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Effect of CYP3A4 inhibitor and induction on the pharmacokinetics and safety of FHND9041, a novel EGFR T790M inhibitor, in healthy Chinese

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Abstract

Background Non-small cell carcinoma is the main pathologic type of lung cancer, and a large number of clinical trials have shown that epidermal growth factor receptor tyrosinase inhibitors exhibit superior clinical efficacy and lower toxicity compared with chemotherapy. FHND9041 is a new irreversible EGFR T790M mutation-selective small molecule kinase inhibitor, a third-generation EGFR inhibitor developed by Nanjing Chuangte Pharmaceutical Technology Co., Ltd. The aim of this study was to evaluate the effects of oral Itraconazole capsules and oral Rifampicin capsules on the pharmacokinetic profile and safety and tolerability of a single oral dose of FHND9041 capsules in healthy Chinese male subjects.

Patients and methods This study employed a single-center, open-label, fixed-sequence design, comprising two parallel groups: Group 1 received FHND9041 40 mg in combination with Itraconazole, while Group 2 received Rifampicin in combination with FHND9041 80 mg. Each group enrolled 16 subjects for a two-period study, with the first period involving monotherapy and the second period involving co-administration. All subjects participating in this clinical trial were healthy adult Chinese males.

Results In healthy subjects, after a single oral administration of 40 mg FHND9041 capsules, the corrected geometric mean ratios (90% confidence intervals) of FHND9041 C_{max}, AUC_{0-last}, and AUC_{0-inf} when co-administered with itraconazole capsules compared to the monotherapy phase were 111.46% (103.26 – 120.30%), 169.53% (156.21 – 183.99%), and 168.25% (156.26 – 181.15%), respectively. The 90% confidence interval for C_{max} fell within the 80-125%

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range, while the 90% confidence intervals for both AUC_{0-last} and AUC_{0-inf} exceeded the 80-125% range. Following a single oral dose of 80 mg FHND9041 capsules, the adjusted geometric mean ratios (90% confidence intervals) of C_{max}, AUC_{0-last}, and AUC_{0-inf} for FHND9041 during co-administration with Rifampicin compared to monotherapy were 52.12% (41.95 – 64.74%), 16.47% (13.34 – 20.31%), and 16.51% (13.56 – 20.09%), respectively. The 90% confidence intervals for C_{max}, AUC_{0-last}, and AUC_{0-inf} all fell outside the 80 – 125% range. No serious adverse events occurred during the trial.

Conclusions Co-administration with Rifampicin significantly reduced the exposure of FHND9041. Therefore, it is recommended to avoid co-administration of FHND9041 with Rifampicin and other potent CYP3A4 inducers. Conversely, co-administration with Itraconazole significantly increased the total exposure of FHND9041. Caution is advised when FHND9041 is co-administered with Itraconazole or other strong CYP3A4 inhibitors. Close monitoring of tolerability during co-administration is essential, and dose reduction may be necessary if required. FHND9041 capsules demonstrated good safety and tolerability when used alone or in combination with strong CYP3A4 inhibitors or inducers.

Trial registration Registered 03/27/2023 (http://www.chinadrugtrials.org.cn/index.html, CTR202300931).

Keywords FHND9041, Non-small cell lung cancer, Pharmacokinetics, Safety assessment

Introduction

According to the International Agency for Research on Cancer's report of 2024, lung cancer is one of the most common diseases worldwide. As of 2022, there were 2.480 million new cases of lung cancer, which jumped to the top of the 2022 cancer incidence spectrum [1].

Depending on the pathological features, lung cancer can be classified as either small cell carcinoma (SCLC) or non-small cell carcinoma (NSCLC). About 85% of all lung tumors are NSCLC, the primary pathological form of lung cancer [2]. According to published research, Asians with non-small cell lung cancer are more likely to have mutations in the gene for the epidermal growth factor receptor (EGFR); for example, in China, more than 50% of lung cancer patients have EGFR mutations [3]. For early-stage lung cancer patients, surgery combined with adjuvant therapy can cure lung cancer [4]. Even though chemotherapy is still the most common treatment for NSCLC, the development of epidermal growth factor receptor tyrosine kinase inhibitors, or EGFR-TKIs, has resulted in major advancements in the care of NSCLC patients [5]. Some clinical trial findings have shown that EGFR-TKIs demonstrate superior clinical outcomes and lower toxicity compared to chemotherapeutic treatments, making them the standard first-line treatment for EGFR-mutated advanced NSCLC. As a key transmembrane protein molecule, EGFR, located on chromosome 7 of the human genome, belongs to the family of tyrosine kinase receptor proteins, whose gene structure consists of 28 exon fragments, capable of transcribing and translating 1,186 amino acids, and whose glycoprotein molecular weight has been determined to be approximately 170 kDa [6]. EGFR has the ability to bind to epidermal growth factor or other growth factors, triggering the dimerization of EGFR itself or with other receptors to activate its intrinsic tyrosine kinase activity. By hydrolyzing ATP, EGFR transfers phosphate groups to downstream substrates, initiating and regulating a series of complex signaling cascades, mainly involving the PI3K/AKT/mTOR、RAS/RAF/MEK/ERK、and JAK/STAT pathways [7, 8]. Cell development, proliferation, and death are all significantly influenced by the EGFR signaling pathway.

FHND9041 is a third-generation EGFR inhibitor developed by Nanjing Chuangte Pharmaceutical Technology Co., Ltd. and is a new irreversible EGFR T790M mutation-selective small molecule kinase inhibitor. It selectively inhibits the phosphorylation of EGFR mutant kinase and the activation of its downstream key signaling molecules, Akt and Erk, thereby inhibiting the proliferation of tumor cells with EGFR T790M resistance or sensitive mutations and inducing apoptosis of tumor cells. As an innovative drug, FHND9041 should undergo evaluation to identify both definite and potential factors contributing to drug-drug interactions (DDIs), such as metabolic enzymes and transporters, and clinical DDI studies should be conducted. The results of these studies would guide subsequent design considerations in clinical research, including drug combination therapies and dosage adjustments. After oral administration, FHND9041 is rapidly absorbed and exhibits high bioavailability. It demonstrates extensive tissue distribution and can penetrate the blood-brain barrier. FHND9041 is primarily metabolized in the body via CYP3A enzymes. Fecal excretion is the main route of elimination for FHND9041, while renal excretion through urine serves as a secondary elimination pathway.

The metabolism and elimination of many drugs (including the majority metabolized via the P450 enzyme system) can be inhibited, activated, or induced by co-administration with other drugs. Changes in metabolism due to drug interactions can be substantial, potentially leading to a tenfold or greater decrease or increase in

the concentration levels of the drug or its metabolites in the blood or tissues. It may also result in the formation of toxic metabolites or an elevation in the exposure levels of toxic parent drugs. These significant alterations in exposure levels can importantly modify the safety and efficacy profiles of some drugs or their active metabolites. Based on the data from Phase I/II studies, and following a comprehensive analysis of efficacy, safety, and pharmacokinetic (PK) data, the sponsor and investigators unanimously selected 80 mg once daily (QD) as the recommended dose for FHND9041.

Itraconazole is a potent inhibitor of the CYP3A4 enzyme, capable of suppressing its activity and thereby increasing the systemic exposure of CYP3A4 substrates. FHND9041 is a substrate of CYP3A4, and when co-administered with itraconazole, the systemic exposure of FHND9041 is anticipated to rise. To ensure the safety of subjects during co-administration and prevent the systemic exposure of FHND9041 from reaching excessively high levels, a lower dose has been selected for this study. It was projected that co-administering 40 mg of FHND9041 with itraconazole would yield an exposure level comparable to that achieved with an 80 mg monotherapy dose of FHND9041. Hence, 40 mg has been chosen as the FHND9041 dose for co-administration with itraconazole. Additionally, to closely simulate the continuous dosing regimen of itraconazole in clinical practice, subjects would receive 200 mg of itraconazole QD for five days prior to the co-administration of FHND9041 and itraconazole. This pre-treatment period is designed to approximate steady-state conditions, maximizing the inhibition of hepatic enzymes. Itraconazole would continue to be administered until the completion of the final pharmacokinetic sampling. The dosing regimen of 200 mg QD itraconazole is commonly utilized in clinical settings.

Rifampicin is a potent inducer of the CYP3A4 enzyme, capable of enhancing its activity and thereby reducing the systemic exposure of CYP3A4 substrates. FHND9041, being a substrate of CYP3A4, is expected to experience a decrease in exposure when co-administered with rifampicin. Therefore, the recommended dose of 80 mg has been selected for FHND9041 when co-administered with rifampicin. Additionally, to closely simulate the continuous dosing regimen of rifampicin in clinical practice, subjects would receive 600 mg of rifampicin QD for nine days prior to the co-administration of FHND9041 and rifampicin. This pre-treatment period is designed to approximate steady-state conditions, maximizing the induction of hepatic enzymes. Rifampicin would continue to be administered until the completion of the final pharmacokinetic sampling. The dosing regimen of 600 mg QD rifampicin is commonly utilized in clinical settings.

In order to maximize the safety and efficacy of patient dosing, this study would examine the effect of a strong inhibitor/strong inducer of CYP3A4 on the pharmacokinetic profile of a single dose of FHND9041 capsules in healthy subjects.

Inhibition or induction of CYP3A4 may alter the exposure parameters of FHND9041, thereby affecting the safety profile of the drug. The aim of this study was to evaluate the effects of oral Itraconazole capsules and oral Rifampicin capsules on the PK profile, safety and tolerability of a single oral dose of FHND9041 capsules in healthy Chinese male subjects.

Methods

Subjects

Eligible subjects were healthy men, aged 18–55 years, with a body mass index of 19.0–28.0 kg/m^2 inclusive and body weight of 50 kg inclusive or more; agree to take effective contraceptive measures from signing the informed con-sent form until 3 months after the infusion of the study drug. Existing preclinical and clinical-stage research results indicate that FHND9041's metabolism has minimal correlation with gender. Given the radiological nature of this drug, male healthy subjects were selected to participate in this study to better protect the rights and well-being of the subjects; it was anticipated that this would have no impact on the trial results.

The main exclusion criteria were as follows: (1) Diseases with abnormal clinical manifestations that need to be excluded, such as neurological, cardiovascular, hematologic and lymphatic, immune, endocrine, respiratory, urinary, digestive, metabolic, and skeletal diseases of any clinical severity, or any other disease that may interfere with the results of the study. (2) History of specific allergies (asthma, urticaria, eczema, etc.) or sensitivities, or allergy to any of the ingredients in FHND9041 capsules or formulations. (3) History of dysphagia or any gastrointestinal disorder that interferes with drug absorption (as determined by the investigator). (4) lactose intolerance. (5) History of substance abuse, drug use, or positive substance abuse screen within 6 months prior to screening. (6) Surgery within 3 months prior to screening, or planned surgery during the study period, and any previous surgery that may affect drug absorption status (e.g., gastrectomy). (7) Smoking more than 5 cigarettes per day on average in the 3 months prior to screening or inability to stop using any tobacco-based product during the trial period. (8) Alcoholics or those who have consumed more than 14 units of alcohol per week in the 3 months prior to screening or have had a positive breathalyzer test result for alcohol, or are unable to abstain from alcohol within 48 h prior to the first dose and for the duration of the trial. (9) Excessive daily consumption of tea, coffee and/or caffeinated beverages in the 3 months prior to

screening. (10) Drugs affecting hepatic metabolism taken 28 days prior to dosing. (11) The subject has taken prescription drugs, over-the-counter medications, dietary supplements, or herbal medicines within 14 days prior to dosing. If the half-life of the previously used medication is relatively long, a longer time interval is required, which should be equivalent to five half-lives of that particular drug. (12) Those who cannot abstain from grapefruit or grapefruit-related citrus fruits (e.g., pomelo) or their juices within 7 days before dosing and during the trial period.

Study design and ethics

This study was a single-center, open, fixed-sequence study.

The study was conducted at the Clinical Research Center of Affiliated Hospital of Bengbu Medical College and in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) and NMPA related laws and regulations. Clinical Research Center of Affiliated Hospital of Bengbu Medical College Ethics Review Committee gave its approval to this study, which is also registered with China Drug Trials (http://www.chinadrugtrials.org.cn/index.html, CTR202300931). Prior to conducting the study, all subjects signed an informed consent form.

FHND9041 has completed the clinical study on food effect, and the results show that food does not affect the drug's absorption/metabolism. This study included two parallel groups: Group 1 received FHND9041 40 mg + Itraconazole; Group 2 received Rifampicin + FHND9041 80 mg. Each group enrolled 16 subjects for a two-period study. This clinical study did not follow conventional statistical assumptions. The sample size was determined based on comprehensive consideration of the CDE's (Center for Drug Evaluation) technical guidelines, preclinical research findings, available human metabolism data, and information on drugs with a similar mechanism of action.

Subjects were admitted to the research center on Day 1 and remained hospitalized until Day 8. They were readmitted on Day 10 and began the second period of dosing, remaining hospitalized until Day 30. The first period was the single-dose phase of FHND9041. On Day 1, subjects in Group 1 received a single oral dose of 40 mg FHND9041 in a fasted state, while subjects in Group 2 received a single oral dose of 80 mg FHND9041 in a fasted state. PK sampling was conducted up to 240 h post-dose. The second period was the co-administration phase. From Day 11 to Day 29, subjects in Group 1 received 200 mg Itraconazole once daily after meals. On Day 16, they also received a single dose of 40 mg FHND9041 (FHND9041 was administered in a fasted state, followed by breakfast 1 h later, and 200 mg Itraconazole was taken within 10 min after the meal). PK sampling began on Day 16 and continued up to 336 h after the administration of FHND9041. Subjects in Group 2 received 600 mg Rifampicin once daily in a fasted state from Day 11 to Day 29. On Day 20, they also received a single dose of 80 mg FHND9041 in a fasted state. PK sampling began on Day 20 and continued up to 240 h after the administration of FHND9041. The flow chart of drug administration in both groups is shown in Figs. 1 and 2.

Assessments

Group 1 received FHND9041 on Day 1 and Day 16, while Group 2 received FHND9041 on Day 1 and Day 20. Both groups had PK blood samples collected at 0 h (pre-dose) and at 1 h ± 5 min, 2 h ± 10 min, 3 h ± 15 min, 4 h ± 20 min, 6 h ± 30 min, 8 h ± 30 min, 10 h ± 1 h, 12 h ± 1 h, 24 h ± 2 h, 48 h ± 4 h, 72 h ± 4 h, 96 h ± 4 h, 120 h ± 4 h, 144 h ± 4 h, 168 h ± 4 h, and 240 h ± 4 h after the administration of FHND9041. During the co-administration phase,

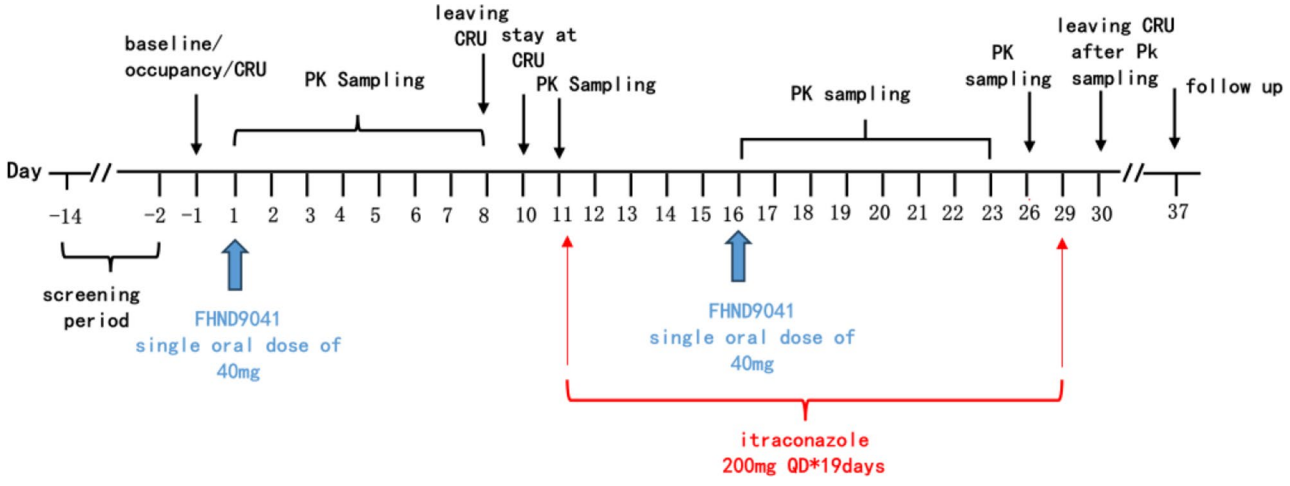

Fig. 1 Flow chart of Itraconazole + FHND9041 group administration

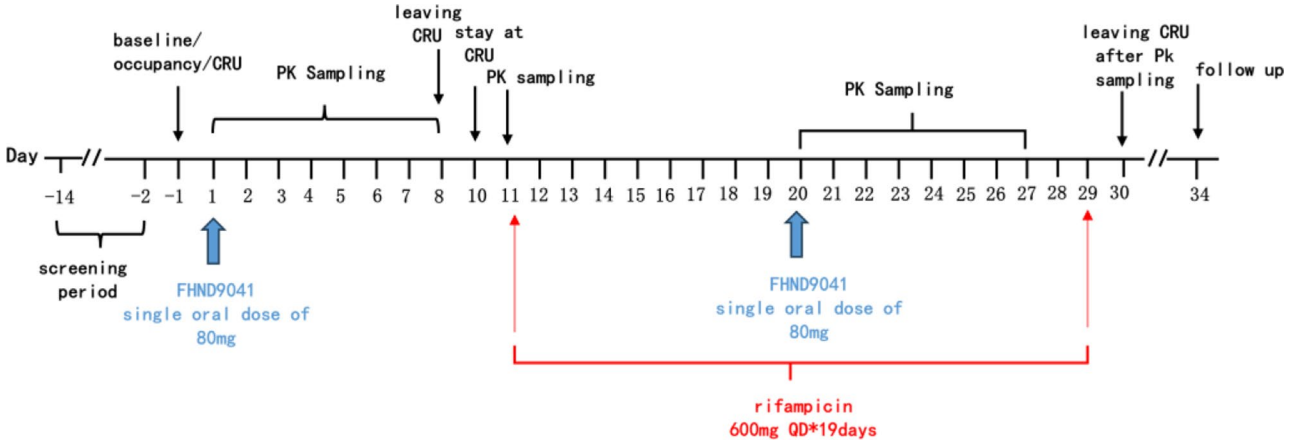

Fig. 2 Flowchart of Rifampicin + FHND9041 group administration

Group 1 had an additional PK blood sample collected at 336 h ± 4 h after dosing to determine the plasma concentration of FHND9041. Approximately 4 mL of venous blood was collected each time. After collection, the blood was immediately and gently inverted 4–6 times to ensure thorough mixing of the contents, and then placed upright in an ice bath. Within 1 h, the blood samples were centrifuged at 4 ℃ for 10 min at 1700 g, and the plasma was separated under ice-water bath conditions. Plasma samples could be temporarily stored in a refrigerator at -20 °C or lower, and then transferred to a -80 °C freezer within 24 h for long-term storage, or directly stored in a -80 °C freezer.

Bioanalytical method: Protein precipitation of the subject plasma samples was performed using acetonitrile, with FHND9041-A as the internal standard. Chromatographic separation was achieved using an Agela Venusil MP C18(2) column, with a mobile phase consisting of 5 mM ammonium acetate aqueous solution containing 0.2% formic acid and acetonitrile: methanol: formic acid (50:50:0.2, v/v/v). Detection was carried out using a Triple Quad™ 5500 tandem mass spectrometer with positive ion electrospray ionization and multiple reaction monitoring mode.

Statistical analysis

Pharmacokinetics

The PK parameters evaluated in this study included maximum plasma concentration (C_{max}), time to reach maximum concentration (T_{max}), area under the concentration-time curve from the time of dosing to the last measurable time point (AUC_{0-last}), area under the concentration-time curve from the time of dosing to infinity (AUC_{0-inf}), apparent clearance (CL/F), apparent volume of distribution (V_Z/F), and elimination half-life ($t_{1/2}$).

In this study, SAS® software (Version 9.4, SAS Institute Inc., North Carolina, US) was used for statistical analysis and graphical presentation of the data, while noncompartmental analysis methods i-n Phoenix™ WinNonlin software (Version 8.2, Certara Inc., New Jersey, US) were employed for the calculation of PK.

For each dataset, a mixed-effects model was employed to analyze the natural logarithm-transformed C_{max}, AUC_{0-last}, and AUC_{0-inf}, with period as a fixed effect and subject as a random effect. The model-derived estimates of the adjusted mean differences (co-administr-ation vs. single administration) and their 90% confidence intervals (CIs) were obtained. The adjusted mean differences and their 90% CIs were then exponentiated to yield the estimated adjusted geometric mean ratios (co-administration/single administration) and their 90% CIs, which were used to assess whether Itraconazole or Rifampicin had an impact on the PK characteristics of FHND9041. If the 90% CI of the $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, C_{max} geometric mean ratios after co-administration of the drugs is in the range of 80–125%, then no pharmacokinetic interaction effect between the drugs can be considered.

Safety

The safety evaluation criteria in this study included physical examination, assessment of vital signs, laboratory tests such as complete blood count, biochemical profile, urinalysis, and coagulation function, 12-lead electrocardiogram (ECG) examination, as well as any adverse events occurring during the study period. All AEs would be graded on a 5-point scale (1–5) of severity by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCICTCAE) v5.0.

Results

Baseline characteristics

As shown in Fig. 3, a total of 92 subjects were screened in this study, with 16 subjects enrolled in the Itraconazole group and 16 subjects in the Rifampicin group, resulting in a total enrollment of 32 subjects. Among them, one

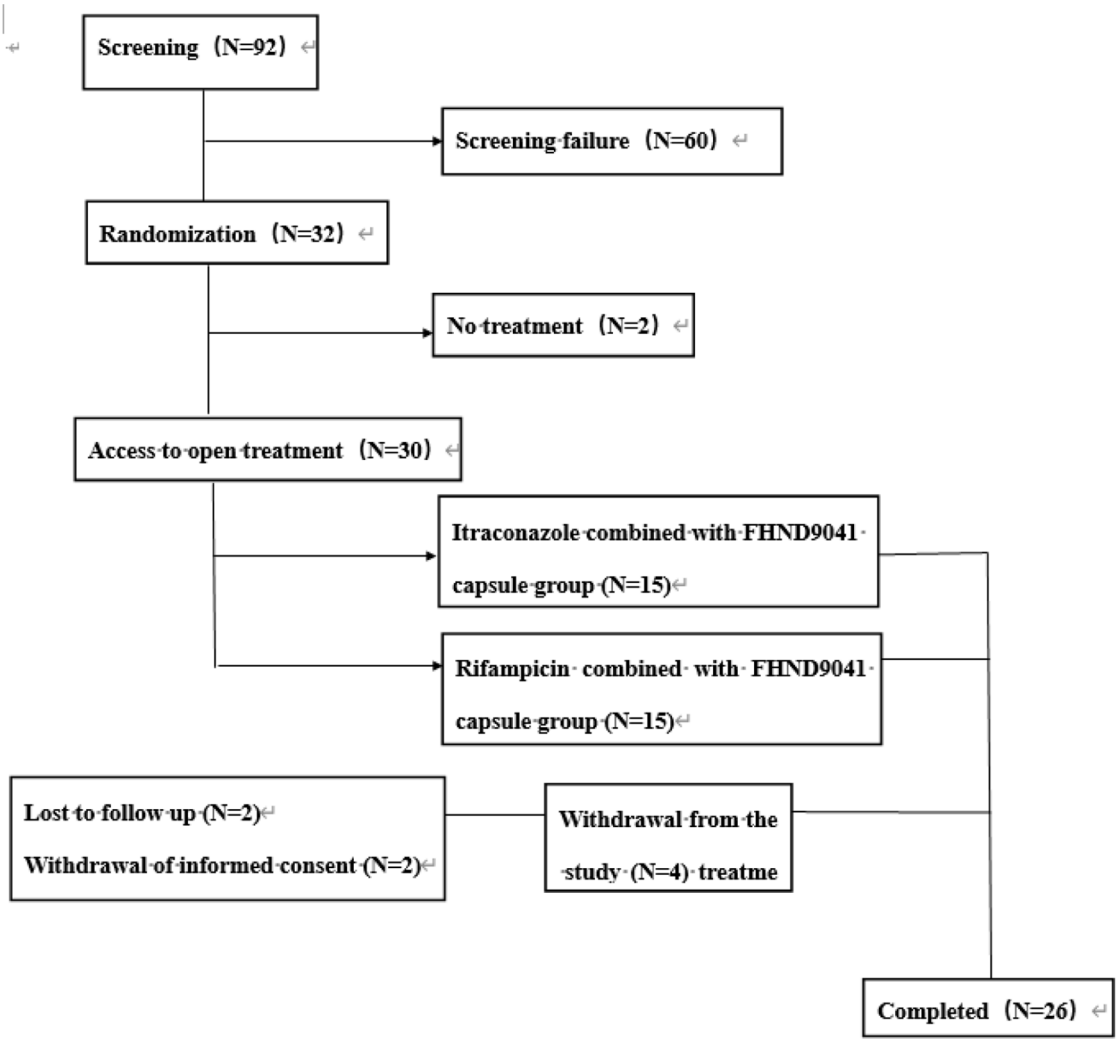

Fig. 3 Subject Disposition Flowchart

subject in the Itraconazole group (RD003) and one subject in the Rifampicin group (RD020), a total of two subjects, withdrew and did not receive the study drug. One subject in the Itraconazole group (RD004) completed a single dose of FHND9041 on Day 1 and withdrew from the study on Day 5. One subject in the Rifampicin group completed a single dose of FHND9041 on Day 1 and QD Rifampicin dosing from Day 11 to Day 13, and withdrew from the study on Day 14. A total of two subjects withdrew from the study after revoking their informed consent. Two subjects in the Itraconazole group (RD005 and RD012) were lost to follow-up. A total of 26 subjects completed the study, with 12 subjects in the Itraconazole group and 14 subjects in the Rifampicin group. Among the 32 enrolled subjects, two subjects (RD003 and RD020) did not receive the study drug. The remaining 30 subjects who received the study drug were included in the Full Analysis Set (FAS), Safety Analysis Set (SS), pharmacokinetic concentration dataset(PKCS), and pharmacokinetic parameter dataset (PKPS). The main reason for subject screening failure in this study was the presence of abnormal values on the enrollment physical examination labs (e.g., abnormal values of test results such as alanine aminotransferase, aspartate aminotransferase, creatinine, total bilirubin, platelet count, etc.), which, in the judgment of the investigator, had clinical significance and made participation in the study of this clinical trial unsuitable. Table 1 summarizes the demographic characteristics of the subjects, with comparable baseline features among the subjects.

Pharmacokinetics

Blood concentration versus drug-time profile of FHND9041(Itraconazole + FHND9041 group)

A total of 15 subjects in the Itraconazole group (Group 1) were included in the PKCS and PKPS. A total of 503 plasma concentration data points for FHND9041 were collected, with no instances of sampling time deviations.

Table 1 Demographics information

	Itraconazole + FHND9041 Group (Group 1)	Rifampicin + FHND9041 Group (Group 2)	Total
N	**15**	**15**	**30**
Age(years)			
Mean ± SD	32.4 ± 7.46	29.9 ± 5.30	31.2 ± 6.48
Min, Max	20,44	19,42	19,44
Gender			
Male	15	15	30
Female	0	0	0
Ethnicity			
Han Chinese	15	15	30
Height(cm)			
Mean ± SD	172.3 ± 4.507	171.73 ± 6.868	172.03 ± 5.716
Min, Max	161.0,178.5	160.0,181.5	160.0,181.5
Weight(kg)			
Mean ± SD	69.63 ± 7.642	74.33 ± 9.711	71.98 ± 8.912
Min, Max	58.4,85.9	53.9,88.6	53.9,88.6
BMI(kg/m^2)			
Mean ± SD	23.45 ± 2.412	25.10 ± 2.017	24.28 ± 2.340
Min, Max	19.6,27.6	20.2,27.5	19.6,27.6

For subject RD010, the pre-dose concentration of FHND9041 exceeded 5% of C_{max} during the co-administration phase with Itraconazole. Plasma concentrations and PK parameters at all time points during this phase were excluded from descriptive statistics. Subject RD004 withdrew informed consent during the monotherapy phase, resulting in early termination of the trial. Only PK samples from pre-dose to 96 h post-dose were collected, and AUC_{0-last} may have been underestimated. These data were excluded from descriptive statistics. Additionally, for this subject, $AUC_{\_\%Extrap}$ was greater than 20%, and λz, as well as other parameters calculated based on λ_z (e.g., AUC_{0-inf}, CL/F, V_z/F, $t_{1/2}$, etc.), could not be accurately calculated and were also excluded from descriptive statistics.

Following a single oral dose of 40 mg FHND9041 capsules in healthy subjects, the superimposed mean plasma concentration-time curves of FHND9041 during monotherapy and co-administration with Itraconazole (200 mg, once daily) are shown in Fig. 4 (presented in both linear and semi-logarithmic coordinates). The results indicate that, compared with monotherapy, co-administration with Itraconazole led to an increase in the mean plasma concentration of FHND9041 at each time point and a decrease in the terminal phase elimination rate.

PK parameters of FHND9041 (Itraconazole + FHND9041 group)

The PK parameters of FHND9041 following a single oral dose of 40 mg FHND9041 capsules in subjects are summarized in Table 2, grouped by different dosing phases (monotherapy and co-administration). After a single oral dose of 40 mg FHND9041 capsules in healthy subjects, the median T_{max} values for FHND9041 during monotherapy and co-administration with Itraconazole (200 mg, QD) were 4.00 h and 8.00 h, respectively, indicating a delay in time to reach maximum concentration of approximately 4 h during the co-administration phase. The mean C_{max} values were 27.5 ng/mL and 31.3 ng/mL,

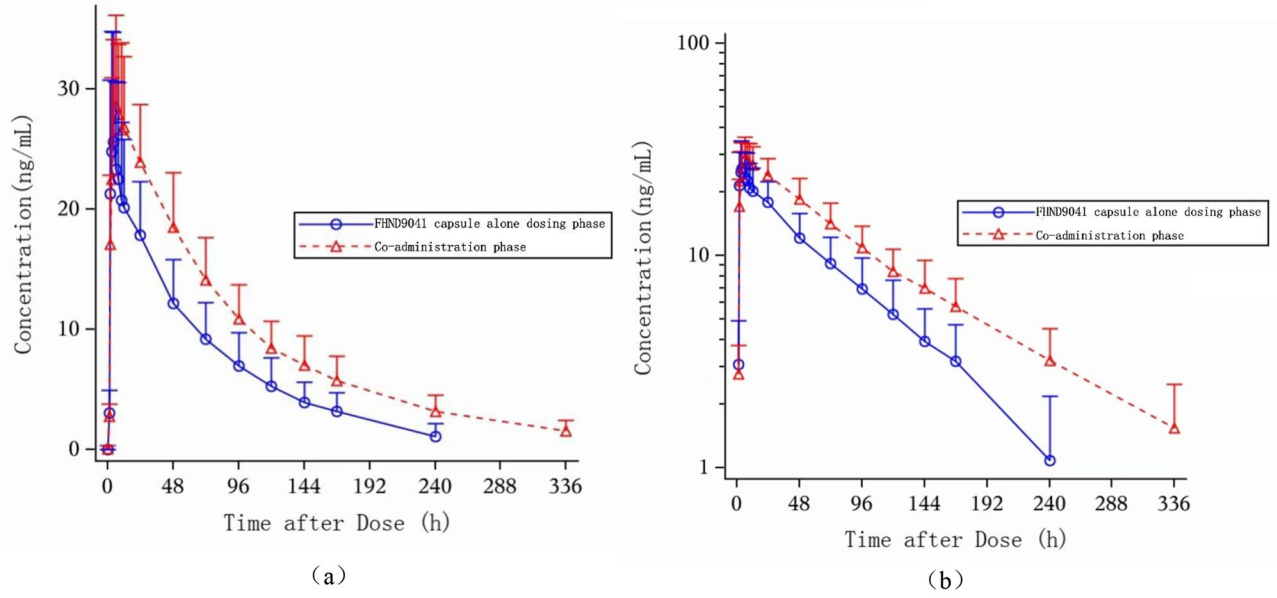

Fig. 4 Mean plasma concentration-time curves of FHND9041 at different stages in healthy subjects (upper panel: linear coordinates; lower panel: semi-logarithmic coordinates) (Itraconazole + FHND9041 group, PKCS)

Table 2 Summary of FHND9041 PK parameters in healthy subjects after single oral administration of FHND9041 capsules at different stages (Itraconazole + FHND9041 group, PKPS)

Phase(*n*)	Descriptive statisticians	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-last} (ng·h/mL)	T_{last} (h)	AUC_{0-inf} (ng·h/mL)	$C_{L/F}$ (L/h)	$V_{z/F}$ (L)	$t_{1/2}$ (h)
Monotherapy Phase(*n* = 15)	n	15	15	14[a]	14[a]	14[a]	14[a]	14[a]	14[a]
		27.5 ± 8.78(32.0%)	4.00 (2.00, 12.00)	1732 ± 567 (32.7%)	239.33 (168.00,239.3)	1896 ± 619 (32.7%)	23.2 ± 7.08 (30.6%)	1911 ± 476 (24.9%)	59.2 ± 12.1 (20.5%)
Co-administration phase(*n* = 14[a])	n	13[b]	13[b]	13[b]	13[b]	13[b]	13[b]	13[b]	13[b]
		31.3 ± 8.1 9 (26.2%)	8.00 (4.00, 23.55)	2850 ± 732 (25.7%)	336.00 (239.33,336.0)	3090 ± 828 (26.8%)	13.7 ± 3.28 (23.9%)	1738 ± 385 (22.2%)	89.5 ± 15.1 (16.9%)

Note: a: Subject RD004 withdrew informed consent during the monotherapy phase and terminated the trial early, without proceeding to the co-administration phase. PK samples were collected only from pre-dose to 96 h post-dose during the monotherapy phase, which may underestimate AUC0-last and Tlast. These parameters were not included in the descriptive statistics. Additionally, since $AUC_{\_\%Extrap} > 20\%$, λ_z and other parameters calculated based on λ_z (e.g., AUC_{0-inf}, CL/F, V_z/F, $t_{1/2}$, etc.) could not be accurately calculated and were also excluded from the descriptive statistics

b: Subject RD010 had a pre-dose concentration of FHND9041 exceeding 5% of Cmax during the co-administration phase with Itraconazole. PK parameters for this subject during this phase were excluded from the descriptive statistics

Table 3 Summary of Pharmacokinetic interaction statistical analysis for FHND9041 (Itraconazole + FHND9041 Group)

PK parameters	Monotherapy Phase		Co-administration Phase**		Mean ratio (combination/alone)	Mean ratio 90%CI	Intra-individual coefficient of variation (%)
	N	Mean	*N*	Mean			
C_{max} (ng/mL)	15	26.2	13[ab]	29.2	111.46	(103.26, 120.30)	11.00
AUC_{0-last} (ng·h/mL)	14[a]	1652	13[ab]	2800	169.53	(156.21, 183.99)	11.78
AUC_{0-inf} (ng·h/mL)	14[a]	1808	13[ab]	3041	168.25	(156.26, 181.15)	10.63

Note: a: Subject RD004 withdrew informed consent during the monotherapy phase and terminated the trial early, without proceeding to the co-administration phase. PK samples were collected only from pre-dose to 96 h post-dose during the monotherapy phase, which may underestimate AUC0-last and Tlast. These parameters were not included in the descriptive statistics. Additionally, since $AUC_{\_\%Extrap} > 20\%$, λ_z and other parameters calculated based on λ_z (e.g., AUC_{0-inf}, CL/F, V_z/F, $t_{1/2}$, etc.) could not be accurately calculated and were also excluded from the descriptive statistics

b: Subject RD010 had a pre-dose concentration of FHND9041 exceeding 5% of Cmax during the co-administration phase with Itraconazole. PK parameters for this subject during this phase were excluded from the descriptive statistics

respectively; mean AUC_{0-last} values were 1732 ng·h/mL and 2850 ng·h/mL, respectively; and mean AUC0-inf values were 1896 ng·h/mL and 3090 ng·h/mL, respectively. The inter-individual variability in exposure parameters (C_{max} and AUC) of FHND9041, expressed as CV%, was 32.0-32.7% during monotherapy and 25.7–26.8% during co-administration with Itraconazole. After a single oral dose of 40 mg FHND9041 capsules in healthy subjects, the mean t1/2 values for FHND9041 during monotherapy and co-administration with Itraconazole were 59.2 h and 89.5 h, respectively; CL/F values were 23.2 L/h and 13.7 L/h, respectively; and V_z/F values were 1911 L and 1738 L, respectively.

Statistical analysis of the impact of multiple oral doses of Itraconazole capsules on the PK parameters of a single oral dose of FHND9041 capsules

Table 3 summarizes the statistical analysis of the impact of co-administration with Itraconazole capsules (200 mg, QD) on plasma exposure (C_{max} and AUC) of FHND9041, following a single oral dose of 40 mg FHND9041 capsules in healthy subjects, with monotherapy as the reference. The adjusted geometric mean ratios (90% CI) of C_{max}, AUC_{0-last}, and AUC_{0-inf} for FHND9041 during co-administration with Itraconazole capsules compared to monotherapy were 111.46% (103.26–120.30%), 169.53% (156.21–183.99%), and 168.25% (156.26–181.15%), respectively.

Blood concentration versus drug-time profile of FHND9041(Rifampicin + FHND9041 group)

A total of 15 subjects in the Rifampicin group (Group 2) were included in the PKCS and PKPS. A total of 493 plasma concentration data points for FHND9041 were collected, with no instances of sampling time deviations. Subject RD022 withdrew informed consent during the monotherapy phase with Rifampicin, resulting in early termination of the trial and no co-administration phase was conducted.

Following a single oral dose of 80 mg FHND9041 capsules in healthy subjects, the superimposed mean plasma concentration-time curves of FHND9041 during monotherapy and co-administration with Rifampicin (600 mg, QD) are shown in Fig. 5 (presented in both linear and semi-logarithmic coordinates). The results indicate that, compared with monotherapy, co-administration with Rifampicin led to a significant decrease in the mean

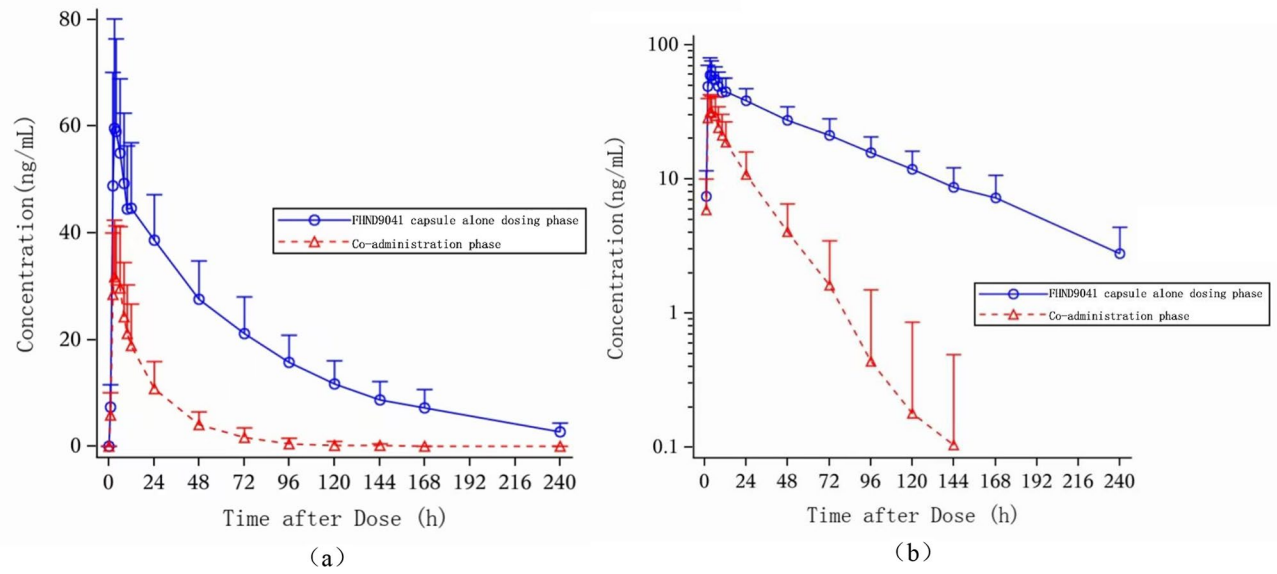

Fig. 5 Mean plasma concentration-time curves of FHND9041 at different stages in healthy subjects (upper panel: linear coordinates; lower panel: semi-logarithmic coordinates) (Rifampicin + FHND9041 group, PKCS)

Table 4 Summary of FHND9041 PK parameters in healthy subjects after single oral administration of FHND9041 capsules at different stages (Rifampicin + FHND9041 group, PKPS)

Phase(*n*)	Descriptive statisticians	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-last} (ng·h/mL)	T_{last} (h)	AUC_{0-inf} (ng·h/mL)	$C_{L/F}$ (L/h)	$V_{z/F}$ (L)	$t_{1/2}$ (h)
Monotherapy Phase(*n* = 15)	n	15	15	15	15	15	15	15	15
		65.6 ± 17.3 (26.4%)	3.00 (2.00, 12.00)	3936 ± 1039 (26.4%)	239.33 (168.00, 239.35)	4206 ± 1122 (26.7%)	20.7 ± 6.89 (33.3%)	1662 ± 512 (30.8%)	57.1 ± 11.4 (20.0%)
Co-administration phase(*n* = 14[a])	n	14	14	14	14	14	14	14	14
		35.0 ± 11.3 (32.3%)	3.00 (2.00, 6.00)	691 ± 339 (49.1%)	71.33 (47.33, 143.33)	732 ± 345 (47.2%)	133 ± 66.3 (49.9%)	3179 ± 1154 (36.3%)	17.9 ± 5.03 (28.1%)

Note: a: Subject RD022 withdrew informed consent during the monotherapy phase with Rifampicin, resulting in early termination of the trial without proceeding to the co-administration phase. Data from this subject were excluded from the statistical analysis of the co-administration phase

plasma concentration of FHND9041 at each time point and an increase in the terminal phase elimination rate.

PK parameters of FHND9041 (Rifampicin + FHND9041 group)

The PK parameters of FHND9041 following a single oral dose of 80 mg FHND9041 capsules in subjects, grouped by different dosing phases (monotherapy and co-administration), are summarized in Table 4. Following a single oral dose of 80 mg FHND9041 capsules in healthy subjects, the median Tmax for FHND9041 was 3.00 h in both the monotherapy and co-administration with Rifampicin (600 mg, QD) phases. The mean C_{max} values were 65.6 ng/mL and 35.0 ng/mL, respectively; mean AUC_{0-last} values were 3936 ng·h/mL and 691 ng·h/mL, respectively; and mean AUC0-inf values were 4206 ng·h/mL and 732 ng·h/mL, respectively. The inter-individual variability in exposure parameters (C_{max} and AUC) of FHND9041, expressed as CV%, was 26.4–26.7% during monotherapy and 32.3–49.1% during co-administration with Rifampicin. Following a single oral dose of 80 mg FHND9041 capsules in healthy subjects, the mean $t_{1/2}$ values for FHND9041 were 57.1 h and 17.9 h, respectively; CL/F values were 20.7 L/h and 133 L/h, respectively; and V_z/F values were 1662 L and 3179 L, respectively, during monotherapy and co-administration with Rifampicin.

Statistical analysis of the impact of multiple oral doses of rifampicin capsules on the PK parameters of a single oral dose of FHND9041 capsules

Table 5 summarizes the statistical analysis of the impact of co-administration with Rifampicin capsules (600 mg, QD) on plasma exposure (C_{max} and AUC) of FHND9041 following a single oral dose of 80 mg FHND9041 capsules in healthy subjects, with monotherapy as the reference. The adjusted geometric mean ratios (90% CI) of C_{max}, AUC_{0-last}, and AUC_{0-inf} for FHND9041 during co-administration with Rifampicin capsules compared to monotherapy were 52.12% (41.95–64.74%), 16.47% (13.34–20.31%), and 16.51% (13.56–20.09%), respectively.The 90% CI for C_{max}, AUC_{0-last}, and AUC_{0-inf} all fell outside the 80–125% range. The results indicate that, compared with monotherapy, co-administration

Table 5 Summary of Pharmacokinetic interaction statistical analysis for FHND9041 (Rifampicin + FHND9041 Group)

PK parameters	Monotherapy Phase		Co-administration Phase		Mean ratio (combination/alone)	mean ratio 90%CI	Intra-individual coefficient of variation (%)
	N	Mean	*N*	Mean			
C_{max} (ng/mL)	15	63.3	14[a]	33.0	52.12	(41.95, 64.74)	33.88
AUC_{0-last} (ng·h/mL)	15	3790	14[a]	624	16.47	(13.34, 20.31)	32.51
AUC_{0-inf} (ng·h/mL)	15	4046	14[a]	668	16.51	(13.56, 20.09	30.30

Note: a: Subject RD022 withdrew informed consent during the monotherapy phase with Rifampicin, resulting in early termination of the trial without proceeding to the co-administration phase. Data from this subject were excluded from the statistical analysis of the co-administration phase

with Rifampicin led to a decrease of approximately 48% in C_{max}, 84% in $AUC_{0\text{-last}}$, and 83% in AUC_{0-inf} for FHND9041.

Safety evaluations

A total of 30 subjects were enrolled in this study, with 15 subjects receiving Itraconazole in combination with FHND9041 capsules (Group 1) and 15 subjects receiving Rifampicin in combination with FHND9041 capsules (Group 2). Upon summarization by dosing phase, one subject in Group 1 withdrew during the monotherapy phase with FHND9041. A total of 14 subjects were evaluated for safety during both the monotherapy and co-administration phases with Itraconazole. One subject in Group 2 withdrew during the monotherapy phase with Rifampicin. A total of 14 subjects were evaluated for safety during the co-administration phase with Rifampicin.

Summary of adverse events in the Itraconazole + FHND9041 group

A total of 15 subjects in the Itraconazole group were included in the SS. Eleven subjects (73.3%) experienced a total of 23 treatment-emergent adverse events (TEAEs). All TEAEs were treatment-related adverse events (TRAEs) and were associated with FHND9041. Among these, 13 TEAEs in 10 subjects (66.7%) were also related to Itraconazole. Except for four TEAEs in four subjects classified as Grade 2, the remaining 19 TEAEs in 11 subjects were Grade 1. The TEAEs were summarized by dosing phase as follows:1) Monotherapy phase with FHND9041: Eight TEAEs occurred in six subjects (40.0%)0.2) Monotherapy phase with Itraconazole: Seven TEAEs occurred in six subjects (42.9%)0.3) Co-administration phase: Eight TEAEs occurred in eight subjects (57.1%)0.4) Except for two TEAEs, all others resolved spontaneously without treatment.

Specifically, one subject (RD002) experienced Grade 1 elevated blood bilirubin on Day 23, which was recorded as "not recovered" due to the subject's refusal to follow up; another subject (RD012) experienced Grade 1 hyperglycemia on Day 23, which was recorded as "not recovered" due to loss to follow-up. Neither event was treated. The incidence of TEAEs during the co-administration phase of FHND9041 with Itraconazole was comparable to that during the monotherapy phase of FHND9041. No serious adverse events (SAEs), TEAEs leading to discontinuation of the study drug or withdrawal from the study, or TEAEs resulting in death were reported in the Itraconazole group. AEs occurring during the trial were summarized using the System Organ Class (SOC) and Preferred Term (PT) from the Medical Dictionary for Regulatory Activities (MedDRA). The summary of all TEAEs in the Itraconazole + FHND9041 group by SOC and PT is presented in Table 6.

Summary of adverse events in the Rifampicin + FHND9041 group

A total of 15 subjects in the Rifampicin group were included in the SS. Ten subjects (66.7%) experienced a total of 23 TEAEs. All TEAEs were TRAEs and were associated with FHND9041. Among these, three TEAEs in three subjects (20.0%) were also related to Rifampicin. Except for three TEAEs in three subjects classified as Grade 2, the remaining 20 TEAEs in 10 subjects were Grade 1. The TEAEs were summarized by dosing phase as follows:1) Monotherapy phase with FHND9041: Sixteen TEAEs occurred in nine subjects (60.0%)0.2) Monotherapy phase with Rifampicin: Three TEAEs occurred in two subjects (13.3%)0.3) Co-administration phase: Four TEAEs occurred in four subjects (28.6%)0.4) One subject (RD027) experienced fever and upper respiratory tract infection (both Grade 1) on Day 3 and Day 4, respectively, and recovered after treatment with combined medications (ibuprofen and cold granules).

One subject (RD018) experienced Grade 1 elevated gamma-glutamyl transferase on Day 20, which was recorded as "not recovered" due to the subject's refusal to follow up; another subject (RD021) experienced Grade 1 positive urine occult blood on Day 30, which was recorded as "unknown" due to the subject's refusal to follow up. Neither event was treated. The remaining TEAEs resolved spontaneously without treatment. The incidence of TEAEs during the co-administration phase of FHND9041 with Rifampicin was lower than that during the monotherapy phase of FHND9041. No SAEs, TEAEs leading to discontinuation of the study drug or withdrawal from the study, or TEAEs resulting in death

Table 6 Summary of adverse events in the Itraconazole + FHND9041 group (SS)

System organ classification Preferred terminology	Monotherapy Phase with FHND9041	Monotherapy Phase with Itraconazole	Co-administration phase	Total
N	**15**	**14**	**14**	**15**
TEAE	6 (40.0%)[8]	6 (42.9%)[7]	8 (57.1%)[8]	11 (73.3%)[23]
Hypertriglyceridemia	4 (26.7%)[4]	3 (21.4%)[3]	2 (14.3%)[2]	7 (46.7%)[9]
Hypoglycaemia	0 (0.0%)[0]	3 (21.4%)[3]	0 (0.0%)[0]	3 (20.0%)[3]
Hyperglycaemia	0 (0.0%)[0]	0 (0.0%)[0]	1 (7.1%)[1]	1 (6.7%)[1]
Elevated blood bilirubin	0 (0.0%)[0]	0 (0.0%)[0]	2 (14.3%)[2]	2 (13.3%)[2]
C Elevated reactive proteins	1 (6.7%)[1]	0 (0.0%)[0]	0 (0.0%)[0]	1 (6.7%)[1]
Elevated gamma-glutamyltransferase	0 (0.0%)[0]	0 (0.0%)[0]	1 (7.1%)[1]	1 (6.7%)[1]
Elevated alanine aminotransferase	0 (0.0%)[0]	0 (0.0%)[0]	1 (7.1%)[1]	1 (6.7%)[1]
Carbon dioxide reduction	0 (0.0%)[0]	1 (7.1%)[1]	0 (0.0%)[0]	1 (6.7%)[1]
Elevated blood alkaline phosphatase	0 (0.0%)[0]	0 (0.0%)[0]	1 (7.1%)[1]	1 (6.7%)[1]
Abnormal liver function	1 (6.7%)[1]	0 (0.0%)[0]	0 (0.0%)[0]	1 (6.7%)[1]
Have a high temperature	1 (6.7%)[1]	0 (0.0%)[0]	0 (0.0%)[0]	1 (6.7%)[1]
Diarrhoea	1 (6.7%)[1]	0 (0.0%)[0]	0 (0.0%)[0]	1 (6.7%)[1]

Note: All adverse events are coded using the MedDRA version 26.0 (Chinese) coding system and are presented in the form of number of cases (percentage) [cases]

Table 7 Summary of adverse events in the Rifampicin + FHND9041 group (SS)

System organ classification Preferred terminology	Monotherapy Phase with FHND9041	Monotherapy Phase with Rifampicin	Co-administration phase	Total
N	**15**	**15**	**14**	**15**
TEAE	9 (60.0%)[16]	2 (13.3%)[3]	4 (28.6%)[4]	10 (66.7%)[23]
Positive Urinary Occult Blood	0 (0.0%)[0]	0 (0.0%)[0]	2 (14.3%)[2]	2 (13.3%)[2]
Elevated Blood Myoglobin	0 (0.0%)[0]	0 (0.0%)[0]	2 (14.3%)[2]	2 (13.3%)[2]
C Elevated Reactive Proteins	1 (6.7%)[1]	0 (0.0%)[0]	0 (0.0%)[0]	1 (6.7%)[1]
Elevated Gamma-Glutamyltransferase	0 (0.0%)[0]	1 (6.7%)[1]	0 (0.0%)[0]	1 (6.7%)[1]
Elevated Alanine Aminotransferase	1 (6.7%)[1]	0 (0.0%)[0]	0 (0.0%)[0]	1 (6.7%)[1]
Elevated LDL	0 (0.0%)[0]	1 (6.7%)[1]	0 (0.0%)[0]	1 (6.7%)[1]
Decreased Lymphocyte Count	1 (6.7%)[1]	0 (0.0%)[0]	0 (0.0%)[0]	1 (6.7%)[1]
Positive Urine White Blood Cells	1 (6.7%)[1]	0 (0.0%)[0]	0 (0.0%)[0]	1 (6.7%)[1]
Elevated Blood Bilirubin	1 (6.7%)[1]	0 (0.0%)[0]	0 (0.0%)[0]	1 (6.7%)[1]
Hypertriglyceridemia	4 (26.7%)[4]	0 (0.0%)[0]	0 (0.0%)[0]	4 (26.7%)[4]
Hyperuricaemia	2 (13.3%)[2]	0 (0.0%)[0]	0 (0.0%)[0]	2 (13.3%)[2]
Hypercholesterolaemia	0 (0.0%)[0]	1 (6.7%)[1]	0 (0.0%)[0]	1 (6.7%)[1]
Upper Respiratory Tract Infection	1 (6.7%)[1]	0 (0.0%)[0]	0 (0.0%)[0]	1 (6.7%)[1]
Have A High Temperature	1 (6.7%)[1]	0 (0.0%)[0]	0 (0.0%)[0]	1 (6.7%)[1]
Haematuria	1 (6.7%)[1]	0 (0.0%)[0]	0 (0.0%)[0]	1 (6.7%)[1]
Oral Mucositis	1 (6.7%)[1]	0 (0.0%)[0]	0 (0.0%)[0]	1 (6.7%)[1]
Anemic	1 (6.7%)[1]	0 (0.0%)[0]	0 (0.0%)[0]	1 (6.7%)[1]

Note: All adverse events are coded using the MedDRA version 26.0 (Chinese) coding system and are presented in the form of number of cases (percentage) [cases]

were reported in the Rifampicin group. The summary of all TEAEs in the Rifampicin + FHND9041 group by SOC and PT is detailed in Table 7.

Discussion

This study was a single-center, open-label, fixed-sequence study designed to evaluate the effects of oral Itraconazole capsules and oral Rifampicin capsules on the PK, safety, and tolerability of a single oral dose of FHND9041 capsules in healthy Chinese male subjects. The study included two parallel groups, each enrolling 16 subjects for a two-period investigation. It explored the PK characteristics, as well as the safety and tolerability of a single oral dose of FHND9041 capsules during both monotherapy and concomitant administration with Itraconazole or Rifampicin capsules.

Following a single oral dose of 40 mg FHND9041 capsules in healthy subjects, co-administration with Itraconazole had no effect on the C_{max} of FHND9041 but increased AUC0-last by approximately 69% and AUC_{0-inf} by approximately 68% compared with monotherapy. Itraconazole is a strong inhibitor of the CYP3A4 enzyme. When co-administered with drugs primarily metabolized by CYP3A4, it significantly reduces the clearance and

markedly increases the systemic exposure of these drugs. In vitro studies using human liver microsomes have shown that CYP3A4 contributes 99.8% to the formation of the major metabolite M10 (accounting for 7.51% of the total), indicating that CYP3A4 is the primary enzyme responsible for the generation of metabolite M10. In the preclinical studies, the primary analyte detected was the parent drug FHND9041, with no other metabolites being monitored. M10, being an inactive metabolite, is not expected to impact the safety and efficacy of the drug. Therefore, PK concentrations of M10 were not measured in the combination study with rifampicin and itraconazole.

As anticipated, co-administration of FHND9041 with Itraconazole in this study resulted in a significant reduction in clearance and an increase in exposure. Compared with monotherapy, co-administration with Itraconazole had no effect on C_{max}, delayed T_{max} by approximately 4 h, and increased AUC by approximately 68–69%. Given the significant increase in exposure, the potential for increased toxicity should be considered when FHND9041 is co-administered with Itraconazole or other strong CYP3A4 inhibitors. Caution is advised, and close monitoring of tolerability during co-administration is essential. Dose reduction may be necessary if required.

Following a single oral dose of 80 mg FHND9041 capsules in healthy subjects, co-administration with Rifampicin resulted in a decrease of approximately 48% in C_{max}, 84% in AUC_{0-last}, and 83% in AUC_{0-inf} compared with monotherapy. Rifampicin is a potent inducer of CYP enzymes, including CYP3A4 and other CYP isoenzymes (e.g., CYP2C8, CYP2C9, CYP2C19). When co-administered with drugs primarily metabolized by these enzymes, it significantly increases their clearance and markedly reduces systemic exposure. As previously described, in vitro studies have shown that CYP3A4 is the primary enzyme responsible for the metabolism of FHND9041 and plays a major role in the formation of the main metabolite M10. As anticipated, co-administration of FHND9041 with Rifampicin in this study resulted in a significant increase in clearance and a marked reduction in exposure. Compared with monotherapy, co-administration with Rifampicin led to a decrease of approximately 48% in C_{max} and 83–84% in AUC. These reductions are clinically significant and may impact the therapeutic efficacy of FHND9041. Therefore, co-administration of FHND9041 with Rifampicin or other potent CYP3A4 inducers should be avoided.

The results of the safety assessment in this study show that: In the Itraconazole group, 11 subjects (73.3%) experienced a total of 23 TEAEs. All TEAEs were TRAEs and were related to FHND9041. During the monotherapy phase with FHND9041, by SOC classification, the common (>20%) TRAE was Metabolism and Nutrition Disorders (26.7%, 4/15). By PT classification, the common (>10%) TRAE was Hypertriglyceridemia (26.7%, 4/15). During the co-administration phase, by SOC classification, the common TRAEs included Various Investigations (35.7%, 5/14) and Metabolism and Nutrition Disorders (21.4%, 3/14). By PT classification, the common TRAEs included Hypertriglyceridemia and Elevated Bilirubin, both at 14.3% (2/14). It can be seen that the incidence of TEAEs and TRAEs during the co-administration phase in the Itraconazole group was comparable to that during the monotherapy phase with FHND9041. All TEAEs during the co-administration phase were of Grade 1 or 2 severity. No SAEs, TEAEs leading to discontinuation of the study drug or withdrawal from the study, or TEAEs resulting in death were reported in the Itraconazole group. In the Rifampicin group, 10 subjects (66.7%) experienced a total of 23 TEAEs. All TEAEs were TRAEs and were related to FHND9041. During the monotherapy phase with FHND9041, by SOC classification, the common (>20%) TRAEs included Metabolism and Nutrition Disorders (40.0%, 6/15) and Various Investigations (26.7%, 4/15). By PT classification, the common (>10%) TRAEs included Hypertriglyceridemia (26.7%, 4/15) and Hyperuricemia (13.3%, 2/15). During the co-administration phase, by SOC classification, the common TRAE was Various Investigations (28.6%, 4/14). By PT classification, the common TRAEs included Positive Urine Occult Blood and Elevated Myoglobin, both at 14.3% (2/14). It can be seen that the incidence of TEAEs and TRAEs during the co-administration phase in the Rifampicin group was lower than that during the monotherapy phase with FHND9041. All TEAEs during the co-administration phase were of Grade 1 severity, with no Grade 2 events occurring. No SAEs, TEAEs leading to discontinuation of the study drug or withdrawal from the study, or TEAEs resulting in death were reported in the Rifampicin group.

The TEAEs reported in this study that were related to FHND9041 alone are consistent with those of similar marketed drugs. The more common TEAEs include hypertriglyceridemia, hyperuricemia, abnormal liver function, fever, and diarrhea. These events were of Grade 1 or 2 severity and had short durations. During the co-administration phase, no new safety issues emerged. The common TEAEs were consistent with the known adverse reactions of FHND9041 and either Itraconazole or Rifampicin. Except for hyperglycemia (observed in the Itraconazole group), which has not been previously reported in the Itraconazole product information or prior FHND9041 studies, all other TEAEs have been documented in prior studies or product information. The potential relationship of unreported TEAEs during both monotherapy and co-administration phases with FHND9041 can be further observed in subsequent studies. In summary, the safety results of this study indicate

that FHND9041 capsules, when used alone or in combination with strong CYP3A4 inhibitors or inducers, demonstrated good safety and tolerability. All TEAEs reported during the study were of Grade 1–2 severity, with no TEAEs of Grade ≥ 3 occurring. No SAEs, adverse events leading to death, or adverse events resulting in withdrawal from the study occurred during the trial. No TEAEs related to cardiac toxicity, such as QT interval prolongation, were reported in this study. The majority of TEAEs had favorable outcomes.

For the population of NSCLC patients treated with first- and second-generation EGFR-TKIs and subsequently progressing, more than half will develop T790M resistance mutations [9, 10]. Compared with first-generation EGFR-TKIs, first-line treatments with third-generation EGFR-TKIs can significantly prolong the median progression-free survival (PFS) of patients with EGFR-sensitive mutations in NSCLC, lay a good foundation for subsequent overall survival (OS) benefit, and improve the quality of life of patients. Among them, the third-generation EGFR-TKI represented by Osimertinib has highlighted better efficacy and safety, and has become the preferred first-line treatment for patients with advanced NSCLC with EGFR mutations. The FLAURA clinical study showed that third-generation EGFR-TKIs Osimertinib significantly prolonged median overall survival compared to first-generation EGFR-TKIs drugs (38.6 months vs. 31.8 months) [11, 12]. Four third-generation EGFR-TKIs, Vorametinib, Ametinib, Osimertinib, and Befotinib, are currently available in China.

FHND9041 is a third-generation EGFR inhibitor with significant inhibitory effects on T790M drug-resistant mutants and various sensitive EGFR mutants in the EGFR signalling pathway. It regulates the proliferation and apoptosis of tumour cells by inhibiting the phosphorylation of EGFR and its downstream signalling molecules, thus inhibiting tumour growth; at the same time, it has a weak inhibitory effect on wild-type EGFR proteins, avoiding the toxicity associated with the inhibition of wild-type EGFR proteins. FHND9041 capsules are mainly metabolised by CYP3A4 enzymes and Itraconazole is a strong inhibitor of CYP3A4 enzymes, which increases the systemic exposure of CYP3A4 substrates [11]. Rifampicin, a strong inducer of CYP3A4 enzyme, decreases the systemic exposure of CYP3A4 substrate, consistent with the results of this experimental study [13].

However, drug resistance inevitably occurs after third-generation EGFR-TKI treatment, and how to overcome drug resistance has become a key issue for third-generation EGFR-TKI to further play a role in the clinic, prolong patients' survival, and improve the quality of patients' survival. In the past, third-generation EGFR-TKI resistance was mainly treated with chemotherapy without considering the patient's resistance mechanism, and the limited efficacy and safety of chemotherapy has limited the long-term survival of patients with advanced EGFR mutations, so there is a huge unmet need for the diagnosis and treatment of this group of patients. Types of third-generation EGFR-TKI resistance include primary resistance and acquired resistance, with acquired resistance being the most common [14, 15]. For resistance after treatment with third-generation TKIs, a variety of therapeutic options are still being explored, including drugs targeting specific mutations (e.g., MET/MEK inhibitors), EGFR-TKI in combination with VEGF inhibitors, immune monotherapy, and EGFR-TKI in combination with immunotherapy [16].

FHND9041, as a third-generation EGFR inhibitor, has demonstrated significant inhibitory efficacy against the T790M resistance mutation and various sensitive EGFR mutations in the EGFR signaling pathway. This drug is primarily metabolized by the CYP3A4 enzyme. Itraconazole, a strong CYP3A4 inhibitor, increases the systemic exposure of CYP3A4 substrates, while Rifampicin, a strong CYP3A4 inducer, decreases it. These findings are consistent with the conclusions of this experimental study. Based on the research data from in vitro inhibition assays, under the tested conditions, FHND9041 exhibited moderate inhibitory effects on CYP1A2 (IC50 = 7.16 μM) and weak inhibitory effects on CYP3A4 (using testosterone as the substrate), CYP2B6, CYP2C8, CYP3A4 (using midazolam as the substrate), CYP2C19, CYP2D6, and CYP2C9, with IC50 values ranging from 11.8 μM to 47.1 μM.

However, due to the limited number of subjects included in the analysis and the short duration of drug exposure, the trial was not sufficient to observe adverse events with an incidence rate of less than 1‰ (such as rare events or those occurring with long-term use). The strict inclusion and exclusion criteria also led to a highly homogeneous subject population, which is not ideal for evaluating drug safety. In addition, because of the radiological properties of this drug, subjects were not included as females, so the lack of PK data in female subjects for this drug interaction trial somewhat affects clinical dosing guidance for female patients. Finally, weak CYP3A4 inducers and inhibitors may also affect the plasma concentration of FHND9041, and further research is needed in the future.

Conclusions

Following a single oral dose of 40 mg FHND9041 capsules in healthy subjects, co-administration with Itraconazole had no effect on the C_{max} of FHND9041 but increased AUC_{0-last} by approximately 69% and AUC_{0-inf} by approximately 68%. The results indicate that co-administration with Itraconazole significantly increased the

total exposure of FHND9041. Caution is advised when FHND9041 is co-administered with Itraconazole or other strong CYP3A4 inhibitors. Close monitoring of tolerability during co-administration is essential, and dose reduction may be necessary if required. Following a single oral dose of 80 mg FHND9041 capsules in healthy subjects, co-administration with Rifampicin led to a decrease of approximately 48% in C_{max}, 84% in AUC_{0-last}, and 83% in AUC_{0-inf} compared with monotherapy. The results indicate that co-administration with Rifampicin significantly reduced the exposure of FHND9041. Co-administration of FHND9041 with Rifampicin or other potent CYP3A4 inducers should be avoided. Healthy male subjects tolerated single oral doses of 40 mg and 80 mg FHND9041 capsules well, with good safety profiles. Co-administration of 40 mg FHND9041 capsules with 200 mg Itraconazole and 80 mg FHND9041 capsules with 600 mg Rifampicin was also well-tolerated, with good safety outcomes.

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Author contributions
Huan Zhou, Jian Gong, and Yongqiang Zhu were involved in the paper conception and experimental design, Chang Lu, Dongmei Cheng, and Yunqiu Xie were involved in writing the manuscript, Minghong Shang, and Rongzhen Chen were involved in the organization and implementation of the study, all authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was carried out in accordance with the principles of the Declaration of Helsinki. Approved by the Clinical Medical Ethics Committee of the First Affiliated Hospital of Bengbu Medical College. Informed consent was obtained for all individual subjects participating in the study.

Competing interests
The authors declare no competing interests.

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