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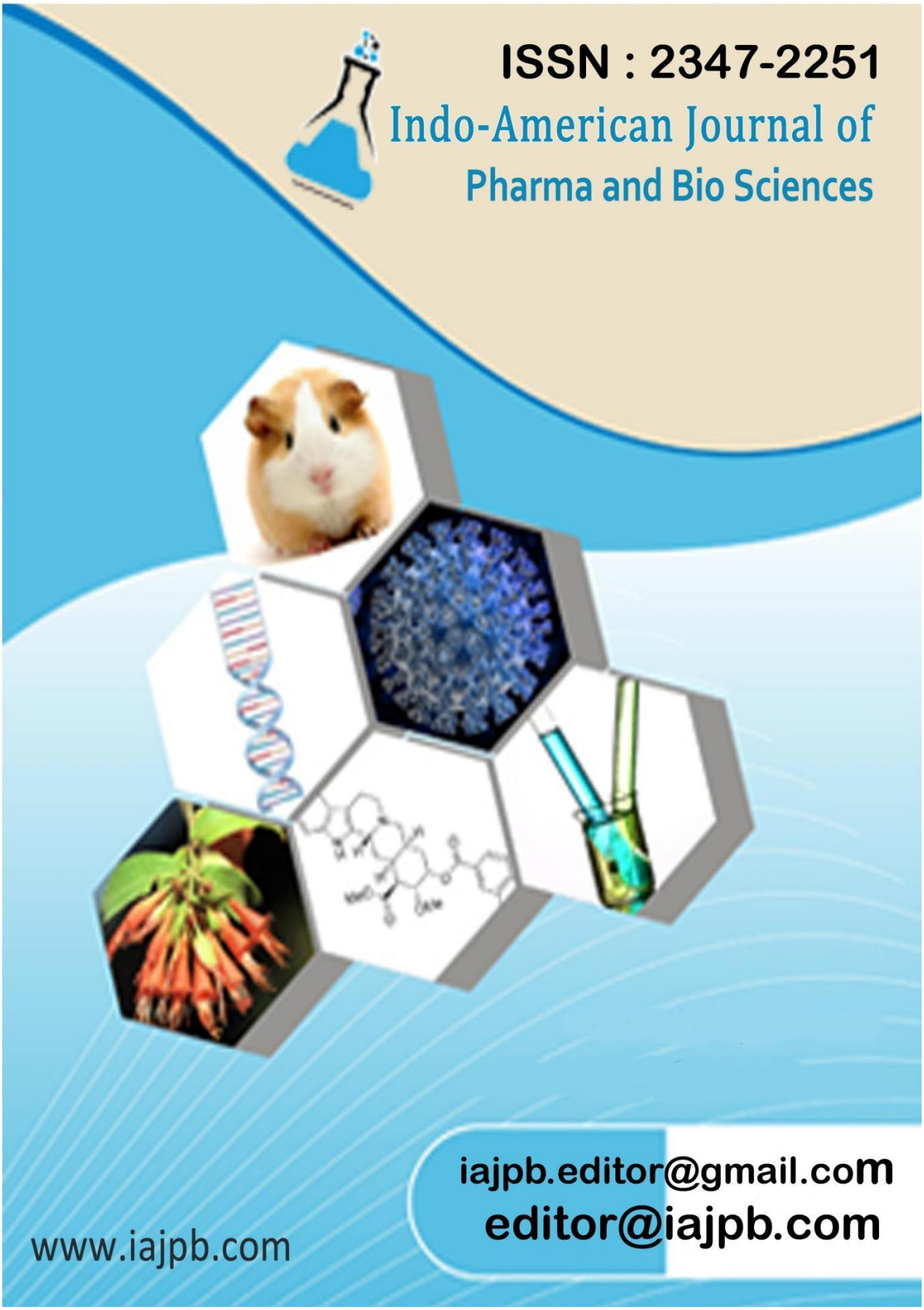

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Interaction Between CYP3A4 Regulators and New EGFR

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Abstract

Context The primary pathologic form of lung cancer is non-small cell carcinoma, and several clinical studies have shown that epidermal growth factor receptor tyrosinase inhibitors are more clinically effective and less hazardous than chemotherapy. Nanjing Chuangte Pharmaceutical Technology Co., Ltd. created the third-generation EGFR inhibitor FHND9041, an irreversible EGFR T790M mutation-selective small molecule kinase inhibitor. This research sought to determine how oral Rifampicin and oral Itraconazole capsules affected the pharmacokinetic profile, safety, and tolerability of a single oral dosage of FHND9041 capsules in healthy male Chinese participants. Patients and techniques A single-center, open-label, fixed-sequence design was used in this trial, with two parallel groups: Group 1 got 40 mg of FHND9041 together with itraconazole, while Group 2 received 80 mg of rifampicin. For a two-period trial, each group recruited 16 participants; the first period was monotherapy, while the second period involved co-administration. Every participant in this clinical study was a healthy adult male Chinese participant. Findings The corrected geometric mean ratios (90% CI) of FHND9041 Cmax, AUC0 − last, and AUC0 − inf in healthy subjects following a single oral administration of 40 mg FHND9041 capsules were 111.46% (103.26 − 120.30%), 169.53% (156.21 − 183.99%), and 168.25% (156.26 − 181.15%) in comparison to the monotherapy phase. Cmax's 90% confidence interval was within the 80–125% range.

range, although the 90% CIs for AUC0 − inf and AUC0 − last were also higher than the 80–125% range. The adjusted geometric mean ratios (90% CI) of Cmax, AUC0 − last, and AUC0 − inf for FHND9041 after a single oral dose of 80 mg capsules were 52.12% (41.95 − 64.74%), 16.47% (13.34 − 20.31%), and 16.51% (13.56 − 20.09%) for FHND9041 when co-administered with Rifampicin as opposed to monotherapy. Cmax, AUC0 − last, and AUC0 − inf all had 90% confidence intervals that were beyond the 80–125% range. During the study, there were no significant adverse effects. Conclusions The exposure of FHND9041 was considerably decreased when co-administered with Rifampicin. Consequently, it is advised to refrain from using FHND9041 concurrently with Rifampicin and other strong CYP3A4 inducers. On the other hand, co-administration of itraconazole considerably raised FHND9041's overall exposure. When FHND9041 is used with itraconazole or other potent CYP3A4 inhibitors, caution is suggested. It is crucial to closely evaluate tolerance during co-administration, and if necessary, dosage decrease may be needed. FHND9041 capsules showed satisfactory safety and acceptability when used either by itself or in conjunction with potent inducers or inhibitors of CYP3A4.

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Introduction

Lung cancer is one of the most prevalent illnesses in the globe, according the 2024 report from the International Agency for Research on Cancer. Lung cancer surged to the top of the 2022 cancer incidence spectrum with 2.480 million new cases as of 2022 [1]. Lung cancer may be categorized as either non-small cell carcinoma (NSCLC) or small cell carcinoma (SCLC) based on the pathological characteristics. NSCLC is the main pathogenic type of lung cancer, accounting for around 85% of all lung malignancies [2]. Published studies have shown that EGFR gene mutations are more common among Asians with non-small cell lung cancer; in China, for instance, EGFR mutations are present in almost 50% of lung cancer patients [3]. Surgery and adjuvant treatment may cure lung cancer in persons with

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early-stage disease [4]. The discovery of epidermal growth factor receptor tyrosine kinase inhibitors, or EGFR-TKIs, has led to significant improvements in the treatment of NSCLC patients, despite the fact that chemotherapy is still the most often used treatment for the disease [5]. According to certain clinical trial results, EGFR-TKIs are the preferred first-line therapy for EGFR-mutated advanced non-small cell lung cancer (NSCLC) because they exhibit better clinical outcomes and less toxicity than chemotherapeutic treatments. The tyrosine kinase receptor protein family includes EGFR, a crucial transmembrane protein molecule found on chromosome 7 of the human genome. Its gene structure is made up of 28 exon fragments, and it can transscribe and translate 1,186 amino acids. Its glycoprotein molecular weight has been estimated to be around 170 kDa [6]. To activate its intrinsic tyrosine kinase activity, EGFR may dimerize itself or with other receptors after binding to epidermal growth factor or other growth factors. By use of hydrolysis

By transferring phosphate groups to downstream substrates via ATP, EGFR starts and controls a number of intricate signaling cascades, mostly including the JAK/STAT and PI3K/AKT/m TOR RAS/RAF/MEK/ERK pathways [7, 8]. The EGFR signaling pathway has a major impact on cell

formation, proliferation, and death. Nanjing Chuangte Pharmaceutical Technology Co., Ltd. created the third-generation EGFR inhibitor FHND9041, a novel irreversible small molecule kinase inhibitor that selectively targets the EGFR T790M mutation. Tumor cells with EGFR T790M resistance or sensitive mutations cannot proliferate, and tumor cells undergo apoptosis as a result of its selective inhibition of EGFR mutant kinase phosphorylation and the activation of its downstream critical signaling molecules, Akt and Erk. Since FHND9041 is a novel medication, it should be evaluated to find specific and possible causes of drug-drug interactions (DDIs), such transporters and metabolic enzymes, and clinical DDI research should be carried out. These studies' findings might direct future clinical study design considerations, such as medication combination therapy and dosage modifications. FHND9041 has a high bioavailability and is quickly absorbed when taken orally. It may cross the blood-brain barrier and has wide tissue distribution. The body mainly uses CYP3A enzymes to break down FHND9041. FHND9041 is mostly eliminated by fecal excretion, with renal excretion via urine acting as a supplementary elimination mechanism.

Co-administration with other pharmaceuticals may inhibit, activate, or induce the metabolism and clearance of numerous medications, including those that are processed by the P450 enzyme system. Drug interactions may cause significant changes in metabolism, which might result in a tenfold or more reduction or increase in he drug's or its metabolites' concentration levels in the tissues or blood. Additionally, it might lead to an increase in exposure levels of harmful parent medications or the formation of toxic metabolites. The safety and effectiveness characteristics of some medications or their active ingredients may be significantly altered by these notable changes in exposure levels. Following a thorough evaluation of effectiveness, safety, and pharmacokinetic (PK) data, the sponsor and investigators unanimously decided that 80 mg once daily (QD) was the recommended dosage for FHND9041 based on the findings from Phase I/II trials.

Itraconazole is a strong CYP3A4 enzyme inhibitor that may increase the systemic exposure of CYP3A4 substrates by inhibiting the enzyme's activity. As a CYP3A4 substrate, FHND9041 is expected to have a higher systemic exposure when used in combination with itraconazole. A lower dosage of FHND9041 has been chosen for this trial in order to protect participants during co-administration and avoid excessively high levels of systemic exposure. It was predicted that an exposure level equivalent to that obtained with an 80 mg monotherapy dosage of FHND9041 would be obtained when 40 mg of FHND9041 and itraconazole were administered together. For this reason, 40 mg has been selected as the FHND9041 dosage to be used in conjunction with itraconazole. Furthermore, patients would receive 200 mg of itraconazole QD for five days before FHND9041 and itraconazole were administered together in order to precisely mimic the continuous dosage schedule of itraconazole in clinical practice. The goal of this pre-treatment phase is to maximize the inhibition of hepatic enzymes by simulating steady-state circumstances. The administration of itraconazole would continue until the last pharmacokinetic sample was finished. In clinical settings, the 200 mg QD itraconazole dosage is often used.

Rifampicin is a strong CYP3A4 enzyme inducer that may increase the enzyme's activity and lower the systemic exposure of CYP3A4 substrates. Since FHND9041 is a CYP3A4 substrate, it is anticipated that exposure will decrease when rifampicin is taken concurrently with it. As a result, the suggested dosage of 80 mg for FHND9041 when used with rifampicin has been chosen. Furthermore, patients would receive 600 mg of rifampicin QD for nine days before FHND9041 and rifampicin were administered together in order to accurately mimic the continuous dosage schedule of rifampicin in clinical practice. The purpose of this pre-treatment phase is to maximize the induction of hepatic enzymes by simulating steady-state circumstances. The administration of rifampicin would continue until the last pharmacokinetic sample was finished. In clinical settings, the 600 mg QD rifampicin dosage is often used.

This research would investigate the impact of a powerful CYP3A4 inhibitor/inducer on the pharmacokinetic profile of a single dosage of FHND9041 capsules in healthy people in order to optimize patient dosing safety and effectiveness. CYP3A4 inhibition or induction may change FHND9041's exposure characteristics and impact the medication's safety profile. Examining the effects of oral Rifampicin and oral Itraconazole capsules on the PK profile, safety, and tolerability of a single oral dosage of FHND9041 capsules in healthy Chinese male participants was the goal of this investigation.

Methods

Subjects

Healthy males between the ages of 18 and 55 who had a body mass index of 19.0 to 28.0 kg/m2 inclusive and a weight of 50 kg inclusive or more were eligible participants. They also agreed to use effective contraceptive methods from the time they signed the informed consent form until three months after the trial medicine was infused. According to preclinical and clinical study findings, there is little association between gender and the metabolism of FHND9041. In order to better safeguard the rights and welfare of the participants, male healthy volunteers were chosen to participate in this research due to the radiological nature of the medicine; it was expected that this would not affect the trial's outcomes. The following were the primary exclusion criteria: neurological, cardiovascular, hematologic and lymphatic,

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immune, endocrine, respiratory, urinary, digestive, metabolic, and skeletal diseases of any clinical severity, as well as any other disease that might affect the study's outcomes, are among the abnormal clinical manifestations that must be ruled out. (2) A history of particular sensitivities, allergies, or conditions (such as eczema, urticaria, asthma, etc.) to any of the components in FHND9041 formulations or capsules. (3) A history of dysphagia or any other gastrointestinal condition that the investigator determines impedes the absorption of drugs. (4) intolerance to lactose. (5) A positive substance abuse test within six months of the screening, or a history of drug use or substance abuse. (6) Any past surgery that could have an impact on medication absorption status, such as a gastrectomy, or surgery scheduled during the research period or performed within three months before screening. (7) The inability to quit using any tobacco-based product throughout the trial period or an average daily cigarette use of more than five cigarettes during the three months before screening. (8) Alcoholics or those who have had a positive breathalyzer test result for alcohol, used more over 14 units of alcohol per week in the three months before to screening, or who are unable to refrain from drinking for the whole trial period and 48 hours before the first dosage. (9) Drinking too much tea, coffee, or other caffeinated drinks every day for the three months before screening. (10) Hepatic metabolism-related medications taken 28 days before dosage. (11) Within 14 days before the dose, the person used prescription meds, over-the-counter medications, nutritional supplements, or herbal remedies. A greater time interval—five half-lives of that specific drug—is necessary if the half-life of the previously used medicine is comparatively lengthy. (12) Individuals unable to avoid grapefruit or citrus fruits linked to grapefruit (such pomelo) or their juices for seven days before to dosage and during the study period.

Study design and ethics

This research was open, single-center, and fixed-sequence. In compliance with the Declaration of Helsinki, Good Clinical Practice (GCP), and NMPA-related rules and regulations, the research was carried out at the Clinical Research Center of Affiliated Hospital of Bengbu Medical College. The research was approved by the Clinical Research Center of Affiliated Hospital of Bengbu Medical College Ethics Review Committee and is registered with China Drug Trials. An informed consent form was completed by each participant before the trial began. The findings of the clinical investigation on the food impact conducted by FHND9041 indicate that food has no influence on the drug's absorption or metabolism. Two parallel groups participated in this study: Group 1 got 40 mg of FHND9041 with itraconazole, whereas Group 2 received 80 mg of rifampin plus FHND9041. For a two-period investigation, 16 subjects were recruited in each group. Conventional statistical assumptions were not followed in this clinical trial. The CDE's (Center for Drug Evaluation) technical criteria, preclinical research results, and available human resources were all carefully considered while determining the sample size. data on metabolism and medications with similar modes of action.

On Day 1, the subjects were brought to the study facility, where they stayed until Day 8. On Day 10, they were readmitted and started the second dosage cycle; they were in the hospital until Day 30. The FHND9041 single-dose phase was the initial time frame. Group 1 participants were given a single oral dosage of 40 mg FHND9041 while fasting on Day 1, and Group 2 participants were given a single oral dose of 80 mg FHND9041 while fasting. Up to 240 hours after the treatment, PK sampling was carried out. The co-administration phase was the second time frame. Subjects in Group 1 were given 200 mg of itraconazole once daily after meals from Day 11 to Day 29. Additionally, patients were given a single dosage of 40 mg of FHND9041 on Day 16 (the medication was given while fasting, followed by breakfast one hour later, and 200 mg of itraconazole ten minutes after the meal). On Day 16, PK sampling started, and it lasted for 336 hours after the administration of FHND9041. From Day 11 through Day 29, subjects in Group 2 were fasted and given 600 mg of Rifampicin once day. Additionally, they were given a single dosage of 80 mg FHND9041 while fasting on Day 20. Beginning on Day 20, PK sampling continued for 240 hours after the injection of FHND9041. Figs. 1 and 2 depict the medication administration flow chart for each group.

Assessments

On Days 1 and 16, FHND9041 was given to Group 1, and on Days 1 and 20, FHND9041 was given to Group 2. PK blood samples were taken from both groups at 0 hours (pre-dose), 1 hour ± 5 minutes, 2 hours ± 10 minutes, 3 hours ± 15 minutes, 4 hours ± 20 minutes, 6 hours ± 30 minutes, 8 hours ± 30 minutes, 10 hours ± 1 hour, 12 hours ± 1 hour, 24 hours ± 2 hours, 48 hours ± 4 hours, 72 hours ± 4 hours, 96 hours ± 4 hours, 120 hours ± 4 hours, 144 hours ± 4 hours, 168 hours ± 4 hours, and 240 hours ± 4 hours following the administration of FHND9041. In the period of co-administration,

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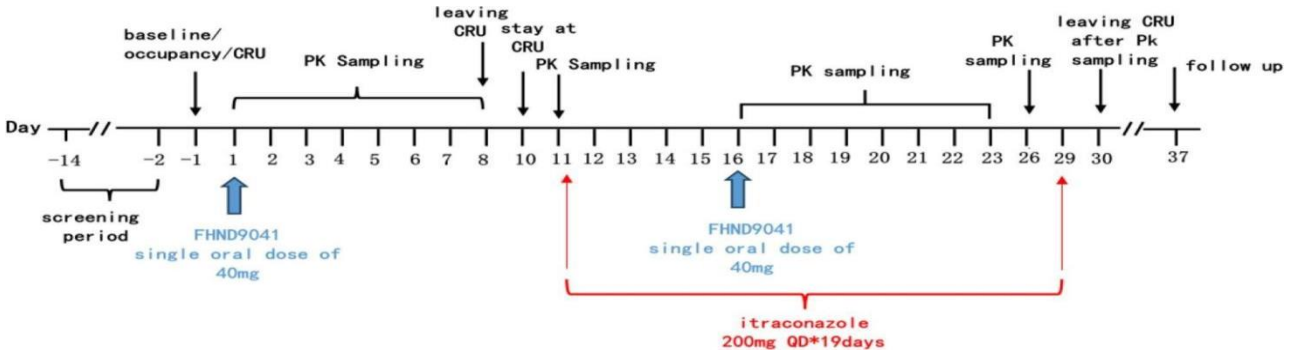

Fig. 1 Flow chart of Itraconazole + FHND9041 group administration

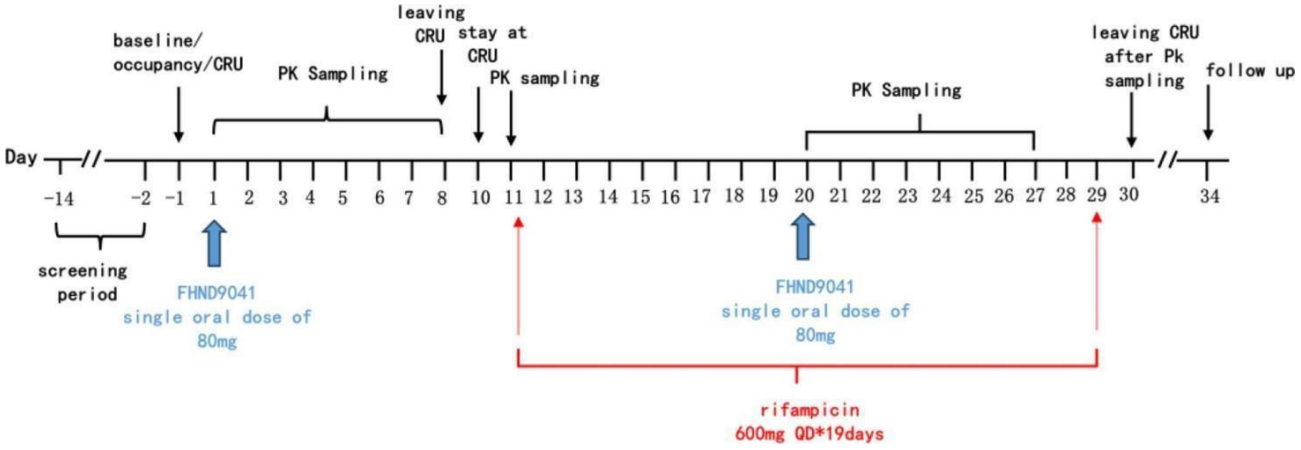

Fig. 2 Flowchart of Rifampicin + FHND9041 group administration

A second PK blood sample was taken from Group 1 336 hours ± 4 hours after the dose in order to measure the plasma concentration of FHND9041. Each time, around 4 mL of venous blood was drawn. Following collection, the blood was put upright in an ice bath after being gently inverted four or six times to guarantee that the contents were well mixed. The plasma was separated in an ice-water bath after the blood samples were centrifuged at 4 °C for 10 minutes at 1700 g in less than an hour. Plasma samples may be either immediately placed in a -80 °C freezer for long-term storage or briefly kept in a refrigerator at -20 °C or lower, followed by a 24-hour transfer to a -80 °C freezer. The bioanalytical approach Acetonitrile was used for protein precipitation of the subject plasma samples, with FHND9041-A serving as the internal standard. A mobile phase of 5 mM ammonium acetate aqueous solution with 0.2% formic acid and acetonitrile: methanol: formic acid (50:50:0.2, v/v/v) was used to accomplish chromatographic separation using an Agela Venusil MP C18(2) column. A Triple QuadTM 5500 tandem mass spectrometer with multiple reaction monitoring mode and positive ion electrospray ionization was used for the detection.

Statistical analysis

Pharmacokinetics

The study assessed several PK parameters, including apparent clearance (CL/F), apparent volume of distribution (VZ/F), elimination half-life (t1/2), area under the concentration-time curve from the time of dosing to the last measurable time point (AUC0 − last), area under the concentration-time curve from the time of dosing to infinity (AUC0 − inf), and maximum plasma concentration (Cmax) and time to reach maximum concentration (Tmax).

SAS® software (Version 9.4, SAS Institute Inc., North Carolina, US) was used in this work to analyze the data statistically and display it graphically, while PK was calculated using noncompartmental analysis techniques in Phoenix™ Win-Nonlin software (Version 8.2, Certara Inc., New Jersey, US).

The natural logarithm-transformed Cmax, AUC0 − last, and AUC0 − inf were analyzed for each dataset using a mixed-effects model, where period was a fixed factor and subject was a random effect. The 90% confidence intervals (CIs) and adjusted mean differences (co-administration vs. single administration) were estimated using the model. To determine whether it was Itraconazole or Rifampicin that affected the PK characteristics of FHND9041, the adjusted mean differences

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and their 90% CIs were then exponentiated to produce the estimated adjusted geometric mean ratios (co-administration/single administration) and their 90% CIs. No pharmacokinetic interaction impact between the medications may be taken into consideration if the 90% CI of the AUC0-last, AUC0-inf, and Cmax geometric mean ratios after co-administration of the pharmaceuticals falls between 80 and 125%.

Safety

Physical examination, vital sign assessment, laboratory tests like complete blood count, biochemical profile, urinalysis, and coagulation function, 12-lead electrocardiogram (ECG) examination, and any adverse events that occurred during the study period were all included in the safety evaluation criteria for this study. The investigator would use the National Cancer Institute Common Terminology Criteria for Adverse Events (NCICTCAE) v5.0 to assess all adverse events on a 5-point (1–5) severity scale.

Results

Baseline characteristics

A total of 92 participants were screened for this research, as seen in Fig. 3. Of these, 32 subjects were recruited, 16 of whom were placed in the Itraconazole group and 16 in the Rifampicin group. Of them, one

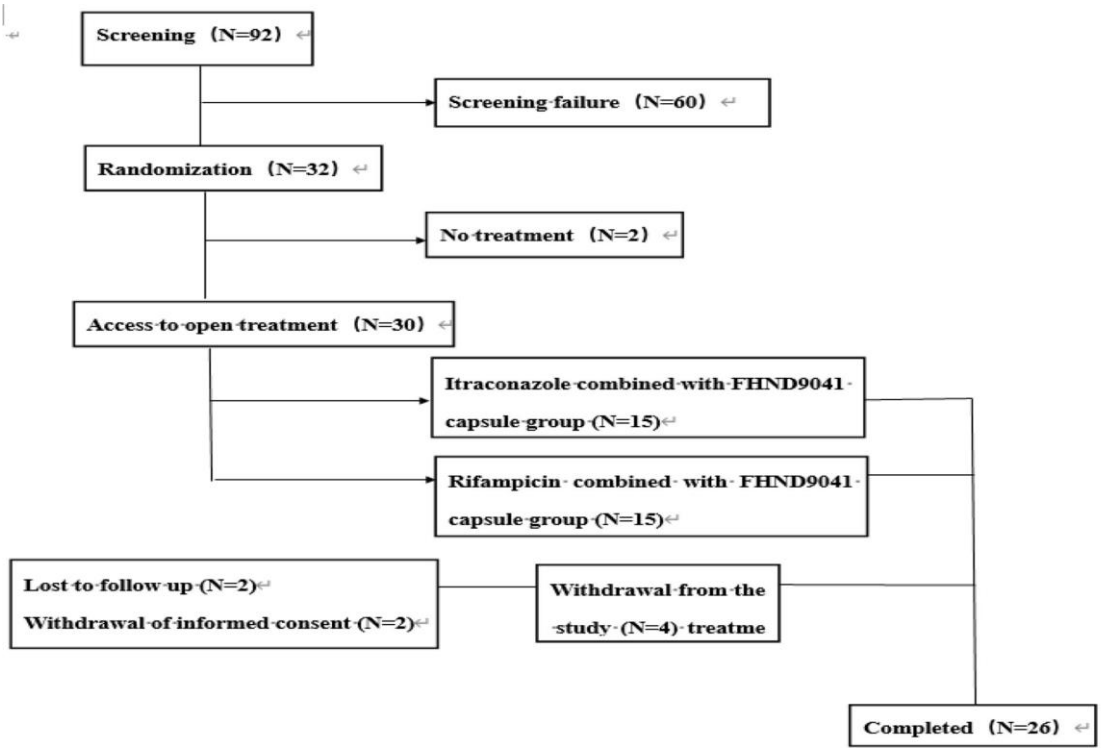

Fig. 3 Subject Disposition Flowchart

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Two subjects, one in the Rifampicin group (RD020) and one in the Itraconazole group (RD003), withdrew and were not given the study medication. On Day 1, one participant in the itraconazole group (RD004) finished a single dose of FHND9041 and left the trial on Day 5. On Day 14, one participant in the Rifampicin group withdrew from the research after completing a single dose of FHND9041 on Day 1 and QD Rifampicin dosing from Days 11 to 13. After withdrawing their informed consent, two participants in all left the research. The Itraconazole group lost two individuals (RD005 and RD012) to follow-up. Twelve participants in the itraconazole group and fourteen in the rifampicin group made up the study's total of 26 participants. Two patients (RD003 and RD020) out of the 32 recruited subjects were not given the study medication. The pharmacokinetic concentration dataset (PKCS), Safety Analysis Set (SS), Full Analysis Set (FAS), and the remaining 30 participants who were administered the trial medication were all included.

dataset of pharmacokinetic parameters (PKPS). 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.) was the primary cause of subject screening failure in this study. The investigator determined that these abnormal values had clinical significance and that participation in this clinical trial was inappropriate. With similar baseline features among individuals, Table 1 provides a summary of the respondents' demo-graphic traits.

Pharmacokinetics

FHND9041's blood concentration against drug-time profile (group receiving itraconazole with FHND9041) The Itraconazole group (Group 1) consisted of 15 participants in all, who participated in the PKCS and PKPS. There were no instances

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

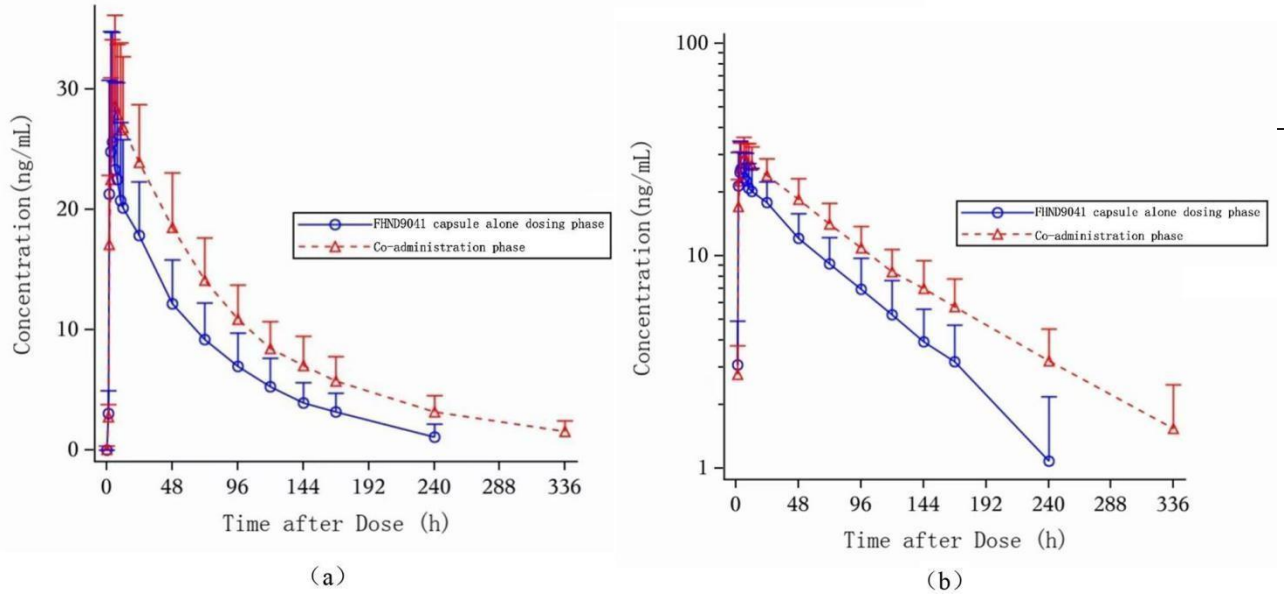
PK parameters of FHND9041(Itraconazole + FHND9041 group)

(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.

Among healthy individuals, the FHND9041 mean plasma concentration-time curves with monotherapy and concurrent treatment with Itracon-

For subject RD010, the pre-dose concentration of FHND9041 exceeded 5% of C_{max} during the co-admin- istration 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

Table 2 summarizes the PK characteristics of FHND9041 in patients after a single oral dosage of 40 mg FHND9041 capsules, categorized by several dosing phases (co-administration and monotherapy). The median Tmax values for FHND9041 during monotherapy and co-administration with Itraconazole (200 mg, QD) were 4.00 h and 8.00 h, respectively, following a single oral dose of 40 mg FHND9041 capsules in healthy subjects. This suggests that there was a delay of about 4 hours in reaching



the maximum concentration during the co-administration phase. 27.5 ng/mL and 31.3 ng/mL were the mean Cmax values.

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	Cmax (ng/mL)	Tmax (h)	AUC_{0-last} (ng·h/mL)	Tlast (h)	AUC_{0-inf} (ng·h/mL)	CL/F (L/h)	Vz/F (L)	t1/2 (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			
Cmax (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

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Note: A Subject RD004 ended the experiment early without moving on to the co-administration phase and revoked informed consent during the monotherapy phase. AUC0-last and Tlast may have been underestimated since PK samples were only taken during the monotherapy phase, from before the administration to 96 hours after the dose. The descriptive statistics did not contain these characteristics. Furthermore, λz and other λz-based parameters (such as AUC0 − inf, CL/F, Vz/F, t1/2, etc.) could not be computed reliably because to AUC_%Extrap > 20%, and they were also not included in the descriptive statistics. b: When taking it with itraconazole, Subject RD010's pre-dose concentration of FHND9041 was higher than 5% of Cmax. The descriptive data did not include the PK parameters for this individual during this phase. 1896 ng·h/mL and 3090 ng·h/mL were the mean AUC0-inf values, respectively; the mean AUC0 − last values were 1732 ng·h/mL and 2850 ng·h/mL, respectively. FHND9041's CV%, or inter-individual variability in exposure parameters (Cmax and AUC), was 25.7–26.8% when co-administered with itraconazole and 32.0-32.7% when used alone. The mean t1/2 values for FHND9041 during monotherapy and co-administration with itraconazole were 59.2 hours and 89.5 hours, respectively; CL/F values were 23.2 L/h and 13.7 L/h, respectively; and Vz/F values were 1911 L and 1738 L, respectively, following a single oral dose of 40 mg FHND9041 capsules in healthy subjects.

The effect of many oral doses of itraconazole capsules on the PK parameters of a single oral dosage of FHND9041 capsules is statistically examined. Following a single oral dosage of 40 mg FHND9041 capsules in healthy participants, Table 3 presents the

statistical analysis of the effect of co-administration with Itraconazole capsules (200 mg, QD) on plasma exposure (Cmax and AUC) of FHND9041, with monotherapy serving as the reference. When FHND9041 was co-administered with itraconazole capsules as opposed to monotherapy, the adjusted geometric mean ratios (90% CI) of Cmax, AUC0 − last, and AUC0 − inf were 111.46% (103.26–120.30%), 169.53% (156.21–183.99%), and 168.25% (156.26–181.15%), respectively. Drug-time profile of FHND9041 vs blood concentration (Rifampicin + FHND9041 group) In the PKCS and PKPS, there were 15 individuals in the Rifampicin group (Group 2). There were no instances of sampling time discrepancies in the 493 plasma concentration data points that were gathered for

FHND9041. The experiment was terminated early because subject RD022 withdrew informed consent during the Rifampicin monotherapy phase; no co-administration phase was carried out. The superimposed mean plasma concentration-time curves of FHND9041 after monotherapy and co-administration with Rifampicin (600 mg, QD) are shown in Fig. 5 (given in both linear and semi-logarithmic coordinates) after a single oral dosage of 80 mg FHND9041 capsules in healthy volunteers. The findings show that co-administration of Rifampicin resulted in a substantial drop in the mean when compared to monotherapy.

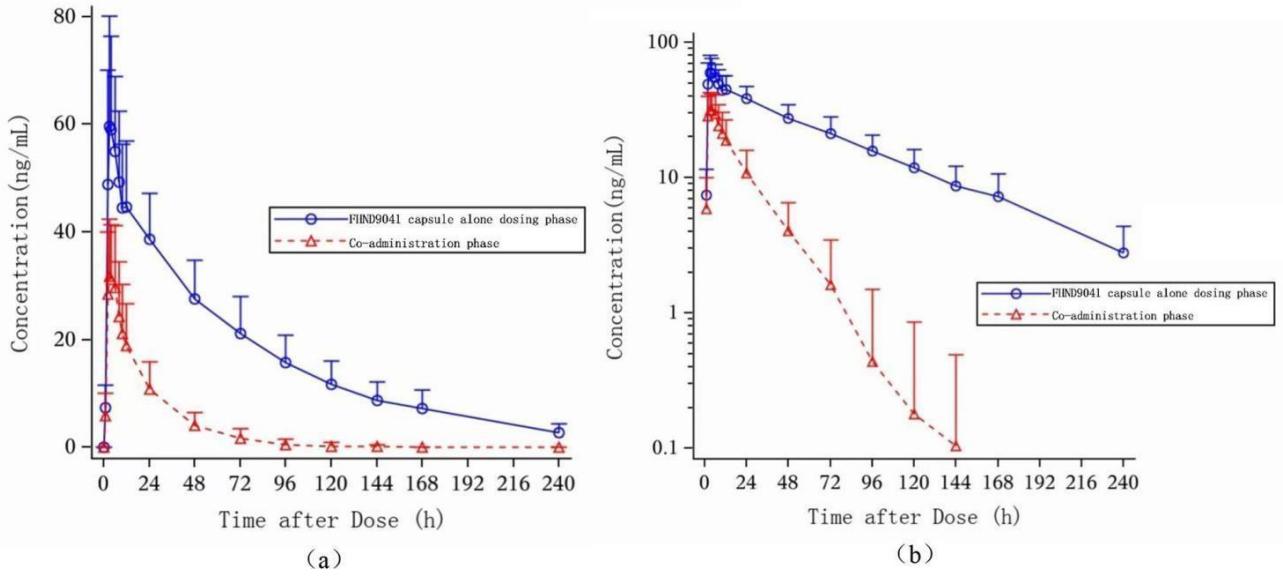

Fig. 5 Mean plasma concentration-time curves of FHND9041 at different stages in healthy subjects (upper panel: linear coordinates; lower panel: semi- logarithmic coordinates) (Rifampicin+FHND9041 group, PKCS)

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)	CL/F (L/h)	Vz/F (L)	t1/2 (h)
Monotherapy	n	15	15	15	15	15	15	15	15

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Phase(*n* = 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: The experiment was terminated early without going to the co-administration phase because Subject RD022 withdrew informed consent while receiving Rifampicin monotherapy. This subject's data were not included in the co-administration phase's statistical analysis.

a rise in the terminal phase elimination rate and the plasma concentration of FHND9041 at every time point.

FHND9041's PK parameters (Rifampicin + FHND9041 group) Table 4 summarizes the PK characteristics of FHND9041 after a single oral dosage of 80 mg FHND9041 capsules in participants categorized by several dosing phases (co-administration and monotherapy). In both the monotherapy and co-administration phases with Rifampicin (600 mg, QD), the median Tmax for

FHND9041 was 3.00 hours after a single oral dosage of 80 mg FHND9041 capsules in healthy subjects. Mean AUC0 − last values were 3936 ng·h/mL and 691 ng·h/mL, respectively; mean AUC0-inf values were 4206 ng·h/mL and 732 ng·h/mL, respectively; and mean Cmax values were 65.6 ng/mL and 35.0 ng/mL, respectively. FHND9041's CV%, or inter-individual variability in exposure parameters (Cmax and AUC), ranged from 26.4 to 26.7% when used alone and from 32.3 to 49.1% when used in combination with rifampicin. After taking 80 mg FHND9041 capsules orally as a single dosage in healthy individuals, the mean t1/2 values for

Vz/F values were 1662 L and 3179 L, respectively, following monotherapy and co-administration of Rifampicin; FHND9041 was 57.1 h and 17.9 h, respectively; and CL/F values were 20.7 L/h and 133 L/h, respectively.

Statistical evaluation of the effects of many oral rifampicin capsule dosages on the PK characteristics of a single oral FHND9041 capsule dosage
With monotherapy as the reference, Table 5 presents the statistical analysis of the effect of co-administration of 600 mg, QD Rifampicin capsules on plasma exposure (Cmax and AUC) of FHND9041 after a single oral dosage of 80 mg FHND9041 capsules in healthy volunteers. When FHND9041 was co-administered with Rifampicin capsules as opposed to monotherapy, the adjusted geometric mean ratios (90% CI) of Cmax, AUC0 − last, and AUC0 − inf were 52.12% (41.95–64.74%), 16.47% (13.34–20.31%), and 16.51% (13.56–20.09%), respectively. Cmax, AUC0 − last, and AUC0 − inf all had 90% CIs that were beyond the 80–125% range. The findings show that, in contrast to 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)		
	N	Mean	*N*	Mean	mean ratio	90%CI	Intra-individual coefficient of variation (%)
Cmax (ng/mL)	15	63.3	14[a]	33.0	52.12	(41.95, 64.74)	33.88
AUC0 – last (ng·h/mL)	15	3790	14[a]	624	16.47	(13.34, 20.31)	32.51
AUC0 – 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.

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Safety evaluations

Thirty patients were recruited for the trial; fifteen of them received FHND9041 capsules and itraconazole (Group 1), while fifteen of them received FHND9041 capsules and rifampicin (Group 2). One participant in Group 1 withdrew during the monotherapy phase with FHND9041, according to the dosing phase summary. Itraconazole's safety in both monotherapy and co-administration phases was assessed in a total of 14 participants. In Group 2, one participant stopped taking Rifampicin during the monotherapy period. 14 participants in all were assessed for safety during the Rifampicin co-administration phase.

Summary of adverse events in the Itraconazole + FHND9041 group

The SS had a total of 15 individuals in the itraconazole group. A total of 23 treatment-emergent adverse events (TEAEs) were reported by 11 individuals (73.3%). Every TEAE was linked to FHND9041 and was a treatment-related adverse event (TRAE). Of these, Itraconazole was also linked to 13 TEAEs in 10 individuals (66.7%). The other 19 TEAEs in 11 courses were Grade 1, with the exception of four in four topics that were categorized as Grade 2. The following is a summary of the TEAEs by dosage phase: 1) FHND9041 monotherapy phase: Six participants (40.0%) experienced eight TEAEs. 0.2) Itraconazole monotherapy phase: Six individuals (42.9%) had seven TEAEs. 0.3) Co-administration phase: Eight individuals (57.1%) experienced eight TEAEs. 0.4) All TEAEs, with the exception of two, resolved on their own without medical intervention.

In particular, on Day 23, one subject (RD002) had Grade 1 elevated blood bilirubin, which was noted as "not recovered" because the subject refused to follow up, and on Day 23, another subject (RD012) had Grade 1 hyperglycemia, which was noted as "not recov- ered" because of loss to follow-up. Neither incident was addressed. TEAEs' frequency during co-administration

phase of Itraconazole-treated FHND9041 was similar to that of FHND9041 monotherapy. The itraconazole group did not have any major adverse events (SAEs), TEAEs that resulted in the discontinuation of the study medication or study withdrawal, or TEAEs that caused death. The System Organ Class (SOC) and Preferred Term (PT) from the Medical Dictionary for Regulatory Activities (MedDRA) were used to summarize adverse events (AEs) that occurred throughout the experiment. Table 6 presents a summary of all TEAEs by SOC and PT in the Itraconazole + FHND9041 group.

Summary of adverse events in the Rifampicin + FHND9041 group

The Rifampicin group had 15 patients in all, according to the SS. A total of 23 TEAEs were experienced by 10 individuals (66.7%). Every TEAE was connected to FHND9041 and was a TRAE. Of these, Rifampin was also linked to three TEAEs in three individuals (20.0%). The remaining twenty TEAEs in ten courses were Grade 1, with the exception of three in three topics that were categorized as Grade 2. The following is a summary of the TEAEs by dosage phase: 1) FHND9041 monotherapy phase: Nine individuals (60.0%) experienced sixteen TEAEs. 0.2) Rifampicin monotherapy phase: Two participants (13.3%) had three TEAEs.
0.3) Co-administration phase: Four participants (28.6%) had four TEAEs. 0.4) On Days 3 and 4, respectively, one participant (RD027) had a fever and an upper respiratory tract infection (both Grade 1), but recovered after treatment with a combination of ibuprofen and cold granules.
Due to the subject's refusal to follow up, one subject (RD018) had Grade 1 elevated gamma-glutamyl transferase on Day 20, which was noted as "not recovered." On Day 30, another subject (RD021) had Grade 1 positive urine occult blood, which was noted as "unknown." Neither incident was addressed. Without medical intervention, the remaining TEAEs resolved on their own. Compared to the monotherapy phase of FHND9041, the incidence of TEAEs was reduced during the co-administration phase of FHND9041 with Rifampicin. Absence of SAEs, TEAEs that resulted in withdrawal from the study or the termination of the study medication, or TEAEs that caused 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]

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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

Evaluation of the effects of oral Itraconazole and oral Rifampicin capsules on the PK, safety, and tolerability of a single oral dosage of FHND9041 capsules in healthy Chinese male volunteers was the aim of this single-center, open-label, fixed-sequence trial. Two parallel groups of 16 subjects each were enrolled in the research for a two-period examination. It investigated the PK features, as well as the single oral dosage of FHND9041 capsules' safety and tolerability whether used as a monotherapy or in combination with Itra-conazole or Rifampicin capsules.

In healthy participants, co-administration of itraconazole after a single oral dosage of 40 mg FHND9041 capsules raised AUC0-last by around 69% and AUC0 – inf by roughly 68% when compared to monotherapy, but had no impact on FHND9041's Cmax. The CYP3A4 enzyme is strongly inhibited by itraconazole. When used with medications that are mostly metabolized by CYP3A4, it dramatically lowers

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the clearance and significantly increases these medications' systemic exposure. According to in vitro experiments using human liver microsomes, CYP3A4 is the main enzyme in charge of producing metabolite M10, as it contributes 99.8% of the principal metabolite M10's synthesis (or 7.51% of the total). The parent medication FHND9041 was the main analyte found in the preclinical investigations; no additional metabolites were tracked. As an inactive metabolite, M10 is not anticipated to affect the medication's effectiveness or safety. As a result, M10 PK concentrations were not assessed in the rifampicin and itraconazole combo trial.

In this investigation, co-administration of FHND9041 with itraconazole led to a substantial decrease in clearance and an increase in exposure, as expected. Co-administration of itraconazole raised AUC by around 68–69%, delayed Tmax by about 4 hours, and had no impact on Cmax when compared to monotherapy. When FHND9041 is used with itraconazole or other potent CYP3A4 inhibitors, the potential for enhanced toxicity should be taken into account due to the substantial increase in exposure. During co-administration, caution is recommended and tolerance must be closely monitored. If necessary, a dose decrease may be

needed. When compared to monotherapy, co-administration of Rifampicin decreased Cmax by around 48%, AUC0 − last by 84%, and AUC0 − inf by 83% after a single oral dosage of 80 mg FHND9041 capsules in healthy volunteers. CYP enzymes, such as CYP3A4 and other CYP iso-enzymes (e.g., CYP2C8, CYP2C9, CYP2C19), are strongly stimulated by rifampicin. It greatly improves the clearance of medications that are mostly processed by these enzymes and dramatically lowers systemic exposure when taken together. As previously mentioned, in vitro research has shown that CYP3A4 is the principal enzyme in charge of FHND9041 metabolism and is crucial to the production of the primary metabolite M10. As expected, in this investigation, co-administration of FHND9041 with Rifampicin led to a notable decrease in exposure and a considerable increase in clearance. Co-administration of Rifampicin resulted in a reduction of around 48% in Cmax and 83–84% in AUC when compared to monotherapy. These decreases are clinically noteworthy and might affect FHND9041's treatment effectiveness. Therefore, it is best to avoid co-adminstrating FHND9041 with Rifampicin or other strong CYP3A4 inducers. The findings of this study's safety evaluation indicate that: A total of 23 TEAEs were experienced by 11 participants (73.3%) in the itraconazole group. Every TEAE had a connection to FHND9041 and was a TRAE. According to SOC categorization, the most prevalent (>20%) TRAE throughout the monother-apy phase with FHND9041 was metabolism and nutrition.

Disorders (4/15, 26.7%). According to PT categorization, hypertriglyceridemia (26.7%, 4/15) was the most common (>10%) TRAE. According to SOC classification, the most prevalent TRAEs during the co-administration period were Metabolism and Nutrition Disorders (21.4%, 3/14) and Various Investigations (35.7%, 5/14). The common TRAEs by PT categorization were elevated bilirubin and hypertriglyceridemia, both of which were 14.3% (2/14). It is evident that the incidence of TEAEs and TRAEs in the Itraconazole group during the co-administration period was similar to that in the FHND9041 monotherapy phase. During the co-administration period, every TEAE was either Grade 1 or Grade 2. The itraconazole group did not have any SAEs, TEAEs that resulted in the discontinuation of the study medication or study withdrawal, or TEAEs that caused death. Ten individuals (66.7%) in the

Rifampicin group had a total of twenty-three TEAEs. Every TEAE had a connection to FHND9041 and was a TRAE. According to SOC categorization, the most common (>20%) TRAEs during the monotherapy phase with FHND9041 were Various Investigations (26.7%, 4/15) and Metabolism and Nutrition Disorders (40.0%, 6/15). According to PT categorization, hypertriglyceridemia (26.7%, 4/15) and hyperuricemia (13.3%, 2/15) were the most prevalent (>10%) TRAEs. According to SOC categorization, Various Investigations was the most prevalent TRAE during the co-administration period (28.6%, 4/14). According to PT classification, elevated myoglobin and positive urine occult blood were the most frequent TRAEs, both occurring at 14.3% (2/14). As can be shown, the Rifampicin group saw a decreased incidence of TEAEs and TRAEs during the co-administration period compared to the FHND9041 monotherapy phase. There were no Grade 2 incidents throughout the co-administration period, and all TEAEs were of

Grade 1 intensity. The Rifampicin group did not have any SAEs, TEAEs that resulted in the study medicine being stopped or withdrawal, or TEAEs that caused mortality. The TEAEs linked to FHND9041 alone that were documented in this investigation are comparable to those of similar medications. Hypertriglyceridemia, hyperuricemia, impaired liver function, fever, and diarrhea are among the most prevalent TEAEs. These brief occurrences were of Grade 1 or 2 intensity. There were no further safety concerns throughout the co-administration stage. The typical TEAEs aligned with the recognized side effects of FHND9041 and either rifampicin or itraconazole. All other TEAEs have been reported in previous studies or product information, with the exception of hyperglycemia (found in the Itraconazole group), which has not been previously described in the Itraconazole product information or previous FHND9041 research. Future research might examine the possible connection between FHND9041 and unreported TEAEs during the monotherapy and co-administration periods. In conclusion, this study's safety findings show found FHND9041 capsules showed satisfactory safety and tolerability when taken either by alone or in combination with potent CYP3A4 inducers or inhibitors. No TEAEs of Grade ≥ 3 occurred throughout the trial; all TEAEs reported were of Grade 1–2 intensity. During the trial, there were no SAEs, adverse events that resulted in mortality, or adverse events that caused study discontinuation. This research did not disclose any TEAEs associated with cardiac toxicity, such as QT interval prolongation.

The results of most TEAEs were positive. T790M resistance mutations will be developed in over half of the population of NSCLC patients treated with first- and second-generation EGFR-TKIs and subsequently progressing [9, 10]. First-line treatments with third-generation EGFR-TKIs can improve patient quality of life, lay a solid basis for future overall survival (OS) benefit, and significantly extend the median progression-free survival (PFS) of patients with EGFR-sensitive mutations in non-small cell lung cancer (NSCLC) when compared to first-generation EGFR-TKIs. Osimertinib, a third-generation EGFR-TKI, has shown superior effectiveness and safety among them, making it the recommended first-line therapy for patients with advanced non-small cell lung cancer (NSCLC) who have EGFR mutations. Osimer-tinib, a third-generation EGFR-TKI, considerably increased median overall survival when compared to first-generation EGFR-TKIs (38.6 months vs. 31.8 months), according to the FLAURA clinical research [11, 12]. China now offers four third-generation EGFR-TKIs: Befotinib, Osimertinib, Ametinib, and Vorametinib. Third-generation EGFR inhibitor FHND9041 significantly inhibits the EGFR signaling pathway's T790M drug-resistant mutants as well as a number of sensitive EGFR mutants. Inhibiting the phosphorylation of EGFR and its downstream signaling molecules prevents tumor growth by controlling the proliferation and apoptosis of tumor cells. It also has a weak inhibitory effect on wild-type EGFR proteins, preventing the toxicity that comes with inhibiting wild-type EGFR proteins. CYP3A4 enzymes are primarily responsible for the metabolism of FHND9041 capsules, and itraconazole is a potent inhibitor of CYP3A4 enzymes, increasing the systemic exposure of CYP3A4 substrates [11]. Consistent with the findings of this experimental investigation, rifampicin, a potent CYP3A4 enzyme inducer, reduces the systemic exposure of CYP3A4 substrate [13]. However, after third-generation EGFR-TKI therapy, drug resistance always develops. Therefore, overcoming drug resistance has become crucial for third-generation EGFR-TKI to continue to play a role in the clinic, extend patient life, and enhance patient survival quality. Chemotherapy was the primary treatment for third-generation EGFR-TKI resistance in the past.

There is a significant unmet need for the identification and treatment of patients with advanced EGFR mutations since chemotherapy's low safety and effectiveness, when combined with the patient's resistance mechanism, has reduced their long-term survival. Primary resistance and acquired resistance are the two types of third-generation EGFR-TKI resistance, with acquired resistance being the more prevalent [14, 15]. Numerous therapeutic options, such as medications that target particular mutations (e.g., MET/MEK inhibitors), EGFR-TKI in combination with VEGF inhibitors, immune monotherapy, and EGFR-TKI in combination with immunotherapy, are still being investigated for resistance following treatment with third-generation TKIs [16]. The T790M resistant mutation and other sensitive EGFR mutations in the EGFR signaling pathway have been shown to be significantly inhibited by FHND9041, a third-generation EGFR inhibitor. The CYP3A4 enzyme is principally responsible for the metabolism of this

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medication. The systemic exposure of CYP3A4 substrates is increased by the potent CYP3A4 inhibitor itraconazole and decreased by the potent CYP3A4 inducer rifampicin. These results are in line with the experimental study's findings. According to research data from in vitro inhibition assays, FHND9041 showed 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. It also showed moderate inhibitory effects on CYP1A2 (IC50 = 7.16 µM) under tested conditions.
However, the study was insufficient to notice adverse events with an incidence rate of less than 1‰ (such as infrequent occurrences or those occurring with long-term usage) because of the small number of participants included in the analysis and the brief length of drug exposure. Additionally, a very homogenous subject group resulted from the stringent inclusion and exclusion criteria, which is not optimal for assessing medication safety. Clinical dosing recommendations for female patients are slightly impacted by the absence of PK data in female participants for this drug interaction experiment, since female individuals were excluded due to the radiological characteristics of this medication. Lastly, more study is required since weak CYP3A4 inducers and inhibitors may potentially impact the plasma concentration of FHND9041.

Conclusions

In healthy participants, co-administration of Itraconazole after a single oral dosage of 40 mg FHND9041 capsules raised AUC0 − inf by about 68% and AUC0 − last by about 69%, but had no impact on FHND9041's Cmax. According to the findings, co-administration of itraconazole considerably raised the total FHND9041 exposure. When FHND9041 is used with itraconazole or other potent CYP3A4 inhibitors, caution is suggested. It is crucial to closely evaluate tolerability during co-administration, and if necessary, dosage reduction may be needed. When compared to monotherapy, co-administration of Rifampicin resulted in a reduction of around 48% in Cmax, 84% in AUC0 − last, and 83% in AUC0 − inf after a single oral dosage of 80 mg FHND9041 capsules in healthy volunteers. The findings show that co-administration of Rifampicin considerably decreased FHND9041 exposure. Avoid using FHND9041 together with Rifampicin or other strong CYP3A4 inducers. Single oral dosages of 40 mg and 80 mg FHND9041 capsules were well tolerated by healthy male volunteers, and their safety profiles were favorable. Additionally, co-administration of 80 mg FHND9041 capsules with 600 mg Rifampicin and 40 mg FHND9041 capsules with 200 mg Itraconazole was well tolerated and had positive safety results.

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