Effect of a strong CYP3A4 inducer rifampin on the pharmacokinetics of SHR2554 in healthy Chinese volunteers: A drug-drug interaction study

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Abstract

Aims: A phase I open-label study assessed the effect of multiple oral doses of a potent CYP3A4 inducer (rifampicin) on the pharmacokinetic profile of SHR2554, a novel enhancer of zeste homolog 2 inhibitor (EZH2) and CYP3A4 substrate. Methods: Eighteen adult Chinese healthy subjects were enrolled in this study. All participants received a single oral dose of SHR2554 (300 mg) on day 1, rifampin (600 mg) from day 4 to day 10 and day 12, the same dose was coadministered with SHR2554 (300 mg) and rifampicin (600 mg) on day 11. The primary endpoints were SHR2554 exposure parameters. Lack of drug–drug interaction was concluded if 90% confidence intervals (CIs) for the ratio of area under the plasma concentration–time curve (AUC) or maximum concentration (Cmax), with/without oral rifampicin, were within a pre-specified interval (0.80–1.25). Results: The Cmax, AUC0-t, and AUC0-[?] of administration alone and coadministration with rifampin were 177.265 ±127.9889 ng/mL, 17.001 ± 8.4759 ng/mL; 672.12 ± 507.390 h*ng/mL, 38.58 ± 19.495 h*ng/mL; and 721.50 ±514.386 h*ng/mL, 46.30 ± 20.750 h*ng/mL, respectively. Coadministration with rifampin decreased the least-squares geometric mean ratios of Cmax, AUC0-t, and AUC0-[?] by 89%, 93%, and 93%, respectively. Well tolerance and acceptable safety profile showed during the trial. Conclusion: The exposure of SHR2554 was significantly decreased when coadministered with rifampicin. It is recommended to avoid concomitant use of SHR2554 and strong inducers of CYP3A4.

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Abstract

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Results : The C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}[?]}$ of administration alone and coadministration with rifampin were 177.265 ±127.9889 ng/mL, 17.001 ± 8.4759 ng/mL; 672.12 ± 507.390 h*ng/mL, 38.58 ± 19.495 h*ng/mL; and 721.50 ±514.386 h*ng/mL, 46.30 ± 20.750 h*ng/mL, respectively. Coadministration with rifampin decreased the least-squares geometric mean ratios of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}[?]}$by 89%, 93%, and 93%, respectively. Well tolerance and acceptable safety profile showed during the trial.

Conclusion : The exposure of SHR2554 was significantly decreased when coadministered with rifampicin. It is recommended to avoid concomitant use of SHR2554 and strong inducers of CYP3A4.

Keywords: SHR2554, cytochrome P450, drug-drug interaction, pharmacokinetics, drug metabolism, drug safety

1 Introduction

Enhancer of zeste homolog 2 (EZH2) is the catalytic subunit of the polycomb repressive complex 2 (PRC2), which regulates its downstream gene expression through tri-methylation of lysine 27 of histone H3 (H3K27)[1]. According to previous research, EZH2 regulates cell progression in three ways including PRC2-dependent H3K27 methylation, PRC2-dependent non-histone protein methylation, and PRC2-independent gene transactivation.[2-4]. EZH2 hyperactivity, overexpression, or expression loss is correlated with cancer initiation[5], progression[6], and immunity regulation[7] due to enhanced cell proliferation and oncogenic capacity. Several cancers are associated with the EZH2 overexpression, such as hepatocellular carcinoma[8], gastric cancer[9], relapsed/refractory follicular lymphoma[10], advanced epithelioid sarcoma[11], etc. A host of studies have demonstrated that specific EZH2 inhibitors or gene knockout could reduce EZH2-related tumors development and progression[12]. Based on these founds, several specific EZH2 inhibitors that ongoing clinical trials of drugs have been developed for treatment, including GSK126, EPZ005687, EI1, tazemetostat, EPZ011989, UNC1999, etc[13].

SHR2554, a novel highly selective oral EZH2 inhibitor which inhibits both wild-type and mutant EZH2 methyltransferase activity, is developed by Jiangsu Hengrui Medicine co., Ltd. Preclinical studies have shown that SHR2554 competitively binds to the catalytic SET domain of EZH2 to inhibit mouse lymphoma cell proliferation and tumor growth[14]. SHR2554 expressed excellent application prospects for EZH2 wild-type Diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) patients with an objective response rate lower by 20% after treatment using EZH2-specific inhibitors[14]. And phase I clinical study indicated aiming to relapsed or refractory lymphoma patients, SHR2554 showed an acceptable safety profile and promising anti-tumor activity[15]. Further clinical trials for SHR2554 administration alone or coadministration with other anti-tumor drugs aimed at malignant tumor, prostate cancer, castration-resistant prostate cancer, solid tumor, and lymphoma are ongoing (NCT05661591, NCT05592262, NCT04407741, NCT05049083). Hence, SHR2554 provides a new therapeutic modality for patients with multiple abnormal EZH2 expression tumors.

The results in the phase I study have demonstrated that 350 mg SHR2554 twice daily is the maximum tolerated dose[15], so the dosage of below 300mg (including 300mg) has good safety without occurring drug-related SAE or dose-limiting toxicity. CYP3A4 enzyme involves in the SHR2554 main oxidative metabolism, considering many drugs could inhibit or induce CYP3A4 expression, coadministration with such medicines

could significantly affect it pharmacokinetics of SHR2554, so it is essential to conduct drug-drug interaction (DDI) clinical trials for CYP3A4 inhibitors or CYP3A4 inducers. In addition, strong index inhibitors or strong index inducers should be urgently prioritized in clinical DDI trials when the investigational drug is substrate based on the guidelines. Therefore, this study is designed to evaluate the concomitant use of rifampin, a potentially potent CYP3A4 inducer, to impact the pharmacokinetics (PK) properties of SHR2554 in healthy Chinese volunteers. Safety and tolerance are assessed during treatment period.

2 Methods

2.1 Trial design and subjects

This single-center, open-label, phase I trial was designed to primarily assess the effect of multiple oral doses of rifampin on the pharmacokinetics of a single oral dose of SHR2554 in healthy Chinese volunteers. Secondly, we assessed the tolerance and safety of the SHR2554 administration alone and when coadministration with rifampin in Chinese healthy volunteers.

The subjects enrolled should age 18 to 45 years (including both ends) with body mass index (BMI) in the range of 19.0-26.0 kg/m^2 (including the critical value), the body weight of male subjects less than 50 kg or that of female subjects less than 45 kg would be excluded. All inclusion and exclusion criteria were provided in the supplementary.

The qualified subjects were admitted to the phase I clinical trial center on D-0, provided light dinner, and fasted but no water for 10 hours. On D1, the subjects were orally administrated SHR2554 at a dose of 300mg; then, all subjects were orally administrated rifampin 600mg quaque die (QD) for 8 days (D4-D9, D12). On D-11, 300mg SHR2554 and 600mg rifampin were orally co-administrated under fasting conditions with 240ml water. Water was forbidden before or after 1 hour, and food was forbidden after 4 hours of administration. The blood samples were collected before administration 60 mins, and 0.5h,1.0h,1.5h,2.0h,2.5h,3.0h,4.0h,6.0h,8.0h,12.0h,24.0h,48.0h after first SHR2554 administration on day 1 and day 11. All subjects were discharged after examination on D-13 and received follow-up visits on D-16 to D-19. The clinical progress is shown in **Figure 1** .

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) and approved by the Institutional Ethics Committee of Xiangya Hospital. Written informed consent was obtained from all subjects prior to the screening. This study was registered at

www.chinadrugtrials.org.cn.

2.2 Assessments

2.2.1 PK

Approximately 4mL of blood was collected into heparin lithium anticoagulant tubes, if the indwelling needle was used, the blood should be withdrawn 0.5-1.0mL in advance. The blood samples should be centrifuged at room temperature for 10 mins (2500 g) for no more than one hour, the plasma samples were collected and stored at -70 (10) for long-stem storage or stored at -20 for no more than 12 hours.

The concentration of SHR2554 in plasma samples was determined by the Shanghai Institute of Pharmacy, Chinese Academy of Sciences (Shanghai), and the analytical method has been verified. High-performance liquid chromatography-tandem mass spectrometry was been used for the concentration of plasma samples. The plasma samples were stored at -70, and should be detected within 176 days. The concentration range of the calibration standard curve was 1.00–500 ng/mL; the regression equation showed linear fitting, and the weight coefficient was W= $1/X^2$. The lower limit of quantification (LLOQ) of SHR2554 was 1.00ng/mL. All concentration which was lower than LLOQ was referred to as blow the detection limit.

2.2.2 Safety

All adverse events (AEs) were recorded from the time of the first dose of SHR2554 until the end of the follow-up whether they were related to investigation drugs or not. Due to the pigment group of rifampicin

metabolites, subjects whose urine, stool, saliva, sputum, or tears appeared orange-red after taking rifampin were not recorded as AEs. All subjects were received the physical examination on day-0 and day 13. All account of physical examination was provided in supplementary.

2.3 Study endpoints

The primary endpoints were maximum plasma concentration of SHR2554 (C_{max}), area under the plasma concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration ($AUC_{0\text{-}t}$), and AUC from time 0 to infinity ($AUC_{0\text{-}[?]}$), the secondary endpoints included other PK parameters, such as time to reach C_{max}(T_{max}), terminal elimination half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (Vz/F); and safety endpoints, including incidence and severity of AEs, and evaluation through laboratory tests, physical examination, vital signs, and 12-lead ECG. The SHR2554 main metabolites were quantitatively analyzed. All the definitions and calculations were provided in the supplementary.

2.4 Statistical analysis

This study enrolled 18 subjects whose sample size were not calculated by statistical power considerations. Based on the analysis set of PK and non-atrioventricular model (NCA) to calculate the PK parameters, including $AUC_{0\text{-}t}$, $AUC_{0\text{-}[?]}$, C_{max}, CL/F, T_{max}, $t_{1/2}$and V_z/F.

Concentrations of SHR2554 will be descriptively summarized The average and median plasma concentration-time curves were plotted according to the scheduled blood collection time. In addition, the actual blood sample collection time was used to plot the blood concentration-time curve of individual subjects. PK parameters of $AUC_{0\text{-}t}$, $AUC_{0\text{-}[?]}$, C_{max}, CL/F, $t_{1/2}$and V_z/F were summarized by using case number, arithmetic mean, arithmetic standard deviation, median, minimum, maximum, geometric mean, geometric standard deviation, coefficient of variation and coefficient of geometric variation

Through natural logarithm transformation, The plasma SHR2554 PK parameters $AUC_{0\text{-}[?]}$ (if applicable), $AUC_{0\text{-}t}$, and C_{max} were estimated by fitting the mixed-effect models to determine the difference between the least-squares means and 90% confidence interval (CI) of SHR2554 combination and monotherapy. In the mixed-effect model, the drugs were considered fixed effects and the subjects were considered random effects. After model fitting, the least-squares mean difference and its 90% confidence interval were converted into the geometric mean ratio (combination/SHR2554 monotherapy) and the 90% confidence interval.

The adverse events, physical examination, vital signs, laboratory results, normal/abnormal changes were recorded during the trial to evaluate the relationship between abnormal changes and the tested drug.

3 Results

3.1 Subject disposition and baseline characteristics

There were 18 subjects enrolling in this study. All 18 subjects completed the phase of a single dose of SHR2554 and the phase of multiple doses of rifampin. 17 subjects completed the coadministration of SHR2554 and rifampin, and 1 subject withdrew from the study due to AEs. All 18 subjects who received investigation drug were included in the safety set and PK concentration set. The subject disposition and baseline characteristics were shown in **Table 1.**

3.2 Compliance

The compliance rate was 100% for both the SHR2554 administration phase and the rifampin administration phase (all 18 subjects received all planned doses of SHR2554 or rifampin). In the coadministration phase, the compliance rate was 94.4%, and 1 subject withdrew from the study due to AEs.

3.3 PK analyses

The plasma concentrations of SHR2554 were significantly decreased and its elimination rate remarkably increased when coadministration with rifampin compared to SHR2554 administration alone **(Figure 2 A,**

B) . The PK parameters of SHR2554 for SHR2554 administration alone and coadministration with rifampin were summarized in**Table 2** .

Compared to administration of SHR2554 as monotherapy and coadministration with rifampin, the geometric mean $AUC_{0\text{-}t}$ of SHR2554 in plasma was 528.0 and 35.5 h*ng/mL, the geometric mean $AUC_{0\text{-}[?]}$ was 581.7 and 42.4 h*ng/mL, the geometric mean C_{max} was 136.7 and 42.4 ng/mL, the median T_{max} was 1.8 hours and 1.6 hours, the mean $t_{1/2}$ was 6.5 and 2.6 hours, the geometric mean of Cl/F was 540.3 and 7468.3 L/h, and the geometric mean of VZ/F was 4829.1 L and 27346.1 L, respectively. According to these results, we could found that concomitant use of rifampin significantly alters the exposure, elimination half-life, and apparent clearance of SHR2554, in addition, combination with rifampin affected the intra-subject variability to varying extents.

The results in the mixed-effect model analysis showed that the least-squares geometric mean ratio (rifampin coadministration/SHR2554 administration) and 90% CI of $AUC_{0\text{-}t}$, $AUC_{0\text{-}[?]}$ and C_{max} of SHR2554 were 0.11 (0.08, 0.15), 0.07 (0.05, 0.09), and 0.07 (0.05, 0.10), respectively, which indicated SHR2554 coadministration with rifampin significantly reducing $AUC_{0\text{-}t}$, $AUC_{0\text{-}[?]}$ and C_{max} of SHR2554 of 89%, 93%, and 93%, respectively (**Table 3)** .

3.4 Safety

3.4.1 TEAEs

There were 15 subjects suffering 28 adverse events during the research. Of the 15 subjects. No subjects reported any TEAEs in the phase of a single dose of SHR2554, 7 subjects reported 8 TEAEs in the phase of multiple doses of rifampin, and 13 subjects reported 20 TEAEs during the phase of coadministration.

The TEAEs recorded in this study were grade 1, grade 2, or grade 3 severity (per the National Cancer Institute Common Criteria for Adverse Events version 5.0). there were 14(77.8%) subjects suffering from 26 grade 1 TEAEs, 1(5.6%) subject suffering from 1 grade 2 TEAEs (Dearticulation reported in the phase of coadministration with rifampin), and 1 subject suffering from 1 grade 3 TEAEs (Epilepsy reported in the phase of coadministration with rifampin). The main grade 1 TEAEs included: nausea, diarrhea (55.6%, reported in the phase of coadministration with rifampin), various examinations (27.8%, reported in the phase of multiple doses of rifampin; 11.1%, reported in the coadministration with rifampin), dizziness and headache (33.3%, reported in the coadministration with rifampin), metabolic and nutritional diseases (11.1%, reported in the phase of multiple doses of rifampin).

There were 15(83.3%) subjects suffering from 26 SHR2554-related TEAEs, including 7 TEAEs reported in the phase of multiple doses of rifampin, and 19 TEAEs reported in the phase of coadministration with rifampin.

There were no TEAEs leading to death in our study, and one subject withdraw from the study due to serious TEAEs. The information could be found in **Tables 4 and 5.**

3.4.2 Other safety endpoints

Table S1 listed all clinically significant changes in laboratory findings, vital signs, and physical examinations. There were no abnormal or clinically significant ECG changes observed during the treatment period.

4 Discussion

Based on The Food and Drug Administration (FDA) and European Medicines Agency's guidelines, strong index metabolic enzyme inhibitors and/or inducers should be preferentially incorporated in drug-drug interactions clinical studies if the investigational drugs have been demonstrated metabolism by such enzymes. In addition, previous pre-clinical studies have demonstrated that CYP3A4 participated in the main oxidative metabolism of SHR2554, and the phase I clinical trial indicated that potent CYP3A4 inhibitor itraconazole could significantly increase the exposure of SHR2554[16]. Therefore, this study was designed to appraise the

potential effect of rifampin on the PK properties of SHR255 in healthy Chinese subjects and assess the safety of drug-drug interactions.

The finding of this DDI study proved that powerful CYP3A4 inducer rifampin significantly impacted the PK characteristics of SHR2554 in Chinese healthy volunteers. Besides, SHR2554 coadministration with rifampin showed good safety and acceptable tolerance with only reported mild to moderate severity TEAEs. Considering the alto-frequency of drug combination in tumor patients, it is notable to take it into account for doctors when concomitant using SHR2554 and potential inducers of CYP3A4.

In general, the recommended introduced dose for rifampin is 600mg daily(about 8-12 mg/kg), with full induction of drug-metabolizing enzymes reached in about 1 week after starting rifampicin treatment[17]. Enzymes and transporters returning to pre-treatment levels may need at least 24 days after the end of treatment[18]. But some patients with several tuberculosis would adjust the dosage to 35mg/kg for high cure rates due to its dose-dependent bactericidal activity, which significantly exceeded the recommended dose[19]. In order to minimize unnecessary drug exposure for subjects and ensure obvious induction to CYP3A4 enzyme at the same time, a dose of 600mg daily for a week was considered in our study. Due to the dose-dependent and concentration-dependent induction for CYP3A4[20], the induction in absorption to co-administered medicines in actual clinical settings by rifampin would be extremely higher than the results expressed in this trial. Therefore, therapeutic strategies should be considered to avoid the combination of these two agents whenever possible.

Compared to reported drug-drug interaction results between rifampin and other drugs, our study founding suggested that concomitant administration of rifampin significantly decreases the exposure process of SHR2554 in vivo, resulting in extremely remarkable decreases in C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}[?]}$by 89%, 93%, and 93%, respectively. This revealed that CYP3A4 plays an important role in the metabolic process of SHR2554 and any DDI with potent CYP3A4 enzyme inducers should be carefully monitored in SHR2554 therapy.

What's more, a nearly 89% decrease in C_{max} indicated that the absorption of SHR2554 may also be affected after coadministration with rifampin, which is similar to the increase of V_Z/F. Preclinical results have demonstrated permeability-glycoprotein (P-gp) may participate in SHR2554 PK process[21]. P-gp is widely distributed on apical membranes of various cells, which limits drug absorption, penetration, and elimination leading to a decrease of drugs in cells[22-24]. Rifampin, as the reported maximal induction of P-gp[25], could reduce the C_{max} of orally administered P-gp substrates by 19-69.5%, thereby reducing the concentration of SHR2554. Despite rifampin-induced P-gp and CYP3A4 expression to a similar extent as well as both being involved in metabolism of SHR2554[26], the magnitude of the decrease of SHR2554 exposure by P-gp is generally lower than CYP3A4 enzyme[27]. Most of the alterations of PK parameters should be attributed to the induction to the CYP3A4 enzyme by rifampin.

Our results suggested a single dose of 300mg SHR2554 performed good safety and well-tolerance in healthy subjects, with no TEAEs happening during the single administration; whereas all TEAEs happened during the phases of multiple doses of rifampin and coadministration with rifampin. However, it is difficult to discriminate TEAEs ascribed to SHR2554 or rifampin because of the commonality of TEAEs for both SHR2554 and rifampin. Generally, in the completed or ongoing clinical trials, the most common non-hematological drug-related TEAEs were nausea, dizziness, diarrhea, and etc.; besides, the drug-related TEAEs in hematology were hypercholesterolemia, anemia, increased alanine aminotransferase, decreased neutrophil, and etc. In contrast to previously published literature in patients with relapsed or refractory mature lymphoid neoplasms and healthy volunteers, there are several differences in the category and incidence of adverse events[15], which may attribute to the effect of rifampin on SHR2554 led to different category and incidence of adverse events, but the most impossible reason might be disease condition and individual factors. Furthermore, this study chose single dose of 300mg, higher than the dose of 50mg in completed tiral in healthy volunteers. Beside, the experimental design and days of administration also should be incorporate into potential factor which cause different adverse events. Overall, it is necessary to monitor the adverse events, especially for hematological toxicity during the treatment coadministration with rifampin or other

CY3A4 induces.

Ingestion with food would decrease the absorption of rifampin and prolong the time to C_{max}, resulting in decrease C_{max} and AUC by 36-40%, and 6-26%, respectively[28-31]. In addition, the instruction of rifampin recommends rifampin be taken before meal to ensure maximal absorption considering to the concentration-lowering influence of food reducing about 30% of absorption of rifampin. And previous clinical trial has demonstrated food effects involved in the absorption of SHR2554(NCT04335266). Therefore, SHR2554 and rifampin were both administrated in fasting condition to keep the administration method consistent, as well as to reduce the variability in absorption.

In order to exclude residual confounding effects to PK process as far as possible, such as comorbidities and concomitant medications, this study was perform in healthy subjects to evaluate the DDI between SHR2554 and rifampin. It indicated that rifampin, a CYP3A4 enzyme inducer, has strong interaction with SHR2554, which could significantly decrease the exposure and promote the elimination of SHR2554. Suggested that patients should avoid drug combination of SHR2554 and rifampin in general or try to reduce the dose of rifampin to guarantee efficacy of SHR2554. Regrettably, lower doses of rifampin or other moderate inducers for CYP3A4 enzyme was not been considered in this study, which should be conducted relevant studies in the future to help researchers understand deeply for DDI potential of the investigational drug. Meanwhile, the induction for SHR2554 could be assessed through modeling and simulation methods or in clinical interaction studies. Given the innovations and prospect, SHR2554 would be frequently used for various tumors, the results could provide some valuable references for researcher to design and conduct subsequent clinical II/III trials and better development of SHR2554.

Conclusion

The results showed that rifampin could significantly impact the properties of SHR2554 in Chinese healthy volunteers. It is recommended to avoid concomitant use of SHR2554 and strong inducers of CYP3A4.

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Author Contributions

Su-Mei Xu, Qiu-Ying Sheng, Xu-Feng Zhong, Xiao-Min Li, Wang-Li Liu, Xiao-Lei Hu and were involved in study design, data analysis and interpretation; Ping-sheng Xu was involved in data analysis and interpretation. Su-mei Xu drafted the manuscript. All authors critically reviewed the manuscript and approved the final draft.

Competing interests

The other authors have no conflicts of interest to declare.

Participant consent

Written informed consent to participate in this trial was provided by all enrolled participants.

Clinical trial registration

This trial is registered at ClinicalTrials.gov, ID: NCT04577885.

Data availability statement The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figure legends

Figure 1. SHR2554 drug–drug interaction study design: effect of coadministration of SHR2554 with rifampicin, compared with SHR2554 alone, on the pharmacokinetic profile of SHR2554 in Chinese healthy male volunteers.

Figure 2. Linear (A) and semilog (B) plasma concentration–time curves for SHR2554 after administration alone (300 mg) and coadministered with rifampicin (600 mg) in Chinese healthy volunteers. When [?]50% of the concentration data at a single time point were defined as BLQ, the mean concentration at that time point was set to BLQ. BLQ data were set to 0 on the linear scale and are not presented on the semilog scale. Error bars represent standard deviation. A Nominal time after dose: planned sampling time postdose. BLQ, below the limit of quantification.

Figure 3. Forest plot of the effect of coadministration of SHR2554 with rifampicin compared with SHR2554 alone on the exposure parameters of SHR2554 in Chinese healthy volunteers. AUC_{0-last}, area under the concentration–time curve from time 0 to the last quantifiable concentration; AUC_{0-inf}, area under the concentration–time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GM, geometric mean.

Table1 Summary of subject baseline and demographic characteristics (full analysis set).

Characteristic	N=18
Age, years, mean ± SD (range)	25.3 ± 4.4 (20-32)
Sex n (%)	
male	11 (61.1%)
female	7 (38.9%)
Ethnicity n (%)	
Han	17 (94.4%)
Other	1 (5.6%)
BMI, kg/m^2, mean ± SD (range)	21.9 ± 1.9 (19.4 -25.4)
Smoking status, n (%)	
Never	15 (83.3%)
Occasional ([?]5 cigarettes/day)	0
Regular	0
Quit	3 (16.7%)
Alcohol consumption,	
Never	14 (77.7%)
Occasional ([?]14 units of alcohol/week)	0
Regular	1 (5.6%)
Abstained	3 (17.7%)
Past medical history[a]	
Epilepsy	1(5.6%)
Past medication	
Magnesium valproate	1(5.6%)

[a]One subject concealed the history of epilepsy and taking magnesium valproate for a long time.

Table 2 Summary of the key pharmacokinetic (PK) parameters of SHR2554.

C_{max}, maximum plasma concentration; T_{max}, time to C_{max}, $AUC_{0\text{-}t}$, area under the concentration-time to the last quantifiable concentration; $AUC_{0\text{-}[?]}$, area under the concentration-time to infinity; $t_{1/2}$, elimination half-life; CL/F, apparent clearance; V_Z/F, apparent volume of distribution

[a]PK parameters are presented as geometric mean (geometric coefficient of variation), with the exception of T_{max}, which is presented as median (range)

[b]In the SHR2554 administration alone phase the $AUC_{0\text{-}[?]}$of 1 subject could not be accurately calculated due to $AUC_{t\text{-}[?]}$ >20%, so the number of subjects was 16.

[c]In the SHR2554 coadministration with rifampin phase the $AUC_{0\text{-}[?]}$ of 2 subjects could not be accurately calculated due to $AUC_{t\text{-}[?]}$ >20%, so the number of subjects was 15.

Treatment period	Parent	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}t}$ (ng*h/mL)	$AUC_{0\text{-}[?]}$ (ng*h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	V_Z/F (
SHR2554 (300mg) alone	N=17	177.2 (72.0%)	1.5 (1.0-4.0)	672.1 (75.4%)	721.5 (71.2%)[b]	6.5 (36.4%)	651.4 (56.8%)	6651.3 (85.4%)
SHR2554 (300mg) + rifampin (600mg)	N=17	17.0 (49.8%)	1.5 (0.5-4.0)	38.5 (50.5%)	46.3 (44.8%)[c]	2.6 (35.0%)	8134.9 (43.1%)	30423.5 (52.4%)

Table 3 Comparison of pharmacokinetic parameters for SHR2554 coadministration with rifampin.

Parameters	SHR2554 alone	SHR2554 alone	Coadministration	Coadministration	GM ratio (90% CI)
	n	GM	n	GM	
C_{max} (ng/mL)	17[b]	136.7	17	15.4	11% (0.08-0.15)
AUC_{0-t} (ng*h/mL)	17	528.0	17	34.5	7% (0.05-0.09)
$AUC_{0-[?]}$(ng*h/mL)	16[c]	581.7	15[d]	42.4	7% (0.05-0.10)

C_{max}, maximum plasma concentration; AUC_{0-t}, area under the concentration-time to the last quantifiable concentration; $AUC_{0-[?]}$, area under the concentration-time to infinity; n, the number of subject enrolled in the PK parameters analysis set; GM, geometric mean; CI, coefficient of variation.

[a]The values after logarithm transformation used PROC MIXED process to carry out analysis of variance. Coadministration or not was introduced into the model as a fixed effect, and individuals were introduced into the model as random effects.

[b]1 subject concealed the history of epilepsy and taking magnesium valproate for a long time, considering potential hepatotoxicity, he was excluded from the PK parameters set.

[c]1 subject could not be enrolled in the analysis of PK parameters set mixed-effects model due to $AUC_{t-[?]}$ >20%.

[d]2 subjects could not be enrolled in the analysis of PK parameters set mixed-effects model due to $AUC_{t-[?]}$>20%.

Table 4 Summary of treatment-emergent adverse events (TEAEs).

Ev (n), number of events; n (%), number of patients (percentage of the treatment group).

To analyze the association between the TEAEs and the study drug, three assessments were made: unrelated or unlikely, potentially, probably, or definitely related.

TEAE summary	A single dose of SHR2554	A single dose of SHR2554	Multiple doses of rifampin	Multipl
	Ev (n)	N (%)	Ev (n)	N (%)
Any TEAE	0	0	8	7(38.9%
TEAEs related to SHR2554	0	0	7	6(33.3%
TEAEs related to rifampin	0	0	8	7(38.9%

AEs	SHR2554 (n=18)	SHR2554 (n=18)	Rifampin (n=18)	Rifampin (n=18)	SHR2554 + Rifampin (n=18)	SHR2554 + Rifampin (n=18)	Total	Total
	Ev (n)	N (%)	Ev (n)	N (%)	Ev (n)	N (%)	Ev (n)	N (%)
Any TEAEs	0	0	8	7 (38.9%)	20	13(72.2%)	28	15 (83.3%)
Nausea	0	0	0	0	9	9 (50.0%)	9	9 (50.0%)
Diarrhea	0	0	0	0	1	1 (5.6%)	1	1 (5.6%
dizziness	0	0	0	0	5	5 (27.8%)	5	5 (27.8%)
Headache	0	0	0	0	1	1 (5.6%)	1	1 (5.6%
Epilepsy	0	0	0	0	1	1 (5.6%)	1	1 (5.6%

AEs	SHR2554 (n=18)	SHR2554 (n=18)	Rifampin (n=18)	Rifampin (n=18)	SHR2554 + Rifampin (n=18)	SHR2554 + Rifampin (n=18)	Total	Total
Anorexia	0	0	1	1 (5.6%)	0	0	1	1 (5.6%
Dearticulation	0	0	0	0	1	1 (5.6%)	1	1 (5.6%
Anemia	0	0	1	1 (5.6%)	0	0	1	1 (5.6%
Hypercholesterolemia	0	0	1	1 (5.6%)	0	0	1	1 (5.6%
Positive urinary leukocyte	0	0	1	1 (5.6%)	2	2 (11.1%)	3	3 (16.7%)
Increased alanine aminotransferase	0	0	2	2 (11.1%)	0	0	2	2 (11.1%)
Positive urinary erythrocyte	0	0	1	1 (5.6%)	0	0	1	1 (5.6%
Decreased neutrophil	0	0	1	1 (5.6%)	0	0	1	1 (5.6%

Table 5 Summary of detailed treatment-emergent adverse events (TEAEs) in different administration phases.

Ev (n), number of events; n (%), number of patients (percentage of the treatment group).