Overview of the Clinical Pharmacology of Ertugliflozin, a Novel Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitor

Vaishali Sahasrabudhe¹, Gianluca Nucci², Vikas Kumar¹, Daryl J Fediuk¹, David L Cutler^{3*}, Neeta B Amin², Steven G Terra⁴, and Rebecca A Boyd^{1*}

¹Pfizer, Inc., Groton, CT, USA; ²Pfizer, Inc., Cambridge, MA, USA; ³Merck & Co., Inc., Kenilworth, NJ, USA*; ⁴Pfizer, Inc., Andover, MA, USA
*At the time of study conduct

Background

- Ertugliflozin (ERTU), a selective sodium glucose co-transporter 2 inhibitor, is being developed for the treatment of type 2 diabetes mellitus (T2DM).^{1,2}
- In Phase 3 trials, ERTU 5 mg and 15 mg improved glycemic control, and reduced body weight and blood pressure in patients with T2DM.³⁻⁶
- Based on dose-response modeling, ERTU 5 mg and 15 mg doses are predicted to achieve >80% and >90% of maximal pharmacological activity, respectively.

Objectives

- To provide an overview of the clinical pharmacology of ERTU, with a focus on:
 - The pharmacokinetics (PK) and pharmacodynamics (PD) measured as 24 h urinary glucose excretion (UGE₂₄) in healthy subjects and T2DM patients
 - The effect of intrinsic (renal or hepatic impairment) and extrinsic (drug interactions, food) factors on PK
 - The effect of ERTU on corrected QT (QTc) interval.

Single- and multiple-dose studies

- Two Phase 1, escalating-dose studies evaluated the PK and PD of ERTU:
 - Single doses of ERTU 0.5 mg, 2.5 mg, 10 mg, 30 mg, 100 mg, 300 mg, or placebo in 24 healthy male subjects under fasted conditions
 - ERTU 1 mg, 5 mg, 25 mg, 100 mg, or placebo dosed once daily (QD) with breakfast for 14 days to 40 healthy obese or overweight subjects in 4 cohorts.
- Oral absorption was rapid with median time to peak plasma concentrations occurring at 1 h (fasted) and 2 h (fed) postdose.
- The terminal phase half-life (t_{1/2}) of ERTU was consistent across doses (11–17 h in both studies).
- Consistent with t_{1/2}, steady state concentrations were achieved by Day 6 after initiating QD dosing in the multiple-dose study.
- Accumulation ratio ranged from 1.2 to 1.4.
- Maximum observed plasma concentration (C_{max}) and area under the plasma concentration–time profile from time 0 extrapolated to infinity (AUC_{inf}) increased with increasing dose over the dose range of 0.5–300 mg (**Figure 1**).

Figure 1. Relationship between ERTU dose-normalized AUC_{inf} values and dose

Open circles are individual subjects and closed circles are geometric means.
AUC_{inf}, area under the plasma concentration–time profile from time 0 extrapolated to infinity.

- A dose-dependent effect was observed on UGE over 0–24 h (**Figure 2**) with maximum effect achieved at ~30 mg.

Figure 2. Cumulative UGE over 0–24 h over 0.5–300 mg dose range

*0 mg dose refers to placebo.
Open circles identify individual subject data; closed circles identify means.
Box plots provide medians, and 25% and 75% quartiles with whiskers extended to the minimum/maximum values.
UGE₂₄, 24 h urinary glucose excretion

Absorption, distribution, metabolism, and excretion (ADME)

- A single-dose study of [¹⁴C] ERTU (25 mg/100 μCi suspension) was conducted in 6 healthy males to characterize the metabolic profile and routes of excretion of ERTU.
- The concentration–time profiles for plasma [¹⁴C] ERTU and plasma ERTU were similar with peak concentrations occurring 1 h postdose; t_{1/2} was similar for ERTU and [¹⁴C] ERTU, averaging ~17 h (**Figure 3**).

Figure 3. Median plasma concentration–time profiles for ERTU (ng/mL) and [¹⁴C] ERTU (ng-eq/mL)

Plasma ERTU lower limit of quantification (LLOQ)=0.5 ng/mL.
Plasma [¹⁴C] ERTU LLOQ = 6.7 ng-eq/mL.

- ERTU underwent minimal Phase 1 metabolism; the major metabolic pathway was glucuronidation to 2 pharmacologically inactive glucuronide metabolites, M5a and M5c.²**
- Mean total recovery of radioactivity in feces (40.9%) and urine (50.2%) was 91.0% of the administered dose.
- Unchanged ERTU excretion in urine accounted for 1.5% of administered dose, indicating renal excretion is not a major clearance mechanism for ERTU.**

Special patient populations

Renal impairment study

- PK and PD of a single dose of ERTU 15 mg were assessed in T2DM patients with renal impairment (mild, n=8; moderate, n=8; severe, n=6) and compared with healthy subjects (n=8) and T2DM patients (n=6) with normal renal function.⁷
- PK of ERTU were generally similar between T2DM and healthy subjects with normal renal function.
- Mean t_{1/2} for ERTU was slightly longer in subjects with renal impairment (23–26 h) compared to T2DM and healthy subjects with normal renal function (15–18 h).
- Predicted mean AUC_{inf} values for mild, moderate, and severe renal impairment T2DM patients were ~1.2-, 1.4-, and 1.7-fold higher, respectively, vs subjects with normal renal function.
- Consistent with decreased glomerular filtration of glucose, UGE₂₄ decreased with decreasing renal function.

Hepatic impairment study

- PK of single-dose ERTU 15 mg was assessed in 8 subjects with moderate hepatic impairment (Child-Pugh Score 7–9) and 8 demographically matched healthy subjects.
- Mean t_{1/2} values for ERTU were similar for those with moderate hepatic impairment (14.6 h) and normal hepatic function (13.8 h).
- In subjects with moderate hepatic impairment, ERTU AUC_{inf} and C_{max} were 13% and 21% lower, respectively, vs those with normal hepatic function.
 - AUC_{inf} and C_{max} for unbound ERTU were similar for subjects with moderate hepatic impairment and normal hepatic function.
- Changes in ERTU exposure in participants with renal or mild/moderate hepatic impairment are not considered clinically relevant and do not require dose adjustments.**

Drug–drug interaction studies

- PK drug–drug interaction potential of ERTU 15 mg when co-administered with common concomitant medications and a prototypical enzyme inducer was assessed in:
 - 4 separate, single-dose, 3-period crossover studies with sitagliptin 100 mg, metformin 1000 mg, glimepiride 1 mg, or simvastatin 40 mg^{8,9}
 - 1 fixed-sequence, 2-period study with rifampin 600 mg, QD for 10 days.¹⁰
- Concomitant administration of metformin, sitagliptin, glimepiride, or simvastatin with ERTU did not have a clinically meaningful effect on ERTU PK (**Figure 4**).
- Co-administration of rifampin decreased ERTU AUC_{inf} and C_{max} by 39% and 15%, respectively, but is unlikely to have a clinically meaningful impact on ERTU efficacy (**Figure 4**).
- ERTU did not have a clinically meaningful effect on the PK of the concomitant medications (**Figure 5**).
 - AUC_{inf} for simvastatin (24%) and simvastatin acid (30%) increased by 24% and 30%, respectively, after co-administration with ERTU; this was not considered clinically relevant.

Figure 4. Effects of commonly co-administered drugs on the PK of ERTU 15 mg

*Relative to ERTU alone (%).
AUC_{inf}, area under the plasma concentration–time profile from time 0 extrapolated to infinity;
CI, confidence interval; C_{max}, maximum observed plasma concentration.

Figure 5. Effects of ERTU 15 mg on the PK of commonly co-administered drugs

*Relative to concomitant medication alone; †Simvastatin 40 mg (n=18).
AUC_{inf}, area under the plasma concentration–time profile from time 0 extrapolated to infinity;
CI, confidence interval; C_{max}, maximum observed plasma concentration.

Absolute bioavailability study

- The absolute bioavailability (F) and fraction absorbed (Fa) of ERTU were estimated in a 2-period study in 8 healthy subjects using a ¹⁴C-microdose approach:¹¹
 - Period 1: ERTU 15 mg oral unlabeled followed 55 min later by [¹⁴C] ERTU 100 μg (400 nCi) IV dose
 - Period 2: ERTU 15 mg oral unlabeled at the same time as [¹⁴C] ERTU 100 μg oral dose.
- Estimates of F (105%) and Fa (111%) indicated complete absorption.**

Food-effect study

- The effect of food on the PK of ERTU 15 mg was evaluated in a 2-period, 2-sequence crossover study in 14 healthy subjects.¹²
- Following an overnight fast of ≥10 h, subjects received the following treatments separated by a washout period: ERTU 15 mg (fasted), or ERTU 15 mg ~30 min after beginning consumption of a standard high-fat, high-calorie breakfast (fed).
- AUC_{inf}: 90% CI for the adjusted geometric mean ratios (90% CI: 88%–95%) fell within the bioequivalence limits (80%–125%).
- C_{max}: decreased by 29% (90% CI: 62%–81%); as efficacy of ERTU is driven by total exposure and not peak exposure, this decrease is not considered to be clinically relevant.
- Administration of the ERTU 15 mg tablet with food did not have a clinically meaningful effect on PK.**

Thorough QT study

- The effect of ERTU on the QT interval was evaluated in 42 healthy subjects receiving ERTU 100 mg (supra-therapeutic dose), placebo, and moxifloxacin (400 mg; positive control).¹³
- The estimated least-squares mean difference between ERTU and placebo in QTc using Fridericia's correction (QTcF) was <5 msec (threshold of potential clinical concern); the upper limits of the 2-sided 90% CI for the difference in QTcF between ERTU and placebo were <10 msec at all postdose time points.
- ERTU was not associated with QTc interval prolongation in healthy subjects.**

Conclusions

- The comprehensive evaluation of the clinical pharmacology of ertugliflozin supports QD administration to patients with T2DM, regardless of food and with no required dose-adjustments for concomitant medication, or renal or hepatic impairment, based on PK.
- Ertugliflozin was well tolerated in all studies.

References

- Kalghatkar AS, et al. *Drug Metab Dispos* 2011;39:1609–19.
- Miao Z, et al. *Drug Metab Dispos* 2013;41:445–56.
- Terra SG, et al. *Diabetes Obes Metab* 2017;19:721–28.
- Rosenstock J, et al. *Diabetes Obes Metab* 2017; doi: 10.1111/dom.13103.
- Dagogo-Jack S, et al. *Diabetes Obes Metab* 2017; doi: 10.1111/dom.13116.
- Pratley R, et al. *EASD 52nd Annual Meeting*, Munich, Germany, 2016 (abstr 728).
- Sahasrabudhe V, et al. *J Clin Pharmacol* 2017;57:1432–43.
- Kumar V, et al. *ASCP Annual Meeting*, San Diego, CA, USA, 2016 (abstr PI-064).
- Sahasrabudhe V, et al. *ASCP Annual Meeting*, San Diego, CA, USA, 2016 (abstr PI-061).
- Kumar V, et al. *ASCP Annual Meeting*, San Diego, CA, USA, 2016 (abstr PI-063).
- Sahasrabudhe V, et al. *ASCP Annual Meeting*, Washington, DC, USA, 2017 (abstr PI-123).
- Sahasrabudhe V, et al. *ADA 75th Scientific Sessions*, Boston, MA, USA, 2015 (abstr 2605-PO).
- Raje S, et al. *ASCP Annual Meeting*, San Diego, CA, USA, 2016 (abstr PI-015).

Acknowledgments

The studies were funded by Pfizer, Inc., Groton, CT, USA and Merck & Co., Inc., Kenilworth, NJ, USA. Medical writing support was provided by Radhika Bhatia, PhD, of Engage Scientific Solutions (Horsham, UK) and was funded by Pfizer.