pKa =Acid dissociation constant; PK = Pharmacokinetics; Qgut = Hybrid term including both villous blood flow and permeability through the enterocyte membrane; Simcyp® = Computer simulation program developed to predict metabolic DDIs; Tlag = Lag time; UGT = Uridine diphosphate-glucuronosyltransferase; Vsac = Volume of single adjusting compartment; Vss = Volume of distribution at steady state; - = Data not available or not applicable.

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Table 2, page 17)

Table 4.4.2-2: Trial Designs for Simcyp® Simulations of Pharmacokinetic and Drug-Drug Interaction Studies

Simulation	Subjects (n) × Trial (n) = Total	Age/ % female	Object Drug	Dose, Regimen	Treatment Day	Precipitant Drug	Dose/Regimen	Treatment Day	Analysis	Reference
1	8 x 10	25-54/0	ertugliflozin	0.1 mg, IV	1	--	--	--	pred vs obs	method dev
2	8 x 10	25-54/0	ertugliflozin	15 mg, SD	1	--	--	--	pred vs obs	method dev
3	8 x 10	20-49/0	ertugliflozin	0.5 mg, SD	1	--	--	--	pred vs obs	
4	8 x 10	20-49/0	ertugliflozin	2.5 mg, SD	1	--	--	--	pred vs obs	
5	8 x 10	20-49/0	ertugliflozin	10 mg, SD	1	--	--	--	pred vs obs	
6	8 x 10	20-49/0	ertugliflozin	30 mg, SD	1	--	--	--	pred vs obs	
7	8 x 10	20-49/0	ertugliflozin	100 mg, SD	1	--	--	--	pred vs obs	
8	7 x 10	20-49/0	ertugliflozin	300 mg, SD	1	--	--	--	pred vs obs	
9	22 x 10	22-53/45	ertugliflozin	5 mg, MD	1-6	--	--	--	pred vs obs	
10	28 x 10	20-45/25	ertugliflozin	15 mg, MD	1-6	--	--	--	pred vs obs	
11	7 x 10	18-45/0	dapagliflozin	10 mg, SD	1	--	--	--	pred vs obs	method dev
12	6 x 10	28-37/0	dapagliflozin	10 mg, MD	1-14	--	--	--	pred vs obs	
13	6 x 10	28-37/0	dapagliflozin	50 mg, MD	1-14	--	--	--	pred vs obs	
14	10 x 10	default	mefenamic acid	500 mg, SD	1	--	--	--	pred vs obs	
15	16 x 10	18-55/44	dapagliflozin	10 mg, SD	2	mefenamic acid	500 mg loading dose, then 250 mg Q6h for 4 days	1-4	pred vs obs	
16	10 x 10	18-55/50	ertugliflozin	15 mg, SD	2	mefenamic acid	500 mg loading dose, then 250 mg Q6h for 4 days	1-4	pred	
17	10 x 10	18-55/50	ertugliflozin	15 mg, SD	2	mefenamic acid, SA, K_i values	500 mg loading dose, then 250 mg Q6h for 4 days	1-4	pred	
18	10 x 10	18-55/50	ertugliflozin, SA, f_m UGT = 0.93	15 mg, SD	2	mefenamic acid	500 mg loading dose, then 250 mg Q6h for 4 days	1-4	pred	

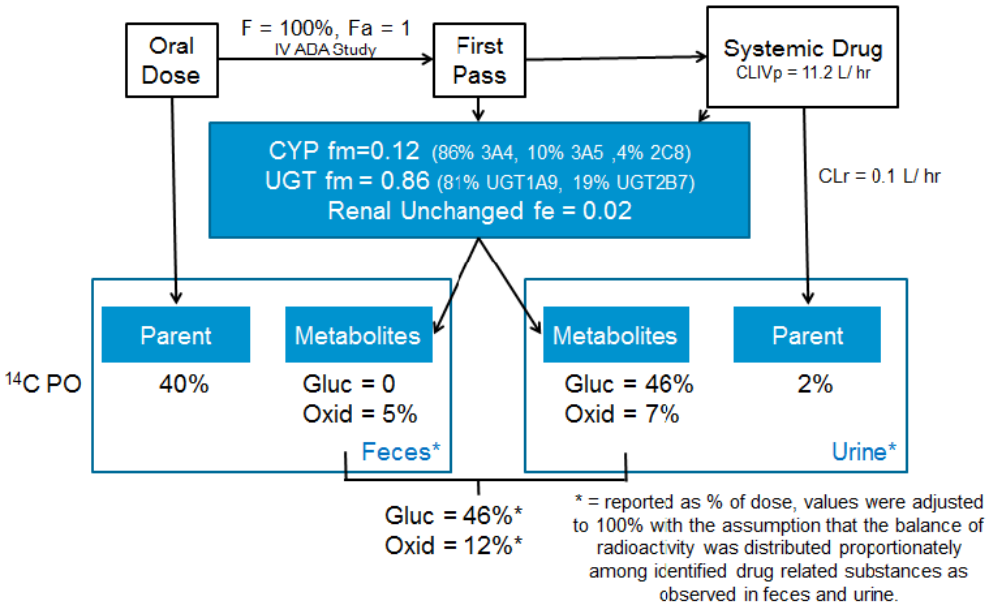
dev = Development; f_m = Fraction metabolized; K_i = Reversible inhibition constant; MD = Multiple dose; obs = Observed; pred = Predicted; Q6h = Once every 6 hours; SA = Sensitivity analysis; SD = Single dose; UGT = Uridine diphosphate-glucuronosyltransferase; vs = Versus; -- = Data not available or not applicable.

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Table 1, pp 15-16)

4.4.3 PBPK Model Development

Ertugliflozin PBPK model was developed based on its physicochemical properties, *in vitro* measurements and clinical PK observations. Human serum concentration-time data, urine data, and fraction absorbed (f_a) data were obtained from mass balance study (P038/1033), an absolute bioavailability study (P020/1043) and a phase I single dose escalation study (P036/1001).

The metabolism and disposition of ertugliflozin is described in Figure 4.4.3-1.

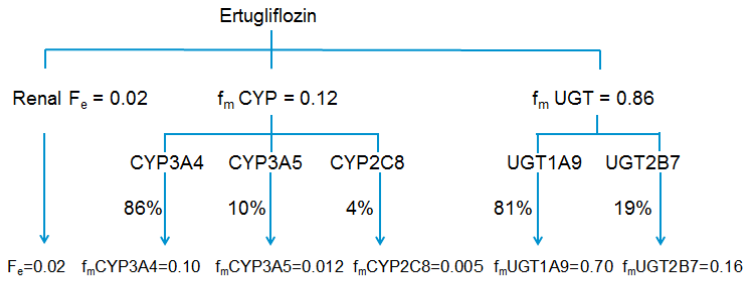


ABA = Absolute bioavailability; B/P = Blood to plasma ratio; $CL_{iv,p}$ = IV plasma clearance; CL_r = Renal clearance; CYP = Cytochrome P450; F = Bioavailability; F_a = Fraction absorbed; f_e = Fraction excreted; f_m = Fraction metabolized; Gluc = Glucuronidation; IV = Intravenous; Oxid = Oxidation; PO = Oral; UGT = Uridine diphosphate-glucuronosyltransferase.

Figure 4.4.3-1: Ertugliflozin Metabolism and Disposition

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Figure 1, Page 23)

Quantitative estimation of enzymatic pathways involved in the metabolism (f_m) and excretion (F_e) of ertugliflozin are summarized in Figure 4.4.3-2.



F_e (fraction excreted), f_m CYP (fraction metabolized by cytochrome P450), and f_m UGT (fraction metabolized by uridine diphosphate-glucuronosyltransferase) data from clinical ertugliflozin ^{14}C ADME study; % CYP and % UGT data from in vitro reaction phenotyping.

Figure 4.4.3-2: Ertugliflozin Fraction Metabolized and Fraction Excreted Values Calculated from Clinical and In Vitro Reaction Phenotyping Data

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Figure 3, Page 25)

4.4.3.1 Ertugliflozin Human Clearance Mechanisms

The systemic plasma clearance of ertugliflozin was 11.2 L/hr and the volume of distribution was 85.5 L following an IV dose. Following oral administration of ertugliflozin, estimates of absolute bioavailability and fraction absorbed were approximately 100% and 1, respectively, suggesting complete absorption. The renal clearance of ertugliflozin was 0.1 L/hr.

Following an oral dose, ertugliflozin is extensively metabolized by glucuronidation and to a lesser extent by oxidation. The oxidative metabolites were estimated to be 12% of total clearance based on scaling of all metabolic pathways with the remainder of metabolism due to glucuronidation. Therefore, overall f_m UGT = 0.86, f_m CYP = 0.12, and urine F_e = 0.02.

From UGT reaction phenotyping studies, UGT1A9 (81%) is the major enzyme and UGT2B7 (19%) is the minor enzyme responsible for metabolism of ertugliflozin. Similarly, *in vitro* CYP reaction phenotyping studies showed that CYP3A4 (86%), CYP3A5 (10%), and CYP2C8 (4%) are the CYP450 enzymes metabolizing ertugliflozin.

4.4.3.2 Distribution Model

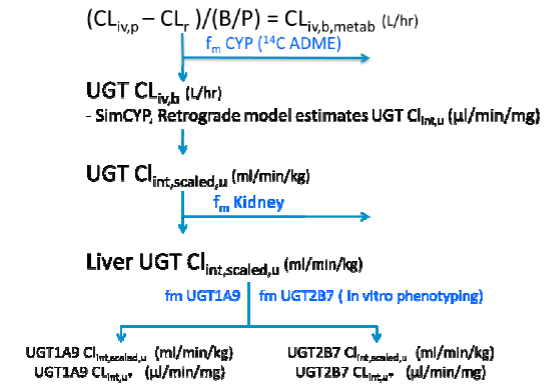
The Applicant used the minimal PBPK model to simulate the PK profile of ertugliflozin after IV administration. The Simcyp input file for ertugliflozin IV was constructed using systemic IV clearance (CL_{iv} = 11.2 L/hr) and renal clearance (CL_r = 0.1 L/hr) from clinical studies. The IV PK profile showed biphasic distribution therefore an additional compartment was modeled. A V_{ss} value of 1.23 L/kg from the IV pharmacokinetic study was used and parameter estimation in Simcyp estimated V_{sac}, k_{in}, k_{out} values to fit the IV PK profile of ertugliflozin.

4.4.3.3 Absorption Model

Based on an absolute bioavailability of 100, the fraction absorbed (F_a) value was set at 1 and the CV was set to 0% to capture AUC. The human P_{eff} was estimated from the *in vitro* Caco-2 results. The K_a value was estimated by comparison of the sensitivity analysis of C_{max} in Simcyp across a K_a range of 0.1 to 2 to the observed C_{max} of the oral 15 mg dose. Based on individual K_a values input into Simcyp, a value of K_a=1.2 captured the observed C_{max} of the clinical studies. Review of the PK profile, sensitivity analysis and subsequent simulations determined that T_{lag} = 0.5 hr captured the T_{max} following a 15 mg oral dose of ertugliflozin.

4.4.3.4 Elimination Model

Using the enzymatic clearance parameters outline in Figure 4.4.3-3, and ertugliflozin input parameters listed in Table 4.4.2-1, the elimination model for ertugliflozin was developed.



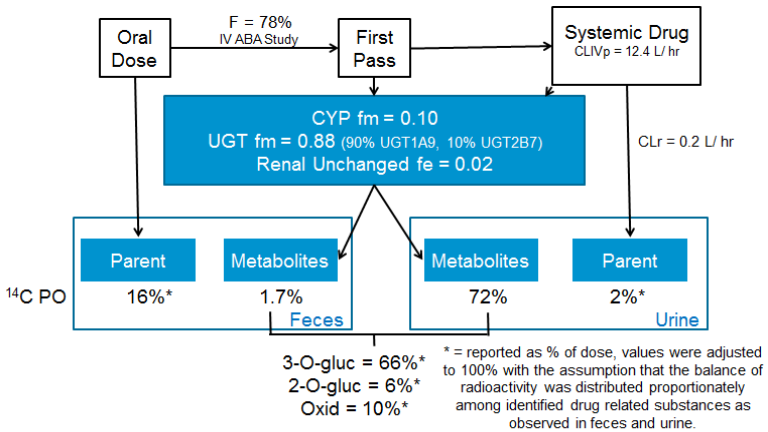
ADME = Absorption, distribution, metabolism and excretion; B/P = Blood to plasma ratio; CL_{int} = Intrinsic clearance; $CL_{int,u}$ = Unbound intrinsic clearance; $CL_{iv,p}$ = Intravenous plasma clearance; $CL_{iv,b,metab}$ = Intravenous metabolic blood clearance; $CL_{iv,b}$ = Intravenous blood clearance; $CL_{int,scaled,u}$ = Unbound intrinsic clearance scaled; f_m = Fraction metabolized; UGT = Uridine diphosphate-glucuronosyltransferase.

Figure 4.4.3-3 Dapagliflozin and Ertugliflozin Elimination Model Development Strategy

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Figure 4, Page 25)

4.4.3.5 Dapagliflozin PBPK Input Parameters and Model Development

Dapagliflozin ADME properties summarized in Figure 4.4.3-4, and input paramaters listed in Table 4.4.3-1 were used to construct the model for Dapagliflozin.



ABA = Absolute bioavailability; B/P = Blood to plasma ratio; $CL_{iv,p}$ = IV plasma clearance; CL_r = Renal clearance; CYP = Cytochrome P450; F = Bioavailability; f_e = Fraction excreted; f_m = Fraction metabolized; Gluc = Glucuronide; IV = Intravenous; Oxid = Oxidation; PO = Oral; UGT = Uridine diphosphate-glucuronosyltransferase.

Figure 4.4.3-4 Dapagliflozin Metabolism and Disposition

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Figure 2, Page 24)

Table 4.4.3-1: Simcyp Input Parameters for Dapagliflozin

Parameter	Value	Method	Reference
Compound	Dapagliflozin	-	-
Molecular Weight	408	-	19
LogP	2.52	-	19
pKa	Neutral	-	-
B/P ratio	0.88	Experimental	18
$f_{u,gut}$	0.09	Assumed	-
$f_{u,plasma}$	0.09	Experimental	18
F_a	0.9	Clinical Data	10
K_a (h^{-1})	1.2	Simcyp® estimate based on clinical data	-
Caco-2 (10^{-6} cm/s)	15.9	Experimental	18
Q_{gut} (L/h)	8.5	Predicted in Simcyp®	-
V_{ss} (L/kg)	1.19	Clinical Data	10
V_{sac} (L/kg)	0.9	Simcyp® parameter estimate	-
Q (L/hr)	10	Simcyp® parameter estimate	
CL_{iv} (L/h)	12.4	Clinical data	10
CL_r (L/h)	0.2	Based on human ^{14}C ADME study	11
Additional HLM Cl_{int} ($\mu L \cdot min^{-1} \cdot mg^{-1}$)	4	Human ^{14}C ADME study	11,12
CL_{int} (UGT) ($\mu L \cdot min^{-1} \cdot mg^{-1}$)	30 (UGT1A9); 3 (UGT2B7)	Predicted based on contribution of UGT1A9 (90%) and UGT2B7 (10%) to systemic CL	-

B/P ratio = Blood to plasma ratio; CL_{int} = Intrinsic clearance; CL_{iv} = Intravenous clearance; CL_r = Renal clearance; F_a = Fraction of dose absorbed from the gut; $f_{u,gut}$ = Fraction unbound in the gut; $f_{u,plasma}$ = Fraction unbound in plasma; HLM = Human liver microsomes; K_a = Absorption rate constant; LogP = Partition coefficient; pKa = Acid dissociation constant; Q = Inter-compartment clearance ; Simcyp® = Computer simulation program developed to predict metabolic DDIs ; V_{sac} = Volume of single adjusting compartment; V_{ss} = Volume of distribution at steady state; UGT = Uridine diphosphate-glucuronosyltransferase; - = Data not available or not applicable.

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Table 3, Page 18)

4.4.3.6 Mefenamic Acid Inhibition of UGT

In vivo fitted UGT1A9 and UGT2B7 K_i values of 0.038 μM and 0.051 μM, respectively, were used in the model following top down scaling.

4.4.4 Model Verification

The developed model for ertugliflozin was verified by comparing the biphasic distribution kinetics of the PBPK distribution model (with later incorporation of absorption and elimination parameters) against oral single and multiple dose PK studies.

In addition, absorption and elimination model parameters were incorporated into the dapagliflozin PBPK model, which was verified with oral single and multiple dose PK studies.

Single dose PK parameters of mefenamic acid were also predicted by the model.

4.4.5 Model Application

The model was utilized to predict the DDI potential od mefenamic acid with ertugliflozin.

4.4.6 Results

4.4.6.1 Single and Multiple Dose PK of ertugliflozin

Model predicted and clinically observed PK parameters of ertugliflozin following single doses (0.5 mg to 300 mg, Study P036/1001) and multiple doses (5 and 15 mg, Study P035/1051) are listed in Table 4.4.6-1 and Table 4.4.6-2, respectively. The predicted plasma *vs.* time profiles of ertugliflozin after a single 10 mg dose and after multiple doses of 15 mg are depicted in Figure 4.4.6-1 and Figure 4.4.6-2, respectively.

The predicted/observed ratios for C_{max} were within 80 to 125% of observed values. Predicted/observed ratios for AUC after single dose studies were within 77 to 84% of observed values across the dose range of 0.5 to 300 mg. Predicted/observed ratios for AUC after multiple doses were within 80 to 125% for multiple dose simulations. PBPK model predicted PK parameters and plasma profiles of ertugliflozin were comparable to the observed clinical data.

Table 4.4.6-1: Simulated vs. Observed Geometric Mean (%CV) Pharmacokinetic Parameters of Ertugliflozin After a Single Dose

Dose (mg)	Predicted C_{max} (ng/ml)	Predicted AUC_{inf} (ng•hr/ml)	Observed C_{max} (ng/ml)	Observed AUC_{inf} (ng•hr/ml)	C_{max} Predicted/ Observed Ratio	AUC Predicted/ Observed Ratio
0.1 (IV[a])	8.46 (63)	9.19 (35)	8.51 (32)	8.48 (15)	0.98	1.08
15 (PO[a])	249 (69)	1140 (50)	256 (14)	1400 (13)	0.97	0.81
0.5 (PO)	8.38 (64)	37.4 (44)	7.23 (11)	45.7 (10)	1.16	0.82
2.5 (PO)	41.9 (64)	187 (44)	42.8 (21)	231 (22)	0.98	0.81
10 (PO)	168 (64)	749 (44)	182 (22)	909 (15)	0.92	0.82
30 (PO)	503 (64)	2250 (44)	545 (24)	2810 (18)	0.92	0.80
100 (PO)	1680 (64)	7490 (44)	1620 (16)	9610 (16)	1.04	0.78
300 (PO)	4890 (66)	22000 (38)	4330 (20)	26400(16)	1.13	0.83

AUC_{inf} = Area under the concentration-time curve from time 0 to infinity; C_{max} = Maximum concentration; %CV = Geometric coefficient of variation; IV = Intravenous; PO = Oral.
a. Method development.

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Table 5, Page 20)

Table 4.4.6-2: Simulated vs. Observed Geometric Mean (%CV) Pharmacokinetic Parameters of Ertugliflozin After Multiple Oral Doses

Dose (mg)	Predicted C_{max} (ng/ml)	Predicted AUC_{24} (ng•hr/ml)	Observed C_{max} (ng/ml)	Observed AUC_{24} (ng•hr/ml)	C_{max} Predicted/ Observed Ratio	AUC Predicted/ Observed Ratio
5	99.3 (61)	410 (47)	81.3 (29)	398 (18)	1.22	1.03
15	279 (61)	1160 (47)	268 (20)	1190 (22)	1.04	0.97

AUC_{24}= Area under the concentration-time curve from time 0 to 24 hours; C_{max} = Maximum concentration; %CV = Geometric coefficient of variation.

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Table 6, Page 20)

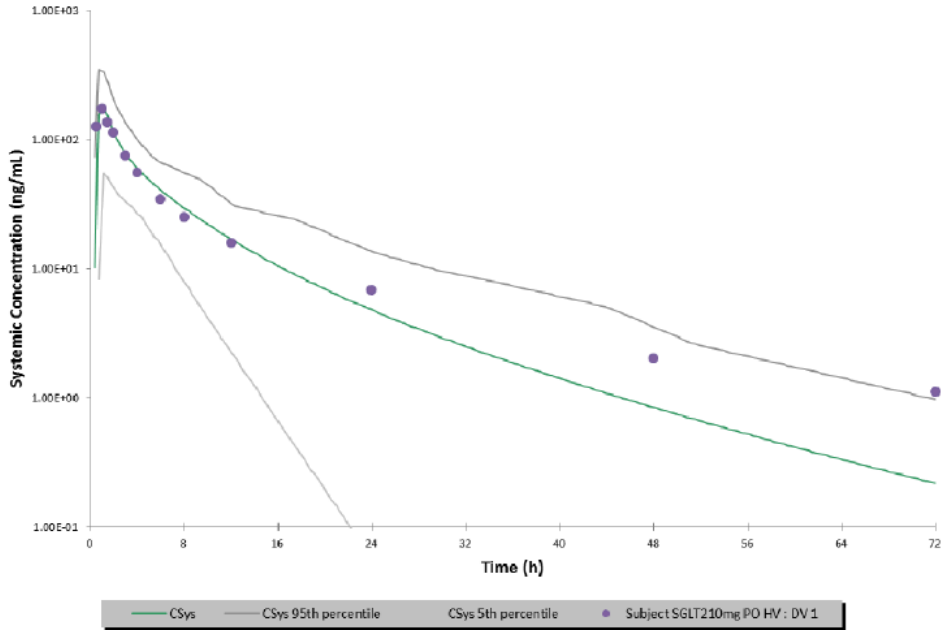


Figure 4.4.6-1 Simcyp Predicted vs Observed Ertugliflozin Plasma Concentration vs Time Profile Following a Single 10 mg Oral Dose

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Figure 5, Page 26)

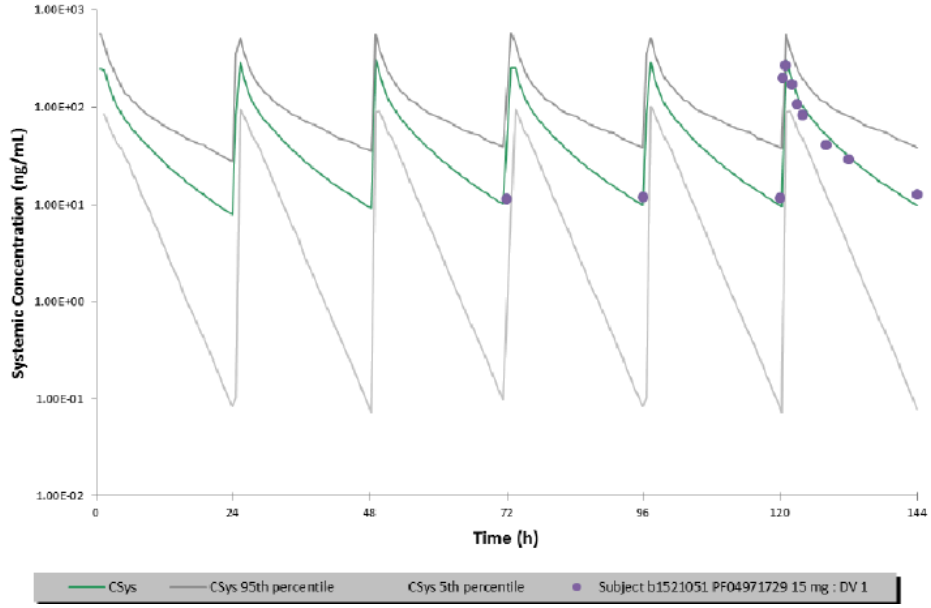


Figure 4.4.6-2 Simcyp Predicted vs Observed Ertugliflozin Plasma Concentration vs Time Profile Following Multiple 15 mg Oral Doses

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Figure 7, Page 28)

Simcyp model estimated f_m and F_e values based on the input parameters were compared with the observed f_m and F_e values. During model development, 10% of the UGT clearance ($CL_{int,scaled,u}$) was attributed to metabolism in the kidney and subtracted from the systemic UGT enzymatic clearance to calculate the liver UGT clearance ($CL_{int,scaled,u}$). Using liver input parameters the model predicted 14% of the UGT

clearance was in the kidney, which was similar to the initial estimation. Additionally, the model estimated f_m UGT1A9 = 0.70 and f_m UGT2B7 = 0.17 were similar to the observed f_m UGT1A9 = 0.70 and f_m UGT2B7 = 0.16 values. Simcyp estimated CYP values, f_m CYP3A4 = 0.10, f_m CYP3A5 = 0.02 and f_m CYP2C8 = 0.01, were similar to observed values, f_m CYP3A4 = 0.1, f_m CYP3A5 = 0.012 and f_m CYP2C8 = 0.005. These simulation results provided verification of the absorption, distribution and mechanistic f_m UGT and f_m CYP assignments of the ertugliflozin PBPK model.

Ertugliflozin PBPK model can therefore be used to simulate the DDI following coadministration with mefenamic acid.

4.4.6.2 Single and Multiple Dose PK of dapagliflozin

Model predicted and clinically observed PK parameters of dapagliflozin following a single dose (10 mg)10 and multiple doses (10 mg and 50 mg)16 are shown in Table 4.4.6-3. Predicted plasma *vs*. time profile of dapagliflozin after a 10 mg single dose is depicted in Figure 4.4.6-3. The Predicted/Observed ratios for dapagliflozin C_{max} and AUC were within 80 to 125% of observed values at all simulated doses.

Table 4.4.6-3: Simulated vs. Observed Geometric Mean Pharmacokinetic Parameters of Dapagliflozin After Single or Multiple Oral Doses

Dose (mg)	Predicted C_{max} (ng/ml)	Predicted AUC[a] (ng•hr/ml)	Observed C_{max} (ng/ml)	Observed AUC[a] (ng•hr/ml)	C_{max} Predicted/ Observed Ratio	AUC Predicted/ Observed Ratio
10 SD	124	580	143	628	0.87	0.92
10 MD	123	537	119	506	1.03	1.06
50 MD	614	2690	728	2540	0.84	1.06

AUC = Area under the concentration-time curve; C_{max} = Maximum concentration; SD= Single dose; MD = Multiple dose.
a = SD is AUC from time 0 to infinity, MD is AUC from time 0 to 24 hours post dose.

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Table 7, Page 20)

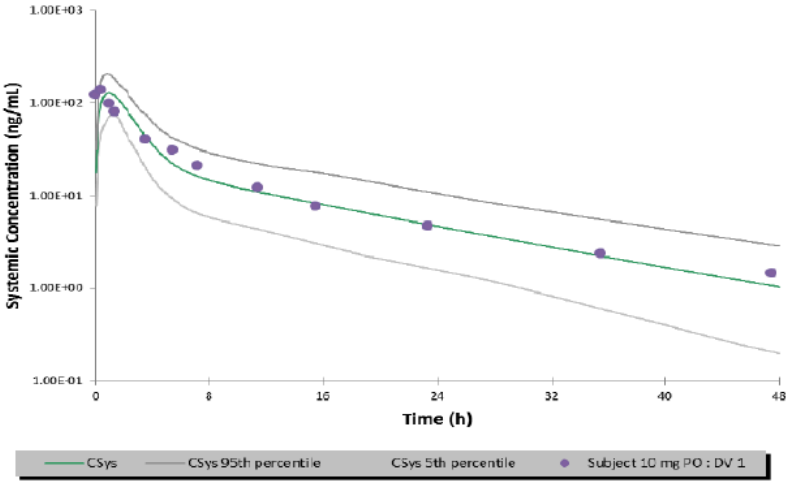


Figure 4.4.6-3 Simcyp Predicted vs Observed Dapagliflozin Plasma Concentration vs Time Profile Following a Single 10 mg Oral Dose

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Figure 8, Page 28)

Simcyp model predicted dapagliflozin f_m and F_e values (f_m UGT1A9 = 0.81, f_m UGT2B7 = 0.076, f_m CYP = 0.094 and urine F_e = 0.018) were similar to the observed values (f_m UGT1A9 = 0.80, f_m UGT2B7 = 0.09, f_m CYP = 0.10, and urine F_e = 0.02) used in initial model development.

PK simulation and predicted clearance values therefore provide verification of the dapagliflozin compound file.

4.4.6.3 Single Doses of Mefenamic Acid

Model predicted and observed PK parameters of mefenamic acid following a single oral dose of 500 mg is summarized in Table 4.4.6-4 and depicted in Figure 4.4.6-4. The predicted/observed ratios for C_{max} and AUC were within 80 to 125% of observed values.

The simulation results provide verification of the observed mefenamic acid PK profile.

Table 4.4.6-4: Simulated vs. Observed Geometric Mean Pharmacokinetic Parameters of Mefenamic Acid After a Single Oral Dose

Dose (mg)	Predicted C_{max} (ng/ml)	Predicted AUC_{inf} (ng•hr/ml)	Observed C_{max} (ng/ml)	Observed AUC_{inf} (ng•hr/ml)	C_{max} Predicted/ Observed Ratio	AUC_{inf} Predicted/ Observed Ratio
500	6370	30400	6900	34200	0.92	0.89

AUC_{inf}= Area under the concentration-time curve from time 0 to infinity; C_{max} = Maximum concentration.

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Table 8, Page 21)

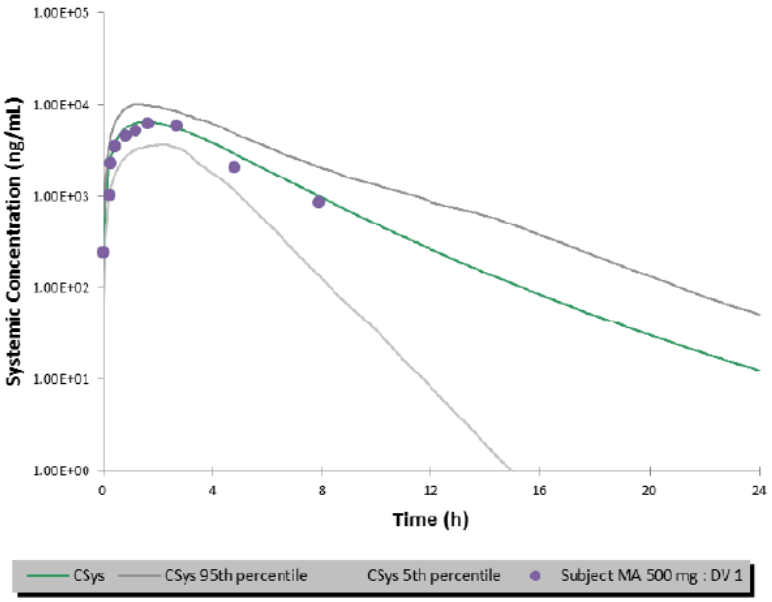


Figure 4.4.6.4 Simcyp Predicted vs Observed Mefenamic Acid Plasma Concentration vs Time Profile Following a Single 500 mg Oral Dose

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Figure 9, Page 29)

4.4.6.4 *Verification of Mefenamic Acid Inhibition of UGT Following Coadministration with Dapagliflozin in a Clinical Study*

The AUC_R = 1.51 and C_{maxR} = 1.13 that was observed in a clinical DDI study, when UGT substrate dapagliflozin was coadministered with UGT inhibitor mefenamic acid, was simulated in the PBPK model. The model predicted AUC_R was 1.52, and that for C_{maxR} was 1.18, which are similar to observed values (Table 4.4.6-5 and Figure 4.4.6-5).

Table 4.4.6-5: Simulated vs Observed DDI Following Coadministration of Dapagliflozin with Mefenamic Acid

	AUC_R Geo Mean (CI[a])	C_{maxR} Geo Mean (CI[a])
Predicted	1.53 (1.50-1.55)	1.18 (1.17-1.19)
Observed	1.51 (1.44-1.58)	1.13 (1.03-1.24)
Predicted/Observed Ratio	1.0	1.0

AUC_R = ratio of AUC_{inf} of substrate drug with coadministration of the interacting drug to AUC_{inf} of substrate drug alone; CI = Confidence interval; C_{maxR} = Ratio of C_{max} of substrate drug with coadministration of the interacting drug to C_{max} of the substrate alone; DDI = Drug-drug interaction; Geo = Geometric.
a. CI Predicted = 95%, CI Observed = 90%.

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Table 9, Page 21)

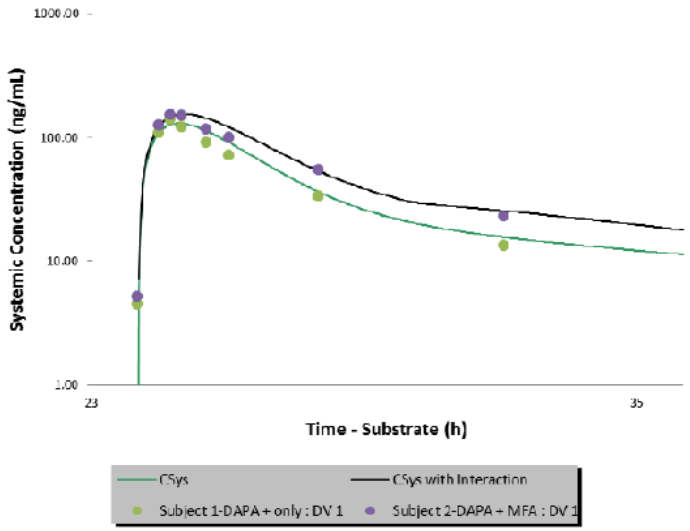


Figure 4.4.6-5 Simcyp Predicted vs Observed Dapagliflozin Plasma Concentration vs Time Profile With or Without Coadministration of Mefenamic Acid

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Figure 10, Page 29)

4.4.6.5 *Simulation of Ertugliflozin PK Following Coadministration with Mefenamic Acid*

The predicted DDI following coadministration of ertugliflozin and UGT inhibitor mefenamic acid was simulated using the verified ertugliflozin and verified mefenamic acid PBPK models. Following coadministration with UGT inhibitor mefenamic acid, the predicted ertugliflozin AUC_R = 1.51 and predicted C_{maxR} = 1.19. The results are summarized in Table 4.4.6-6 and Figure 4.4.6-6.

Table 4.4.6-6: Simulated DDI Following Coadministration of Ertugliflozin and Mefenamic Acid

	AUC_R Geo Mean (95% CI)	C_{maxR} Geo Mean (95% CI)
Predicted	1.51 (1.48-1.54)	1.19 (1.17-1.20)

AUC_R = Ratio of AUC_{0-72} of substrate drug with coadministration of the interacting drug to AUC_{0-72} of substrate drug alone; CI = Confidence interval; C_{maxR} = Ratio of C_{max} of substrate drug with coadministration of the interacting drug to C_{max} of the substrate alone; DDI = Drug-drug interaction; Geo = Geometric.

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Table 10, Page 21)

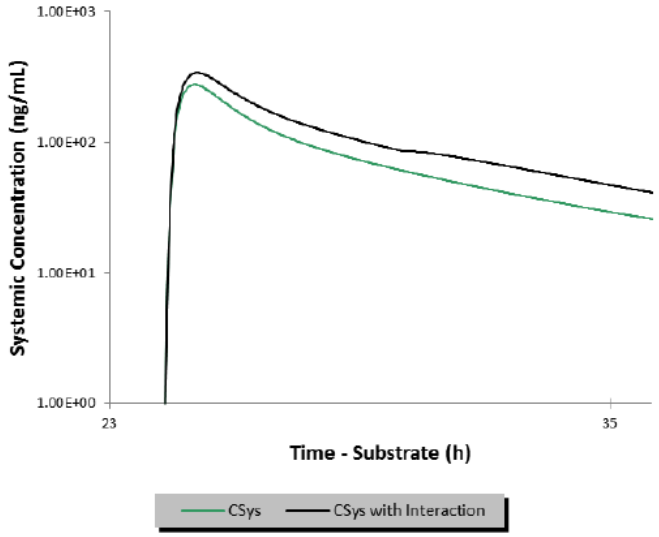


Figure 4.4.6-6 Simcyp Predicted Ertugliflozin Plasma Concentration vs Time Profile With or Without Coadministration of Mefenamic Acid

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Figure 11, Page 30)

4.4.6.5.1 Sensitivity Analysis

The Sponsor conducted a sensitivity analysis of mefenamic acid UGT1A9 and UGT2B7 inhibition to evaluate the impact of (a) K_i values and (b) UGT f_m values on the DDI following coadministration of ertugliflozin and mefenamic acid,

Assuming a worst-case scenario of a 50% reduction in the mefenamic acid UGT1A9 (K_i = 0.019 µM) and UGT2B7 (K_i = 0.026 µM), the Simcyp model-predicted DDI following administration of ertugliflozin and mefenamic acid resulted in an AUC_R = 1.88 and C_{maxR} = 1.27 (Table 4.4.6-7). Simcyp model-predicted DDI following coadministration of ertugliflozin (f_m UGT = 0.93) and mefenamic acid estimated the AUC_R = 1.55 and the C_{maxR} = 1.20 (Table 4.4.6-7).

Table 4.4.6-7: Sensitivity Analysis for Ertugliflozin and Mefenamic Acid DDI Prediction

Simulated DDI Following Coadministration of Ertugliflozin and Mefenamic Acid (K_i UGT1A9 = 0.019 µM, UGT2B7 = 0.026 µM)		
	AUC_R Geo Mean (95% CI)	**C_{maxR} Geo Mean (95% CI)**
Predicted	1.88 (1.82-1.93)	1.27 (1.25-1.29)

AUC_R = Ratio of AUC_{0-72} of substrate drug with coadministration of the interacting drug to AUC_{0-72} of substrate drug alone; CI = Confidence interval; C_{maxR} = Ratio of C_{max} of substrate drug with coadministration of the interacting drug to C_{max} of the substrate alone; DDI = Drug-drug interaction; Geo = Geometric; K_i = Inhibition constant.

Simulated DDI Following Coadministration of Ertugliflozin (fm UGT = 0.93) and Mefenamic Acid		
	AUC_R Geo Mean (± 95% CI)	**C_{maxR} Geo Mean (± 95% CI)**
Predicted	1.55 (1.52-1.59)	1.20 (1.19-1.22)

AUC_R = Ratio of AUC_{0-72} of substrate drug with coadministration of the interacting drug to AUC_{0-72} of substrate drug alone; CI = Confidence interval; C_{maxR} = Ratio of C_{max} of substrate drug with coadministration of the interacting drug to C_{max} of the substrate alone; DDI = Drug-drug interaction; f_m = Fraction metabolized; Geo = Geometric.

(Source: eCTD for NDA 209803, Module 4.2.2.6 SimCYP® Prediction of Interaction between Ertugliflozin (PF-04971729) and UGT Inhibitor Mefenamic Acid, Tables 11 and 12, pp 21-22)

Reviewer's Comments

The applicant was able to predict the DDI between ertugliflozin and UGT inhibitor mefenamic acid by utilizing verified PBPK models using Simcyp. The robustness of the model was verified by comparing the predicted and observed PK interaction between dapagliflozin, another drug in the same SGLT2 class, and mefenamic acid. The predicted and observed values for dapagliflozin were very similar.

The model was also able to predict the single-dose and multiple-dose PK of ertugliflozin, which were similar to the observed values from Phase 1 studies.

PBPK modeling and simulation results indicated that the expected drug interaction between ertugliflozin and mefenamic acid would be less than 2-fold and similar to that between dapagliflozin and mefenamic acid.

Based on a successful model development, the application of PBPK modeling would support a waiver for the conduct of a clinical DDI study with ertugliflozin and a UGT inhibitor.

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/s/

SURYANARAYANA M SISTA
08/17/2017

LIAN MA
08/18/2017

JINGYU YU
08/18/2017
On behalf of Yaning Wang

MANOJ KHURANA
08/18/2017

CHANDRAHAS G SAHAJWALLA
08/18/2017

Office of Clinical Pharmacology Review

NDA Number	209805
Link to EDR	\\CDSESUB1\EVSPROD\NDA209805\209805.enx
Submission Date	12/19/2016
Submission Type	505(b)(2), Standard
Brand Name	Steglujan
Generic Name	Ertugliflozin and Sitagliptin
Dosage Form and Strength	Film-coated tablets: • (b) (4) • Ertugliflozin 5 mg/ Sitagliflozin 100 mg • (b) (4) • Ertugliflozin 15 mg/ Sitagliflozin 100 mg
Route of Administration	Oral administration, QD
Proposed Indication	It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate. Limitations of Use: • Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis. • Has not been studied in patients with a history of pancreatitis.
Applicant	Merck
Associated IND	IND 122330
OCP Review Team	Lei He, Ph.D., Manoj Khurana, Ph.D.

Table of Contents

1. EXECUTIVE SUMMARY

Merck has submitted three NDA submissions in parallel seeking the marketing approval for ertugliflozin tablets (5 mg and 15 mg) (NDA 209803), ertugliflozin/sitagliptin fixed-dose combination (FDC) tablets ((b) (4) 5 mg/100 mg, (b) (4) 15 mg/100 mg) (NDA 209805), ertugliflozin/metformin FDC tablets (2.5mg/500mg, 2.5mg/1000mg, 7.5mg/500mg, 7.5mg/1000mg) (NDA 209806) for the treatment of type 2 diabetes mellitus (T2DM) as adjunct to diet and exercise therapy. The proposed dosing regimens for the three products are as below:

- Ertugliflozin tablets: 5 mg or 15 mg once daily (QD) with or without food
- Ertugliflozin/sitagliptin FDC tablets: up to 15 mg ertugliflozin/100 mg sitagliptin QD dose with or without food
- Ertugliflozin/metformin FDC tablets: up to 7.5 mg ertugliflozin/1000 mg metformin twice daily (BID) dose with meals

A comprehensive clinical program has been conducted to support the approval of ertugliflozin as a stand-alone product, as well as ertugliflozin/sitagliptin and ertugliflozin/metformin FDCs, including twenty-nine Phase 1 studies, two Phase 2 studies, and nine Phase 3 studies.

A total of six clinical Pharmacology studies and three Phase 3 studies has been submitted to support the ertugliflozin/ sitagliptin FDC. The clinical pharmacology studies include four bioequivalence (BE) studies (Studies P025/1038, (b) (4) P048/1056, and (b) (4) one food-effect study (Study P026/1050), and one 2-way pharmacokinetic (PK) drug-drug interaction (DDI) study (Study P022/1033). Note that only the six Phase 1 studies will be reviewed in this review. Regarding other relevant studies, refer to the Clinical Pharmacology Review for NDA 209803 by Drs Sury Sista and Lian Ma.

Results indicate that each strength of the proposed ertugliflozin/sitagliptin FDC tablets is bioequivalent to co-administration of individual components, which was used in Phase 3 studies. There is no clinically meaningful food effect for both individual components. The systemic exposure for both individual components remains similar following the administration of FDC and each of the individual components alone, suggesting no clinically meaningful PK interaction between ertugliflozin and sitagliptin.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 209805 Clinical Pharmacology data submitted on December 19, 2016 and found the results of submitted studies are acceptable to support approval. However, the final determination of the approval will be made based on the efficacy/safety assessment of ertugliflozin in NDA 209803.

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Summary of Important Clinical Pharmacology Findings

Ertugliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor. Sitagliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4).

Four BE studies were conducted to bridge the proposed four strengths of commercial FDC tables and the co-administration of individual components in Phase 3 studies. Results indicate that following the single dose administration of each strength of FDC tablet and co-administration of individual tablets used in Phase 3 studies, the 90% CIs of the geometric mean ratios of Cmax, AUC0-t, and AUC0-inf of both ertugliflozin and sitagliptin are all well within 80-125% range, suggesting the BE demonstration of the each strength of FDC tablets and the co-administration of individual components used in Phase 3 studies.

In the food effect study (Study P026/1050) in healthy subjects (n=14), for ertugliflozin, following the administration of ertugliflozin/sitagliptin FDC with high-fat, high-calorie breakfast, ertugliflozin AUCs are similar while Cmax was about 30% lower compared to fasted condition. Median Tmax was delayed from 1 hour to 2 hours in the presence of food. Mean terminal phase t1/2 for ertugliflozin remains similar, 12.89 hours and 11.64 hours for fasted and fed conditions, respectively. For sitagliptin, following the administration of ertugliflozin/sitagliptin FDC with high-fat, high-calorie breakfast, sitagliptin AUCs and Cmax are all similar compared to fasted condition. Median Tmax was 3.00 hours under the fasted condition and 1.77 hours in under fed condition. Mean terminal phase t1/2 for sitagliptin remains similar, 11.49 hours and 12.07 hours for fasted and fed conditions, respectively.

In the PK interaction study (Study P022/1033), following the administration of FDC and each of the individual components alone, the systemic exposure (Cmax, AUC0-t, and AUC0-inf) for both individual components remains unchanged, suggesting no clinically meaningful PK interaction between ertugliflozin and sitagliptin.

2.2 Summary of Labeling Recommendations

Summary of labeling recommendation for different sections are listed below:

- Section 2: The proposed general dosing recommendations are acceptable. Dosing recommendations for renal impaired patients depend on (b) (4) the efficacy/safety assessment of ertugliflozin component in renal impairment subgroups in NDA 209803.
- Section 7: The proposed labeling statements are acceptable.
- Section 8: The labeling statements for hepatic impaired patients are acceptable. Recommendations for the labeling statements for renal impaired patients depend on the

[redacted] efficacy/safety assessment of ertugliflozin component in renal impairment subgroups in NDA 209803.

- Section 12.3: The labeling statements regarding the [redacted] are recommended to be removed.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Merck has submitted three NDA submissions in parallel seeking the marketing approval for ertugliflozin tablets (5 mg and 15 mg) (NDA 209803), ertugliflozin/sitagliptin FDC tablets [redacted] 5 mg/100 mg, [redacted] 15 mg/100 mg) (NDA 209805), ertugliflozin/metformin FDC tablets (2.5mg/500mg, 2.5mg/1000mg, 7.5mg/500mg, 7.5mg/1000mg) (NDA 209806) for the treatment of T2DM as adjunct to diet and exercise therapy.

Ertugliflozin is a new molecular entity under NDA 209803. Sitagliptin is currently available in the US market as JANUVIA (sitagliptin) tablets (NDA 021995, by Merck) or as one component in JANUMET (metformin and sitagliptin) tablets (NDA 022044, by Merck) and JANUMET XR (metformin and sitagliptin) extended release tablets (NDA 202270, by Merck).

To support the application of ertugliflozin/sitagliptin FDC, six Phase 1 studies and three Phase 3 studies were submitted. Only the six Phase 1 studies as shown in Table 1 will be reviewed in this review. Regarding other relevant studies, refer to the Clinical Pharmacology Review for NDA 209803 by Drs. Sury Sista and Lian Ma.

Table 1. Summary of Clinical Pharmacology Studies Supporting NDA 209805

Protocol No.	Objective(s)	Design	Number of Healthy Subjects	Dose and Formulations
P022/1033	Drug-Drug Interaction	Open-label, randomized, 3-period, 6-sequence single oral dose crossover	N=12 (5 males/ 7 females)	Ertugliflozin 15 mg tablet (single dose) Sitagliptin 100 mg tablet (single dose) Ertugliflozin 15 mg + sitagliptin 100 mg tablets (single dose of each administered within 5 minutes of each other)
P026/1050	Definitive food effect	Open-label, randomized, 2-period, 2-sequence crossover, single-dose	N=14 (11 males/ 3 females)	ertugliflozin 15 mg/sitagliptin 100 mg tablet
P025/1038	Bioequivalence	Open-label, randomized, 2-period, 2-sequence crossover, single-dose	N=18 (15 males/ 3 females)	15 mg ertugliflozin (administered as one 10 mg tablet + one 5 mg tablet) and sitagliptin 100 mg tablet co-administered ertugliflozin 15 mg/sitagliptin 100 mg tablet
[redacted]				(b) (4)
P048/1056	Bioequivalence	Open-label, randomized, 2-period, 2-sequence crossover, single-dose	N=18 (17 males/ 1 female)	5 mg ertugliflozin tablet and sitagliptin 100 mg tablet co-administered ertugliflozin 5 mg/sitagliptin 100 mg tablet
[redacted]				(b) (4)

(Source: Summary of Clinical Pharmacology Studies, Table 1)

3.2 Clinical Pharmacology Review Questions

3.2.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Three Phase 3 studies were conducted to support the efficacy and safety of ertugliflozin/sitagliptin FDC. For more detailed information, refer to the Clinical Pharmacology Review for NDA 209803 by Drs. Sury Sista and Lian Ma, and the Clinical Review by Dr. Frank Pucino.

Since the co-administration of the corresponding doses of the individual components was used in Phase 3 studies, four BE studies were conducted to bridge the co-administered individual components and the proposed ertugliflozin/sitagliptin FDC tablet. See Section 3.2.2 or Individual Study Review for more information.

3.2.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

The proposed to-be-marketed product is ertugliflozin/sitagliptin FDC tablet at four strengths (b) (4) (b) (4) 5 mg/100 mg, (b) (4) and 15 mg/100 mg. However, in Phase 3 studies, the co-administration of the corresponding doses of the individual components, ertugliflozin and sitagliptin, was used. Therefore, four BE studies (Studies P025/1038, (b) (4) P048/1056, and (b) (4) were conducted in healthy subjects to bridge each strength of the ertugliflozin/sitagliptin FDC tablet and co-administration of individual components. Results of BE studies indicated that each strength of the proposed ertugliflozin/sitagliptin FDC tablet is bioequivalent to co-administration of individual components, which was used in Phase 3 studies (see statistical analysis results for ertugliflozin 15 mg/sitagliptin 100 mg in Tables 2 and 3, for (b) (4) for ertugliflozin 5 mg/sitagliptin 100 mg in Tables 6 and 7, (b) (4)

Also note that the clinical facility has been requested to be inspected. The OSIS recommends accepting data without an on-site inspection since the requested inspection site was classified as NAI based on recent inspections. For more detailed information, refer to the OSIS memorandum dated 04/17/2017.

Statistical Analysis Results for Ertugliflozin 15 mg/Sitagliptin 100 mg FDC tablet:

Table 2. Ertugliflozin PK parameters following single oral dose administration of ertugliflozin 15 mg/sitagliptin 100 mg FDC tablet and co-administration of the individual components: ertugliflozin 15 mg (administered as one 10 mg tablet + one 5 mg tablet) and sitagliptin 100 mg tablet under fasted conditions (Study P025/1038)

Parameter (units)	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Sitagliptin 100 mg/ Ertugliflozin 15 mg FDC (Test)	Sitagliptin 100 mg + Ertugliflozin 15 mg Co-administered (Reference)		
AUC_{inf} (ng.hr/mL)	1188	1209	98.25	95.07, 101.54
AUC_{last} (ng.hr/mL)	1162	1184	98.18	95.17, 101.30
C_{max} (ng/mL)	202.4	198.1	102.13	92.32, 112.99

Source: Table 14.4.3.3.1
Abbreviations: CI = confidence interval; FDC = Fixed Dose Combination; PK = pharmacokinetic(s).
a. The ratios (and 90% CIs) are expressed as percentages.
Parameters are defined in Table 5.
The intra-subject variability values based on mixed effects model for ertugliflozin AUC_{inf} and C_{max} were 5.46% and 17.49%, respectively.

(Source: Study P025/1038 CSR, Table 10)

Table 3. Sitagliptin PK comparison following single oral dose administration of ertugliflozin 15 mg/sitagliptin 100 mg FDC tablet and co-administration of the individual components: ertugliflozin 15 mg (administered as one 10 mg tablet + one 5 mg tablet) and sitagliptin 100 mg tablet under fasted conditions (Study P025/1038)

	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
Parameter (units)	Sitagliptin 100 mg/ Ertugliflozin 15 mg FDC (Test)	Sitagliptin 100 mg + Ertugliflozin 15 mg Co-administered (Reference)		
AUC_{inf} (µM.hr)	7.343	7.171	102.40	99.51, 105.38
AUC_{last} (µM.hr)	7.241	7.058	102.60	99.78, 105.50
C_{max} (nM)	661.1	579.2	114.14	108.35, 120.24

Source: Tables 14.4.3.3.2
Abbreviations: CI = confidence interval; FDC = Fixed Dose Combination; PK = pharmacokinetic(s).
Parameters are defined in Table 5.
a. The ratios (and 90% CIs) are expressed as percentages.
The intra-subject variability values based on mixed effects model for sitagliptin AUC_{inf} and C_{max} were 4.81% and 9.01%, respectively.

(Source: Study P025/1038 CSR, Table 12)

(b) (4)

Statistical Analysis Results for Ertugliflozin 5 mg/Sitagliptin 100 mg FDC tablet

Table 6. Ertugliflozin PK comparison following single oral dose administration of ertugliflozin 5 mg/sitagliptin 100 mg FDC tablet and co-administration of the individual components: ertugliflozin 5 mg and sitagliptin 100 mg under fasted conditions (Study P048/1056)

Parameter (units)	Adjusted (Least-Squares) Geometric Means: Ertugliflozin 5 mg/Sitagliptin 100 mg FDC tablet (Test)	Adjusted (Least-Squares) Geometric Means: Ertugliflozin 5 mg + Sitagliptin 100 mg Co-administered (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{inf} (ng.hr/mL)	386.8	382.1	101.23	97.15, 105.49
AUC_{last} (ng.hr/mL)	371.7	364.3	102.01	97.89, 106.32
C_{max} (ng/mL)	73.44	71.19	103.17	93.76, 113.52

Source: Table 14.4.3.3.1
Abbreviations: CI = confidence interval; FDC = fixed dose combination; PK = pharmacokinetic(s).
a. The ratios (and 90% CIs) are expressed as percentages.
Parameters are defined in Table 5.
The intra-subject variability (sqrt[exp(MSE)-1], where MSE is the mean square error) values based on mixed effects model for ertugliflozin AUC_{inf}, AUC_{last} and C_{max} were 0.0708, 0.0710, and 0.1654, respectively.

(Source: Study P048/1056 CSR, Table 10)

Table 7. Sitagliptin PK comparison following single oral dose administration of ertugliflozin 5 mg/sitagliptin 100 mg FDC tablet and co-administration of the individual components: ertugliflozin 5 mg and sitagliptin 100 mg under fasted conditions (Study P048/1056)

Parameter (units)	Adjusted (Least-Squares) Geometric Means: Ertugliflozin 5 mg/Sitagliptin 100 mg FDC tablet (Test)	Adjusted (Least-Squares) Geometric Means: Ertugliflozin 5 mg + Sitagliptin 100 mg Co-administered (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{inf} (µM.hr)	7.136	7.151	99.80	98.12, 101.51
AUC_{last} (µM.hr)	7.061	7.078	99.77	98.05, 101.52
C_{max} (nM)	673.8	675.5	99.76	93.63, 106.28

Source: Table 14.4.3.3.2
Abbreviations: CI = confidence interval; FDC = fixed dose combination; PK = pharmacokinetic(s).
Parameters are defined in Table 5
a. The ratios (and 90% CIs) are expressed as percentages.
Sitagliptin data in ertugliflozin 5 mg + sitagliptin 100 mg co-administered treatment for Subject 10011002 were excluded due to occurrence of vomiting within 2 × median sitagliptin T_{max} for the treatment.
The intra-subject variability (sqrt[exp(MSE)-1], where MSE is the mean square error) values based on mixed effects model for sitagliptin AUC_{inf}, AUC_{last} and C_{max} were 0.0282, 0.0289, and 0.1056, respectively.

(Source: Study P048/1056 CSR, Table 12)

(b) (4)

3.2.3 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing is reasonable from a clinical pharmacology perspective. The proposed starting dose of the ertugliflozin/sitagliptin FDC is 5 mg/100 mg QD, to be taken in the morning, with or without food. In patients tolerating the FDC, the dose may be increased to 15 mg/100 mg, QD, if additional glycemic control is needed.

3.2.4 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic or extrinsic factors?

Per relevant information of ertugliflozin and JANUVIA (sitagliptin), no dosage adjustment of the ertugliflozin/sitagliptin FDC is required based on race, gender, age, body weight/BMI, UGT1A9 polymorphism, mild or moderate hepatic impairment, or concomitant administration of drugs that impact the metabolism and/or transport of ertugliflozin or sitagliptin. No dosage adjustment of the ertugliflozin/sitagliptin FDC is also required for patients with mild renal impairment. (b) (4)

3.2.5 Are there clinically relevant food effects and what is the appropriate management strategy?

The food effect on ertugliflozin 15 mg/sitagliptin 100 mg FDC was evaluated in Study P026/1050 and no clinically meaningful food effects were identified for both individual components.

Study P026/1050 is a Phase 1, open-label, randomized, 2-period, 2-sequence single dose crossover study in healthy subjects (n=14). For ertugliflozin, following the administration of ertugliflozin/sitagliptin FDC with high-fat, high-calorie breakfast, ertugliflozin AUCs are similar while Cmax was about 30% lower compared to fasted condition (Table 10). Median Tmax was delayed from 1 hour to 2 hours in the presence of food. Mean terminal phase $t_{1/2}$ for ertugliflozin remains similar, 12.89 hours and 11.64 hours for fasted and fed conditions, respectively. For sitagliptin, following the administration of ertugliflozin/sitagliptin FDC with high-fat, high-calorie breakfast, sitagliptin AUCs and Cmax are all similar compared to fasted condition (Table 11). Median Tmax was 3.00 hours under the fasted condition and 1.77 hours in under fed condition. Mean terminal phase $t_{1/2}$ for sitagliptin remains similar, 11.49 hours and 12.07 hours for fasted and fed conditions, respectively.

Table 10. Statistical summary of treatment comparisons for plasma ertugliflozin PK parameters

Parameter (Units)	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Ertugliflozin 15 mg/Sitagliptin 100 mg FDC-Fed (Test)	Ertugliflozin 15 mg/Sitagliptin 100 mg FDC-Fasted (Reference)		
AUC_{inf} (ng•h/mL)	1108	1171	94.64	(91.62, 97.75)
AUC_{last} (ng•h/mL)	1090	1150	94.81	(91.79, 97.93)
C_{max} (ng/mL)	157.1	223.0	70.47	(63.34, 78.39)

Source: Table 14.4.3.3.1
PK parameters are defined in Table 5.
Values were back-transformed from the log scale.
The model was a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect.
The intra-subject variability (sqrt[exp(MSE)-1], where MSE is the mean square error) values based on mixed effects model for ertugliflozin AUC_{inf}, AUC_{last} and C_{max} were 0.0481, 0.0481 and 0.1592, respectively.
Abbreviations: CI = confidence interval; FDC = fixed dose combination; PK = pharmacokinetic(s).
a. The ratios (and 90% CIs) are expressed as percentages.

(Source: Study P026/1050 CSR, Table 10)

Table 11. Statistical summary of treatment comparisons for plasma sitagliptin PK parameters

Parameter (Units)	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Ertugliflozin 15 mg/Sitagliptin 100 mg FDC-Fasted (Test)	Ertugliflozin 15 mg/Sitagliptin 100 mg FDC-Fed (Reference)		
AUC_{inf} (μM•h)	7.105	7.352	96.64	(93.99, 99.37)
AUC_{last} (μM•h)	7.015	7.277	96.40	(93.79, 99.08)
C_{max} (nM)	721.3	750.7	96.09	(82.38, 112.09)

Source: Table 14.4.3.3.2
PK parameters are defined in Table 5.
Values were back-transformed from the log scale.
The model was a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect.
The intra-subject variability (sqrt[exp(MSE)-1], where MSE is the mean square error) values based on mixed effects model for sitagliptin AUC_{inf}, AUC_{last}, and C_{max} were 0.0413, 0.0408 and 0.2316, respectively.
Abbreviations: CI = confidence interval; FDC = fixed dose combination; PK = pharmacokinetic(s).
a. The ratios (and 90% CIs) are expressed as percentages.

(Source: Study P026/1050 CSR, Table 12)

3.2.6 Are there clinically relevant drug-drug interactions and what is the appropriate management strategy?

The PK interaction between individual components, ertugliflozin and sitagliptin, was evaluated in Study P022/1033. This was a Phase 1, open-label, randomized, 3-period, 6-sequence single oral dose crossover drug-drug interaction study to estimate the PK interaction between ertugliflozin and sitagliptin in 12 healthy volunteers. Results indicated that, for both individual components, the systemic exposure remains similar following the administration of FDC and each of the individual components alone, suggesting no clinically meaningful PK interaction between ertugliflozin and sitagliptin (Tables 12 and 13).

Table 12. Statistical comparisons for plasma ertugliflozin PK parameters

PK parameters	Geometric means		GMR (%) (90% CI) (Test/Reference)
	Ertugliflozin 15 mg + Sitagliptin 100 mg (Test)	Ertugliflozin 15 mg (Reference)	
AUC0-inf (h*ng/mL)	1482	1455	101.89 (97.24, 106.76)
AUC0-t (h*ng/mL)	1449	1428	101.46 (97.06, 106.07)
Cmax (ng/mL)	258	262	98.18 (91.86, 104.94)

(Reviewer's analysis)

Table 13. Statistical comparisons for plasma sitagliptine PK parameters

PK parameters	Geometric means		GMR (%) (90% CI) (Test/Reference)
	Ertugliflozin 15 mg + Sitagliptin 100 mg (Test)	Sitagliptin 100 mg (Reference)	
AUC0-inf (h*ng/mL)	7299	7192	101.48 (98.27, 104.79)
AUC0-t (h*ng/mL)	7214	7123	101.28 (98.04, 104.63)
Cmax (ng/mL)	814	792	101.65 (91.51, 112.91)

(Reviewer's analysis)

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Determinations of ertugliflozin and sitagliptin in human plasma were performed using fully validated high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) assays. For ertugliflozin bioanalytical method validation and performance, refer to the Clinical Pharmacology Review for NDA 209803 by Dr. Sury Sista. The key descriptive parameters of the bioanalytical assay for sitagliptin measurement were summarized in Table 1.

The bioanalytical facilities have been requested to be inspected. The OSIS recommends accepting data without an on-site inspection since the requested inspection site was classified as NAI based on recent inspections. For more detailed information, refer to the OSIS memorandum dated 04/17/2017.

Table 1. Summary of key descriptive parameters for sitagliptin bioanalytical assay

Assay Conditions	
Sample Storage Temperature	Pooled QC Samples: -20°C
Extraction Method	Protein Precipitation
Detection Method	HPLC-MS/MS
Sample Aliquot Volume	0.100 µL
Regression Weighting	Linear, $1/conc^2$
Quantification	Peak Area Ratios
Calibration Range (nominal)	1.00 to 1000 ng/mL
ULOQ	1000 ng/mL
LLOQ	1.00 ng/mL
Validation (VQC) Sample Concentrations	1.00, 3.01, 100.30, 802.40 and 10030.00 (VS-DIL) ng/mL
Assay Performance	
Intra-assay Validation (VQC) Sample Statistics	
Precision (%CV)	≤13.28%
Accuracy (%RE)	8.66% to 6.51%
Recovery	
Mean Analyte Recovery	74.71%, 83.69% and 85.55%
Mean Internal Standard Recovery	82.58%
Selectivity	
Matrix	4 out of 6 Human K_2EDTA Plasma Lots Passed
Ionization Effects	2 out of 2 Hyperlipidemic Human K_2EDTA Plasma lots passed 2 out of 2 Hemolyzed Human K_2EDTA Plasma lots passed
Analyte Carryover	≤9.25%

Batch Size	The maximum batch size investigated within this validation was 288
Stability	
Primary Stock Solution	20 hours and 25 minutes at room temperature (25°C) 453 days at -20°C
High Working Solution	74 days at -4°C
Low Working Solution	91 days at 4°C
Internal Standard solution	20 hours and 20 minutes at room temperature 372 days at -20°C
Ambient Matrix Stability	26 hours at room temperature in human K_2EDTA plasma
Frozen Matrix Storage Stability	628 days at -20°C
Freeze/Thaw Matrix Stability	4 Cycles at -20°C and 3 Cycles at -80°C in human K_2EDTA Plasma
Extract Stability	107 hours at room temperature in human K_2EDTA plasma
Re-injection Reproducibility Stability	94 hours at room temperature in human K_2EDTA plasma
Whole Blood Stability	180 minutes at room temperature (25°C) (human K_2EDTA plasma) 230 minutes in an ice/water bath (human K_2EDTA plasma)

Source: [Ref. 5.3.1.4: 04H3RQ].
Abbreviations: K_2EDTA=potassium ethylenediaminetetraacetic acid; HPLC-MS/MS=High Performance Liquid Chromatography-Tandem Mass Spectrometry; LLOQ=lower limit of quantification; QC=quality control; ULOQ=upper limit of quantification; VS-DIL=validation sample – dilution QC; VQC=validation quality control.

(Source: Summary of biopharmaceutical studies and associated analysis methods-ertugliflozin/sitagliptin FDC, Table 9)

4.2 Summary of Individual Studies

Study P025/1038 (BE Study)

Title: A Phase 1, Single Dose, Open-Label, Randomized, Crossover Bioequivalence Study of a Sitagliptin 100 mg/Ertugliflozin 15 mg Fixed Dose Combination Tablet vs Co-Administration of the Individual Components (Sitagliptin and Ertugliflozin) in Healthy Subjects

Objectives:

- **Primary:** to demonstrate the BE of sitagliptin 100 mg/ertugliflozin 15 mg FDC tablet to the co-administration of the individual components: sitagliptin 100 mg tablet and ertugliflozin 15 mg (administered as one 10 mg tablet + one 5 mg tablet) under fasted conditions
- **Secondary:** safety and tolerability

Study Design

This was a pivotal, Phase 1, open-label, randomized, 2-period, 2-sequence single dose crossover study to demonstrate the bioequivalence of ertugliflozin 15 mg/sitagliptin 100 mg FDC tablet to the co-administration of the individual components: ertugliflozin 15 mg (administered as one 10 mg tablet + one 5 mg tablet) and sitagliptin 100 mg tablet under fasted conditions in healthy subjects. Each subject received 2 treatments in a randomized manner as outlined in Table 2. Subjects received a single dose of the assigned trial medication in the morning of Day 1 in the fasted state (minimum 10-hour fast). Dosing in each period was separated by a washout period of at least 7 days.

Table 2. Treatment sequence in Study P025/1038

Sequence	Period 1	Period 2
1 (n = 9)	SITA+ERTU-Coadm	SITA/ERTU-FDC
2 (n = 9)	SITA/ERTU-FDC	SITA+ERTU-Coadm

Source: Section 16.1.1

Abbreviation: Coadm = co-administered; FDC = fixed dose combination; n = number of subjects.

SITA+ERTU-Coadm: sitagliptin 100 mg and ertugliflozin 15 mg (one 10 mg tablet + one 5 mg tablet) co-administered (within 5 minutes of each other with the ertugliflozin being administered first) under fasted conditions (Reference)

SITA/ERTU-FDC: sitagliptin 100 mg/ertugliflozin 15 mg FDC tablet, single dose, under fasted conditions (Test)

(Source: Study P025/1038 CSR, Table 1)

PK Sampling Schedule

Blood samples for determination of sitagliptin and ertugliflozin concentrations were collected from each subject predose, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours post-dose.

Results and Conclusions

A total of 18 healthy male and/or female subjects (9 in each treatment sequence) were enrolled and all of them completed this study. Results indicated that the BE was demonstrated for both ertugliflozin (Figure 1 and Tables 3, 4) and sitagliptin (Figure 2 and Tables 5, 6).

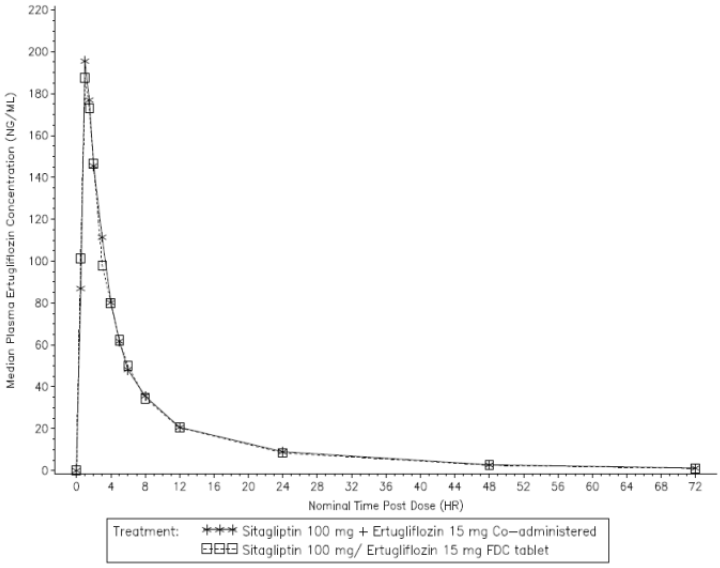

Figure 1. Median plasma ertugliflozin concentration-time profiles following single oral doses of ertugliflozin 15 mg /sitagliptin 100 mg FDC and ertugliflozin 15 mg+sitagliptin 100 mg co-administered

(Source: adapted from Figure 1 of Study P025/1038 CSR)

Table 3. Summary of plasma ertugliflozin PK parameters

	Parameter Summary Statistics[a] by Treatment	
Parameter (units)	Sitagliptin 100 mg/ Ertugliflozin 15 mg FDC	Sitagliptin 100 mg + Ertugliflozin 15 mg Co-administered
N, n	18, 18	18, 17
AUC_{inf} (ng.hr/mL)	1188 (22)	1242 (22)
AUC_{last} (ng.hr/mL)	1162 (23)	1184 (23)
C_{max} (ng/mL)	202.4 (34)	198.1 (24)
T_{max} (hr)	1.01 (0.500, 4.00)	1.01 (0.500, 5.00)
$t_{½}$ (hr)	13.38 ±3.05	13.84 ±2.73

Source: Table 14.4.3.1.1

Abbreviations: %CV = percent coefficient of variation; FDC = Fixed Dose Combination; N = Number of subjects in the treatment and contributing to the descriptive summary statistics; n = number of subjects with reportable $t_{½}$ and AUC_{inf}; PK = pharmacokinetic(s); SD = standard deviation.

Parameters are defined in Table 5.

a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ±SD for $t_{½}$.

(Source: Study P025/1038 CSR, Table 9)

Table 4. Statistical summary of treatment comparisons for plasma ertugliflozin PK parameters

	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
Parameter (units)	Sitagliptin 100 mg/ Ertugliflozin 15 mg FDC (Test)	Sitagliptin 100 mg + Ertugliflozin 15 mg Co-administered (Reference)		
AUC_{inf} (ng.hr/mL)	1188	1209	98.25	95.07, 101.54
AUC_{last} (ng.hr/mL)	1162	1184	98.18	95.17, 101.30
C_{max} (ng/mL)	202.4	198.1	102.13	92.32, 112.99

Source: Table 14.4.3.3.1

Abbreviations: CI = confidence interval; FDC = Fixed Dose Combination; PK = pharmacokinetic(s).

a. The ratios (and 90% CIs) are expressed as percentages.

Parameters are defined in Table 5.

The intra-subject variability values based on mixed effects model for ertugliflozin AUC_{inf} and C_{max} were 5.46% and 17.49%, respectively.

(Source: Study P025/1038 CSR, Table 10)

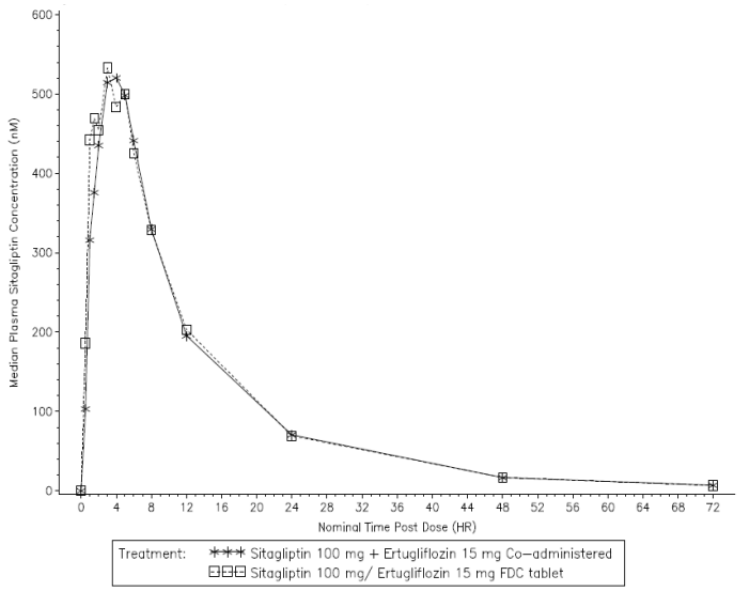

Figure 2. Median plasma sitagliptin concentration-time profiles following single oral doses of ertugliflozin 15 mg /sitagliptin 100 mg FDC and ertugliflozin 15 mg+sitagliptin 100 mg co-administered

(Source: adapted from Figure 4 of Study P025/1038 CSR)

Table 5. Summary of plasma sitagliptin PK parameters

	Parameter Summary Statistics[a] by Treatment	
Parameter (units)	**Sitagliptin 100 mg/ Ertugliflozin 15 mg FDC**	**Sitagliptin 100 mg + Ertugliflozin 15 mg Co-administered**
N, n	18, 18	18, 17
AUC_{inf} (µM.hr)	7.343 (15)	7.239 (14)
AUC_{last} (µM.hr)	7.241 (15)	7.058 (14)
C_{max} (nM)	661.1 (22)	579.2 (20)
T_{max} (hr)	3.00 (0.500, 6.02)	3.98 (1.98, 5.00)
$t_{½}$ (hr)	12.16 ±2.02	12.53 ±1.28

Source: Table 14.4.3.1.2

Abbreviations: %CV = percent coefficient of variation; FDC = Fixed Dose Combination; N = Number of subjects in the treatment and contributing to descriptive summary statistics; n = number of subjects with reportable $t_{½}$ and AUC_{inf}; PK = pharmacokinetic(s); SD = standard deviation.

Parameters are defined in Table 5.

a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ±SD for $t_{½}$.

(Source: Study P025/1038 CSR, Table 11)

Table 6. Statistical summary of treatment comparisons for plasma sitagliptin PK parameters (Study P025/1038)

	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
Parameter (units)	**Sitagliptin 100 mg/ Ertugliflozin 15 mg FDC (Test)**	**Sitagliptin 100 mg + Ertugliflozin 15 mg Co-administered (Reference)**		
AUC_{inf} (µM.hr)	7.343	7.171	102.40	99.51, 105.38
AUC_{last} (µM.hr)	7.241	7.058	102.60	99.78, 105.50
C_{max} (nM)	661.1	579.2	114.14	108.35, 120.24

Source: Tables 14.4.3.3.2

Abbreviations: CI = confidence interval; FDC = Fixed Dose Combination; PK = pharmacokinetic(s).

Parameters are defined in Table 5.

a. The ratios (and 90% CIs) are expressed as percentages.

The intra-subject variability values based on mixed effects model for sitagliptin AUC_{inf} and C_{max} were 4.81% and 9.01%, respectively.

(Source: Study P025/1038 CSR, Table 12)

Study P048/1056 (BE Study)

Title: A Phase 1, Single Dose, Open-Label, Randomized, Crossover Bioequivalence Study of a Sitagliptin 100 mg/Ertugliflozin 5 mg Fixed Dose Combination Tablet vs Co-Administration of the Individual Components (Sitagliptin and Ertugliflozin) in Healthy Subjects

Objectives:

- **Primary:** To demonstrate bioequivalence of ertugliflozin 5 mg/sitagliptin 100 mg FDC tablet to the co-administration of the individual components: ertugliflozin 5 mg and sitagliptin 100 mg, under fasted conditions
- **Secondary:** safety and tolerability

Study Design

This was a pivotal, Phase 1, open-label, randomized, 2-period, 2-sequence single dose crossover study to demonstrate the bioequivalence of ertugliflozin 5 mg/sitagliptin 100 mg FDC tablet to the co-administration of the individual components: ertugliflozin 5 mg and sitagliptin 100 mg tablet under fasted conditions in healthy subjects. Each subject received 2 treatments in a randomized manner as outlined in Table 12. Subjects received a single dose of the assigned trial medication in the morning of Day 1 in the fasted state (minimum 10-hour fast). Dosing in each period was separated by a washout period of at least 7 days.

Table 12. Treatment sequence in Study P048/1056

Sequence	Period 1	Period 2
1 (N = 9)	ERTU+SITA -Coadm	ERTU/SITA -FDC
2 (N = 9)	ERTU/SITA -FDC	ERTU+SITA -Coadm

Source: Section 16.1.1

Abbreviations: Coadm = co-administered; FDC = fixed dose combination; N = number of subjects.

ERTU+SITA -Coadm: ertugliflozin 5 mg tablet and sitagliptin 100 mg tablet co-administered (within 5 minutes of each other with the ertugliflozin being administered first) under fasted conditions (Reference)
ERTU/SITA-FDC: ertugliflozin 5 mg/sitagliptin 100 mg FDC tablet, single dose, under fasted conditions (Test)

(Source: Study P048/1056 CSR, Table 1)

PK Sampling Schedule

Blood samples for determination of sitagliptin and ertugliflozin concentrations were collected from each subject predose, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours post-dose.

Results and Conclusions

A total of 18 healthy male and/or female subjects (9 in each treatment sequence) were enrolled and all of them completed this study. Results indicated that the BE was demonstrated for both ertugliflozin (Figure 5 and Tables 13, 14) and sitagliptin (Figure 6 and Tables 15, 16).

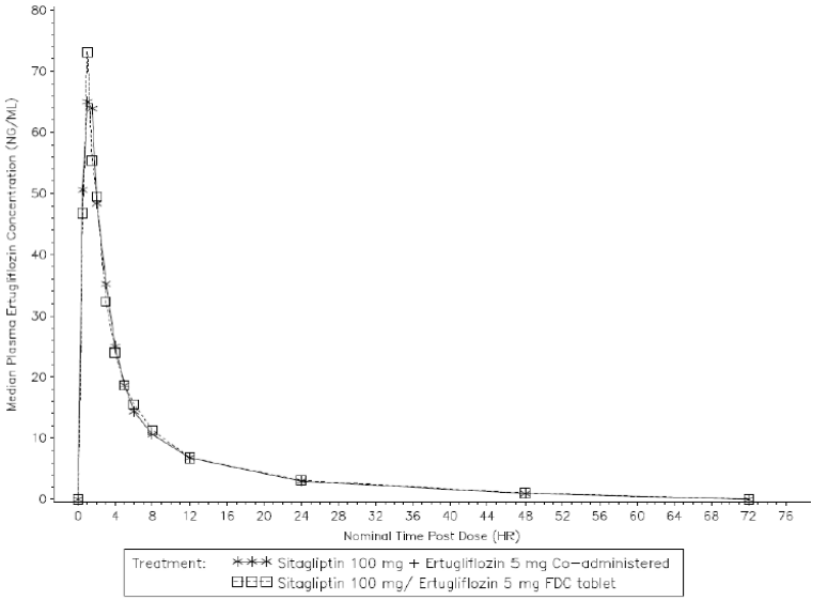

Figure 5. Median plasma ertugliflozin concentration-time profiles following single oral doses of ertugliflozin 5 mg /sitagliptin 100 mg FDC and ertugliflozin 5 mg+sitagliptin 100 mg co-administered

(Source: adapted from Figure 1 of Study P048/1056 CSR)

Table 13. Summary of plasma ertugliflozin PK parameters

Parameter (units)	Parameter Summary Statistics[a] by Treatment	
	Ertugliflozin 5 mg/Sitagliptin 100 mg FDC tablet	Ertugliflozin 5 mg + Sitagliptin 100 mg Co-administered
N	18	18
AUC_{inf} (ng.hr/mL)	386.8 (22)	382.1 (22)
AUC_{last} (ng.hr/mL)	371.7 (23)	364.3 (23)
C_{max} (ng/mL)	73.44 (24)	71.19 (23)
T_{max} (hr)	1.01 (0.500, 3.00)	1.01 (0.500, 4.00)
$t_{½}$ (hr)	12.99 ± 3.53	11.84 ± 2.60

Source: Table 14.4.3.1.1

Abbreviations: %CV = percent coefficient of variation; FDC = fixed dose combination; N = number of subjects in the treatment group and contributing to the summary statistics; PK = pharmacokinetic(s); SD = standard deviation.

Parameters are defined in Table 5.

a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ±SD for $t_{½}$.

(Source: Study P048/1056 CSR, Table 9)

Table 14. Statistical summary of treatment comparisons for plasma ertugliflozin PK parameters

Parameter (units)	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Ertugliflozin 5 mg/Sitagliptin 100 mg FDC tablet (Test)	Ertugliflozin 5 mg + Sitagliptin 100 mg Co-administered (Reference)		
AUC_{inf} (ng.hr/mL)	386.8	382.1	101.23	97.15, 105.49
AUC_{last} (ng.hr/mL)	371.7	364.3	102.01	97.89, 106.32
C_{max} (ng/mL)	73.44	71.19	103.17	93.76, 113.52

Source: Table 14.4.3.3.1

Abbreviations: CI = confidence interval; FDC = fixed dose combination; PK = pharmacokinetic(s).

a. The ratios (and 90% CIs) are expressed as percentages.

Parameters are defined in Table 5.

The intra-subject variability (sqrt[exp(MSE)-1], where MSE is the mean square error) values based on mixed effects model for ertugliflozin AUC_{inf}, AUC_{last} and C_{max} were 0.0708, 0.0710, and 0.1654, respectively.

(Source: Study P048/1056 CSR, Table 10)

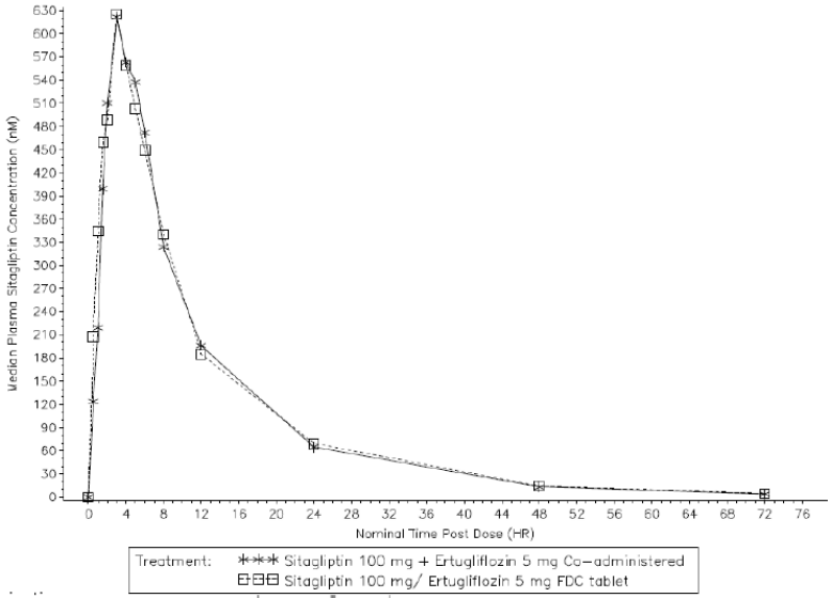

Figure 6. Median plasma sitagliptin concentration-time profiles following single oral doses of ertugliflozin 5 mg /sitagliptin 100 mg FDC and ertugliflozin 5 mg+sitagliptin 100 mg co-administered

(Source: adapted from Figure 4 of Study P048/1056 CSR)

Table 15. Summary of plasma sitagliptin PK parameters

Parameter (units)	Parameter Summary Statistics[a] by Treatment	
	Ertugliflozin 5 mg/Sitagliptin 100 mg FDC tablet	Ertugliflozin 5 mg + Sitagliptin 100 mg Co-administered
N	18	17
AUC_{inf} (µM.hr)	7.136 (17)	7.077 (16)
AUC_{last} (µM.hr)	7.061 (17)	7.005 (16)
C_{max} (nM)	673.8 (32)	659.5 (26)
T_{max} (hr)	3.00 (1.00, 4.08)	2.98 (0.483, 5.00)
$t_{½}$ (hr)	11.56 ± 0.92	11.18 ± 1.19

Source: Table 14.4.3.1.2
Abbreviations: %CV = percent coefficient of variation; FDC = fixed dose combination; N = number of subjects in the treatment group and contributing to the summary statistics; PK = pharmacokinetic(s); SD = standard deviation.
Parameters are defined in Table 5.
a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ±SD for $t_{½}$. Sitagliptin data in ertugliflozin 5 mg + sitagliptin 100 mg co-administered treatment for Subject 10011002 were excluded due to occurrence of vomiting within 2 × median sitagliptin T_{max} for the treatment.

(Source: Study P048/1056 CSR, Table 11)

Table 16. Statistical summary of treatment comparisons for plasma sitagliptin PK parameters

Parameter (units)	Adjusted (Least-Squares) Geometric Means: Ertugliflozin 5 mg/Sitagliptin 100 mg FDC tablet (Test)	Adjusted (Least-Squares) Geometric Means: Ertugliflozin 5 mg + Sitagliptin 100 mg Co-administered (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{inf} (µM.hr)	7.136	7.151	99.80	98.12, 101.51
AUC_{last} (µM.hr)	7.061	7.078	99.77	98.05, 101.52
C_{max} (nM)	673.8	675.5	99.76	93.63, 106.28

Source: Table 14.4.3.3.2
Abbreviations: CI = confidence interval; FDC = fixed dose combination; PK = pharmacokinetic(s).
Parameters are defined in Table 5
a. The ratios (and 90% CIs) are expressed as percentages.
Sitagliptin data in ertugliflozin 5 mg + sitagliptin 100 mg co-administered treatment for Subject 10011002 were excluded due to occurrence of vomiting within 2 × median sitagliptin T_{max} for the treatment.
The intra-subject variability (sqrt[exp(MSE)-1], where MSE is the mean square error) values based on mixed effects model for sitagliptin AUC_{inf}, AUC_{last} and C_{max} were 0.0282, 0.0289, and 0.1056, respectively.

(Source: Study P048/1056 CSR, Table 12)

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Study P026/1050 (Food Effect Study)

Title: A Phase 1, Randomized, Open-Label, 2-Sequence, 2-Period Crossover Study to Estimate the Effect of Food on the Pharmacokinetics of Sitagliptin and Ertugliflozin When Administered as a Fixed Dose Combination Tablet to Healthy Subjects

Objectives:

- Primary: To estimate the effect of food on the PK of sitagliptin and ertugliflozin following administration of the ertugliflozin 15 mg/sitagliptin 100 mg FDC tablet
- Secondary: safety and tolerability

Study Design

This is a Phase 1, open-label, randomized, 2-period, 2-sequence single dose crossover study in healthy subjects. Each subject received 2 treatments in a randomized manner according to 1 of 2 sequences as outlined in the Table as below.

Table 22. Treatment Sequence of Study P026/1050

Sequence	Period 1	Period 2
1 (N = 7)	ERTU/SITA-Fasted	ERTU/SITA-Fed
2 (N = 7)	ERTU/SITA-Fed	ERTU/SITA-Fasted

Source: Section 16.1.1

Abbreviations: ERTU/SITA-Fasted = ertugliflozin 15 mg/sitagliptin 100 mg FDC tablet, single dose under fasted conditions (Reference); ERTU/SITA-Fed = ertugliflozin 15 mg/sitagliptin 100 mg FDC tablet, single dose under fed conditions (Test); FDC = fixed dose combination; N = total number of subjects.

(Source: Study P026/1050 CSR, Table 1)

ERTU/SITA–Fasted: After an overnight fast of at least 10 hours, subjects were dosed with the ertugliflozin 15 mg/sitagliptin 100 mg FDC tablet.

ERTU/SITA-Fed: After an overnight fast of at least 10 hours, subjects were dosed with the ertugliflozin 15 mg/sitagliptin 100 mg FDC tablet approximately 30 minutes after beginning consumption of a standard high-fat (approximately 50% of total caloric content of the meal),

high-calorie high-calorie (approximately 800 to 1000 calories) breakfast. The subjects were instructed to consume the entire meal within 25 minutes.

PK Sampling Schedule
Blood samples for determination of sitagliptin and ertugliflozin concentrations were collected from each subject predose, and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours post-dose.

Results and Conclusions
A total of 14 subjects were assigned to and received study treatments. All subjects completed the study and were analyzed for PK and safety.

For ertugliflozin, following the administration of ertugliflozin/sitagliptin FDC with high-fat, high-calorie breakfast, ertugliflozin AUCs are similar while Cmax was about 30% lower compared to fasted condition (Figure 9 and Table 23). Median Tmax was delayed from 1 hour to 2 hours in the presence of food. Mean terminal phase t1/2 for ertugliflozin remains similar, 12.89 hours and 11.64 hours for fasted and fed conditions, respectively.

For Sitagliptin, following the administration of ertugliflozin/sitagliptin FDC with high-fat, high-calorie breakfast, sitagliptin AUCs and Cmax are all similar compared to fasted condition (Figure 10 and Table 24). Median Tmax was 3.00 hours under the fasted condition and 1.77 hours in under fed condition. Mean terminal phase t1/2 for sitagliptin remains similar, 11.49 hours and 12.07 hours for fasted and fed conditions, respectively.

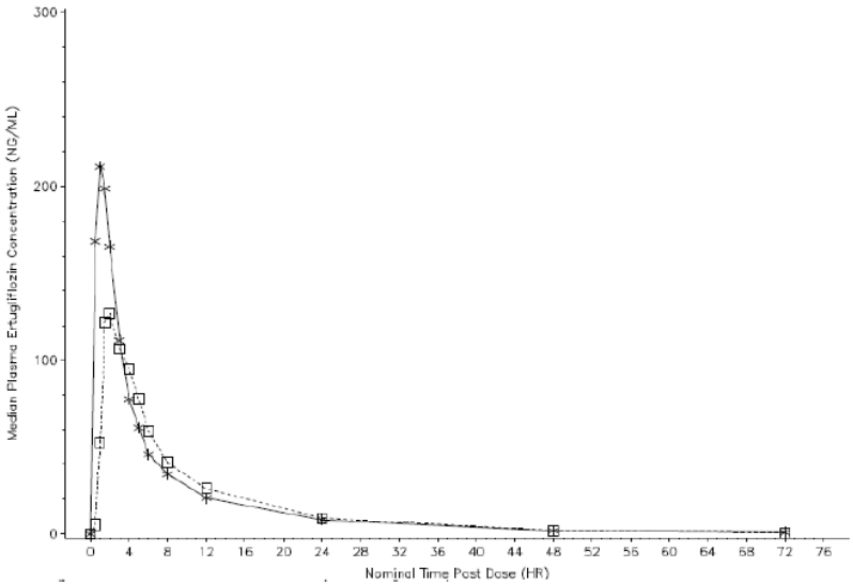

Figure 9. Median plasma ertugliflozin concentration-time profiles following single oral doses of ertugliflozin 15 mg/sitagliptin 100 mg FDC under fed and fasting conditions
(Source: Adapted from Figure 1 of Study P026/1050 CSR)

Table 23. Statistical summary of treatment comparisons for plasma ertugliflozin PK parameters

Parameter (Units)	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Ertugliflozin 15 mg/Sitagliptin 100 mg FDC-Fed (Test)	Ertugliflozin 15 mg/Sitagliptin 100 mg FDC-Fasted (Reference)		
AUC_{inf} (ng•h/mL)	1108	1171	94.64	(91.62, 97.75)
AUC_{last} (ng•h/mL)	1090	1150	94.81	(91.79, 97.93)
C_{max} (ng/mL)	157.1	223.0	70.47	(63.34, 78.39)

Source: Table 14.4.3.3.1
PK parameters are defined in Table 5.
Values were back-transformed from the log scale.
The model was a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect.
The intra-subject variability (sqrt[exp(MSE)-1], where MSE is the mean square error) values based on mixed effects model for ertugliflozin AUC_{inf}, AUC_{last} and C_{max} were 0.0481, 0.0481 and 0.1592, respectively.
Abbreviations: CI = confidence interval; FDC = fixed dose combination; PK = pharmacokinetic(s).
a. The ratios (and 90% CIs) are expressed as percentages.

(Source: Study P026/1050 CSR, Table 10)

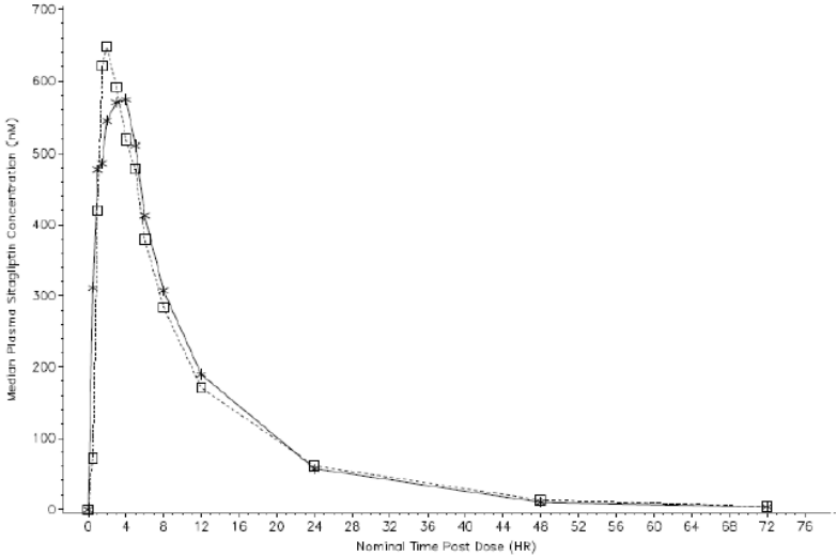

Figure 10. Median plasma sitagliptin concentration-time profiles following single oral doses of ertugliflozin 15 mg/sitagliptin 100 mg FDC under fed and fasting conditions
(Source: Adapted from Figure 4 of Study P026/1050 CSR)

Table 24. Statistical summary of treatment comparisons for plasma sitagliptin PK parameters

Parameter (Units)	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Ertugliflozin 15 mg/Sitagliptin 100 mg FDC-Fasted (Test)	Ertugliflozin 15 mg/Sitagliptin 100 mg FDC-Fed (Reference)		
AUC_{inf} (µM•h)	7.105	7.352	96.64	(93.99, 99.37)
AUC_{last} (µM•h)	7.015	7.277	96.40	(93.79, 99.08)
C_{max} (nM)	721.3	750.7	96.09	(82.38, 112.09)

Source: Table 14.4.3.3.2
PK parameters are defined in Table 5.
Values were back-transformed from the log scale.
The model was a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect.
The intra-subject variability (sqrt[exp(MSE)-1], where MSE is the mean square error) values based on mixed effects model for sitagliptin AUC_{inf}, AUC_{last}, and C_{max} were 0.0413, 0.0408 and 0.2316, respectively.
Abbreviations: CI = confidence interval; FDC = fixed dose combination; PK = pharmacokinetic(s).
a. The ratios (and 90% CIs) are expressed as percentages.

(Source: Study P026/1050 CSR, Table 12)

Study P022/1033 (PK Interaction Study)

Title: A Phase 1, Randomized, Open-Label, 3-Period, 6-Sequence Study to Estimate the Pharmacokinetic Interaction between Ertugliflozin and Sitagliptin in Healthy Subjects

Objectives:

- **Primary:** to estimate the effect of sitagliptin on ertugliflozin PK and the effect of ertugliflozin sitagliptin PK
- **Secondary:** safety and tolerability

Study Design

This was a Phase 1, open-label, randomized, 3-period, 6-sequence single oral dose crossover drug-drug interaction study to estimate the PK interaction between ertugliflozin and sitagliptin in 12 healthy volunteers. Each enrolled subject received 3 treatments (A, B and C) in a randomized manner according to 1 of 6 sequences as outlined in Table as below. Subjects received the assigned trial medication (Treatment A, B or C) in the morning of Day 1 in each period after an overnight fast of at least 8 hours. Dosing in consecutive crossover periods was separated by a washout period of at least 5 days.

Table 25. Treatment sequence of Study P022/1033

Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	A	C	B
3	B	A	C
4	B	C	A
5	C	A	B
6	C	B	A

Source: Section 16.1.1
Abbreviation: SD = single dose
Treatment A: 15 mg ertugliflozin (SD).
Treatment B: 100 mg sitagliptin (SD).
Treatment C: 15 mg ertugliflozin (SD) + 100 mg sitagliptin (SD) administered within 5 minutes of each other with the ertugliflozin being administered first.

(Source: Study P022/1033 CSR, Table 1)

PK Sampling Schedule

Blood samples for determination of sitagliptin and ertugliflozin concentrations were collected from each subject predose, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours post-dose.

Results and Conclusions

A total of 12 subjects were assigned to and received study treatments and all of them completed the study. Results indicated that, for both individual components, the systemic exposure remains similar following the administration of FDC and each of the individual components alone, suggesting no clinically meaningful PK interaction between ertugliflozin and sitagliptin (Figures 11 and 12, Tables 26-29).

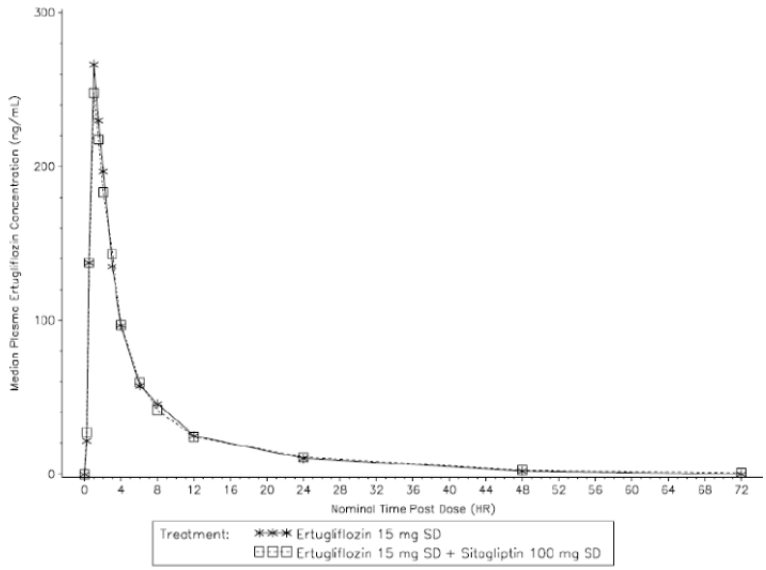

Figure 11. Median plasma ertugliflozin concentration-time profiles following a single oral dose of ertugliflozin alone and co-administered with sitagliptin
(Source: Adapted from Figure 1 of Study P022/1033 CSR)

Table 26. Summary of plasma ertugliflozin PK parameters

Parameter (unit)	Parameter Summary Statistics[a] for Ertugliflozin by Treatment	
	Ertugliflozin 15 mg SD	Ertugliflozin 15 mg SD +Sitagliptin 100 mg SD
N, n	12, 12	12, 12
AUC_{inf} (ng·hr/mL)	1413 (26)	1445 (25)
AUC_{last} (ng·hr/mL)	1385 (26)	1412 (24)
C_{max} (ng/mL)	262.9 (25)	258.1 (26)
T_{max} (hr)	1.00 (1.00 - 3.00)	1.00 (0.500 - 2.10)
CL/F (mL/min)	177.0 (26)	173.1 (25)
V_z/F (L)	181.4 (41)	203.3 (21)
$t_{½}$ (hr)	12.63 ± 5.15	14.17 ± 4.55

Source: Table 14.4.3.1.1.1
PK parameters are defined in Table 5.
Abbreviations: %CV = percent coefficient of variation; hr = hour(s); N = number of subjects in the treatment group; n = number of subjects contributing to the summary statistics; PK = pharmacokinetic(s); SD = single dose.
a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± standard deviation for $t_{½}$.
(Source: Study P022/1033 CSR, Table 10)

Table 27. Statistical comparisons for plasma ertugliflozin PK parameters

PK parameters	Geometric means		GMR (%) (90% CI) (Test/Reference)
	Ertugliflozin 15 mg + Sitagliptin 100 mg (Test)	Ertugliflozin 15 mg (Reference)	
AUC0-inf (h*ng/mL)	1482	1455	101.89 (97.24, 106.76)
AUC0-t (h*ng/mL)	1449	1428	101.46 (97.06, 106.07)
Cmax (ng/mL)	258	262	98.18 (91.86, 104.94)

(Reviewer's analysis)

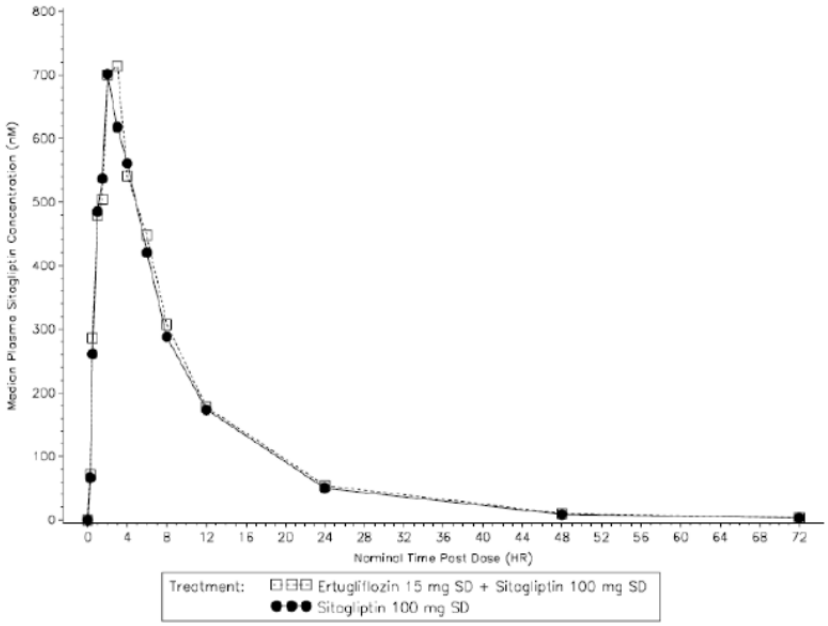

Figure 12. Median plasma sitagliptin concentration-time profiles following a single oral dose of sitagliptin alone and co-administered with ertugliflozin
(Source: Adapted from Figure 4 of Study P022/1033 CSR)

Table 28. Summary of plasma sitagliptin PK parameters

Parameter (unit)	Parameter Summary Statistics[a] for Sitagliptin by Treatment	
	Sitagliptin 100 mg SD	Ertugliflozin 15 mg SD + Sitagliptin 100 mg SD
N, n	12, 12	12, 12
AUC_{inf} (uM·hr)	6.882 (21)	6.997 (20)
AUC_{last} (uM·hr)	6.814 (21)	6.912 (21)
C_{max} (nM)	792.0 (24)	805.3 (24)
T_{max} (hr)	2.00 (1.00-4.00)	3.00 (1.00-6.00)
CL/F (mL/min)	594.4 (21)	584.4 (20)
Vz/F (L)	548.2 (28)	579.3 (23)
$t_{½}$ (hr)	11.00 ± 2.89	11.79 ± 2.98

Source: Table 14.4.3.1.1.2
PK parameters are defined in Table 5.
Abbreviations: %CV = percent coefficient of variation; hr = hour(s); N = Number of subjects in the treatment group; n = Number of subjects with reportable $t_{½}$ and AUC_{inf}; SD = single dose.
a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean (± standard deviation) for $t_{½}$.
(Source: Study P022/1033 CSR, Table 12)

Table 29. Statistical comparisons for plasma sitagliptin PK parameters

PK parameters	Geometric means		GMR (%) (90% CI) (Test/Reference)
	Ertugliflozin 15 mg + Sitagliptin 100 mg (Test)	Sitagliptin 100 mg (Reference)	
AUC0-inf (h*ng/mL)	7299	7192	101.48 (98.27, 104.79)
AUC0-t (h*ng/mL)	7214	7123	101.28 (98.04, 104.63)
Cmax (ng/mL)	814	792	101.65 (91.51, 112.91)

(Reviewer's analysis)

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/s/

LEI HE
08/07/2017

MANOJ KHURANA
08/07/2017

Office of Clinical Pharmacology Review

NDA Number	209806
Link to EDR	\\CDSESUB1\EVSPROD\NDA209806\209806.enx
Submission Date	12/19/2016
Submission Type	505(b)(2), Standard
Brand Name	Segluromet
Generic Name	Ertugliflozin and Metformin
Dosage Form and Strength	Film-coated tablets: • Ertugliflozin 2.5 mg/ Metformin 500 mg • Ertugliflozin 2.5 mg/ Metformin 1000 mg • Ertugliflozin 7.5 mg/ Metformin 500 mg • Ertugliflozin 7.5 mg/ Metformin 1000 mg
Route of Administration	Oral administration, BID
Proposed Indication	It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) Limitations of Use: • Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
Applicant	Merck
Associated IND	IND 122329
OCP Review Team	Lei He, Ph.D., Lian Ma, Ph.D., Manoj Khurana, Ph.D.

Table of Contents

1. EXECUTIVE SUMMARY

Merck has submitted three NDA submissions in parallel seeking the marketing approval for ertugliflozin tablets (5 mg and 15 mg) (NDA 209803), ertugliflozin/sitagliptin fixed-dose combination (FDC) tablets [redacted] (b) (4) 5 mg/100 mg, [redacted] (b) (4) 15 mg/100 mg) (NDA 209805), ertugliflozin/metformin FDC tablets (2.5mg/500mg, 2.5mg/1000mg, 7.5mg/500mg, 7.5mg/1000mg) (NDA 209806) for the treatment of type 2 diabetes mellitus (T2DM) as adjunct to diet and exercise therapy. The proposed dosing regimens for the three products are as below:

- Ertugliflozin tablets: 5 mg or 15 mg once daily (QD) with or without food
- Ertugliflozin/sitagliptin FDC tablets: up to 15 mg ertugliflozin/100 mg sitagliptin QD dose with or without food
- Ertugliflozin/metformin FDC tablets: up to 7.5 mg ertugliflozin/1000 mg metformin twice daily (BID) dose with meals

A comprehensive clinical program has been conducted to support the approval of ertugliflozin as a stand-alone product, as well as ertugliflozin/sitagliptin and ertugliflozin/metformin FDCs, including twenty-nine Phase 1 studies, two Phase 2 studies, and nine Phase 3 studies.

To support the application of ertugliflozin/metformin FDC, six clinical pharmacology studies were submitted, including two bioequivalence (BE) studies, one PK interaction study, one food effect study, two PK/PD studies, and four Phase 3 studies. Only the clinical pharmacology studies will be reviewed in this review.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 209806 Clinical Pharmacology data submitted on December 19, 2016 and found the results of submitted studies are acceptable to support approval. However, the final determination of the approval will be made based on the efficacy/safety assessment of ertugliflozin in NDA 209803.

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Summary of Important Clinical Pharmacology Findings

Ertugliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor. Metformin hydrochloride is an anti-hyperglycemic agent (AHA) that improves glucose tolerance in patients with T2DM by lowering both basal and post-prandial plasma glucose (PPG).

Six clinical pharmacology studies were submitted to support the application of ertugliflozin/metformin FDC, including two bioequivalence (BE) studies, one PK interaction study, one food effect study, two PK/PD studies.

- The Sponsor conducted one pivotal PK/PD study (Study P035/1051) in healthy subjects and a model based meta-analysis (MBMA) to support the bridge between QD and BID dosing regimen.
    - Following 6-day ertugliflozin administration with QD or BID dosing regimen, the steady state exposure of ertugliflozin (AUC0-24h) and PD (UGE0-24h) are both comparable between QD and BID dosing regimen.
    - Dose-response (UGE and HbA1c) relationship of ertugliflozin indicated that, with the same total daily dose of ertugliflozin, the proposed BID dosing regimens (2.5 mg BID and 7.5 mg BID) are expected to produce similar treatment effect as compared to the QD dosing regimens (5 mg QD and 15 mg QD).

- Two BE studies were conducted to bridge the co-administered individual components which was used in Phase 3 studies and the proposed highest (7.5 mg/1000 mg) and lowest (2.5 mg/500 mg) strengths of ertugliflozin/metformin FDC tablets. Results indicated that both strengths of the proposed ertugliflozin/metformin FDC tablet are bioequivalent to co-administration of individual components. Regarding the other two strengths (7.5 mg/500 mg and 2.5 mg/1000 mg), the Sponsor has requested BE study waiver.

- The food effect on ertugliflozin/metformin FDC was evaluated in Study P028/1049 and no clinically meaningful food effects were identified for both individual components.

- The PK interaction between individual components, ertugliflozin and metformin, was evaluated in Study P019/1032. Results indicated that, for both individual components, the systemic exposure remains unchanged with GMR and 90%CI within the 80-125% limits following the administration of FDC and each of the individual components alone, suggesting no clinically meaningful PK interaction between ertugliflozin and sitagliptin

2.2 Summary of Labeling Recommendations

Summary of labeling recommendation for different sections are listed below:

- Section 2: The proposed general dosing recommendations are acceptable. Dosing recommendations for renal impaired patients depend on the efficacy/safety assessment of ertugliflozin component in renal impairment subgroups in NDA 209803.
- Section 7: The proposed labeling statements are acceptable.
- Section 8: The labeling statements for hepatic impaired patients are acceptable. Dosing recommendations for renal impaired patients depend on the efficacy/safety assessment of ertugliflozin component in renal impairment subgroups in NDA 209803.
- Section 12.3: The labeling statements about the (b) (4) are recommended to be removed.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Merck has submitted three NDA submissions in parallel seeking the marketing approval for ertugliflozin tablets (5 mg and 15 mg) (NDA 209803), ertugliflozin/sitagliptin FDC tablets ([(b) (4)] [(b) (4)] 5 mg/100 mg, [(b) (4)] 15 mg/100 mg) (NDA 209805), ertugliflozin/metformin FDC tablets (2.5mg/500mg, 2.5mg/1000mg, 7.5mg/500mg, 7.5mg/1000mg) (NDA 209806) for the treatment of T2DM as adjunct to diet and exercise therapy.

Ertugliflozin is a new molecular entity under NDA 209803. Metformin is currently available in the US market as GLUCOPHAGE (metformin) tablets (NDA 020357, by Bristol Myers Squibb), GLUCOPHAGE XR (metformin) extended release tablets (NDA 021202, by Bristol Myers Squibb), or as one component in JANUMET (metformin and sitagliptin) tablets (NDA 022044, by Merck), JANUMET XR (metformin and sitagliptin) extended release tablets (NDA 202270, by Merck), and many other products.

While ertugliflozin will be dosed QD, the ertugliflozin-metformin FDC will be dosed BID. The applicant proposed a PK/PD study comparing the BID and QD ertugliflozin dose regimens (2.5 mg BID vs 5 mg QD and 7.5 mg BID vs 15 mg QD) in healthy subjects for bridging the two dosing regimens of ertugliflozin. In the Pre-IND meeting requested on May 09, 2014, for Question 1a regarding whether the proposed PK/PD study is sufficient for bridging the two dosing regimens of ertugliflozin, the Agency provided responses that "*Your approach to use PK/PD study to bridge ertugliflozin once daily (q.d.) and twice daily (b.i.d.) dosing regimens seems reasonable. Please submit any data you have linking the PD endpoint, urinary glucose excretion (UGE), with the clinical endpoint, HbA1c. Also submit exposure-response analysis evaluating relationship between ertugliflozin exposure and HbA1c response.*" The rationale to accept the sponsor's approach to use PK/PD study to bridge ertugliflozin QD and BID dosing regimens was as below:

- *"For canagliflozin sponsor conducted a trial comparing BID vs. placebo, results from which were compared with QD in a cross-trial comparison. The review for this application is completed (final regulatory decision pending) which concludes that efficacy for canagliflozin is not lost when switching patients from QD to BID dosing regimen.*
- *For dapagliflozin, a head-to-head comparison of QD vs. BID was conducted in a 16 week study D1691C00003. The results for primary endpoint HbA1c are shown below, which confirms that patients do not lose efficacy when switching from QD to BID dosing regimen.*
- *Given the rich prior information demonstrating that efficacy for SGLT-2 inhibitors is retained between QD and BID dosing regimen, we agreed to accept the sponsor's proposal of bridging based on just the steady state PK and PD (UGE0-24 at steady state) measurements."*

The Agency also concurred that the BE studies can be conducted in the fasted state and the food effect study can be conducted with the highest strength FDC product. For more detailed information, refer to the Clinical Pharmacology Review for IND 122329 by Dr. Zhihong Li dated July 22, 2014.

To support the application of ertugliflozin/metformin FDC, six clinical pharmacology studies and four Phase 3 studies were submitted. Only the six clinical pharmacology studies as shown in Table 1 will be reviewed in this review. Regarding Phase 3 studies, refer to the Clinical Pharmacology Review for NDA 209803 by Drs Sury Sista and Lian Ma.

Table 1. Summary of Clinical Pharmacology Studies Supporting NDA 209805

Protocol No.	Objective(s)	Design	Number of Healthy Subjects	Dose and Formulations
P019/1032	Drug-Drug Interaction	Open-label, randomized, 3-period, 6-sequence, single-dose crossover	N=18 (10 males/ 8 females)	15 mg ertugliflozin administered as three 5 mg tablets 1000 mg metformin administered as two 500 mg tablets 15 mg ertugliflozin administered as three 5 mg tablets + 1000 mg metformin administered as two 500 mg tablets
P040/1007	PK/PD	Randomized, double-blind, sponsor-open, 2 cohort, 2-period, 2-way crossover	N=52[a] (45 males/ 7 females)	Ertugliflozin 1 mg tablet 2 mg ertugliflozin administered as two 1 mg tablets 4 mg ertugliflozin administered as four 1 mg tablets
P035/1051	PK/PD	Open-label, multiple-dose, randomized, 2-period, 2-way crossover	N=70 (51 males/ 19 females)	Ertugliflozin 2.5 mg tablet Ertugliflozin 5 mg tablet 7.5 mg ertugliflozin administered as one 5 mg tablet + one 2.5 mg tablet 15 mg ertugliflozin administered as one 10 mg tablet + one 5 mg tablet
P028/1049	Definitive food effect	Open-label, randomized, 2-period, 2-sequence crossover, single-dose	N=14 (10 Males/ 4 Females)	ertugliflozin 7.5 mg/metformin 1000 mg tablet
P027/1041	Bioequivalence	Open-label, randomized, 2-period, 2-sequence crossover, single-dose	N=32 (26 Males/ 6 Females)	7.5 mg ertugliflozin administered as one 5 mg tablet + one 2.5 mg tablet and US-sourced Glucophage® 1000 mg tablet co-administered ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet
P050/1058	Bioequivalence	Open-label, randomized, 2-period, 2-sequence crossover, single-dose	N=32 (29 Males/ 3 Females)	2.5 mg ertugliflozin and US-sourced Glucophage® 500 mg tablet co-administered ertugliflozin 2.5 mg/metformin 500 mg FDC tablet
P046/1054	Bioequivalence	Open-label, randomized, 2-period, 2-sequence crossover, single-dose	N=34 (20 Males/ 14 Females)	7.5 mg ertugliflozin administered as one 5 mg tablet + one 2.5 mg tablet and EU-sourced Glucophage® 850 mg tablet co-administered ertugliflozin 7.5 mg/metformin 850 mg FDC tablet
P047/1055	Bioequivalence	Open-label, randomized, 2-period, 2-sequence crossover, single-dose	N=34 (21 Males/ 13 Females)	7.5 mg ertugliflozin administered as one 5 mg tablet + one 2.5 mg tablet and EU-sourced Glucophage® 1000 mg tablet co-administered ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet

(Source: Summary of Clinical Pharmacology Studies, Table 1)

3.2 Clinical Pharmacology Review Questions

3.2.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Four Phase 3 studies were conducted to support the efficacy and safety of ertugliflozin/metformin FDC, including two placebo-controlled studies and two active-controlled studies. For more detailed information, refer to the Clinical Pharmacology Review for NDA 209803 by Drs. Sury Sista and Lian Ma, and the Clinical Review by Dr. Frank Pucino.

The clinical pharmacology information has been provided to bridge the QD and BID dosing regimen as well as the co-administration of individual components in Phase 3 studies and the proposed FDC tablets.

Bridging QD (studied) vs. BID (proposed) dosing regimen

Given that Glucophage **(**metformin) immediate release formulation is recommended to be administered BID, the ertugliflozin/metformin FDC has also been proposed to be given BID. However, in Phase 3 studies, ertugliflozin was administered QD. Therefore, the QD dosing regimen of ertugliflozin used in the Phase 3 clinical development program need to be bridged to the proposed BID dosing regimen of ertugliflozin as a component of the ertugliflozin/metformin FDC. As such, the Sponsor conducted one pivotal PK/PD study (Study P035/1051) and model based meta-analysis (MBMA) to support bridging between QD and BID dosing regimen.

- PK/PD study (Study P035/1051)
  This was a Phase 1, open-label, multiple-dose, randomized, 2-period, 2-way crossover study in 3 cohorts in 70 healthy subjects. Eligible subjects received ertugliflozin 5 mg QD and 2.5 mg BID (Cohort A and C) or 15 mg QD and 7.5 mg BID (Cohort B) for 6 days. Morning dose was administered after an overnight fast of at least 10 hours and evening dose (for BID dosing regimen) was administered ~12 hours after the morning dose and 1 hour before dinner. Results indicated that following 6-day ertugliflozin administration with QD or BID dosing regimen, the steady state exposure of ertugliflozin (AUC0-24h) and PD (UGE0-24h) were both comparable between QD and BID dosing regimen (Table 2).

Table 2. Statistical comparisons for AUC0-24 and UGE0-24 on Day 6 following QD and BID dosing regimen

Parameter (unit)	Comparison (Test vs Reference)	Adjusted (Least-Squares) Geometric Means		Ratio (BID/QD) of Adjusted Means	90% CI for Ratio†
		BID (Test)	QD (Reference)		
AUC_{0-24} (ng•hr/mL)	Ertugliflozin 2.5 mg BID vs ertugliflozin 5 mg QD	401.0	397.9	100.78	98.76, 102.83
	Ertugliflozin 7.5 mg BID vs ertugliflozin 15 mg QD	1190	1193	99.73	97.08, 102.45
UGE_{0-24} (g)	Ertugliflozin 2.5 mg BID vs ertugliflozin 5 mg QD	57.00	51.74	110.16	(102.96, 117.87)
	Ertugliflozin 7.5 mg BID vs ertugliflozin 15 mg QD	58.84	57.26	102.77	(97.69, 108.12)

†The ratios (and 90% CIs) are expressed as percentages.
AUC_{0-24} = area under the plasma concentration-time curve from 0 to 24 hours; BID = twice daily; CI = confidence interval; QD = once daily; UGE_{0-24} = urinary glucose excretion during 24 hours.

Source: [Ref. 5.3.4.1: P035: Table 12] [Ref. 5.3.4.1: P035: Table 15]

(Source: Clinical Overview-Ertugliflozin/Metformin FDC, Table 3)

- Dose-response (UGE and HbA1c) relationship of ertugliflozin

  The Sponsor has performed MBMA to quantify the link between the dose response relationship for UGE in healthy subjects after multiple dose administration (steady-state) and glycated hemoglobin (HbA1C) in T2DM patients in order to support the use of UGE measured at steady-state in healthy subjects as a biomarker to predict HbA1C in T2DM patients. An MBMA model has been developed using UGE or HbA1C data from 96 randomized placebo-controlled trials of SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ipragliflozin or luseogliflozin) and 8 ertugliflozin studies. Of the 104 trials, 82 reported HbA1C results and 29 reported UGE data.

  The developed model has been identified to characterize the observed treatment effect for UGE and HbA1C in ertugliflozin trials well and the treatment plateau of ertugliglozin appears to be reached at the total daily dose of 5 mg and above (Figure 1). The ED50s for UGE_{24h} and HbA1C were estimated to be 0.75 mg and 1 mg, respectively, which are both much lower as compared to the proposed total daily doses of 5 mg and 15 mg (Table 3). In addition, even assuming 2.5 mg and 7.5 mg was given as single dose administration, ~75-80% and >90% of maximum response was expected to be achieved, respectively, for both UGE and HbA1C. Therefore, with the same total daily dose of ertugliflozin, the proposed BID dosing regimens (2.5 mg BID and 7.5 mg BID) are expected to produce similar treatment effect as compared to the QD dosing regimens (5 mg QD and 15 mg QD).

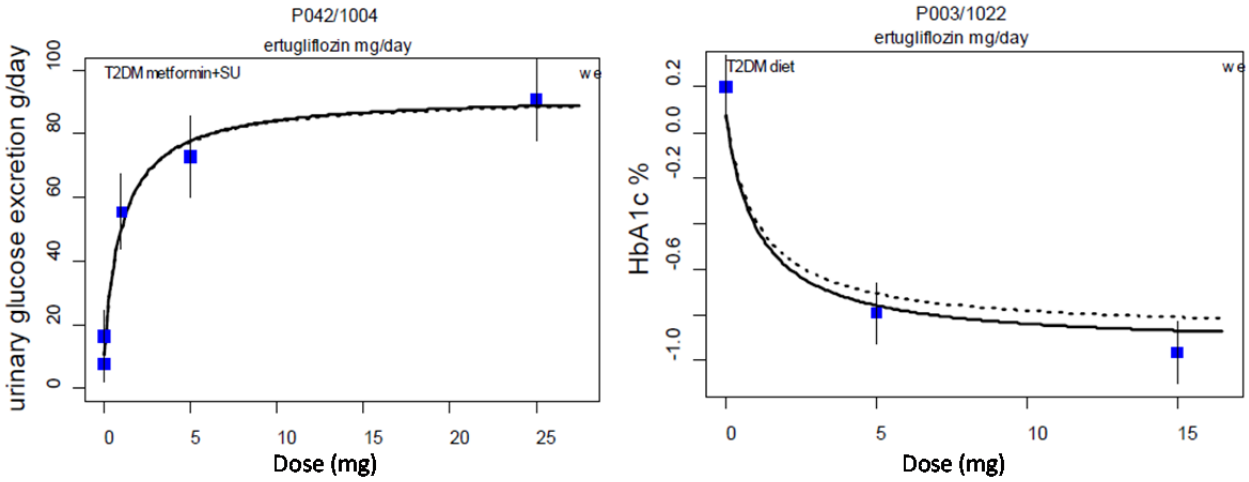


Figure 1. Estimated and observed dose response of UGE and HbA1C in T2DM patients for ertugliflozin trials

Note: Symbols represent observed effects and whiskers represent 95% CIs. Solid and dotted lines represent trial specific and population estimates, respectively.

(Source: adapted from Figures 13 and 14 of Model-Based Meta Analysis Report)

Table 3. Estimated response (UGE_{24h} and HbA1C) achieved by 5 mg and 15 mg ertugliflozin

Ertugliflozin dose	UGE_{24h} (g)	HbA1C(%)
	ED50=0.75 mg Emax=71.5g	ED50=1.0 mg Emax=-0.77%
5 mg	62.5	-0.64
15 mg	68.9	-0.72

Bridging co-administration of individual components (studied) to the FDC tablets (proposed)

Since the co-administration of the corresponding doses of the individual components was used in Phase 3 studies, two BE studies were conducted to bridge the co-administered individual components and the proposed highest (7.5 mg/1000 mg) and lowest (2.5 mg/500 mg) strengths of ertugliflozin/metformin FDC tablet. Results indicated that both strengths of the proposed ertugliflozin/metformin FDC tablet are bioequivalent to co-administration of individual components, which was used in Phase 3 studies. See Section 3.2.2 or Individual Study Review for more information. Regarding the other two strengths (7.5 mg/500 mg and 2.5 mg/1000 mg), the Sponsor has requested BE study waiver. For more detailed information, refer to the Biopharmaceutics Review.

3.2.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

The proposed to-be-marketed product is ertugliflozin/metformin FDC tablet at four strengths of 2.5 mg/500 mg, 2.5 mg/1000 mg, 7.5 mg/500 mg, and 7.5 mg/1000 mg. However, in Phase 3 studies, the co-administration of the corresponding doses of the individual components, ertugliflozin and Glucophage (metformin), was used. Therefore, two BE studies (Studies P027/1041 and P050/1058) were conducted in healthy subjects to bridge the highest (7.5 mg/1000 mg) and lowest (2.5 mg/500 mg) strengths of the ertugliflozin/metformin FDC tablet and co-administration of individual components. Results of BE studies indicated that both of the

highest and lowest strengths of the proposed ertugliflozin/metformin FDC tablet are bioequivalent to co-administration of individual components, which was used in Phase 3 studies (see statistical analysis results for ertugliflozin 7.5 mg/metformin 1000 mg in Tables 4 and 5, for ertugliflozin 2.5 mg/metformin 500 mg in Tables 6 and 7).

Regarding the other two strengths (7.5 mg/500 mg and 2.5 mg/1000 mg), the Sponsor has requested BE study waiver. For more detailed information, refer to the Biopharmaceutics Review.

Also note that the clinical facility has been requested to be inspected. The OSIS recommends accepting data without an on-site inspection since the requested inspection site was classified as NAI based on recent inspections. For more detailed information, refer to the OSIS memorandum dated 04/17/2017.

Statistical Analysis Results for Ertugliflozin 7.5 mg/Metformin 1000 mg FDC tablet

Table 4. Ertugliflozin PK comparison following single oral dose administration of ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet and co-administration of the individual components: ertugliflozin 7.5 mg and metformin 1000 mg tablet under fasted conditions (Study P027/1041)

	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
Parameter (unit)	Ertugliflozin 7.5 mg/Metformin 1000 mg FDC (Test)	Ertugliflozin 7.5 mg + Metformin 1000 mg (US) COADM (Reference)		
AUC_{inf} (ng•hr/mL)	651.5	653.9	99.64	97.04, 102.30
AUC_{last} (ng•hr/mL)	638.0	637.7	100.05	97.31, 102.87
C_{max} (ng/mL)	124.1	119.9	103.50	97.85, 109.47

Source: Table 14.4.3.3.1
PK parameters are defined in Table 5.
Values have been back-transformed from the log scale.
The model was a mixed effects model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. The intra-subject variability values based on mixed effects model for ertugliflozin AUC_{inf} and C_{max} were 6.22% and 13.3%, respectively.
Abbreviations: CI = confidence interval, COADM = co-administered, FDC = fixed dose combination, hr = hour, PK = pharmacokinetic(s), US = United States.
a. The ratios (and 90% CIs) are expressed as percentages.
(Source: Study P027/1041 CSR, Table 10)

Table 5. Metformin PK comparison following single oral dose administration of ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet and co-administration of the individual components: ertugliflozin 7.5 mg and metformin 1000 mg tablet under fasted conditions (Study P027/1041)

	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
Parameter (unit)	Ertugliflozin 7.5 mg/Metformin 1000 mg FDC (Test)	Ertugliflozin 7.5 mg + Metformin 1000 mg (US) COADM (Reference)		
AUC_{inf} (ng•hr/mL)	11230	11560	97.14	89.98, 104.87
AUC_{last} (ng•hr/mL)	10870	11130	97.72	91.31, 104.58
C_{max} (ng/mL)	1648	1661	99.20	92.06, 106.90

Source: Tables 14.4.3.3.2
PK parameters are defined in Table 5.
Values have been back-transformed from the log scale.
The model was a mixed effects model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. The intra-subject variability values based on mixed effects model for metformin AUC_{inf} and C_{max} were 15.8% and 17.8%, respectively.
Abbreviations: CI = confidence interval; COADM = co-administered; FDC = fixed dose combination, hr = hour, PK = pharmacokinetic(s), US = United States.
a. The ratios (and 90% CIs) are expressed as percentages.
(Source: Study P027/1041 CSR, Table 12)

Statistical Analysis Results for Ertugliflozin 2.5 mg/Metformin 500 mg FDC tablet

Table 6. Ertugliflozin PK comparison following single oral dose administration of ertugliflozin 2.5 mg/metformin 500 mg FDC tablet and co-administration of the individual components: ertugliflozin 2.5 mg and metformin 500 mg tablet under fasted conditions (Study P050/1058)

	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
Parameter (units)	Ertugliflozin 2.5 mg/Metformin 500 mg FDC tablet (Test)	Ertugliflozin 2.5 mg + Metformin 500 mg (US) Co-administration (Reference)		
AUC_{inf} (ng.hr/mL)	176.9	180.0	98.26	96.62, 99.94
AUC_{last} (ng.hr/mL)	165.3	167.6	98.62	96.82, 100.44
C_{max} (ng/mL)	34.94	34.86	100.22	94.76, 106.00

Source: Table 14.4.3.5.1
Abbreviations: CI = confidence interval, FDC = fixed dose combination, hr = hour, PK = pharmacokinetic(s), US = United States.
The intra-subject variability values (sqrt[exp(MSE)-1], where MSE is the mean square error) based on mixed effects model for ertugliflozin AUC_{inf}, AUC_{last}, and C_{max} were 0.0399, 0.0433 and 0.1327, respectively.
PK parameters are defined in Table 5.
a. The ratios (and 90% CIs) are expressed as percentages.
(Source: Study P050/1058 CSR, Table 10)

Table 7. Metformin PK comparison following single oral dose administration of ertugliflozin 2.5 mg/metformin 500 mg FDC tablet and co-administration of the individual components: ertugliflozin 2.5 mg and metformin 500 mg tablet under fasted conditions (Study P050/1058)

Parameter (units)	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Ertugliflozin 2.5 mg/Metformin 500 mg FDC tablet (Test)	Ertugliflozin 2.5 mg + Metformin 500 mg (US) Co-administration (Reference)		
AUC_{inf} (ng.hr/mL)	6934	6717	103.24	96.16, 110.83
AUC_{last} (ng.hr/mL)	6819	6794	100.36	93.28, 107.98
C_{max} (ng/mL)	1030	1015	101.49	93.83, 109.76

Source: Table 14.4.3.5.2
Abbreviations: CI = confidence interval, FDC = fixed dose combination, hr = hour, PK = pharmacokinetic(s), US = United States.
The intra-subject variability values (sqrt[exp(MSE)-1], where MSE is the mean square error) based on mixed effects model for metformin AUC_{inf}, AUC_{last}, and C_{max} were 0.1495, 0.1737 and 0.1864, respectively.
PK parameters are defined in Table 5.
a. The ratios (and 90% CIs) are expressed as percentages.
(Source: Study P050/1058 CSR, Table 12)

3.2.3 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is reasonable from a clinical pharmacology perspective. Given that Glucophage (metformin) immediate release formulation is recommended to be administered BID, the ertugliflozin/metformin FDC has also been proposed to be given BID with meals, with gradual dose escalation for those initiating metformin to reduce the gastrointestinal side effects due to metformin.

3.2.4 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic or extrinsic factors?

Per relevant information of ertugliflozin and Glucophage (metformin), no dosage adjustment of the ertugliflozin/metgormin FDC is required based on age, body weight, gender, race, UGT1A9 polymorphism, and concomitant administration of drugs that impact the metabolism and/or transport of ertugliflozin and metformin.

(b) (4)

(b) (4). The final determination will depend on the efficacy/safety assessment of ertugliflozin in NDA 209803.

For patients with mild or moderate hepatic impairment, although no dosage adjustment is recommended for ertugliflozin component, the approved metformin labels recommend to avoid the use of metformin in patients with clinical and laboratory evidence of hepatic disease, as the usehas been associated with some cases of lactic acidosis. Therefore, the ertugliflozin/metformin FDC is not recommended in patients with hepatic impairment. In addition, although food has no clinically meaningful impact on the PK of ertugliflozin or metformin when administered as the

FDC tablet, the ertugliflozin/metformin FDC should be administered BID with meals to reduce the gastrointestinal adverse effects due to metformin.

3.2.5 Are there clinically relevant food effects and what is the appropriate management strategy?

The food effect on ertugliflozin 7.5 mg /metformin 1000 mg FDC was evaluated in Study P028/1049 and no clinically meaningful food effects were identified for both individual components.

Study P028/1049 is a Phase 1, open-label, randomized, 2-period, 2-sequence single dose crossover study in healthy subjects (n=14).

For ertugliflozin, following the administration of ertugliflozin 7.5 mg/metformin 1000 mg FDC with high-fat, high-calorie breakfast, ertugliflozin AUCs are similar while Cmax was about 41% lower compared to fasted condition (Table 8). Median Tmax was delayed from 1.5 hour to 2.5 hours in the presence of food. Mean terminal phase t1/2 for ertugliflozin remains similar, 11.18 hours and 12.10 hours for fasted and fed conditions, respectively.

For metformin, following the administration of ertugliflozin 7.5 mg/metformin 1000 mg FDC with high-fat, high-calorie breakfast, metformin AUCs remains similar while Cmax was about 29% lower compared to fasted condition (Table 9). Median Tmax for metformin was delayed from 2.25 hours to 4.00 hours in the presence of food. The mean terminal phase t1/2 for metformin was 11.75 hours and 12.34 hours with and without food, respectively.

Table 8. Comparisons of plasma ertugliflozin PK following the single oral dose administration of ertugliflozin 7.5 mg/metformin 1000 mg FDC under fasted and fed conditions

	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
Parameter (units)	**Ertugliflozin 7.5 mg/ Metformin 1000 mg FDC-Fed (Test)**	**Ertugliflozin 7.5 mg/ Metformin 1000 mg FDC-Fasted (Reference)**		
AUC_{inf} (ng•hr/mL)	614.3	654.8	93.81	(90.09, 97.69)
AUC_{last} (ng•hr/mL)	599.6	639.5	93.75	(90.03, 97.63)
C_{max} (ng/mL)	75.16	126.5	59.41	(51.06, 69.11)

Source: Table 14.4.3.3.1.1
PK parameters are defined in Table 5.
Values were back-transformed from the log scale.
The model was a mixed effects model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. The intra-subject variability values (sqrt[exp(MSE)-1], where MSE is the mean square error) based on mixed effects model for ertugliflozin AUC_{inf}, AUC_{last}, and C_{max} were 0.0574, 0.0574, and 0.2186, respectively.
Abbreviations: CI = confidence interval; FDC = fixed dose combination; hr = hour (s); PK = pharmacokinetic(s).
a. The ratios (and 90% CIs) are expressed as percentages.

(Source: Study P028/1049 CSR, Table 10)

Table 9. Comparisons of plasma metformin PK following the single oral dose administration of ertugliflozin 7.5 mg/metformin 1000 mg FDC under fasted and fed conditions

Parameter (units)	Adjusted Geometric Means: Ertugliflozin 7.5 mg/ Metformin 1000 mg FDC-Fed (Test)	Adjusted Geometric Means: Ertugliflozin 7.5 mg/ Metformin 1000 mg FDC-Fasted (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{inf} (ng•hr/mL)	11630	12530	92.82	(85.07, 101.26)
AUC_{last} (ng•hr/mL)	11740	12420	94.53	(86.97, 102.76)
C_{max} (ng/mL)	1442	2040	70.68	(63.62, 78.51)

Source: Table 14.4.3.3.1.2
PK parameters are defined in Table 5.
Values were back-transformed from the log scale.
The model was a mixed effects model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. The intra-subject variability values (sqrt[exp(MSE)-1], where MSE is the mean square error) values based on mixed effects model for metformin AUC_{inf}, AUC_{last}, and C_{max} were 0.1175, 0.1190, and 0.1504, respectively.
Abbreviations: CI = confidence interval; FDC = fixed dose combination; hr = hour(s); PK = pharmacokinetic(s).
a. The ratios (and 90% CIs) are expressed as percentages.
(Source: Study P028/1049 CSR, Table 12)

3.2.6 Are there clinically relevant drug-drug interactions and what is the appropriate management strategy?

The PK interaction between individual components, ertugliflozin and metformin, was evaluated in Study P019/1032. This was a Phase 1, open-label, randomized, 3-period, 6-sequence single oral dose crossover drug-drug interaction study to estimate the PK interaction between ertugliflozin and metformin in 18 healthy volunteers. Results indicated that, for both individual components, the systemic exposure remains unchanged with GMR and 90%CI within the 80-125% limits following the administration of FDC and each of the individual components alone, suggesting no clinically meaningful PK interaction between ertugliflozin and sitagliptin (Tables 10 and 11).

Table 10. Statistical comparisons for plasma ertugliflozin PK parameters following a single oral dose of ertugliflozin alone and co-administered with ertugliflozin

Parameter (Units)	Adjusted (Least-Squares) Geometric Means: Ertugliflozin 15 mg + Metformin 1000 mg (Test)	Adjusted (Least-Squares) Geometric Means: Ertugliflozin 15 mg (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{inf} (ng.h/mL)	1380	1376	100.34	97.43, 103.34
AUC_{last} (ng.h/mL)	1367	1346	101.52	98.65, 104.48
C_{max} (ng/mL)	264.5	272.3	97.14	88.77, 106.30

Source: Table 14.4.3.3.1
The intra-subject variability based on the statistical model for AUC_{inf} and C_{max} were 0.0469 and 0.1552, respectively.
AUC_{inf} = area under the plasma concentration-time profile from time 0 extrapolated to infinite time, AUC_{last} = area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}), C_{max} = maximum observed plasma concentration.
CI = confidence interval.
a. The ratios (and 90% CIs) are expressed as percentages.
(Source: Study P019/1032 CSR, Table 10)

Table 11. Statistical comparisons for plasma metformin PK parameters following a single oral dose of metformin alone and co-administered with ertugliflozin

Parameter (Units)	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Ertugliflozin 15 mg + Metformin 1000 mg (Test)	Metformin 1000 mg (Reference)		
Data excluded due to vomiting[b]				
AUC_{inf} (ng.h/mL)	12490	12370	100.94	90.62, 112.44
AUC_{last} (ng.h/mL)	12270	12560	97.75	89.46, 106.82
C_{max} (ng/mL)	1835	1952	94.00	82.94, 106.55
All Data Included				
AUC_{inf} (ng.h/mL)	12490	12370	100.94	90.62, 112.44
AUC_{last} (ng.h/mL)	12270	12550	97.81	89.99, 106.31
C_{max} (ng/mL)	1835	1983	92.52	81.99, 104.39

Source: Tables 14.4.3.3.2 and 14.4.3.3.3

The intra-subject variability based on the statistical model for AUC_{inf} and C_{max} were 0.1365 and 0.2189, respectively.

AUC_{inf} = area under the plasma concentration-time profile from time 0 extrapolated to infinite time, AUC_{last} = area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}), C_{max} = maximum observed plasma concentration, CI = confidence interval.

a. The ratios (and 90% CIs) are expressed as percentages.

b. Metformin 1000 mg treatment data for Subject 10011018 has been excluded due to vomiting. Only AUC_{last} and C_{max} are affected since AUC_{inf} was not reportable for this subject and treatment.

(Source: Study P019/1032 CSR, Table 12)

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Determinations of ertugliflozin and metformin in human plasma were performed using fully validated high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) assays. Regarding the bioanalytical method validation and performance for ertugliflozin, refer to the Clinical Pharmacology Review for NDA 209803 by Dr. Sury Sista. The key descriptive parameters of the bioanalytical assay for metformin measurement were summarized in Table 1.

The bioanalytical facilities have been requested to be inspected. The OSIS recommends accepting data without an on-site inspection since the requested inspection site was classified as NAI based on recent inspections. For more detailed information, refer to the OSIS memorandum dated 04/17/2017.

Table 1. Summary of key descriptive parameters for metformin bioanalytical assay

Assay Conditions	
Sample Storage Temperature	Pooled QC Samples: -20°C
Extraction Method	Protein Precipitation
Detection Method	HPLC-MS/MS
Sample Aliquot Volume	50 µL
Regression Weighting	Linear, $1/conc^2$
Quantification	Peak Area Ratios
Calibration Range	2.00 to 1000 ng/mL
ULOQ	1000 ng/mL
LLOQ	2.00 ng/mL
Validation (VQC) Sample Concentrations	2.00, 6.00, 60.0, 400, 800 ng/mL and 2000 (VS-DIL) ng/mL
Assay Performance	
Intra-assay Validation (VQC) Sample Statistics	
Precision (%CV)	≤4.4%
Accuracy (%RE)	-2.3% to 0.2%
Recovery	
Mean Analyte Recovery	101.3%
Mean Internal Standard Recovery	101.8%
Selectivity	
Matrix	6 out of 6 Human K_2EDTA Plasma Lots Passed
Ionization Effects	6 out of 6 Normal Human K_2EDTA Plasma Lots Passed 1 out of 1 Hyperlipidemic Human K_2EDTA Plasma lots passed 1 out of 1 Hemolyzed Human K_2EDTA Plasma lots passed
Analyte Carryover	≤12.5%

Stability	
Primary Stock Solution	24 hours at room temperature (25±5°C) 106 days at -15°C
High Working Solution	24 hours at room temperature (25±5°C) 106 days at -2°C to 8°C
Low Working Solution	24 hours at room temperature (25±5°C) 106 days at -2 to 8°C
Ambient Matrix Stability	23.54 hours at 25°C in human K_2EDTA plasma
Frozen Storage Matrix Stability Established at Validation	212 days at -20°C and 104 days at -70°C
Freeze/Thaw Matrix Stability	5 Cycles at -20°C and -80°C in human K_2EDTA Plasma
Extract Stability	65.7 hours at 10°C in human K_2EDTA plasma
Re-injection Reproducibility Stability	72.6 hours at 10°C in human K_2EDTA plasma
Whole Blood Stability	Stable after 3 hours at room temperature (25°C) followed by centrifugation at both 4°C and ambient conditions

Source: [Ref. 5.3.1.4: 04GRSW], [Ref. 5.3.1.4: 04GRSS].
Abbreviations: %CV=percent coefficient of variation; %RE=percent relative error; K_2EDTA=potassium ethylenediaminetetraacetic acid; HPLC-MS/MS=High Performance Liquid Chromatography-Tandem Mass Spectrometry; LLOQ=lower limit of quantification; QC=quality control; ULOQ=upper limit of quantification; VQC=validation quality control; VS-DIL=validation sample – dilution QC.

(Source: Summary of biopharmaceutical studies and associated analysis methods-ertugliflozin/metformin FDC, Table 11)

4.2 Summary of Individual Studies

Study P019/1032 (PK Interaction Study)

Title: A Phase 1, Randomized, Open-Label, 3-Period, 6-Sequence Study to Estimate the Pharmacokinetic Interaction between Ertugliflozin and Metformin in Healthy Subjects

Objectives:

- **Primary:** to estimate the effect of ertugliflozin on metformin PK and the effect of metformin on ertugliflozin PK
- **Secondary:** safety and tolerability

Study Design

This was a Phase 1, open-label, randomized, 3-period, 6-sequence single oral dose crossover drug-drug interaction study to estimate the PK interaction between ertugliflozin and metformin in healthy volunteers. Each enrolled subject received 3 treatments (A, B and C) in a randomized manner according to 1 of 6 sequences as outlined in Table as below. Subjects received the assigned trial medication (Treatment A, B or C) in the morning of Day 1 in each period under fasted condition. Dosing in each period was separated by a washout period of at least 5 days.

Table 2. Treatment sequence of Study P019/1032

Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	A	C	B
3	B	A	C
4	B	C	A
5	C	A	B
6	C	B	A

Source: Section 16.1.1
Treatment A: 15 mg ertugliflozin (single dose).
Treatment B: 1000 mg metformin (single dose).
Treatment C: 15 mg ertugliflozin + 1000 mg metformin (single dose of each administered within 5 minutes of each other).

(Source: Study P019/1032 CSR, Table 1)

PK Sampling Schedule

Blood samples for determination of metformin and ertugliflozin concentrations were collected from each subject predose, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 48, and 72 hours post-dose.

Results and Conclusions

A total of 18 subjects were assigned to and received study treatments and all of them completed the study. Results indicated that, for both individual components, the systemic exposure remains similar following the administration of FDC and each of the individual components alone, suggesting no clinically meaningful PK interaction between ertugliflozin and metformin (Figures 1 and 2, Tables 3-6).

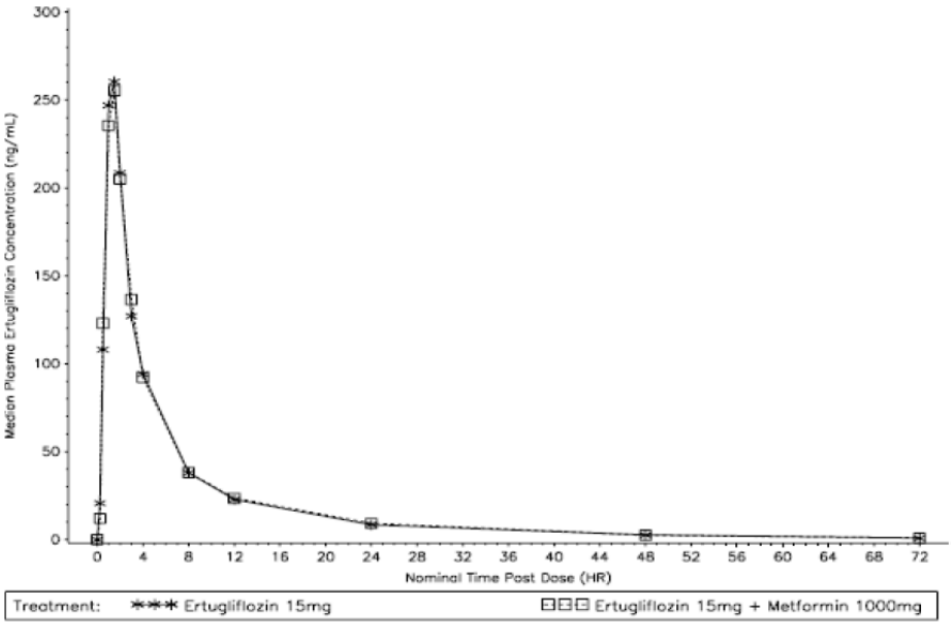


Figure 1. Median plasma ertugliflozin concentration-time profiles following a single oral dose of ertugliflozin alone and co-administered with metformin
(Source: Adapted from Figure 1 of Study P019/1032 CSR)

Table 3. Summary of plasma ertugliflozin PK parameters

Parameter (units)	Parameter Summary Statistics[a] by Treatment	
	Ertugliflozin 15 mg	Ertugliflozin 15 mg + Metformin 1000 mg
N, n	18, 17	18, 17
AUC_{inf} (ng.h/mL)	1363 (24)	1388 (23)
AUC_{last} (ng.h/mL)	1346 (23)	1367 (22)
C_{max} (ng/mL)	272.3 (24)	264.5 (20)
T_{max} (h)	1.02 (1.00, 2.00)	1.29 (1.00, 3.00)
$t_{½}$ (h)	11.79 ± 2.34	13.48 ± 4.65
CL/F (mL/min)	183.8 (24)	180.0 (23)
V_z/F (L)	183.7 (33)	201.7 (31)

Source: Table 14.4.3.1.1.1
AUC_{inf} = area under the plasma concentration-time profile from time 0 extrapolated to infinite time, AUC_{last} = area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}), C_{max} = maximum observed plasma concentration, CL/F = apparent clearance, N = number of subjects; n = number of subjects for $t_{½}$, AUC_{inf}, CL/F and V_z/F, $t_{½}$ = terminal half-life, T_{max} = time for C_{max}, V_z/F = apparent volume of distribution.
a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ±SD for $t_{½}$.
(Source: Study P019/1032 CSR, Table 9)

Table 4. Statistical comparisons for plasma ertugliflozin PK parameters

Parameter (Units)	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Ertugliflozin 15 mg + Metformin 1000 mg (Test)	Ertugliflozin 15 mg (Reference)		
AUC_{inf} (ng.h/mL)	1380	1376	100.34	97.43, 103.34
AUC_{last} (ng.h/mL)	1367	1346	101.52	98.65, 104.48
C_{max} (ng/mL)	264.5	272.3	97.14	88.77, 106.30

Source: Table 14.4.3.3.1
The intra-subject variability based on the statistical model for AUC_{inf} and C_{max} were 0.0469 and 0.1552, respectively.
AUC_{inf} = area under the plasma concentration-time profile from time 0 extrapolated to infinite time, AUC_{last} = area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}), C_{max} = maximum observed plasma concentration.
CI = confidence interval.
a. The ratios (and 90% CIs) are expressed as percentages.

(Source: Study P019/1032 CSR, Table 10)

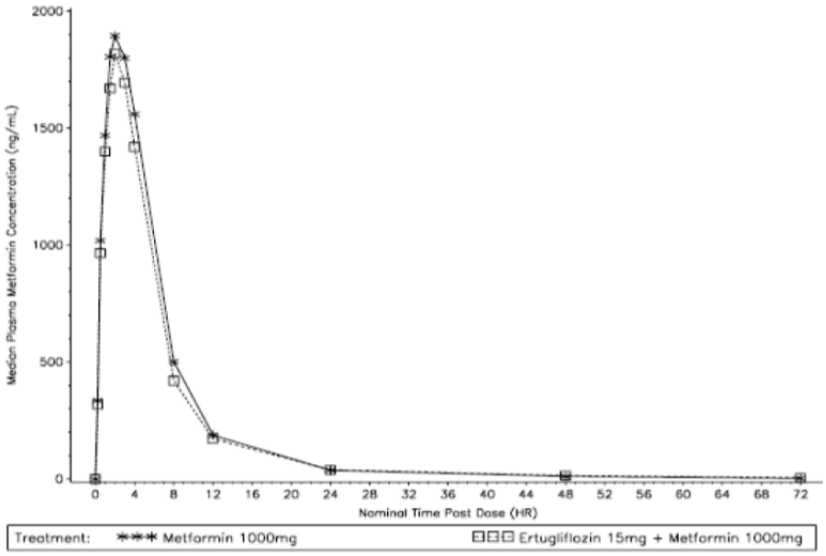


Figure 2. Median plasma metformin concentration-time profiles following a single oral dose of metformin alone and co-administered with ertugliflozin
(Source: Adapted from Figure 4 of Study P019/1032 CSR)

Table 5. Summary of plasma metformin PK parameters

Parameter (Units)	Parameter Summary Statistics[a] by Treatment	
	Metformin 1000 mg	Ertugliflozin 15 mg + Metformin 1000 mg
N, n	18, 13	18, 13
AUC_{inf} (ng.h/mL)	12770 (27)	12260 (27)
AUC_{last} (ng.h/mL)	12550 (26)	12270 (23)
C_{max} (ng/mL)	1983 (26)	1835 (26)
T_{max} (h)	2.00 (0.50, 4.00)	2.00 (1.00, 3.00)
$t_{½}$ (h)	10.23 ± 2.39	14.47 ± 6.94
CL/F (mL/min)	1305 (27)	1359 (26)
V_z/F (L)	1126 (43)	1577 (51)

Source: Table 14.4.3.1.1.2
AUC_{inf} = area under the plasma concentration-time profile from time 0 extrapolated to infinite time, AUC_{last} = area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}), C_{max} = maximum observed plasma concentration, CL/F = apparent clearance, N = number of subjects; n = number of subjects for $t_{½}$, AUC_{inf}, CL/F and V_z/F, $t_{½}$ = terminal half-life, T_{max} = time for C_{max}, V_z/F = apparent volume of distribution.
a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ±SD for $t_{½}$.
(Source: Study P019/1032 CSR, Table 11)

Table 6. Statistical comparisons for plasma metformin PK parameters

Parameter (Units)	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Ertugliflozin 15 mg + Metformin 1000 mg (Test)	Metformin 1000 mg (Reference)		
Data excluded due to vomiting[b]				
AUC_{inf} (ng.h/mL)	12490	12370	100.94	90.62, 112.44
AUC_{last} (ng.h/mL)	12270	12560	97.75	89.46, 106.82
C_{max} (ng/mL)	1835	1952	94.00	82.94, 106.55
All Data Included				
AUC_{inf} (ng.h/mL)	12490	12370	100.94	90.62, 112.44
AUC_{last} (ng.h/mL)	12270	12550	97.81	89.99, 106.31
C_{max} (ng/mL)	1835	1983	92.52	81.99, 104.39

Source: Tables 14.4.3.3.2 and 14.4.3.3.3

The intra-subject variability based on the statistical model for AUC_{inf} and C_{max} were 0.1365 and 0.2189, respectively.

AUC_{inf} = area under the plasma concentration-time profile from time 0 extrapolated to infinite time, AUC_{last} = area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}), C_{max} = maximum observed plasma concentration, CI = confidence interval.

a. The ratios (and 90% CIs) are expressed as percentages.

b. Metformin 1000 mg treatment data for Subject 10011018 has been excluded due to vomiting. Only AUC_{last} and C_{max} are affected since AUC_{inf} was not reportable for this subject and treatment.

(Source: Study P019/1032 CSR, Table 12)

Study P040/1007 (PK/PD Study)

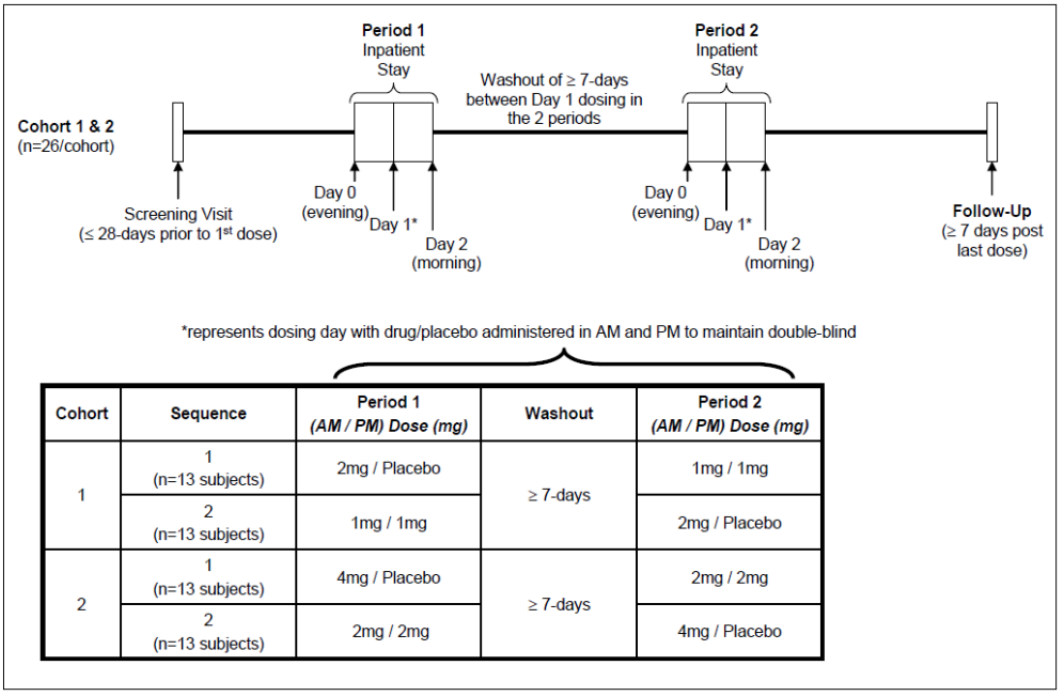
Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, 2-Period, Cross-Over Single Day Evaluation of the Pharmacokinetic-Pharmacodynamic Effect of Once and Twice Daily Oral Administration of PF-04971729 in Patients with Type 2 Diabetes Mellitus

Objectives:

- To evaluate the PD effects of single day dosing of 2 mg and 4 mg doses of PF-04971729 each administered once and split into twice daily dosing in adults with T2DM
- To characterize the safety and tolerability of PF-04971729
- To characterize PK of PF-04971729
- To investigate the relationship of PK and PD of PF-04971729

Study Design

This was a randomized, double-blind, sponsor-open, 4-arm study using 2 cohorts and 2-way crossover. Each subject was randomized to receive 2 of the planned 4 dosing regimens. For each subject, the study included a total of 2 outpatient visits (ie, Screening and Follow-up) to the study center as well as 2 inpatient stays, each lasting 2 overnight days. Dosing between the 2 periods was separated by a washout of ≥7 days. Total participation in the study for each subject, excluding Screening, was approximately 3 weeks.



Cohort	Sequence	Period 1 *(AM / PM) Dose (mg)*	Washout	Period 2 *(AM / PM) Dose (mg)*
1	1 (n=13 subjects)	2mg / Placebo	≥ 7-days	1mg / 1mg
	2 (n=13 subjects)	1mg / 1mg		2mg / Placebo
2	1 (n=13 subjects)	4mg / Placebo	≥ 7-days	2mg / 2mg
	2 (n=13 subjects)	2mg / 2mg		4mg / Placebo

Figure 3. Overall Study Design
(Source: Study P040/1007 CSR, Figure 1)

PK and PD sampling schedule
PK sampling: blood samples were collected predose and at 0.5, 1, 2, 3, 4, 5, 5.5, 6, 7, 8, 10, 12, 18, 24 hours post-dose in each period.

PD sampling:

- For urine glucose: Urine collected during windows of 0-4, 4-8, 8-12, and 12-24 hours relative to AM dose with forced voids before start and at the end of each window in each period.
- For plasma glucose: blood samples were collected predose and at 0.5, 1, 2, 3, 4, 5, 5.5, 6, 7, 8, 10, 12, 12.5, 13, 14, 15, 16, 18, 24 hours post-dose in each period.
- For analysis of C-peptide: blood samples were collected predose and at 24 hours post-dose.

Results and Conclusions
Overall, 52 subjects (26 per cohort) were enrolled at 4 study centers to ensure that a minimum of 44 subjects (22 per cohort) completed the study.

PK:
The PK of PF-04971729 was assessed following QD administration and split into twice-daily administration (0 and 5 hours, described as BID or split dosing). All PK parameter calculations were performed using actual times relative to the AM dose. Following split dosing (BID) of PF-04971729, peak plasma PF-04971729 concentrations generally occurred after the second dose, with a median Tmax of 6 hours for split dosing as compared to 1 hour for QD dosing. Peak concentration for split dosing was ~30% lower than that observed in the QD dose, with

geometric mean Cmax values of 19.51 ng/mL and 34.80 ng/mL for 1 mg and 2 mg BID doses, respectively, as compared to 26.98 ng/mL and 50.83 ng/mL for 2 mg and 4 mg QD doses, respectively. However, total PF-04971729 exposure following split dose and QD dose was comparable, as supported by nearly identical geometric mean AUClast values for equivalent total doses (Figure 4 and Table 7).

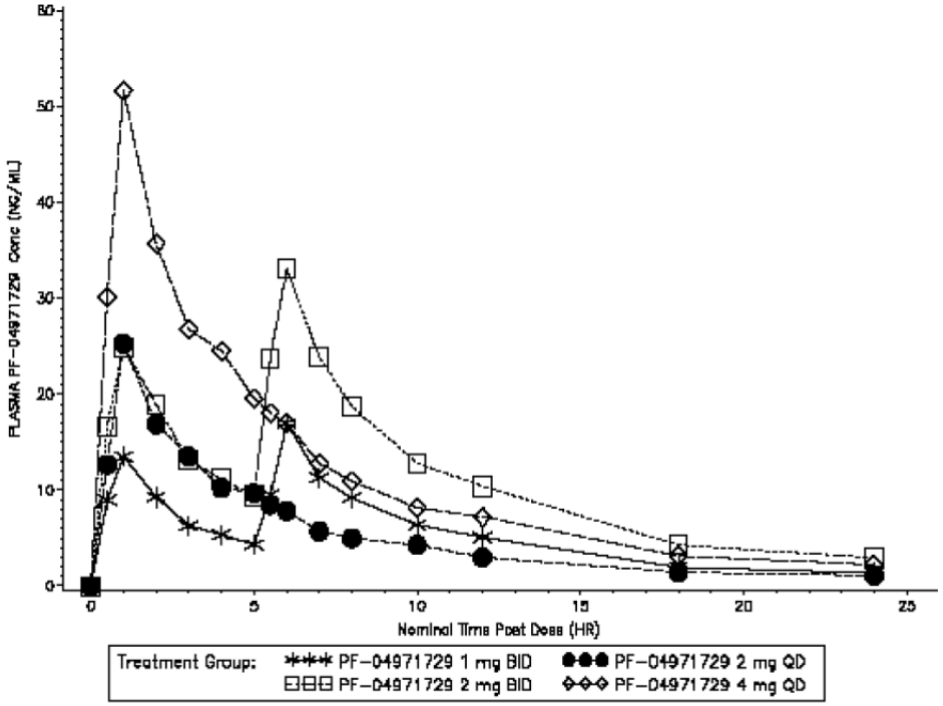


Figure 4. Median Plasma PF-04971729 PK Concentration-Time Plot (Linear Scale)
(Source: Study P040/1007 CSR, Figure 3)

Table 7. Summary of Plasma PF-04971729 PK Parameter Following QD and BID Dosing

Parameter, Units	Parameter Summary Statistics[a] by PF-04971729 Treatment			
	Cohort 1		Cohort 2	
Treatment	1 mg BID	2 mg QD	2 mg BID	4 mg QD
Total Dose	2 mg	2 mg	4 mg	4 mg
N, n	25, 25	26, 26	26, 25	26, 26
AUC_{last}, ng•hr/mL	131.8 (26)	132.7 (28)	272 (19)	270.5 (20)
C_{max}, ng/mL	19.51 (39)	26.98 (37)	34.80 (23)	50.83 (25)
T_{max}, hr	6.00 (0.500-12.0)	1.00 (0.500-5.50)	6.00 (0.500-8.00)	1.00 (0.500-6.00)

Source: Table 14.4.3.1
Abbreviations: AUC_{last} = area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}), BID = twice daily, C_{max} = maximum observed plasma concentration, %CV = percent coefficient of variation, hr = hour(s), N = Number of subjects, n = number of subjects where AUC_{last} was determined, QD = daily, T_{max} = time for C_{max}
[a] Geometric mean (%CV) for all except median (range) for T_{max}.
(Source: Study P040/1007 CSR, Table 25)

PD
Overall, PD effects (UGE, plasma glucose, and C-peptide) were similar for all treatment groups

following single day dosing of 2 mg and 4 mg doses of PF-04971729 administered QD or split into BID dosing in adults with T2DM (Tables 8-10).

Table 8. Statistical Summary of Cumulative Urinary Glucose Excretion (Grams) Over 0 to 24 Hours

Time Post Dose	Treatment	N	Least Squares Mean		90% CI (%)
			Mean	SE	
Cohort 1					
0 to 24 hours	PF-04971729 1 mg BID	25	69.45	9.08	(54.20, 84.70)
	PF-04971729 2 mg QD	25	70.43	9.08	(55.19, 85.68)
Cohort 2					
0 to 24 hours	PF-04971729 2 mg BID	24	78.29	9.77	(61.87, 94.72)
	PF-04971729 4 mg QD	24	80.54	9.81	(64.05, 97.02)

Source: Table 14.2.1.4

Abbreviation: BID = twice daily, CI = confidence interval, N = number of subjects, QD = daily, SE = standard of error

(Source: Study P040/1007 CSR, Table 21)

Table 9. Summary of Weighted Mean Plasma Glucose (mg/dL) Over 0 to 24 Hours

Parameter	PF-04971729 1 mg BID	PF-04971729 2 mg QD	PF-04971729 2 mg BID	PF-04971729 4 mg QD
N	23[a]	25[b]	23[c]	24[d]
Arithmetic mean	173.6	175.7	169.1	170.4
Standard deviation	26.94	29.88	35.91	41.26
Coefficient of variation (%)	16	17	21	24
Median	165.6	176.8	163.1	166.7
Minimum	128.2	123.3	99.8	104.8
Maximum	226.5	231.7	235.6	253.7

Source: Table 14.2.2.1

Abbreviations: BID = twice daily, N = number of subjects, QD = daily

[a] Two subjects (10021008 and 10021012) did not have mean plasma glucose over 0 to 24 hours.

[b] One subject (10021010) did not have mean plasma glucose over 0 to 24 hours.

[c] Three subjects (10011051, 10011052, and 10021007) did not have mean plasma glucose over 0 to 24 hours.

[d] One subject (10021026) did not have mean plasma glucose over 0 to 24 hours.

(Source: Study P040/1007 CSR, Table 23)

Table 10. Summary of serum C-peptide (ng/mL)

		PF-04971729 1 mg BID (N=25)	PF-04971729 2 mg QD (N=26)	PF-04971729 2 mg BID (N=26)	PF-04971729 4 mg QD (N=26)
0 H	N	25	26	26	26
	Arithmetic Mean	2.82	2.76	2.36	2.57
	Standard Deviation	0.873	0.877	0.899	0.842
	Coefficient of Variation (%)	31	32	38	33
	Median	3.0	2.7	2.3	2.4
	Minimum	1.3	0.8	0.8	1.1
	Maximum	5.4	5.1	4.7	4.8
24 H	N	25	26	24	26
	Arithmetic Mean	3.01	2.99	2.59	2.41
	Standard Deviation	1.148	0.997	0.916	0.973
	Coefficient of Variation (%)	38	33	35	40
	Median	3.0	2.9	2.4	2.3
	Minimum	1.5	1.3	1.2	1.0
	Maximum	6.6	5.6	4.8	5.3

(Source: Study P040/1007 CSR, Table 14.2.4.1)

Study P035/1051 (pivotal PK/PD Study)

Title: An Open-Label, Randomized, 2-Period, Crossover, Steady State Evaluation of the Pharmacokinetics and Pharmacodynamics of Once Daily and Twice Daily Oral Administration of Ertugliflozin in Healthy Subjects

Objectives:

- Primary:
  - To demonstrate equivalence of exposure (AUC24h) on Day 6 of ertugliflozin
    - at total daily dosing of 5 mg when administered QD vs. BID in healthy subjects (5 mg QD and 2.5 mg BID)
    - at total daily dosing of 15 mg when administered QD vs. BID in healthy subjects (15 mg QD and 7.5 mg BID)
  - To demonstrate similar steady state PD effect (UGE0-24) of ertugliflozin
    - at total daily dosing of 5 mg when administered QD vs. BID in healthy subjects (5 mg QD and 2.5 mg BID)
    - at total daily dosing of 15 mg when administered QD vs. BID in healthy subjects (15 mg QD and 7.5 mg BID)

- **Secondary:** safety and tolerability

Study Design

This was a Phase 1, open-label, multiple-dose, randomized, 2-period, 2-way crossover study in 3 cohorts. Approximately 60 (20 per cohort) healthy subjects were planned to be enrolled in the study.

In Cohorts A and C, each subject received ertugliflozin 5 mg QD and 2.5 mg BID for 6 days. In Cohort B, each subject received ertugliflozin 15 mg QD and 7.5 mg BID for 6 days. Cohorts were enrolled and analyzed independently and subjects were assigned to 1 of the 2 sequences within a cohort as outlined in Table 11 as below. Eligible subjects received the assigned study medication in either the morning or the morning and evening (as applicable) on Days 1 to 6. Morning dose was administered after an overnight fast of at least 10 hours. Evening dose (for BID dosing regimen) was administered approximately 12 hours after the morning dose and 1 hour before dinner.

Table 11. Treatment Sequence

Cohort[a]	Sequence	Period 1 Ertugliflozin	Washout	Period 2 Ertugliflozin
A and C	1 (N = 10)	5 mg QD	≥7 days	2.5 mg BID
	2 (N = 10)	2.5 mg BID		5 mg QD
B	1 (N = 10)	15 mg QD		7.5 mg BID
	2 (N = 10)	7.5 mg BID		15 mg QD

Source: Section 16.1.1

Abbreviations: BID = twice daily; N = number of planned subjects for each treatment sequence; QD = once daily.

a. For each cohort, all subjects received the assigned study medication in each period for 6 days.

(Source: Study P035/1051 CSR, Table 1)

PK and PD sampling schedule

PK sampling for ertugliflozin measurement: In each period, blood samples were collected predose on Days 4, 5, 6, and at 0.5, 1, 2, 3, 4, 8, 10, 12, 12.5, 13, 14, 15, 16, 20, 24 hours post-dose.

PD sampling:

- For plasma glucose: blood samples were collected predose and at 1, 2, 5, 6, 12, 13, 14, 24 hours post-dose on Day 6 in each period.
- For urine glucose: Urine collected during windows of 0-4, 4-8, 8-12, and 12-24 hours post-morning dose on Day 6 in each period.

Results and Conclusions

A total of 70 subjects were assigned to and received at least 1 dose of study medication. 8 additional subjects were enrolled in Cohort B and 2 additional subjects were enrolled in Cohort C. 3 subjects (1 from Cohort B and 2 from Cohort C) discontinued from the study due to protocol deviation, personal reasons, or adverse event (not related to study medication).

PK results:

Following oral administration of ertugliflozin 2.5 mg BID and 5 mg QD for 6 days, the geometric mean AUC_{24} was similar for both BID and QD treatments, whereas the geometric mean C_{max} after the morning dose was higher for the QD treatment than BID treatment. Also, the geometric mean C_{max} for 2.5 mg BID treatment after the morning dose was slightly higher than the evening dose. Median T_{max} following the morning dose was 1.00 hour for both treatments, 2.5 mg BID and 5 mg QD (Figure 5 and Tables 12, 13).

Similarly, following oral administration of ertugliflozin 7.5 mg BID and 15 mg QD for 6 days, the geometric mean AUC_{24} was similar for both BID and QD treatments, whereas the geometric mean C_{max} after the morning dose was higher for the QD treatment than that for the BID treatment. Also, the geometric mean C_{max} for 7.5 mg BID treatment after the morning dose was slightly higher than the evening dose. Median T_{max} following the morning dose was 1.00 hour for both treatments, ertugliflozin 7.5 mg BID and 15 mg QD (Figure 5 and Tables 12, 13).

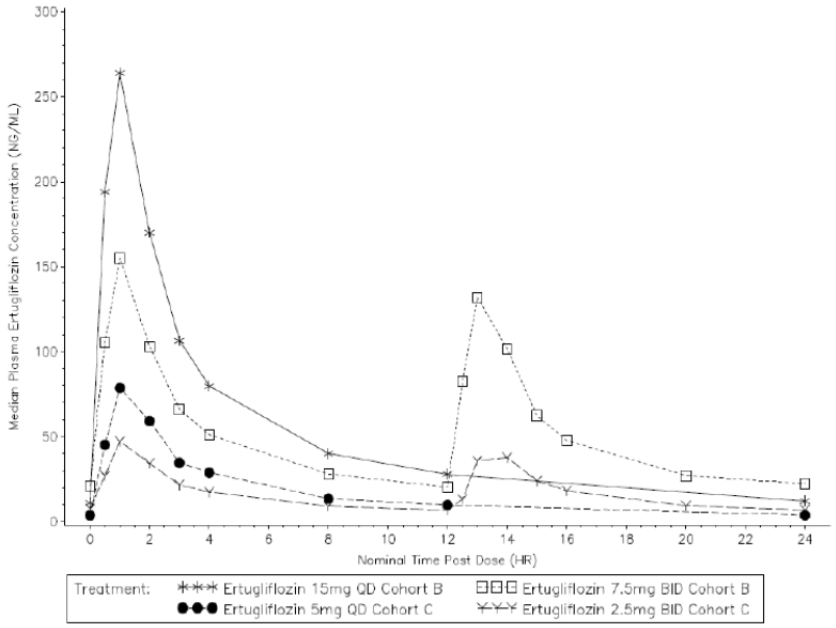


Figure 5. Median Plasma Ertugliflozin Concentration-Time Profiles on Day 6 Following Multiple QD or BID Oral Doses

(Source: Study P035/1051 CSR, Figure 1)

Table 12. Summary of Plasma Ertugliflozin PK on Day 6

	Parameter Summary Statistics[a] by Treatment			
Parameters (units)	**Ertugliflozin 7.5 mg BID Cohort B**	**Ertugliflozin 15 mg QD Cohort B**	**Ertugliflozin 2.5 mg BID Cohort C**	**Ertugliflozin 5 mg QD Cohort C**
N, n	27, 26	28, 28	22, 20	22, 22
AUC_{24} (ng•hr/mL)	1192 (20)	1193 (22)	399.2 (18)	397.9 (18)
C_{max1} (ng/mL)	154.2 (20)	268.2 (20)	47.49 (25)[b]	81.27 (29)
T_{max1} (hr)	1.00 (0.500, 2.02)	1.00 (0.500, 2.07)	1.00 (0.500, 1.10)[b]	1.00 (0.500, 2.05)
C_{max2} (ng/mL)	140.1 (21)	NA	42.81 (28)	NA
T_{max2} (hr)	1.00 (1.00, 2.00)	NA	2.00 (1.00, 2.10)	NA

Source: Table 14.4.3.1.1

PK parameters are defined in Table 5.

Abbreviations: %CV = percent coefficient of variation; BID = twice daily; hr = hour(s); N = number of subjects for the treatment; n = number of subjects contributing to summary statistics; NA = not applicable; PK = pharmacokinetic; QD = once daily.

a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}.

b. Twenty-one (21) subjects were included in summary statistics for C_{max1} and T_{max1}.

(Source: Study P035/1051 CSR, Table 11)

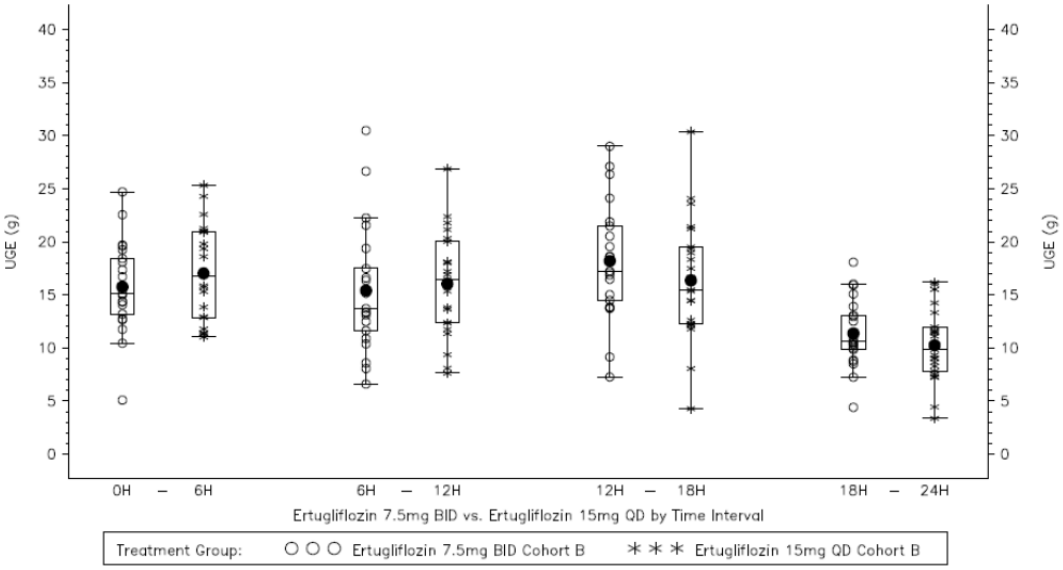
Table 13. Comparisons of Plasma Ertugliflozin AUC24 on Day 6

Parameter (Unit)	Comparison (Test vs. Reference)	Adjusted (Least-Squares) Geometric Means BID (Test)	QD (Reference)	Ratio (BID/QD) of Adjusted Means[a]	90% CI for Ratio
AUC_{24} (ng•hr/mL)	Ertugliflozin 2.5 mg BID vs. ertugliflozin 5 mg QD	401.0	397.9	100.78	98.76, 102.83
	Ertugliflozin 7.5 mg BID vs. ertugliflozin 15 mg QD	1190	1193	99.73	97.08, 102.45

Source: Tables 14.4.3.3.1 and 14.4.3.3.2
AUC_{24} is defined in Table 5.
The intra-subject variability values (sqrt [exp {MSE}-1]) based on mixed effects model for ertugliflozin AUC_{24} for 2.5 mg BID vs. 5 mg QD (Cohort C) and 7.5 mg BID vs. 15 mg QD (Cohort B) were 0.0367 and 0.0569, respectively.
Abbreviations: BID = twice daily; CI = confidence interval; hr = hour(s); MSE = mean square error; QD = once daily; vs. = versus.
a. The ratios (and 90% CIs) are expressed as percentages.
(Source: Study P035/1051 CSR, Table 12)

PD results
The mean UGE over the intervals of 0 to 6, 6 to 12, 12 to 18, and 18 to 24 hours was comparable between the QD and BID treatments (Figure 6 and Table 14). Results of the statistical comparisons for UGE-24 indicated that the UGE0-24 at steady state was similar between ertugliflozin BID and QD administration of total daily dosing of 5 mg (5 mg QD and 2.5 mg BID) as well as 15 mg (15 mg QD and 7.5 mg BID) (Tables 15, 16).

Note that included in the primary statistical analysis were UGE0-24 values obtained from all the subjects in Cohorts B and C who consumed 100% of the meals (breakfast, lunch, dinner, and snack) on Day 6 in at least 1 period and there was no deviation in the type of meals offered. Included in the secondary statistical analysis were UGE0-24 values obtained from all the subjects in Cohorts B and C who consumed 100% of the meals (breakfast, lunch, dinner, and snack) on Day 6 in both periods and there was no deviation in the type of meals offered.



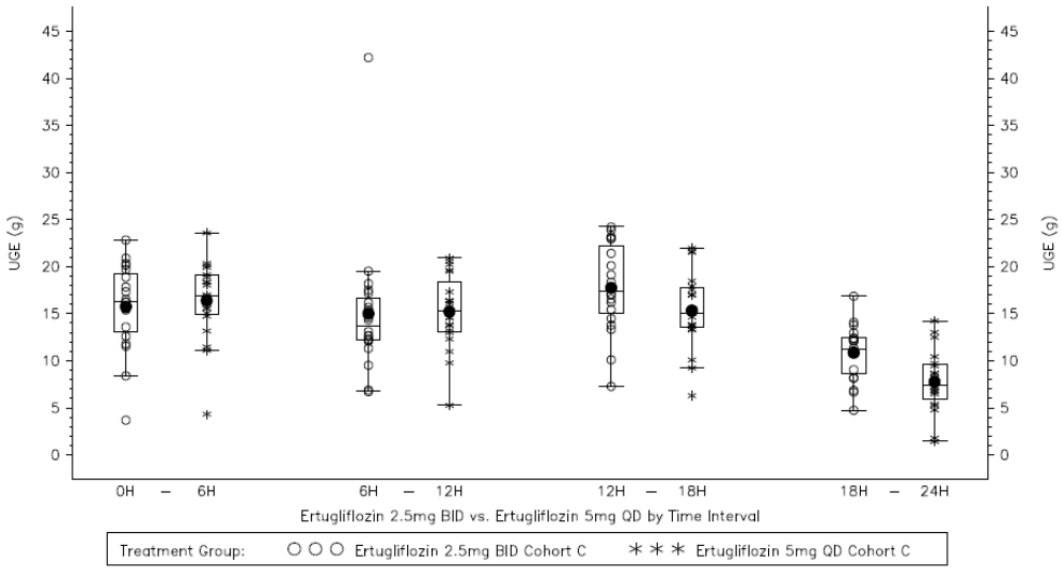


Figure 6. Individual and Arithmetic Mean UGE (g) vs. Time Intervals for QD and BID Treatments
(Source: Study P035/1051 CSR, Figure 5)

Table 14. Descriptive Summary of UGE (g) by Time Intervals – Primary Analysis

Collection Interval		Ertugliflozin 7.5 mg BID Cohort B	Ertugliflozin 15 mg QD Cohort B	Ertugliflozin 2.5 mg BID Cohort C	Ertugliflozin 5 mg QD Cohort C
0 to 6 hours	N	21	23	20	20
	Arithmetic Mean	15.76	17.03	15.76	16.39
	%CV	28	26	29	26
6 to 12 hours	N	21	23	20	20
	Arithmetic Mean	15.41	16.04	15.02	15.24
	%CV	39	30	48	26
12 to 18 hours	N	21	23	20	20
	Arithmetic Mean	18.21	16.36	17.76	15.34
	%CV	31	35	26	26
18 to 24 hours	N	21	23	20	20
	Arithmetic Mean	11.38	10.27	10.87	7.78
	%CV	28	33	27	43

Source: Table 14.4.7.1.1
Abbreviations: BID = twice daily; %CV = percent coefficient of variation; N = number of subjects; QD = once daily; UGE = urinary glucose excretion.
(Source: Study P035/1051 CSR, Table 13)

Table 15. Descriptive Summary of UGE0-24 (g) and IGRA (%)

Parameters (units)		Ertugliflozin 7.5 mg BID Cohort B	Ertugliflozin 15 mg QD Cohort B	Ertugliflozin 2.5 mg BID Cohort C	Ertugliflozin 5 mg QD Cohort C
Primary Analysis					
UGE_{0-24} (g)	N	21	23	20	20
	Geometric Mean	58.58	57.63	57.09	52.46
	%CV	28	28	31	34
IGRA (%)	N	21	23	20	20
	Arithmetic Mean	42.01	40.56	40.26	38.48
	%CV	26	26	27	29
Secondary Analysis					
UGE_{0-24} (g)	N	18	18	18	18
	Geometric Mean	59.01	57.32	58.25	52.94
	%CV	29	29	32	33
IGRA (%)	N	18	18	18	18
	Arithmetic Mean	43.16	41.23	40.79	38.76
	%CV	26	28	27	26

Source: Tables 14.4.7.1.3.1.1, 14.4.7.1.3.1.2, 14.4.7.3.1 and 14.4.7.3.2
Pharmacodynamics parameters are defined in Table 6.
Abbreviations: BID = twice daily; %CV = percent coefficient of variation; N = number of subjects; QD = once daily.
(Source: Study P035/1051 CSR, Table 14)

Table 16. Statistical Summary of Treatment Comparisons for UGE0-24 (g) on Day 6

Parameter (Unit)	Comparison (Test vs. Reference)	Adjusted (Least-Squares) Geometric Means BID (Test)	QD (Reference)	Ratio (BID/QD) of Adjusted Means[a]	90% CI for Ratio
Primary Analysis					
UGE_{0-24} (g)	Ertugliflozin 2.5 mg BID vs. ertugliflozin 5 mg QD	57.00	51.74	110.16	(102.96, 117.87)
	Ertugliflozin 7.5 mg BID vs. ertugliflozin 15 mg QD	58.84	57.26	102.77	(97.69, 108.12)
Secondary Analysis					
UGE_{0-24} (g)	Ertugliflozin 2.5 mg BID vs. ertugliflozin 5 mg QD	58.25	52.94	110.03	(102.80, 117.76)
	Ertugliflozin 7.5 mg BID vs. ertugliflozin 15 mg QD	59.01	57.32	102.95	(97.80, 108.37)

Source: Tables 14.4.7.1.4.1.1, 14.4.7.1.4.1.2, 14.4.7.1.4.2.1 and 14.4.7.1.4.2.2
UGE_{0-24} is defined in Table 6.
The model was a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect.
Values were back-transformed from the log scale.
The intra-subject variability values (sqrt [exp {MSE}-1]) based on mixed effects model for ertugliflozin UGE_{0-24} for 2.5 mg BID vs. 5 mg QD (Cohort C) and 7.5 mg BID vs. 15 mg QD (Cohort B) were 0.1172 and 0.0881, respectively.
Abbreviations: BID = twice daily; CI = confidence interval; MSE = mean square error; QD = once daily; vs. = versus.
a. The ratios (and 90% CIs) are expressed as percentages.
(Source: Study P035/1051 CSR, Table 15)

Study P028/1049 (Food Effect Study)

Title: A Phase 1, Single Dose, Randomized, Open-Label, Crossover Study to Estimate the Effect of Food on the Pharmacokinetics of Ertugliflozin and Metformin When Administered as a Fixed Dose Combination Tablet to Healthy Subjects

Objectives:

- **Primary:** To estimate the effect of food on the PK of ertugliflozin and metformin following administration of the ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet
- **Secondary:** safety and tolerability

Study Design

This was a Phase 1, open-label, randomized, 2-sequence, 2-period single dose crossover study to evaluate the effect of food on the PK of ertugliflozin and metformin following administration of the ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet to healthy subjects. Each subject received 2 treatments in a randomized manner as outlined in Table 17. Dosing in each period was separated by a washout period of at least 7 days.

Table 17. Treatment sequence in Study P028/1049

Sequence	Period 1	Period 2
1 (N = 7)	ERTU/MET-Fasted	ERTU/MET-Fed
2 (N = 7)	ERTU/MET-Fed	ERTU/MET-Fasted

Source: Section 16.1.1
ERTU/MET-Fasted: ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet, single dose under fasted conditions (Reference)
ERTU/MET-Fed: ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet, single dose under fed conditions (Test)
(Source: Study P028/1049 CSR, Table 1)

ERTU/MET-Fasted: After an overnight fast of at least 10 hours, subjects were dosed with 1 FDC tablet containing ertugliflozin 7.5 mg/metformin 1000 mg with ~240 mL of ambient temperature water.

ERTU/MET-Fed: After an overnight fast of at least 10 hours, subjects were administered a standard high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) breakfast ~30 minutes prior to administration of 1 FDC tablet containing ertugliflozin 7.5 mg/metformin 1000 mg. The entire breakfast was consumed within ~25 minutes or less. The FDC tablet was administered with ~240 mL of ambient temperature water.

PK Sampling Schedule

Blood samples for determination of ertugliflozin and metformin concentrations were collected from each subject predose, and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, and 72 hours post-dose.

Results and Conclusions

A total of 14 subjects were assigned to and received study treatments, and 13 of them completed the study and were analyzed for PK and safety. One subject withdrew the study due to personal reasons.

For ertugliflozin, following the administration of ertugliflozin 7.5 mg/metformin 1000 mg FDC with high-fat, high-calorie breakfast, ertugliflozin AUCs are similar while Cmax was about 41% lower compared to fasted condition. Median Tmax was delayed from 1.5 hour to 2.5 hours in the presence of food. Mean terminal phase t1/2 for ertugliflozin remains similar, 11.18 hours and 12.10 hours for fasted and fed conditions, respectively (Figure 7 and Tables 18, 19).

For metformin, following the administration of ertugliflozin 7.5 mg/metformin 1000 mg FDC with high-fat, high-calorie breakfast, metformin AUCs remains similar while Cmax was about 29% lower compared to fasted condition. Median Tmax for metformin was delayed from 2.25 hours to 4.00 hours in the presence of food. The mean terminal phase t½ for metformin was 11.75 hours and 12.34 hours with and without food, respectively (Figure 8 and Tables 20, 21).

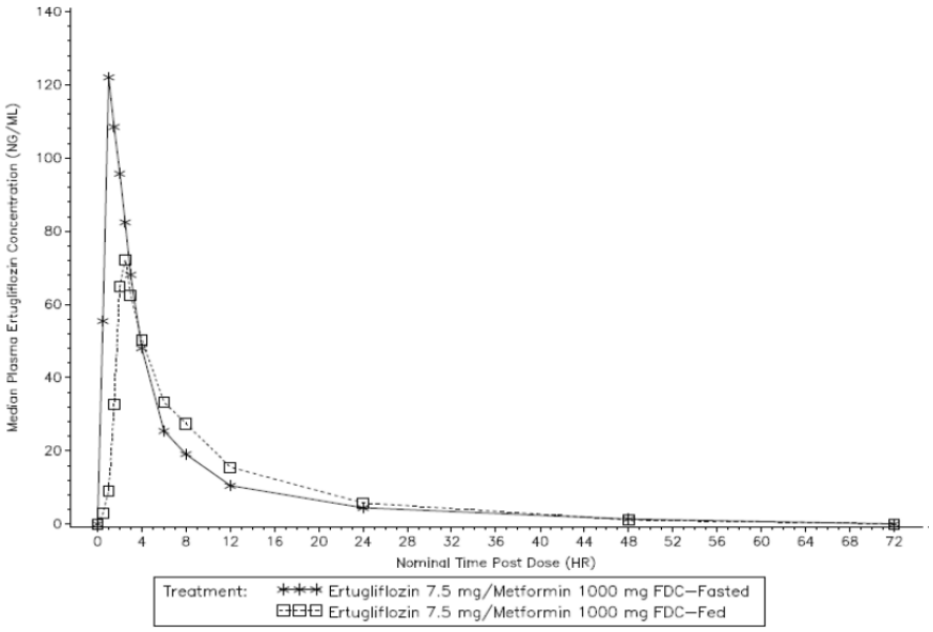


Figure 7. Median plasma ertugliflozin concentration-time profiles following single oral doses of ertugliflozin 7.5 mg /metformin 1000 mg FDC under fasted and fed conditions
(Source: adapted from Figure 1 of Study P028/1049 CSR)

Table 18. Summary of plasma ertugliflozin PK parameters

Plasma PK Parameter Summary Statistics[a] for ertugliflozin by Treatment		
Parameter (units)	**Ertugliflozin 7.5 mg/ Metformin 1000 mg FDC-Fed (Test)**	**Ertugliflozin 7.5 mg/ Metformin 1000 mg FDC-Fasted (Reference)**
N	13	14
AUC_{inf} (ng•hr/mL)	602.3 (26)	654.8 (24)
AUC_{last} (ng•hr/mL)	587.4 (26)	639.5 (25)
C_{max} (ng/mL)	75.30 (44)	126.5 (27)
T_{max} (hr)	2.50 (1.00, 8.02)	1.50 (1.00, 2.50)
$t_{½}$ (hr)	11.18 ± 4.54	12.10 ± 2.56

Source: Table 14.4.3.1.1.1
PK parameters are defined in Table 5.
Abbreviations: %CV = percent coefficient of variation; FDC = fixed dose combination; hr = hour (s); N = total number of subjects in the treatment group and contributing to the descriptive summary statistics; PK = pharmacokinetic(s); SD = standard deviation.

a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for $t_{½}$.

(Source: Study P028/1049 CSR, Table 9)

Table 19. Statistical summary of treatment comparisons for plasma ertugliflozin PK parameters

Parameter (units)	Adjusted Geometric Means: Ertugliflozin 7.5 mg/ Metformin 1000 mg FDC-Fed (Test)	Adjusted Geometric Means: Ertugliflozin 7.5 mg/ Metformin 1000 mg FDC-Fasted (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{inf} (ng•hr/mL)	614.3	654.8	93.81	(90.09, 97.69)
AUC_{last} (ng•hr/mL)	599.6	639.5	93.75	(90.03, 97.63)
C_{max} (ng/mL)	75.16	126.5	59.41	(51.06, 69.11)

Source: Table 14.4.3.3.1.1
PK parameters are defined in Table 5.
Values were back-transformed from the log scale.
The model was a mixed effects model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. The intra-subject variability values (sqrt[exp(MSE)-1], where MSE is the mean square error) based on mixed effects model for ertugliflozin AUC_{inf}, AUC_{last}, and C_{max} were 0.0574, 0.0574, and 0.2186, respectively.
Abbreviations: CI = confidence interval; FDC = fixed dose combination; hr = hour (s); PK = pharmacokinetic(s).
a. The ratios (and 90% CIs) are expressed as percentages.

(Source: Study P028/1049 CSR, Table 10)

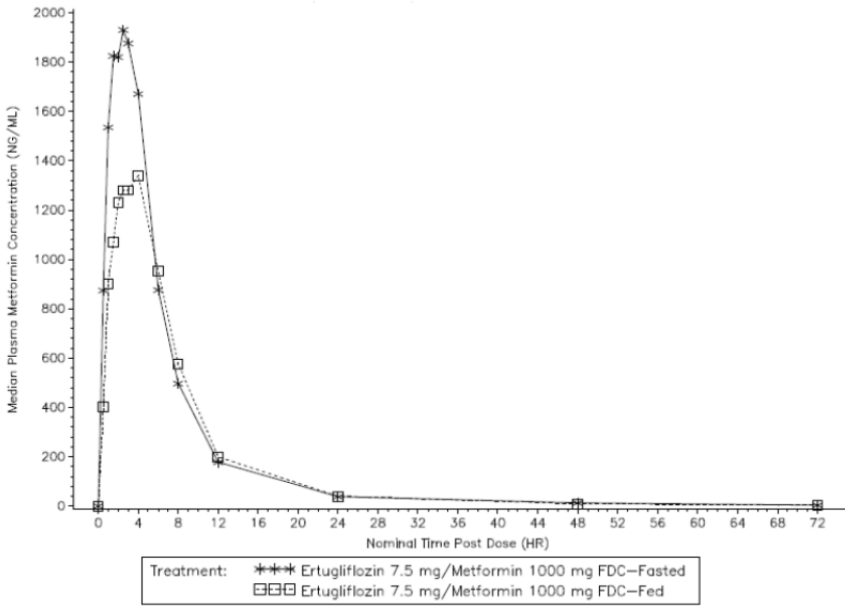


Figure 8. Median plasma metformin concentration-time profiles following single oral doses of ertugliflozin 7.5 mg /metformin 1000 mg FDC under fasted and fed conditions
(Source: adapted from Figure 4 of Study P028/1049 CSR)

Table 20. Summary of plasma metformin PK parameters

Plasma PK Parameter Summary Statistics[a] for metformin by Treatment		
Parameter (units)	**Ertugliflozin 7.5 mg/Metformin 1000 mg FDC-Fed (Test)**	**Ertugliflozin 7.5 mg/Metformin 1000 mg FDC-Fasted (Reference)**
N, n	13, 12	14, 14
AUC_{inf} (ng•hr/mL)	11550 (29)	12530 (26)
AUC_{last} (ng•hr/mL)	11760 (29)	12420 (26)
C_{max} (ng/mL)	1461 (32)	2040 (31)
T_{max} (hr)	4.00 (0.500, 8.02)	2.25 (1.00, 4.00)
$t_{½}$ (hr)	11.75 ± 3.82	12.34 ± 5.82

Source: Table 14.4.3.1.1.2
PK parameters are defined in Table 5.
Abbreviations: %CV = percent coefficient of variation; FDC = fixed dose combination; hr = hour(s); N = total number of subjects in the treatment group and contributing to the descriptive summary statistics; n = number of subjects with reportable $t_{½}$ and AUC_{inf}; PK = pharmacokinetic(s); SD = standard deviation.
a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for $t_{½}$.

(Source: Study P028/1049 CSR, Table 11)

Table 21. Statistical summary of treatment comparisons for plasma metformin PK parameters

Parameter (units)	Adjusted Geometric Means: Ertugliflozin 7.5 mg/ Metformin 1000 mg FDC-Fed (Test)	Adjusted Geometric Means: Ertugliflozin 7.5 mg/ Metformin 1000 mg FDC-Fasted (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{inf} (ng•hr/mL)	11630	12530	92.82	(85.07, 101.26)
AUC_{last} (ng•hr/mL)	11740	12420	94.53	(86.97, 102.76)
C_{max} (ng/mL)	1442	2040	70.68	(63.62, 78.51)

Source: Table 14.4.3.3.1.2
PK parameters are defined in Table 5.
Values were back-transformed from the log scale.
The model was a mixed effects model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. The intra-subject variability values (sqrt[exp(MSE)-1], where MSE is the mean square error) values based on mixed effects model for metformin AUC_{inf}, AUC_{last}, and C_{max} were 0.1175, 0.1190, and 0.1504, respectively.
Abbreviations: CI = confidence interval; FDC = fixed dose combination; hr = hour(s); PK = pharmacokinetic(s).
a. The ratios (and 90% CIs) are expressed as percentages.

(Source: Study P028/1049 CSR, Table 12)

Study P027/1041 (BE Study)

Title: A Phase 1, Single Dose, Open-Label, Randomized, Crossover Bioequivalence Study of an Ertugliflozin 7.5 mg/Metformin 1000 mg Fixed Dose Combination Tablet vs Co-Administration of the Individual Components (Ertugliflozin and US-Sourced Metformin) in Healthy Subjects

Objectives:

- **Primary:** to demonstrate the BE of ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet to the co-administration of the individual components: ertugliflozin 7.5 mg (administered as one 5 mg tablet + one 2.5 mg tablet)and US-sourced Glucophage (metformin hydrochloride) 500 mg under fasted conditions
- **Secondary:** safety and tolerability

Study Design

This was a pivotal, Phase 1, open-label, randomized, 2-period, 2-sequence, single dose, crossover study to demonstrate the bioequivalence of the ertugliflozin 2.5 mg/metformin 500 mg FDC tablet to the co-administration of the individual components: ertugliflozin 2.5 mg and metformin 500 mg (US) tablets under fasted conditions in healthy subjects. Each subject received 2 treatments in a randomized manner as outlined in Table 22. In each period, subjects received a single dose of the assigned trial medication in the morning on Day 1 in the fasted state (minimum 10-hour fast). Dosing in each period was separated by a washout period of at least 7 days.

Table 22. Treatment sequence in Study P027/1041

Sequence	Period 1	Period 2
1 (n = 16)	ERTU+MET-COADM	ERTU/MET-FDC
2 (n = 16)	ERTU/MET-FDC	ERTU+MET-COADM

Source: Section 16.1.1
ERTU+MET-COADM: ertugliflozin 7.5 mg (administered as one 5 mg tablet + one 2.5 mg tablet) and metformin 1000 mg (US) co-administered under fasted conditions (Reference).
ERTU/MET-FDC: ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet, single dose, under fasted conditions (Test).
Abbreviations: COADM = co-administered, FDC = fixed dose combination, n = number of planned subjects, US = United States.
(Source: Study P027/1041 CSR, Table 1)

PK Sampling Schedule
Blood samples for determination of ertugliflozin and metformin concentrations were collected from each subject predose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours post-dose.

Results and Conclusions
A total of 32 healthy male and female subjects (16 in each treatment sequence) were enrolled and all of them completed this study. Results indicated that for both ertugliflozin and metformin, the 90% CI of the geometric mean ratios for Cmax, AUC0-t, and AUC0-inf are all well within the 80-125% range, suggesting the BE was demonstrated between ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet and the co-administration of the individual components: ertugliflozin 7.5 mg tablet and US-sourced Glucophage (metformin hydrochloride) 1000 mg under fasted conditions (Figures 9, 10 and Tables 23-26).

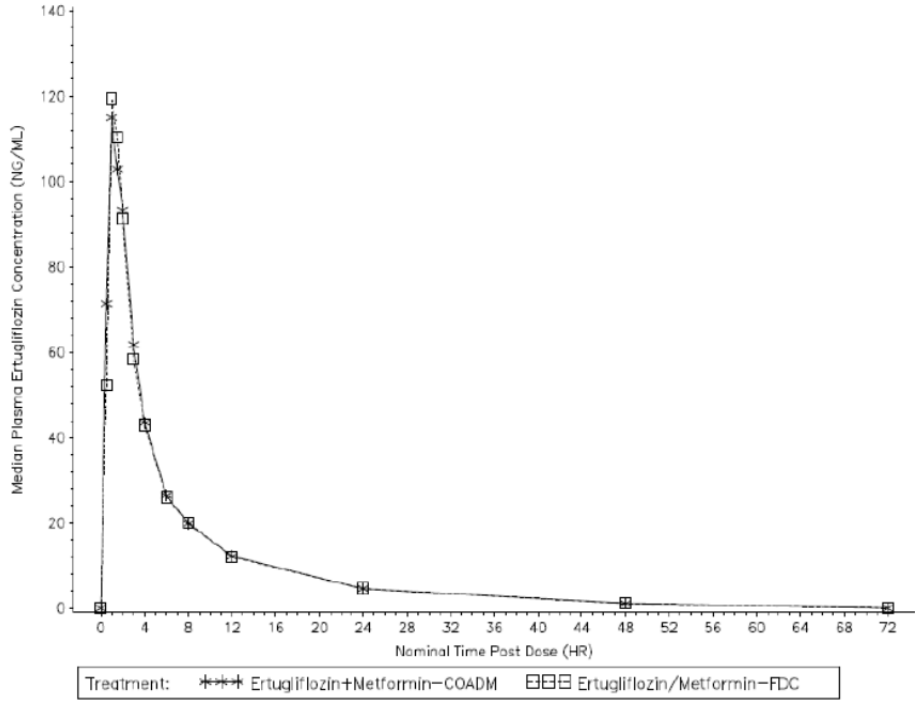


Figure 9. Median plasma ertugliflozin concentration-time profiles following single oral doses of ertugliflozin 7.5 mg /metformin 1000 mg FDC and ertugliflozin 7.5 mg+ Metformin 1000 mg (US) co-administration
(Source: adapted from Figure 1 of Study P027/1041 CSR)

Table 23. Summary of plasma ertugliflozin PK parameters

Parameter (unit)	Parameter Summary Statistics[a] by Treatment	
	Ertugliflozin 7.5 mg/Metformin 1000 mg FDC (Test)	Ertugliflozin 7.5 mg + Metformin 1000 mg (US) COADM (Reference)
N, n	32, 32	32, 32
AUC_{inf} (ng•hr/mL)	651.5 (28)	653.9 (27)
AUC_{last} (ng•hr/mL)	638.0 (29)	637.7 (28)
C_{max} (ng/mL)	124.1 (24)	119.9 (23)
T_{max} (hr)	1.03 (1.00, 3.00)	1.00 (0.500, 2.02)
$t_{½}$ (hr)	11.00 ± 2.70	11.19 ± 3.28

Source: Table 14.4.3.1.1
PK parameters are defined in Table 5.
Abbreviations: %CV = percent coefficient of variation, COADM = co-administered, FDC = fixed dose combination, hr = hour, N = number of subjects for the treatment and contributing to the descriptive summary statistics, n = number of subjects with reportable $t_{½}$ and AUC_{inf}, PK = pharmacokinetic(s), SD = standard deviation, US = United States.
a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for $t_{½}$.
(Source: Study P027/1041 CSR, Table 9)

Table 24. Statistical summary of treatment comparisons for plasma ertugliflozin PK parameters

Parameter (unit)	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Ertugliflozin 7.5 mg/Metformin 1000 mg FDC (Test)	Ertugliflozin 7.5 mg + Metformin 1000 mg (US) COADM (Reference)		
AUC_{inf} (ng•hr/mL)	651.5	653.9	99.64	97.04, 102.30
AUC_{last} (ng•hr/mL)	638.0	637.7	100.05	97.31, 102.87
C_{max} (ng/mL)	124.1	119.9	103.50	97.85, 109.47

Source: Table 14.4.3.3.1
PK parameters are defined in Table 5.
Values have been back-transformed from the log scale.
The model was a mixed effects model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. The intra-subject variability values based on mixed effects model for ertugliflozin AUC_{inf} and C_{max} were 6.22% and 13.3%, respectively.
Abbreviations: CI = confidence interval, COADM = co-administered, FDC = fixed dose combination, hr = hour, PK = pharmacokinetic(s), US = United States.
a. The ratios (and 90% CIs) are expressed as percentages.
(Source: Study P027/1041 CSR, Table 10)

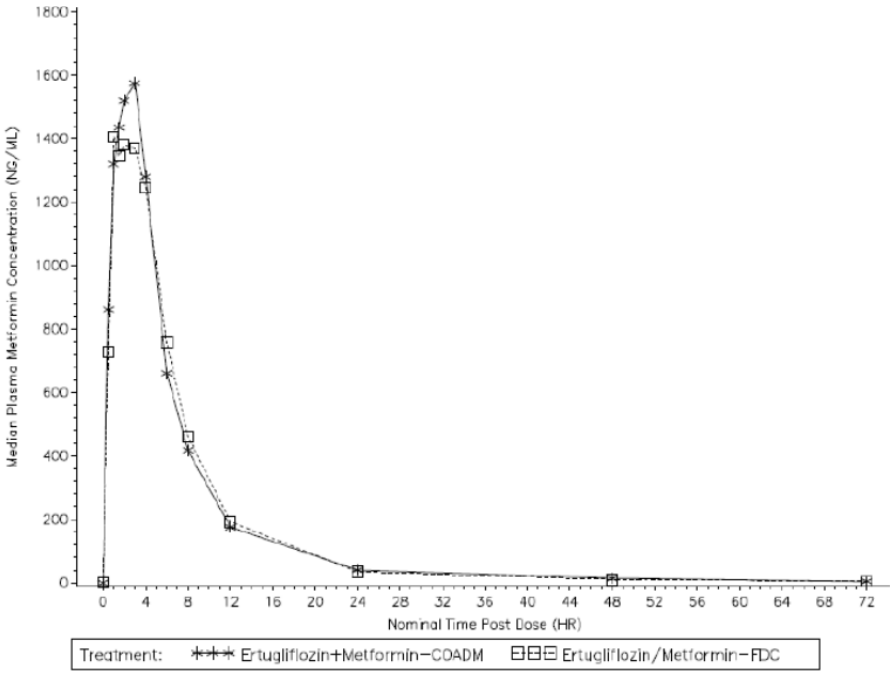


Figure 10. Median plasma metformin concentration-time profiles following single oral doses of ertugliflozin 7.5 mg /metformin 1000 mg FDC and ertugliflozin 7.5 mg+ Metformin 1000 mg (US) co-administered

(Source: adapted from Figure 4 of Study P027/1041 CSR)

Table 25. Summary of plasma metformin PK parameters

	Parameter Summary Statistics[a] by Treatment	
Parameter (unit)	**Ertugliflozin 7.5 mg/Metformin 1000 mg FDC (Test)**	**Ertugliflozin 7.5 mg + Metformin 1000 mg (US) COADM (Reference)**
N, n	32, 27	32, 26
AUC_{inf} (ng•hr/mL)	11180 (26)	11600 (24)
AUC_{last} (ng•hr/mL)	10870 (26)	11130 (26)
C_{max} (ng/mL)	1648 (25)	1661 (29)
T_{max} (hr)	2.01 (1.00, 4.10)	1.98 (0.517, 3.98)
$t_{½}$ (hr)	16.20 ± 11.65	16.42 ± 12.51

Source: Table 14.4.3.1.2
PK parameters are defined in Table 5.
Abbreviations: %CV = percent coefficient of variation, COADM = co-administered, FDC = fixed dose combination, hr = hour, N = number of subjects for the treatment and contributing to the descriptive summary statistics, n = number of subjects with reportable $t_{½}$ and AUC_{inf}, PK = pharmacokinetic(s), SD = standard deviation, US = United States.
a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for $t_{½}$.

(Source: Study P027/1041 CSR, Table 11)

Table 26. Statistical summary of treatment comparisons for plasma metformin PK parameters

	Adjusted (Least-Squares) Geometric Means		Ratio	
Parameter (unit)	**Ertugliflozin 7.5 mg/Metformin 1000 mg FDC (Test)**	**Ertugliflozin 7.5 mg + Metformin 1000 mg (US) COADM (Reference)**	**(Test/Reference) of Adjusted Means[a]**	**90% CI for Ratio**
AUC_{inf} (ng•hr/mL)	11230	11560	97.14	89.98, 104.87
AUC_{last} (ng•hr/mL)	10870	11130	97.72	91.31, 104.58
C_{max} (ng/mL)	1648	1661	99.20	92.06, 106.90

Source: Tables 14.4.3.3.2
PK parameters are defined in Table 5.
Values have been back-transformed from the log scale.
The model was a mixed effects model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. The intra-subject variability values based on mixed effects model for metformin AUC_{inf} and C_{max} were 15.8% and 17.8%, respectively.
Abbreviations: CI = confidence interval; COADM = co-administered; FDC = fixed dose combination, hr = hour, PK = pharmacokinetic(s), US = United States.
a. The ratios (and 90% CIs) are expressed as percentages.

(Source: Study P027/1041 CSR, Table 12)

Study P050/1058 (BE Study)

Title: A Phase 1, Single Dose, Open-Label, Randomized, Crossover Bioequivalence Study of an Ertugliflozin 2.5 mg/Metformin 500 mg Fixed Dose Combination Tablet vs Co-Administration of the Individual Components (Ertugliflozin and US-Sourced Metformin) in Healthy Subjects

Objectives:

- **Primary:** to demonstrate the BE of ertugliflozin 2.5 mg/metformin 500 mg FDC tablet to the co-administration of the individual components: ertugliflozin 2.5 mg tablet and US-sourced Glucophage (metformin hydrochloride) 500 mg under fasted conditions
- **Secondary:** safety and tolerability

Study Design

This was a pivotal, Phase 1, open-label, randomized, 2-period, 2-sequence, single dose, crossover study to demonstrate the bioequivalence of the ertugliflozin 2.5 mg/metformin 500 mg FDC tablet to the co-administration of the individual components: ertugliflozin 2.5 mg and metformin 500 mg (US) tablets under fasted conditions in healthy subjects. Each subject received 2 treatments in a randomized manner as outlined in Table 27. In each period, subjects received a single dose of the assigned trial medication in the morning on Day 1 in the fasted state (minimum 10-hour fast). Dosing in each period was separated by a washout period of at least 7 days.

Table 27. Treatment sequence in Study P050/1058

Sequence	Period 1	Period 2
1 (N = 16)	ERTU+MET-COADM	ERTU/MET-FDC
2 (N = 16)	ERTU/MET-FDC	ERTU+MET-COADM

Source: Section 16.1.1
Abbreviations: COADM = co-administered, FDC = fixed dose combination, N = number of subjects, US = United States.
ERTU+MET-COADM: ertugliflozin 2.5 mg tablet and metformin 500 mg (US) co-administered under fasted conditions (Reference)
ERTU/MET-FDC: ertugliflozin 2.5 mg/metformin 500 mg FDC tablet, single dose, under fasted conditions (Test)
(Source: Study P050/1058 CSR, Table 1)

PK Sampling Schedule

Blood samples for determination of ertugliflozin and metformin concentrations were collected from each subject predose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours post-dose.

Results and Conclusions

A total of 32 healthy male and female subjects (16 in each treatment sequence) were enrolled and all of them completed this study. Results indicated that for both ertugliflozin and metformin, the 90% CI of the geometric mean ratios for Cmax, AUC0-t, and AUC0-inf are all well within the 80-125% range, suggesting the BE was demonstrated between ertugliflozin 2.5 mg/metformin 500 mg FDC tablet and the co-administration of the individual components: ertugliflozin 2.5 mg

tablet and US-sourced Glucophage (metformin hydrochloride) 500 mg under fasted conditions (Figures11, 12 and Tables 28-31).

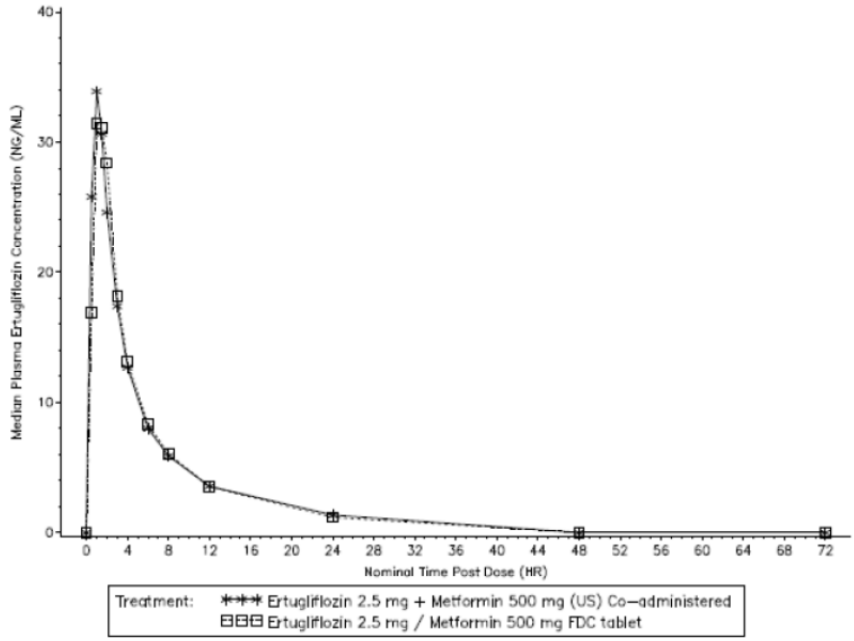


Figure 11. Median plasma ertugliflozin concentration-time profiles following single oral doses of ertugliflozin 2.5 mg /metformin 500 mg FDC and ertugliflozin 2.5 mg+ Metformin 500 mg (US) co-administered

(Source: adapted from Figure 1 of Study P050/1058 CSR)

Table 28. Summary of plasma ertugliflozin PK parameters

	Parameter Summary Statistics[a] by Treatment	
Parameter (units)	**Ertugliflozin 2.5 mg/Metformin 500 mg FDC tablet (Test)**	**Ertugliflozin 2.5 mg + Metformin 500 mg (US) Co-administered (Reference)**
N, n	32, 32	32, 32
AUC_{inf} (ng.hr/mL)	176.9 (24)	180.0 (25)
AUC_{last} (ng.hr/mL)	165.3 (23)	167.6 (25)
C_{max} (ng/mL)	34.94 (23)	34.86 (24)
T_{max} (hr)	1.00 (1.00, 2.00)	1.00 (0.500, 3.00)
$t_{½}$ (hr)	7.117 ± 1.340	7.728 ± 1.865

Source: Table 14.4.3.1.1

Abbreviations: %CV = percent coefficient of variation, FDC = fixed dose combination, hr = hour, N = Number of subjects in the treatment group and contributing to the descriptive summary statistics, n = number of subjects with reportable $t_{½}$ and AUC_{inf}, PK = pharmacokinetic(s), SD = standard deviation, US = United States.

PK parameters are defined in Table 5.

a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for $t_{½}$.

(Source: Study P050/1058 CSR, Table 9)

Table 29. Statistical summary of treatment comparisons for plasma ertugliflozin PK parameters

Parameter (units)	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Ertugliflozin 2.5 mg/Metformin 500 mg FDC tablet (Test)	Ertugliflozin 2.5 mg + Metformin 500 mg (US) Co-administration (Reference)		
AUC_{inf} (ng.hr/mL)	176.9	180.0	98.26	96.62, 99.94
AUC_{last} (ng.hr/mL)	165.3	167.6	98.62	96.82, 100.44
C_{max} (ng/mL)	34.94	34.86	100.22	94.76, 106.00

Source: Table 14.4.3.5.1
Abbreviations: CI = confidence interval, FDC = fixed dose combination, hr = hour, PK = pharmacokinetic(s), US = United States.
The intra-subject variability values (sqrt[exp(MSE)-1], where MSE is the mean square error) based on mixed effects model for ertugliflozin AUC_{inf}, AUC_{last}, and C_{max} were 0.0399, 0.0433 and 0.1327, respectively.
PK parameters are defined in Table 5.
a. The ratios (and 90% CIs) are expressed as percentages.

(Source: Study P050/1058 CSR, Table 10)

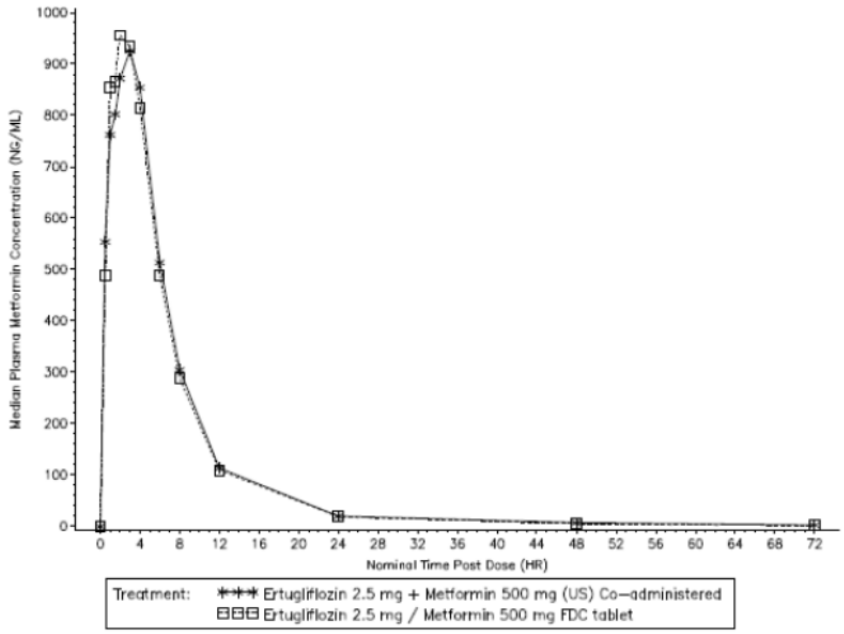


Figure 12. Median plasma metformin concentration-time profiles following single oral doses of ertugliflozin 2.5 mg /metformin 500 mg FDC and ertugliflozin 2.5 mg+ Metformin 500 mg (US) co-administered

(Source: adapted from Figure 4 of Study P050/1058 CSR)

Table 30. Summary of plasma metformin PK parameters

Parameter (units)	Parameter Summary Statistics[a] by Treatment	
	Ertugliflozin 2.5 mg/Metformin 500 mg FDC tablet (Test)	Ertugliflozin 2.5 mg + Metformin 500 mg (US) Co-administered (Reference)
N, n	32, 29	32, 27
AUC_{inf} (ng.hr/mL)	6953 (28)	6784 (21)
AUC_{last} (ng.hr/mL)	6819 (27)	6794 (20)
C_{max} (ng/mL)	1030 (30)	1015 (20)
T_{max} (hr)	2.00 (1.00, 4.02)	1.98 (0.483, 4.10)
$t_{½}$ (hr)	13.45 ± 8.29	14.08 ± 7.78

Source: Table 14.4.3.1.2
Abbreviations: %CV = percent coefficient of variation, FDC = fixed dose combination, hr = hour, N = Number of subjects in the treatment group and contributing to descriptive summary statistics, n = number of subjects with reportable $t_{½}$ and AUC_{inf}, PK = pharmacokinetic(s), SD = standard deviation, US = United States.
PK parameters are defined in Table 5.
a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for $t_{½}$.

(Source: Study P050/1058 CSR, Table 11)

Table 31. Statistical summary of treatment comparisons for plasma metformin PK parameters

Parameter (units)	Adjusted (Least-Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Ertugliflozin 2.5 mg/Metformin 500 mg FDC tablet (Test)	Ertugliflozin 2.5 mg + Metformin 500 mg (US) Co-administration (Reference)		
AUC_{inf} (ng.hr/mL)	6934	6717	103.24	96.16, 110.83
AUC_{last} (ng.hr/mL)	6819	6794	100.36	93.28, 107.98
C_{max} (ng/mL)	1030	1015	101.49	93.83, 109.76

Source: Table 14.4.3.5.2
Abbreviations: CI = confidence interval, FDC = fixed dose combination, hr = hour, PK = pharmacokinetic(s), US = United States.
The intra-subject variability values (sqrt[exp(MSE)-1], where MSE is the mean square error) based on mixed effects model for metformin AUC_{inf}, AUC_{last}, and C_{max} were 0.1495, 0.1737 and 0.1864, respectively.
PK parameters are defined in Table 5.
a. The ratios (and 90% CIs) are expressed as percentages.

(Source: Study P050/1058 CSR, Table 12)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEI HE
08/07/2017

LIAN MA
08/07/2017

MANOJ KHURANA
08/07/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	209805	**SDN**	1
Applicant	Merck	**Submission Date**	12/19/2016
Generic Name	Ertugliflozin and Sitagliptin	**Brand Name**	NA
Drug Class	Ertugliflozin is a sodium-glucose co-transporter 2 inhibitor Sitagliptin is a dipeptidyl peptidase-4 inhibitor		
Indications	It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate. Limitations of Use: • Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. • Has not been studied in patients with a history of pancreatitis.		
Dosage Regimen	• The recommended starting dose is 5 mg ertugliflozin/100 mg sitagliptin once daily, taken in the morning, with or without food. • Dose may be increased to 15 mg ertugliflozin/100 mg sitagliptin once daily in those tolerating ertugliflozin/sitagliptin and needing additional glycemic control. • Initiation of administration is not recommended in patients with an eGFR less than (b) (4) mL/min/1.73 m^2. • (b) (4) • (b) (4) • (b) (4)		
Dosage Form	Tablets • (b) (4) • Ertugliflozin 5 mg and Sitagliptin 100 mg • Ertugliflozin 15 mg and Sitagliptin 100 mg	**Route of Administration**	Oral
OCP Division	DCP2	**OND Division**	Metabolism and Endocrinology Products

OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader
Division	Lei He, PhD	Manoj Khurana, PhD
Pharmacometrics		
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	2/17/2017	**74-Day Letter Date**	3/3/2017
Review Due Date	8/19/2017	**PDUFA Goal Date**	12/19/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

If yes explain

As the proposed ertugliflozin/sitagliptin fixed-dose combination (FDC) products were not administered in Phase 3 studies, 4 pivotal BE studies (Studies P025/1038, (b) (4) P048/1056, and (b) (4) were conducted under fasted conditions to bridge each strength of the proposed ertugliflozin/sitagliptin FDC commercial tablets (15 mg/100 mg, (b) (4) 5 mg/100 mg, (b) (4) and the co-administration of the respective doses of the individual tablets used in Phase 3 studies. The BE studies will be used to support the bridging of PK, efficacy and safety data obtained with the co-administered tablets used in the Phase 3 studies to the FDC commercial tablet. Therefore, we request that both the clinical site and analytical site be inspected for this submission.

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☑ Bioequivalence		4	Studies P025/1038, (b) (4) P048/1056, (b) (4)
☑ Food Effect		1	Study 026/1050
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		

☐ Mass Balance Study		
☐ Other (e.g. dose proportionality)		
Intrinsic Factors		
☐ Race		
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☑ Effects on Primary Drug	1	Study 022/1033
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies	**In Vitro**		**In Vivo**	6
Total Number of Studies to be Reviewed				

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☐N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☑No ☐N/A	

Filing Memo
See Attachment: Presentation slides in filing meeting.

U.S. FOOD & DRUG ADMINISTRATION

NDA 209805 ERTUGLIFLOZIN/SITAGLIPTIN FDC

Sponsor:
Merck Sharp & Dohme Corp.,
(subsidiary of Merck & Co., Inc.)
Submitted: 19 Dec 2016

FILING MEETING

Clin Pharm Reviewers: Lei He, PhD (Primary)
Manoj Khurana, PhD (Team Leader)

Clinical Pharmacology Summary

- **Application is fileable from a clinical pharmacology perspective.**
- **OSIS consults for 1 clinical sites and 2 bioanalytical sites:**
  - 4 BE Studies P025, (b) (4) 048, (b) (4)
- **Topline Results**
  1. No clinically meaningful PK interaction between the individual components.
  2. No clinically meaningful food effect on each of individual components.
  3. Since the proposed FDC product was not administered in Phase 3 studies, BE studies bridged the individual tablets used in Phase 3 studies and the proposed commercial FDC tablets.

2

Clinical Pharmacology Program

Study	NDA209805	
	# of studies	Protocol #
DDI study	1	P022
Food effect Study	1	P026
BE study	4	P025 (b) (4) P048 (b) (4)
PK/PD study	--	--
Model based meta-analysis	--	--
Total	**6**	

3

Summary

- Application is fileable
- Mid-cycle deliverables
  - Any approvability issues
  - Confirm PK results
- OSI inspection for BE study clinical sites and bioanalytical sites will be requested

4

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/s/

LEI HE
02/07/2017

MANOJ KHURANA
02/07/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	209806	**SDN**	1
Applicant	Merck	**Submission Date**	12/19/2016
Generic Name	Ertugliflozin and Metformin	**Brand Name**	NA
Drug Class	Ertugliflozin is a sodium-glucose co-transporter 2 inhibitor Metformin is a biguanide		
Indications	It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [redacted (b) (4)] Limitations of Use: • Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.		
Dosage Regimen	• Individualize the starting dose based on the patient's current regimen. • The maximum recommended dose is 7.5 mg ertugliflozin/1000 mg metformin twice daily. • Take twice daily with meals, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin. • It is contraindicated in patients with an eGFR < 30 mL/min/1.73 m^2. • Initiation is not recommended in patients with an eGFR between 30 and [redacted (b) (4)] mL/min/1.73 m^2. • [redacted (b) (4)] • [redacted (b) (4)] • It may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures.		
Dosage Form	Tablets • Ertugliflozin 2.5 mg and metformin hydrochloride 500 mg • Ertugliflozin 2.5 mg and metformin hydrochloride 1000 mg • Ertugliflozin 7.5 mg and metformin hydrochloride 500 mg • Ertugliflozin 7.5 mg and metformin hydrochloride 1000 mg	**Route of Administration**	Oral
OCP Division	DCP2	**OND Division**	Metabolism and Endocrinology Products

OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader
Division	Lei He, PhD	Manoj Khurana, PhD
Pharmacometrics		
Genomics		
Review Classification	☑ Standard ☐ Priority ☐ Expedited	

Filing Date	2/17/2017	**74-Day Letter Date**	3/3/2017
Review Due Date	8/19/2017	**PDUFA Goal Date**	12/19/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

If yes explain

In Phase 3 studies supporting ertugliflozin/metformin fixed-dose combination (FDC) clinical development program, the FDC products were not used, and ertugliflozin was administered once daily (QD) on a background of metformin twice daily (BID) using separate tablets. Two pivotal BE studies (Study P027/1041 and Study P050/1058) were conducted comparing the highest and lowest strengths of the proposed ertugliflozin/metformin commercial tablets with the co-administration of ertugliflozin and Glucophage tablets used in the Phase 3 studies. The combination of BE study data and in vitro dissolution data will be used to support the bridging of PK, efficacy and safety data obtained with the co-administered tablets used in the Phase 3 studies to the FDC commercial tablet. Therefore, we request that both the clinical site and analytical site be inspected for this submission.

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		
☐ Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
☐ Absolute Bioavailability		
☐ Relative Bioavailability		
☑ Bioequivalence	4	Studies P027/1041, P050/1058, P046/1054, P047/1055
☑ Food Effect	1	Study P028/1049
☐ Other		
Human Pharmacokinetics		
Healthy ☐ Single Dose		

Subjects	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☑ Effects on Primary Drug	1	Study P019/1032	
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☑ Healthy Subjects	1	Study 035/1051	
☑ Patients	1	Study 040/1007	
☐ QT			
Pharmacometrics			
☑ Population Pharmacokinetics	1	Model-Based Meta-Analysis to Quantify the Relationship Between Urinary Glucose Excretion and A1C for SGLT2 Inhibitors	
☐ Exposure-Efficacy			
☐ Exposure-Safety			
Total Number of Studies	**In Vitro**		**In Vivo** 9
Total Number of Studies to be Reviewed			

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☐N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☑No ☐N/A	

Filing Memo

See Attachment: Presentation slides in filing meeting.

U.S. FOOD & DRUG ADMINISTRATION

NDA 209806 ERTUGLIFLOZIN/METFORMIN FDC

Sponsor:
Merck Sharp & Dohme Corp.,
(subsidiary of Merck & Co., Inc.)
Submitted: 19 Dec 2016

FILING MEETING

Clin Pharm Reviewers: Lei He, PhD (Primary)
Manoj Khurana, PhD (Team Leader)

Clinical Pharmacology Summary

- **Application is fileable from a clinical pharmacology perspective.**
- **OSIS consults for 1 clinical sites and 1 bioanalytical sites:**
  - 2 BE Studies P027, 050.
- **Topline Results**
  1. No clinically meaningful PK interaction between the individual components.
  2. No clinically meaningful food effect on each of individual components.
  3. Since the proposed FDC product was not administered in Phase 3 studies,
     - BE studies and in-vitro dissolution studies bridged the individual tablets used in Phase 3 studies and the proposed commercial FDC tablets
     - PK/PD study and model based meta-analysis bridged QD and BID dosing regimen of ertugliflozin

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Clinical Pharmacology Program

Study	NDA209806	
	# of studies	Protocol #
DDI study	1	P019
Food effect Study	1	P028
BE study	4	P027 P050 P046 P047
PK/PD study	2	P040 P035
Model based meta-analysis	1	Report 04J75J
Total	**9**	

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Summary

- Application is fileable
- Mid-cycle deliverables
  - Any approvability issues
  - Confirm PK results
- OSI inspection for BE study clinical sites and bioanalytical sites will be requested

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/s/

LEI HE
02/07/2017

MANOJ KHURANA
02/07/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	209803	**SDN**	0000
Applicant	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	**Submission Date**	19 Dec 2016
Generic Name	Ertugliflozin	**Brand Name**	STEGLATRO (Proposed)
Drug Class	Sodium glucose co-transporter 2 (SGLT2) inhibitor		
Indication	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.		
Dosage Regimen	• The recommended starting dose of TRADEMARK is 5 mg once daily, taken in the morning, with or without food • Dose may be increased to TRADEMARK 15 mg once daily in those tolerating TRADEMARK and needing additional glycemic control • Assess renal function before initiating TRADEMARK. Initiation of TRADEMARK is not recommended in patients with an eGFR less than (b) (4) mL/min/1.73 m^2 • (b) (4) • (b) (4) (b) (4)		
Dosage Form	Film-coated tablets: 5 mg and 15 mg	**Route of Administration**	Oral
OCP Division	DCP 2	**OND Division**	DMEP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Suryanarayana Sista, PhD	Manoj Khurana, PhD
Pharmacometrics	Lian Ma, PhD	Nitin Mehrotra, PhD
PBPK	Suryanarayana Sista, PhD	Manuela Grimstein, PhD
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	1/30/2017	**74-Day Letter Date**	3/3/2017
Review Due Date	8/19/2017	**PDUFA Goal Date**	12/19/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

If yes explain: Study P023 is a pivotal clinical pharmacology bridging study establishing bioequivalence between the clinical trial material used in Phase 3 studies and the to-be-marketed commercial batch. Therefore, an inspection of the bioanalytical and clinical trial sites is requested.

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies		
Study Type	**Count**	**Comment(s)**
In Vitro Studies		
☑ Metabolism Characterization	3	pk045mk8835 (PF-04971729/31Mar09/162240), pk046mk8835 (PF-04971729_06Oct15_130356), pk047mk8835 (PF-04971729_01Dec15_044314)
☑ Transporter Characterization	2	pk062mk8835 (PF-0497 I 729_09 Mar I I 081536), pk063mk8835 (PF-04971729_30Mar11_162655)
☑ Distribution	2	pk036mk8835 (PF-04971729/07May09/102049), pk038mk8835 (PF-04971729/04Jun09/143527)
☑ Drug-Drug Interaction	24	pk050mk8835 (PF-04971729/14JUN09/125135), pk050mk8835 (PF-04971729_11Mar15_122850), pk052mk8835 (PF-06481944_01Jul15_101545), pk053mk8835 (PF-06685948_01Jul15_101636), pk054mk8835 (PF-04971729/19Nov08/125201), pk055mk8835 (PF-04971729_30Jan15_120553), pk056mk8835 (PF-06481944_04Sep15_120049), pk057mk8835 (PF-06685948_04Sep15_120321), pk058mk8835 (PF-04971729_21May15_113856), pk060mk8835 (PF-06481944_29Jun15_151558), pk061mk8835 (PF-06685948_29Jun15_155303), pk064mk8835 (PF-04971729 _13Jul11_131709), pk065mk8835 (PF-04971729_25Mar14_114705), pk066mk8835 (PF-04971729_30Sep15_140916), pk067mk8835 (PF-04971729_10Oct12_115403), pk068mk8835 (PF-04971729_05Nov15_032208), pk069mk8835 (PF-04971729_06Sep11_153120), pk070mk8835 (PF-04971729/18Aug09/143816), pk071mk8835 (PF-04971729_09Marl1_081536), pk072mk8835 (PF-04971729_20Dec10_144638), pk073mk8835 (PF-04971729_10Jun11_140913), pk074mk8835 (PF-04971729_06Aug10_111034), pk075mk8835 (PF-06481944_04Nov15_013302), pk076mk8835 (PF-06685948_04Nov15_013350)
In Vivo Studies		
Biopharmaceutics		
☑ Absolute Bioavailability	1	P020/1043
☑ Relative Bioavailability	1	P011/1034
☑ Bioequivalence	1	P023/1037
☑ Food Effect	1	P024/1048
☐ Other		
Human Pharmacokinetics		
Healthy Subjects – ☑ Single Dose	1	P036/1001
Healthy Subjects – ☑ Multiple Dose	2	P037/1002, P035/1051
Patients – ☑ Single Dose	1	P040/1007
Patients – ☐ Multiple Dose		
☑ Mass Balance Study	1	P038/1003
☐ Other (e.g. dose proportionality)		
Intrinsic Factors		
☑ Race	1	P041/1009
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☑ Hepatic Impairment	1	P014/1024
☑ Renal Impairment	1	P009/1023
☐ Genetics		
Extrinsic Factors		
☑ Effects on Primary Drug	5	P019/1032, P021/1040, P022/1033, P030/1036, P032/1044

☑ Effects of Primary Drug	4	P019/1032, P022/1033, P030/1036, P032/1044
Pharmacodynamics		
☑ Healthy Subjects		
☑ Patients		
Pharmacokinetics/Pharmacodynamics		
☑ Healthy Subjects	1[a]	P035/1051[a]
☐ Patients		
☑ QT		P010/1025
Pharmacometrics		
☑ Population Pharmacokinetics	1	04J75F
☑ Exposure-Efficacy	2	04J759, 04J75J
☐ Exposure-Safety		
☑ Other	2	04J75L[b], 04J9DB[c]

Total Number of Studies	**57**	**In Vitro**		**In Vivo**	
Total Number of Studies to be Reviewed: 57			31		26

[a]Study numbers repeated
[b]Non-Compartmental Meta-Analysis of Ertugliflozin PK Parameters
[c]Relationship between Urinary Glucose Excretion and Ertugliflozin Dose

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☐N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	**Human Plasma:** B1529001 [04GRNY], B1529003 [04GRPY, 04GRPX], B1529004 [04GRPZ], B1529005 [04GRQV], B1529008 [04GRQY, 04H3RN, 04J0Z2, 04J0ZT] **Human Urine** B1529002 [04GRNZ], B1529006 [04GRQW] **Human Plasma Dialysate** B1529007 [04GRQX]
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input	☑Yes ☐No ☐N/A	

files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	The initial Pediatric Study Plan (iPSP) for ertugliflozin was agreed on August 26, 2013, which includes (a) a waiver for pediatric subjects 0 to < 10 years, and (b) a deferral of a study in pediatric subjects 10 to < 18 years until the completion of the adult core Phase 3 glycemic efficacy studies confirming efficacy and safety
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

The sponsor's clinical development program for ertugliflozin includes a combination of Phase I, Phase II and Phase III studies. Several meetings were held between the Agency and the Sponsor (see IND 106447) for the development program of ertugliflozin. The Phase I clinical pharmacology program for ertugliflozin comprised of 19 Phase 1 studies, 2 Phase 2 studies with sparse PK sampling (Studies P042/1004, P016/1006), and 4 Phase 3 studies with sparse PK sampling (Studies P001/1016, P007/1017, P005/1019, P003/1022). In addition, the following reports were submitted to the NDA: (a) PopPK, (b) exposure-response, (c) meta-analysis to quantify the relationship between urinary glucose excretion and A1C for SGLT2 inhibitors, (d) non-compartmental meta-analysis of ertugliflozin PK parameters in healthy subjects, (e) characterization of the relationship between urinary glucose excretion and ertugliflozin dose in T2DM subjects

Filing slides are listed in Appendix

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?	☑Yes ☐No

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comments to Sponsor:	None

Suryanarayana M. Sista 03 February 2017
Reviewing Clinical Pharmacologist Date

Manoj Khurana 03 February 2017
Acting Team Leader Date

Appendix

APPEARS THIS WAY ON ORIGINAL

U.S. FOOD & DRUG ADMINISTRATION

NDA 209803 FILING MEETING

ERTUGLIFLOZIN

Sponsor:
Merck Sharp & Dohme Corp.,
(subsidiary of Merck & Co., Inc.)
Submitted: 19 Dec 2016

OCP Review Team:
Sury Sista, Lian Ma, Manuela Grimstein, Manoj Khurana, Nitin Mehrotra

Clinical Pharmacology Summary

- **Application is filable from Clinical Pharmacology perspective**
- **OSIS consults:**
  - Inspection of Studies P023 (P3 IMP *versus* Commercial batch)
- **Request for Sponsor:**
  - None at present
- **Topline Results**
  - **SD and MD PK in Healthy Subjects**:
    - Oral bioavailability ~ 100%
    - Median T_{max} : 1 hour (fasted); 2 hours (fed)
    - $t_{1/2}$ 15.3 hours based on Pop PK analysis and similar to the estimated elimination half-life of 16.6 hours in T2DM subjects with normal renal function
    - Food does not have a clinically meaningful effect on the pharmacokinetics of ertugliflozin, and therefore ertugliflozin may be administered without regard to meals
  - **Once Daily vs Twice Daily Dosing:**
    - At total daily doses of 2, 4, 5, and 15 mg, there were no meaningful differences in AUC values for the bid vs corresponding qd regimens.
  - **Dose Proportionality:**
    - Dose-proportional over the dose range of 0.5 to 300 mg
  - **Intrinsic Factors:**
    - Age, body weight, gender, race, UGT1A9 polymorphism, renal impairment, and mild or moderate hepatic impairment do not have a clinically meaningful effect on the pharmacokinetics of ertugliflozin
  - **Dose-Response:**
    - Dose-response modeling indicates that ertugliflozin 5 mg and 15 mg result in near maximal urinary glucose excretion (PD effect) and HbA1c lowering (glycemic efficacy), with the 15 mg dose providing incrementally greater urinary glucose excretion and HbA1c lowering relative to the 5 mg dose

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Clinical Pharmacology Program

- **Clinical Pharmacology Information from:**
  - 19 Phase 1, 2 Phase 2, and 4 Phase 3 studies

Ertugliflozin Clinical Pharmacology Studies

Category	Study Description	Study Number
PK/PD/Safety	Single escalating oral dose, including initial assessment of food effect	P036/1001[a]
	Multiple escalating dose	P037/1002[a]
	[^{14}C]ADME study	P038/1003
	qd vs bid regimen after single day dose in T2DM subjects; 1 mg bid vs 2 mg qd, 2 mg bid vs 4 mg qd	P040/1007[a]
	qd vs bid regimen at steady state in healthy subjects; 2.5 mg bid vs 5 mg qd, 7.5 mg bid vs 15 mg qd	P035/1051[a]
	Thorough QT study	P010/1025
Biopharmaceutics[b]	Absolute BA	P020/1043
	BE between Phase 3 and commercial tablet	P023/1037
	Food effect of commercial tablet	P024/1048
	Relative BA of amorphous form vs cocrystal	P011/1034
	Relative BA of MR vs IR tablets[c]	P039/1005
Special Population	Single escalating dose and multiple dose study in Japanese vs Western subjects	P041/1009[a]
	PK in moderate hepatic impairment	P014/1024
	PK and PD in mild, moderate and severe renal impairment	P009/1023[a]
DDI	Ertugliflozin 15 mg and sitagliptin 100 mg	P022/1033
	Ertugliflozin 15 mg and metformin 1000 mg	P019/1032
	Ertugliflozin 15 mg and glimepiride 1 mg	P032/1044
	Ertugliflozin 15 mg and simvastatin 40 mg	P030/1036
	Ertugliflozin 15 mg and rifampin 600 mg qd x 10 days	P021/1040

- Two Phase 2 studies with sparse PK sampling (Studies P042/1004, P016/1006)
- Four Phase 3 studies with sparse PK sampling (Studies P001/1016, P007/1017, P005/1019, P003/1022)

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Overview of PK of Ertugliflozin

- **Pharmacokinetics**
  - Ertugliflozin is a BCS Class 1 drug (high permeability and high solubility)
  - Absolute bioavailability ~ 100%
  - T_{max}: 1 h in fasted state; 2 h in fed state
  - $t_{1/2}$ ~ 16.6 h in T2DM patients with normal renal function
  - Time-independent PK; steady-state in 4-6 days following once-daily dosing
  - Plasma protein binding – 93.6%
  - Exposure increases in a dose-proportional manner over the dose range of 0.5 to 300 mg
  - Primarily metabolized by glucuronidation (UGT1A9, UGT2B7)
  - No clinically meaningful effect on PK of Ertugliflozin by intrinsic factors age, body weight, gender, race, UGT1A9 polymorphism, renal impairment, and mild or moderate hepatic impairment
  - Low DDI potential
  - No clinically meaningful effect of food - may be administered without regard to meals

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Overview of PD of Ertugliflozin

- **Pharmacodynamics**
  - Dose-response modeling indicates that ertugliflozin 5 mg and 15 mg result in near maximal urinary glucose excretion (PD effect) and HbA1c lowering (glycemic efficacy)
    - 15 mg dose provides incrementally greater urinary glucose excretion and HbA1c lowering relative to the 5 mg dose
  - A lack of an effect of ertugliflozin on the QTc interval was demonstrated in the thorough QT study at the ertugliflozin dose of 100 mg

Dose Selection Rationale

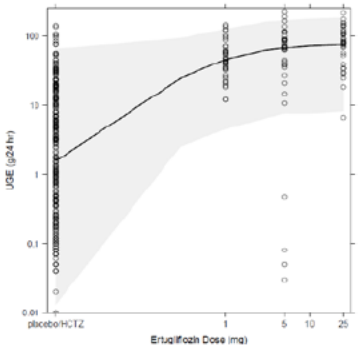
- Single oral doses as high as 300 mg, multiple doses of 100 mg qd up to 14 days and 25 mg qd up to 12 weeks were associated with an acceptable safety profile in the Phase 1 and Phase 2 studies
- Dose-response relationships for the change from baseline in A1C, FPG, and body weight in T2DM subjects from a 12-week Phase 2 dose-ranging study (Study P016/1006) was the key driver for Phase 3 dose selction
- Relationship between change from baseline in HbA1c or FPG or body weight at Week 12 vs dose was described by an maximum effect (E_{max}) model that included dose as a continuous variable

Model-Predicted Placebo-adjusted Change from Baseline Responses for Key Endpoints Based on Phase 2 Studies

Ertugliflozin Dose (mg)	A1C (%) ED_{50}=1.0 mg E_{max}=-0.77%	FPG (mg/dL) ED_{50}=1.1 mg E_{max}=-34.8 mg/dL	Body weight (%) ED_{50}=0.8 mg E_{max}=-2.11%	UGE_{24} (g) ED_{50}=0.75 mg E_{max}=71.5 g
5	-0.64	-28.4	-1.81	62.5
15	-0.72	-32.4	-2.00	68.9

- Dose-response modeling of the PD marker, 24-hour UGE, in subjects with T2DM from the 4-week Phase 2 Study P042/1004 also contributed towards dose selection in Phase 3 studies

Dose Selection Rationale



UGE versus Ertugliflozin Dose in T2DM Subjects

- Model estimated a maximal baseline-adjusted UGE(0-24) response [95% CI] of 71.5 [57.9 to 87.3] g/day and an ED_{50} [95% CI] of 0.752 [0.299, 1.58] mg
- Baseline UGE (95% CI) was estimated as 2.37 [1.69, 3.37] g/day and 0.622 [0.381, 1.03] g/day, respectively, for males and females
- Predictions of UGE [90% CI] following 28 days of administration:
  - For the 5 mg ertugliflozin dose, the mean UGE prediction was 62.5 [54.9, 69.7] g/day
  - For the 15 mg ertugliflozin dose, the mean UGE prediction was 68.9 [58.9, 78.7] g/day

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Results – *in vitro* Studies

Absorption

- Ertugliflozin is a substrate for both P-gp and BCRP efflux transporters

Distribution

- Mean in vitro plasma protein binding was 93.6% at concentration of 2.3 µM and 94.7% at a concentration of 23 µM
- In human whole blood, ertugliflozin distributed preferentially into plasma relative to red blood cells with a blood-to-plasma concentration ratio of 0.66

Metabolism

- Glucuronidation of ertugliflozin accounts for approximately 86% of ertugliflozin metabolism in humans
- Two groups of isomeric glucuronides were detected, the first group included M5a, M5b, and M5c derived directly from parent and the second group, M6a, M6b, and M6c, resulted from glucuronidation and desethylation
- Primary enzyme involved in the glucuronidation of ertugliflozin was UGT1A9 (≥81%) with minor contributions from UGT2B7 (≤19%)
- CYP3A4 was the predominant CYP enzyme involved in the minor oxidative metabolism of ertugliflozin to M1, M2, and M3, accounting for 85% to 100% of the CYP metabolism. Minor contributions by CYP2C8 (0% to 4%) and CYP3A5 (0% to 10%) were also observed

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Results – *in vitro* Studies

***In vitro* DDI**

- ***Inhibition of CYP Enzymes***
  - Ertugliflozin demonstrated little or no inhibition for the CYP enzyme activities tested, with half maximal inhibitory concentration (IC_{50}) >30 µM and a calculated inhibition constant (K_i) of >15 µM, assuming competitive inhibition
  - Ertugliflozin did not demonstrate time-dependent inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 at concentrations of 100 µM or greater
  - Metabolites M5c and M5a demonstrated little or no change (<20%) in time-dependent inhibitory potential for these isozymes at concentrations up to 100 µM
- ***Induction of CYP Enzymes***
  - Ertugliflozin did not cause induction of CYP3A4, CYP2B6, or CYP1A2 activity, however, weak mRNA induction was observed in hepatocytes at concentrations ≥50 µM
  - The glucuronide metabolites did not cause induction of CYP3A4, CYP2B6, or CYP1A2 mRNA expression or enzyme activity in hepatocytes up to the highest concentration evaluated
- ***Inhibition of UGT enzymes***
  - Ertugliflozin demonstrated little or no reversible inhibition of UGT1A6, UGT1A9, and UGT2B7 catalyzed activities (IC_{50} >100 µM)
  - Ertugliflozin inhibited UGT1A1 and UGT1A4 activities in the presence of 0.1% bovine serum albumin with unbound IC_{50} values of 39 and 45 µM, respectively
  - Glucuronides M5c and M5a demonstrated little or no reversible inhibition of UGT-catalyzed activities for all UGTs evaluated

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Results – *in vitro* Studies

***In vitro* DDI**

- ***Inhibition of Efflux Transporters***
  - The IC_{50} of ertugliflozin-mediated inhibition of P-gp or BCRP was estimated to be 176 µM and ~100 µM, respectively (K_i of 176 µM and ~100 µM, respectively)
  - M5c and M5a demonstrated little to no inhibition of P-gp or BCRP at concentrations up to 100 µM
- ***Inhibition of Hepatic Uptake Transporters***
  - Ertugliflozin inhibited the OATP1B1-, OATP1B3-, and OCT1-mediated transport of the respective probe substrate, with IC_{50} values of 35.4, 141, and 53 µM, respectively (K_i of 17.7, 141, and 53 µM, respectively)
  - M5c inhibited OATP1B1-mediated uptake of rosuvastatin, with a corresponding IC_{50} of 59.3 µM (Ki = 29.7 µM)
  - M5c and M5a did not inhibit OATP1B3, and M5a demonstrated little to no inhibition of OATP1B1-mediated uptake of rosuvastatin at concentrations up to 100 µM
- ***Inhibition of Renal Uptake Transporters***
  - Ertugliflozin did not inhibit OAT1 at the highest concentration evaluated (250 µM)
  - Ertugliflozin was a weak inhibitor of OAT3- and OCT2-mediated transport, with estimated IC_{50} of 70 µM (K_i of 70 µM) for OAT3 and 917 µM (K_i of 917 µM) for OCT2
  - M5c and M5a had little to no inhibition of OAT1-, OAT3-, or OCT2-mediated uptake of the respective probe substrate at concentrations up to 100 µM
- ***Transporter Substrate Potential - Hepatic Uptake Transporters***
  - Hepatic uptake transporters OATP1B1, OATP1B3, and OATP2B1 do not contribute significantly in facilitating the entry of ertugliflozin into hepatocytes
  - Ertugliflozin was not a substrate for OCT1
- ***Transporter Substrate Potential - Renal Uptake Transporters***
  - Ertugliflozin was not a substrate for human OAT1, OAT3, and OCT2

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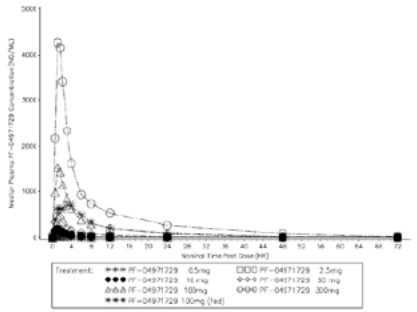
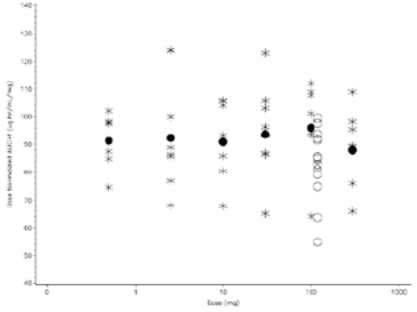
Phase 1 Safety, Tolerability of SAD Study and Food-Effect

Median Plasma Ertugliflozin Concentration-Time Plot

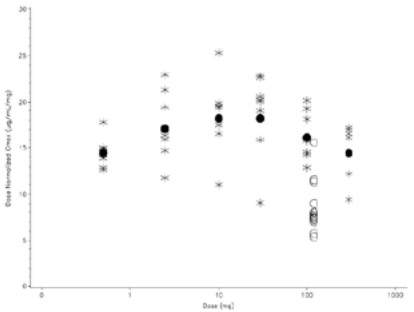


Individual and Mean Dose-Normalized Ertugliflozin AUC_{inf} by Treatment

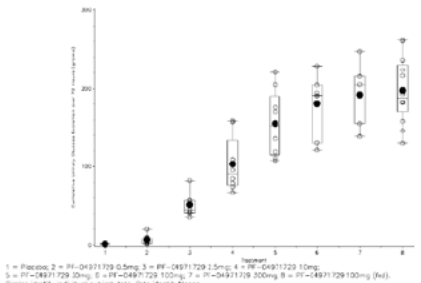


Phase 1 Safety, Tolerability of SAD Study and Food-Effect

Individual and Mean Dose-Normalized Ertugliflozin C_{max} by Treatment



Box and Whisker Plot of Urinary Glucose Excretion over 0-72 hours



Summary of Plasma and Urine PF-04971729 PK Parameter Values Following Single Oral Doses

Parameter, Units	Parameter Summary Statistics[a] by PF-04971729 Dose						
	0.5 mg Cohort 1	2.5 mg Cohort 2	10 mg Cohort 1	30 mg Cohort 2	100 mg Cohort 1	300 mg Cohort 2	100 mg Fed Cohort 1
N[b]	8	8	8	8	8	7	12
AUC_{inf}, ng*hr/mL	45.7 (10)	231 (22)	909 (15)	2810 (18)	9610 (16)	26400 (16)	8230 (16)
C_{max}, ng/mL	7.25 (11)	42.8 (21)	182 (22)	343 (24)	1620 (16)	4330 (29)	824 (15)
T_{max}, hr	1.0 (0.5-1.5)	1.0 (0.5-1.1)	1.0 (0.5-1.5)	1.0 (0.5-1.5)	1.0 (0.5-1.5)	1.0 (0.5-1.5)	3.5 (0.5-6.0)
$t_{½}$, hr	11.4 (19)	13.1 (24)	17.4 (42)	15.2 (33)	16.2 (36)	13.8 (13)	15.8 (21)
Ae_{72},	0.879 (29)	1.08 (43)	0.888 (17)	1.10 (46)	0.964 (20)	1.15 (17)	0.977 (26)

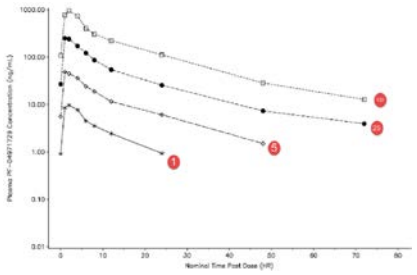
Abbreviations: PK = pharmacokinetic, CV = coefficient of variation

[a] Geometric mean (CV%) for all except median (range) for T_{max} and arithmetic mean (CV%) for $t_{½}$

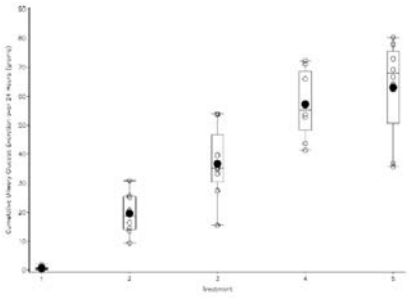
[b] N = number of subjects evaluated against criteria

Phase 1 Safety, Tolerability of MAD Study

Median Plasma Ertugliflozin Concentration-Time Plot



Cumulative UGE (g) Over 0-24 Hours, Days 1 and 14

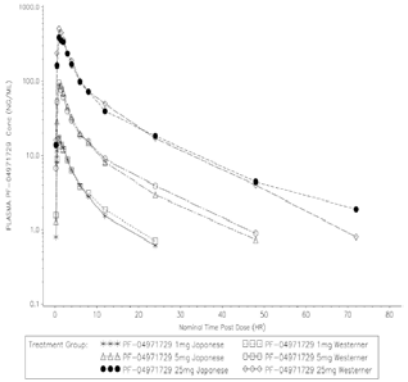


Day 14

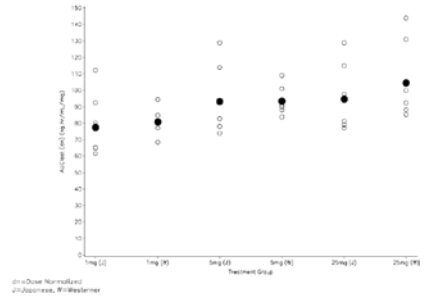
1 Placebo; 2 1 mg; 3 5 mg; 4 25 mg; 5 100 mg

Intrinsic Factors: Ethnicity

Median Plasma Ertugliflozin Concentration-Time Profiles in Japanese and Western Healthy Subjects Following Single Oral Doses



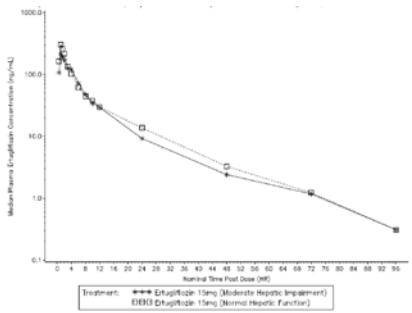
Relationship Between Ertugliflozin Dose-Normalized $AUCl_{ast}$ Values and Dose by Population



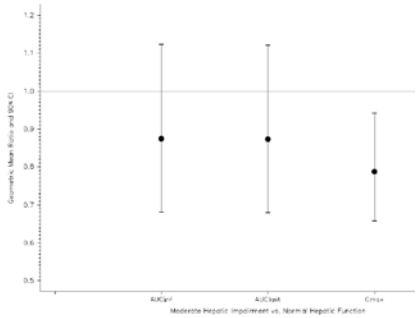
There were no meaningful ethnic differences in Ertugliflozin exposure (C_{max} and AUC_{last}) and Ertugliflozin - induced UGE between Japanese and Western healthy subjects

Intrinsic Factors: Hepatic Impairment

Median Plasma Ertugliflozin Concentration-Time Profiles by Hepatic Function Group Following Single Oral Doses of Ertugliflozin 15 mg



GMR and 90% CI for Ertugliflozin AUCinf, AUClast, and Cmax (Moderate Hepatic Impairment versus Normal Hepatic Function)



Moderate hepatic impairment did not result in an increase in the exposure of ertugliflozin. The slight decrease in C_{max} and AUC observed in subjects with moderate hepatic impairment compared to subjects with normal hepatic function is not anticipated to be clinically relevant

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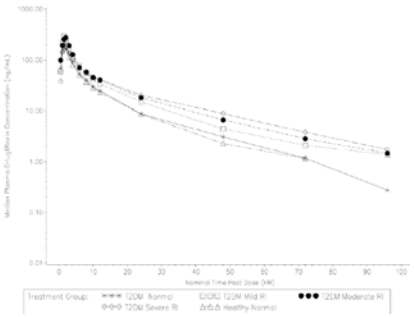
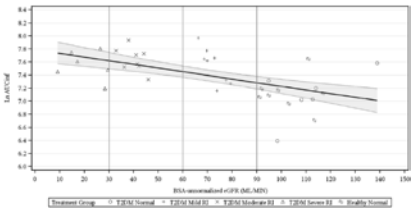
Intrinsic Factors: Renal Impairment

Median Plasma Ertugliflozin Concentration-Time Profiles Following a Single 15-mg Oral Dose by Renal Function Group



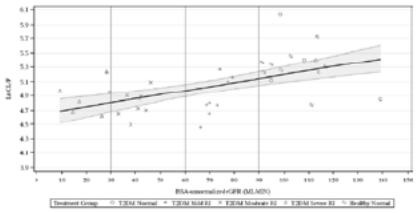
Regression and 90% CI of Ln AUCinf After Oral Administration of Ertugliflozin Versus BSA-unnormalized eGFR in Subjects with Varying Degrees of Renal Function



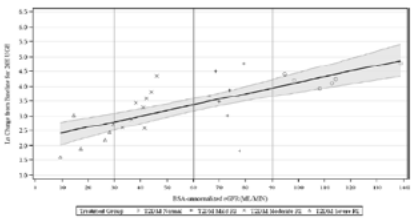
16

Intrinsic Factors: Renal Impairment

Regression and 90% CI of Ln CL/F After Oral Administration of Ertugliflozin Versus BSA-unnormalized eGFR in Subjects with Varying Degrees of Renal Function



Ln Change from Baseline in 24-Hour UGE Versus BSA-Unnormalized eGFR



- **Ertugliflozin pharmacokinetics were similar between healthy and T2DM subjects with normal renal function.**
- **Systemic exposure (AUC_{Inf}) of ertugliflozin was higher in subjects with mild, moderate and severe renal impairment. The mean increases in exposures were less than 2-fold and are not anticipated to be clinically meaningful**
- **The change from baseline in 24-hour UGE on Day 1 for T2DM subjects with mild, moderate and severe renal impairment decreased with decline in renal function compared to T2DM subjects with normal renal function**

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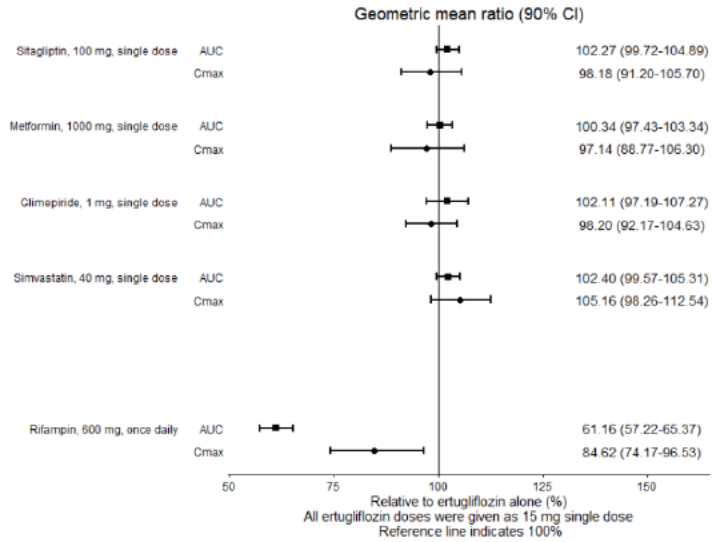
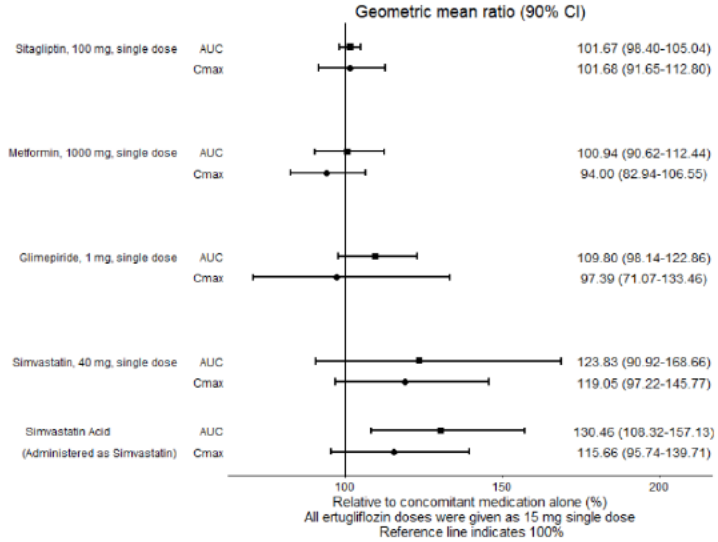
DDI - Effects of Commonly Co-administered Drugs on the PK of Ertugliflozin



18

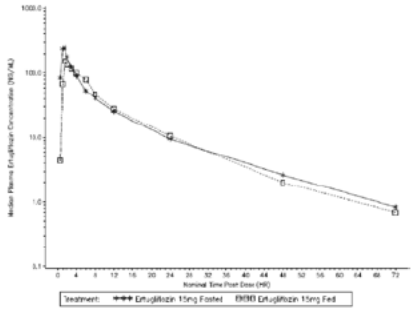
DDI - Effects of Ertugliflozin on the PK of Commonly Co-administered Drugs



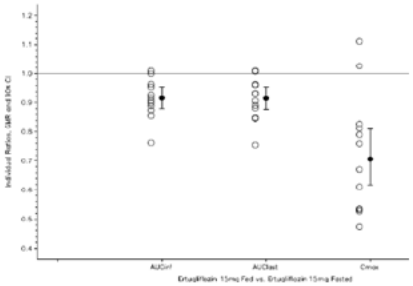
19

Food-Effect (Commercial Image Tablet)

Median Plasma Ertugliflozin Concentration-Time Profiles Following Single Oral Doses



Individual Ratios, Geometric Mean Ratio and 90% CI for Ertugliflozin AUC_{inf}, AUC_{last} and C_{max}



Food delayed median T_{max} by 1 hour and reduced mean C_{max} by approximately 29% compared to fasted conditions. The decrease in ertugliflozin C_{max} with food is not anticipated to be clinically relevant. Ertugliflozin may be administered without regard to meals

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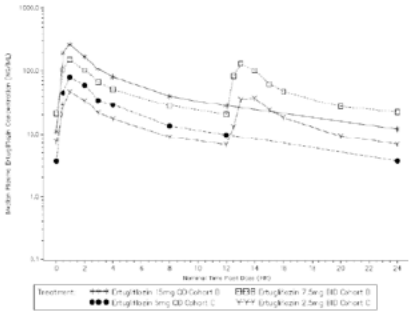
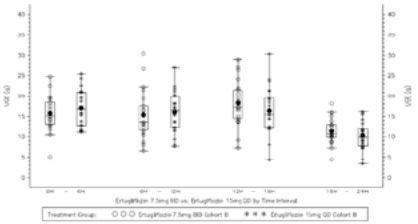
Steady-State PK/PD: 5 mg and 15 mg qd *versus* 2.5 mg and 7.5 mg bid

Median Plasma Ertugliflozin Concentration-Time Profiles on Day 6 Following Multiple QD or BID Oral Doses



Individual and Arithmetic Mean UGE (g) vs. Time Intervals for Ertugliflozin 15 mg qd and 7.5 mg bid



- **Ertugliflozin steady state exposure was equivalent when administered as 2.5 mg BID vs. 5 mg QD and as 7.5 mg BID vs. 15 mg QD**
- **UGE0-24 at steady state was similar when administered as 2.5 mg BID vs. 5 mg QD and as 7.5 mg BID vs. 15 mg QD**

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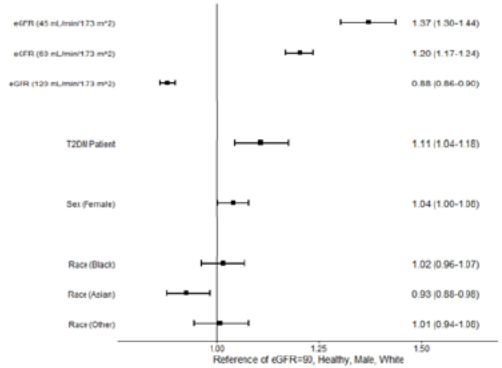
PopPK Analysis

Relative Covariate Effects on Ertugliflozin AUC_{tau} (95% CI)



- **Ertugliflozin pharmacokinetics were adequately characterized by a 2-compartment model with lag time, first-order absorption, and first-order elimination**
- **Apparent clearance was estimated to be 12.0 L/hr for the reference subject: a 65 year-old, healthy, white male with a baseline body weight of 85 kg, an eGFR of 90 mL/min/1.73 m^2, and taking ertugliflozin in the fasted state**
- **Covariates that were determined to be predictive of ertugliflozin CL/F included baseline body weight, baseline eGFR, T2DM status, female sex, and Asian race. Apparent clearance increased with increasing body weight and eGFR. Apparent clearance was slightly lower in T2DM patients (vs healthy subjects) and females, and slightly higher in Asian subjects. These covariate effects are not anticipated to be clinically relevant**

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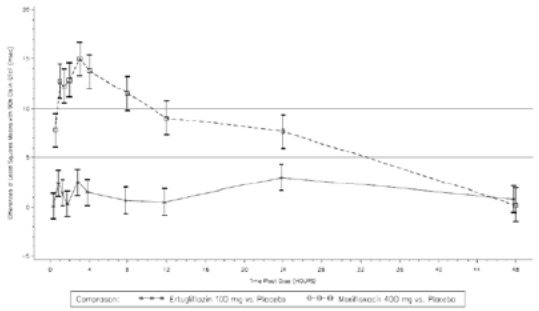
Effect on QT/QTc Interval

Plot of Estimated Mean Differences of QTcF With 90% Confidence Intervals Between Ertugliflozin and Placebo, and Moxifloxacin and Placebo



- **A lack of an effect on QTc interval was demonstrated with a single supratherapeutic oral dose of ertugliflozin 100 mg**
- **The study was adequately sensitive to assess the effect of ertugliflozin on QTc interval, as the lower bound of the 2-sided 90% CIs for the mean difference in QTcF between moxifloxacin (positive control) and placebo was greater than the predefined cutoff of 5 msec at each pre-specified time point (2, 3, or 4 hours) post dose**

Exposure-Response Modeling for Ertugliflozin

Final Model Parameter Estimates for the Reference Subject

Parameter	Estimate (%RSE)	Lower 95% Bound	Upper 95% Bound
$k_{deg,PBO}$ (day^{-1})	0.0113 (11.9)	0.00879	0.0146
$k_{deg,Ertu}$ (day^{-1})	0.0353 (12.4)	0.0269	0.0433
PBO (%)	-0.135 (42.1)	-0.223	-0.00412
E0 (%)	8.19 (0.260)	8.14	8.23
E_{max} (%)	-0.745 (8.81)	-0.899	-0.624
ED_{50} (mg)	1.20 (45.0)	0.0699	2.64
E0 ~ E_{max}	1.47 (28.9)	0.772	2.45
E0 ~ PBO	3.41 (8.84)	2.82	3.93
eGFR ~ E_{max}	0.368 (38.6)	0.104	0.658
Age ~ ED_{50}	3.25 (40.9)	0.648	16.7
WT ~ ED_{50}	0.417 (444)	<1.0	6.37
FDUR ~ E_{max}	-0.0265 (21.2)	-0.0373	-0.0161
Other ~ E_{max}	0.729 (16.9)	0.511	0.999
Diet ~ E_{max}	0.882 (7.37)	0.750	1.01
ω^2_{PBO}	0.545 (11.5)	0.434	0.705
ω^2_{E0}	0.013 (3.34)	0.012	0.014
σ^2	0.115 (4.03)	0.106	0.124

Predicted Mean Ertugliflozin Change from Baseline and Placebo-Adjusted Change from Baseline A1C Response [95% Confidence Intervals] for the Representative Patient at Week 26

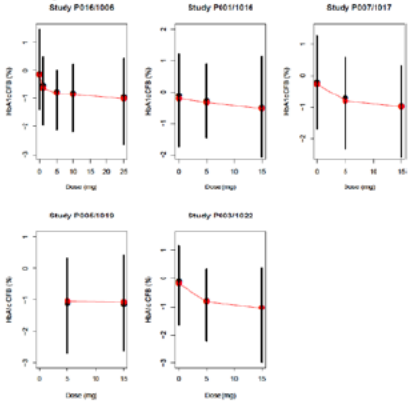
Response	Mean CFB [95% CI]	Mean Placebo-Adjusted CFB [95% CI]
Placebo Response (%)	-0.113 [-0.201, -0.00398]	...
5 mg Response (%)	-0.788 [-0.855, -0.723]	-0.674 [-0.805, -0.565]
15 mg Response (%)	-0.849 [-0.905, -0.794]	-0.735 [-0.869, -0.626]
5/15 mg Difference (%)	-0.0611 [-0.134, -0.000960]	-0.0611 [-0.134, -0.000960]
5 mg Response, Effect of Rifampin (%)	-0.739 [-0.846, -0.633]	-0.625 [-0.783, -0.482]
15 mg Response, Effect of Rifampin (%)	-0.826 [-0.875, -0.772]	-0.713 [-0.841, -0.604]

Exposure-Response Modeling for Ertugliflozin

Predicted Effect of Renal Function on Mean Ertugliflozin Placebo-Adjusted Change from Baseline A1C Response at Week 26

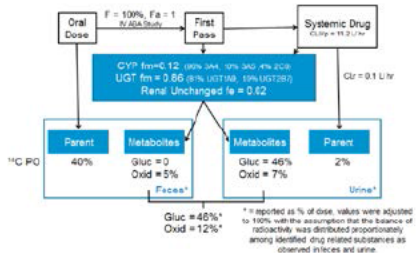
Group	Estimate	Lower 95% Bound	Upper 95% Bound
5 mg Normal Renal Function: eGFR of 105 mL/min/1.73 m^2, baseline A1C 8.34%, diabetes duration 6.51 years (%)	-0.725	-0.902	-0.559
15 mg Normal Renal Function: eGFR of 105 mL/min/1.73 m^2, baseline A1C 8.34%, diabetes duration 6.51 years (%)	-0.820	-0.985	-0.693
5 mg Mild Renal Impairment: eGFR of 75 mL/min/1.73 m^2, baseline A1C 8.19%, diabetes duration 7.03 years (%)	-0.614	-0.797	-0.482
15 mg Mild Renal Impairment: eGFR of 75 mL/min/1.73 m^2, baseline A1C 8.19%, diabetes duration 7.03 years (%)	-0.695	-0.839	-0.577

Observed and Final Model-Predicted Mean A1C Response versus Ertugliflozin Dose by Study at Week 26

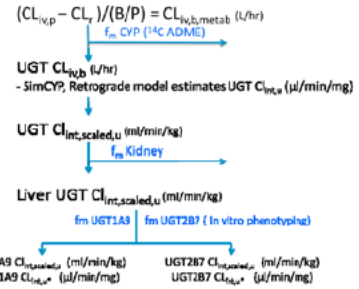


PBPK Modeling to Estimate UGT-mediated DDI for Ertugliflozin

Ertugliflozin Metabolism and Disposition

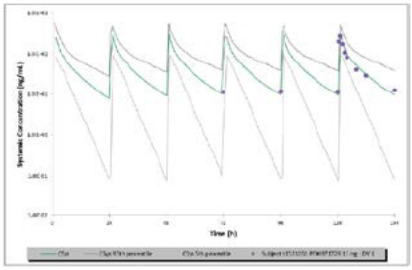


Dapagliflozin and Ertugliflozin Elimination Model Development Strategy

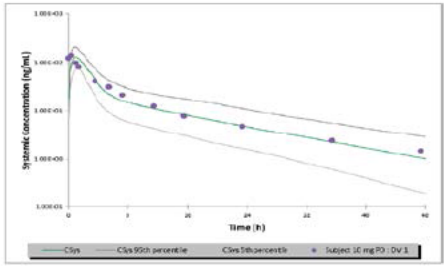


PBPK Modeling to Estimate UGT-mediated DDI for Ertugliflozin

Simcyp® Predicted vs Observed Ertugliflozin Plasma Concentration vs Time Profile Following Multiple 15 mg Oral Doses



Simcyp® Predicted vs Observed Dapagliflozin Plasma Concentration vs Time Profile Following a Single 10 mg Oral Dose



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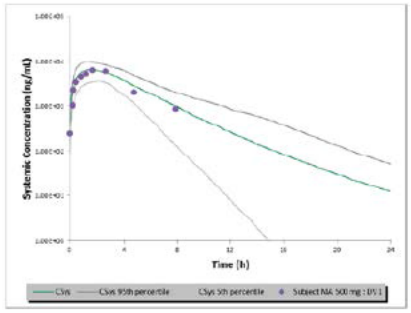
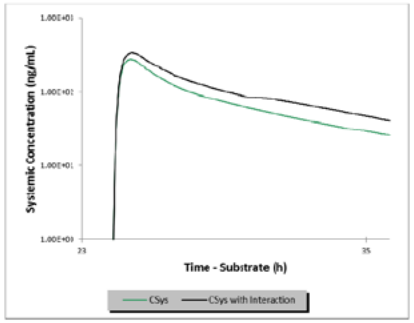
PBPK Modeling to Estimate UGT-mediated DDI for Ertugliflozin

Simcyp® Predicted vs Observed Mefenamic Acid Plasma Concentration vs Time Profile Following a Single 500 mg Oral Dose



Simcyp® Predicted Ertugliflozin Plasma Concentration vs Time Profile With or Without Coadministration of Mefenamic Acid



- **The modeling and simulation results indicated that the expected drug interaction between ertugliflozin and mefenamic acid would be less than 2-fold and similar to that between dapagliflozin and mefenamic acid**
- **The application of PBPK modeling would support a waiver for the conduct of a clinical DDI study with ertugliflozin and a UGT inhibitor**

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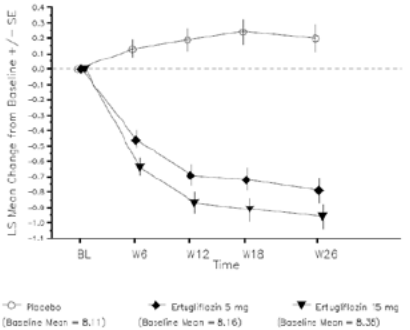
Phase 3 Program

Study	Randomized Population	N	Study Design	Treatment Groups and Number of Subjects Randomized	Treatment Duration
Monotherapy					
P003/1122 Monotherapy	Adult subjects ≥18 years of age with T2DM and inadequate glycemic control (A1C 7.0% to 10.5%, inclusive) on diet and exercise	461	Multicenter, randomized (1:1:1), double-blind, placebo-controlled	Placebo (n=153) Ertugliflozin 15 mg (n=152) Ertugliflozin 5 mg (n=156) Subjects receiving placebo who did not receive glycemic rescue therapy in Phase A were switched to metformin in Phase B	52 weeks Phase A: 26 weeks Phase B: 26 weeks
Add-on to metformin					
P007/1117 Placebo-controlled add-on to metformin	Adult subjects ≥18 years of age with T2DM and inadequate glycemic control (A1C 7.0% to 10.5%, inclusive) on background of metformin	821	Multicenter, randomized (1:1:1), double-blind, placebo-controlled	Placebo (n=208) Ertugliflozin 15 mg (n=205) Ertugliflozin 5 mg (n=207) Subjects receiving placebo who did not receive glycemic rescue therapy in Phase A were switched to glimepiride in Phase B	104 weeks Phase A: 26 weeks Phase B: 78 weeks
P002/1103 Ertugliflozin vs glimepiride as add-on to metformin	Adult subjects ≥18 years of age with T2DM and inadequate glycemic control (A1C 7.0% to 9.0%, inclusive) on background of metformin	1326	Multicenter, randomized (1:1:1), double-blind, active-controlled	Glimepiride up to 8 mg (n=437) Ertugliflozin 15 mg (n=441) Ertugliflozin 5 mg (n=448)	104 weeks Phase A: 52 weeks Phase B: 52 weeks
P005/1109 Ertugliflozin plus sitagliptin factorial	Adult subjects ≥18 years of age with T2DM and inadequate glycemic control (A1C 7.5% to 11.0%, inclusive) on background of metformin	1233	Multicenter, randomized (1:1:1:1:1), double-blind, factorial	Sitagliptin 100 mg (n=247) Ertugliflozin 15 mg (n=248) Ertugliflozin 5 mg (n=250) Ertugliflozin 15 mg/sitagliptin 100 mg (n=245) Ertugliflozin 5 mg/sitagliptin 100 mg (n=243)	52 Weeks Phase A: 26 weeks Phase B: 26 weeks
Add-on to metformin plus sitagliptin					
P009/1113 Add-on to metformin plus sitagliptin	Adult subjects ≥18 years of age with T2DM and inadequate glycemic control (A1C 7.0% to 10.5%, inclusive) on background of metformin and sitagliptin	463	Multicenter, randomized (1:1:1), double-blind, placebo-controlled	Placebo (n=232) Ertugliflozin 15 mg (n=154) Ertugliflozin 5 mg (n=156)	52 Weeks Phase A: 26 weeks Phase B: 26 weeks
Co-administration with sitagliptin in subjects on diet and exercise alone					
P017/1047 Ertugliflozin plus sitagliptin initial combination	Adult subjects ≥18 years with T2DM and inadequate glycemic control (A1C 5.0% to 10.5%, inclusive) on diet and exercise	291	Multicenter, randomized (1:1:1), double-blind, placebo-controlled	Placebo (n=97) Ertugliflozin 15 mg/sitagliptin 100 mg (n=96) Ertugliflozin 5 mg/sitagliptin 100 mg (n=98)	26 weeks
Studies in special populations					
P001/1016 Moderate renal impairment	Adult subjects ≥25 years of age with T2DM, Stage 3 chronic kidney disease, and inadequate glycemic control (A1C 7.0% to 10.5%, inclusive) on treatment with standard diabetes therapy(-ies)	468[1]	Multicenter, randomized (1:1:1), double-blind, placebo-controlled	Placebo (n=154) Ertugliflozin 15 mg (n=156) Ertugliflozin 5 mg (n=158)	52 Weeks Phase A: 26 weeks Phase B: 26 weeks
Phase 3 study not included in SCE					
P004/1021 CV outcomes[2]	Adults subjects ≥40 years of age with T2DM and inadequate glycemic control (A1C 7.0% to 10.5%, inclusive) on background standard of care and with established vascular disease involving the coronary, cerebral and/or peripheral vascular systems	8000[3]	Multicenter, randomized (1:1:1), double-blind, placebo-controlled	Placebo (n=2666[3]) Ertugliflozin 5 mg (n=2667[3]) Ertugliflozin 15 mg (n=2667[3])	Event driven, approximately 5 to 6 years

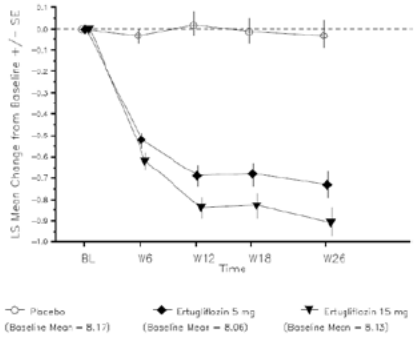
[1] Randomization was stratified by eGFR ≥45 to <60 mL/min/1.73 m² (Stage 3A chronic kidney disease; 309 subjects) and eGFR ≥30 to <45 mL/min/1.73 m² (Stage 3B chronic kidney disease; 159 subjects).
[2] The study is ongoing with the final results expected in the post-approval period. Therefore, the efficacy data for this study and for the subsets are not part of the SCE. Three glycemic efficacy substudies are part of this study: addon to SU monotherapy, add-on to metformin with SU, and add-on to insulin with or without metformin.
[3] Approximate number of subjects planned to be randomized.
Abbreviations: A1C=glycosylated hemoglobin A_{1c}; CV=cardiovascular; eGFR=estimated glomerular filtration rate; n=number of subjects randomly assigned to study medication; N=overall number of subjects randomly assigned to study medication; SCE=Summary of Clinical Efficacy; SU=sulfonylurea; T2DM=type 2 diabetes mellitus

Phase 3 Results: A1C (%): LS Mean Change from Baseline Over Time

Study P003: 52-Week Monotherapy in T2DM

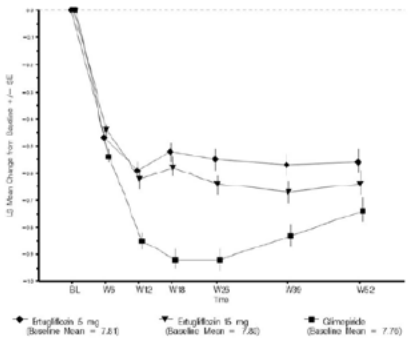


Study P007: Placebo-Controlled Add-On to Metformin Study

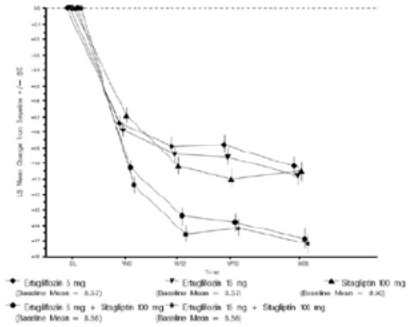


Phase 3 Results: A1C (%): LS Mean Change from Baseline Over Time

Study P002: Ertugliflozin vs Glimepiride as Add-On to Metformin Study



Study P005: Ertugliflozin Plus Sitagliptin Factorial Study



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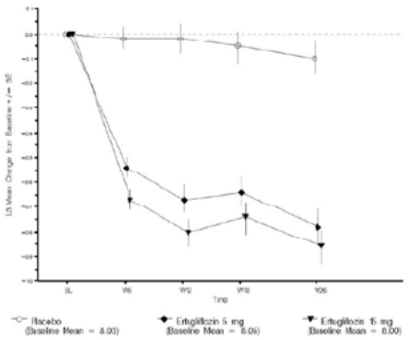
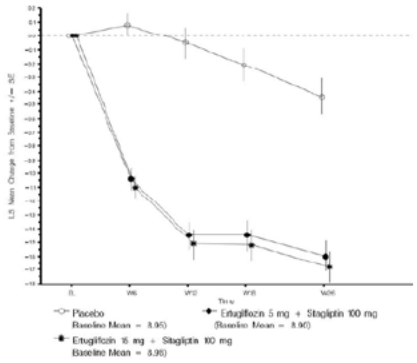
Phase 3 Results: A1C (%): LS Mean Change from Baseline Over Time

Study P006: Add-On to Metformin Plus Sitagliptin Study



Study P017: Ertugliflozin Plus Sitagliptin Initial Combination Study



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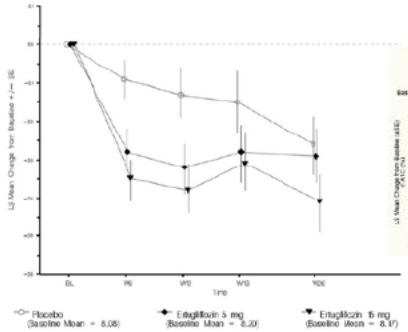
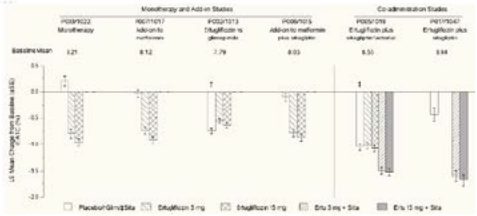
Phase 3 Results: A1C (%): LS Mean Change from Baseline Over Time

Study P001: Moderate Renal Impairment Study

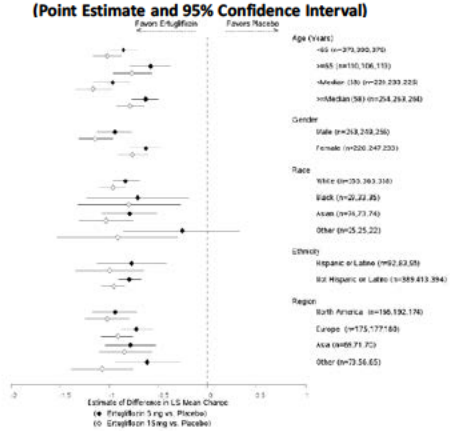


A1C (%): Change from Baseline at Primary imepoint by Study



Phase 3 Results: A1C (%): LS Mean Change from Baseline Over Time

A1C (%): Forest Plot of Change from Baseline at Week 26 for All Subgroups (Point Estimate and 95% Confidence Interval)



(n = n1,n2,n3): n1 = number of subjects in the placebo group,
n2 = number of subjects in the Ertugliflozin 5 mg group,
n3 = number of subjects in the Ertugliflozin 15 mg group.

Review Deliverables

- Confirm PK/PD Results
- Dose Selection
- Exposure Response
- Pop PK
- PBPK for DDI

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/s/

SURYANARAYANA M SISTA
02/06/2017

MANOJ KHURANA
02/06/2017