

# Effects of Ketoconazole on the Pharmacokinetics of Lenvatinib (E7080) in Healthy Participants

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## Abstract

**Background:** Lenvatinib is an oral, multitargeted, tyrosine kinase inhibitor under clinical investigation in solid tumors. In vitro evidence indicates that lenvatinib metabolism may be modulated by ketoconazole, an inhibitor of CYP3A4 and p-glycoprotein.

**Methods:** In this Phase I, single-center, randomized, open-label, two-period, crossover study, healthy adults (18–55 years; N = 18) were randomized to one of two sequences (ketoconazole → placebo or vice versa). Ketoconazole (400 mg) or placebo was administered orally once daily for 18 days; a 5 mg dose of lenvatinib was orally administered on Day 5 of each treatment period. Blood samples were collected over 14 days and lenvatinib plasma concentrations measured by high-performance liquid chromatography/tandem mass spectrometry.

**Results:** Systemic exposure to lenvatinib increased slightly (15–19%) with coadministration of ketoconazole. Although the 90% confidence interval (CI) for area under the plasma concentration–time curve (AUC) was within the prespecified bioequivalence interval of 80–125%,  $C_{max}$  slightly exceeded the 125% CI bound (134%). No changes in  $t_{max}$ ,  $t_{lag}$ , or  $t_{1/2}$  were observed. Thirteen subjects (72%) experienced treatment-emergent adverse events (11 mild, 2 moderate), most commonly headache (22%) and diarrhea (17%).

**Conclusions:** Lenvatinib exposure was slightly increased by ketoconazole; however, the magnitude of the change was relatively small, and likely not clinically meaningful.

## Keywords

E7080, lenvatinib, CYP3A4, pharmacokinetics, ketoconazole

Aberrant tyrosine-kinase-mediated signaling of multiple pathways critical for the regulation of apoptosis, cell proliferation, cellular metabolism, and angiogenesis has been implicated in tumorigenesis and progression in several solid tumor types.<sup>1</sup> These pathways include those mediated by vascular endothelial growth factor receptors (VEGFRs), fibroblast growth factor receptors (FGFRs), and platelet-derived growth factor receptors (PDGFRs). Several tyrosine kinase inhibitors (TKIs) of these pathways are currently available or in development for the treatment of multiple malignancies.<sup>1</sup> Drug interaction studies have shown that many TKIs are primarily metabolized by cytochrome P450 3A4 (CYP3A4), resulting in significant changes in drug exposure during concomitant use with strong CYP3A4 inducers or inhibitors.<sup>2–6</sup>

Lenvatinib is an orally active, multitargeted TKI that blocks VEGFRs 1,2,3, FGFRs 1,2,3,4, PDGFR- $\alpha$ , RET, and KIT.<sup>7,8</sup> Lenvatinib is currently being clinically evaluated in several solid tumor types. In Phase I and

II studies, lenvatinib has demonstrated antitumor activity and manageable toxicity as a single agent at a maximum tolerated dose of 25 mg/day.<sup>9–11</sup>

Lenvatinib pharmacokinetics (PK) have been studied in humans following single- and multiple-dose oral administration. Following a single dose, lenvatinib is

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rapidly absorbed with an observed time to maximum concentration ( $t_{\max}$ ) typically occurring between 1 and 4 hours.<sup>12</sup> Oral clearance is similar for doses between 0.8 mg to 32 mg and ranges from 4.2 L/h to 7.1 L/h. Renal clearance is a minor contributor to oral clearance ( $\sim 1\text{--}2\%$ ). The terminal exponential half-life ( $t_{1/2,z}$ ) is  $\sim 28$  hours. The terminal volume of distribution across these doses ranges from 50.5 L to 163 L. Upon multiple dosing, exposure (area under the plasma concentration–time curve [AUC]) and maximum plasma concentration ( $C_{\max}$ ) increases proportionally with dose. A Phase I dose-escalation study of lenvatinib determined that at steady-state for clinically relevant doses (12- to 32-mg dose range) there is minimal accumulation (mean accumulation ratios 0.96–1.28, Eisai data on file).

In vitro and in vivo studies have shown that lenvatinib is eliminated via both the liver and kidney, primarily by excretion in bile.<sup>13,14</sup> A radiolabeled human mass balance study of lenvatinib found that  $\sim 64\%$  of the radioactive dose was recovered in the feces and  $\sim 25\%$  in urine.<sup>13</sup> Intact lenvatinib, either recovered in urine or feces, accounted for only  $\sim 2\%$  of the administered dose.<sup>13</sup> In human liver microsomes, the demethylated metabolite of lenvatinib (M2) was identified as the major metabolite. Although in vitro data indicated that lenvatinib is a substrate for P-glycoprotein, recent results showed that there were no clinically important alterations in lenvatinib exposure following coadministration of lenvatinib with rifampin.<sup>15</sup> In an in vitro study using human liver microsomes and human recombinant CYPs over a lenvatinib concentration range of 0.1–10  $\mu\text{g/mL}$ , CYP3A4 was the predominant ( $>80\%$ ) CYP isoform involved in the CYP-mediated metabolism of lenvatinib (Eisai data on file).

The broad-spectrum antifungal agent ketoconazole is a potent and specific inhibitor of CYP3A4,<sup>16</sup> and a p-glycoprotein inhibitor.<sup>17</sup> At therapeutic doses, ketoconazole has been shown to significantly alter plasma concentrations of CYP3A4 substrates.<sup>18,19</sup> Assuming CYP3A4-mediated metabolism accounts for  $\sim 80\%$  of lenvatinib total clearance, ketoconazole inhibition of CYP3A4 could result in a  $\geq 90\%$  reduction in CYP3A4-mediated metabolism of lenvatinib<sup>19</sup> and increase lenvatinib half-life ( $t_{1/2}$ )  $\geq 3$ -fold. Ketoconazole was routinely used to evaluate drug interactions involving CYP3A4 inhibition mechanisms, including TKIs,<sup>2–4,20,21</sup> until October 16th 2013, when the United States Food and Drug Administration (FDA) recommended the use of alternate CYP3A inhibitors due to the risk of serious side effects with ketoconazole use. This study was designed and conducted prior to the FDA advisory.

The objective of this Phase I study was to evaluate the influence of ketoconazole on the PK profile of lenvatinib. The study followed the 2006 United States Food and Drug Administration Guidance for drug-interaction studies.<sup>21</sup>

## Methods

### Study Design

This was a single-center, randomized, open-label, 2-period, crossover study conducted at the Charles River Clinical Services Northwest, Inc., Tacoma, WA, USA. The study was conducted in accordance with the International Conference on Harmonisation guidelines and in compliance with local and national regulations. The protocol and informed consent form received approval from a duly constituted institutional review board (Alpha Independent Review Board, San Clemente, CA) before any subjects were enrolled. All subjects provided written informed consent.

### Subjects

Healthy, nonsmoking, male or female (not pregnant or lactating) subjects between the ages of 18 and 55 years who had a body mass index of  $\geq 18\text{--}30 \text{ kg/m}^2$  were enrolled. Women of childbearing potential, and men who were partners of women of childbearing potential, agreed to use a medically acceptable contraceptive method for at least 30 days after the last dose of study drug. Subjects with clinically significant systemic diseases or abnormalities, or a known history of any gastrointestinal surgery that could impact the PK of lenvatinib were excluded. Additional exclusion criteria included clinically significant illness within 8 weeks of lenvatinib administration or infection within 4 weeks, clinically significant electrocardiogram (ECG) abnormality, history of drug or food allergies or current seasonal allergy, use of prescription drugs within 4 weeks or over-the-counter medications within 2 weeks, history of drug or alcohol misuse, positive test for human immunodeficiency virus or hepatitis A, B, or C, recent weight change  $>10\%$  or participation in heavy exercise, or hemoglobin levels  $<12.0 \text{ g/dL}$ . Individuals who had taken CYP3A4 inhibitors/inducers within 2 weeks (e.g., alcohol, grapefruit, grapefruit juice, grapefruit-containing beverages, apple or orange juice, vegetables from the mustard green family [kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard], and charbroiled meats) of study drug administration were excluded from participating.

### Treatments

Subjects were randomly allocated to one of two treatment sequences with a 14-day washout between treatments, and with 33 days between administrations of lenvatinib. Excluding the fifth day of each period, ketoconazole (single 400-mg capsule formulation) or placebo was administered orally once daily, 1 hour before breakfast, for 18 days. A single oral 5-mg dose of lenvatinib ( $1 \times 4\text{-mg} + 1 \times 1\text{-mg}$  capsule formulation) was co-administered with 400-mg ketoconazole on the fifth day of each treatment period. Subjects were

administered lenvatinib and ketoconazole (or placebo) after a 10-hour fast, were not allowed to eat for 4 hours thereafter, and were required to maintain an upright position. The 5-mg lenvatinib dose was selected to provide an adequate safety margin in case of a significant interaction with ketoconazole. All drugs were administered with 8 ounces (240 mL) of water.

### Blood Sampling

Serial blood samples in heparinized tubes for lenvatinib analysis were collected predose and at 0.5, 1, 2, 3, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, 168, 240, 288, and 336 hours after dosing in each treatment period.

### Bioanalytical Methods

Blood samples for the determination of plasma concentrations of lenvatinib were collected in heparinized tubes, and plasma samples were stored at  $\leq -20^{\circ}\text{C}$  prior to analysis by WuXi AppTec, Inc., Shanghai, China using a validated assay. For each sample, 100  $\mu\text{L}$  plasma volume was prepared by solid phase extraction using Waters MCX (10 mg, 30  $\mu\text{m}$ ) cartridges in a 96-well plate format with an analog internal standard, followed by separation of the analyte using high-performance liquid chromatography (HPLC) on a C18 column. A gradient flow was set up with mobile phases consisting of 0.5% formic acid in water and 0.5% formic acid in acetonitrile/methyl alcohol (25:75, v/v). Eluting compounds were detected by tandem mass spectrometry in the multiple reaction monitoring (MRM) positive ion mode using atmospheric pressure chemical ionization (APCI). Lenvatinib mass transition was from 427.10  $\rightarrow$  370.10; the analog internal standard from 431.10  $\rightarrow$  372.10. The total run time was 3.7 minutes. The linear range for lenvatinib was 0.250–250 ng/mL in plasma. The accuracy and precision based on interday and intraday measurements were within 86.0–115.2% and 0.7–8.8%, respectively. The interference check for ketoconazole was tested with no impact on the quantitation of lenvatinib.

### Pharmacokinetic Methods

PK parameters were calculated using a non-compartmental PK analysis with WinNonlin<sup>®</sup> version 6.2 (Pharsight Corporation, Mountain View, CA).<sup>22</sup> Samples below the lower limit of quantification were treated as 0 for the estimation of the mean concentration–time profile. The terminal exponential rate constant ( $\lambda_z$ ) was determined using linear least-squares regression of the terminal phase of the log concentration–time profile. The  $t_{1/2,z}$  was obtained as  $0.693/\lambda_z$ .  $\text{AUC}_{0-t}$  was determined up to the last observed quantifiable concentration, using the linear-up and log-down trapezoidal rule.  $\text{AUC}_{0-\infty}$  was the sum of  $\text{AUC}_{0-t}$  and  $\text{AUC}_{\text{ext}}$  and was obtained based on the last observed quantifiable plasma concentration and  $\lambda_z$ .  $C_{\text{max}}$  and  $t_{\text{max}}$  were determined from visual inspection of the

concentration–time data. The lag time ( $t_{\text{lag}}$ ) was determined as the time point immediately prior to the first quantifiable concentration. Apparent oral clearance ( $\text{CL}/F$ ) and the apparent terminal volume of distribution ( $V_z/F$ ), uncorrected for bioavailability, were determined using standard equations.

### Safety Assessments

Adverse events (AEs) were monitored on a daily basis and were graded by the investigator on a 3-point scale (mild, moderate, severe) in terms of severity, and in terms of causality related to the study drug. Vital signs (blood pressure, heart rate, body temperature, respiratory rate) were recorded prior to PK blood samples collection. Additional safety assessments, including clinical laboratory testing, 12-lead ECGs, and physical examinations, were made during baseline periods, before each dose, and prior to discharge.

### Statistics

Statistical analyses were performed using SAS software, version 9.2 (Cary, NC). A linear mixed-effects model with log-transformed PK parameters as response was used to estimate the ratios of geometric means and associated two-sided 90% confidence intervals (CIs) for AUC and  $C_{\text{max}}$ . The model included terms for treatment, sequence and period as fixed effects and subject nested within sequence as a random effect. If the 90% CIs fell within the range of 80–125%, then the test was considered to be bioequivalent to the reference and an absence of drug interaction could be concluded. Assuming a ratio of 1.05 between treatments and an intrasubject coefficient of variance of 14% for lenvatinib  $C_{\text{max}}$  (Phase 1 dose-escalation study, Eisai data on file), a sample size of 14 completing subjects would provide a power of 90% to conclude bioequivalence. Other PK parameters and plasma lenvatinib concentrations by time point were summarized using descriptive statistics.

Safety parameters were evaluated descriptively for all subjects who received study drug and had at least one safety assessment postdose. AEs were classified into standardized terminology using the Medical Dictionary for Regulatory Activities (version 14.0). Other parameters, including baseline subject characteristics, were also evaluated descriptively.

## Results

### Subjects

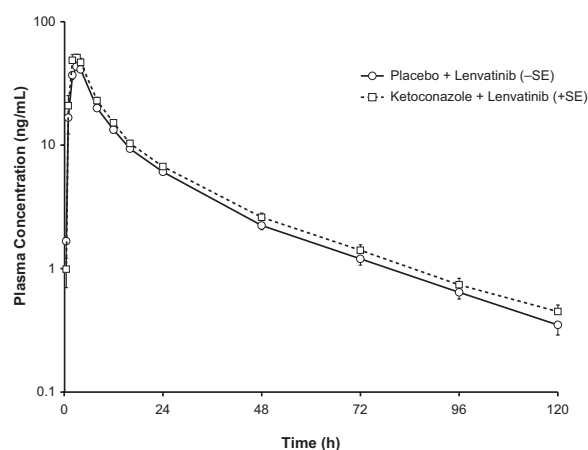
Eighteen subjects were randomized, with 16 subjects completing both periods of the study. One subject was discontinued before entering treatment Period 2 due to a positive drug test and one withdrew informed consent after receiving three doses of ketoconazole in Period 2. The pharmacokinetic analysis set therefore included

16 subjects, while the safety analysis set consisted of 17 subjects in the lenvatinib + placebo group, and 18 subjects in the lenvatinib + ketoconazole group. The median age of the enrolled subjects was 28.5 years (range: 19–53 years), and the subjects were predominantly male (83%) and white (61%). The median weight of the subjects was 78.5 kg (range: 58–93 kg), with a median body mass index of 24.3 kg/m<sup>2</sup> (range, 20–28 kg/m<sup>2</sup>). Overall, demographic and baseline characteristics were similar across treatment sequences.

### Pharmacokinetics

Lenvatinib was rapidly absorbed under both treatment conditions (placebo or ketoconazole), with  $C_{max}$  achieved at a median of 3 hours (Table 1). Plasma concentrations were quantifiable for >50% of subjects for up to 144 hours after dosing (Fig. 1). Lenvatinib plasma concentration-time profile appeared biphasic following achievement of the peak concentration with a  $t_{1/2,z}$  of approximately 29 hours for each treatment. The percent extrapolation of  $AUC_{0-\infty}$  was <4% across all subjects.

Mean  $AUC_{0-\infty}$  and  $AUC_{0-t}$  were about 15% greater following coadministration of ketoconazole with lenvatinib than placebo (Table 1). Similarly, exposure based on the observed  $C_{max}$  was 19% greater in the lenvatinib plus



**Figure 1.** Semi-log plot of mean (standard error [SE]) lenvatinib plasma concentration versus time by treatment following oral administration of 5 mg of lenvatinib plus placebo or 5 mg of lenvatinib plus 400 mg of ketoconazole.

ketoconazole treatment. The 90% CIs of the geometric least squares mean ratios for the AUCs were within the 80–125% CI, which is generally considered to denote bioequivalence, while the upper bound of the interval for

**Table 1.** Pharmacokinetic Parameters for Lenvatinib (5 mg) When Administered in Combination With Ketoconazole (400 mg/day) or Placebo

Parameter	5 mg Lenvatinib + Placebo [A] (n = 16)	5 mg Lenvatinib + Ketoconazole [B] (n = 16)
	Arithmetic mean (SD)	
$C_{max}$ (ng/mL)	45.08 (11.70)	54.56 (20.30)
$AUC_{(0-t)}$ (ng • h/mL)	571.19 (99.26)	661.00 (146.92)
$AUC_{(0-\infty)}$ (ng • h/mL)	584.31 (100.85)	675.69 (147.63)
$t_{max}$ (h)	3.13 (0.81) <sup>a</sup>	2.56 (0.51) <sup>d</sup>
$t_{lag}$ <sup>a</sup> (h)	0.16 (0.24) <sup>b</sup>	0.06 (0.17) <sup>e</sup>
$t_{1/2}$ (h)	27.82 (6.97) <sup>c</sup>	28.33 (7.75) <sup>f</sup>
CL/F (L/h)	8.78 (1.40)	7.70 (1.49)
Vz/F (L)	347.13 (89.07)	313.09 (101.73)
	Geometric mean (%CV)	
$C_{max}$ (ng/mL)	43.74 (25.66)	51.22 (38.31)
Geometric LS mean ratio (90% CI)	B/A: 118.69 (105.34–133.74)	
$AUC_{(0-t)}$ (ng • h/mL)	563.56 (16.85)	647.05 (21.18)
Geometric LS mean ratio (90% CI)	B/A: 114.52 (108.21–121.20)	
$AUC_{(0-\infty)}$ (ng • h/mL)	576.59 (16.77)	661.88 (20.83)
Geometric LS mean ratio (90% CI)	B/A: 114.51 (108.48–120.88)	

AUC, area under the plasma concentration–time curve; CI, confidence interval; CL/F, oral clearance;  $C_{max}$ , maximum plasma concentration; CV, coefficient of variation; LS, least squares;  $t_{lag}$ , lag time;  $t_{1/2}$ , terminal exponential half-life;  $t_{max}$ , time the maximum concentration occurred; Vz/F, terminal volume of distribution, uncorrected for bioavailability.

<sup>a</sup> $t_{max}$  median (range) 3.00 (2.00–4.00).

<sup>b</sup> $t_{lag}$  median (range) 0.00 (0.00–0.50).

<sup>c</sup> $t_{1/2}$  median (range) 28.96 (9.00–36.17).

<sup>d</sup> $t_{max}$  median (range) 3.00 (2.00–3.00).

<sup>e</sup> $t_{lag}$  median (range) 0.00 (0.00–0.50).

<sup>f</sup> $t_{1/2}$  median (range) 29.21 (8.21–40.60).

$C_{\max}$  was 133.7%. Based on visual assessment, no difference in  $t_{\max}$ ,  $t_{1/2}$ , or  $t_{\text{lag}}$  was observed between the two treatments. Consistent with the slightly higher lenvatinib exposure, a slightly lower apparent mean clearance ( $\sim 12\%$ ) and volume of distribution ( $\sim 10\%$ ) were observed in the ketoconazole treatment group (Table 1).

### Safety

Thirteen (72%) subjects reported treatment-emergent AEs (TEAEs), including eight subjects (44%) following the administration of ketoconazole with lenvatinib and 10 subjects (59%) following the administration of placebo with lenvatinib, most commonly headache (22%) and diarrhea (17%). Four subjects (22%) had treatment-related TEAEs: three subjects following the administration of ketoconazole with lenvatinib (nausea, increased alanine aminotransferase [ALT], increased aspartate aminotransferase [AST], and dysmenorrhea) and one subject following the administration of placebo with lenvatinib (dry mouth and dyspnea). All TEAEs were mild in severity except for one subject in the ketoconazole group with moderate dysmenorrhea and one subject in the placebo group with moderate presyncope. No serious TEAEs were reported.

Overall, no treatment-related trends were observed in any safety parameters. Mean vital sign measurements after dosing were similar to those at baseline, and all ECG results were either normal or considered not clinically significant. Mean hematology and clinical chemistry values were within reference ranges, and mean values before each dose of study drug were similar to those at the end of the study. Shift analyses from normal at baseline to abnormal at study termination revealed no shifts of clinical concern for hematology, clinical chemistry, or urinalysis parameters. Furthermore, except for one ketoconazole subject with increased ALT and AST, no abnormal clinical laboratory results were reported as TEAEs.

### Discussion

The PK profile of lenvatinib following administration of a single 5-mg dose in this study was generally consistent with previous observations in healthy volunteers where the median  $t_{\max}$  was 2 hours (range: 1–4 hours), the mean  $t_{1/2}$  was 27.6 hours (range: 11–57 hours), the mean  $C_{\max}$  was 144.5 ng/mL, and  $AUC_{0-\infty}$  was 1409 ng·h/mL.<sup>12</sup> Although earlier in vitro studies indicated that oxidative metabolism of lenvatinib was primarily mediated via CYP3A4, oxidative metabolism does not appear to be a major pathway involved in lenvatinib clearance since changes in oral clearance in this study and in another study with rifampin<sup>15</sup> are minimal. It may be possible that there are multiple pathways involved in lenvatinib metabolism.

In this study, coadministration of ketoconazole with lenvatinib increased lenvatinib  $C_{\max}$  by 19% and both  $AUC_{0-t}$  and  $AUC_{0-\infty}$  by 15% compared with placebo. These increases are lower than increases observed for other TKIs in similar Phase I studies. For example, ketoconazole coadministration increased imatinib  $C_{\max}$  by 26% and AUC by 40%,<sup>3</sup> and nilotinib  $C_{\max}$  by 84% and AUC by more than 200%.<sup>2</sup> The slight increase in lenvatinib exposure with ketoconazole may be related to a decrease in first-pass (intestinal and/or hepatic) metabolism since no change in  $t_{1/2}$  was observed.

Safety data from this study indicated that single-dose lenvatinib (5 mg) had an acceptable safety profile when administered to healthy subjects alone or in combination with ketoconazole. There were no clinically significant safety or laboratory changes associated with the dosing combination. Mild or moderate headache and gastrointestinal toxicities were the most common TEAEs. Hypertension, which has been reported in lenvatinib studies in patients with advanced solid tumors<sup>9,10</sup> and for other VEGFR inhibitors, was not observed.

In conclusion, the results of this study show that exposure to single-dose lenvatinib in healthy volunteers increased by 15–19% when taken in combination with ketoconazole. Based on the minimal changes in lenvatinib systemic exposure, CYP3A4 (and other CYP)-mediated metabolism appears to not have a major role in lenvatinib's overall metabolism/total clearance in humans. Based on these results, the coadministration of lenvatinib with CYP3A4 inhibitors appears not likely to result in clinically important alterations in lenvatinib exposure.

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### Declaration of Conflicting Interests

J. Fan is now an employee of Boehringer-Ingelheim Pharmaceuticals, Inc., Ridgefield, CT. R. Shumaker, J. Aluri, G. Martinez, and M. Ren are employees of Eisai, Inc. J. Fan is a former employee of Eisai, Inc. G.A. Thompson is a consultant to Eisai, Inc. and a Fellow of the American College of Clinical Pharmacology.

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