# Pharmacokinetics, bioequivalence, and safety studies of gefitinib tablet formulations: a randomized, open-label, two-period, two-sequence crossover study in Chinese healthy volunteers

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**Abstract**

Aims: A randomized, open-label, two-period, two-sequence crossover study was carried out for evaluating the bioequivalence of test (T) and reference (R) formulation of gefitinib in healthy Chinese volunteers. Methods: A total of eighty subjects were enrolled and randomized into two sequence groups. All subjects were orally administered of T or R formulation at dose of 250 mg. The plasma samples were obtained at before and after administration until post-dose 168 hour, and the drug concentrations were analyzed using validated high-performance liquid chromatography-tandem mass spectrometry method. Results: The 90% confidence interval of the geometric mean ratios were all within the range of 0.80-1.25 under fasting and fed conditions. As for the safety of both formulations, no serious or unexpected adverse events occurred during the study. Conclusions: Overall, the T formulation was bioequivalent with R formulation under fasting and fed conditions.

## Introduction

Cancer is a primary public health concern throughout the world and its occurrence significantly reduces people's quality of life and leads to a range of medical problems [1, 2]. Cancer treatment has undergone tremendous changes, from previous chemotherapy and surgery to current molecular targeted drug therapy, onco-immunology therapy and combination therapy. Among them, the clinical practice of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) has significantly improved the benefit-risk ratio of cancer patients. Gefitinib, a first-generation EGFR-TKI, was authorized by the U.S. Food and Drug Administration (FDA) in 2003 and launched in China for treatment of non-small cell lung cancer (NSCLC) in February 2005. As the latest reported literature shows, gefitinib alone or chemotherapy with gefitinib plus pemetrexed may be cost-effective for patients with advanced EGFR mutated NSCLC in China [3, 4]. Evaluating the bioequivalence or substitutability of the tested formulation with the reference formulation will undoubtedly facilitate the treatment and recovery of cancer patients. The purpose of this open-label, randomized, two-period crossover, comparative pharmacokinetic study is to explore the bioequivalence of gefitinib in reference (R) or test (T) formulation in healthy Chinese subjects under fasting and fed conditions.

## Methods

### Ethics

This study was approved and performed at the Beijing Chao-Yang hospital, Capital Medical University (BCYH-CMU). The study protocol and informed consent form were endorsed by the BCYH-CMU Ethics

Committee with the ethical approval number 2017-drug-2 (April 10, 2017). This clinical study was implemented according to Good Clinical Practice and the Declaration of Helsinki, International Council for Harmonization Guidelines. Besides, this study was registered at the website of Clinical Trial Registry (Identifier: CTR20180968, http://www.chinadrugtrials.org.cn) and was conducted from July 2018.

Formulations

The test and reference formulations were evaluated simultaneously. The test formulation was provided by Zhejiang Hisun Pharmaceutical Co., Ltd. (250 mg/pill; Lot: 21803261; Purity: 95.0%-105.0%; Production date: March 26, 2018; expiry date: February, 2020). The reference formulation was from AstraZeneca UK Limited (IRESSA®, 250 mg/pill; Lot: MC979; Purity: 95.0%-105.0%; Production date: 2016.03; expiry date: February 2019).

Subjects

Eighty healthy male volunteers were screened and enrolled according to the inclusive criteria: (1) age[?]18 years; (2) body mass index (BMI) of 19-26 kg/$m^2$ (weight[?]50 kg); (3) healthy conditions as confirmed by the detailed medical history, comprehensive physical examination, vital signs (e.g., systolic and diastolic blood pressure, body temperature, pulse rate), 12-lead electrocardiogram (12-ECG), virus antigen (hepatitis B and C, HIV and syphilis tests), chest X-ray and laboratory examinations (biochemistry, hematology, urinalysis, coagulation function tests); (4) restricted by concomitant drugs, tobacco, alcohol, and food supplements around the whole study. Taking any drugs that change the activity of CYP3A4 liver drug enzymes (e.g., inducers-phenobarbital, carbamazepine, phenytoin, rifampin, etc.; inhibitors-ketoconazole, itraconazole) within 28 days before taking the study drug, posaconazole, voriconazole, etc.) were excluded. All participants were supplied with a written informed consent form (ICF) prior to enrollment and were able to comply with the study constraints as published by the Phase I clinical trial center protocol. The subjects available to withdraw whenever necessary. Eighty male subjects were enrolled to explore the bioequivalence of gefitinib.

Study Design and Clinical Study Procedures

Under the fasting and fed conditions, a randomized, single-dose, and 2-period crossover study was implemented to investigate the bioequivalence of test formulation with a reference formulation in adult healthy volunteers. Subjects were screened within 14 days prior to dosing and orally treated at the dose of 250 mg.

Compared with the fasting group, the high-fat (providing about 50% of the calories in food), high-calorie (about 800˜1000 kcal) meal was allocated no more than 30 min before dosing in the fed trial. For both two groups, subjects were orally administered T or R formulation with 240 +- 5 mL water. Conventional standardized meals were given at post-4 and post-10 hours to manipulate the feeding status of the subjects. The water intake restriction was strictly followed at 1 hour prior to drug administration and at 1 hour post-drug administration. Grapefruits, grapefruit juice, oranges, alcohol, coffee and strenuous exercise are not permitted during the study from 48 hours to 168 hours prior to dosing.. According to the $t_{1/2}$ of gefitinib from previous reports, the washout period was fixed to 21 days[5, 6].

Estimating of sample size

In accordance with FDA requirements for bioequivalence study, the geometric mean ratio (GMR) is usually set at 95-105% under these conditions (80% power, $\alpha$=5%). The intra-subject variability (intra-CV) for gefitinib is described to be 17-30%[7], and the sample size calculation was carried out based on the smallest even number of subjects. Additionally, considering the subject withdrawal of 10%, thus forty healthy male subjects were enrolled in the fasting or fed group. Random order list was calculated by SAS statistical software (version 9.4, SAS Institute, Cary, North Carolina), and all participants were allocated into either a T or R group.

Blood Sampling

For both fasting and fed conditions, peripheral venous blood samples (approximate 4 mL) from each subject were drawn at 0 hour (within 60min pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, 72, 96,120, 144, and 168 hours post-administration in $K_2$EDTA anticoagulated tubes, mixed upside down gently, and transferred in ice-water bath. Sample were centrifuged at 3500 rpm at 2-8 for 10 minutes, and supernatant plasma was equally pipetted into assay parts and backup parts. All plasma samples were stored in ultra-low temperature refrigerators (-80 ). All blood samples were centrifuged within 30 min after collection, and the plasma samples were frozen within 1 hours after centrifugation.

Safety Assessment

Vital signs will be measured at various time points (1, 3, 6, 8, 12, 24, 72, 120, 168 hours) before and after drug administration. Medical staff will closely monitor and report adverse events throughout the trial. Safety assessment was conducted throughout the entire study period, and laboratory examinations, physical examinations, 12-ECG were performed before dosing and after blood sampling.

On the one hand, all the AEs were evaluated and recorded pertaining to seriousness, intensity, time course, outcome, relationship to the study formulation [8]. On the other hand, AEs were coded to a preferred term and system organ class according to the Medical Dictionary for Regulatory Activities [8]. All clinical occurrences and clinically meaningful laboratory adverse reactions will be evaluated according to the Common Adverse Events Evaluation Criteria (CTCAE) version 4.03. To reveal the relationship between AEs and formulations, five description types were documented (not relevant, unlikely, possible, probable, or definitely relevant).

Bioanalysis

The high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) assay has been developed and fully validated to support the bioequivalence study. Gefitinib was obtained from European Directorate for the Quality of Medicines with purity of 99.5%. Gefitinib-d3 (Internal standard, IS, purity: 98%; expiration date: May 6, 2021) was purchased from Toronto Research Chemicals. Chromatography was performed at 40 using ultrafast liquid chromatography system (UFLC 20AD, Shimadzu, Japan) equipped with Luna HILIC column (5μm, 100×2 mm, Phenomenex). Mobile phase for gradient elution composed of water (A, 0.4% formic acid, pH=3.2) and acetonitrile (B) delivered at a flow rate of 0.4 mL/min. The whole analytical time was 5 min. QTRAP 5500 mass spectrometer (SCIEX) equipped with an positive electrospray ionization (ESI) source was adopted. Multiple reaction monitoring (MRM) transitions were at *m/z* 447.3-128.0 for gefitinib, 453.2-127.9 for IS, respectively. Plasma sample were prepared using liquid-liquid extraction using acetonitrile: water (1:1, *v/v* ). The linearity range of HPLC-MS/MS was 1-1000 ng/mL with lower limit of quantification of 1 ng/mL and with good linearity of $r^2$ =0.999. The results of bioanalytical method validation meet the criteria of FDA Guidelines, such as accuracy and precision, matrix effect, stability, linearity, recovery, incurred sample reanalysis.

Pharmacokinetic Parameters and Statistical Analysis

Non-compartmental model was carried out to calculate the pharmacokinetic parameters using Phoenix WinNonLin (Pharsight Corporation, version 8.1, Mountain View, CA). The pharmacokinetic parameters were as follows: the peak plasma concentration ($C_{max}$) and the time to reach $C_{max}$ ($T_{max}$) were obtained directly from the concentration-time profile. The areas under the plasma concentration-time curve ($AUC_{0\text{-}t}$ or $AUC_{0\text{-}[?]}$) were calculated from time 0 to the end time of the concentration-time profile or infinity. The first-order terminal rate constant ($k_{el}$) was estimated using linear regression of the terminal log-linear decay phase. Statistical analysis was executed using SAS software and $C_{max}$, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}[?]}$ were compared between two formulations using 1-way analysis of variance (ANOVA) on log-transformed pharmacokinetic values. The p value of $< 0.05$ was considered statistically significant. According to FDA guidance, the T and R were considered bioequivalent if the 90% confidence interval (CI) for the ratio of the geometric least-squares means was within the equivalence limits (80.0-125.0%) for the primary end points $C_{max}$, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}[?]}$[9]..

## Results

### Participants

A total of 250 healthy male volunteers were screened for this bioequivalent study, and eighty subjects satisfied the inclusive criteria and enrolled in the study. The mean age of fasting and fed group were 30.85+-7.97 and 31.28+-7.62 years old, respectively. Most participants were Han Chinese. The mean BMI of fasting and fed condition was 22.77+-1.91, 22.34+-2.17 kg/m$^2$. The demographic data of all enrolled subjects are summarized in **Table 1** . Five subjects were dropped off due to adverse reactions and other reasons (e.g., positive urine screen) that occurred during the trials. The screening and enrollment flow chart of all subjects was shown in**Figure 1** .

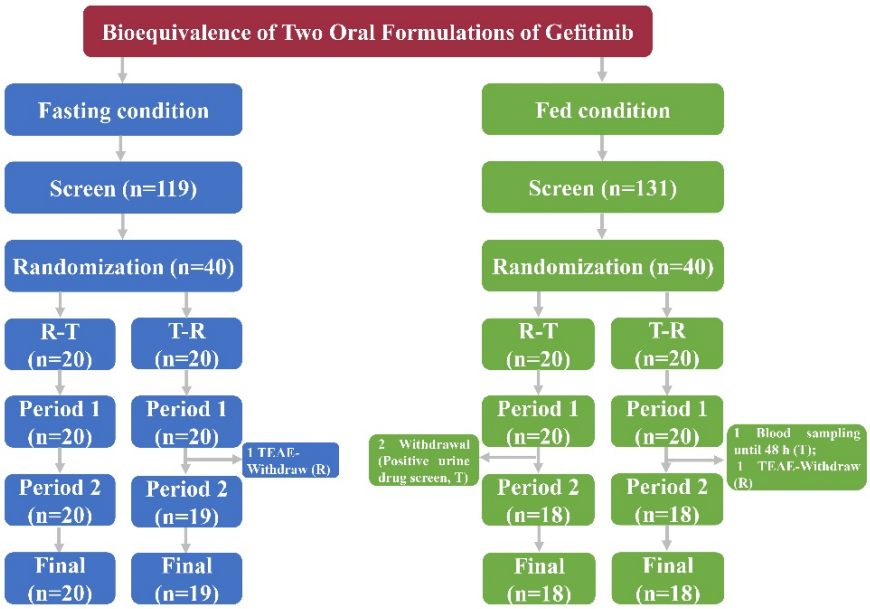


**Figure 1** The flow diagram for this pharmacokinetic and bioequivalence study of gefitinib.

**Table 1** Demographic and baseline characteristics of all participants

| Parameter | Fasting condition (N=40) | Fed condition (N=40) |
|---|---|---|
| Age (year, mean±SD) | 30.85±7.97 | 31.28±7.62 |
| Sex (Male) | 40(100.00%) | 40(100.00%) |
| Ethnicity (Han, Other) | 38, 2 | 38, 2 |
| Height (cm, mean±SD) | 168.06±6.06 | 169.81±5.43 |
| Body weight (kg, mean±SD) | 64.18±4.89 | 64.54±8.03 |
| BMI (kg/m$^2$), mean±SD) | 22.77±1.91 | 22.34±2.17 |

### Pharmacokinetics

The mean plasma concentration-time curves are illustrated in**Figure 2** (fasting) and **Figure 3** (fed). A biphasic decline manner was shown, which initially decrease rapidly and described a somewhat decrease. Besides, the concentration-time curve of gefitinib was similar as for R and T formulations. Pharmacokinetic parameters of gefitinib under fasting and fed conditions were presented in**Table 2** . $AUC_{0\text{-}t}$ accounted for [?]90% of the total $AUC_{0\text{-}[?]}$ for all subjects, indicating that the plasma concentration-time profiles were

represented nicely. The CV values of the pharmacokinetic parameters were similar with more than 50%. It is noted that the mean $C_{max}$ and AUC were in the range of 208.01-260.05 ng/mL, 6520.42-7334.52 h*ng/mL. In addition, the meant $t_{1/2}$ was in the range of 29.50-35.10 hour. Moreover, no significant differences were detected in either the absorption or elimination phases of the R- and T-formulations of gefitinib, with similar values of pharmacokinetic parameters under fasting and feeding conditions. **Figure 2 and Figure 3** also demonstrated the generally consistent absorption as described using concentration-time curve of post-administration of 12 hour.

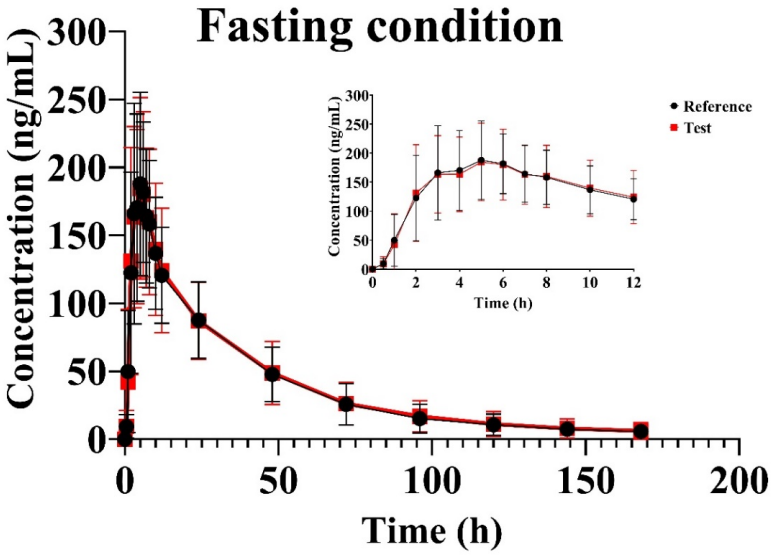


**Figure 2** The mean plasma concentration-time profile of gefitinib in two periods after single dose under fasting condition.

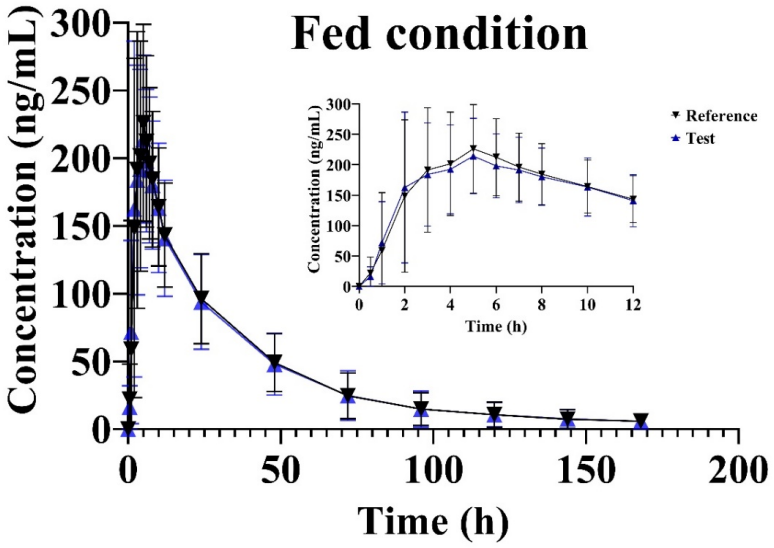

**Figure 3** The mean plasma concentration-time profile of gefitinib in two periods after single dose under fed condition.

**Table 2** Pharmacokinetic parameters of gefitinib under fasting and fed conditions

| **Parameters** | **Fasting condition (M** |
|---|---|
| | **Test (N=40)** |
| $T_{max}$ (hour)* | 5.00 (2-23.99) |
| $C_{max}$(ng/mL) | 208.01±70.19(33.75) |
| $AUC_{0\text{-}t}$ (h*ng/mL) | 6520.42±2830.07(43.40) |
| $AUC_{0\text{-}[?]}$ (h*ng/mL) | 6883.55±3274.47(47.57) |
| $t_{1/2}$ (hour) | 35.10±14.31(40.78) |
| Median (range), **C003 subject had only the first cycle $C_{max}$ and $T_{max}$ as valid PK parameters. | * Median (range), **C0 |

Bioequivalence Analysis

The detailed pharmacokinetic parameters and the 90% CI for the ratio of the logarithmically transformed pharmacokinetic parameters are described in **Table 3** . Based on the multivariate ANOVA no significant difference was found in both $C_{max}$ and $AUC_{0\text{-}t}$ between the test and reference formulations. It is shown that the 90% CIs were 91.40-107.57% for $C_{max}$, 91.69-103.63% for $AUC_{0\text{-}t}$, 92.27-104.37% for $AUC_{0\text{-}[?]}$. In addition, the GMRs for $C_{max}$and AUC were all within 0.80-1.25, and $T_{max}$ values were comparable between test and reference formulations under fasting or fed condition. The detailed results are shown in **Table 3** . As indicated in **Figure 4** , the individual difference of log $C_{max}$ and log $AUC_{0\text{-}t}$ values was in a narrow range for the T and T formulations. Therefore, the test formulation was considered bioequivalent to the reference formulation.

**Table 3** Bioequivalence evaluation for the main pharmacokinetic parameters of gefitinib under fasting and fed conditions

| **Parameter** | **GM (Test)** |
|---|---|
| **Fasting condition** | |
| $C_{max}$(ng/mL) (N=40) | 194.27 |
| $AUC_{0\text{-}t}$(h*ng/mL) (N=40) | 5871.87 |
| $AUC_{0\text{-}[?]}$(h*ng/mL) (N=40) | 6115.71 |
| **Fed condition** | |
| $C_{max}$(ng/mL) (N=40) | 232.47 |
| $AUC_{0\text{-}t}$(h*ng/mL) (N=38) | 6341.16 |
| $AUC_{0\text{-}[?]}$(h*ng/mL) (N=38) | 6530.76 |
| CV, coefficient of variation; GM, geometric mean; GMR, geometric mean ratio | CV, coefficient of variation; GM, geometri |

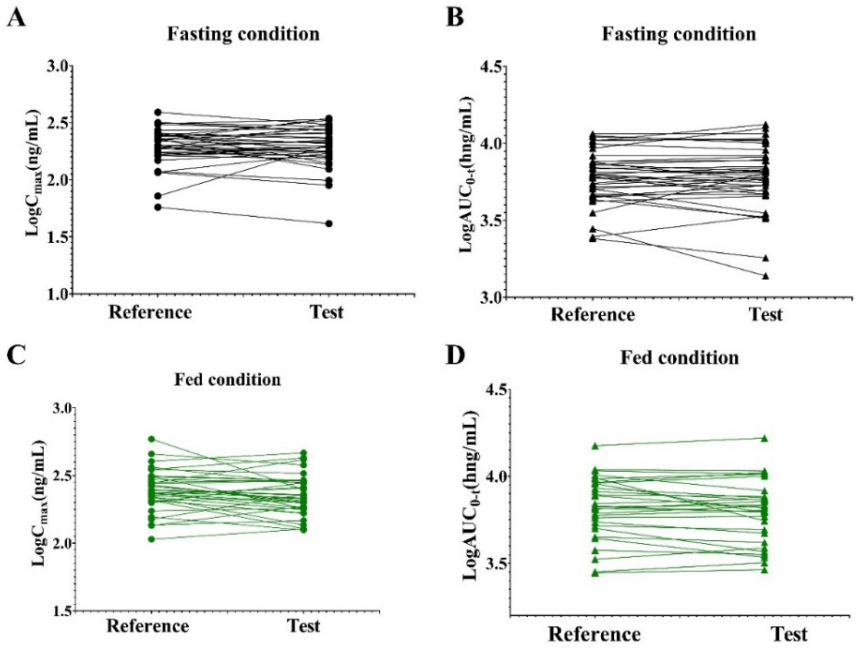


**Figure 4** Individual comparison of log $C_{max}$ (A, C) and log $AUC_{0\text{-}t}$ (B, D) between reference and test formulations.

Safety

Seventeen AEs occurred in eleven subjects in the fasting condition, and the incidence rate of AEs was 27.50% (11/40); among them, six cases (15.00%, 6/40) and 9 cases occurred in the test formulation, seven subjects of eight cases (17.95%, 7/39) occurred in the reference formulation. In addition, as for the fed condition, a total of sixteen AEs occurred in thirteen subjects in the postprandial test in this study, and the incidence rate of adverse events was 32.50% (13/40); among them, eight cases (21.05%, 8/38) and nine cases occurred in the test formulation, five cases (13.16%, 5/38) and seven cases occurred in the reference formulation. The more common AEs in this trial included rosacea, oral ulcers, urticaria, elevated glutathione and glutathione transaminases, elevated bilirubin, and elevated uric acid. Collectively, neither serious safety attentions nor unexpected Ars of the T or R formulation was observed during this study.

## Discussion

This randomized, open-label, and two-period crossover studies were firstly investigated under both fasted and fed conditions in healthy male volunteers. In this bioequivalent study, a total of 250 volunteers were screeded, and the baseline characteristics of all subjects were similar regarding age and BMIs. As demonstrated in **Figure 2 and Figure 3** , the concentration-time profiles of fasting and fed states were constant in both absorptive rates and degrees. It was observed that gefitinib absorbs slowly and undergoes rapid plasma clearance, with the $T_{max}$ of 4-5 hour after single administration. Moreover, the results of the main pharmacokinetic parameters were generally similar to those of the published literatures[10, 11].

Generally speaking, the variations of the primary pharmacokinetic parameters (e.g., $C_{max}$, AUC, $t_{1/2}$) are due to food-facilitated variation in physiological processes (e.g., gastric emptying rate, fluctuations in gastrointestinal pH, increase luminal fluids, release of bile salts, inhibition of transporters)[12]. Besides, several literatures have reported that CYP2D6 was associated with gefitinib exposure and may contribute to the high inter-subject variability, but it did not influence the bioequivalence result [13].

Undoubtedly, the property of Biopharmaceutics Classification System (BCS) class II for gefitinib-high permeability and low solubility-may influence the oral absorption [14]. Gefitinib dissolves rapidly in acidic agents, but the solubilityreduces with increasing pH until neutral pH in the intestinal tract. In the present study, our results conclusively show higher exposure under feeding conditions compared with studies conducted in the fasted state. In addition, feeding conditions can alter the pH of the stomach, which can increase dissolution and absorption by approximately 10%. Although some literature has reported studies on the bioequivalence of gefitinib in healthy subjects, these have shortcomings such as limited sample size (25 cases[15], 50 cases[16]).

Besides, the range of Intra-CV was less than 22% (ranged from 10.68% to 21.61%, Table 3) and was constant with previous literature[7, 17], which suggests that the various aspects of quality control of this protocol are well established. The statistical requirements were fully satisfied in the forty healthy volunteers. Furthermore, for both formulations, rosacea, oral ulcers, and urticaria were the most commonly reported treatment emergent adverse event (TEAEs). The incidence of TEAEs was in agreement with what is known for commercial formulations. [10].

It has to be admitted that there are several limitations in this study. Firstly, according to our previous study, we partially determined the genotypes of metabolic enzymes or transporters (e.g., CYP3A4, CYP3A5, CYP2D6, ABCG2) that metabolize gefitinib, so we could not analyze the variation of pharmacokinetic parameters completely[18]. Secondly, we conducted bioequivalence studies only in healthy subjects and did not evaluate the equivalence of T to R formulation in cancer patients. Besides, other dosage regimens should be integrated to fully assess the comparative pharmacokinetics.

## Conclusion

Collectively, the assessment of pharmacokinetics demonstrated that the R and T formulations were bioequivalent under fasting and fed conditions. The 90% CIs for $C_{max}$, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}[?]}$ were within the acceptable range for bioequivalence (80.00-125.00%) as issued by the Pharmacopoeia of the People's Republic of China (ChP) guidelines. All subjects were well tolerated for the two formulations of gefitinib, and there were no major side effects. Thus, an alternative formulation of gefitinib would provide an affordable, tolerable, and meaningful access to the drug for cancer patients.

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## Declaration of Conflicting Interests

The sponsor and all authors declare no conflicts of interests in this work.

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## Data availability statement

The data supporting the findings of this study are available from the principal investigator for this paper, Lihong Liu, upon reasonable request.

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