Transl Clin Pharmacol. 2021 Sep;29(3):171-179
https://doi.org/10.12793/tcp.2021.29.e17
pISSN 2289-0882·eISSN 2383-5427

Translational and Clinical Pharmacology TCP

Bioequivalence Report

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Pharmacokinetic properties and bioequivalence of gefitinib 250 mg in healthy Korean male subjects

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OPEN ACCESS

Received: Aug 16, 2021
Revised: Sep 9, 2021
Accepted: Sep 16, 2021

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Reviewer
This article was reviewed by peer experts who are not TCP editors.

Conflict of Interest
- Authors: Shin-Jung Park is a paid employee of Chong Kun Dang Pharmaceutical Corp., Korea. All other authors declare that they have no conflicts of interest.
- Reviewers: Nothing to declare
- Editors: Nothing to declare

ABSTRACT

Gefitinib is an anti-cancer drug used to treat non-small cell lung cancer. The objective of this study was to compare the pharmacokinetics and evaluate the bioequivalence of 2 orally administered gefitinib 250 mg tablets in healthy Korean subjects. A randomized, open-label, single-dose, crossover bioequivalence study was conducted. A total of 50 healthy male volunteers were randomized into 2 sequence groups. During each treatment, the subjects received the test or reference formulation of 250 mg gefitinib with a washout period of 21 days. The plasma samples were collected at pre-dose and up to 144 hours post-dose, and plasma drug concentrations were measured using validated liquid chromatography-tandem mass spectrometry. Pharmacokinetic parameters were calculated, and the formulations were considered as bioequivalent if the 90% confidence intervals (CIs) of the geometric mean ratios were within the bioequivalence limits of 0.8 to 1.25. Forty-one subjects completed the study and were included in the pharmacokinetic analysis. The 90% CIs of the geometric mean ratios of the test formulation to the reference formulation were 0.8115 to 0.9993 for maximum plasma concentration and 0.9119 to 1.0411 for area under the plasma concentration versus time curve from dosing to the last measurable concentration. There were no serious or unexpected adverse events during the study. In healthy Korean adult subjects, the test and reference formulations of gefitinib 250 mg had similar pharmacokinetic parameters and similar plasma concentration-time profiles. The test formulation of gefitinib met the regulatory criteria for assuming bioequivalence. Both formulations were safe and well-tolerated.

Keywords: Gefitinib; Non-small Cell Lung Cancer; Pharmacokinetics; Bioequivalence; Iressa

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer and approximately 85% of lung malignancies are advanced or metastatic NSCLC at the time of diagnosis [1]. Currently, the main treatment approach for NSCLC targets epidermal growth factor receptor (EGFR), which is involved in the control of cell growth, proliferation, migration, metastasis, angiogenesis, and apoptosis inhibition [2]. Gefitinib is an orally administered EGFR-tyrosine kinase (TK) inhibitor that blocks EGFR phosphorylation [3,4].

Author Contributions

Conceptualization: Kim MG; Formal analysis: Kim Y, Jeon JY; Methodology: Jeon JY, Kim MG; Writing - original draft: Moon SJ, Kim Y; Writing - review & editing: Moon SJ, Park SJ, Kwak YG, Kim MG.

Since the expression of EGFR has been identified in a wide range of human cancers and has been frequently correlated with poor prognostic factors, EGFR represents an important target for novel anti-cancer agents [5].

Gefitinib inhibits EGFR-TK by binding to the adenosine triphosphate-binding site of the enzyme [6]. Thus, the function of EGFR-TK in activating the anti-apoptotic Ras signal transduction cascade is inhibited, and the proliferation of malignant cells is inhibited. Gefitinib has demonstrated anti-cancer activity in patients with advanced NSCLC after failure to respond to both platinum-based and docetaxel chemotherapies [7-9]. In particular, gefitinib showed a high therapeutic response rate in Asian, female, and nonsmoker patients [10]. These studies led to gefitinib approval in many countries as a new therapeutic option for patients with advanced NCSLC who failed to respond to prior chemotherapy.

Gefitinib is an anilinoquinazoline (4-quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-amine) with a molecular weight of 446.9 g/mol. Gefitinib is mainly metabolized by the liver, and its excretion occurs mostly through bile excrement. The major cytochrome P450 (CYP) enzyme predominantly involved in the extensive hepatic metabolism of gefitinib is CYP3A4, although the formation of the major circulating human metabolite of gefitinib has been shown to be catalyzed primarily by CYP2D6 [11,12]. A recent bioequivalence study reported that the median time to maximum plasma concentration (T_{max}) was 4–5 hours, and the mean elimination half-life ($t_{1/2}$) was 18–26 hours [13]. The plasma concentration profiles after oral administration showed that gefitinib was suitable for once-daily oral administration, with a steady-state being achieved after 7 days of multiple dosing [6,14]. No dosage adjustment is required for patient age, body weight, sex, ethnicity or moderate to severe hepatic impairment due to liver metastases [15].

Iressa® (ZD1839; AstraZeneca Co., Ltd., Seoul, Korea), a formulation of gefitinib 250 mg tablets, received accelerated approval by the USA Food and Drug Administration (FDA) in 2003 [6]. Iressa is a targeted therapy tablet taken orally once daily that was designed to treat patients with NSCLC that has spread beyond the lungs, and who have certain types of EGFR mutations [16]. Iretinib, a generic drug for gefitinib, was developed by Chong Kun Dang Pharmaceutical Corp. in Korea, and data on the pharmacokinetic properties and comparative bioavailability of the new drug formulations are required before marketing. This study was designed to compare the pharmacokinetic parameters and to assess the bioequivalence of the test drug, Iretinib, with those of a branded reference drug, Iressa, in healthy Korean subjects.

MATERIALS AND METHODS

This study was approved by the Ministry of Food and Drug Safety (Cheongju, Korea) and the Institutional Review Board of Jeonbuk National University Hospital (Jeonju, Korea; CUH2014-02-004) and was conducted according to the principles of the Declaration of Helsinki for biomedical research involving human subjects and the Guidelines for Good Clinical Practice. A detailed explanation of the study was provided, and then written informed consent was obtained from all participants prior to screening.

Subjects

Healthy male adult volunteers aged 19 to 55 years were enrolled who had a body mass index between 17.5 and 30.5 kg/m^2 and a total body weight ≥ 45 kg. The subjects were screened by

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medical history, physical examination, measurement of vital signs, 12-lead electrocardiogram (ECG), clinical laboratory tests (i.e., serology, blood chemistry, urinalysis), and chest X-ray. The subjects were excluded if they had participated in another clinical study within 3 months prior to taking the first dose of investigational product and if they had received any medication within 10 days before the study that could significantly alter the pharmacokinetics of the study drugs.

Study design

A randomized, open-label, single-dose and crossover bioequivalence study was conducted in healthy male subjects (**Fig. 1**). A total of 50 subjects were randomly assigned to one of the 2 sequence groups and were administered one of the following treatments in each period according to the sequence group: the test formulation (Iretinib, Chong Kun Dang Pharmaceutical Corp., Seoul, Korea) and the reference formulation (Iressa®, AstraZeneca Co.) drug as gefitinib 250 mg. There was a 21 day washout interval, which was at least 5 times the elimination half-life, to ensure that there was no carryover from the previous dose [17].

The subjects were hospitalized at the study institution on the day before the study drug administration for baseline evaluations. On day 1, each subject received the investigational product with 240 mL of water. The subjects were administered the drugs according to the assigned treatment sequence after an overnight fast of at least 10 hours supervised by the investigators. All subjects maintained the fasting state until 4 hours after study drug administration, which included limiting water intake for 1 hour before and after dosing. The subjects were discharged after blood collection at 24 hours after dosing and revisited the study site for scheduled evaluations at 48, 72, 96, 120, and 144 hours. The subjects returned for a follow-up visit 12±2 days after the last blood collection of period 2. During the study period, taking any medication, intense physical activity, drinking alcohol, smoking, and excessive caffeine intake were not allowed. Blood samples were collected at pre-dose and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, 48, 72, 96, 120, and 144 hours after a single administration of gefitinib 250 mg. The blood samples were immediately centrifuged for 10 minutes at 3,000 rpm (1,800 ×g) at 4°C, and the plasma aliquots were stored at −70°C until analysis.

Pharmacokinetic assessment

Plasma sample concentrations of gefitinib were analyzed by high-performance liquid chromatography combined with tandem mass spectrometry, which consisted of HPLC

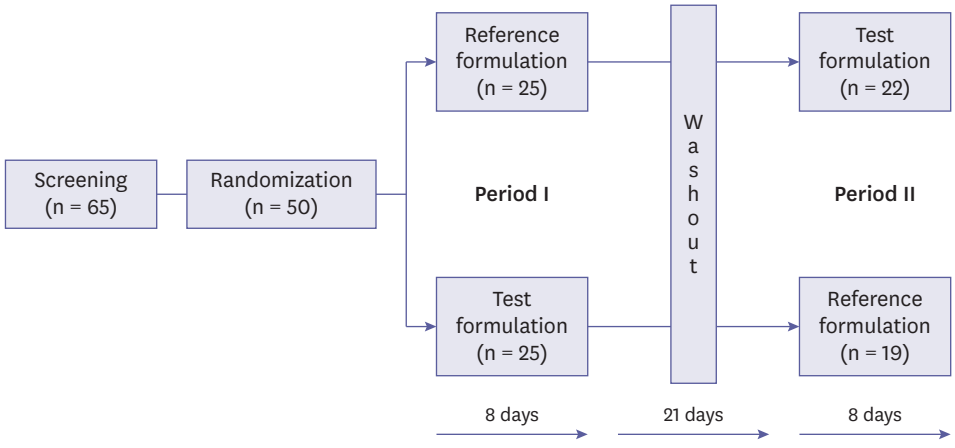

Figure 1. Design for bioequivalence study of gefitinib in healthy male Korean volunteers.

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(Thermo Dionex UltiMate 3000; Thermo Scientific, Waltham, MA, USA) coupled with MS/MS (Thermo TSQ Endura; Thermo Scientific) [18]. Separation was achieved on a 50 × 2.1 mm Hypersil GOLD column (Thermo Scientific). An aliquot of 5 μL of the sample was injected into the column and the mobile phase consisted of a mixture of 10 mM ammonium formate and acetonitrile in gradient mode at a flow rate of 0.35 mL/min. Ion pairs from *m/z* 447.22 → 128.22 for gefitinib and from *m/z* 386.33 → 122.22 for the internal standard (IS) were selected for quantitation. Buspirone was used as the IS for the analyte, and the drug-to-IS ratios were used to create a linear calibration curve using a $1/x^2$ weighted least squares regression analysis. The validated quantification range was between 1 and 1000 ng/mL for gefitinib. Each analytical run included appropriate standards and quality-control samples. The lower limit of quantification (LLOQ) was 1 ng/mL for gefitinib. The method was fully validated according to the FDA guidance for the validation of bioanalytical methods [19]. The calibration curves were linear over the concentration range from 1 to 1000 ng/mL for gefitinib ($r^2 \geq 0.99450$). The accuracy was 94.61–103.89% (LLOQ, 108.27–114.51%) and the precision, expressed as %CV, was 1.90–5.03% (LLOQ, 3.95–5.36%) in the within-run and between-run, respectively.

The individual pharmacokinetic parameters were determined by non-compartmental analysis methods using Phoenix® WinNonlin® software (version 6.3; Pharsight Corporation, Sunnyvale, CA, USA). These properties included the following: maximum plasma concentration (C_{max}), T_{max}, area under the plasma concentration-time curve to the last sampling time (AUC_{last}), area under the plasma concentration-time curve to infinity (AUC_{inf}), and $t_{1/2}$. The linear trapezoidal rule was used to calculate the $AUC_{last,}$ and the C_{max} and T_{max} were directly obtained from the measured values. The AUC_{inf} was calculated as $AUC_{last} + C_{last}/k_e$, where C_{last} was the last measured concentration, and k_e, the elimination rate constant, was the slope of the linear regression of the log-transformed plasma concentration-time in the terminal phase. The $t_{1/2}$ of a substance, the time required for the blood plasma concentration to be reduced by half, was calculated as $\ln 2/k_e$. Only data from subjects who completed the study were included in the statistical analysis of the pharmacokinetic properties.

Safety assessments

Subjects who received at least one dose of investigational product during the study were included in the safety analysis. Safety was assessed by monitoring adverse events (AEs), physical examinations, laboratory tests (hematology, blood chemistry, and urinalysis), vital sign measurements (blood pressure, pulse rate, and body temperature), ECG, and chest X-ray. AEs were identified by asking the subjects about their condition during the study period. AE data were recorded from the pre-dose until the follow-up visit. AEs were summarized by treatment groups in terms of severity (mild, moderate, or severe) and relationship to the investigational products. Physical examinations, laboratory tests, and vital sign measurements were conducted at screening, pre-dose, 144 hours post-dose, and at the follow-up visit.

Statistical analysis

Statistical analysis was performed using SAS® (version 9.3; SAS Institute Inc., Cary, NC, USA). Descriptive statistics of the plasma gefitinib concentrations, as well as for the derived pharmacokinetic parameters, were calculated for each treatment.

Descriptive statistics, including the mean ± standard deviation (SD), were used to summarize the demographic and pharmacokinetic data for the 2 formulations. Natural log-transformed C_{max} and AUC_{last} were analyzed separately using an analysis of variance (ANOVA) model with

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sequence, subject within sequence, period, and treatment as factors. The point estimates and 90% confidence intervals (CIs) of the geometric mean ratios (test drug/reference drug) of the log-transformed C_{max} and AUC_{last} were compared. The formulations were assumed to be bioequivalent if the 90% CIs of the geometric mean ratios of C_{max} and AUC_{last} (test formulation to the reference formulation) were 0.8 to 1.25 [20]. A *p*-value of < 0.05 for C_{max} and AUC_{last} was considered statistically significant [21].

All AEs were statistically presented in terms of the number, percentage, and incidence of AEs in the treatment group. The results of the laboratory tests and vital signs were reviewed descriptively by treatment group at each examination point. The physical examination and ECG results were summarized according to the time of each examination.

RESULTS

Subjects

A total of 50 healthy Korean male subjects were enrolled in the study and randomized to 2 sequences. The demographics of the subjects (mean ± SD) included a mean age of 24.0 ± 2.3 years, height of 174.0 ± 5.3 cm, and weight of 69.9 ± 8.6 kg. There were no relevant differences in demographic characteristics among groups undergoing different treatment sequences. Ultimately, 41 subjects completed the study. Two subjects withdrew due to taking concomitant medication to treat AEs, and 7 subjects withdrew their participation consent after drug administration. Therefore, a total of 9 subjects were excluded from the pharmacokinetic analysis.

Pharmacokinetic analysis

Fig. 2 shows the mean plasma concentration-time curves of the test or reference formulations following a single 250 mg dose of gefitinib, and **Table 1** shows the values of the pharmacokinetic parameters for the test and reference formulations. Both formulations

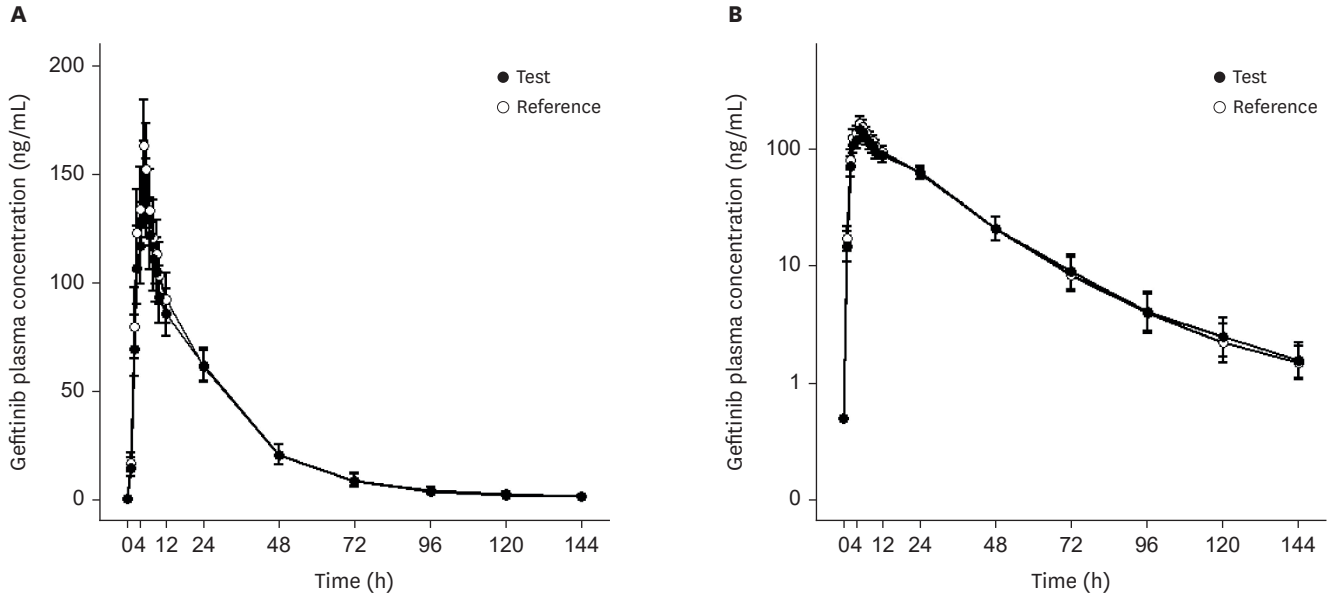

Figure 2. Plasma concentration-time curve (geometric mean ± 95% confidence interval) of gefitinib after administration of a single oral dose of the test or reference drug to healthy male subjects. Data are represented on a (A) linear scale and (B) log scale.

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Table 1. Pharmacokinetic parameters of gefitinib after single oral administration of 2 formulations

Parameters (units)	Test	Reference
AUC_{last} (hr × ng/mL)	4,279.995 ± 2,032.756	4,354.838 ± 1,904.361
C_{max} (ng/mL)	163.942 ± 64.614	180.758 ± 63.958
AUC_{inf} (hr × ng/mL)	4,417.408 ± 2,150.011	4,470.836 ± 2,000.004
T_{max} (hr)	5.00 (2.00–6.00)	5.00 (3.00–6.00)
$t_{1/2}$ (hr)	24.62 ± 9.97	22.64 ± 8.49

Values are represented as the arithmetic mean ± standard deviation except T_{max} (median [range]).
AUC_{last}, area under the plasma concentration-time curve to the last sampling time; C_{max}, maximum plasma concentration; AUC_{inf}, area under the plasma concentration-time curve to the infinity; T_{max}, time to reach C_{max}; $t_{1/2}$, terminal half-life.

Table 2. Bioequivalence assessment of the 2 formulations of gefitinib after administration of a single dose

Pharmacokinetic parameter (unit)	Geometric LS mean		Geometric LS mean ratio (test/reference)	
	Test	Reference	Point estimate	90% CI
AUC_{last} (ng × hr/mL)	3,865.376	3,966.969	0.9744	0.9119–1.0411
C_{max} (ng/mL)	151.940	168.728	0.9005	0.8115–0.9993

LS, least squares; AUC_{last}, area under the plasma concentration-time curve to the last sampling time; C_{max}, maximum plasma concentration; CI, confidence interval.

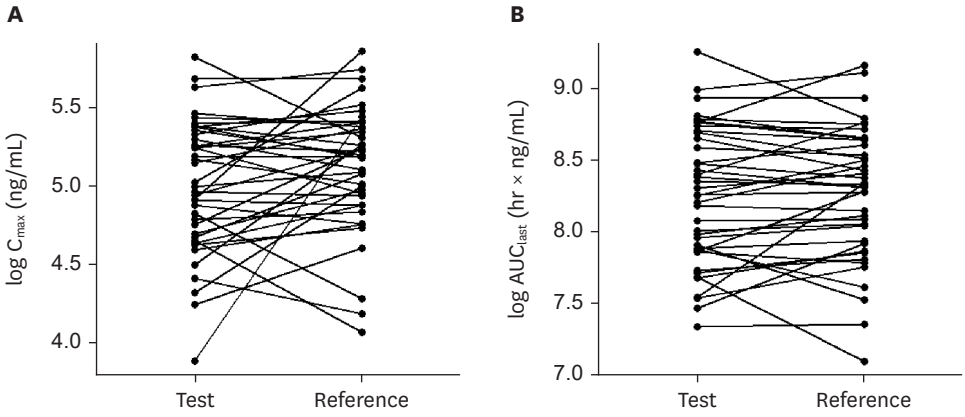

Figure 3. Comparison of log C_{max} (A) and log AUC_{last} (B) between reference and test formulations, in each subject.
AUC_{last}, area under the plasma concentration-time curve to the last sampling time; C_{max}, maximum plasma concentration.

showed comparative AUC, C_{max}, $t_{1/2}$, and T_{max} values, and the figure also shows that the 2 formulations showed similar absorption and elimination profiles. **Table 2** shows the pharmacokinetic parameters, including AUC_{last} and C_{max}, which were calculated and the 90% CIs of the ratio (test/reference) of the parameters were obtained by ANOVA on logarithmically transformed data. Bioequivalence was assessed by a general linear mixed model with sequence, treatment, and period effects as fixed effects and sequence nested subject effects as random effects. The point estimates and 90% CIs for the geometric mean ratios of the test to reference formulations were as follows: 0.9744 (0.9119–1.0411) for AUC_{last}, and 0.9005 (0.8115–0.9993) for C_{max}. The 90% CIs for these pharmacokinetic parameters of gefitinib met the acceptance interval of 0.80–1.25 for bioequivalence. The changes in log C_{max} and log AUC_{last} values after administration of 2 formulations of gefitinib in each subject are shown in **Fig. 3**. For most subjects, both log C_{max} and log AUC_{last} of each subject changed in a narrow range for the reference and test formulations. Oral administration of the test drug showed comparative C_{max} and AUC_{last} values for gefitinib compared to the reference drug.

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Safety

Fifty subjects who were enrolled in the study and received at least one dose of the investigational product were monitored for safety. A total of 10 subjects (20%) experienced 13 cases of AEs. There were 3 cases of AEs that were either probably related or possibly related to the investigational products, which were 2 cases of diarrhea and one case of folliculitis. The other 10 cases of AEs were unlikely to be related or not related to the investigational products.

Two subjects who had to take concomitant medication to treat their AEs were withdrawn from the study; one subject had an injury to the left wrist, and another subject had acute rhinitis and masticatory muscle disorder. The injury to the left wrist was not related to the investigational products, and the other 2 AEs were considered to be unlikely to be related; however, these AEs needed medical attention and the 2 subjects were dropped out from the study.

All of the AEs were of mild or moderate intensity, except one AE of a masticatory muscle disorder, which was of severe intensity. All subjects with AEs recovered without sequelae, and no serious AEs were observed.

DISCUSSION

A clinical study was conducted to evaluate the pharmacokinetics and safety of 2 formulations of gefitinib 250 mg for bioequivalence in healthy Korean male subjects.

The bioavailability of gefitinib is approximately 60% in humans when taken orally, regardless of food intake [22]. In previous pharmacokinetic studies, the C_{max} following a single oral dose of the original drug for gefitinib 250 mg was 141–183 ng/mL [13,23]. In this study, the C_{max} was 180.76 ng/mL for the reference formulation and 163.94 ng/mL for the test formulation. Additionally, the T_{max} with this dose was 5 hours (median value) for both reference and test formulations in this study. The $t_{1/2}$ of gefitinib was approximately 22–25 hours with a 250 mg single dose, which agreed with the literature-reported $t_{1/2}$ in healthy subjects [24]. Compared to previous studies, the pharmacokinetic parameters of this study demonstrated similar results. Furthermore, the 90% CIs for these pharmacokinetic parameters were within the commonly accepted bioequivalence limit of log 0.8 to log 1.25. The findings of this study suggest that the test and reference formulations of gefitinib 250 mg have similar pharmacokinetic characteristics. The test formulation met the regulatory criteria for assuming bioequivalence to the reference formulation for both AUC_{last} and C_{max}.

Most of the AEs associated with gefitinib therapy were mild or moderate in severity, such as diarrhea, dry skin, rash, nausea, and vomiting, and were usually reversible and manageable with appropriate intervention. Gefitinib is known to be well-tolerated in a phase 1 study, as the most frequent drug-related AEs were acne-like rash and diarrhea [14,25]. Both AEs were generally mild or moderate and reversible upon the cessation of treatment and even with continued use.

In this study, suspected drug-related AEs (2 cases of headache and one case of folliculitis) recovered without any additional medical treatment. In other words, the 2 formulations had no major safety issues and were well tolerated. However, this study was a bioequivalence study and had a limitation of targeting healthy Korean male subjects because of practical reasons; recruiting and assigning separate hospital wards for female subjects were difficult at

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the study site. Therefore, further studies in various populations, such as patients with NSCLC and women, are needed to fully evaluate the clinical efficacy and safety of gefitinib.

The intra-subject variability of gefitinib was reported mostly between 17% to 30%, with the largest value of 31.9% [13], and when sample size was calculated using the largest value, a sample size of 35 subjects would be adequate to assess the bioequivalence between the 2 drugs with a power of 80% at the significance level of 0.05. In this study, the drop-out rate was taken into consideration and 50 subjects were enrolled, and because 41 subjects had completed the study, this sample size was considered as adequate. Also, the washout interval in this study was set as 21 days because gefitinib has large inter-subject variability; even though most bioequivalence studies report $t_{1/2}$ of gefitinib between 18 to 26 hours, a few pharmacokinetic studies report the $t_{1/2}$ values as large as 32 to 40 hours [17,24] with high inter-subject variability up to 70% [13]. It is already known that polymorphisms in various metabolic enzymes such as CYP3A4 and 2D6 can contribute to the large inter-subject variability [11], but in this study, we did not investigate the effect of such polymorphism on gefitinib pharmacokinetics. Instead, to assure the complete washout of previously administered gefitinib, 21 days were selected as the washout interval.

In conclusions, the results of this study suggest that the test and reference formulation of 250 mg of gefitinib have similar pharmacokinetic characteristics and plasma concentration-time profiles. The test formulation met the regulatory criteria for assuming bioequivalence to the reference formulation for both AUC_{last} and C_{max}. As such, the test formulation Iretinib can be regarded as safe and well-tolerated in healthy Korean volunteers. It can be anticipated that the gefitinib test formulation will contribute to the treatment of Korean NCSLC patients.

REFERENCES

1. Kim HR, Jang JS, Sun JM, Ahn MJ, Kim DW, Jung I, et al. A randomized, phase II study of gefitinib alone versus nimotuzumab plus gefitinib after platinum-based chemotherapy in advanced non-small cell lung cancer (KCSG LU12-01). Oncotarget 2017;8:15943-15951.
PUBMED | CROSSREF
2. Salomon DS, Brandt R, Ciardiello F, Normanno N. Epidermal growth factor-related peptides and their receptors in human malignancies. Crit Rev Oncol Hematol 1995;19:183-232.
PUBMED | CROSSREF
3. Mitsui H, Nakajima J, Maruyama T, Hanajiri K, Omata M. Clinical efficacy and toxiciy of gefitinib in patients with lung cancer. Lancet 2003;361:1993.
PUBMED | CROSSREF
4. Simon GR, Ruckdeschel JC, Williams C, Cantor A, Chiappori A, Rocha Lima CM, et al. Gefitinib (ZD1839) in previously treated advanced non-small-cell lung cancer: experience from a single institution. Cancer Contr 2003;10:388-395.
PUBMED | CROSSREF
5. Nicholson RI, Gee JM, Harper ME. EGFR and cancer prognosis. Eur J Cancer 2001;37 Suppl 4:S9-S15.
PUBMED | CROSSREF
6. Cohen MH, Williams GA, Sridhara R, Chen G, Pazdur R. FDA drug approval summary: gefitinib (ZD1839) (Iressa) tablets. Oncologist 2003;8:303-306.
PUBMED | CROSSREF
7. Luo J, Ni L, Wang M, Zhong W, Xiao Y, Zheng K, et al. Pharmacokinetic analysis of gefitinib in a patient with advanced non-small cell lung cancer undergoing hemodialysis. Thorac Cancer 2016;7:251-253.
PUBMED | CROSSREF
8. Tanović A, Alfaro V. Gefitinib: current status in the treatment of non-small cell lung cancer. Drugs Today (Barc) 2004;40:809-827.
PUBMED | CROSSREF

9. Thomas SM, Grandis JR. Pharmacokinetic and pharmacodynamic properties of EGFR inhibitors under clinical investigation. Cancer Treat Rev 2004;30:255-268.
PUBMED | CROSSREF
10. Thatcher N, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 2005;366:1527-1537.
PUBMED | CROSSREF
11. Cantarini MV, Bailey CJ, Collins B, Smith RP. The relative bioavailability of gefitinib administered by granular formulation. Cancer Chemother Pharmacol 2008;62:203-208.
PUBMED | CROSSREF
12. Chen Y, Zhou D, Tang W, Zhou W, Al-Huniti N, Masson E. Physiologically based pharmacokinetic modeling to evaluate the systemic exposure of gefitinib in CYP2D6 ultrarapid metabolizers and extensive metabolizers. J Clin Pharmacol 2018;58:485-493.
PUBMED | CROSSREF
13. Zhang H, Li Q, Zhu X, Wu M, Li C, Li X, et al. Association of variability and pharmacogenomics with bioequivalence of gefitinib in healthy male subjects. Front Pharmacol 2018;9:849.
PUBMED | CROSSREF
14. Baselga J, Rischin D, Ranson M, Calvert H, Raymond E, Kieback DG, et al. Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. J Clin Oncol 2002;20:4292-4302.
PUBMED | CROSSREF
15. Culy CR, Faulds D. Gefitinib. Drugs 2002;62:2237-2248.
PUBMED | CROSSREF
16. Wu SG, Shih JY. Management of acquired resistance to EGFR TKI-targeted therapy in advanced non-small cell lung cancer. Mol Cancer 2018;17:38.
PUBMED | CROSSREF
17. Cantarini MV, McFarquhar T, Smith RP, Bailey C, Marshall AL. Relative bioavailability and safety profile of gefitinib administered as a tablet or as a dispersion preparation via drink or nasogastric tube: results of a randomized, open-label, three-period crossover study in healthy volunteers. Clin Ther 2004;26:1630-1636.
PUBMED | CROSSREF
18. Zhao M, Hartke C, Jimeno A, Li J, He P, Zabelina Y, et al. Specific method for determination of gefitinib in human plasma, mouse plasma and tissues using high performance liquid chromatography coupled to tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 2005;819:73-80.
PUBMED | CROSSREF
19. U.S. Department of Health and Human Services, Food Drug Administration (FDA), Center for Drug Evaluation Research (CDER), Center for Veterinary Medicine (CVM). Guidance for industry, bioanalytical method validation. Rockville (MD): FDA, CDER, CVM; 2001.
20. Ministry of Food and Drug Safety. Bioequivalence guideline in Korea. Cheongju: Ministry of Food and Drug Safety; 2011.
21. Kutner MH. Applied linear statistical models. Boston (MA): McGraw-Hill Irwin; 2005.
22. Rahman AF, Korashy HM, Kassem MG. Gefitinib. Profiles Drug Subst Excip Relat Methodol 2014;39:239-264.
PUBMED | CROSSREF
23. Chhun S, Verstuyft C, Rizzo-Padoin N, Simoneau G, Becquemont L, Peretti I, et al. Gefitinib-phenytoin interaction is not correlated with the C-erythromycin breath test in healthy male volunteers. Br J Clin Pharmacol 2009;68:226-237.
PUBMED | CROSSREF
24. Greenhalgh J, Dwan K, Boland A, Bates V, Vecchio F, Dundar Y, et al. First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. Cochrane Database Syst Rev 2016:CD010383.
PUBMED | CROSSREF
25. Herbst RS, Maddox AM, Rothenberg ML, Small EJ, Rubin EH, Baselga J, et al. Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in non-small-cell lung cancer and other solid tumors: results of a phase I trial. J Clin Oncol 2002;20:3815-3825.
PUBMED | CROSSREF