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Pharmacokinetic Properties of Single and Multiple Doses of Ertugliflozin, a Selective Inhibitor of SGLT2, in Healthy Chinese Subjects

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Abstract

Ertugliflozin, a sodium-glucose cotransporter 2 inhibitor for the treatment of type 2 diabetes mellitus, prevents renal glucose reabsorption resulting in urinary glucose excretion. This open-label, parallel cohort, randomized study conducted in healthy Chinese adults residing in China assessed the pharmacokinetics, tolerability, and safety of 5 mg and 15 mg of ertugliflozin following single (fasted condition) and multiple-dose (fed condition) administration. Sixteen subjects were randomized and completed the study. Ertugliflozin absorption was rapid, with maximum plasma concentrations observed 1 hour after dosing under fasted conditions and 2 to 4 hours after dosing under fed conditions. Following single- and multiple-dose administration, ertugliflozin exhibited dose-proportional exposures with an apparent mean terminal half-life of approximately 9.5 to 11.9 hours. Steady state was reached after 4 once-daily doses. The accumulation ratio based on the area under the plasma concentration–time curve after multiple-dose administration was approximately 1.3 and 1.2 for ertugliflozin 5 mg and 15 mg, respectively. Ertugliflozin was generally well tolerated following administration of single and multiple oral doses of 5 mg and 15 mg in healthy Chinese subjects. Pharmacokinetic comparison with non-Asian subjects indicated that there are no clinically meaningful racial differences and no dose modification of ertugliflozin is required based on race or body weight.

Keywords

ertugliflozin, pharmacokinetics

Diabetes mellitus (DM) is a highly prevalent disease, and the number of affected individuals is increasing each year. Following current trends, DM could affect 693 million adults worldwide by the year 2045.[1] China has the highest number of adults with DM (114.4 million) in the world, with type 2 diabetes (T2DM) accounting for >90% of these cases, and the prevalence is projected to increase to 119.8 million (~10% of the Chinese population) by 2045.[2] T2DM carries a significant global health and economic burden, including an increased risk of microvascular (eg, neuropathy, retinopathy) and macrovascular disease (eg, coronary artery disease, peripheral arterial disease, and stroke).[2] China had 842,993 deaths due to DM in 2017, and one third of these occurred in people under 60 years of age.[1] In a Report on the Status of Nutrition and Chronic Diseases of Chinese Residents in 2015, the rise in prevalence of T2DM was linked with changes in social and economic factors, diet, behavior, and lifestyle.[3] There has been a shift in the traditional Chinese diet of a high consumption of rice, pork, and vegetables to a reduced intake of rice and vegetables and an increased intake of fat and carbohydrates, linked to greater risk of obesity,[3] which in turn is linked to an increased

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risk of T2DM. Along with lifestyle management, new pharmacologic treatments to manage T2DM in China and reduce the associated risks of micro- and macrovascular disease are therefore needed.

Currently, metformin (a biguanide oral antihyperglycemic agent targeted to lower blood glucose by reducing hepatic glucose output and improving peripheral insulin resistance) is recommended as the basis of monotherapy or combined therapy for T2DM in China.[4] This is in line with most worldwide treatment guidelines for T2DM. In combination with lifestyle intervention, there are many oral or injectable antihyperglycemic agents available as add-ons to metformin, providing dual, triple, or multiple therapies to improve glycemic control. Ertugliflozin is a selective sodium-glucose cotransporter 2 (SGLT2) inhibitor[5,6] recently approved in the United States, the European Union, and other regions including Canada and Australia, for the treatment of adult patients with T2DM. By inhibiting SGLT2, ertugliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion. Recent phase 3 trials have demonstrated that ertugliflozin alone or when used in combination with metformin or metformin and sitagliptin is associated with statistically significant reductions in hemoglobin A_{1c}, fasting plasma glucose, body weight, and blood pressure.[7–14]

Ertugliflozin is rapidly absorbed following oral administration, with maximal plasma concentration (C_{max}) occurring after approximately 1 hour when administered in the fasted state.[6,15–19] The absolute bioavailability of ertugliflozin is approximately 100%[15]; its exposure increases in a dose-proportional manner over a dose range of 0.5 to 300 mg[5,6]; and administration with food does not have a clinically meaningful effect on pharmacokinetics (PK).[19] The terminal elimination half-life ($t_{½}$) of ertugliflozin ranges from 11 to 17 hours.[5,6,15–22] The PK of ertugliflozin are similar in healthy subjects and in patients with T2DM.[20]

The major clearance pathway of ertugliflozin is metabolism via glucuronidation (86%) with minor contribution from oxidative metabolism (12%). Urinary excretion of unchanged drug accounts for 1.5% of the administered dose.[22] The primary uridine diphosphate-glucuronosyltransferase (UGT) enzymes involved in the glucuronidation of ertugliflozin to the pharmacologically inactive metabolites are UGT1A9 and UGT2B7, respectively.[5] Cytochrome P450 (CYP) 3A4 is the predominant enzyme involved in the relatively minor oxidative metabolism of ertugliflozin, with contributions from CYP2C8 and CYP3A5. In vitro, ertugliflozin is highly bound to plasma proteins (93.6%). A phase 1 study in subjects with mild, moderate, and severe renal impairment showed that, based on PK, no dose adjustments of ertugliflozin are necessary in patients with renal impairment.[20] PK results from a phase 1 study in healthy subjects and those with moderate hepatic impairment also showed that no dose adjustments of ertugliflozin are necessary in patients with mild or moderate hepatic impairment.[21]

Given the increasing incidence of T2DM in China, and the regulatory requirement from the National Medical Product Administration (NMPA) for a new drug approval in China, it is important to characterize the PK profile of ertugliflozin in the Chinese population. The primary objective of this study was to investigate the single- and multiple-dose PK of ertugliflozin 5 mg and 15 mg in healthy Chinese adults. The secondary objective was to investigate the tolerability and safety. The ertugliflozin doses of 5 mg and 15 mg assessed in this study are the clinical doses evaluated in the global phase 3 studies of ertugliflozin[7–14] and now approved for use in the United States, European Union, and other regions. The results of this study will support the NMPA regulatory filing requirements for the approval of ertugliflozin for treatment of T2DM in China.

Methods

Study Design

An open-label, parallel-cohort, randomized, single- and multiple- dose phase 1 study was conducted in healthy male and female Chinese adults to evaluate the PK profile, tolerability, and safety of ertugliflozin 5 mg and 15 mg. A sample size of 16 subjects (8 in each cohort) with equal numbers of males and females was planned based on the NMPA requirement for a China PK study.[23] Subjects were randomized, in blocks for sex, to receive 5 mg or 15 mg (provided as one 5-mg tablet and one 10-mg tablet) of oral ertugliflozin once daily in single (in 1 day) and multiple (6 days) doses. The study sponsor provided a randomization schedule to the investigator and, in accordance with the randomization numbers, the subject received the study medication regimen assigned to the corresponding randomization number. Eligible subjects were admitted to the study center on day 0. Each subject received a single dose (5 mg or 15 mg) under fasted conditions (at least 10 hours) on day 1 and then 6 doses (5 mg or 15 mg) over consecutive days under fed conditions (immediately after breakfast) on days 6 to 11 (multiple doses). Subjects remained at the study center until the last PK sample was collected (day 14). Screening evaluation took place within 28 days of day 1 dosing. Safety laboratory tests (chemistry, hematology, and urinalysis) were conducted at screening, day 0, and at discharge.

The study was conducted in compliance with the ethical principles of the Declaration of Helsinki and in compliance with all International Conference on Harmonisation Good Clinical Practice guidelines. The

study was approved and reviewed by the Ethics Committee of the study site, 307 Hospital of People's Liberation Army. All subjects provided written informed consent before their participation in the study.

Subjects

Healthy Chinese men and women (residing in mainland China who were born in China and had both parents of Chinese descent), aged 18 to 45 years inclusive, with a body mass index of 19 to 24 kg/m^2 (according to the rounding algorithm of the equipment used at the study site to measure height and weight) and total body weight >50 kg were eligible to take part in the study. Healthy subjects were defined as having no clinically relevant abnormalities as identified by a detailed medical history, full physical examination including blood pressure and pulse rate measurement, 12-lead electrocardiogram (ECG), and clinical laboratory tests. Female subjects of childbearing potential agreed to take suitable precaution (abstinence from sexual activity or use of 2 methods of specified contraception) to prevent pregnancy during and up to 14 days after the last dose of study medication.

Subjects with the following were not eligible to participate: evidence or history of clinically significant hematologic, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including drug allergies but excluding untreated, asymptomatic, seasonal allergies at time of dosing); history of alcohol abuse or binge drinking; use of prescription or nonprescription drugs (hormonal contraception in the form of oral, subcutaneous, intrauterine, and intramuscular agents, and cutaneous patch contraception was allowed); positive urine screen for drugs of abuse or recreation and/or any other illicit drug use or dependence within 6 months of screening; clinically significant malabsorption condition; an estimated glomerular filtration rate of <90 mL/min/1.73 m^2; and known hypersensitivity or intolerance to any SGLT2 inhibitor. Females who were pregnant or breastfeeding, males/females who had given a blood donation of ≥500 mL within 56 days prior to dosing, and individuals who had used tobacco or nicotine-containing products (≥5 cigarettes a day) or used vitamins/dietary supplements within 7 days or herbal supplements/teas within 28 days prior to study were also excluded. Subjects with elevated blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic) or 12-lead ECG demonstrating QT interval corrected for heart rate >450 milliseconds at screening were to have repeat assessments to determine eligibility.

Assessments

Blood samples (4 mL) were collected to provide a minimum of 1.5 mL of plasma for determination of ertugliflozin concentrations. For the single dose on day 1, blood samples were collected before dosing and then at 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 hours after dosing. For assessment of multiple-dose PK, blood samples were collected on day 6 before dosing and then at 0.5, 1, 2, 4, 6, 8, 12, and 24 hours after dosing; days 9 and 10 before dosing; and day 11 before dosing and then at 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 hours after dosing. To standardize the conditions on days of dense PK sampling (days 1, 6, and 11), all subjects were required to refrain from lying down (except when required for blood pressure, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

Plasma samples were analyzed for ertugliflozin concentrations using a validated high-performance liquid chromatography–tandem mass spectrometric method.[16] The following PK parameters were calculated for each participant for each treatment using noncompartmental analysis of plasma concentration–time data using a validated in-house software system (eNCA, version 2.2.4): C_{max}; time to C_{max} (T_{max}); area under curve (AUC) from time 0 to the time of the last quantifiable concentration (AUC_{last}); AUC from time zero extrapolated to infinite time (AUC_{inf}); AUC from time 0 to time tau (the dosing interval) at steady state, where tau = 24 hours ($AUC_{tau,ss}$), apparent oral clearance (CL/F, determined by dose/AUC_{inf} for single dose and dose/$AUC_{tau,ss}$ for multiple doses), $t_{½}$, and observed accumulation ratio (R_{ac}, determined by day 11 $AUC_{tau,ss}$/day 6 AUC from time 0 to 24 hours after dosing [AUC_{24}]).

Safety

The safety and tolerability of ertugliflozin were assessed via adverse event (AE) monitoring, 12-lead ECGs, physical examination, blood pressure and pulse rate, and measurement of clinical laboratory parameters, which were performed from screening and throughout the duration of study participation. Subjects received a follow-up phone call 14 ± 3 days after administration of the last dose of the multiple-dose study medication to assess for AEs. AEs were coded using the Medical Dictionary for Regulatory Activities, Version 19.0.

Statistical Analysis

Plasma concentrations below the limit of quantification were set to zero for analysis. PK parameters were summarized by treatment and study day. For mean (standard deviation) plots by sampling time, the nominal PK sampling time was used. Safety data were presented in tabular format and summarized descriptively, where appropriate.

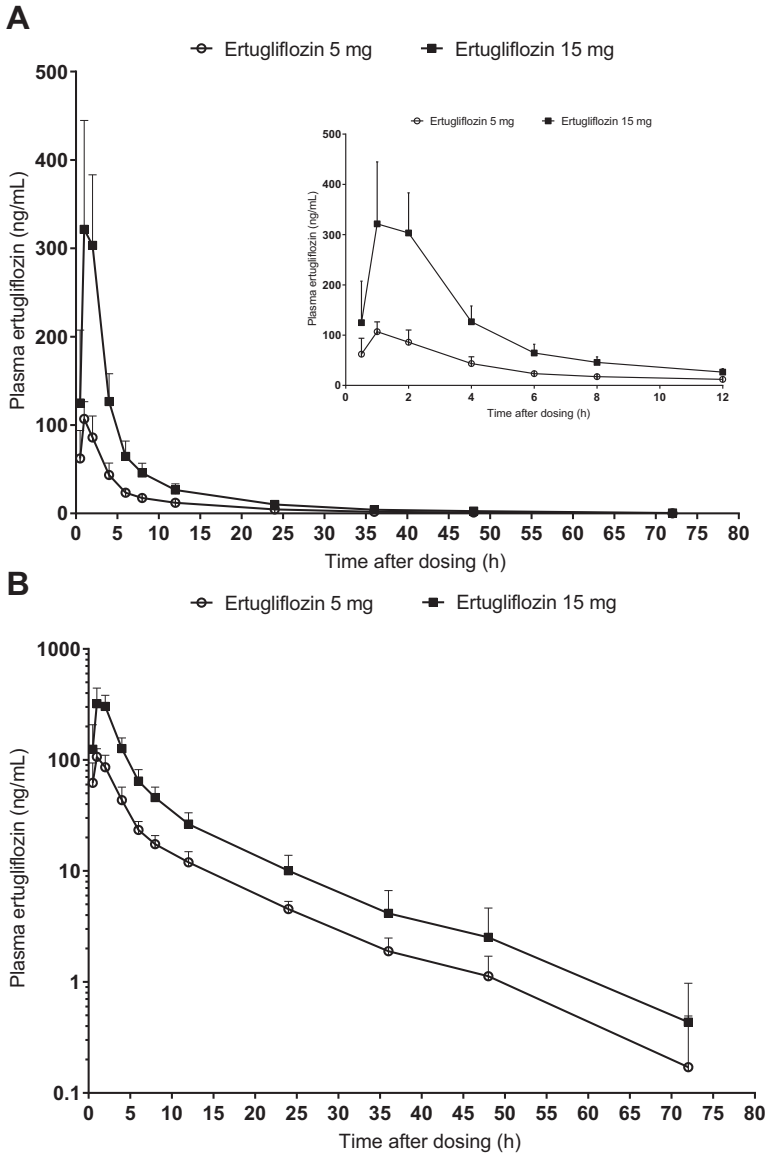

Figure 1. Mean (standard deviation) plasma ertugliflozin concentration–time profiles following a single oral dose of ertugliflozin 5 mg and 15 mg under fasted conditions (day 1) in (A) linear (principal plot) with the 0- to 12-hour interval on an expanded time scale (inset plot) and (B) semilogarithmic scales. h, hour.

Results

Subject Demographics

A total of 16 subjects (8 subjects in each cohort) with equal numbers of males and females were randomized. All subjects completed the study and were included in the analysis. The mean (range) age was 29.1 (22–39) years. The mean (range) body weight and body mass index were 59.6 (50.3–73.2) kg and 22.4 (19.8–24.1) kg/m^2, respectively.

PK Properties

Following a single oral dose of 5 mg or 15 mg ertugliflozin under fasted conditions (day 1), ertugliflozin was rapidly absorbed (Figure 1) with T_{max} occurring at 1-hour post-dose (Table 1). In fed conditions following multiple doses (day 11; Figure 2), median T_{max} was 4 hours and 2 hours after dosing for ertugliflozin 5 mg and 15 mg, respectively; the range for T_{max} was similar for both ertugliflozin 5 mg and 15 mg (Table 1). The apparent $t_{½}$ of ertugliflozin ranged from approximately 9.5 to 11.9 hours following single- and multiple-dose administration and was independent of dose.

Ertugliflozin exposure increased in a dose-proportional manner following single-dose (Figure 3) and multiple-dose administration (Figure 4). Arithmetic mean of R_{ac} was similar for the 2 doses (1.3

Table 1. Descriptive Summary of Plasma Ertugliflozin Pharmacokinetic Parameter Values Following Single (Days 1 and 6) and Multiple Once-Daily (Day 11) Dosing

	Parameter Summary Statistics[a] by Treatment	
	ERTU 5 mg (n = 8)	ERTU 15 mg (n = 8)
Day 1, fasted		
AUC_{inf} (ng·h/mL))	599.3 (15)	1606 (26)
	605.5 ± 94.48	1651 ± 419.6
AUC_{last} (ng·h/mL)	586.8 (15)	1594 (26)
	592.9 ± 92.21	1639 ± 417.3
CL/F (mL/min)	139.2 (15)	155.8 (26)
	140.6 ± 21.02	160.1 ± 39.39
C_{max} (ng/mL)	112.9 (18)	360.8 (24)
	114.5 ± 19.83	369.3 ± 83.92
$t_{½}$ (h)	10.41 ± 2.434	9.521 ± 2.294
T_{max} (h)	1.00 (1.00–2.02)	1.00 (1.00–2.02)
Day 6, fed		
AUC_{24} (ng·h/mL)	453.5 (10)	1263 (18)
	455.3 ± 42.16	1281 ± 235.8
C_{max} (ng/mL)	72.65 (17)	191.4 (26)
	73.55 ± 12.35	196.8 ± 48.63
T_{max} (h)	2.00 (1.98–4.02)	2.01 (1.98–4.02)
Day 11, fed		
$AUC_{tau,ss}$ (ng·h/mL)	586.0 (20)	1542 (22)
	595.6 ± 114.9	1578 ± 380.6
CL/F (mL/min)	142.3 (19)	162.0 (23)
	144.6 ± 28.06	165.4 ± 33.92
C_{max} (ng/mL)	78.48 (26)	236.5 (26)
	80.79 ± 20.64	243.1 ± 60.42
R_{ac}	1.291 (12)	1.225 (10)
	1.299 ± 0.158	1.230 ± 0.123
$t_{½}$ (h)	11.88 ± 3.234	10.60 ± 2.776
T_{max} (h)	4.00 (1.00–4.02)	2.00 (1.00–4.00)

AUC, area under the plasma concentration–time curve; AUC_{24}, AUC from time 0 to 24 hours after dosing; AUC_{inf}, AUC from time 0 extrapolated to infinite time; AUC_{last}, AUC from time 0 to the time of last measurable concentration; $AUC_{tau,ss}$, AUC from time 0 to time tau (the dosing interval) at steady state; CL/F, apparent oral clearance; dose/AUC_{inf} for single dose and dose/$AUC_{tau,ss}$ for multiple doses; C_{max}, maximum observed plasma concentration; ERTU, ertugliflozin; R_{ac}, observed accumulation ratio; SD, standard deviation; $T_{½}$, terminal half-life; T_{max}, time to C_{max}.

[a]Values are geometric mean (geometric %CV) and arithmetic mean ± SD for all except: median (range) for T_{max}, arithmetic mean ± SD for $t_{½}$.

and 1.2 for ertugliflozin 5 mg and 15 mg, respectively). Steady state was reached by day 9 (after 4 once-daily doses) based on similar median trough (predose) concentrations on days 9, 10, 11, and 12 (24 hours after last dose on day 11).

Safety

Treatment-emergent and treatment-related AEs are summarized in Table 2. There were no deaths, serious AEs, or discontinuations of study medication due to AEs. All treatment-emergent AEs were mild in severity and all resolved. The most frequently reported treatment-emergent AEs were glucosuria (ertugliflozin 5 mg: 3; ertugliflozin 15 mg: 4) followed by nausea (ertugliflozin 5 mg: 1; ertugliflozin 15 mg: 2). All other treatment-emergent AEs were reported in no more than 1 subject after receiving either treatment. There were no abnormal laboratory findings or changes in blood pressure or pulse rate of clinical significance.

Discussion

In order to address the increasing disease burden of T2DM in China and worldwide, novel therapeutic strategies are required along with lifestyle management. Phase 3 studies have demonstrated the efficacy and safety of ertugliflozin in patients with T2DM with statistically significant reductions in glycated hemoglobin (HbA_{1c}), fasting plasma glucose, body weight, and blood pressure.[7–14] Given the NMPA regulatory requirement for new drug approval in China, it is important to characterize the PK profile of ertugliflozin in the Chinese population. The objectives of this study were to evaluate the PK, safety, and tolerability of ertugliflozin in healthy Chinese adults.

In a phase 1 study evaluating the PK and pharmacodynamics of single 1-, 5-, and 25-mg doses of ertugliflozin in Japanese and Western subjects, there were no meaningful differences in exposure (C_{max} and AUC) or urinary glucose excretion between Japanese and Western subjects.[24] Urinary glucose excretion was therefore not evaluated in this current study because Japanese and Western subjects showed no meaningful racial difference for urine glucose excretion in these populations.

In Chinese subjects, absorption of ertugliflozin 5 mg and 15 mg was rapid, with a median T_{max} of 1 hour after dosing under fasted conditions and 2 to 4 hours after dosing under fed conditions. Following both single- and multiple-dose administration, exposure of ertugliflozin increased in a dose-proportional manner. Consistent with the $t_{½}$ of 9.5 to 11.9 hours, steady state was reached after 4 once-daily doses, and the R_{ac} was approximately 1.3 and 1.2 for ertugliflozin 5 mg and 15 mg, respectively. This is similar to the accumulation ratio of 1.2 to 1.4 observed in single- and multiple-dose studies of ertugliflozin conducted in the West in healthy subjects.[6] Ertugliflozin AUC_{inf} and C_{max} values following 15-mg dosing in the current study of Chinese subjects are comparable with those in Western subjects (AUC_{inf}: 1113–1636 ng·h/mL; C_{max}: 169–319 ng/mL, in Western subjects) after receiving the same single doses of 15 mg of ertugliflozin.[15,17–21]

A pooled analysis of the current study of Chinese subjects together with 16 other phase 1 studies

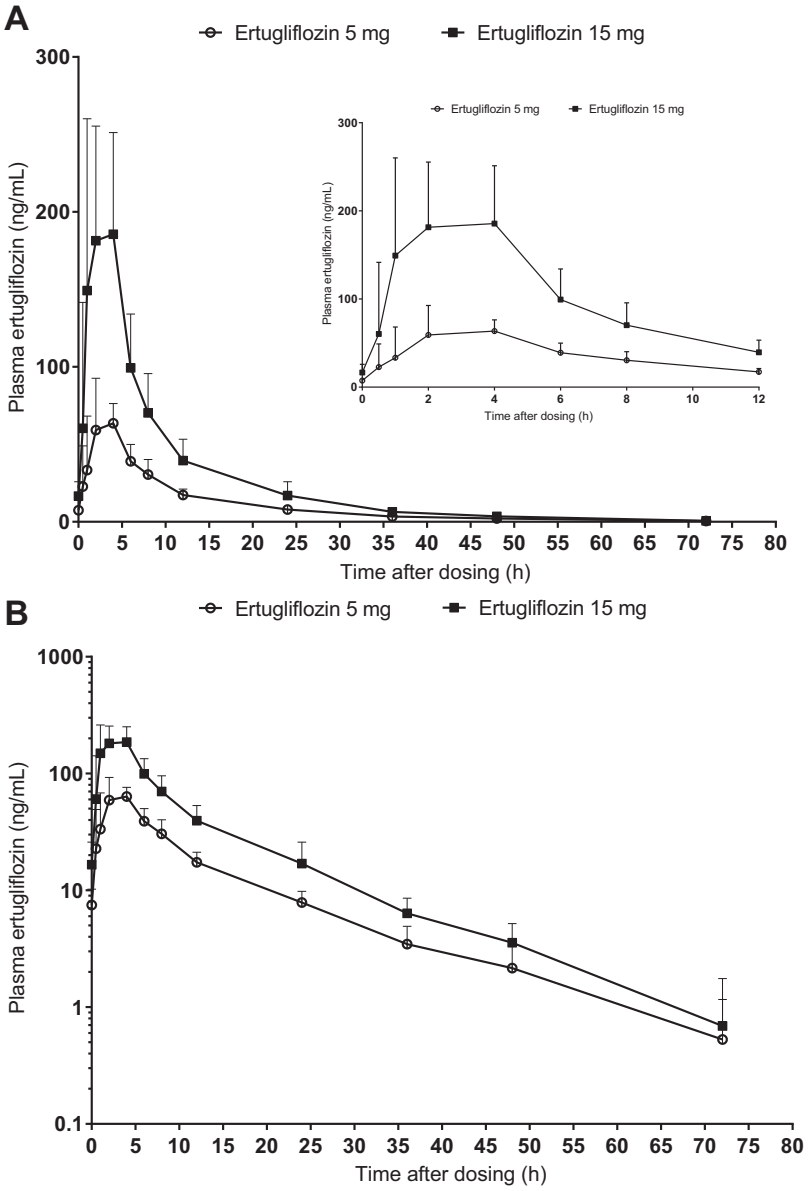

Figure 2. Mean (standard deviation) plasma ertugliflozin concentration–time profiles following multiple oral doses of ertugliflozin 5 mg and 15 mg (once daily) under fed conditions (day 11) in (A) linear (principal plot) with the 0- to 12-hour interval on an expanded time scale (inset plot) and (B) semilogarithmic scales.

conducted in healthy subjects showed geometric means of dose normalized AUC_{inf} and C_{max} after single-dose administration in Chinese subjects are 1.20- and 1.34-fold of those in non-Asian subjects, respectively (data on file). Similarly, following multiple-dose administration of ertugliflozin under fed conditions in 3 studies, geometric mean of dose normalized AUC_{tau} and C_{max} in Chinese subjects are 1.33- and 1.50-fold of those in non-Asian subjects, respectively. However, after body weight correction, these ratios fell within the range of 0.97 to 1.05, indicating the differences in exposures are likely due to differences in body weight instead of racial differences between the 2 populations. Chinese subjects in the current study had a mean body weight of 59.6 kg; however, mean body weight in the non-Asian studies were 76.2 and 90.5 kg, respectively, for pooled single- and multiple-dosing populations. The lower mean body weight for the Chinese subjects observed in this study compared with the other non-Asian studies may, in part, be due to a higher proportion of female Chinese subjects in the current study (50%) vs pooled non-Asian populations receiving single (27.2%) and multiple (3.1%) ertugliflozin doses. Results from a population PK analysis of ertugliflozin indicate that sex does not have a clinically relevant effect on the PK of ertugliflozin.[25] Similar to ertugliflozin, lower body

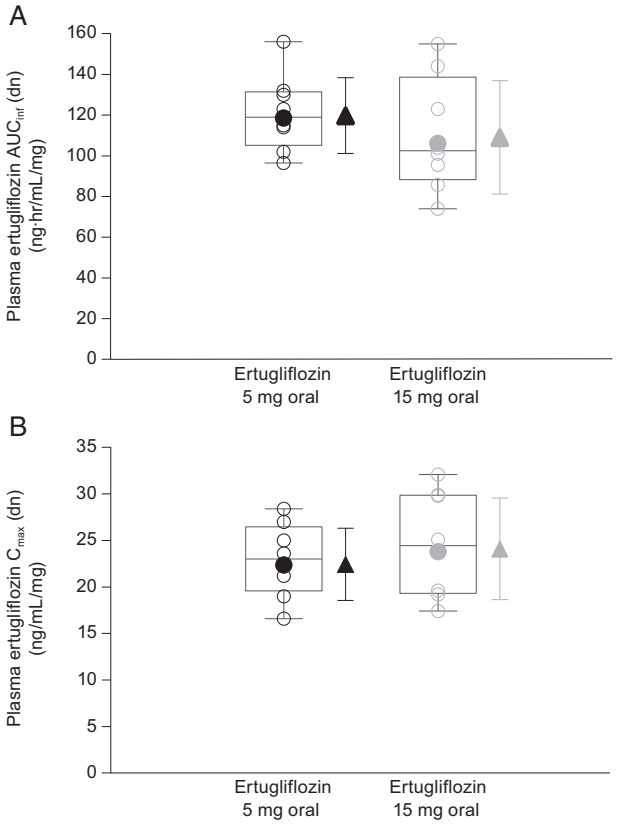

Figure 3. Individual, geometric, and arithmetic mean plasma ertugliflozin dose-normalized AUC_{inf} (A) and C_{max} (B) values by doses on day 1 (fasted). Open circles identify individual subject data; closed circles identify geometric means. Offset closed triangles identify arithmetic mean (with standard deviation). Box plots provide medians, and 25% and 75% quartiles with whiskers extended to the minimum/maximum values. AUC_{inf}, area under the curve from time 0 extrapolated to infinite time; C_{max}, maximum observed plasma concentration; dn, dose-normalized.

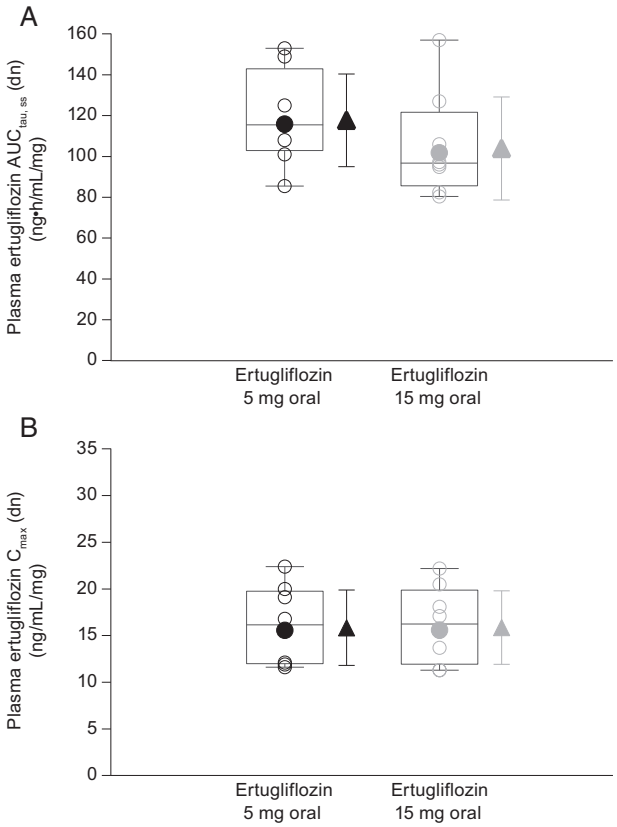

Figure 4. Individual, geometric, and arithmetic mean plasma ertugliflozin dose-normalized steady state $AUC_{tau,ss}$ (A) and C_{max} (B) values by doses on day 11 (fed). Open circles identify individual subject data; closed circles identify geometric means. Offset closed triangles identify arithmetic mean (with standard deviation). Box plots provide medians and 25% and 75% quartiles with whiskers extended to the minimum/maximum values. $AUC_{tau,ss}$, area under the curve from time 0 to time tau (the dosing interval) at steady state; C_{max}, maximum observed plasma concentration; dn, dose-normalized.

weight is associated with higher exposures of both empagliflozin[26] and canagliflozin[27] in Chinese subjects compared with Western counterparts. Nevertheless, the observed exposure differences in ertugliflozin AUC and C_{max} are $\leq$50% between Chinese and non-Asian populations and are not considered clinically meaningful.

Differences in variant allele frequencies within genes important to the clinical pharmacology of ertugliflozin could potentially influence race-based responses to treatment. As such, polymorphisms in UGT1A9 and UGT2B7, the primary enzymes involved in ertugliflozin glucuronidation,[5] could potentially affect UGT activity and ultimately ertugliflozin metabolism. The minor allele frequency UGT1A9*1b, reported to be 40% in European, 57% in Japanese/East Asian, and 46% in African American populations (National Center for Biotechnology Information, database of Single Nucleotide Polymorphisms), has been associated with increased expression of UGT1A9, which in turn can decrease exposure to drugs metabolized by this pathway.[28] However, a pooled analysis of AUC values from 20 phase 1 studies revealed that mean effects of the allelic variants of UGT1A9 on AUC were within $\pm$ 10% of the wild type and are not clinically relevant.[29] Furthermore, with the lack of reports regarding UGT2B7 polymorphisms of clinical significance,[30] genetic polymorphisms in UGT2B7 are not expected to have a clinically meaningful impact on the PK of ertugliflozin. While CYP3A4 (with contributions from CYP2C8 and CYP3A5) is involved in the relatively minor oxidative metabolism of ertugliflozin,[5] molecular variations in CYP3A do not appear to contribute substantially to interindividual differences in drug disposition.[31] The low fraction of elimination attributed to CYP3A4, CYP3A5, and CYP2C8 makes it unlikely that any differences would arise from polymorphism of these enzymes. Taken

Table 2. Summary of Adverse Events

	ERTU 5 mg (n = 8)	ERTU 15 mg (n = 8)
Number of all-causality treatment-emergent AEs	6	11
Number of treatment-related AEs	5	8
Number of subjects with all-causality treatment-emergent AEs	4	6
Number of subjects with treatment-related AEs	4	5
SAEs	0	0
Severe AEs	0	0
Discontinuation due to AEs	0	0
Dose reduced or temporary discontinuation due to AEs	0	0

AE, adverse event; ERTU, ertugliflozin; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.
Except for the number of AEs, subjects were counted only once per treatment in each row. Included all data collected since the first dose of study medication. SAEs were determined according to the investigator's assessment. Severity counts were based on the maximum severity or grade of events. MedDRA (version 19.0) coding dictionary applied.

together, it is unlikely that genetic polymorphisms in enzymes that metabolize ertugliflozin will have a clinically meaningful impact on the PK of ertugliflozin and further suggest racial differences in metabolism and subsequent efficacy and tolerability are unlikely.

Reducing renal glucose reabsorption and lowering the renal threshold for glucose excretion increases urinary glucose excretion, thereby reducing plasma glucose and HbA_{1c} in patients with T2DM. Although in this study of healthy volunteers glucosuria was reported as a mild AE by investigators, it is an expected outcome of ertugliflozin administration based on the mechanism of action. While caution should be taken when drawing conclusions regarding the general clinical applicability of data from small phase 1 studies, no specific tolerability issues were identified with ertugliflozin dosing in healthy Chinese subjects, and there were no treatment discontinuations due to AEs in this study.

This phase 1 study enrolled healthy subjects and evaluated the PK of ertugliflozin. The PK findings reported here in Chinese subjects residing in China are comparable with those observed in other populations[15–22] and are supported by results from a recently conducted phase 3 study exploring the efficacy and safety of ertugliflozin in Asian patients with T2DM.[32] This longer-term study (with the same ertugliflozin doses of 5 mg and 15 mg assessed in the current phase 1 study) demonstrated that ertugliflozin improved glycemic control and reduced body weight and systolic blood pressure in Asian patients with T2DM inadequately controlled on metformin monotherapy, including Chinese patients from mainland China.[32] Taken together, the comparable efficacy and safety across the ertugliflozin phase 3 studies in varied populations including Chinese patients and the PK findings from the phase 1 studies suggest no clinically meaningful PK differences, and no dose modification of ertugliflozin is required based on race or body weight.

Conclusions

In healthy Chinese subjects, exposure (C_{max}, AUC_{inf}, and $AUC_{tau,ss}$) of ertugliflozin increased in a dose-proportional manner following single- and multiple-dose administration. The apparent $t_{½}$ of ertugliflozin ranged from approximately 9.5 to 11.9 and the R_{ac} of ertugliflozin exposure after multiple-dose administration was approximately 1.3 and 1.2 for ertugliflozin 5 mg and 15 mg, respectively. PK comparison with non-Asian subjects indicated that there are no clinically meaningful racial differences, and no dose modification of ertugliflozin is required based on race or body weight. Ertugliflozin was generally well tolerated when administered as single and multiple oral doses of 5 mg and 15 mg in healthy Chinese subjects.

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Declaration of Conflicting Interests

Z.Liu. declares no conflict of interest. Y. Li, Y.Mu, H.Shi, K.Matschke, A.Hickman, and V.Sahasrabudhe are employees of Pfizer Inc. R.Krishna is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.. Y. Liang was an employee of Pfizer Inc. at the time the study was conducted.

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Data Accessibility

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will

provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States and/or European Union or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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