Single- and Multiple-Dose Pharmacokinetics of Ertugliflozin in Healthy Chinese Subjects

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Background

- In China, the prevalence of type 2 diabetes mellitus (T2DM) is projected to reach 150.7 million people by 2040.¹
- Ertugliflozin (ERTU) is a highly selective and potent sodium-glucose co-transporter 2 (SGLT2) inhibitor currently in development for the treatment of T2DM.^{2,3}
- The pharmacokinetics (PK) of ERTU are predictable and reproducible across healthy, non-T2DM obese, and T2DM study populations.
- In Phase 3 studies, ERTU 5 mg and 15 mg once daily (QD) doses were associated with reductions in glycated hemoglobin, body weight, and blood pressure, and were well tolerated in patients with T2DM.^{4–7}

Objectives

- To investigate the single- and multiple-dose PK, tolerability, and safety of ERTU 5 mg and 15 mg in healthy Chinese subjects.

Methods

Subjects enrolled

- Healthy male and/or female Chinese subjects (residing in mainland China who were born in China and had both parents of Chinese descent) aged 18–45 years with body mass index (BMI) 19–24 kg/m² and total body weight >50 kg.
- The sample size of 8 Chinese subjects per cohort was based on the Chinese Food and Drug Administration requirement for a PK study in China.

Study design and treatment

- The design of this Phase 1, open-label, parallel-cohort, randomized study is shown in **Figure 1**.

Figure 1. Study design

^aOvernight fast of ≥10 h; ^bWithin 5 min after breakfast (approximately 650 calories). ERTU, ertugliflozin; QD, once daily.

Assessments

- Blood samples were collected for PK analysis:
 - Single dose: Day 1 – 0 (predose), 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 h after dosing
 - Multiple dose: Day 6 – 0 (predose), 0.5, 1, 2, 4, 6, 8, 12, and 24 h after dosing; Days 9 and 10 – 0 h (predose); Day 11 – 0 (predose), 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 h after dosing.
- Plasma samples were analyzed for ERTU concentrations using a validated, sensitive, and specific high-performance liquid chromatography–tandem mass spectrometric method with a lower limit of quantification of 0.500 ng/mL.
- ERTU PK parameters after single and multiple doses were calculated from the plasma concentration–time data using non-compartmental methods. PK parameters were summarized descriptively by treatment and study day.
- Safety assessments were conducted from screening and throughout study participation. A follow-up phone call 14 ± 3 days after the last dose of study medication assessed for adverse events (AEs).

Results

Table 1. Descriptive summary of plasma ERTU PK parameter values following single (Days 1 and 6) and multiple QD (Day 11) dosing

	Parameter summary statistics ^a	ERTU 5 mg (n=8)	ERTU 15 mg (n=8)
Day 1; fasted	AUC _{inf} , ng·h/mL	599.3 (15)	1606 (26)
	AUC _{last} , ng·h/mL	586.8 (15)	1594 (26)
	CL/F, mL/min	139.2 (15)	155.8 (26)
	C _{max} , ng/mL	112.9 (18)	360.8 (24)
	t _{1/2} , 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)
	C _{max} , ng/mL	72.65 (17)	191.4 (26)
	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)
	CL/F, mL/min	142.3 (19)	162.0 (23)
	C _{max} , ng/mL	78.48 (26)	236.5 (26)
	R _{ac}	1.291 (12)	1.225 (10)
	t _{1/2} , h	11.88 ± 3.234	10.60 ± 2.776
	T _{max} , h	4.00 (1.00–4.02)	2.00 (1.00–4.00)

^aGeometric mean (geometric %CV) for all except: median (range) for T_{max}, arithmetic mean ± SD for t_{1/2}. %CV, percent coefficient of variation; AUC, area under the plasma concentration–time profile; AUC₂₄, AUC from 0 to 24 h postdose; AUC_{inf}, AUC from time 0 extrapolated to infinity; AUC_{last}, AUC from time 0 to time of last measurable concentration; AUC_{tau,ss}, AUC from time 0 to tau (dosing interval) at steady state; CL/F, apparent oral clearance; C_{max}, maximum observed plasma concentration; ERTU, ertugliflozin; QD, once daily; R_{ac}, observed accumulation ratio; SD, standard deviation; t_{1/2}, terminal half-life; T_{max}, time for C_{max}.

Figure 2. Median plasma ERTU concentration–time profiles following a single oral dose of ERTU 5 mg and 15 mg under fasted conditions (Day 1) (A) and multiple oral doses of ERTU 5 mg and 15 mg QD under fed conditions (Day 11) (B)

Linear (principal plots) and semi-logarithmic (inset plots) scales are shown. Summary statistics were calculated by setting concentration values <LLOQ to 0 ng/mL (LLOQ=0.500 ng/mL). ERTU, ertugliflozin; LLOQ, lower limit of quantification; QD, once daily.

Figure 3. Individual and geometric mean plasma ERTU dose-normalized AUC_{inf} (A) and C_{max} (B) values by dose on Day 1 (fasted)

AUC_{inf}, AUC from time 0 extrapolated to infinite time; C_{max}, maximum observed plasma concentration; dn, dose-normalized; ERTU, ertugliflozin.

Figure 4. Individual and geometric mean plasma ERTU dose-normalized steady state AUC_{tau,ss} (A) and C_{max} (B) values by dose on Day 11 (fed)

AUC_{tau,ss}, AUC from time 0 to time tau (the dosing interval) at steady state; C_{max}, maximum observed plasma concentration; dn, dose-normalized; ERTU, ertugliflozin.

Safety

- No deaths, serious AEs, or discontinuations were reported.
- The most frequently reported treatment-emergent AE was glucosuria (occurring in 3 and 4 subjects for ERTU 5 mg and 15 mg, respectively), which is related to the mechanism of action of SGLT2 inhibitors.

Conclusions

- In healthy Chinese subjects, absorption of ertugliflozin was rapid, with a median time for maximum observed plasma concentration of 1 h postdose under fasted conditions and 2–4 h postdose under fed conditions.
- Following single- and multiple-dose administration:
 - Exposure of ertugliflozin increased in a dose-proportional manner
 - Apparent mean terminal half-life of ertugliflozin ranged from approximately 9.5 to 11.9 h.
- The accumulation ratio of ertugliflozin exposure based on AUC after multiple-dose administration was approximately 1.3 and 1.2 for ertugliflozin 5 mg and 15 mg, respectively.
- Single- and multiple-oral doses of ertugliflozin 5 mg and 15 mg were well tolerated in healthy Chinese subjects.

References

1. International Diabetes Federation. *Diabetes Atlas*. Seventh Edition. Brussels, Belgium. 2015. 2. Kalgutkar AS, et al. *Drug Metab Dispos* 2011;39:1609–19. 3. Miao Z, et al. *Drug Metab Dispos* 2013;41:445–56. 4. Dagogo-Jack S, et al. *Diabetes Obes Metab* 2017; doi: 10.1111/dom.13116. 5. Pratley R, et al. EASD 52nd Annual Meeting, Munich, Germany, 2016 (abstr 728). 6. Rosenstock J, et al. *Diabetes Obes Metab* 2017; doi: 10.1111/dom.13103. 7. Terra SG, et al. *Diabetes Obes Metab* 2017;19(5):721–8.

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