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CLINICAL TRIAL REPORT

Effect of Efavirenz on the Pharmacokinetics of SHR6390 in Healthy Volunteers

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Purpose: SHR6390 is an oral, potent and selective small-molecule CDK4/6 inhibitor for the treatment of human breast, ovarian and colon cancer. Previous studies have shown that SHR6390 in combination with rifampicin, a potent inducer of CYP3A4, significantly reduces exposure levels. Therefore, we further investigated the effect of efavirenz, a moderate CYP3A4 inducer, on a single oral dose of SHR6390 in healthy volunteers.

Patients and Methods: Twenty healthy subjects were enrolled in this single-center, open, single-dose, self-controlled DDI study. On Day 1, subjects received a single oral dose of 150mg SHR6390; on Day 8-26, subjects received 600 mg efavirenz orally at night, with a single dose of 150 mg SHR6390 on Day 22. Blood samples for pharmacokinetic analyses were collected.

Results: The geometric mean ratios of the maximum concentration(C_{max}) and the area under the concentration curve from zero to infinity ($AUC_{0\text{-}inf}$) between combination therapy and SHR6390 monotherapy (combination therapy/SHR6390 monotherapy) and their 90% confidence intervals were 0.562 (0.482, 0.654) and 0.328 (0.278, 0.386), respectively. This indicates that the Cmax and AUC0 inf of SHR6390 decreased by approximately 43.8% and 67.2%, respectively. Oral administration of 150 mg SHR6390 alone or together with efavirenz was safe and tolerable in healthy subjects.

Conclusion: It is suggested that under the action of the moderate CPY3A4 inducer efavirenz, the exposure AUC of SHR6390 exhibits a moderate level of induction. It is recommended to avoid concomitant administration of moderate inducers of CYP3A4 during treatment with SHR6390.

Trial Registration: http://www.chinadrugtrials.org.cn/index.html, CTR20211571/ https://classic.clinicaltrials.gov, NCT04973020.

Keywords: SHR6390, efavirenz, drug-drug interaction, pharmacokinetics, tolerability

Introduction

Cyclin-dependent kinase (CDK) is a type of serine/threonine kinase that forms dimers with the corresponding cyclin, phosphorylates downstream protein molecules, promotes the orderly progression of the cell cycle at all stages, and achieves cell growth and proliferation.[1] CDK4/6 belongs to the CDK kinase family and plays a critical role in the process of cell transition from the G1 phase to the S phase by interacting with cyclin D, phosphorylating Rb protein, dissociating Rb-E2F complex, releasing free E2F into the nucleus, and regulating protein transcription.[2,3] In most tumors, various genetic or epigenetic changes cause high activity of CDK4/6, leading to hyperphosphorylation and inhibition of Rb protein, ultimately leading to disordered cell proliferation.[4] CDK4/6 has therefore become an important molecular target for tumor treatment.[5,6]

SHR6390 is an oral, efficient, and selective small molecule CDK4/6 inhibitor, that can induce the inhibition of phosphorylated Rb and cell cycle arrest at the G1 phase in both cell lines and xenografts.[7] In vivo,pharmacodynamics studies show thats SHR6390 can significantly inhibit tumor growth in mouse models of transplanted tumors[8] (including human breast cancer, ovarian cancer, and colon cancers). Pharmacokinetic studies have shown that SHR6390 has high bioavailability in rats and dogs, with a larger apparent volume of distribution, and no significant accumulation after continuous administration. Safety studies have shown that SHR6390 has moderate toxicity in rats and dogs, mainly manifested in bone marrow suppression, immune system suppression, gastrointestinal and hepatic changes.

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The pharmacokinetics (PK) of SHR6390 have been investigated and clarified in both advanced breast cancer patients and healthy subjects.[9,10] The approved dose of SHR6390 is 150 mg once daily, which is below the maximum tolerated dose observed in advanced breast cancer patients and well tolerated in healthy subjects.[9,10] After oral administration, the median time to reach the maximum observed concentration (Tmax) of SHR6390 in plasma was approximately 6h, and it is eliminated with a half-life (T1/2) of approximately 42.4h.[10]

Preclinical studies have shown that CYP3A4 is the major metabolic enzyme of SHR6390 in the liver.[9] Therefore, it is necessary to conduct clinical studies on the effects of CYP3A4 inducers on the pharmacokinetics and safety of SHR6390. A study (CTR20201240) was conducted to investigate the pharmacokinetic effects of the CYP3A4 strong inducer rifampicin on SHR6390 in healthy subjects. The data show that the combination of SHR6390 and rifampicin reduces $AUC_{0\text{-}t}$, $AUC_{0\text{–}\infty}$, and C_{max} by approximately 80.5%, 80.7%, and 64.0%, respectively. According to the FDA guidelines[11] on drug-drug interactions, the sponsor may conduct clinical trials with moderate-intensity inducers if necessary to better understand the characteristics of the studied drug. Therefore, this study is designed to evaluate the effect of a moderate-intensity CYP3A4 inducer on the pharmacokinetics and safety of SHR6390. The FDA website in the United States lists five moderate-intensity inducers for drug-drug interaction(DDI) clinical research, namely Bosentan, Efavirenz, Etravirine, Phenobarbital, and Primidone. Referring to the DDI clinical trials of CYP3A4 medium intensity inducers for other drugs already conducted by ClinicalTrails.org (such as NCT04459598, NCT01867996, NCT01268839), this study selected efavirenz as the CYP3A4 medium intensity inducer.

Materials and Methods

Ethics Statement

The clinical registration numbers are CTR20211571 (http://www.chinadrugtrials.org.cn/index.html), and NCT04973020 (https://classic.clinicaltrials.gov). All applicable documents including protocol and informed consent form were submitted to the Ethic Committees of Xuanwu Hospital of Capital Medical University for review and written approval. This study was conducted by the ethical principles, that have their origin in the Declaration of Helsinki, and with Good Clinical Practice guidelines. All subjects provided written informed consent.

Study Design

This study is a single-center, open-label, single-dose, self-controlled DDI study. The entire study lasted 34 days, with subjects receiving a single dose of 150 mg SHR6390 on day 1, and then received a dose of efavirenz 600 mg from day 8 to day 26, once daily at night. On day 22, the subjects received another dose of 150 mg SHR6390, the two SHR6390 doses were separated by a washout interval of 21 days. A standard lunch and dinner were provided at least 4 hours and at least 10 hours, respectively, after taking SHR6390. After completing the safety check, the subjects were discharged on Day 27 and followed up by phone or outpatient service once on Day 32 to 34. The schematic of the study protocol is shown in Figure 1.

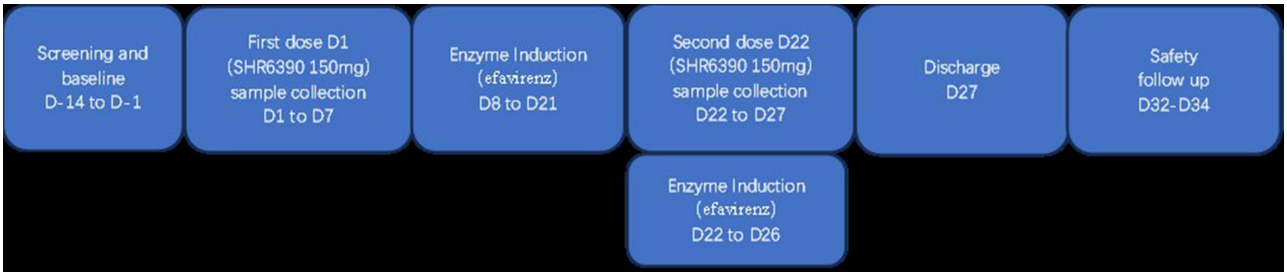

Figure 1 Study flow chart.

Study Population and Inclusion Criteria

Twenty subjects were enrolled in the study, not less than one-third of female subjects. The age varied from 18 to 45 years and body mass index (BMI) from 19 to 26 kg/m^2. All subjects were considered healthy based on a detailed medical history, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory tests. Subjects were excluded if they had any clinically significant disease such as the circulatory system, endocrine system, nervous system, digestive system, respiratory system, urogenital system, hematology, immunology, psychiatry, and metabolic abnormalities, or any other disease that can affect the study results were excluded from this study. In addition, subjects were excluded if they had taken any medicine within 4 weeks before the first administration (including prescription medicines, non-prescription medicines, Chinese herbal medicines, vitamins, calcium tablets, and other food supplements), especially the drugs that have any effect on CYP3A4 were also excluded.

Pharmacokinetic Assessment

For the pharmacokinetic assessment, 4 mL of blood samples were collected in heparin-lithium anticoagulant tubes at different time points: pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 24, 36, 48, 72, 96 and 144 after the administration of SHR6390 (blood samples were collected for the second administration of SHR6390 up to 120 h). The collected blood samples were centrifuged at 2–8 °C, 2000 g for 10 minutes, and the plasma was collected separately and stored in a −80 °C freezer before analysis. Shanghai Frontage Biotechnology Co., Ltd. (located in Shanghai) detected and analysed the concentration samples, and the analytical method was validated. In this method, d8-pabocillin was used as an internal standard, and the concentration of SHR6390 in plasma was determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) with LC-30AD (Shimadzu) and Sciex Triple Quad 6500+(Sciex). The calibration range of the SHR6390 was 0.390–390 ng/mL. The lower limit of quantification was 0.390 ng/mL.[10] The accuracy of the assay was −2.4% to 2.3%, and the precision was within 7.9% of the coefficient of variation. The following pharmacokinetic parameters were calculated using a non-compartmental method with WinNonlin™ software (version 8.0): maximum plasma concentration (Cmax), area under the plasma concentration-time curve calculated from 0 to the last measurement point (AUC_{0-t}), AUC to infinity (AUC_{0-inf}), terminal elimination half-life ($t_{1/2}$), time to Cmax (T_{max}), apparent clearance (CL/F) and apparent volume of distribution (Vz/F).

Safety Assessment

Adverse events (AEs) were recorded by subject reporting, investigator observation, examination of physiology, vital signs, 12-lead ECG, and/or clinical laboratory tests, we recorded the adverse events (AEs) to assess the safety and tolerability. All significant abnormalities observed during the study were carefully recorded and followed up until resolution or clinical stability. The AEs were described according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grading system (version 5.0).

Statistical Analysis

The sample size estimation of this study is not based on statistical hypothesis testing. A total of 16 subjects are planned to be enrolled, allowing for a dropout rate of 25%. A total of 20 subjects are planned to be enrolled. After natural logarithmic transformation, the plasma SHR6390 PK parameters AUC0-inf, AUC0-t, and Cmax were estimated by fitting a mixed effect model to obtain the least squares mean difference and 90% confidence interval between the combination therapy and SHR6390 monotherapy. The drug group was a fixed effect, and the subjects were included in the model fitting as a random effect. The least squares mean difference and its 90% confidence interval obtained from this analysis are then converted into a geometric mean ratio (combination therapy/SHR6390 monotherapy) and its 90% confidence interval by taking the negative number.

Results

Subjects

Twenty healthy subjects (7 male and 13 female) were included in the study. The mean age was 30.8 ± 6.39 years (range 22–42), the mean body weight was 60.45 ± 9.026 kg (range 48.3–75.9) and the mean BMI was 22.57 ± 1.695 kg m2 (range 20.0–25.2).17 subjects completed the study as planned while one subject withdrew consent on day 17, and 2 subjects were discontinued by the investigator due to an AE on day 16, day 19.

Effect of Efavirenz on SHR6390 PK

The non-compartmental pharmacokinetic parameters are summarized in Table 1. The concentration-time profiles of plasma SHR6390 from subjects receiving a single oral dose of 150 mg SHR6390 alone or in combination with efavirenz are shown in Figure 2. The analysis results showed that for the combination therapy and SHR6390 monotherapy, the geometric mean ratios of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$, were 0.562 (0.482, 0.654), 0.340 (0.289, 0.400), and 0.328 (0.278, 0.386) respectively. The 90% confidence intervals were 0.562 (0.482, 0.654), 0.340 (0.289, 0.400), and 0.328 (0.278, 0.386), all of which were outside the equivalent interval range of 80.00%-125.00%, indicating that co-administration with efavirenz affects the pharmacokinetic profile of SHR6390. Treatment ratio estimates are shown in Table 2.

Safety

Fifty-nine AEs occurred in 19 subjects during the treatment period (Table 3). The severity of all AEs was 55 cases at grade 1, and 4 cases at grade 2. A total of 12 AEs related to SHR6390 and 30 AEs related to efavirenz. There were a total of 2 AEs leading to withdrawal from the trial and no serious AE. The most common AE in the SHR6390 monotherapy and co-administration (SHR6390 plus efavirenz) groups was decreased white blood cell count (four subjects, four events). The most common AE in the efavirenz monotherapy groups was dizziness (fourteen subjects, fourteen events).

Discussion

Patients with tumors often take multiple drugs simultaneously, which can lead to DDIs, serious adverse reactions or altered treatment outcomes. Therefore, it is necessary to conduct a scientific assessment of the likelihood, severity, and impact of DDI occurrence. There are no clinical studies of drug-drug interactions between moderate-intensity inducers and SHR6390. Here, the effect of the moderate CYP3A inducer efavirenz with SHR6390 was evaluated in this study. Previous clinical studies have shown no dose-limiting toxicities(DLT) events were observed in the 25 mg to 175 mg dose range for SHR6390.[9] The recommended dosage for SHR6390 in Phase III clinical trials is 150 mg (QD) administered on an empty stomach.[12] The 150 mg dose of SHR6390 was chosen for this study to ensure the safety of healthy volunteers, and because co-administration with efavirenz may reduce exposure to SHR6390, it does not increase the risk to volunteers.

The choice of inducers was based on previous relevant studies. Efavirenz has been classified by the FDA as a moderate CYP3A4 inducer, as it reduces the AUC of CYP3A-sensitive index substrates by ≥50% and <80%. Although the stable state of efavirenz was achieved after continuous administration for 6–10 days, according to the

Table 1 Plasma Pharmacokinetic Parameters of SHR6390 Following Monoadministration and Coadministration with Efavirenz

Pharmacokinetic parameters (Unit)	Mean±SD (CV %)	
	SHR6390 (N=20)	SHR6390 with efavirenz (N=17)[b]
C_{max}(ng/mL)	62.7±16.2 (25.9%)	35.3±9.8 (27.8%)
AUC_{0-t} (h*ng/mL)	1970±436 (22.1%)	688±204 (29.6%)
$AUC_{0-\infty}$ (h*ng/mL)	2140±495 (23.2%)	719±215 (29.9%)
Tmax (h)[a]	5.0 (2.0, 6.0)	4.0 (1.0, 8.0)
$t_{1/2}$ (h)	43.7±5.66	29.3±4.33
CL/F (L/h)	74.4±20.3	234±97.8
Vd (L)	4610±970	9600±3250

Notes: *SD* standard deviation, *CV%* percent coefficient of variation of mean, *N* number of subjects with available data in pharmacokinetic analysis, $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity, AUC_{0-t} area under the plasma concentration-time curve from the time zero to the last measurable plasma concentration, C_{max} maximum observed plasma concentration, T_{max} time to maximum plasma concentration, $t_{1/2}$ half-life. [a]Presented as median (minimum-maximum). [b]Three subjects dropped out before the administration of SHR6390 with efavirenz.

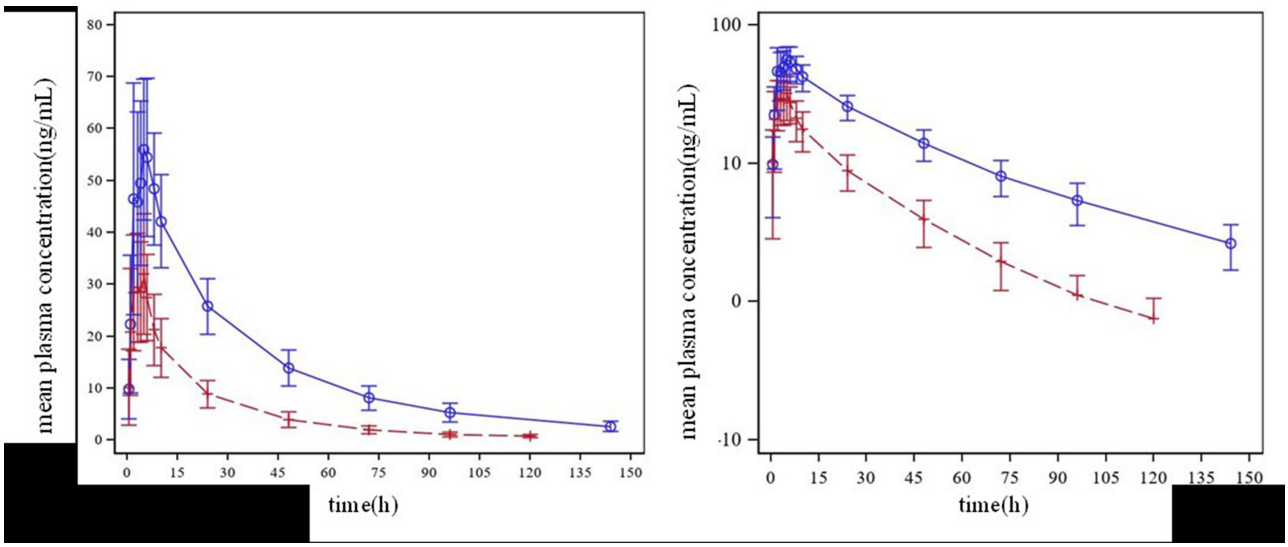

Figure 2 The linear and semilogarithmic scales of mean plasma concentration-time curves after subjects received a single dose (150 mg) of SHR6390 orally and together with 600 mg efavirenz. —○— SHR6390. —+— SHR6390 with efavirenz.

FDA guidelines[13] it may take approximately 2 weeks of daily drug administration to achieve the maximum level of induction. The effect of efavirenz on SHR6390 was within the expected range, reducing the AUC of CYP3A-sensitive index substrates by ≥50% and <80%.

The safety analysis in this study showed that well tolerable. However, it is noteworthy that 14 subjects (70%) experienced dizziness, all of which were related to efavirenz and were the most frequent adverse events, with a higher incidence rate than stated in instructions of efavirenz (5–9%). In this study, 3 subjects experienced rash, and 2 withdrew. In another drug-drug interaction study (CTR20202107), efavirenz is also an inducer with the same dosage and duration. A total of 20 subjects were recruited, and 2 subjects experienced rash and withdrew in the study (CTR20202107). We found that the average time from oral efavirenz to rash is 8 days;[14] The initial symptoms of the rash are skin itching, mainly occurring in the limbs and back, without any other accompanying symptoms or laboratory abnormalities. Four subjects who withdrew from the trial were treated with anti-allergic therapy for 5–7 days, and the rash subsided. Therefore, the above-mentioned adverse events need our attention in future studies if efavirenz is an inducer.

In this study, the dose of efavirenz is according to the highest recommended dose in clinical treatment. However, after the end of the visit in this study, Chinese Guidelines for Diagnosis and Treatment of HIV/AIDS (2021 edition) have required that the dose of efavirenz be reduced to 400 mg per day according to relevant studies[15–17] to reduce the

Table 2 Treatment Ratio Geometric Mean Ratios (GMR, SHR6390+efavirenz versus SHR6390 Alone) with 90% Confidence Interval for SHR6390

PK parameters	Geometric mean[a]			
	SHR6390 with efavirenz (N=17)	SHR6390 (N=20)	Ratio	90% CI
C_{max}(ng/mL)	34.026	60.567	0.562	0.482, 0.654
AUC_{0-t} (h*ng/mL)	652.682	1917.808	0.340	0.289, 0.400
$AUC_{0-\infty}$ (h*ng/mL)	681.868	2079.714	0.328	0.278, 0.386

Notes: $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity, AUC_{0-t} area under the plasma concentration-time curve from time zero to the last time point with a measurable concentration, *CI* confidence interval, C_{max} maximum observed plasma concentration. [a]Least squares method.

Table 3 Summary of Adverse Events After the Study Drug Administration

Treatment / Adverse event	SHR6390 (N=20)	Efavirenz (N=20)	SHR6390 + efavirenz (N=17)	Total (N=20)
Dizziness	0 (0)	14 (14)	0 (0)	14 (14)
Hypoesthesia[a]	0 (0)	1 (1)	0 (0)	1 (1)
Headache	0 (0)	1 (1)	0 (0)	1 (1)
White blood cell count decrease	1 (1)	0 (0)	3 (3)	4 (4)
Neutrophil count decrease	1 (1)	0 (0)	1 (1)	2 (2)
Blood pressure increase[a]	1 (1)	1 (1)	0 (0)	1 (2)
Alanine aminotransferase increase	0 (0)	1 (1)	0 (0)	1 (1)
Aspartate aminotransferase increase	0 (0)	0 (0)	1 (1)	1 (1)
QRS interval prolong[a]	0 (0)	1 (1)	0 (0)	1 (1)
Heart rate increase[a]	1 (1)	0 (0)	0 (0)	1 (1)
Blood non-binding bilirubin increase	1 (1)	0 (0)	0 (0)	1 (1)
Oral ulcer[a]	1 (1)	4 (4)	1 (1)	4 (6)
Nausea	0 (0)	3 (3)	0 (0)	3 (3)
Constipation[a]	0 (0)	1 (1)	0 (0)	1 (1)
Non-infectious gingivitis[a]	0 (0)	1 (1)	0 (0)	1 (1)
Abnormal dreaming	0 (0)	4 (5)	0 (0)	4 (5)
Insomnia	0 (0)	1 (1)	0 (0)	1 (1)
Upper respiratory tract infection[a]	0 (0)	2 (2)	1 (1)	3 (3)
Conjunctivitis[a]	0 (0)	1 (1)	0 (0)	1 (1)
Allergic dermatitis	0 (0)	2 (2)	0 (0)	2 (2)
Rash	0 (0)	1 (1)	0 (0)	1 (1)
Acne[a]	0 (0)	1 (1)	0 (0)	1 (1)
Anemia[a]	0 (0)	0 (0)	2 (2)	2 (2)
Anorexia	0 (0)	1 (1)	0 (0)	1 (1)
Cough[a]	0 (0)	0 (0)	2 (2)	1 (1)
Ventricular extrasystole	1 (1)	0 (0)	0 (0)	1 (1)
Total	4 (7)	16 (42)	7 (10)	19 (59)

Notes: Data are presented as the number of subjects (number of events). [a]Considered as "not related" to the study drugs.

occurrence of related adverse reactions.[18] Therefore, this situation should be noted when efavirenz is used as an inducer in future DDI studies in the future.

The results of the pharmacokinetic study showed that after oral administration of SHR6390 with efavirenz in subjects, the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of subjects decreased by 43.8%, 66.0% and 67.2%, respectively, suggesting that the effect of efavirenz on the exposure of SHR6390 is weaker than that of rifampicin. It is recommended to avoid concomitant administration of moderate inducers of CYP3A4 during treatment with SHR6390.

Conclusion

Our study suggests that the moderate CYP3A4 inducer efavirenz has a significant influence on the PK behavior of SHR6390, the exposure level AUC of SHR6390 exhibits a moderate level of induction effect. It is recommended to avoid using CYP3A4 moderate inducers simultaneously in clinical medication. It was well tolerated to oral a dose of 150 mg SHR6390 and its combination with 600 mg efavirenz in healthy subjects.

Data Sharing Statement

The data that support the findings of this study are not available due to confidentiality.

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Disclosure

The authors report no conflict of interest in this work.

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