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CLINICAL TRIAL REPORT

# Pharmacokinetics and Safety of HRS-1780 in Renal Impaired Subjects: A Multicenter, Non-Randomized, Open-Label Study

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**Purpose:** HRS-1780 is a selective non-steroidal mineralocorticoid receptor antagonist developed for the treatment of chronic kidney disease. This study aimed to assess the pharmacokinetics (PK) and safety profiles of HRS-1780 in subjects with renal impairment.

**Patients and Methods:** Eligible participants were enrolled in the healthy (glomerular filtration rate [GFR] of ≥90 mL/min), mild (GFR of 60–89 mL/min), and moderate renal impairment (GFR of 30–59 mL/min) groups with 9 subjects each and orally received 20 mg HRS-1780. Concentrations of HRS-1780 and its main metabolites were measured in plasma and urine. PK profiles between healthy and renal impairment subjects were compared using analysis of variance.

**Results:** A total of 27 subjects completed the study. HRS-1780 was rapidly absorbed and eliminated, with $T_{max}$ of 0.50–0.52 hour and $t_{1/2}$ of 2.06–2.56 hours. Exposure ($AUC_{0\text{-inf}}$) to HRS-1780 was comparable between mildly and moderately renal impaired subjects, while higher, but not significantly than that in healthy subjects. Similar plasma protein binding among different renal function groups suggested a consistent effect of renal function on total and unbound HRS-1780. Renal clearance of HRS-1780 decreased with severity of renal impairment, but renal elimination of HRS-1780 was minimal. Exposure to SX2183-M3 was significantly increased in the moderate renal impairment subjects. Renal impairment did not appear to be associated with an increased risk of adverse events.

**Conclusion:** HRS-1780 PK and safety profiles did not differ significantly between healthy and renal impairment subjects. This supports the drug dose regimen for renal impairment patients in clinical practice.

**Keywords:** mineralocorticoid receptor antagonist, pharmacokinetics, renal impairment, chronic kidney disease

## Introduction

Chronic kidney disease (CKD) is a progressive disease with damaged kidney function as the main manifestation.[1] It is characterized by proteinuria, hematuria, edema, and hypertension.[2,3] The leading causes of CKD include diabetes, hypertension, and chronic glomerulonephritis.[4] The global prevalence of CKD was estimated to be 14.3%, and the prevalence is rising with the growing aging population and increasing incidence of diabetes and hypertension.[5] The progression of CKD brings a series of complications, such as hypertension, anemia, renal osteodystrophy, ventricular hypertrophy, and heart failure.[6,7]

CKD is closely related to the renin-angiotensin-aldosterone system (RAAS), which regulates body fluid homeostasis.[8,9] In RAAS, the binding of aldosterone to the mineralocorticoid receptors (MRs) results in sodium reabsorption and potassium excretion.[10] MRs are mainly expressed in the distal nephron of the kidney, as well as in the heart and blood vessels.[11] Overactivation of MR will lead to sodium and fluid retention, which promotes hypertension

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and pathological changes including inflammation, fibrosis, and oxidative stress in the kidney, heart, and vascular system, thereby contributing to the progression of CKD and cardiovascular diseases.[12–14]

The main medications for CKD treatment act on the RAAS, among which angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are the primary options for CKD patients with urine albumin-to-creatinine ratio of >300 mg/g.[15] Mineralocorticoid receptor antagonists (MRAs) are recommended as add-on treatment for CKD patients with type 2 diabetes mellitus.[16,17] By inhibiting MR overactivation, MRAs can increase potassium retention and sodium excretion and improve the prognosis of CKD. The first-generation non-selective steroidal MRAs and second-generation selective steroidal MRAs have demonstrated renal and cardiovascular protective effects, but they are underutilized because of the risk of hyperkalemia.[18] Moreover, patients with impaired renal function are more susceptible to hyperkalemia when steroidal MRAs are given on top of ACEIs or ARBs.[19,20] Thus, the development of non-steroidal MRAs is imperative.[21,22]

HRS-1780 is a selective non-steroidal MRA with greater MR binding affinity developed for the treatment of CKD. An earlier phase 1 first-in-human study has demonstrated good safety and tolerability following a single oral dose of HRS-1780 from 5 to 80 mg in healthy men.[23] However, it is unknown whether impaired kidney function would affect the metabolism and excretion of HRS-1780. This study aimed to assess the difference in pharmacokinetics (PK) and safety of a single oral dose of 20 mg HRS-1780 and its primary metabolites between healthy subjects and subjects with mild or moderate renal impairment. The study will help guide further development of HRS-1780 clinical regimen in patients with impaired renal function.

# Materials and Methods

## Study Population

Eligible subjects were males or females aged 18–70 years with a body mass index (BMI) of 18–30 kg/m$^2$. Healthy subjects with normal renal function were included if they had a glomerular filtration rate (GFR) of ≥90 mL/min. Mild and moderate renal impairment was defined by a GFR of 60–89 mL/min and a GFR of 30–59 mL/min at both screening and baseline (GFR at both screening and baseline should be allocated to the same GFR range of renal function category). Subjects with renal impairment were required to be medically stable based on medical history, physical examination, vital signs, laboratory evaluations, and 12-lead electrocardiogram (ECG), in addition, to have a stable renal function for at least 3 months before dosing. Key exclusion criteria included severe infections, injuries, or major surgeries within 3 months before screening; clinically significant disorders deemed not suitable to participate in the study; clinically significant abnormalities in ECG; a history or suspected of being allergic to the study drug or any of its components; participation in another clinical study within 3 months or 5 half-lives, whichever is longer, before screening; or use of the following drugs within 2 weeks before screening, including strong or moderate CYP3A4 inducers and inhibitors, or strong CYP2C8 inhibitors; receiving RAAS interventions other than ACEIs and ARBs, potassium supplements, or potassium-sparing diuretics within 4 weeks before screening. Subjects with impaired renal function were also excluded if they had a history of kidney transplant or needed for kidney transplant or renal dialysis during the study; severe uncontrolled hypertension (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg); serum potassium >5.0 mmol/L or at high risk of hyperkalemia.

The protocol and all amendments were approved by the Ethics Committee of The Second Affiliated Hospital of Guangzhou Medical University (leading site; Y2023-34-01) and the ethics committees of the other study centers. The study was conducted according to the Declaration of Helsinki, Guidelines for Good Clinical Practice, and local laws and regulations. The study was performed in accordance with the US Food and Drug Administration and China's National Medicines and Pharmaceutical Administration Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function. All participants provided informed written informed consent prior to the commencement of the study.

## Study Design and Intervention

This was a multicenter, non-randomized, open-label phase 1 study of HRS-1780 to characterize the PK and safety of a single oral dose of HRS-1780 in subjects with normal renal function and mild or moderate renal impairment in China (ClinicalTrials.gov, NCT06039254).

Three study groups were planned (healthy subject group, mild renal impairment group, and moderate renal impairment group), each containing nine subjects. The gender ratio, age, and weight in healthy subjects were generally matched to that in the renal impairment groups (age within the range of ±10 years; weight within the range of ±10 kg). On Day 1, subjects orally received a single dose of HRS-1780 20 mg after an overnight fast and then were hospitalized and observed until Day 4, during which blood and urine samples were collected. A telephone safety follow-up was conducted on Day 8. During the study period, all enrolled subjects received equal and controlled standard meal at site. Smoking/tobacco products, alcohol, caffeinated beverages, and grapefruit/grapefruit juice were prohibited within 48 hours prior to Day 1 until the end of study.

## Endpoints

The primary endpoints were the plasma PK parameters of HRS-1780 and its primary metabolites (SX2183-C, SX2183-M2, and SX2183-M3). The secondary endpoints were the urinary PK parameters of HRS-1780 and its metabolite SX2183-C, the plasma protein binding rate of HRS-1780, and safety.

## PK Assessments

Blood samples were collected pre-dose (within 60 min before dosing) and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours post-dose. Urine samples were collected pre-dose, 0–4, 4–8, 8–12, 12–24, 24–48, and 48–72 hours post-dose. Plasma and urine samples were analyzed using a high-performance liquid chromatography-tandem mass spectrometry (HPLC/MS/MS) method (Exion LC, Triple Quad 6500 Plus, HPLC-30AD [Pump] and Exion-30ACMP Autosampler, SCIEX, Toronto, Canada) to determine the concentrations of HRS-1780 and its metabolites at Triapex Biotechnology (Shanghai, China).

The bio-analytical method was validated with respect to the matrix selectivity, sensitivity, matrix effect, linear range, accuracy and precision of quality control samples, extraction recovery, dilution experiment, hemolytic effect, high lipid effect, interference of analyte on internal standard, interference of internal standard on analyte, mutual interference between analytes, sample freeze-thaw stability, short-term and long-term stability of sample/stock solution/working solution, reproducibility of sample injection after treatment, stability of sample after treatment, whole blood stability, residue evaluation, maximum number of injections in analytical batches, and methodological durability experiment of different laboratory technicians or different batches of instruments.

Plasma protein binding of HRS-1780 was assessed by using the blood sample at the 1-hour collection time point, and the fraction of HRS-1780 bound to plasma proteins was measured on spiked samples by the rapid equilibrium dialysis method.

Analyte concentrations were evaluated using the internal standard method. Standard curves were calculated from the peak area ratio of analyte/internal standard and the nominal concentrations of HRS-1780 and its metabolites using linear regression $y = ax + b$ with $1/x^2$ weighting. At each concentration level (except lower limit of quantification [LLOQ]), the intra-batch accuracy of plasma HRS-1780 ranged from −1.7% to 5.1% with the inter-batch accuracy of −1.1% to 3.5%. Both the intra-batch and inter-batch precision were ≤2.7%. The intra-batch accuracy of plasma SX2183-C ranged from −2.9% to 7.1% with the precision of ≤4.0% while the inter-batch accuracy ranged from −1.6% to 4.0% with the precision of ≤3.6%. At the LLOQ quality control level, the intra-batch accuracy of plasma HRS-1780 ranged from −2.8% to 6.0% with the precision of ≤5.7%, while the inter-batch accuracy was 2.8% with the precision of 5.8%; the intra-batch accuracy of plasma SX2183-C ranged from −3.6% to 9.2% with the inter-batch accuracy of 3.2%. Both the intra-batch and inter-batch precision were ≤7.0%. At each concentration level (except LLOQ), the intra-batch accuracy of plasma SX2183-M2 ranged from −2.8% to 2.1% with the precision of ≤5.3% while the inter-batch accuracy ranged from −1.4% to 0.6% with the precision of ≤4.7%; the intra-batch accuracy of plasma SX2183-M3 ranged from −2.7% to 2.6% with the precision ≤5.8%, while the inter-batch accuracy ranged from −1.1% to 1.1% with the precision of ≤4.2%. At the LLOQ quality control level, the intra-batch accuracy of plasma SX2183-M2 ranged from −4.6% to 7.2% with the precision of ≤11.9% while the inter-batch accuracy was 2.0% with the precision of 10.0%; the intra-batch accuracy of plasma SX2183-M3 ranged from −4.6 to 8.4% with the precision of ≤5.2%, while the inter-batch accuracy was 2.0% with the precision of 6.5%.

At each concentration level (except LLOQ), the intra-batch accuracy of urine HRS-1780 ranged from −4.1% to 6.9% with the precision of ≤5.2% while the inter-batch accuracy ranged from −1.7% to 4.1% with the precision of ≤3.6%; the intra-batch accuracy of urine SX2183-C ranged from −3.7% to 6.6% with the precision of ≤4.6% while the inter-batch accuracy ranged from −1.7% to 4.2% with the precision of ≤3.9%. At the LLOQ quality control level, the intra-batch accuracy of urine HRS-1780 ranged from 2.5% to 9.6% with the precision of ≤4.6% while the inter-batch accuracy was 7.0% with the precision of 5.1%; the intra-batch accuracy of urine SX2183-C ranged from 1.0% to 5.4% with the precision of ≤8.8%, while the inter-batch accuracy was 3.3% with the precision of 6.5%.

The calibration range (LLOQ - upper limit of quantification [ULOQ]) in plasma was 0.250 −500.000 ng/mL for HRS-1780 and SX2183-C and 0.500–1000.000 ng/mL for SX2183-M2 and SX2183-M3. The calibration range was 1.000–500.000 ng/mL for HRS-1780 in mixed matrix (plasma-phosphate buffered saline) while 1.000–2000.000 ng/mL for HRS-1780 and SX2183-C in urine.

## Safety Assessments

Safety assessments included incidence and severity of adverse events (AEs), including treatment-emergent AEs (TEAEs), treatment-related AEs (TRAEs), and serious AEs (SAEs), vital signs, physical examinations, laboratory tests, and 12-lead ECG. AEs were classified according to the Medical Dictionary for Regulatory Activities (Version 26.0). AE severity was graded as mild, moderate, or severe.

## Statistical Analysis

Based on the earlier study, the inter-individual coefficient of variation was assumed to be 35%. Enrolment of eight subjects in each renal function group provides an 80% probability that the 95% confidence interval (CI) of relevant PK parameters is within the range of 60% and 140% of the geometric mean estimates. Assuming a dropout rate of 10%, nine subjects were needed in each of the healthy, mild renal impairment, and moderate renal impairment groups, resulting in a total of 27 subjects in the study.

PK analysis was performed on subjects who received the study treatment and had at least one PK concentration or PK parameter value. Safety was assessed in all subjects who received the study treatment. The plasma concentration-time profile of HRS-1780 and its metabolites was presented graphically by study groups. PK parameters were calculated using non-compartmental model analysis and summarized using descriptive statistics. PK parameters included maximum plasma concentration ($C_{max}$), time to reach maximum plasma concentration ($T_{max}$), area under the curve from zero to last measurable concentration ($AUC_{0\text{-last}}$), area under the curve from zero to infinity ($AUC_{0\text{-inf}}$), terminal elimination half-life ($t_{1/2}$), apparent total clearance (CL/F), apparent volume of distribution ($V_z$/F), as well as cumulative amount excreted in the urine ($Ae_{,ur}$), cumulative percentage excreted in the urine (%$Ae_{,ur}$), and renal clearance (CLr). To compare the PK profiles between healthy and renal impaired subjects, the least squares (LS) geometric mean of the PK parameters ($C_{max}$, $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$) of HRS-1780 and metabolites were calculated for each study group, along with the corresponding LS geometric mean ratio (mild impairment/healthy, moderate impairment/healthy) and 90% CI using analysis of variance model. The urinary excretion of HRS-1780 and SX2183-C were presented graphically by study groups. The relationship between GFR and CLr was analyzed using a regression model, the estimated slopes and corresponding 95% CIs were provided with CLr as the dependent variable and GFR as the covariate. HRS-1780 plasma protein binding rate and safety data were summarized descriptively.

The PK analysis was conducted using Phoenix WinNonlin (Version 8.3). Other statistical analyses were conducted using SAS (Version 9.4).

# Results

## Participants

A total of 27 subjects were enrolled in this study (n = 9 in each renal function group). All subjects received a single dose of oral HRS-1780 20 mg and completed the follow-up. Among all the subjects, 22 (81.5%) were male and 5 (18.5%) were female. The mean (standard deviation) age and BMI were 48.3 (11.6) years and 24.2 (2.9) kg/$m^2$. Healthy and renal

**Table 1** Demographics and Baseline Characteristics

| | Healthy Subjects (N = 9) | Mild Renal Impairment (N = 9) | Moderate Renal Impairment (N = 9) | Total (N = 27) |
|---|---|---|---|---|
| **Age, years** | 46.2 (3.1) | 42.3 (12.7) | 56.4 (12.1) | 48.3 (11.6) |
| **Sex, n (%)** | | | | |
| **Male** | 7(77.8) | 9 (100.0) | 6 (66.7) | 22 (81.5) |
| **Female** | 2 (22.2) | 0 | 3 (33.3) | 5 (18.5) |
| **Height, cm** | 165.0 (5.1) | 165.6 (4.9) | 160.6 (10.0) | 163.7 (7.2) |
| **Weight, kg** | 63.5 (6.5) | 69.3 (7.0) | 61.6 (7.9) | 64.8 (7.7) |
| **BMI, kg/m$^2$** | 23.4 (2.7) | 25.3 (2.9) | 23.9 (3.1) | 24.2 (2.9) |
| **GFR, mL/min** | 101.0 (4.9) | 76.5 (10.6) | 44.7 (6.6) | 74.0 (24.6) |

**Notes**: Data are presented as mean (SD) unless otherwise specified. GFR (mL/min) = eGFR × BSA ÷ 1.73. eGFR=141×min (Scr/κ, 1)$^{\alpha}$×max (Scr/κ, 1)$^{-1.209}$×0.993$^{Age}$. BSA (m$^2$) = 0.0061 × height (cm) + 0.0124 × weight (kg) - 0.0099.
**Abbreviations**: BMI, body mass index; BSA, body surface area; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate.

impairment groups were well matched for sex, age, and BMI, as shown in the key demographic and baseline characteristics. Among the 18 subjects with renal impairment, the medical histories of renal and urinary disorders included chronic kidney disease, glomerulonephritis chronic, diabetic nephropathy, nephrolithiasis, IgA nephropathy, nephrotic syndrome, and glomerulonephritis. Some of these subjects also had medical histories such as type 2 diabetes mellitus, hypertension, hyperuricemia, hyperlipidemia, congenital cystic kidney disease, arteriosclerosis, hypothyroidism, and gout, which might also contribute to their CKD (Supplemental Table S1). There were 6 enrolled subjects who had ongoing concomitant diseases of type 2 diabetes mellitus, 3 in mild renal impairment group and 3 in moderate renal impairment group. Concomitant medications were taken by 13 renal impaired subjects during the study. The mean (standard deviation) GFR was 101.0 (4.9), 76.5 (10.6), and 44.7 (6.6) mL/min in the healthy, mild impairment, and moderate impairment subjects, respectively (Table 1).

## Plasma PK Characteristics

All 27 subjects were included in the PK analysis. The HRS-1780 plasma concentration-time curves are presented in Figure 1, and plasma PK parameters of HRS-1780 are summarized in Table 2. In general, HRS-1780 was rapidly absorbed and eliminated. The median $T_{max}$ ranged 0.50–0.52 hour, and the mean $t_{1/2}$ ranged 2.06–2.56 hours. $T_{max}$, $t_{1/2}$, and $C_{max}$ were comparable between the three renal function groups. The geometric means of $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ in subjects with normal renal function, mild, and moderate renal impairment were 624, 720, and 821 h×ng/mL and 629, 818, and 827 h×ng/mL, respectively. There was a slight increase in HRS-1780 exposure (AUC) with increased severity of renal impairment, but relatively comparable between renal impaired groups (Supplemental Figure S1).

For HRS-1780, the LS geometric mean ratios (mild vs healthy and moderate vs healthy) of $C_{max}$ were 0.98 (90% CI, 0.80, 1.21) and 1.02 (90% CI, 0.83, 1.25). The LS geometric mean ratios of $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ were 1.15 (90% CI, 0.79, 1.69) and 1.30 (90% CI, 0.91, 1.87) in mild impairment subjects and 1.32 (90% CI, 0.90, 1.93) and 1.31 (90% CI, 0.93, 1.87) in moderate impairment subjects, respectively (Supplemental Table S2). There was no significant effect of mild and moderate renal impairment on the exposure to HRS-1780. The geometric mean of HRS-1780 plasma protein binding rate was comparable across three renal function groups, ranging from 94.1%-95.0%, not affected by renal impairment.


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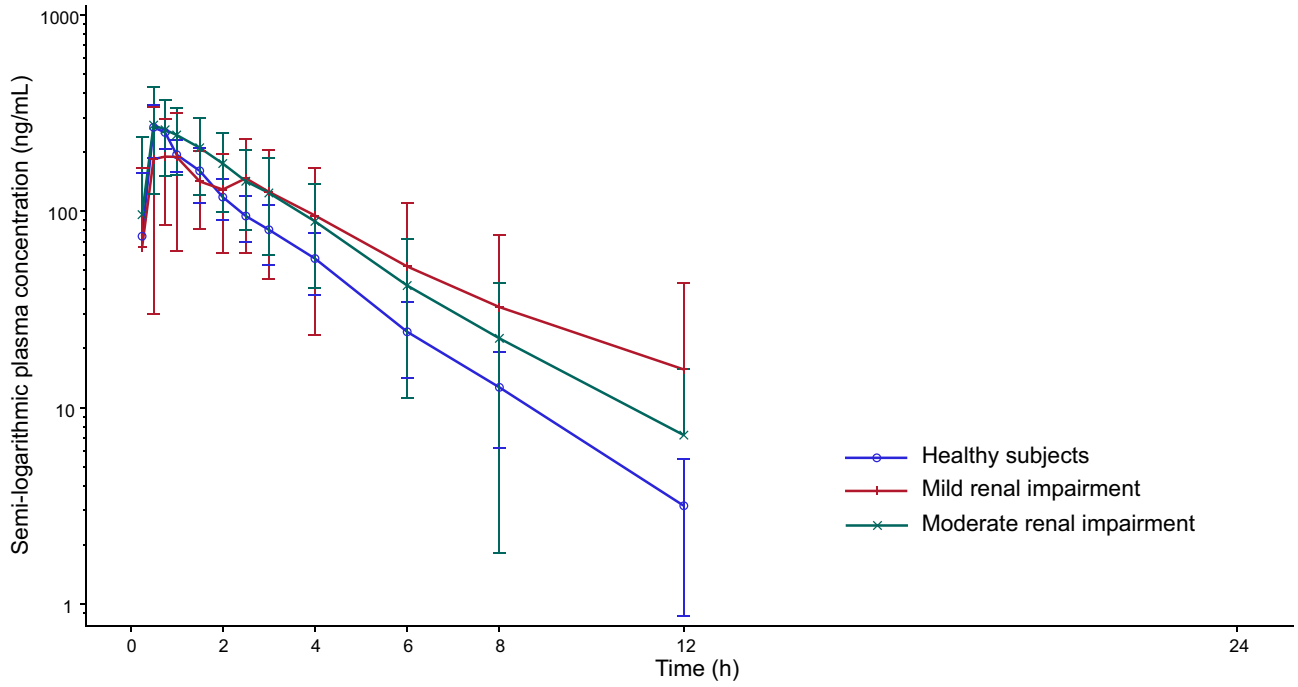


**Figure 1** Plasma concentration-time curve of HRS-1780 (semi-log). Error bars show standard deviation.

Meanwhile, the PK profiles of metabolites SX2183-C, SX2183-M2, and SX2183-M3 demonstrated a slower absorption and elimination compared with HRS-1780. Renal function did not influence the exposure of SX2183-C and SX2183-M2, similar to the parent compound. However, exposure to SX2183-M3 was significantly increased in the moderate renal impairment group, where there was an approximately increase of 131.1%, 219.3%, and 218.0% in $C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$, respectively compared to those in healthy subjects (Supplemental Table S2).

**Table 2** Plasma PK Parameters of HRS-1780

| | Healthy Subjects (N = 9) | Mild Renal Impairment (N = 9) | Moderate Renal Impairment (N = 9) |
|---|---|---|---|
| **$C_{max}$, ng/mL** | 302 (8.3) | 297 (29.1) | 307 (33.5) |
| **$T_{max}$, h** | 0.517 (0.500, 1.47) | 0.500 (0.500, 2.50) | 0.500 (0.250, 1.50) |
| **$AUC_{0\text{-last}}$, h×ng/mL** | 624 (22.4) | 720 (71.5) | 821 (48.8) |
| **$AUC_{0\text{-inf}}$, h×ng/mL** | 629 (22.2) | 818 (61.5) | 827 (48.8) |
| **$t_{1/2}$, h** | 2.06 (24.0) | 2.56 (69.9) | 2.13 (33.8) |
| **$V_z/F$, L** | 92.2 (23.1) | 78.1 (8.8) | 71.0 (25.3) |
| **CL/F, L/h** | 31.8 (22.2) | 24.4 (61.5) | 24.2 (48.8) |
| **PPB, %** | 95.0 (0.3) | 94.2 (0.5) | 94.1 (0.9) |

**Notes**: $T_{max}$ is presented as median (min, max). $t_{1/2}$ is presented as mean (CV%). Other parameters are presented as Geomean (GeoCV%).

**Abbreviations**: $AUC_{0\text{-inf}}$, area under the curve from zero to infinity; $AUC_{0\text{-last}}$, area under the curve from zero to last measurable concentration; CL/F, apparent total clearance; $C_{max}$, maximum plasma concentration; $T_{max}$, time to reach maximum plasma concentration; $t_{1/2}$, terminal elimination half-life; PPB, plasma protein binding; $V_z/F$, and apparent volume of distribution.

## Urinary PK Characteristics

The cumulative amount of HRS-1780 excretion ($Ae_{,ur}$) in the urine in different groups tended to reach plateau after 24 hours post-dose (Figure 2A and Supplemental Table S3), while the $Ae_{,ur}$ of metabolite SX2183-C showed a slow increment until 72 hours post-dose (Figure 2B and Supplemental Table S3). The geomean of total $Ae_{,ur}$ for HRS-1780 were 212000 ng, 176000 ng, 138000 ng in healthy subjects, mild renal impairment and moderate renal impairment subjects, while the geometric mean of total

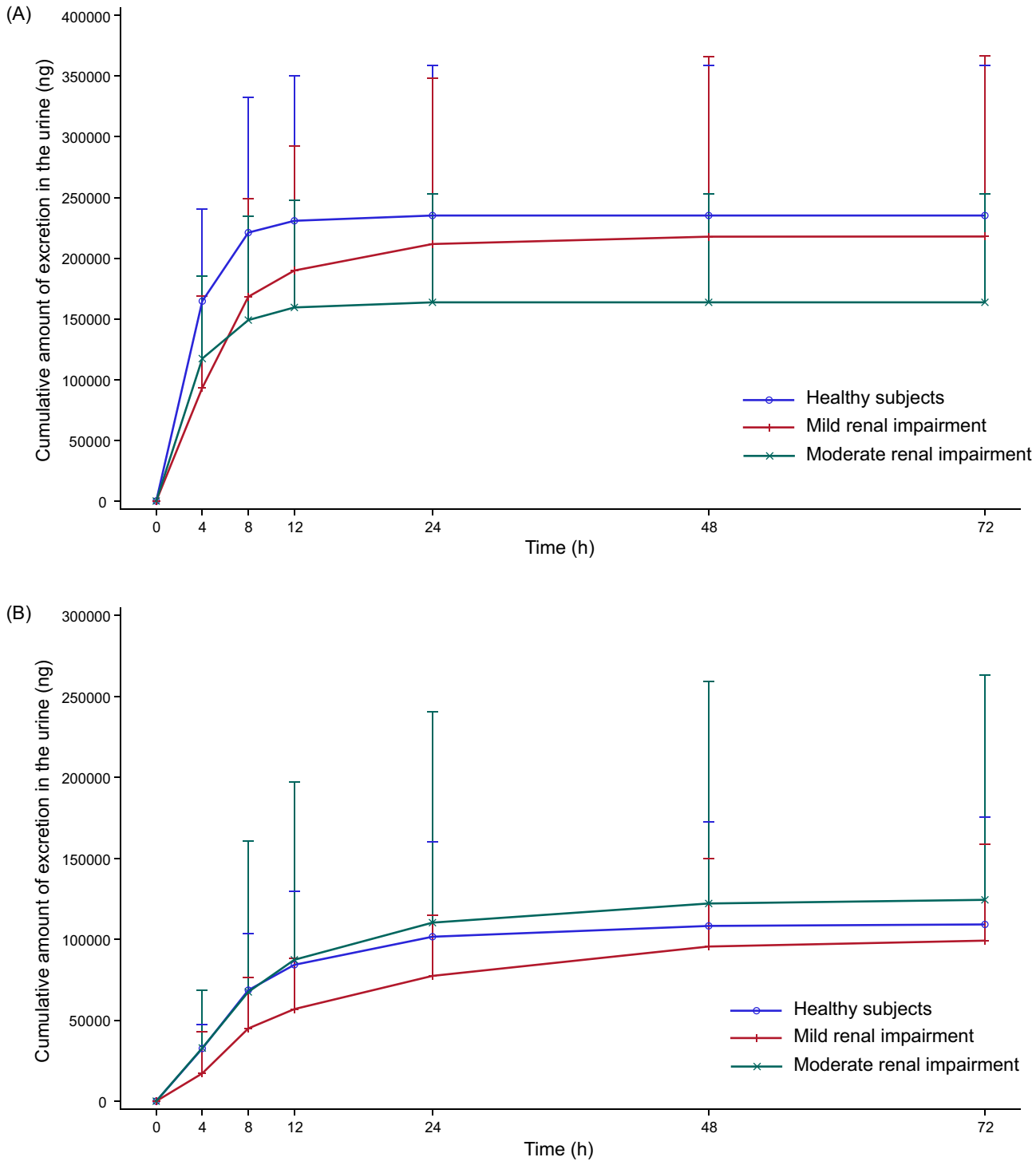


**Figure 2** Cumulative urinary excretion of (**A**) HRS-1780 and (**B**) SX2183-C. Error bars show standard deviation.


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**Table 3** Urinary PK Parameters of HRS-1780 and SX2183-C

| | PK Parameters | Healthy Subjects (N = 9) | Mild Renal Impairment (N = 9) | Moderate Renal Impairment (N = 9) |
|---|---|---|---|---|
| **HRS-1780** | $Ae_{,ur}$, ng | 212000 (48.2) | 176,000 (82.5) | 138,000 (76.2) |
| | $\%Ae_{,ur}$ | 1.060 (48.2) | 0.878 (82.5) | 0.690 (76.2) |
| | CLr (L/h) | 0.341 (38.9) | 0.244 (62.6) | 0.168 (62.0) |
| **SX2183-C** | $Ae_{,ur}$, ng | 95500 (56.0) | 82,000 (77.3) | 82,700 (119.6) |
| | CLr (L/h) | 0.0319 (52.0) | 0.0302 (125.9) | 0.0191 (100.4) |

**Notes**: Data are presented as Geomean (GeoCV%).
**Abbreviations**: $Ae_{,ur}$, cumulative amount excreted in the urine; $\%Ae_{,ur}$, cumulative percentage excreted in the urine; CLr, renal clearance.

$Ae_{,ur}$ for SX2183-C were 95500 ng, 82000 ng, 82700 ng in healthy, mild renal impairment, and moderate renal impairment subjects, respectively (Table 3). The HRS-1780 geometric mean $\%Ae_{,ur}$ decreased with the severity of renal impairment, which was 1.060%, 0.878%, and 0.690%, in healthy, mildly impaired, and moderately impaired groups, respectively, meanwhile, renal clearance of HRS-1780 decreased as well, giving geometric mean CLr of 0.341, 0.244, and 0.168 L/h in the three renal function groups (Table 3). A similar trend was observed for SX2183-C, with a small amount excreted in the urine while a decreased renal clearance with decreasing renal function. Regression analysis suggested that GFR was associated with the renal clearance of HRS-1780 (p=0.0099), but not with that of SX2183-C (p=0.5626) (Supplemental Table S4).

## Safety

All 27 subjects were included in the safety analysis, among which, 13 (48.1%) reported at least one TEAE, including 5 (55.6%) in the healthy subject group, 4 (44.4%) in the mild impairment group, and 4 (44.4%) in the moderate impairment group. The incidence of TEAEs was comparable among different renal function groups and was not apparently associated with renal function. Most TEAEs were mild in severity, except that two subjects in the mild impairment group had moderate TEAEs but were not considered to be drug-related. Five (55.6%) healthy subjects and 1 (11.1%) mild impairment subject reported TRAEs, all of which were mild in severity and recovered without intervention. There was one SAE in the mild impairment group (moderate syncope) due to the medical history of the subject, which was determined possibly unrelated to the study drug and recovered after corrective treatment. No TEAEs or TRAEs led to death or treatment discontinuation (Table 4).

**Table 4** Safety Summary and Most Common Treatment-Emergent Adverse Events

| | Healthy Subjects (N = 9) | Mild Renal Impairment (N = 9) | Moderate Renal Impairment (N = 9) | Total (N = 27) |
|---|---|---|---|---|
| **Any TEAE** | 5 (55.6) | 4 (44.4) | 4 (44.4) | 13 (48.1) |
| **Mild** | 5 (55.6) | 2 (22.2) | 4 (44.4) | 11 (40.7) |
| **Moderate** | 0 | 2 (22.2) | 0 | 2 (7.4) |
| **Severe** | 0 | 0 | 0 | 0 |
| **Any TRAE** | 5 (55.6) | 1 (11.1) | 0 | 6 (22.2) |
| **Mild** | 5 (55.6) | 1 (11.1) | 0 | 6 (22.2) |
| **Moderate** | 0 | 0 | 0 | 0 |
| **Severe** | 0 | 0 | 0 | 0 |
| **SAE** | 0 | 1 (11.1) | 0 | 1 (3.7) |
| **Most common TEAEs** | | | | |
| **Blood uric acid increased** | 2 (22.2) | 0 | 1 (11.1) | 3 (11.1) |
| **Blood triglycerides increased** | 1 (11.1) | 1 (11.1) | 0 | 2 (7.4) |

**Notes**: Data are presented as n (%). Most common TEAEs are those reported by ≥5% of the total subjects during the study.
**Abbreviations**: SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

The most common TEAEs were increased blood uric acid (3 [11.1%], 2 healthy and 1 moderate impairment) and increased blood triglycerides (2 [7.4%], healthy and mild impairment each). Two increased blood uric acid events in the healthy subject group and all increased triglyceride events reported were determined related to HRS-1780 treatment.

Laboratory test results were mainly normal for healthy subjects at baseline and post-dose. For mild and moderate renal impairment subjects, most clinically significant abnormalities were attributed to the patient's underlying conditions. Specifically, two healthy subjects had a clinically significant increase in uric acid that was determined to be possibly related to the study drug. The clinically significant increase in serum triglyceride, experienced by one healthy subject and one subject with mild renal impairment, was deemed possibly HRS-1780-related. Other abnormalities in biochemistry lab results, including changes in serum total protein, serum albumin, glucose, serum urea, uric acid, serum lipids, and serum creatinine, were determined to be related to the underlying diseases of renal impaired subjects rather than the HRS-1780 treatment. Serum potassium levels did not differ between healthy and renal impaired subjects. No abnormalities were observed in serum potassium at baseline or post-dose. In general, vital signs and 12-lead ECG were not affected by HRS-1780, except one healthy subject experienced treatment-related decreased blood pressure and sinus bradycardia. There were no treatment-related ECG abnormalities among subjects with renal impairment, and most of the ECG abnormalities were non-clinically significant. Three subjects with moderate renal impairment had clinically significant ECG abnormalities, including increased P-wave terminal force in lead V1 (PTFV1) and T wave changes, which were deemed related to their medical history of hypertension by the investigator, rather than study treatment (Supplemental Table S5).

## Discussion

In this phase 1 study, the PK and safety profiles of HRS-1780 and the main metabolites were compared between healthy subjects and subjects with mild or moderate renal impairment to investigate if there is a need for dose adjustments in CKD patients. Following a single oral administration of 20 mg HRS-1780, the maximum plasma concentration was reached in 0.50–0.52 hour, and the mean half-life was 2.06–2.56 hours, which were comparable between renal impaired subjects and healthy matched controls, and was consistent with that from the first-in-human study of HRS-1780 in healthy men.[23] There was no significant association between different renal function status and the exposure of HRS-1780 in blood, although renal impairment groups demonstrated slightly higher levels of exposure (AUC) than that in the healthy subjects. In addition, the exposure of HRS-1780 was comparable between mild and moderate renal impairment groups with relatively high inter-individual variability. It is also important to note that HRS-1780 has not been evaluated in patients with severe renal impairment or end-stage renal disease requiring a kidney transplant or renal dialysis, the study results need to be explained with cautions.

The plasma protein binding of HRS-1780 was relatively high and also similar among subjects of different renal functions with little inter-individual variability. Therefore, the degree of kidney damage seems not to heavily impact the total and unbound drug exposure. Renal clearance of HRS-1780 declined with the increased severity of renal impairment. The preclinical evidence suggested that HRS-1780 underwent extensive metabolism in the human liver microsomal incubation system. The main metabolic pathways were double oxidation and hydrogenation, dehydrogenation, trioxidation and hydrogenation, single oxidation and dehydrogenation and double oxidation, mainly catalysed by Cytochrome P450 (CYP)3A4 and CYP2C8 enzymes. Thus, renal elimination of HRS-1780 was a minor route, which was further confirmed in this study that HRS-1780 was not mainly eliminated in its parent form through urine. Hence, mild or moderate renal impairment had a limited effect on the overall PK profile of HRS-1780. The effect of renal impairment on non-renal clearance should be further explored in future studies.

A similar study was performed for a same-class drug, marketed non-steroidal MRA, finerenone, to evaluate the pharmacokinetic profile for a single oral dose of finerenone and its metabolites in individuals with renal impairment compared with healthy individuals. The study suggested no effect on the exposure (AUC) to finerenone with mild renal impairment. Although an increased exposure to finerenone was found to be associated with moderate and severe renal impairment compared with normal renal function, the results were with moderate-to-high inter-individual variability, meanwhile, no relevant effect on $C_{max}$ was observed. Moreover, compared with the parent compound, more pronounced increases in exposure to its metabolites were observed with increasing renal impairment, which however, was not

anticipated to have any clinical implications considering the inactivity of these metabolites.[24] Our current study had similar findings. The recommended dosage of HRS-1780 for renal impaired patients will be decided with more patients with renal impairment included in later phase trials.

The absorption and elimination of main metabolites SX2183-C, SX2183-M2, and SX2183-M3 were slower than that of HRS-1780, which was consistent across different renal function groups. The effect of renal impairment was not statistically observed in the exposure change of SX2183-C and SX2183-M2 but the exposure to SX2183-M3 was significantly increased in subjects with moderate renal impairment. Our study suggested that the PK of the main metabolites of HRS-1780 might not be fully independent of renal function given a higher exposure of SX2183-M3 was observed with renal impairment. However, SX2183-C, SX2183-M2 and SX2183-M3 showed no inhibitory activity on MR, androgen receptor (AR), glucocorticoid receptor (GR), progesterone receptor (PR), estrogen receptors (ERa and ERβ) at the highest concentration of 10 uM in the ex vivo studies. Considering that none of these main metabolites demonstrated pharmacological activity in the preclinical study, no clinical implications of the significantly increased exposure of SX2183-M3 would be expected.

In general, HRS-1780 20 mg demonstrated good safety and tolerability in healthy subjects, as well as subjects with mild and moderate renal impairment. No moderate or severe TEAE was reported in this study and no clear association was found between the incidence of TEAE and renal impairment. The most common TRAEs were increased blood uric acid and increased blood triglyceride. The reported significant abnormities in laboratory tests and 12-lead ECG in some participants showed no treatment-related trend and were determined mostly related to the underlying diseases of the subjects with renal impairment, rather than HRS-1780.

## Conclusion

In conclusion, the results of this study indicate that the PK profile of HRS-1780 is independent of renal function. There was limited effect of mild and moderate renal impairment on the exposure to HRS-1780 although renal clearance of HRS-1780 decreased with the degree of kidney damage. The influence of renal impairment on the exposure of HRS-1780 metabolites had limited clinical or safety impact considering a lack of pharmacological activity of these metabolites. In general, HRS-1780 at 20mg single-dose level demonstrated good safety and tolerability in mild and moderate renal impairment groups. The severity of renal impairment in this trial did not appear to be associated with an increased risk of AEs. The study results further support the development of HRS-1780 for CKD treatment but need to be interpreted with caution without severe renal impairment subjects included.

## Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

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## Disclosure

Yue Fei, Na Li, Rong Huang, Gang Cheng, Quanren Wang, and Kai Shen are employees of Hengrui. The authors declare no other conflicts of interest in this work.

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