Intrapulmonary Pharmacokinetics and Pharmacodynamics of Posaconazole at Steady State in Healthy Subjects

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ABSTRACT

We evaluated the pharmacokinetics (PK) and pharmacodynamics (PD) of posaconazole (POS) in a prospective, open-label study. Twenty-five healthy adults received 14 doses of POS oral suspension 400 mg twice daily with a high-fat meal over 8 days. Pulmonary epithelial lining fluid (ELF) and alveolar cell (AC) samples were obtained via bronchoalveolar lavage, and blood samples were collected during the 24 h after the last dose. POS concentrations were determined using liquid chromatography with tandem mass spectrometry parameters. The maximum concentrations ($C_{\text{max}}$) (mean ± SD) in plasma, ELF, and AC were 2.08 ± 0.93, 1.86 ± 1.30, and 87.7 ± 65.0 µg/ml. POS concentrations in plasma, ELF, and AC did not decrease significantly, indicating slow elimination after multiple dosing. Mean concentrations of POS in plasma, ELF, and AC were above the MIC$_{90}$ (0.5 µg/ml) for Aspergillus species over the 12-h dosing interval and for 24 hours following the last dose. Area under the curve (AUC$_{0-12h}$) ratios for ELF/plasma and AC/plasma were 0.84 and 33. AUC$_{0-24h}$ /MIC$_{90}$ ratios in plasma, ELF, and AC were 87.6, 73.2, and 2860. Nine (36%) of 25 subjects had treatment-related adverse events during the course of the study, which were all mild or moderate. We conclude that a dose of 400 mg BID resulted in sustained plasma, ELF, and AC concentrations above the MIC$_{90}$ for Aspergillus spp. during the dosing interval. The intrapulmonary PK/PD of POS is favorable for treatment or prevention of aspergillosis, and oral POS was well tolerated in healthy adults.

INTRODUCTION

Posaconazole (POS) is a triazole antifungal agent with broad-spectrum activity against Aspergillus, Cryptococcus, Candida, Histoplasma, and Blastomyces spp. and others (12,
Use of POS has been approved for prophylaxis of invasive aspergillosis and candidiasis in immunocompromised patients and the treatment of refractory oropharyngeal candidiasis in the United States and is undergoing clinical development for the treatment of pulmonary and disseminated mycoses.

The pharmacokinetics (PK) of POS has been extensively studied. The oral bioavailability of POS is increased significantly by divided dosing and administration with a high-fat meal (11, 13). POS is metabolized in the liver to glucuronides that are microbiologically inactive; however, POS does not have any major circulating CYP450-mediated metabolites. POS is primarily excreted unchanged in feces (14). A high apparent volume of distribution of 1774 L suggests that posaconazole is widely distributed into body tissues (Krishna, G., and A. Sansone-Parsons. 41st American Society of Health-System Pharmacists Midyear Clinical Meeting and Exhibition. December 3-7, 2006, Anaheim, Calif). It has a long half-life of approximately 35 h at steady state (Krishna, G., and A. Sansone-Parsons. 41st American Society of Health-System Pharmacists Midyear Clinical Meeting and Exhibition. December 3-7, 2006, Anaheim, Calif). Mild to moderate renal impairment has no significant effect on the PK parameters, and dose correction is not required for patients with renal impairment (10). Protein binding in humans is >98%.

POS exhibits dose-proportional kinetics up to a daily dose of 800 mg. Increasing the dose of posaconazole to 1200 mg per day results in no further increase in the plasma concentrations; therefore absorption is saturated at a daily dose of 800 mg (9). Although POS is approved in the European Union and in clinical development in the United States for the treatment of pulmonary aspergillosis, the intrapulmonary PK and pharmacodynamics (PD) of POS have not been reported.
METHODS

Study design and subjects. This was a randomized, open-label study to measure the steady state plasma, epithelial lining fluid (ELF), and pulmonary alveolar cell (AC) concentrations of POS. Participation of subjects was voluntary and willingness to comply with study procedures was expressed through written informed consent. The study was conducted in the General Clinical Research Center (GCRC) at the University of California, San Francisco. Subjects were randomized to five groups of five subjects each, with bronchoscopy times at 3, 5, 8, 12, and 24 h post final dose. The 24-h sampling period was selected to evaluate the possibility of an extended intrapulmonary half-life. Volunteers received a total of 14 doses of POS, administered as an oral suspension of 400 mg every 12 h for 8 days.

Subjects were required to be 21 to 55 years of age; have a body mass index (BMI) of 18 to 29 kg/m²; be in good health based on a normal screening evaluation; and be using contraception. The screening evaluation included a medical history and physical examination, electrocardiography, and clinical laboratory tests (complete blood count with differential, platelet count, blood urea nitrogen, serum creatinine, alkaline phosphatase, total bilirubin, albumin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], serum pregnancy test for women of child-bearing age, and urinalysis, including microscopy and screening for abuse of drugs). Subjects were excluded who were taking any medication other than vitamins and hormonal contraceptives; had a significantly abnormal electrocardiogram (ECG); had laboratory test results significantly out of normal range; had a positive result for drug screening, history of substance abuse, or smoking within 1 year before study enrollment; had a
positive test result for HIV, hepatitis C antibody, or hepatitis B surface antigen;
underwent major surgery within the 6 months preceding study enrollment; had a positive
pregnancy test result or planned to be pregnant or breast-feeding within 30 days after the
study; had an allergy or sensitivity to POS or other azole or triazole drugs or to lidocaine;
were participating in another clinical study or used an investigational product or drug in
the 30 days preceding enrollment.

Enrolled subjects were seen for a second visit at the GCRC no more than 28 days after the
screening visit. At the second visit, subjects received their first dose of study drug, were
observed for 30 min for adverse effects (AEs), and were given written instructions to take
the drug after a high-fat meal, every 12 h, for the following 6 days. The subjects were also
given a study diary to record, twice daily, the time at which they completed the high-fat
meal, the time that the dose of posaconazole was taken and symptoms that were
experienced after taking the study drug. The diary was collected and reviewed at the third
visit. At visit 3, on the eighth day, subjects received their last dose of study medication in
the GCRC; the laboratory tests and electrocardiography were repeated; and blood samples
were drawn for each subject at 0, 3, 5, 8, 12, and 24 h after the final dose. Each subject
underwent one bronchoscopy after the last dose at a time determined by the
randomization schedule. The subjects were then given a form with instructions that
included body temperature monitoring and symptom reporting every 4 hours for 24 hours
post-BAL. This form was returned to the investigators by mail.

Bronchoscopy and bronchoalveolar lavage. Standardized bronchoscopy and
bronchoalveolar lavage (BAL) (4-7) were performed in the GCRC at 3, 5, 8, 12, or 24 h
after the administration of the last dose of POS. Topical anesthesia with lidocaine was
used. As we previously reported, systemic sedation was not administered (4-7). A fiber-
optic bronchoscope (PENTAX FB-18BS; Montvale, New Jersey) was inserted into the
right middle lobe. Four 50-ml aliquots of sterile 0.9% saline were infused, and each
aliquot was immediately aspirated into a trap. The average duration of bronchoscopy was
approximately 4 min. The first aspirate was discarded. The aspirates from the second,
third, and fourth instillations were pooled and iced. The volume of the BAL was
measured and recorded. A measured volume (30 ml) of the BAL was immediately spun in
a polypropylene tube at 400 × g for 5 min in a refrigerated (4°C) centrifuge (Sigma
4K15). The supernatants and the cell pellet were separated into two equal samples and
frozen at –70°C until assay. A small aliquot of the supernatant was frozen separately for
urea assay.

**Blood samples.** Blood was obtained for drug assay before administration of the first dose
and the last dose and at the completion of BAL. Blood samples (10 ml each) were
collected into ethylenediaminetetraacetate salt–containing tubes and placed in ice until
centrifugation. The tubes were then spun at 1300 g for 10 minutes in a Sigma 4K15
refrigerated centrifuge (4°C). Plasma was separated and frozen at least –20°C until assay.

**POS Assay.** POS concentrations in plasma, BAL fluid, and AC were assayed using
sensitive and specific validated liquid chromatography with tandem mass spectrometry
(LC-MS/MS). Lung aspirates and cell pellets were quantitated against a human plasma
calibration curve. These samples were analyzed using the human plasma method, but the
extraction was different. A 100-µl sample of lung aspirate fluid was divided in aliquot
portions into a separate tube. To each aliquot, 67 µl methanol was added and mixed, and a
100-µl aliquot was taken for extraction. A dilution factor of 1.67 was applied to the
results. To analyze the cell pellets, 200 µl methanol was added directly to the sample tubes. The samples were subjected to vortex, subjected to sonication for 10 min, and transferred to a centrifuge snap-cap tube. The samples were centrifuged at 13860 g (estimated) for 10 min. The liquid layer of the sample was then transferred to a 96-well block, and 50 µl reagent water was added to each sample before injection. The samples were analyzed using an LC-MS/MS method at PPD Inc (Richmond, Virginia). The lower limit of quantitation for this assay was 1.00 ng/ml, and the calibration range was 1.00 to 4000 ng/ml. For calibration standards, the accuracy (%bias) ranged from –7.02% to 5.93%, and precision (percentage coefficient of variation) ranged from 2.51% to 12.0%. For quality control runs (5 levels: 3.00, 150, 750, 1500, and 3000 ng/ml), accuracy ranged from –4.17% to 12.8% and precision ranged from 2.29% to 14.8%. The percentage of unbound drug in plasma was calculated from the following formula:

unbound fraction = 0.015 × total concentration. Unbound drug concentrations in ELF and AC were not calculated because the extent of protein binding in these compartments is unknown.

The BAL supernatant was assayed for urea concentration using a modified enzymatic assay (Infinity BUN Reagent, enzymatic determination No. 63-UV, Sigma Diagnostics, St. Louis, MO). The assay was linear throughout the range of urea concentrations present in the BAL samples (data not shown).

The volume of ELF in BAL fluid, the concentration of antibiotics in the ELF, and the concentration of antibiotics in alveolar cells were derived using methods and calculations that we have previously reported (4-7).
PK and PD analysis. The analysis was performed using the Pharsight® knowledgebase Server™: Version 2.0.1 with WinNonlin® Version 4.0.1 (Pharsight Corporation, Cary, North Carolina). The plasma concentration–time data set for each individual was used to calculate the maximum observed concentration ($C_{\text{max}}$), the time to the maximum concentration ($T_{\text{max}}$), the area under the concentration–time curve over the dosing interval ($\text{AUC}_{0-12h}$), trough concentration immediately before the last dose ($C_{\text{min}}$), and the terminal phase half-life ($t_{\frac{1}{2}}$). For ELF and AC, the individual subject concentrations at each collection time point were averaged, and the mean data were used to calculate $C_{\text{max}}$, $T_{\text{max}}$, AUC, $C_{\text{min}}$, and $t_{\frac{1}{2}}$.

The analysis was performed using a model-independent method. For each subject, the terminal phase rate constant ($k$) was calculated as the negative of the slope of the log-linear terminal portion of the plasma concentration–time curve using linear regression. The $\text{AUC}_{0-\infty}$ was calculated using the linear trapezoidal method and was extrapolated to infinity. The $t_{\frac{1}{2}}$ was calculated from $0.693/k$, and the value was not reported because the extrapolated portion of the AUC was greater than 25% of the $\text{AUC}_{0-\infty}$.

The $C_{\text{max}}$, $\text{AUC}_{0-12h}$, and the concentration–time data were used to calculate the PD parameters: $C_{\text{max}}/\text{MIC}_{90}$ ratio, $\text{AUC}_{0-12h}/\text{MIC}_{90}$ ratio, and time above MIC$_{90}$ ($T>\text{MIC}_{90}$) in plasma, ELF, and AC. The PD parameters in plasma were derived from the free (i.e., unbound) drug concentrations as well as from total (i.e., unbound plus bound) drug concentrations. The MIC$_{90}$ value for Aspergillus spp. were obtained from the recent literature (19).

RESULTS
Twenty-five subjects were enrolled in the study. Mean age (± standard deviation [SD]) of the 25 subjects was 30.4 ± 7.9 years; 15 were men and 10 were women; 17 were white, 4 were Asian, 5 were Hispanic, 2 were multiracial, and 1 was African American. Mean weight (± SD) of the subjects was 66.11 kg ± 10.0 kg.

Of the 25 subjects enrolled in the study, 21 completed BAL. Twenty of the subjects who completed BAL received 14 doses and one received 13 doses. Of the four subjects who did not complete the study, two withdrew for reasons unrelated to the study drug, and two were withdrawn from the study because of AEs possibly related to the study drug. This resulted in the following BAL schedule: three subjects 3 h after the last dose; four subjects at 5 h; four subjects at 8 h; five subjects at 12 h; and five subjects at 24 h.

The 14 doses of oral POS 400 mg taken BID over 8 days were safe and well tolerated. By protocol-set criteria, nine (36%) of 25 subjects had treatment-related AEs during the course of the study, which were all mild or moderate. Three subjects experienced nausea associated with the study drug, three subjects experienced fatigue, two subjects experienced headache, and two subjects reported diarrhea. The study drug had no clinically relevant effect on blood chemistry, hematology, urinalysis, vital signs, or ECGs, including QTc intervals.

The recovery of alveolar cells from the BAL fluid in the different time groups ranged from $7.1 \times 10^7 \pm 3.1 \times 10^7$ to $1.2 \times 10^7 \pm 5.5 \times 10^7$. The volume of ELF recovered ranged from $0.8 \pm 0.1$ to $1.0 \pm 0.3$ mL. None of the differences between groups in cell recovery or ELF volume were statistically significant (data not shown). The concentrations of POS in plasma, AC, and ELF and the AC/plasma and ELF/plasma ratios at the time of BAL are summarized in Table 1. The ELF/plasma and AC/plasma ratios ranged from...
0.589 to 1.08 and 27.3 to 44.3, respectively. The T > MIC90 (mean ± SD) in plasma was 22.3 ± 5.34 h. In two of the 21 subjects, individual plasma concentrations were not greater than the MIC90 for Aspergillus spp. (Fig. 1). However, the concentration of POS in ACs in these subjects was substantially greater (17- and 25fold, respectively) than the MIC90. The T > MIC90 in ELF and AC was 24 h and 24 h, respectively. The free Cmax/MIC90 and total Cmax/MIC90 ratios in plasma were 0.06 and 4.15, respectively.

The median Tmax in plasma was 3.6 h and the mean Cmax and AUC0-12h in plasma were 2.08 ± 0.93 μg/ml and 21.9 μg · h/ml (Table 2), respectively, and are comparable to the exposure reported previously (9). In plasma, ELF, and ACs, the drug concentrations did not decrease significantly, indicating slow elimination of POS from these compartments (Fig. 1) after dosing to steady state.

The Cmax values in ELF and AC were 1.86 ± 1.30 μg/ml and 87.7 ± 65.0 μg/ml, and both occurred at a Tmax of 5 h (Table 2). The AUC0-12h in ELF and AC were 18.3 and 715 μg · h/ml. While POS concentrations were similar in plasma and ELF, they were substantially higher in ACs. The AUC0-24/MIC90 ratios in plasma, ELF, and AC were 43.8, 36.6, and 1430, respectively. This observation is consistent with the lipophilic nature and high membrane permeability of POS. POS concentrations in AC were several-fold greater than the MIC90 of Aspergillus spp. for the dosing interval of 12 h and for up to 24 h after the last dose.

DISCUSSION

We previously reported the intrapulmonary PK/PD of itraconazole (ITRA) in healthy
human subjects (5). In that study ITRA was administered in a dose of 200 mg every 12 h for 5 days. The ITRA and hydroxyitraconazole (OH-IT) $C_{\text{max}}$ values (mean ± SD) in plasma, ELF, and AC were 2.1 ± 0.8 and 3.3 ± 1.0 µg/ml, 0.5 ± 0.7 and 1.0 ± 0.9 µg/ml, and 5.5 ± 2.9 and 6.6 ± 3.1 µg/ml, respectively. The ITRA and OH-IT AUC$_{0-24\text{h}}$ for plasma, ELF, and AC were 34.4 and 60.2 µg · h/ml, 7.4 and 18.9 µg · h/ml, and 101 and 134 µg · h/ml respectively. In the current study, we administered 400 mg POS every 12 h for 7 days. The $C_{\text{max}}$ values (mean ± SD) for POS in plasma, ELF, and AC were 2.08 ± 0.93, 1.86 ± 1.30, and 87.7 ± 65.0 µg/ml. The AUC$_{0-12\text{h}}$ for POS in plasma, ELF, and AC were 21.9, 18.3, and 715 µg · h/ml. Thus, while the $C_{\text{max}}$ of ITRA and POS in plasma and ELF were roughly comparable, the $C_{\text{max}}$ of POS in AC was 16-fold greater than the $C_{\text{max}}$ of ITRA in AC and 7-fold greater than the $C_{\text{max}}$ for ITRA and OH-IT in AC combined. This differential penetration into AC was also reflected in the AUC values. The AUC$_{0-24\text{h}}$ for POS in AC was approximately 28-fold greater than the AUC$_{0-24\text{h}}$ for ITRA in AC and approximately 12-fold greater than the AUC$_{0-24\text{h}}$ for ITRA and OH-IT combined.

In a study of 12 lung transplant recipients who received at least six oral doses of voriconazole as antifungal prophylaxis before undergoing surveillance bronchoscopy, ELF/plasma ratios ranged from 2 to 28 (2). Alveolar cell concentrations were not measured (2). In our study, the ELF/plasma ratios were less variable and ranged from 0.67 to 1.17; the AC/plasma ratios ranged from 31.1 to 42.2. Methodologic differences may account for the differences observed in ELF penetration in these studies. The subjects in the former study were lung transplant recipients; ours were normal volunteers. The current study was performed in a Clinical Research Unit using standardized procedures. There also may be true biological differences among the azoles in the
penetration into ELF and AC. A comparison of POS ELF and AC levels in our study with previously published data for ITRA (5) may be clinically more relevant because both the POS and the ITRA studies were conducted in healthy subjects, used the same standard methods, and reported levels in ELF and AC.

These observations have clinical significance because it has been demonstrated that the conidia of *Aspergillus* spp. are ingested by alveolar macrophages in the early phase of infection (20, 21). In an immunosuppressed rabbit model and children with AIDS, the antiphagocytic function of alveolar macrophages is impaired (3, 18). The ability of POS to inhibit *Candida* spp. is concentration-dependent and best correlated with the AUC/MIC ratio (1), and a similar relationship may exist for *Aspergillus* spp. Thus, greater AC drug concentrations are likely to be important in preventing or treating *Aspergillus* pulmonary infection in humans. This is also supported by the results in animal models and humans in which the efficacy of POS has been superior to that of ITRA (1, 8, 15).

In a neutropenic rabbit model, a sustained total concentration of 1.0 µg/ml in plasma was judged to be the minimally effective concentration (15). In our study in humans, a total ELF concentration greater than 1.0 µg/ml and a total AC concentration greater than 40 µg/ml were maintained for the dosing interval of 12 h and for 24 h after the last dose. The total AUC$_{0-12}$/MIC$_{90}$ ratios for *Aspergillus* spp. in plasma, ELF, and AC were 43.8, 36.6, and 1430, respectively. The total AUC/MIC ratio is a more appropriate PK/PD parameter for POS since, in a prospective, randomized trial in neutropenic patients, POS was more effective than fluconazole or ITRA for prophylaxis, prevention of invasive fungal
infections, and increased overall survival (8). The high AUC/MIC ratio in the current
study provides additional PK/PD support for the clinical observations that the efficacy of
POS is superior to that of ITRA.

In addition, in the current study, POS 400 mg taken BID administered orally over 8 days
had no clinically relevant effect on blood chemistry, hematology, urinalysis, vital signs,
or ECGs, including QTc intervals in healthy volunteers.

A limitation of the current study is that its 24-hour sampling interval was short in
comparison with the long half-life of POS in AC, plasma, and ELF. This resulted in a flat
concentration-time curve which made it impossible to calculate POS half-life in any
compartment. There are also differences between the pharmacokinetics determined in this
study and those in the other literature. We feel this is most likely a result of within-study
variability (11). A final limitation is that the randomization schedule did not allow study
dropouts to be replaced, resulting in fewer subjects in some time groups than in others.
We consider it unlikely that this last limitation affected our results, because groups were
comparable and there was a flat concentration-time profile in all groups.

We conclude that (i) an oral dosing regimen of POS 400 mg twice daily resulted in
sustained plasma, ELF, and AC concentrations above the MIC$_{90}$ for Aspergillus spp.
during the entire 12 hour dosing interval, (ii) the high intrapulmonary AUC$_{0-12h}$/MIC$_{90}$
ratio observed in this study is favorable for the treatment or prevention of
aspergillosis, and (iii) oral POS was well tolerated in healthy adults.

Acknowledgments
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References


TABLE 1. POS concentrations in plasma, AC, and ELF at the time of BAL

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>n</th>
<th>Plasma Concentration$^a$ (µg/ml)</th>
<th>AC Concentration$^b$ (µg/ml)</th>
<th>AC/Plasma ratio</th>
<th>ELF Concentration$^b$ (µg/ml)</th>
<th>ELF/Plasma ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>3</td>
<td>1.93 (47)</td>
<td>46.2 ± 26.3</td>
<td>34.5 ± 25.8</td>
<td>1.66 ± 1.05</td>
<td>1.08 ± 0.47</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>1.93 (48)</td>
<td>87.7 ± 65.0</td>
<td>44.3 ± 44.2</td>
<td>1.86 ± 1.30</td>
<td>0.75 ± 0.38</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>1.73 (48)</td>
<td>60.9 ± 32.3</td>
<td>32.5 ± 14.0</td>
<td>1.69 ± 0.82</td>
<td>0.95 ± 0.20</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>1.62 (52)</td>
<td>49.0 ± 49.7</td>
<td>27.3 ± 18.0</td>
<td>1.02 ± 0.97</td>
<td>0.59 ± 0.35</td>
</tr>
<tr>
<td>24</td>
<td>5</td>
<td>1.28 (56)</td>
<td>60.7 ± 49.2</td>
<td>34.9 ± 18.6</td>
<td>1.80 ± 1.71</td>
<td>0.92 ± 0.65</td>
</tr>
</tbody>
</table>

$^a$Mean values (%CV) are shown.

$^b$Mean values ± standard deviation are shown.

AC = alveolar cells; ELF = epithelial lining fluid; BAL = bronchoalveolar lavage.

TABLE 2. Plasma, ELF and AC PK/PD$^a$ parameters

<table>
<thead>
<tr>
<th>Parameter →</th>
<th>Compartments ↓</th>
<th>$C_{\text{min}}$ (µg/ml)</th>
<th>$C_{\text{max}}$ (µg/ml)</th>
<th>$C_{\text{max}}$/MIC ratio</th>
<th>$T_{\text{max}}$ (h)</th>
<th>AUC$^{0-12\text{h}}$ (µg · h/ml)</th>
<th>AUC$^{0-24\text{h}}$/MIC ratio$^c$</th>
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</thead>
<tbody>
<tr>
<td>Plasma</td>
<td></td>
<td>1.54</td>
<td>2.08 ± 0.93</td>
<td>4.15</td>
<td>3.6</td>
<td>21.9</td>
<td>87.6</td>
</tr>
<tr>
<td>ELF</td>
<td></td>
<td>1.02</td>
<td>1.86 ± 1.30</td>
<td>3.72</td>
<td>5.0</td>
<td>18.3</td>
<td>73.2</td>
</tr>
<tr>
<td>AC</td>
<td></td>
<td>46.2</td>
<td>87.7 ± 65.0</td>
<td>175</td>
<td>5.0</td>
<td>715</td>
<td>2860</td>
</tr>
</tbody>
</table>

$^a$The parameters were derived using total (i.e., unbound plus bound) drug concentrations.
(see text).

\[ b \text{ Mean values ± standard deviation are shown.} \]

\[ c \text{ Based on AUC}_{0-24h} that was } 2 \times \text{AUC}_{0-12h}. \]

\[ \text{AC = alveolar cells; ELF = epithelial lining fluid; PK = pharmacokinetics; PD = pharmacodynamics.} \]
FIG. 1. Mean ± SD POS concentrations ELF, and AC Concentration-Time Profiles of Posaconazole on Day 8 After Healthy Subjects Received Posaconazole 400 mg (40 mg/mL Oral Suspension) BID With Food (10 Minutes After Eating a High-Fat Meal) for a Total of 14 Doses Note: Only the plasma data has error bars as the data were obtained in multiple subjects at the same time. The ELF and AC data were obtained as one data value per subject. The MIC\textsubscript{90} value for *Aspergillus* spp. was obtained from the recent literature (19). ELF = epithelial lining fluid; AC = alveolar cells; BAL = bronchoalveolar lavage.