

## ARTICLE

# Effect of renal impairment on the pharmacokinetics and safety of dorzagliatin, a novel dual-acting glucokinase activator

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**Abstract**

Dorzagliatin is a novel allosteric glucokinase activator targeting both pancreatic and hepatic glucokinase currently under clinical investigation for treatment of type 2 diabetes (T2D). This study aimed to investigate the effect of renal impairment (RI) on dorzagliatin's pharmacokinetics (PKs) and safety, and to guide appropriate clinical dosing in patients with diabetic kidney disease, including end-stage renal disease (ESRD). Based on the results from physiologically-based pharmacokinetic modeling, the predicted outcome of RI on dorzagliatin PK property would be minimum that the plasma exposure area under concentration (AUC) of dorzagliatin in patients with ESRD would increase at about 30% with minimal change in peak concentration ( $C_{max}$ ) comparing to those in healthy volunteers (HVs). To definitively confirm the prediction, a two-part RI study was designed and conducted based on regulatory guidance starting with the patients with ESRD matched with HVs. Results of the RI study showed minimum difference between patients with ESRD and HVs with respect to dorzagliatin exposure with geometric mean ratio of ESRD to HV at 0.81 for  $C_{max}$  and 1.11 for AUC. The elimination half-life, volume of distribution, and systemic clearance for dorzagliatin were similar between the two groups. Dorzagliatin was well-tolerated in patients with ESRD during the study. Therefore, RI showed no significant impact on dorzagliatin PK, suggesting that dorzagliatin can be readily used in patients with T2D at all stages of RI without need for dose adjustment.

**Study Highlights****WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**

Currently, there are limited safe and effective anti-hyperglycemia treatments for patients with diabetic kidney disease (DKD) and end-stage renal disease

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(ESRD). Dorzagliatin has exhibited favorable absorption, distribution, metabolism, and excretion/drug metabolism and pharmacokinetic properties with good safety and efficacy profiles in multiple preclinical and clinical studies, demonstrating its potential as a novel glucose sensitizer for the treatment of type 2 diabetes.

#### **WHAT QUESTION DID THIS STUDY ADDRESS?**

The impact of renal impairment (RI) on dorzagliatin pharmacokinetics (PKs). Whether dorzagliatin can be used in patients with DKD without dose adjustment.

#### **WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?**

RI had no significant impact on dorzagliatin PKs. Dorzagliatin can be used without dose adjustment in patients with DKD at any stage, including ESRD.

#### **HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?**

A reduced study was designed based on regulatory guidance. Physiologically-based pharmacokinetic (PBPK) modeling accurately predicted minimal impact of RI on dorzagliatin exposure, further supporting the study design. Subsequent clinical study results confirmed *in silico* prediction and validated the PBPK model. Therefore, integrating computational approach using scientifically well-founded PBPK models can be powerful in critical decision making in drug development to reduce expenses and increase confidence.

## **INTRODUCTION**

Diabetes mellitus (DM) is the leading cause of chronic kidney disease and end-stage renal disease (ESRD) worldwide. The alarming rise in the prevalence of DM parallels an increasing prevalence of diabetic kidney disease (DKD), a leading cause of morbidity and mortality in diabetes.<sup>1-3</sup> In fact, about 40% of patients with diabetes will eventually develop DKD, a diabetic complication defined as either a glomerular filtration rate (GFR) below 60 ml/min/1.73 m<sup>2</sup> or a urinary albumin to creatinine ratio greater than 30 mg/g.<sup>4-6</sup>

Although optimal glycemic control is essential to prevent the onset and delay disease progression, patients with DKD have only limited anti-hyperglycemia treatment options. Many commonly used standard therapies for type 2 diabetes (T2D) are either contraindicated or not recommended in DKD at late stage of renal impairment (RI) or with ESRD, or require dose adjustment with frequent monitoring of renal function.<sup>7-19</sup> Thus, there is still a high unmet need for safe and effective glucose management agent for patients with DKD.

Glucokinase activator (GKA) has recently emerged as a promising novel class of oral antidiabetic treatment through targeting glucokinase, a critical glucose sensor plays a central role in the regulation of glucose homeostasis in humans.<sup>20,21</sup> Dorzagliatin is a new generation of allosteric GKA acting on both pancreas and liver, and recently completed phase III clinical trials in Chinese patients with T2D.<sup>22,23</sup> Dorzagliatin has demonstrated favorable pharmacokinetics (PKs), pharmacodynamics

(PDs), and safety profiles in multiple clinical studies conducted thus far, both in healthy as well as patients with T2D.<sup>24-26</sup> Results from a single ascending dose (SAD) study in healthy volunteers (HVs)<sup>24</sup> and a multiple ascending dose study in patients with T2D<sup>26</sup> demonstrated that absorption of dorzagliatin is rapid, reaching peak plasma concentration ( $C_{max}$ ) within 1.25–2.5 h postdose, the elimination half-life ( $t_{1/2}$ ) for dorzagliatin is 4.5–8.6 h following a single oral dose, and dorzagliatin displayed a linear dose-exposure relationship. The metabolism of dorzagliatin is predominantly mediated by cytochrome P450 (CYP) 3A4.<sup>27,28</sup> Additionally, a mass balance study in HVs in the United States (unpublished data, ClinicalTrials.gov identifier: NCT03158506) revealed that dorzagliatin was mainly eliminated through metabolism, and the proportion of unchanged drug excreted through urine is 8.15% (unpublished data), indicating minimal renal excretion.

On the basis of its excretion pathways, we hypothesized that RI would likely have only a minor impact on dorzagliatin exposure, thus dose adjustment would not be needed in patients with DKD. Nonetheless, it is well-recognized that patients with T2D are at high risk of complicated pathological changes, including impaired kidney function, which sometimes is coupled with delayed or defective gastrointestinal transport and absorption, resulting in altered PKs. In addition, RI can also cause changes in drug absorption, liver metabolism, as well as plasma protein binding, and all these defects may be particularly prominent in patients with severely impaired renal

function, even when the renal excretion is not the main elimination pathway.

In order to test the feasibility of the clinical use of dorzagliatin in the DKD population, especially in patients with ESRD with T2D, a previously established mechanistic physiologically-based pharmacokinetic (PBPK) model<sup>27,28</sup> was utilized to quantitatively predict the impact of RI on dorzagliatin PK. Afterward, a dedicated clinical study was designed to rigorously assess the impact of RI in human subjects according to the regulatory guidance.<sup>29–31</sup>

## METHODS

This study (ClinicalTrials.gov identifier: NCT04324424) was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines issued by the International Conference on Harmonization, and the published guidance for PK studies in patients with RI.<sup>32,33</sup> The study protocol was approved by the independent ethics committee at the study site (Clinical Research Center, West China Hospital of Sichuan University, Chengdu, Sichuan, China). All participants provided written informed consent before any study-related procedures.

### Prediction of impact of RI on dorzagliatin PK using PBPK modeling

We have previously proposed a model-based drug development methodology to engage computer learning of PK/PD profiles of dorzagliatin during first-in-human studies by utilizing a learn–research–confirm cycle,<sup>27</sup> and reported the development and validation of a mechanistic PBPK model for dorzagliatin by integrating allometric scaling, *in vitro* to *in vivo* exploration, and steady-state concentration–mean residence time methods to provide mechanistic insight into dorzagliatin PK properties in humans.<sup>28</sup> Thereafter, we further optimized the original PBPK model based on additional clinical data collected from human mass balance study and two drug–drug interaction studies (unpublished data). Hereby, we assessed the effect of RI on the PKs of dorzagliatin using the updated PBPK model using the Simcyp (version 16.0; Certara, Sheffield, UK) in moderate or severe RI populations (refer to Supplementary Material for the details).

### Clinical RI study design

This clinical RI study was designed as an open-label, single-dose, single-center, sequential two-part, parallel-group study, aiming to assess the PKs and safety of dorzagliatin

in subjects with RI versus HVs. Based on the regulatory guidance, we adopted a reduced study design starting with the enrollment of patients with non-dialysis ESRD as a worst-case scenario.<sup>32</sup> An interim analysis was conducted after completing the part 1 study, which enrolled patients with non-dialysis ESRD plus matched healthy controls. In the subsequent part 2, if needed, we planned to enroll patients with mild, moderate, and severe RI, although the part 2 study will be conducted only if the ratio of AUC (area under the concentration–time curve from time of administration up to the time of the last quantifiable concentration [ $AUC_{last}$ ] or AUC to infinity [ $AUC_{inf}$ ]) geometric mean between patients with ESRD and HVs is greater than 100% based on results from part 1.

As for the dose selection, because the maximum single dose of dorzagliatin previously tested in HVs was 50 mg, which was well-tolerated, as shown in the phase I SAD study<sup>24</sup> and the mass balance study. Additionally, dorzagliatin exhibited similar PK characteristics in healthy subjects and patients with T2D with no significant gender difference. Furthermore, dorzagliatin demonstrated linear PKs within a wide range of doses, either given as a single dose or as multiple doses up to 200 mg b.i.d. without significant accumulation.<sup>26</sup> Taken altogether, we therefore chose a single oral dose of 25 mg dorzagliatin to ensure an adequate safety margin while still meeting the purpose of the study.

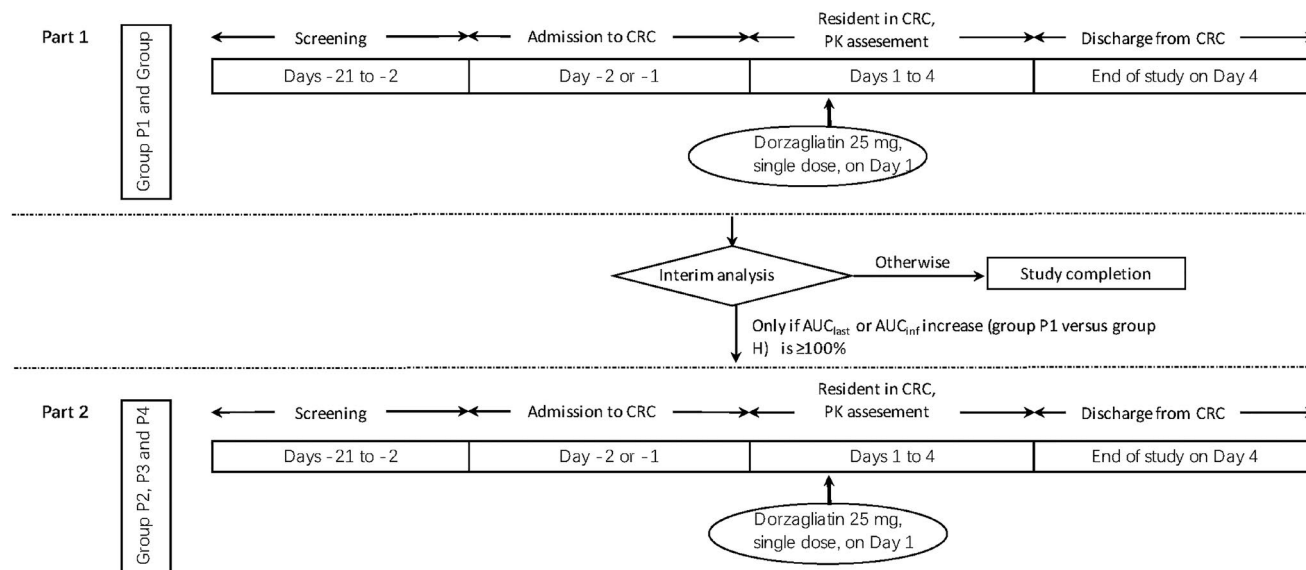
Furthermore, the part 1 study enrolled patients with non-dialysis ESRD who were paired with HVs in 1:1 ratio, matched based on gender, age (within  $\pm 5$  years), and body mass index (BMI; within  $\pm 15\%$ ). Last, because previous studies have shown that an oral dose taken at 1 h prior to a standardized diabetic meal has no significant effect on dorzagliatin PKs, we therefore decided to give dorzagliatin to study participants as a single oral dose at 1 h prior to the standardized breakfast out of practical operational consideration.

All participants were admitted to the clinical unit and received baseline examination on day  $-1$ . Eligible subjects received a single 25 mg oral dose of dorzagliatin on day 1 after overnight fasting, thereafter a standardized meal was served at 1 h postdose. Blood samples were collected at various intervals up to 72 h postdose for PKs and safety analysis. Subjects were then discharged after the end-of-study (EOS) examination (Figure 1).

Because dorzagliatin is a substrate of CYP3A4 or P-gp, concomitant medications for treatment of RI and comorbidities that interact with CYP3A4 or P-gp were not allowed during the study.

### Study participants

Eligible subjects were Chinese men and infertile women aged 18–65 years, weighing greater than or equal to 50 kg



**FIGURE 1** Study design. Group H, group P1, group P2, group P3, and group P4 represent healthy volunteers ( $n = 8$ ), end-stage renal disease not yet on dialysis ( $n = 8$ ), severe ( $n = 6-8$ ), moderate ( $n = 6-8$ ), and mild ( $n = 6-8$ ) renal impairment, respectively.  $AUC_{last}$ , area under the plasma concentration against time curve from time zero to the last quantifiable concentration;  $AUC_{inf}$ , area under the plasma concentration against time curve from time zero to infinity; CRC, clinical research center; PK, pharmacokinetic

for men and greater than or equal to 45 kg for women with a BMI between 18.5 and 35 kg/m<sup>2</sup>. RI severity was classified according to estimated GFR (eGFR) value, as calculated with the Modification of Diet in Renal Disease formula for Chinese population:  $175 \times \text{serum creatinine}^{-1.234} \times \text{age}^{-0.179} \times (0.79 \text{ if female})$ . Accordingly, subjects were categorized into five groups per guidance<sup>32</sup>: normal renal function (eGFR  $\geq 90$  ml/min/1.73 m<sup>2</sup>), ESRD not yet on dialysis (eGFR  $< 15$  ml/min/1.73 m<sup>2</sup>), severe RI (eGFR 15–29 ml/min/1.73 m<sup>2</sup>), moderate RI (eGFR 30–59 ml/min/1.73 m<sup>2</sup>), and mild RI (eGFR 60–89 ml/min/1.73 m<sup>2</sup>). The number of subjects for either gender should be greater than or equal to 3 in each category. For the part 1 study, control subjects with normal renal function were pair-wisely matched with the patients with ESRD based on gender, age ( $\pm 5$ ), and BMI ( $\pm 15\%$ ). Similar design would apply to the part 2 study if needed, where the patient groups with mild, moderate, and severe RI would be matched with HVs in group mean.

Key exclusion criteria included acute kidney failure; type 1 diabetes; congestive heart failure class III or IV according to the New York Heart Association (NYHA) Functional Classification system; history of significant cardiovascular or cerebrovascular disease within 6 months prior to screening; severe anemia with hemoglobin less than 6.0 g/dl; alanine aminotransferase or aspartate aminotransferase elevation to greater than two-fold of the upper normal limit. Medications defined as an inhibitor or inducer of CYP3A4 or P-gp were prohibited

within 14 days or within five half-lives of that medication (whichever is longer) prior to dorzagliatin administration.

## PK sample collection and bioanalysis

Blood samples were drawn from a forearm vein into dipotassium ethylenediamine tetra acetic acid (K<sub>2</sub>EDTA) vacuum tubes at predose (within 1 h prior to dose), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, and 72 h postdose for PK assessment. Blood samples at predose and 1 h postdose were collected for plasma protein binding evaluation. Plasma samples were prepared by centrifugation for 10 min at 1500 g at 4°C within 30 min after blood sample collection.

Urine samples were collected only for the part 1 study at predose (within 1 h prior to dose) and over 72 h postdose consecutive intervals: 0–4, 4–8, 8–12, 12–24, 24–36, 36–48, and 48–72 h.

Dorzagliatin concentration was determined in plasma and urine samples using validated high performance liquid chromatography-tandem mass spectrometric (LC-MS/MS) methods. Dorzagliatin was extracted from plasma samples by protein precipitation with acetonitrile using a sample volume of 100  $\mu$ l, and from urine samples by liquid-liquid extraction with methyl-tert butyl ether using a sample volume of 50.0  $\mu$ l. For both plasma and urine samples, dorzagliatin concentrations were calculated using peak area ratios and calibration curves were generated using weighted ( $1/x^2$ ) linear regression. The quantitation ranges were 1.00–1200 ng/ml in plasma and

5.00–5000 ng/ml in urine, respectively, with the lower limit of quantitation at 1.00 ng/ml in plasma and 5.00 ng/ml in urine.

Because renal failure may also affect drug plasma protein binding, and potentially lead to PK alteration,<sup>34,35</sup> and dorzagliatin has a relatively high plasma protein binding,<sup>36</sup> hence it is possible that dorzagliatin efficacy and/or safety profiles may be influenced by the changes in plasma unbound fraction in clinical setting. Consequently, plasma unbound fraction ( $f_u$ ) as well as unbound exposure parameters  $C_{max,u}$ ,  $AUC_{last,u}$ , and  $AUC_{inf,u}$  were further measured and analyzed in this study. Specifically, plasma protein binding samples were analyzed using a validated method. An aliquot of 200  $\mu$ l plasma samples were dialyzed against phosphate buffered saline (37°C, 5 h) in the equilibrium dialysis device to separate unbound dorzagliatin. An aliquot of 50  $\mu$ l post-dialyzed plasma/buffer mixed samples were extracted using protein precipitation followed by LC-MS/MS analysis. The calibration curve of dorzagliatin was in the range of 0.125–250 ng/ml in the plasma/buffer mixed matrix.<sup>36</sup>

## Safety assessments

Adverse events (AEs) were recorded throughout the study based on the Medical Dictionary for Drug Regulatory Activities (MedDRA) version 22.1. The other safety evaluations included physical examination, vital signs, 12-lead electrocardiogram (ECG), and laboratory tests (hematology, clinical chemistry, and urine analysis) assessed at the screening, baseline, 24 and 48 h postdose, and at EOS.

## Statistical analysis

Dorzagliatin PK parameters were calculated with the non-compartmental analysis model using Phoenix WinNonlin software version 7.0 (Certara Inc., Princeton, NJ, USA).

The primary PK parameters were  $C_{max}$ ,  $AUC_{last}$ , and  $AUC_{inf}$ . Other PK parameters included  $f_u$  and associated unbound PK parameters  $C_{max,u}$ ,  $AUC_{last,u}$ ,  $AUC_{inf,u}$ , time to reach maximum plasma concentration ( $T_{max}$ ),  $t_{1/2}$ , apparent volume of distribution ( $V_z/F$ ), apparent systemic clearance ( $CL/F$ ), cumulative amount excreted into urine ( $A_e$ ), and renal clearance ( $CL_R$ ).

SAS software version 7.1 (SAS Institute Inc., Cary, NC, USA) was used to perform statistical analyses.

The log-transformed primary PK variables ( $C_{max}$ ,  $AUC_{last}$ , and  $AUC_{inf}$ ) were compared by using an analysis of variance (ANOVA) model between each RI group and HV group, respectively. The estimates were back-transformed to yield least squares geometric mean ratios (GMR) and their two-sided 90% confidence intervals (90% CIs). ANOVA was also applied in between-group

comparison of  $f_u$  and, if statistically significant difference was identified, similar statistical comparison between each RI group and HV group for unbound PK variables ( $C_{max,u}$ ,  $AUC_{last,u}$ , and  $AUC_{inf,u}$ ) was performed thereafter.

Safety results were summarized using descriptive statistics. Treatment-emergent adverse events (TEAEs) were summarized by group.

## RESULTS

### PBPK modeling and simulation to predict impact of RI on dorzagliatin PKs

Quantitative PBPK modeling and simulation showed that when dorzagliatin is given as a single oral dose of 75 mg, the ratios of plasma exposure as measured by  $C_{max}$  and AUC in subjects with moderate and severe RI relative to HVs are 1.01 and 0.90, respectively, for plasma  $C_{max}$ , and 1.31 and 1.24, respectively, for plasma AUC (Table 1).

### Participant disposition and characteristics

A total of 17 Chinese subjects were enrolled and exposed to a single oral dose of 25 mg dorzagliatin. Eight subjects were enrolled in the ESRD group, including one with T2D. Nine subjects were initially enrolled in the HV group, with one deemed ineligible later on due to a mismatch in age with the corresponding ESRD group, thereby dropped out on day 1.

**TABLE 1** PBPK modeling simulation of dorzagliatin exposure in different populations

	Population		
	Sim-HVs	Sim-moderate-RI	Sim-severe-RI
$C_{max}$ (mg/L)	0.92	0.93	0.83
$C_{max}$ ratio <sup>a</sup>	\	1.01	0.90
AUC (mg/L*h)	5.15	6.73	6.37
AUC ratio <sup>a</sup>	\	1.31	1.24
CL (L/h)	17.10	12.80	13.50
CL ratio <sup>a</sup>	\	0.75	0.79
$CL_R$ (L/h)	0.98	0.39	0.20
$CL_R$ ratio <sup>a</sup>	\	0.40	0.20

Note: Sim-HV: White healthy population; Sim-moderate-RI: Sim-RenalGFR-30–60 (population with moderate renal impairment); Sim-severe-RI: Sim-RenalGFR-less 30 (population with severe renal impairment).

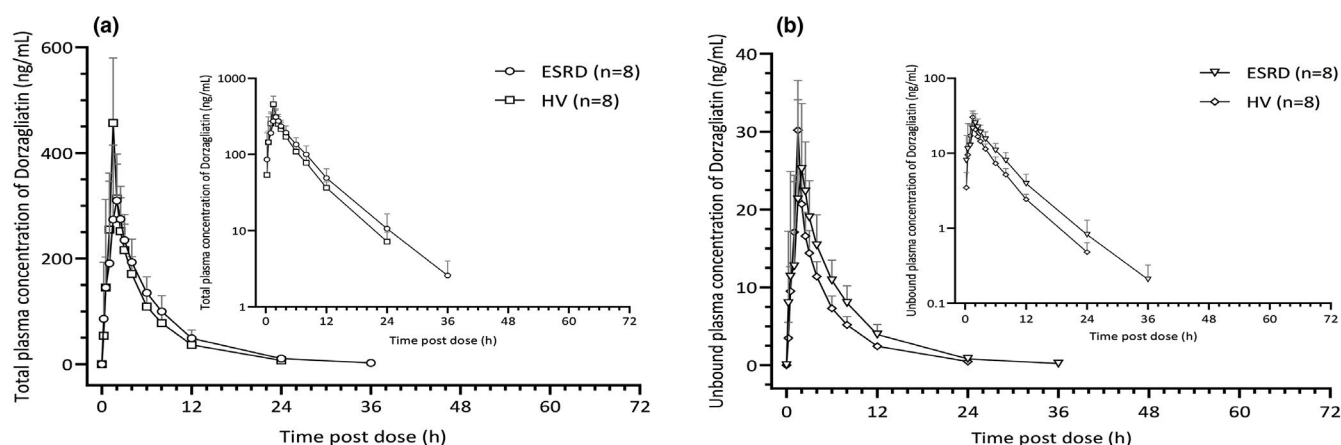
Abbreviations: AUC, area under concentration-time curve; CL, clearance;  $CL_R$ , renal clearance;  $C_{max}$ , peak concentration; HVs, healthy volunteers; PBPK, physiologically-based pharmacokinetic; RI, renal impairment.

<sup>a</sup>Ratio is defined as relative to the healthy population.

**TABLE 2** Demographic and baseline characteristics of participants

Demographic variable	HVs	ESRD	Total
N	9	8	17
Sex			
Male, n (%)	4 (44.4)	3 (37.5)	7 (41.2)
Female, n (%)	5 (55.6)	5 (62.5)	10 (58.8)
Age, years			
Mean (min-max)	43.3 (23–60)	44.5 (22–63)	43.9 (22–63)
Weight, kg/m <sup>2</sup>			
Mean (min-max)	54.71 (47.2–71.4)	60.40 (48.3–82.0)	57.39 (47.2–82.0)
BMI, kg/m <sup>2</sup>			
Mean (min-max)	21.89 (18.8–23.9)	23.25 (18.6–26.8)	22.53 (18.6–26.8)
eGFR, ml/min/1.73 m <sup>2</sup>			
Mean (min-max)	127 (91–176)	8.63 (5–12)	–

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HVs, healthy volunteers; max, maximum; min, minimum.

**FIGURE 2** Mean plasma concentration against time profiles (insert: semi-log plot) in patients with ESRD versus HVs after a single oral dose of 25 mg dorzagliatin (a, total dorzagliatin; b, unbound dorzagliatin). ESRD, end-stage renal disease; HVs, healthy volunteers

All 17 subjects were included in the safety analysis set, and 16 subjects who completed the study were included in the PK analysis set. Demographic and baseline characteristics of the enrolled subjects are summarized in Table 2. Five female subjects were enrolled in each group. The overall mean (range) of age was 44.5 years (22–63 years) and 43.3 years (23–60 years) for patients with ESRD and HVs, respectively. The overall mean (range) of BMI was 23.25 kg/m<sup>2</sup> (18.6–26.8 kg/m<sup>2</sup>) and 21.89 kg/m<sup>2</sup> (18.8–23.9 kg/m<sup>2</sup>) for patients with ESRD and HVs, respectively.

All eight subjects in the HV group completed the study and were well matched with the subjects in the ESRD group by sex, age, and BMI, as predefined in the study protocol.

All subjects in the ESRD group, but none in the HV group, received at least one concomitant medication during the study. The most common concomitant medication classes reported were blood pressure-lowering agents

(e.g., calcium channel blockers,  $\beta$ -blockers, peripheral antiadrenergic agent, and peripheral vasodilator), nutrition supplement, and gout suppressants. Their uses were reviewed and approved by the investigator and the pharmacist beforehand and was considered to have no impact on the PKs or safety evaluation in the study.

### Clinical assessment of impact of RI on dorzagliatin PKs

After a single oral dose of 25 mg dorzagliatin administration, the mean plasma concentration of dorzagliatin versus time profiles appeared to be comparable between the ESRD and HV groups (Figure 2). Dorzagliatin was rapidly absorbed in subjects of both groups with medium  $T_{max}$  being 1.75 and 1.5 h for patients with ESRD and HVs, respectively. The plasma concentration dropped below

**TABLE 3** Comparison of PK parameters for dorzagliatin in patients with ESRD and HVs after a single oral dose of 25 mg dorzagliatin

Parameter, unit	Arithmetic mean (SD)		Geometric mean			90% CI for GMR	
	HVs	ESRD	HVs	ESRD	GMR	Lower limit	Upper limit
	n = 8	n = 8	n = 8	n = 8	ESRD/HVs		
$C_{\max}$ , ng/ml	457 (123)	364 (78.2)	442	356	0.81	0.64	1.01
$AUC_{\text{last}}$ , ng/ml*h	1870 (277)	2090 (420)	1857	2056	1.11	0.95	1.29
$AUC_{\text{inf}}$ , ng/ml*h	1900 (287)	2110 (423)	1887	2074	1.10	0.94	1.28
$C_{\max,u}$ , ng/ml <sup>a</sup>	30.2 (6.37)	28.4 (7.92)	29.5	27.5	0.93	0.74	1.17
$AUC_{\text{last},u}$ , ng/ml*h <sup>a</sup>	124 (10.4)	166 (40.2)	124	162	1.30	1.12	1.52
$AUC_{\text{inf},u}$ , ng/ml*h <sup>a</sup>	127 (11.2)	167 (40.2)	126	163	1.29	1.11	1.51
$f_u$ , % <sup>a</sup>	6.72 (0.717)	8.06 (0.928)	$p = 0.0081^b$				
$T_{\max}$ , h <sup>c</sup>	1.50 (1.50–1.50)	1.75 (0.50–2.50)					
$t_{1/2}$ , h	5.02 (1.26)	5.42 (1.69)					
$V_z/F$ , L	96.8 (27.9)	94.1 (28.9)					
CL/F, L/h	13.4 (1.76)	12.3 (2.64)					
$A_e$ , mg	2.01 (0.516)	0.300 (0.0982)					
$CL_R$ , L/hr	1.11 (0.366)	0.148 (0.0506)					

Abbreviations:  $A_e$ , cumulative amount excreted into urine;  $AUC_{\text{inf}}$ , area under the concentration-time curve to infinity;  $AUC_{\text{last}}$ , area under the concentration-time curve from time of administration up to the time of the last quantifiable concentration; CI, confidence interval; CL/F, apparent systemic clearance;  $CL_R$ , renal clearance;  $C_{\max}$ , maximum concentration; ESRD, end-stage renal disease;  $f_u$ , plasma unbound fraction; GMR, geometric mean ratio; HVs, healthy volunteers; PK, pharmacokinetic;  $t_{1/2}$ , elimination half-life;  $T_{\max}$ , time to reach maximum plasma concentration;  $V_z/F$ , apparent volume of distribution.

<sup>a</sup>There were seven for the ESRD group,  $f_u$  of one subject is missing.

<sup>b</sup>The  $p$  value is calculated and displayed for between-group comparison of  $f_u$ .

<sup>c</sup>Data are presented as median (minimum-maximum).

quantitative limit of 1.00 ng/ml after 48 h postdose. The mean  $t_{1/2}$  in patients with ESRD was 5.42 h, comparable to 5.02 h in HVs. As expected, the  $CL_R$  of dorzagliatin in patients with ESRD showed dramatically decrease, resulting in a reduced  $A_e$ . Nonetheless, the mean CL/F was similar between the two groups (Table 3).

Following ANOVA analysis, the least square GMRs (90% CI) of ESRD-to-HV of  $C_{\max}$ ,  $AUC_{\text{last}}$ , and  $AUC_{\text{inf}}$  were 0.81 (0.64–1.01), 1.11 (0.95–1.29), and 1.10 (0.94–1.28), respectively, showing that mean  $C_{\max}$  mildly decreased by 19%, whereas mean  $AUC_{\text{last}}$  and  $AUC_{\text{inf}}$  slightly increased by 11% and 10%, respectively, in patients with ESRD as compared with the paired HVs (Table 3). Because we observed significant difference in dorzagliatin plasma  $f_u$  between the two groups with mean  $f_u$  values being 8.06% for the ESRD group and 6.72% for the HV group ( $p = 0.0081$ ), we therefore performed additional ANOVA analysis using the corresponding unbound PK parameters. The results showed that the least square GMRs (90% CI) for the  $C_{\max,u}$ ,  $AUC_{\text{last},u}$ , and  $AUC_{\text{inf},u}$  were 0.93 (0.74–1.17), 1.30 (1.12–1.52), and 1.29 (1.11–1.51), respectively, when the ESRD group was compared to the control HV group, indicating that the mean  $C_{\max,u}$  values were similar between the two groups, while mean  $AUC_{\text{last},u}$  and  $AUC_{\text{inf},u}$  increased by

30% and 29%, respectively, in patients with ESRD relative to the HV controls (Table 3).

Although the  $f_u$  value of dorzagliatin demonstrated significant difference in the between-group comparison analysis (8.06% vs. 6.72% for ESRD vs. HV,  $p = 0.0081$ ), the corresponding  $C_{\max,u}$  in the ESRD group relative to the HV control group appeared similar (Table 3). Table 4 is a summary comparison of the results from PBPK modeling with that from the current clinical RI study.

## Safety assessment

A single oral dose of 25 mg dorzagliatin was well-tolerated in both patients with non-dialysis ESRD and HVs. No deaths, serious AEs, or discontinuations due to TEAEs occurred during the study. The overall TEAEs are displayed in Table 5. Twelve TEAEs were reported in eight subjects, all were mild in severity. Two TEAEs in patients with ESRD, one with blood alkaline phosphatase increase (102–114 IU/L, normal range <100 IU/L) and one with headache, both were considered to be possibly related to the study drug by the investigator. In the HV group, two TEAEs were reported to be possibly drug-related, one with

**TABLE 4** Effect of RI on PKs of dorzagliatin—comparison of results from PBPK modeling with the clinical RI study

	PBPK modeling		Clinical study	
	Sim-moderate-RI	Sim-severe-RI	ESRD	ESRD ( $f_u$ )
$C_{max}$ ratio <sup>a</sup>	1.01	0.90	0.81	0.93
AUC ratio <sup>a</sup>	1.31	1.24	1.10	1.30

Note: Sim-moderate-RI: Sim-RenalGFR-30–60 (Population with moderate renal impairment).

Sim-severe-RI: Sim-RenalGFR-less 30 (population with severe renal impairment).

ESRD: Plasma dorzagliatin in the patients with end-stage renal disease.

ESRD ( $f_u$ ): Plasma unbound fraction of dorzagliatin in the patients with end-stage renal disease.

Abbreviations: AUC, area under the concentration-time curve;  $C_{max}$ , maximum concentration; ESRD, end-stage renal disease;  $f_u$ , plasma unbound fraction; PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetic; RI, renal impairment.

<sup>a</sup>Ratio is defined as relative to the healthy population.

**TABLE 5** TEAEs reported by subjects

System organ class and preferred term	Number of subjects with TEAEs (number of TEAEs)		
	HV	ESRD	Total
Overall TEAEs	2 [3]	6 [9]	8 [12]
Investigations			
White blood cells urine positive	0	2 [2]	2 [2]
Red blood cells urine positive	0	1 [1]	1 [1]
Protein urine present	1 [1]	0	1 [1]
Blood alkaline phosphatase increased	0	1 [1]	1 [1]
Metabolism and nutrition disorders			
Hypoalbuminemia	0	1 [1]	1 [1]
Hypoglycemia	1 [1]	0	1 [1]
Hyperphosphatemia	0	1 [1]	1 [1]
Hypermagnesemia	0	1 [1]	1 [1]
Nervous system disorders			
Headache	0	1 [1]	1 [1]
Respiratory, thoracic, and mediastinal disorders			
Epistaxis	1 [1]	0	1 [1]
Gastrointestinal disorders			
Dry mouth	0	1 [1]	1 [1]

Abbreviation: TEAEs, treatment-emergent adverse events.

protein urine and one with asymptomatic hypoglycemia (blood glucose level: 3.81 mmol/L). There were no other clinically significant changes related to dorzagliatin treatment in physical examination, vital signs, 12-lead ECG, or laboratory tests (hematology, clinical chemistry, and urine analysis) during the study.

As described previously, the part 2 study will only be conducted only if the ratio of AUC ( $AUC_{last}$  or  $AUC_{inf}$ ) geometric mean between patients with non-dialysis ESRD

and HVs exceeds 100% based on the results from the part 1 study. Consistent with in silico prediction, we observed the GMR within 11%, thus the part 2 study was deemed unnecessary.

## DISCUSSION

This current study was aimed to investigate the impact of RI on dorzagliatin PKs and safety and to provide guidance in the clinical use of dorzagliatin to control hyperglycemia in patients with DKD with various stages of RI.

On the basis of absorption, distribution, metabolism, and excretion/drug metabolism and pharmacokinetic properties of, predictable dose-response relationship, as well as favorable efficacy and safety profiles of dorzagliatin,<sup>24–26</sup> it was hypothesized that RI is not expected to significantly alter its PK properties, thus dorzagliatin may not require dose adjustment in patients with DKD. To confirm this hypothesis, we first used quantitative PBPK modeling and simulation<sup>28</sup> which further predicted no clinical meaningful impact of RI on the PK characteristics of dorzagliatin, as indicated by about 30% increases in drug exposure levels in patients with ESRD relative to the HVs with normal renal function.

Results from the part 1 clinical study are consistent with the quantitative prediction based on PBPK modeling, as indicated in the summary Table 5, further validating the in silico model and supporting the notion that RI will not alter the PK characteristics of dorzagliatin significantly, thus no dose adjustment is considered necessary when given to patients with DKD with various stages of RI. Here, PBPK modeling accurately predicted  $CL_R$  (refer to Supplementary Material for details) and minimal impact of RI on dorzagliatin exposure, which further provided strong support for the reduced study design. Therefore, integrating a computational approach,



such as utilizing scientifically well-founded PBPK models, can play an important role in critical decision making in drug development to help reduce uncertainty and increase confidence.

Dorzagliatin has demonstrated a sufficiently large safety margin, linear PKs, and highly predictable dose-response relationship in multiple early and late-stage clinical studies<sup>22–26</sup> across a wide range of doses of 5–150 mg b.i.d., a 30% increase in exposure AUC should not result in clinically meaningful changes in efficacy and safety when given at 75 mg b.i.d., which is the standard dose used in the phase III registration trials. Plasma protein binding is often altered in patients with impaired renal function,<sup>32</sup> the change in  $f_u$  between the ESRD and HV groups (8.06% vs. 6.72%) is speculated to be related to the change in albumin (refer to Supplementary Material for details). The parameters of  $V_z/F$ ,  $CL/F$ , and  $t_{1/2}$  of dorzagliatin were similar between the two groups, indicating that RI had minimal impact on the overall PK profile of dorzagliatin despite apparent low  $CL_R$  in the patients with ESRD. Consequently, there should be no need for dose adjustment of dorzagliatin in patients with DKD with various levels of RI.

In the current study, after 25 mg single dose, the geometric mean of  $C_{max}$  in the ESRD group was 356 ng/ml, 19% lower than the HV control group, whereas comparable to the value (350 ng/ml) obtained previously from the 25 mg dose HV cohort in the phase I SAD study.<sup>24</sup> In addition, RI is generally considered to have minimal impact on  $C_{max}$ .<sup>32</sup> Therefore, the observed 19% decrease of  $C_{max}$  in the ESRD group relative to the control group in this study may be attributed to the relatively small sample size, as well as the individual differences rather than to renal insufficiency.

In conclusion, systemic exposure of dorzagliatin is not clinically significantly effected by end-stage RI based on clinical assessment. Therefore, dorzagliatin represents a new oral treatment option for T2D patients with RI and ESRD without a need for dosage adjustment.

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## CONFLICTS OF INTEREST

The authors declared no competing interests for this work.

## AUTHOR CONTRIBUTIONS

P.L., Y.S., X.J., and S.R. wrote the manuscript. J.M., P.F., S.R., C.H., Y.W., and L.C. designed the research. J.M., P.F., C.H., Y.W., S.R., C.J., P.L., Y.Z., J.R., and Y.W. performed the research. Y.Q., C.T., R.Y., and Y.D. analyzed the data.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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