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Pharmacokinetics and Safety of Chiglitazar in Patients with Renal Impairment: A Multicenter, Open-label, Parallel-controlled Phase I Clinical Trial

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Abstract: Background: Chiglitazar is a novel pan-agonist that can activate all three subtypes of peroxisome proliferator-activated receptor. It was approved for the treatment of type 2 diabetes mellitus as monotherapy on October 19, 2021, and as combination therapy with metformin when using metformin alone failed in blood glucose control on July 16, 2024, by the National Medical Products Administration (NMPA) in China. However, pharmacokinetic (PK) study of this product in patients with renal impairment have not yet been conducted. The purpose of this study is to evaluate the effects of renal impairment on the PK and safety after a single oral dose of Chiglitazar. *Methods:* This multicenter, open-label, parallel-controlled, single-dose Phase I clinical trial (NCT 05515458) enrolled 24 participants (12/group) with severe renal impairment (SRI) or normal renal function (NRF). All participants received a single oral dose of 48 mg chiglitazar after breakfast and the PK and safety was evaluated. *Results:* The median T_{max} was similar in both SRI and NRF groups (5.01 vs. 5.02 hours). The geometric mean ratios (GMR) for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 0.807 (90% confidence interval [CI]: 0.697–0.935), 0.853 (90% CI: 0.713–1.02), and 0.855 (90% CI: 0.716–1.02), respectively, indicating that SRI did not significantly affect the exposure of chiglitazar. The C_{max} was weakly positively correlated with eGFR (r= 0.4798, P= 0.0177) and creatinine clearance rate (r= 0.4667, P= 0.0215). Urinary excretion of chiglitazar was negligible in the SRI group, with average values of Ae_{0-t}=2,900 ng, Fe_{0-t}=0.0060%, and CL_R=0.323 mL/h within 0–72 hours post-dose. The treatment-

emergent adverse event (TEAE) incidence in the SRI group (16.7%, 2/12) was comparable to that in the NRF group (25%, 3/12). All TEAEs were of mild severity and were adjudicated by the investigators to be unrelated to chiglitazar. No serious AE were reported. Chiglitazar exhibits a favorable safety profile. *Conclusion:* Severe renal impairment does not significantly affect the PK and safety of chiglitazar, and no dose adjustment for mild, moderate, and severe renal impairments is required.

Keywords: Chiglitazar; Pharmacokinetics; Renal impairment; Safety

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1. Introduction

Diabetic nephropathy is the predominant cause of end-stage kidney disease within developed nations, responsible for nearly 40% of new cases that necessitate kidney replacement therapy [1, 2]. In patients with Diabetic nephropathy, the use of antidiabetic medications may require dosage adjustments due to reduced renal function to prevent drug accumulation and potential safety issues. Accordingly, PK studies of antidiabetic agents in patients with renal impairment are warranted to clarify appropriate dosing regimens for this patient population.

Chiglitazar, a pan-agonist for all three subtypes of peroxisome proliferator-activated receptor (PPAR), can fully activate PPARγ with minimal reverse effect due to its strong and specific binding affinity [3–5]. Chiglitazar preferentially regulates the gene expressions of angiopoietin-like 4 (ANGPTL4) and pyruvate dehydrogenase kinase 4 (PDK4), which are involved in glucose and lipid metabolism, through conformational restricted binding and phosphorylation inhibition of PPARγ [6]. Clinical trials have confirmed that chiglitazar improves blood glucose control, reverse insulin resistance, regulates lipid metabolism and alleviates liver injury while maintaining a favorable safety profile in patients with type 2 diabetes mellitus (T2DM) and metabolic dysfunction-associated steatohepatitis (MASH) [7].

To date, there is a paucity of research investigating the use of chiglitazar in the context of renal impairment. The pharmacokinetics (PK) properties of chiglitazar in vitro and in vivo indicated that the relatively high distribution of the drug is in the liver, pancreas, and skeletal muscles, with minimal excretion through the kidneys [4]. The plasma exposure and peak levels of chiglitazar after repeated doses were comparable between elderly (≥ 65 years old) and younger patients [8]. It is recommended to evaluate the PK for the drugs that may be used in patients with renal impairment to provide reasonable usage and dose regimen [9, 10]. The purpose of this study is to evaluate effects of renal impairment on the PK and safety after a single oral dose of chiglitazar.

2. Materials and results

2.1. Study design

This multicenter, open-label, parallel-controlled, single-dose Phase I clinical trial is conducted from November 17, 2022 to July 19, 2023, including four centers: the First Affiliated Hospital of Soochow University, the First Affiliated Hospital of Zhengzhou University, the Second People's Hospital of Hefei, and the Second Affiliated Hospital of Soochow University. The screening phase spanned from day -14 to day -2. Subsequently, the baseline is established on day -1. The observation period, comprising day 1 to day 4, allowed for detailed data collection. Finally, on day 7, a telephone follow-up is implemented to gather additional information. A simplified PK study

design is employed. Initially, the study cohort comprises 12 subjects exhibiting severe renal impairment, followed by the recruitment of 12-14 subjects with NRF. The study would not proceed with further PK investigation in subjects with mild to moderate renal dysfunction if it was confirmed that severe renal impairment resulted in a less than 1.5-fold increase (The 1.5-fold exposure was based on the previous clinical study results that a single dose of 96 mg chiglitazar are safe and well-tolerated) in chiglitazar exposure. Conversely, a comprehensive PK study would be initiated, encompassing subjects across various renal function classifications. The mean weight, age, and gender distribution of the NRF group are matched with the renal impairment cohort within ±10 kg, ±10 years, and ±1 subject per gender, respectively. The institutional review board or independent ethics committee of each participating research center approved the study protocol and all participants provided written informed consent. The study has been registered in the ClinicalTrials.gov database (NCT 05515458) and is conducted complying with the Declaration of Helsinki.

2.2. Participants

Subjects in the renal impairment group should meet the following criteria:

(1) Aged 18–79 years old

(2) Males having a body weight of no less than 50 kg and females of no less than 45 kg, with a body mass index (BMI) ranging from 18 to 30 kg/m²

(3) Not having taken any drugs within 2 weeks before screening or having had a stable medication for at least 4 weeks for the treatment of renal impairment and/or other comorbidities

(4) The absolute estimated glomerular filtration rate (eGFR) meets the standard of 15–29 mL/min for severe renal impairment

(5) Subjects (including their partners) are willing to voluntarily take effective contraceptive measures from the screening period until 6 months after the administration of the study drug. The inclusion criteria for subjects in the NRF group are as follows: body weight, age, and gender were matched with those in the renal imparement group; the absolute eGFR was ≥ 90 mL/min and < 130 mL/min.

Participants with the following conditions should be excluded:

(1) Allergic constitution, or allergic to PPAR agonist drugs, or allergic to any component of chiglitazar tablets

(2) Having taken PPAR agonist drugs within 2 weeks before the start of the trial

(3) Having undergone or planning to receive surgery that might affect the absorption, distribution, metabolism, and excretion of drugs

(4) Acute hepatitis, chronic liver disease, or any one of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin greater than 2 times the upper limit of the normal value

(5) Female subjects who are pregnant, lactating, or have a positive serum pregnancy test result during the screening period or the trial process

2.3. Intervention

Chiglitazar tablets, manufactured by Chengdu Chipscreen Pharmaceutical Co., Ltd, were utilized for oral administration. In the Phase I, II, and III clinical trials conducted in China, the results have demonstrated that 48 mg exhibits favorable efficacy and safety. Even at a dose of 96 mg, it remains safe and well-tolerated in the healthy population. Additionally, since the PK characteristics after multiple dosing were consistent with those observed after the first administration. A single oral dose of 48 mg was selected as the trial dosage. Moreover, food intake

had no significant effect on the PK of the drug. Consequently, the dosing is scheduled to be taken after meals. On the morning of day 1, subjects received a single 48 mg dose of chiglitazar after breakfast. Extra consumption of water is prohibited within a 1-hour window prior to and following drug intake, while food intake is permitted 4 hours after administration. The participants are dismissed following sample collection and a safety assessment on day 4, with a follow-up telephone call conducted on the 7 th day.

2.4. Outcomes

The primary outcomes of the study focused on the pharmacokinetic (PK) profile of a single oral dose of chiglitazar in subjects with either impaired or normal renal function. Key PK parameters assessed in plasma included the maximum plasma concentration (C_{max}), area under the concentration-time curve from time zero to the last measurable concentration (AUC_{0-t}), area under the concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$), time to reach maximum plasma concentration (T_{max}), apparent volume of distribution (Vz/F), apparent clearance (CL/F), terminal elimination half-life ($t_{1/2}$), mean residence time from time zero to the last measurable concentration (MRT_{0-t}), mean residence time extrapolated to infinity ($MRT_{0-\infty}$), and the unbound fraction (fu). Additionally, the study investigated the correlations between plasma PK parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) and renal function indices, including estimated glomerular filtration rate (eGFR) and creatinine clearance rate (CCR).

Urinary PK parameters included the cumulative amount of drug excreted from time zero to the last measurable concentration (Ae_{0-t}), fraction of dose excreted unchanged in urine (fe), and CL_R. Secondary outcomes comprised the evaluation of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), alongside safety assessments including complete blood count, serum biochemistry, urinalysis, coagulation profile, 12-lead electrocardiogram (ECG), vital signs, and physical examination. The severity of all adverse events was classified according to the Adverse Event and Serious Adverse Event Guidelines (2018) issued by the National Institute on Aging [11].

2.5. Pharmacokinetic sampling

For PK blood sampling, the time points are as follow: before drug administration (-60 min to 0 h) and 0.5 h ± 3 min, 1 h ± 3 min, 2 h ± 3 min, 3 h ± 5 min, 4 h ± 5 min, 5 h ± 5 min, 6 h ± 5 min, 8 h ± 5 min, 12 h ± 5 min, 24 h ± 10 min, 36 h ± 10 min, 48 h ± 10 min, and 72 h ± 10 min after drug administration. When there was a conflict between PK blood sampling points and other examinations, priority is given to ensuring blood sampling time. For PK urine sample collection, urine specimens are collected respectively before drug administration (-24 h to 0 h, random urine) and in the periods of 0–4 h, 4–8 h, 8–12 h, 12–24 h, 24–48 h, and 48–72 h after drug administration.

2.6. Statistics

Descriptive statistics for quantitative data are expressed as the mean ± the standard deviation or median (minimum, maximum), while count data are described using frequency and proportion. The 90% confidence interval (CI) is calculated for the observed indicators. The full analysis set (FAS) included all subjects who received at least one dose of the study drug and was used for demographic and baseline characteristic analysis. The PK parameter analysis set (PKPS) included subjects who received at least one correct dose of the study drug and had at least one evaluable PK parameter. The PK concentration analysis set (PKCS) included subjects who received at least one correct dose of the study drug, had at least one evaluable drug concentration data, and are not affected by related factors that influenced the PK concentration data. The safety analysis set (SS) included all subjects who received at

least one dose of the study drug. Based on PKPS, an equivalence test method is adopted to evaluate comparison of the main PK parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$) of chiglitazar after natural logarithm transformation among severe renal impairment (SRI) and normal renal function (NRF) groups, and calculate the geometric mean ratio (GMR) of the PK parameters and the corresponding 90% CI. Also based on PKPS, the formula $\log(y) = \beta 0 + \beta 1 * \log(x)$ is adopted to evaluate the quantitative relationship between each PK parameter and each renal function index (where y represents the PK parameter and x refers to the renal function index) with $\log(x)$ as the fixed effect term. $P < 0.05$ (two-sides) is set as a significant difference. Phoenix WinNonlin 8.3 software is used for PK analysis, and the statistical software is SAS 9.4.

3. Results

3.1. Demographic and baseline characteristics

A total of 96 subjects were screened in the trial, out of which 72 failed the screening. Eventually, 24 subjects were enrolled, including 12 subjects in the SRI group and 12 subjects in the NRF group, and all these subjects completed the trial (**Figure 1**).

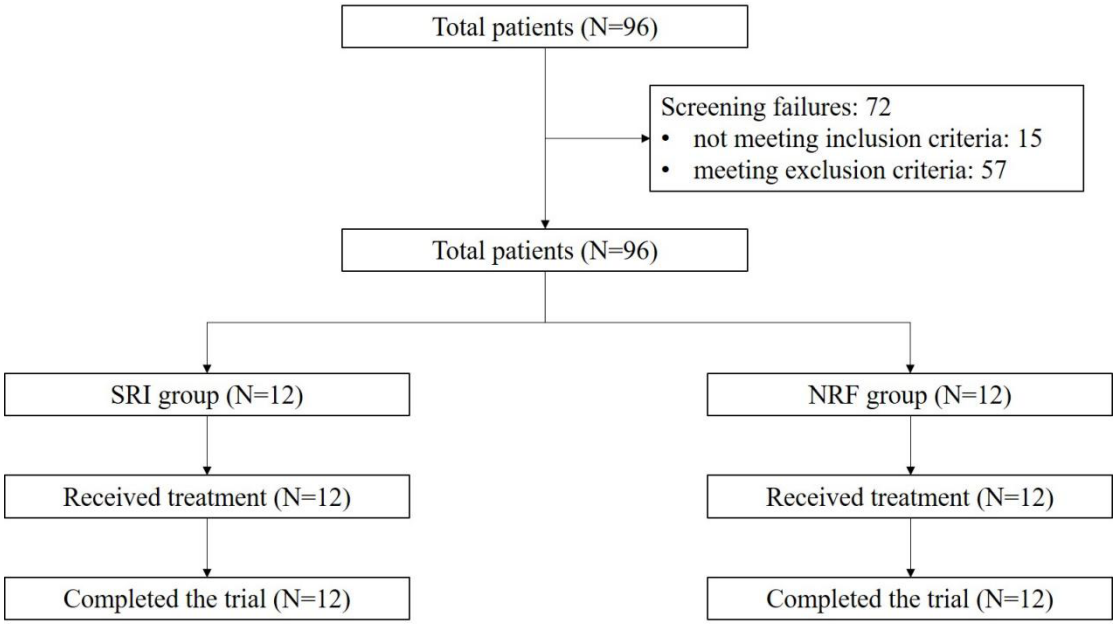

Figure 1. Flowgraph of NRF and SRI group

The mean age was 55.9 ± 6.93 years old; the average height was 162.42 ± 6.58 cm; the average weight was 66.00 ± 8.53 kg; and the average BMI was 24.95 ± 2.22 kg/m². There were 17 males (70.8%) and 7 females (29.2%). All 24 subjects were of Han ethnicity. The average ages in the SRI group and NRF group were 57.8 ± 9.15 years old and 54.0 ± 2.95 years old respectively; the average body weights were 66.33 ± 11.27 kg and 65.67 ± 4.98 kg respectively; and the proportions of male subjects were 75.0% (9/12) and 66.7% (8/12) respectively. The demographic information, such as age, body weight, and gender composition of the two groups was comparable (**Table 1**).

Concomitant medications were presented in Supplementary **Table 1**, and none of the prohibited drugs per the protocol were involved.

Table 1. Demographic and baseline characteristics

Group		SRI (N = 12)	NRF (N = 12)	Total (N = 24)
Gender	Male n (%)	9 (75.0)	8 (66.7)	17 (70.8)
	Female n (%)	3 (25.0)	4 (33.3)	7 (29.2)
Ethnicity	Han n (%)	12 (100)	12 (100)	24 (100)
	Others n (%)	0	0	0
Age (years)	n (Missing)	12 (0)	12 (0)	24 (0)
	Mean (SD)	57.8 (9.15)	54.0 (2.95)	55.9 (6.93)
Height (cm)	n (Missing)	12 (0)	12 (0)	24 (0)
	Mean (SD)	161.88 (7.453)	162.96 (5.852)	162.42 (6.577)
Weight (kg)	n (Missing)	12 (0)	12 (0)	24 (0)
	Mean (SD)	66.33 (11.269)	65.67 (4.980)	66.00 (8.527)
BMI (kg/m²)	n (Missing)	12 (0)	12 (0)	24 (0)
	Mean (SD)	25.15 (2.716)	24.74 (1.671)	24.95 (2.215)
Smoking status	Never smoked n (%)	9 (75.0)	11 (91.7)	20 (83.3)
	Used to smoke n (%)	2 (16.7)	1 (8.3)	3 (12.5)
	Still smoking currently n (%)	1 (8.3)	0	1 (4.2)
Drinking status	Never drank n (%)	7 (58.3)	9 (75.0)	16 (66.7)
	Used to drink n (%)	5 (41.7)	1 (8.3)	6 (25.0)
	Still drinking currently n (%)	0	2 (16.7)	2 (8.3)

*BMI: Body mass index; NRF: Normal renal function group; SRI: Severe renal impairment group.

3.2. Pharmacokinetics in plasma

Following a single oral administration of 48 mg chiglitazar, the median T_{max} was documented at 5.01 and 5.02 hours for two groups, respectively, with the average C_{max} of 1010 ng/mL and 1240 ng/mL. Moreover, the mean AUC_{0-t} was 8110 ng*h/mL and 9240 ng*h/mL, while the average $AUC_{0-\infty}$ was 8230 ng*h/mL and 9360 ng*h/mL, respectively (**Table 2**).

It indicates that although there is a difference in C_{max} between the two cohorts, the reduction amplitude is relatively modest. Upon comparison between the two groups, no significant variations were observed in T_{max} and $t_{1/2}$ in the SRI group. Notably, the plasma f_u in the SRI group (3.76%) exhibited a slight increase relative to that in the NRF group (1.45%). Furthermore, the V_z/F and CL/F in the SRI group were elevated by approximately 22.0% and 19.6%, respectively, when compared to those in the NRF group (**Table 2**).

The average C_{max} was recorded as 1,010 ng/mL and 1,240 ng/mL, while the average AUC_{0-t} was 8,110 ng*h/mL and 9,240 ng*h/mL, and the average $AUC_{0-\infty}$ was 8,230 ng*h/mL and 9,360 ng*h/mL, respectively. The GMR for the exposure parameters of chiglitazar (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) were 0.807 (90% CI 0.697–0.935), 0.853 (90% CI 0.713–1.02), and 0.855 (90% CI 0.716–1.02), respectively. Compared with NRF group, the C_{max} was reduced by approximately 19.3%, the AUC_{0-t} by approximately 14.7%, and the $AUC_{0-\infty}$ by approximately 14.5% in the SRI group, indicating that SRI did not markedly impact the PK profile of chiglitazar (**Table 3**, **Figure 2**).

Table 2. The PK parameters after a single oral administration of 48 mg of chiglitazar (PKPS)

PK	SRI(N=12)	NRF(N=12)
	Plasma PK parameters[#]	
T_{max} (h)	5.01 (3.00, 6.02)	5.02 (3.00, 6.00)
C_{max} (ng/mL)	1010 ± 222 (22.0)	1240 ± 231 (18.7)
AUC_{0-t} (ng*h/mL)	8110 ± 2670 (32.9)	9240 ± 1710 (18.5)
$AUC_{0-\infty}$ (ng*h/mL)	8230 ± 2680 (32.5)	9360 ± 1720 (18.4)
$t_{1/2}$ (h)	12.3 ± 3.98 (32.5)	12.4 ± 3.72 (30.1)
V_z/F (mL)	111000 ± 49400 (44.3)	91000 ± 18900 (20.7)
CL/F (mL/h)	6340 ± 1740 (27.5)	5300 ± 1040 (19.6)
f_u(%)	3.76 ± 1.10 (29.3)	1.45 ± 0.58 (40.0)
MRT_{0-t} (h)	11.0 ± 2.36 (21.4)	10.5 ± 1.66 (15.8)
$MRT_{0-\infty}$ (h)	12.1 ± 2.42 (20.0)	11.4 ± 1.79 (15.6)
	Urinary PK Parameters[*]	
Ae_{0-t} (ng) #	2900 ± 1500 (51.9)	/
Fe (%)#	0.0060 ± 0.0031 (51.9)	/
CL_R (mL/h) #	0.323 ± 0.166 (51.5)	/

[#]Except that T_{max} is presented as Median (Min, Max), all the other parameters are expressed as Mean ± SD (CV%). [*]All the indicators are expressed as Mean ± SD (CV%). [#]N = 6. Only the urinary drug concentration values of 6 subjects in the severe renal impairment group can be evaluated. The urinary drug concentrations of the remaining subjects in all periods are all below the lower limit of quantification (4.00 ng/mL), and their urinary drug parameters cannot be calculated. Ae_{0-t}: Amount excreted from time 0 to the last measurable concentration; $AUC_{0-\infty}$: Area under the curve from time 0 to infinity; AUC_{0-t}: Area under the curve from time 0 to the last measurable concentration; CL_R: Renal clearance; CL/F: Apparent clearance; C_{max}: Maximum concentration; CV: Coefficient of variation; Fe: Fraction excreted; fu:Fraction unbound; $MRT_{0-\infty}$:Mean residence time from time 0 to infinity; MRT_{0-t}:Mean residence time from time 0 to the last measurable concentration; NRF: Normal renal function; PK: pharmacokinetic; PKPS: PK parameter analysis set; SRI: Severe renal impairment; $t_{1/2}$:Terminal half-life; T_{max}:Time to maximum concentration; V_z/F:Apparent volume of distribution.

Table 3. Comparison of the main PK parameters(PKPS)

PK	Group	GM	GMR (90% CI)
C_{max} (ng/mL)	SRI	985	0.807(0.697, 0.935)
	NRF	1220	
AUC_{0-t} (ng*h/mL)	SRI	7750	0.853(0.713, 1.02)
	NRF	9090	
$AUC_{0-\infty}$ (ng*h/mL)	SRI	7880	0.855(0.716, 1.02)
	NRF	9210	

*$AUC_{0-\infty}$: Area under the curve from time 0 to infinity; AUC_{0-t}: Area under the curve from time 0 to the last measurable concentration; C_{max}: Maximum concentration; GM: Geometric mean; GMR: Geometric mean ratio; NRF: Normal renal function; PK: Pharmacokinetics; PKPS: Pharmacokinetic parameter analysis set; SRI: Severe renal impairment.

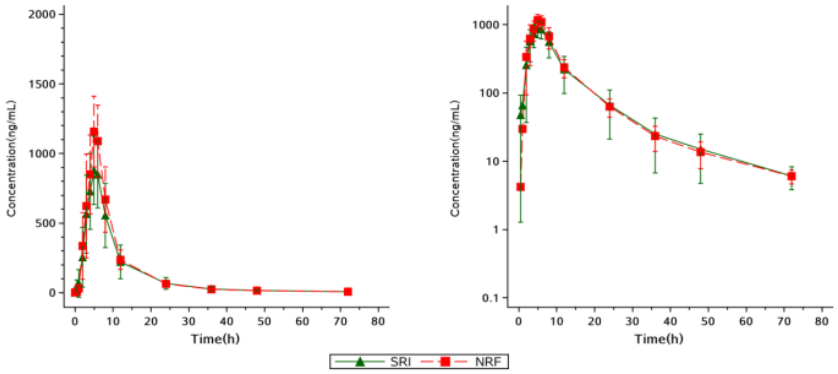

Figure 2. The average concentration-time curves of the drug in plasma for the SRI and NRF groups (linear and semi-logarithmic, PKCS).

*NRF: Normal renal function group; PKCS: Pharmacokinetic concentration analysis set; SRI: Severe renal impairment group.

The C_{max} exhibited a significant weakly positive correlation with eGFR (r = 0.4798, P = 0.0177) and creatinine clearance rate (r = 0.4667, P = 0.0215). Regarding the AUC, it presented a weakly positive correlation without significance with both eGFR and creatinine clearance rate. A lower C_{max} and AUC were observed in the SRI group. Collectively, these findings suggest that SRI does not lead to an elevation in peak plasma drug concentration and drug accumulation (**Figure 3**).

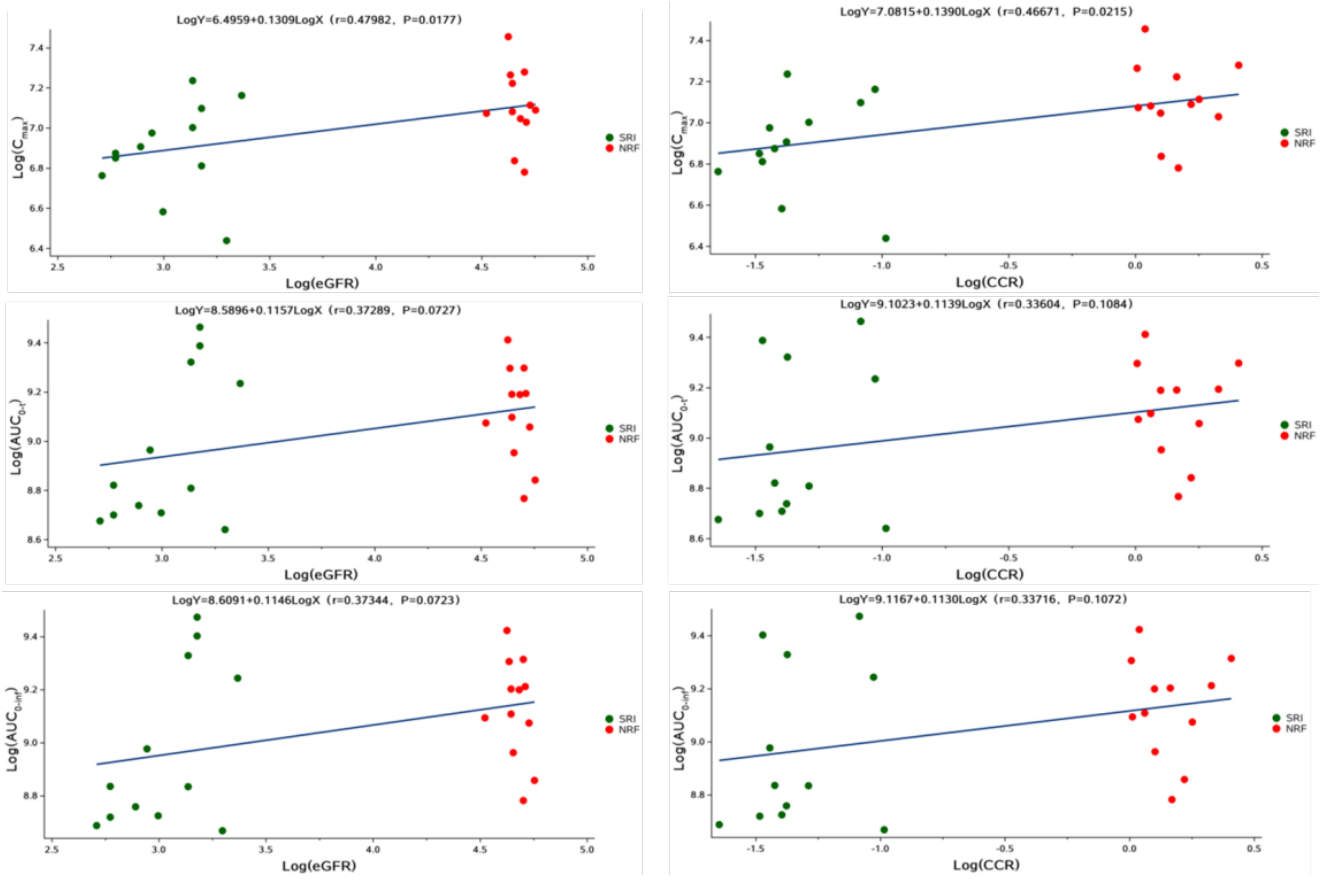

Figure 3. The correlation regression fitting line graphs between the exposure of chiglitazar and renal function indicators.

*AUC: Area under the curve; CCR: creatinine clearance rate; C_{max}: Maximum concentration; eGFR: Estimated glomerular filtration rate; NRF: Normal renal function group; SRI: Severe renal impairment group.

3.3. Pharmacokinetics in urine

The urinary drug concentrations in six subjects from the SRI group and in all participants from the NRF group remained below the lower limit of quantification (< 4.00 ng/mL) throughout the urine collection periods, precluding the calculation of their urinary PK. For the remaining six subjects in the SRI group, within 0–72 hours after administration of chiglitazar, the average values of the Ae_{0-t}, Fe_{0-t}, and CCR of chiglitazar were 2,900 ng, 0.0060%, and 0.323 mL/h, respectively, indicating that the fractional excretion of chiglitazar via urine was negligible in the SRI patients (Table 2).

3.4. Safety assessment

Mild TEAEs occurred in 5 of 24 subjects (20.8%), with the investigator determining no causal relationship to chiglitazar. The TEAE incidences were comparable between the SRI (16.7%, 2/12) and the NRF groups (25%, 3/12). All TEAEs resolved spontaneously, without requiring therapeutic intervention (**Table 4**). Chiglitazar demonstrated good safety among subjects with SRI.

Table 4. Summary of adverse events(SS)

Adverse events	SRI (N=12),n (%)	NRF (N=12),n (%)	Total(N=24)
TEAE	2(16.7)	3(25)	5(20.8)
TEAE related to chiglitazar	0	0	0
SAE	0	0	0
TEAE leading to withdrawal	0	0	0
		Count the TEAE according to SOC and PT	
Various examinations	1(8.3)	3(25)	4(16.7)
Elevated C-reactive protein	0(0)	2(16.7)	2(8.3)
Abnormal T-wave	1(8.3)	0(0)	1(4.2)
Elevated blood triglycerides	0(0)	1(8.3)	1(4.2)
Cardiac organ diseases	1(8.3)	0(0)	1(4.2)
Ventricular extrasystoles	1(8.3)	0(0)	1(4.2)

*The judgment results of clinical significance after treatment are statistically analyzed based on the worst result after treatment. TEAE: treatment-emergent adverse event; SAE: serious adverse event; SRI: severe renal impairment; NRF: normal renal function; SOC: system organ class; PT: preferred term; SS: safety analysis set.

4. Discussion

This study revealed that individuals with SRI exhibited lower GM of C_{max} and AUC compared to those with NRF, indicating that severe renal status has no obvious impact on the chiglitazar exposure. Urinary PK data indicated trivial amounts are excreted in the urine even in patients with SRI. All TEAEs were mild, and no SAEs were reported. The findings suggest that metabolism and excretion of chiglitazar are not significantly compromised by renal impairment, thus no dose adjustment is necessary for patients with mild, moderate, and severe renal impairment.

The C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ in the SRI group were relatively lower than NRF group, as well as the minimal

excretion of unchanged chiglitazar in the urine, indicating that renal function status has little impact on the PK. The results of this trial also aligned with the data from the previous study: The phase I study in healthy Chinese subjects showed that when a single oral dose of 8–72 mg was administered, the C_{max} and AUC increased proportionally with low inter-subject variability, and there was no significant change in $t_{1/2}$. After multiple administrations of 16 mg for 9 days, a steady state was achieved on the 6 th day with no significant accumulation [12]. The PK outcomes from a 7-day consecutive chiglitazar in T2DM patients revealed no significant age-related disparities in AUC, T_{max}, and $t_{1/2}$ parameters. Even after continuous medication, the AUC increment in subjects aged 65 and older was only marginal. Both cohorts exhibited commendable tolerability towards chiglitazar [8].

According to the prescribing information, approximately 92.69% ± 4.29% of chiglitazar is excreted via feces, while only 4.03% ± 0.66% is excreted through the kidneys. The amount of unchanged drug in the urine is minimal (0.01%) [13]. The results of previous in vitro studies showed that the free rate of chiglitazar in human plasma was approximately 0.5%. In this study, the free rates of chiglitazar in plasma samples at 5 hours after a single dose in subjects with SRI and NRF were 3.76 ± 1.10% and 1.45 ± 0.58%, respectively. The free rate in the SRI group was slightly increased compared with that in the NRF group. The observed discrepancies in free fraction may lack clinical significance, attributable to methodological limitations. This study used ultracentrifugation to determine free fraction; however, extreme centrifugal forces may disrupt drug-protein equilibrium and introduce sampling bias, thereby compromising the accuracy of free fraction. Differences between this study and prior in vitro data probably due to the methodological variations. Additionally, a pharmacokinetic study in hepatic subjects using the same ultracentrifugation method reported a 5-hour free fraction of 2.81±0.81% in normal hepatic function subjects, which is similar to the free fraction of chiglitazar in severe renal impairment subjects. Thus, the differences of free fraction may not translate to clinical meaningful differences in drug efficacy and safety. As chiglitazar's PK are not significantly altered by renal impairment, PK studies are not required in mild or moderate cases per guidelines [9, 10].

Enzymes and transporters at the sites of drug distribution and absorption influence the PK parameters of the drug [14]. PPAR agonists are typically involved in a variety of physiological processes, including enhancing insulin sensitivity, regulating lipid metabolism, as well as exerting anti-inflammatory and antioxidant effects [5, 15–17]. Therefore, this extensive distribution may represent a significant factor influencing the non-renal excretion of chiglitazar. The liver is the primary organ for drug metabolism, where the majority of drugs are metabolized into active or inactive forms and subsequently excreted into the intestines via bile, ultimately being eliminated through feces. Chiglitazar is also predominantly metabolized in the liver and excreted via feces, therefore, the liver plays a significant role in the non-renal metabolism of chiglitazar [4, 13]. Concurrently, PPAR agonists suggested its potential protective role in renal diseases including acute kidney injury, DN, and chronic kidney disease (CKD) [18]. Son *et al.* also revealed that pan PPAR agonist effectively prevented the progression of renal fibrosis in in vitro and in vivo fibrotic kidney models, by mitigating inflammatory responses and inhibiting fibroblast activation [19]. This study also validated that SRI limitedly affects the PK of chiglitazar.

In terms of AEs, previous study has also confirmed the good tolerability of chiglitazar in the elderly diabetic population [8]. This study further confirmed the safety profile in patients with SRI. There was no significant difference in the incidence of AE between the NRF group and the SRI group. Most AEs were mild or moderate, and no severe AE occurred. This indicates that chiglitazar has good tolerance in patients with different renal functions. Renal impairment does not increase the risk of drug-related AEs. Chiglitazar has demonstrated promising therapeutic effects in various conditions such as T2DM, dyslipidemia, and MASH [7, 17]. This research further confirms the safety profile in patients with SRI, expands the potential patient population for chiglitazar

treatment, and holds significant value for the management of DN.

5. Conclusion

The plasma and urinary PK profiles of chiglitazar were minimally affected in subjects with severe renal impairment. The occurrence of AEs in subjects with severe renal impairment was comparable to the normal population. It is safe and no dose adjustment is required for the population with mild to severe renal impairment.

Disclosure statement

The authors declare no conflict of interest.

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