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APPLICATION NUMBER:

22-003

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-003	Submission Date(s): 12/22/2005
Drug	Posaconazole
Trade Name	Noxafil
Reviewer	Seong H, Jang, Ph.D. (Primary and Pharmacometrics (PM)) Dakshina Chilukuri, Ph.D. (PM: Population PK)
OCP Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
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OCP Division	DCP 4
OND division	ODE IV DSPTP
Sponsor	Schering-Plough Corp.
Relevant IND(s)	51,662
Submission Type; Code	Original, 1S (NME)
Formulation; Strength(s)	Oral suspension 40 mg/mL (105 mL)
Indication	<ul style="list-style-type: none"> • Prophylaxis in patients, 13 years of age and older, who are at high risk of developing these infections, such as hematopoietic stem cell transplant (HSCT) recipients or those with prolonged neutropenia • Treatment of oropharyngeal candidiasis, including infections refractory to itraconazole and fluconazole
Dosage and Administration	Prophylaxis: 200 mg TID Oropharyngeal Candidiasis: Loading dose of 200 mg QD, then 100 mg QD for 13 days Refractory Oropharyngeal Candidiasis: 400 mg BID with a meal or with a nutritional supplement in patients who cannot tolerate a full meal

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1. Executive Summary

Posaconazole (POS, SCH 56592) is a triazole antifungal agent and, like other azoles such as fluconazole, itraconazole, and voriconazole, blocks ergosterol biosynthesis of yeast and filamentous fungi by inhibiting the enzyme lanosterol 14 α -demethylase (CYP51, Erg1p). The drug formulation in this NDA is an oral suspension (40 mg/mL) and the proposed indications are prophylaxis

_____ in patients, 13 years of age and older, who are at high risk of developing these infections, such as hematopoietic stem cell transplant (HSCT) recipients or those with prolonged neutropenia, and treatment of oropharyngeal candidiasis, including infections refractory to itraconazole and fluconazole. Priority review was granted for prophylaxis of _____.

The sponsor cross-referenced _____, for the clinical pharmacology information. All clinical pharmacology studies _____ have been previously reviewed by the FDA Clinical Pharmacology review team. Accordingly, most of the clinical pharmacology information to support the labeling of the current NDA 22-003 was based on the Clinical Pharmacology review of _____, dated May 24, 2005. In the Approvable letter, dated June 10, 2005, the sponsor was asked to address three unresolved clinical pharmacology issues regarding effect of severe hepatic impairment on the pharmacokinetics of POS and drug-drug interactions as pre-approval recommendations. However, none of these issues were addressed in the current NDA.

The efficacy and safety of posaconazole for the prophylaxis of IFIs were evaluated in two pivotal Phase 3 studies (Studies C98316 and P01899). These two pivotal Phase 3 study reports were reviewed to evaluate potential exposure-response relationships with POS.

The exposure-response analyses revealed a strong relationship between a higher incidence of Clinical Failure and lower plasma exposure to POS, suggesting that ensuring high plasma exposure to POS appears to be needed especially for patients whose steady state average concentration (C_{avg}) is low (see Figure 1). Further analyses showed:

- (a) The exposure-response relationship for POS effectiveness for the prophylaxis against IFIs was not significantly confounded with any patient demographic covariates
- (b) POS concentration of 350 ng/mL determined at 3 to 5 hours post dose on Day 2 after the beginning of POS treatment would result in a steady-state C_{avg} of 700 ng/mL and subsequently result in the incidence of Clinical Failure of <25%. Plasma concentration monitoring of POS may be used as a tool to identify those patients who will have lower than desired plasma exposure.

- (c) The increase of POS dose from 200 mg TID to 400 mg TID is most likely to result in an increase in plasma exposure to POS by at least 2 fold when POS is given either with food or under fasting conditions.
- (d) There would be expected to be no additional safety findings with 400 mg TID for those patients whose C_{avg} was ≤ 700 ng/mL (i.e., those who receive 200 mg TID initially). Based on the dose-proportional PK of POS, following 400 mg TID administration to patients whose C_{avg} was ≤ 700 ng/mL (i.e., those who receive 200 mg TID initially), C_{avg} would not be expected to be greater than 3650 ng/mL, which is the highest C_{avg} observed in patients treated with 200 mg TID in Study C98316.

Collectively, it is recommended that POS dose be adjusted based on plasma concentrations of POS on Day 2.

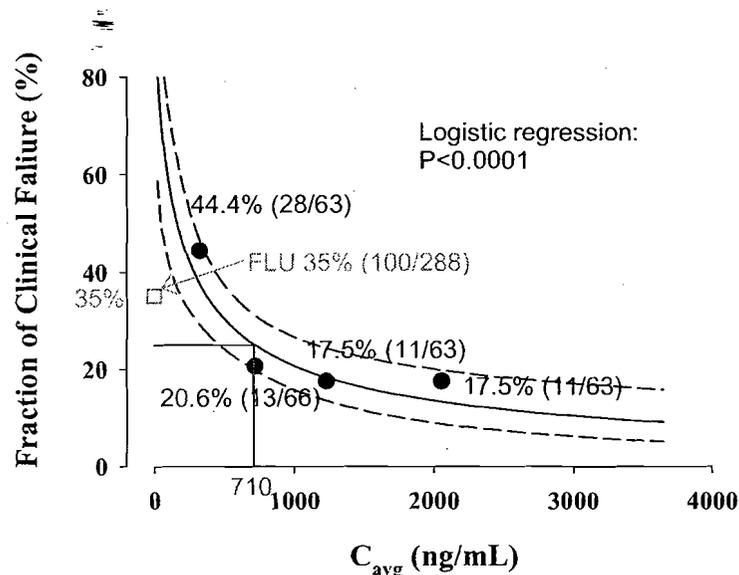


Figure 1. POS exposure-response relationship for patients in the All Treated population during the Primary Time Period (N=252) (Study C98316). Logistic regression was performed using natural log of average concentrations per patient ($\log(C_{avg})$) as a continuous variable and the Clinical Failure as a binary variable (yes or no). The solid line represents the regression fit. The dashed lines represent 95% Confidence Interval. Subsequent to the logistic regression, the response rates in each of the 4 quartiles of C_{avg} (closed circles) are plotted to assess the goodness-of-fit. The response rate for patients treated with fluconazole (FLU, open square) is plotted as a reference. The blue lines showed that 710 ng/mL of C_{avg} is required to achieve 25% Clinical Failure rate.

1.1. Recommendation

It is strongly recommended to determine POS dose according to its plasma concentrations. The summary of dose adjustment, based on the monitoring of POS plasma concentrations, is illustrated as a flow chart below.

Initial dose: 200 mg TID for all patients

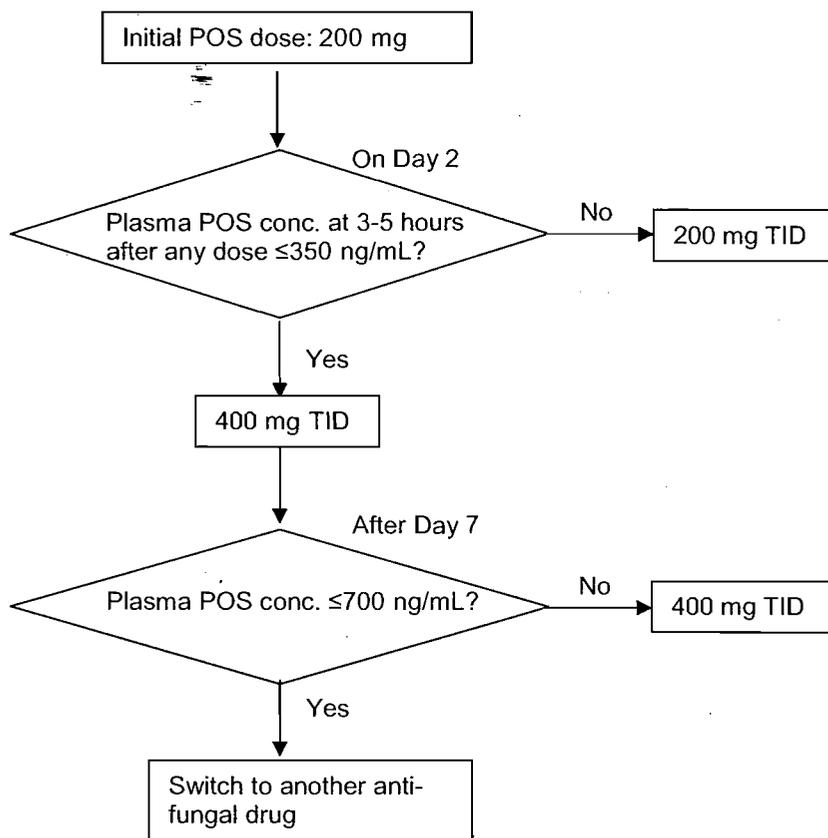
Monitoring of plasma concentration(s) of POS on Day 2:

Plasma samples should be collected at 3 to 5 hours after any dose on Day 2.

- (a) If plasma concentration(s) of POS is ≤ 350 ng/mL, then give 400 mg TID
- (b) If plasma concentration(s) of POS is > 350 ng/mL, then give 200 mg TID

Monitoring of plasma concentration(s) of POS after Day 7 for patients who received 400 mg TID:

- (a) If plasma concentration(s) of POS is > 700 ng/mL, then give 400 mg TID
- (b) If plasma concentration(s) of POS is ≤ 700 ng/mL, then switch to another anti-fungal drug



Scheme of POS Dose recommendation based on plasma concentrations of POS

1.2 Phase 4 Commitments

Not applicable.

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1.3. Summary of Important Clinical Pharmacology Findings

Exposure-response relationship-Effectiveness

The exposure-response analyses revealed a strong relationship between a higher incidence of Clinical Failure and lower plasma exposure to POS, suggesting that ensuring high plasma exposure to POS appears to be needed especially for patients whose steady state average concentration (C_{avg}) is low (See Figure 1 on page 3). Table S1 shows the Clinical Failure rate and Proven/Probable IFIs in the All Treated population during the Primary Time Period for 4 quartiles of POS C_{avg} .

Table S1. Incidence of Clinical Failure and Proven/Probable IFIs in the All Treated population during the Primary Time Period in 4 quartiles of POS C_{avg} (Study C98-316).

Quartiles	Q1	Q2	Q3	Q4
C_{avg} (ng/mL)	21.5-557	557-915	915-1563	1563-3650
Clinical Failure	44.4% (28/63)	20.6% (13/63)	17.5% (11/63)	17.5% (11/63)
Proven/probable IFI	4.76% (3/63)	4.76% (3/63)	1.59% (1/63)	3.17% (2/63)

Dose recommendation based on the exposure-response relationship

There are no patient demographic covariates (or combination of those covariates) that can successfully categorize the patients who will attain low plasma concentrations of POS. Therefore, measuring plasma concentrations of POS is considered by this reviewer to be the most reliable way to identify those patients who will attain low concentrations of POS.

Based on the relationship between C_{avg} of POS and Clinical Failure (See Figure 1 on page 3), a Clinical Failure rate of <25% is considered to be acceptable by the reviewing medical officer as a target clinical outcome that should be achieved with POS and C_{avg} should be greater than 700 ng/mL to achieve this target outcome. Thus, 700 ng/mL is the lower threshold value for C_{avg} to determine if the POS dosage needs to be increased for a given patient. Subsequently, the concentration on Day 2 which would result in a C_{avg} of 700 ng/mL at steady state was calculated using an accumulation factor of 8 obtained from a multiple dose-escalating PK study (Study I96089). Based on this, a concentration of 350 ng/mL measured at 3 to 5 hours post dose on Day 2 is recommended as a cutoff plasma concentration of POS to determine if the POS dosage needs to be increased for a given patient.

The threshold concentration of 700 ng/mL as C_{avg} also appears appropriate in terms of the incidence of Proven/Probable IFIs, because the incidence of Proven/Probable IFIs also tended to be greater for patients whose C_{avg} was \leq 700 ng/mL compared with patients whose C_{avg} was >700 ng/mL. Tables S2 and S3 shows the incidence of Prove/Probable IFIs between group of patients whose C_{avg} was \leq 700 ng/mL and group of patients whose C_{avg} was >700 ng/mL in Study C98316 and P01899, respectively.

Table S2. Incidence of Proven/Probable IFIs between those patients whose POS C_{avg} was ≤ 700 ng/mL and those patients whose POS C_{avg} was >700 ng/mL (Study C98316).

C_{avg} (ng/mL)	≤ 700 ng/mL (N=92)	>700 ng/mL (N=160)
Incidence of Prove/Probable IFIs	6.52% (6/92)	1.88% (3/160)
Incidence of Aspergillosis	4.35% (4/92)	0.63% (1/160)

Table S3. Incidence of Proven/Probable IFIs between those patients whose C_{avg} was ≤ 700 ng/mL and those patients whose C_{avg} was >700 ng/mL (Study P01899).

C_{avg} (ng/mL)	≤ 700 ng/mL (N=155)	>700 ng/mL (N=60)
Incidence of Prove/Probable IFIs	3.87% (6/155)	0% (0/60)

Four clinical pharmacology studies (i.e., single and multiple dose escalating studies and food effect studies following 200 mg and 400 mg of POS) support that the increase of POS dose from 200 mg TID to 400 mg TID is most likely to result in an increase in plasma exposure to POS by at least 2 fold when POS is given either with food or under fasting conditions.

When dose is adjusted from 200 mg TID to 400 mg TID, based on the threshold C_{avg} of 700 ng/mL, the percent of patients whose C_{avg} is ≤ 700 ng/mL would be decreased from 37% (92/252) to 14% (35/252). The Clinical Failure rate for patients whose C_{avg} was ≤ 700 ng/mL (i.e., with 200 mg TID) would be reduced from 37% (34/92) to 25% (23/92) (Table S4).

Table S4. Percent of patients whose C_{avg} is ≤ 700 ng/mL and Clinical Failure rate as a function of POS dosing regimen

$C_{avg} \leq 700$ ng/mL	200 mg TID	400 mg TID (projection)
% of patients whose C_{avg} is ≤ 700 ng/mL	37% (92/252)	14% (35/252)
Clinical Failure rate in patients whose C_{avg} was ≤ 700 ng/mL	37% (34/92)	25% (23/92)

For patients whose plasma concentrations of POS cannot be high enough to ensure desirable clinical outcomes with 400 mg TID, other antifungal treatment for prophylaxis of IFIs may be needed. Thus, it is recommended to use other antifungal treatment instead of POS for patients who receive 400 mg TID and if plasma concentrations of POS after Day 7 (presumed steady state) are ≤ 700 ng/mL.

Collectively, the following dose administration and plasma concentration monitoring scheme is recommended by this reviewer.

Initial dose: 200 mg TID for all patients

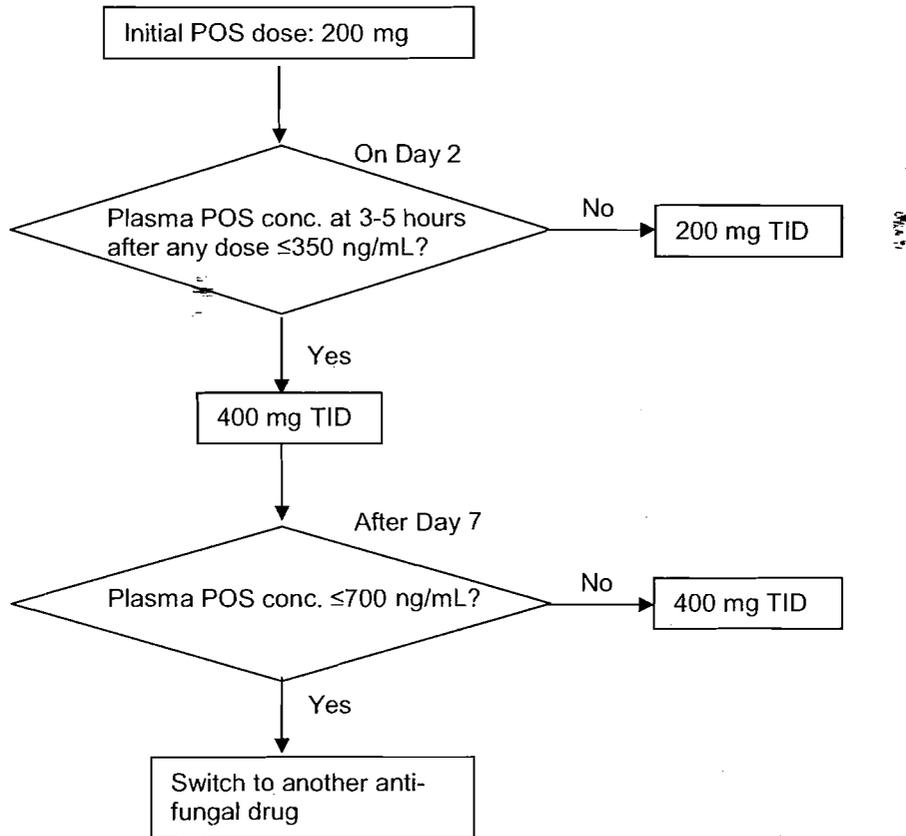
Monitoring of plasma concentration(s) of POS on Day 2:

Plasma samples should be collected at 3 to 5 hours after any dose on Day 2.

- (a) If plasma concentration(s) of POS is ≤ 350 ng/mL, then give 400 mg TID
- (b) If plasma concentration(s) of POS is >350 ng/mL, then give 200 mg TID

Monitoring of plasma concentration(s) of POS after Day 7 for patients who received 400 mg TID:

- (a) If plasma concentration(s) of POS is >700 ng/mL, then give 400 mg TID
- (b) If plasma concentration(s) of POS is ≤ 700 ng/mL, then switch to another anti-fungal drug



Scheme of POS Dose recommendation based on plasma concentrations of POS

Exposure-response relationship-Safety

The most common treatment-related (Possible and Probable) treatment-emergent adverse events were nausea, vomiting, diarrhea, hypokalemia, rash and elevations in hepatic enzymes (SGOT and SGPT increase). For exposure-response relationship regarding safety, data from Study C98316 and P01899 were pooled. Although the incidence of most treatment-related adverse events tended to be lower in the first quartile of C_{avg} compared with the fourth quartile of C_{avg} , the incidence rates of adverse events were not significantly dependent on plasma drug concentration.

There would be expected to be no additional safety findings with 400 mg TID for those patients whose C_{avg} was ≤ 700 ng/mL (i.e., those who receive 200 mg TID initially). Based on the dose-proportional PK of POS, following 400 mg TID administration to patients whose C_{avg} was ≤ 700 ng/mL (i.e., those who receive 200 mg TID initially), C_{avg}

would not be expected to be greater than 3650 ng/mL, which is the highest C_{avg} observed in patients treated with 200 mg TID in Study C98316.

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2. Question Based Review

Exposure-response Analysis

The relationship between plasma exposure to posaconazole (POS) and its effectiveness and safety was analyzed by the FDA Clinical Pharmacology reviewer using data from two pivotal Phase 3 studies (Study C/I98-316 and P01899) which were conducted using POS for the prevention of IFIs in high-risk patients.

C98-316 was a double-blind, active-controlled trial, that compared POS (200 mg TID) with fluconazole (FLU, 400 mg QD) as prophylactic therapy to reduce the incidence of IFIs in high-risk allogeneic hematopoietic stem cell (HSCT) recipient with acute graft versus host disease (GVHD) or chronic GVHD. A total of 600 patients were enrolled (301 POS, 299 FLU). A Data Review Committee (DRC) of experts in antifungal therapy reviewed the blinded results of this study to make assessments of potential IFIs. The primary efficacy analysis was the DRC-adjudicated incidence of proven and probable IFI for All Randomized Subjects during the Primary Time Period (112-day fixed time period). The mean duration of therapy was comparable between the two treatment groups (80 days, POS; 77 days, fluconazole).

P01899 is a Phase 3, randomized, open-label, evaluator-blinded, active control, parallel group, multicenter study comparing POS (200 mg TID) versus standard azole (FLU 400 mg QD or itraconazole (ITZ) 200 mg BID) for prophylaxis against IFIs in subjects with profound, prolonged neutropenia due to remission-induction chemotherapy for AML or MDS. A total of 602 subjects were enrolled (304 POS, 298 standard azoles [240 FLU, 58 ITZ]). A blinded panel of external expert evaluators (DRC) reviewed all identified suspected cases of IFIs to determine the final number of proven, probable, and possible IFIs and to confirm the diagnosis (including the onset date of the infection and primary pathogen) based on EORTC/MSG criteria. The primary efficacy analysis was the DRC-adjudicated incidence of Proven/Probable IFIs in All Randomized Subjects during the Oral Treatment Phase (on-treatment period). The mean duration of therapy was comparable between the two treatment groups (29 days, POS; 25 days, fluconazole).

The primary efficacy variable specified in the protocol was not considered to be appropriate by the reviewing medical officer to evaluate efficacy of POS for prophylaxis against IFIs because the incidence of Proven or Probable IFIs are too rare to be compared. Thus, the FDA review team used Clinical Outcome as a primary endpoint to evaluate a treatment effect of POS regarding clinical failures for All Treated population defined as subjects who were randomized and received at least one dose of study drug. Clinical Failure was defined in the protocol as the occurrence of a proven or probable IFI, receipt of more than 5 days of empiric treatment with a systemic antifungal drug other than the study drug during the Primary Time Period, deaths from all causes, discontinuation of study drugs from the Primary Time Period (i.e., subject not followed for the entire duration of the period), or lost to follow up.

The exposure-relationship for safety was analyzed using the incidence of nausea, vomiting, diarrhea, elevations in hepatic enzymes (SGOT and SGPT increase or bilirubenemia), rash, and treatment discontinuation as the endpoints.

The exposure-response analysis for effectiveness and safety were evaluated by logistic regression which was performed using concentrations as a continuous variable and the clinical response or incidence of toxicity as a binary variable (yes or no). The SAS system for Windows V8 was used for the data manipulation and exposure-response analysis.

2.1. Exposure-response relationship-Effectiveness

2.1.1. Is posaconazole (POS) oral suspension, 200 mg TID, effective for the prophylaxis of invasive fungal infections (IFIs) in patients 13 years and older who are at high risk such as hematopoietic stem cell transplant recipients or those with prolonged neutropenia?

The efficacy of POS for prophylaxis against IFIs in patients who are at high risk such as hematopoietic stem cell transplant recipients (Study C98316) or those with prolonged neutropenia (P01899) was compared with the control group of subjects treated with fluconazole (FLU) and/or itraconazole (ITZ). The results based on the primary efficacy endpoint (i.e., Clinical Outcome) are summarized in Tables 1 and 2 (from Clinical Review from an FDA Medical Officer, Dr. Tierney Maureen). On the basis of Clinical Outcome, the results from Study C98316 supported noninferiority but not significant for superiority to the control group of subjects treated with FLU. On the other hand, the results from Study P01899 supported the superiority of POS to the control group of subjects treated with FLU and ITZ. Thus, collectively, POS is considered to be effective for the prophylaxis against IFIs in patients who are at high risk such as hematopoietic stem cell transplant recipients or those with prolonged neutropenia.

Table 1. Primary efficacy analysis for the prophylaxis against invasive fungal infections in high-risk allogeneic hematopoietic stem cell recipient with acute graft versus host disease (GVHD) or chronic GVHD. (Study C98316: All Treated Population).

	POS		Fluconazole		P value	Difference	95% CI
	N	%	N	%			
Clinical Success	202	69	188	65	0.29	4%	-3.5%, 11.7%
Clinical Failure	89	31	100	35			
Total	291		288				

Table 2. Primary efficacy analysis for the prophylaxis against invasive fungal infections in subjects with profound, prolonged neutropenia. (Study P01899: All Treated Population).

	POS		Fluconazole		P value	Difference	95% CI
	N	%	N	%			
Clinical Failure	107	46	137	58	0.01	11.8%	2.9%, 20.8%
Clinical Success	127	54	101	42			
Total	234		238				

	POS		Itraconazole		P value	Difference	95% CI
	N	%	N	%			
Clinical Failure	37	59	37	69	0.27	9.8%	-7.5%, 27%
Clinical Success	26	41	17	31			
Total	63		54				

2.1.2. Is the effectiveness of POS for the prophylaxis against IFIs dependent upon the plasma exposure to posaconazole?

This reviewer found that there is a strong relationship between a higher incidence of Clinical Failure and the lower plasma exposure to POS, suggesting that clinical response to POS is dependent upon its plasma concentrations.

The plasma POS concentrations were measured in 265 patients of total 291 patients in POS-treated arm. However, plasma POS concentrations were collected only at more than 24 hours after the last dose of POS in 13 patients of the 265 patients.. Thus, these 13 patients were excluded from the PK dataset (N=252). The Clinical Failure rate in the PK dataset (63/252=25%) was comparable with that in the All Treated Population (89/291=31%), indicating that the PK dataset represents All Treated Population adequately.

A total of 870 plasma samples were collected for the measurement of POS concentration from 252 patients at no later than 24 hours after the last dose of POS. An average of 3.5 POS concentrations per patient were determined and the individual average concentration values (C_{avg}) were used to relate the plasma exposure to POS and response. See 2.1.10 to find the rationale for the use of C_{avg} as a PK parameter for the exposure-response analysis.

Figure 2 shows the exposure-effectiveness relationship of POS for prophylaxis of IFIs in hematopoietic stem cell transplant recipients (Study C98316). Table 3 shows the Clinical Failure rate in the All Treated population during the Primary Time Period for 4 quartiles of POS C_{avg} . Additionally, the reasons for Clinical Failure were analyzed for 4 quartiles of POS C_{avg} (Table 3). The incidence of Proven/Probable IFIs tended to be greater in the lower two quartiles (i.e., Q1 and Q2) compared with the higher two quartiles (i.e., Q3 and Q4), but no statistical significance was observed between the incidence of Prove/Probable IFIs and POS C_{avg} (p=0.3). The results showed that the major reason for Clinical Failure was death. The statistical results of logistic regression analysis, using the Clinical Failure

as the dependent binary variable (i.e., yes or no) and C_{avg} as the independent continuous variable, are summarized in Table 4.

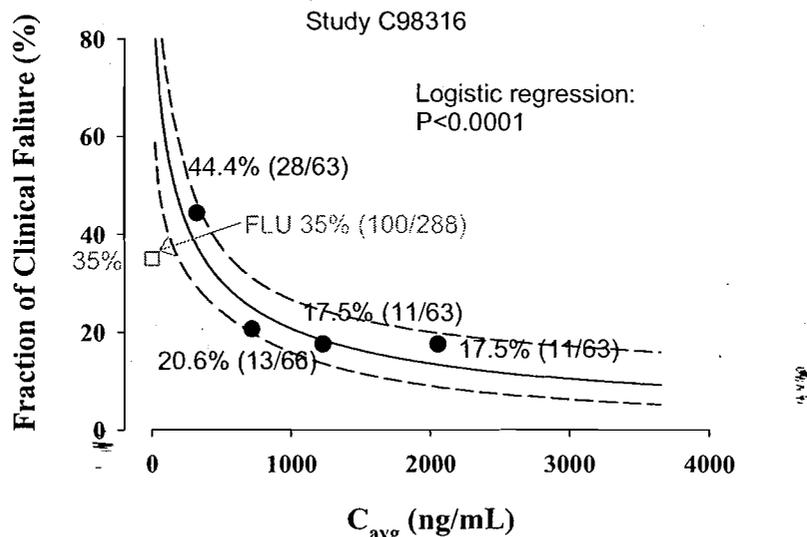


Figure 2. POS exposure-response relationship for patients in the All Treated population during the Primary Time Period (N=252) (Study C98-316). Logistic regression was performed using natural log of average concentrations per patient ($\log(C_{avg})$) as a continuous variable and the Clinical Failure as a binary variable (yes or no). The solid line represents the regression fit. The dashed lines represent 95% Confidence Interval. Subsequent to the logistic regression, the response rates in each of the 4 quartiles of C_{avg} (closed circles) are plotted to assess the goodness-of-fit. The response rate for patients treated with fluconazole (FLU, open square) is plotted as a reference.

Table 3. Incidence of Clinical Failure in the All Treated population during the Primary Time Period in 4 quartiles of POS C_{avg} (Study C98-316).

Quartiles	Q1	Q2	Q3	Q4
C_{avg} (ng/mL)	21.5-557	557-915	915-1563	1563-3650
Clinical Failure	44.4% (28/63)	20.6% (13/63)	17.5% (11/63)	17.5% (11/63)
Proven/probable IFI	4.76% (3/63)	4.76% (3/63)	1.59% (1/63)	3.17% (2/63)
Empirical use of Sys. Antifungal ^a	17.5% (11/63)	3.17% (2/63)	6.35% (4/63)	4.76% (3/63)
Death	34.9% (22/63)	20.6% (13/63)	17.5% (11/63)	11.1% (7/63)
Discontinuation ^b	23.8% (15/63)	14.3% (9/63)	9.52% (6/63)	9.52% (6/63)

There is some overlap in the rows.

^a: Use of systemic antifungal agents in addition to study drug more than 5 days, from all causes

^b: Discontinuation due to any reason

Table 4. Parameter estimates of the logistic regression model for the relationship between $\log(C_{avg})$ and the Clinical Failure in the All Treated population during the Primary Time Period (Study C98-316).

Parameter		Estimate	SE	P-value
Clinical Failure	Intercept	3.7466	1.0713	0.005
	Slope	-0.7369	0.1634	<0.0001

There was a significant difference in Clinical Failure rate between patients who belong to Q1 (i.e., $C_{avg} < 557$ ng/mL) and patients who belong to Q2- Q4 (i.e., $C_{avg} > 557$ ng/mL), i.e., 44% (28/63) vs. 19% (35/189). Based on the results of this analysis, ensuring high plasma exposure to POS appears to be needed for patients whose C_{avg} is low. It should be noted that the Clinical Failure rate for patients who belonged to Q1 was even higher compared with patients who received FLU (See Figure 2).

The same exposure-effectiveness analysis was performed using data from Study P01899. The similar results, i.e., a strong relationship between lower C_{avg} of POS and higher Clinical Failure rate was obtained in subjects with profound, prolonged neutropenia due to remission-induction chemotherapy for AML or MDS (Figure 3 and Tables 5 and 6).

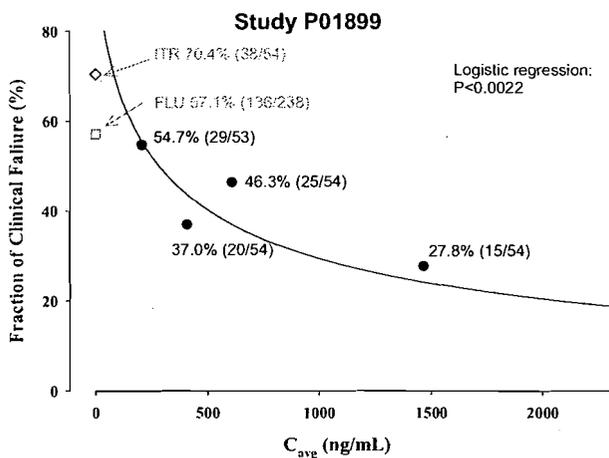


Figure 3. POS exposure-response relationship for patients in the All Treated population during the Oral Treatment Phase (n=215) (Study P01899). Logistic regression was performed using natural log of average concentrations per patient ($\log(C_{avg})$) as a continuous variable and the Clinical Failure as a binary variable (yes or no). The solid line represents the regression fit. Subsequent to the logistic regression, the response rates in each of the 4 concentration quartiles (closed circles) are plotted to assess the goodness-of-fit. The response rates in patients treated with fluconazole (FLU, open square) and itraconazole (ITZ, open diamond) are plotted as references.

Table 5. Incidence of Clinical Failure and Proven/Probable IFIs in the All Treated population during the Oral Treatment Phase in 4 concentration quartiles of POS (Study P01899).

C_{avg} (ng/mL)	Clinical Failure	Proven/probable IFI
89.65-322	54.7% (29/53)	3.77% (2/53)
322-490	37.0% (20/54)	1.85 % (1/54)
490-733.5	46.3% (25/54)	5.56% (3/54)
733.5-2200	27.8% (15/54)	0% (0/54)

Table 6. Parameter estimates of the logistic regression model for the relationship between $\log(C_{avg})$ and Clinical Failure in the All Treated population during the Oral Treatment Phase (Study P01899).

Parameter		Estimate	SE	P-value
Clinical Failure	Intercept	3.9179	1.3969	0.005
	Slope	-0.6938	0.2267	0.0022

As mentioned above, Study P01899 was designed as an open-label study. Additionally, the range of individual C_{avg} values was observed to be wider in Study C-98-316 as compared with Study P01899. Thus, further exposure-effectiveness analyses were performed using data obtained from Study C98316.

2.1.3. Is the above exposure-effectiveness relationship confounded with any other patient demographic covariates?

The exposure-response relationship for POS effectiveness for the prophylaxis against IFIs was not significantly confounded with any patient demographic covariates.

The reviewer investigated if the exposure-effectiveness relationship was confounded with any patient characteristics. The analysis showed some trends such as (a) higher incidence of death in Q1, (b) shorter treatment duration in Q1, (c) less patients with Acute III GVHD at baseline in Q4, (d) more patients with Acute II GVHD at baseline in Q1, (e) less female patients in Q1, (f) more frequent incidence of diarrhea in Q1, and (g) more African-American patients in Q1 (Table 7). However, none of these covariates could identify the patients to all 4 quartiles as significantly as C_{avg} .

Table 7. Comparison of patient demographic covariates in All Treated population as a function of plasma POS concentration (Study C98-316: N=252).

Quartile	Q1 (n=63)	Q2 (N=63)	Q3 (N=63)	Q4 (N=63)
C _{avg} (ng/mL) ^a	296±170 322 [22-549]	740±102, 718 [565-913]	1232±200, 1231 [917-1562]	2146±492, 2056 [1563-3650]
Death	22	13	12	7
Tx Duration (Days)	69.2±44.6	92.2±32.5	101±26.4	91.0±37.3
GVHDBS				
Acute II or Chronic Extensive	77.8%	68.2%	82.5%	85.7%
Acute III	17.5%	23.8%	14.3%	7.94%
Acute IV	3.17%	3.17%	3.17%	3.17%
Acute II	60.3%	46.7%	47.6%	28.6%
Extensive	17.5%	22.6%	34.9%	57.1%
Gender (female)	20.6%	33.3%	36.5%	34.9%
Age (years)	40±13	41±10	43±11	45±11
Diarrhea ^b	14.3%	6.35%	4.76%	3.17%
Vomit ^b	3.17%	6.15%	1.59%	4.76%
Race (Cauc.)	85.7%	81.0%	87.3%	84.1%
Race (AA)	9.52%	6.35%	0%	0%

^a: Mean±SD, median [range] ^b: incidence on the day of plasma sample

The major reason for the shorter duration of therapy in Q1 was the greater incidence of death in Q1. As mentioned in 2.1.2, death is the major reason for Clinical Failure. Thus, a short duration of therapy in Q1 was most likely to be an effect of low plasma exposure to POS but not a cause for low plasma exposure to POS. The Clinical Failure rate for African-American patients was 20% (2/10), indicating more African-American patients in Q1 was not confounded with exposure-effectiveness relationship of POS. Although the incidence of diarrhea appears to be related to low plasma exposure to POS, only 14% of patients who belong to Q1 had diarrhea. Thus, it is not likely to be a major reason for low plasma exposure to POS.

After discussion of this analysis with the sponsor on May 26, 2006, the sponsor identified three risk factors (i.e., Acute GVHD at baseline, male, and CMV positive) which were strongly correlated with Clinical Failure using a logistic regression analysis (backward selection). The sponsor defined a sub population of patients with the three identified risk factors named above (n=51) and showed that there were relatively more patients (46%) who belonged to Q1 in this “high risk” sub population. However, the further exposure-response analysis performed by the Clinical Pharmacology reviewer showed that the Clinical Failure rate is greater in patients who belonged to Q1 compared with Q2-Q4 within the “high risk” sub population group. In addition, an almost identical exposure-effectiveness relationship was observed within a sub population which excluded the high risk sub population (N=240), indicating that the exposure-response relationship for POS effectiveness for the prophylaxis against IFIs was not confounded with any patient demographic covariates (See Appendix).

2.1.4. Is there any way to identify the patients who attain low plasma concentrations of POS?

Measuring POS plasma concentration is considered by this reviewer to be the most reliable way to identify patients who attain low plasma concentrations of POS.

As discussed in 2.1.3, there are no patient demographic covariates (any combination of those covariates) that can successfully identify the patients who will attain low plasma concentrations of POS. Therefore, measuring plasma concentration is considered to be the most reliable way to identify patients who will attain low plasma concentrations of POS. Currently, the sponsor does not have a commercial assay method to monitor plasma concentrations of POS. Thus, it is recommended that the sponsor develop a commercial assay method to monitor plasma concentrations of POS.

2.1.5. What will be the cutoff or threshold concentration of POS to determine if a patient needs an increase in the POS dosage?

It is recommended to use a POS plasma concentration of 350 ng/mL measured at 3 to 5 hours post dose on Day 2 as a cutoff plasma concentration of POS.

This is based on the relationship between C_{avg} of POS and Clinical Failure (See Figure 2 on page 13). A Clinical Failure rate of <25% is considered by the reviewing medical officer to be acceptable as a target clinical outcome. Figure 1 on page 13 shows that C_{avg} should be greater than 700 ng/mL to achieve this target outcome. Thus, 700 ng/mL is the lower threshold value for C_{avg} at steady state to determine if the POS dosage needs to be increased for a given patient.

POS PK can be described appropriately by a one compartment open model with a first order rate of absorption and a first order rate of elimination (See Section 5. Population PK analysis). Thus, the plasma concentrations of POS before it reaches a steady state (i.e., during the first week after the beginning of POS treatment) could be calculated from steady state plasma concentrations using an accumulation factor of 8 obtained from a multiple dose-escalating PK study (Study I96089). Table 8 shows that the calculated average plasma concentrations of POS before C_{avg} reaches 700 ng/mL at Day 7 (presumed steady state) following oral administration of POS 200 mg TID.

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Table 12. Calculated plasma concentrations of POS before C_{avg} reaches 700 ng/mL at Day 7 (presumed at steady state) following oral administration of POS 200 mg TID.

Day	No. of Dose	Plasma concentration of POS (ng/mL)
1	1	67
	2	186
	3	238
2	4	286
	5	331
	6	371
3	7	408
	8	442
	9	474
4	10	503
	11	529
	12	553
5	13	576
	14	596
	15	615
6	16	632
	17	648
	18	663
7	19	676
	20	689
	21	700

For the calculation, 7.6 ± 2.8 of accumulation ratio (R_{0-12h}) obtained following oral administration of POS 200 mg BID for 14 days (Study I96089) were used.

Based on the above results, a POS plasma concentration of 350 ng/mL measured at 3 to 5 hours post dose on Day 2 is recommended as a cutoff plasma concentration of POS to determine if the POS dosage needs to be increased for a given patients.

For Day 1, plasma concentrations of POS vary substantially. Thus, the plasma concentrations of POS on Day 1 are not recommended to be used as criteria to predict C_{avg} at steady state. It should be noted that plasma concentrations of POS should be measured at 3 to 5 hours after each dose considering median value of T_{max} , 3 hour.

2.1.6. How can plasma concentrations of POS be increased in patients who cannot achieve high plasma exposure to POS (i.e., patients who belongs to Q1)?

The increase of POS dose from 200 mg TID to 400 mg TID is most likely to result in an an increase in plasma exposure to POS by at least 2 fold when POS is given either with food or under fasting conditions.

The reviewer recommends that POS dose regimen be adjusted to 400 mg TID from 200 mg TID for patients whose plasma concentrations of POS need to be increased. This

recommendation is based on the following results obtained from clinical pharmacology studies conducted in healthy subjects

A multiple dose escalating study (Study I96089) showed that 400 mg BID dose resulted in 2.3-fold increase in plasma exposure to POS (i.e., AUC and C_{max}) compared with 200 mg BID dose when it is given with a high-fat meal (Table 9). A single dose escalating study (Study I95098) also showed that a single dose of 400 mg POS resulted in about 2-fold increase in both AUC and C_{max} compared with a single dose of 200 mg POS dose when it given with a high-fat meal (Table 10). No dose escalating study was conducted under fasting conditions. However, two studies to evaluate the effect of food on the POS PK (Studies I96099 and I95099) showed that the magnitude of the increase in oral POS bioavailability by a high-fat meal was similar (i.e., ~4 fold) following oral administration of both 200 mg and 400 mg (Tables 11 and 12). Collectively, these data support that 400 mg dose can increase plasma exposure to POS by at least 2-fold compared with 200 mg dose when POS is given under fasting conditions as well as when it is given with a high-fat meal. Thus, the increase of POS dose from 200 mg TID to 400 mg TID is most likely to result in an increase in plasma exposure to POS by at least 2 fold when POS is given either with food or under fasting conditions.

Table 9. Pharmacokinetic parameters (Mean±SD [range]) of POS tablets on Day 14 after oral (Q12 hr) administration of POS tablets for 14 days (n=9/Dose) (Study I96-089)

	200 mg BID	400 mg BID	Fold Difference
C_{max} (ng/mL)	1753±466 [1020-2230]	4150±816 [2920-5710]	2.37
AUC ₀₋₁₂ (ng·hr/mL)	16801±4319 [8929-21960]	39206±8020 [24475-47985]	2.33

Table 10. Pharmacokinetic parameters (Mean±SD [range]) of POS following single oral administration of POS tablets to healthy male volunteers (n=6 for each dose). (Study I95-098)

	200 mg	400 mg	Fold Difference
C_{max} (ng/mL)	332±70.8 [273-470]	611±190 [424-964]	1.84
AUC _{inf} (ng·hr/mL)	10896±3411 [5650-14634]	20264±6781 [12716-29387]	1.86

Table 11. Pharmacokinetic parameters (Mean±SD [range]) of POS (n=20) after a single oral administration of 400 mg oral suspension after a 10-hr fast or a high-fat breakfast (Study I96099)

	Suspension (fasted)	Suspension (high-fat meal)	Fold Difference
C _{max} (ng/mL)	132±65.8 [45.7-267]	512±176 [241-1016]	3.88
AUC _{inf} (ng·hr/mL)	4179±1285 [2705-7269]	13885±5655 [7854-34824]	3.3

Table 12. Pharmacokinetic parameters (Mean (CV%)) of POS (n=20) after a single oral administration of 200 mg oral capsule after a 10-hr fast or a high-fat breakfast (Study I95099)

	Capsules (fasted)	Capsules (high-fat meal)	Fold Difference
C _{max} (ng/mL)	102.3 (39%)	531.4 (32%)	5.2
AUC _{inf} (ng·hr/mL)	3588 (37%)	14293 (38%)	3.98

Briefly, the oral absorption of POS is dose-limited presumably due to low solubility of POS in aqueous and acidic media and significantly dependent upon food intake. The plasma exposure to POS after a single dose administration is increased by about 2.6-fold when given with a non fat meal (~14g fat) or a nutrient supplement (Boost Plus®: ~14 g fat) and by about 4-fold when given with a high-fat meal (~50 g fat). In fasted healthy subjects, the bioavailability of a total daily dose of POS 800 mg was increased by 80% when the dose was administered as 200 mg QID compared with when the dose administered as 400 mg BID.

One way to enhance the oral absorption of POS is to administer POS oral suspension with a nutritional supplement in patients who cannot tolerate a full meal. According to the study protocol, however, POS oral suspension should be administered with food and, therefore, administering POS with food appears to have been attempted as much as possible in the Study. In addition, as discussed in 2.1.3, the baseline disease sickness, which may represent patient status for food intake, did not correlate significantly with plasma exposure to POS. Thus, administering POS with a meal or a nutritional supplement does not appear to be a practically feasible way to increase plasma exposure to POS for patients whose plasma concentrations of POS need to be increased, because those patients may already take POS with food or liquid nutritional supplement, or because those patients may not be able to tolerate either food or oral liquid supplement.

An increase in the frequency of dosing, such as 200 mg QID, may be another way to increase plasma exposure to POS. However, QID dosing regimen is not likely to be preferred to TID dosing regimen in terms of coincidence of the timing of meals and compliance.

2.1.7. Is it appropriate to use Clinical Failure, instead of the incidence of Proven/Probable IFIs, for the determination of the cutoff concentration of POS to identify out the patients whose plasma concentrations of POS need to be increased?

It appears appropriate to use Clinical Failure as an end point to determine dose recommendation because the incidence of Proven/Probable IFIs also tended to be greater for patients whose C_{avg} was ≤ 700 ng/mL compared with patients whose C_{avg} was >700 ng/mL.

As mentioned above, the primary efficacy endpoint specified in the protocol was the incidence of Proven or Probable IFIs. However, since the study was designed to evaluate the efficacy of POS for the prophylaxis against IFIs, the FDA Medical Officers and Statistical reviewers considered that the incidence of Proven/probable IFIs per se is not appropriate to evaluate the efficacy of POS for the prophylaxis against IFIs. In addition, the incidence of Proven/Probable IFIs was too rare to be compared with statistical significance. Thus, Clinical Failure which associated with several factors (See 2. on page 10) was used as a primary end point to evaluate the efficacy of POS for prophylaxis against IFIs. The analysis using Clinical Failure as a primary end point supported the non-inferiority of POS compared with the control group (fluconazole) with statistical significance as the analysis using the incidence of Proven/Probable IFIs as an end point did. Similarly, the use of Clinical Failure for the recommendation of POS dose and administration should be validated in terms of the incidence of Proven/Probable IFIs.

As discussed in 2.1.2, the relationship between the incidence of Proven/Probable IFIs and C_{avg} of POS was not significantly significant ($p=0.3$; logistic regression), but the relationship between Clinical Failure and C_{avg} of POS was ($P<0.0001$). This may be due to the insufficient number of incidence of Proven/Probable IFIs to have statistical significance. Due to the same reason, there was no substantial difference in the incidence of Proven/Probable IFIs for 4 quartiles of POS C_{avg} (See Table 3 on page 13). Thus, alternatively, the incidence of Proven/Probable IFIs was compared between Q1-Q2 and Q3-Q4. Table 13 shows POS C_{avg} in patients who had Proven/Probable IFIs and Table 14 shows that the incidence of Proven/Probable IFIs and Aspergillus infection in Q1-Q2 vs. Q3-Q4. The results support that a higher incidence of Proven/Probable IFIs is most likely to be related with lower plasma exposure to POS.

Table 13. POS C_{avg} in patients who has Proven/Probable IFIs (Study C98316)

Subject ID	C_{avg} (ng/mL)	Quartile	Pathogen
I004000048	99	Q1	Aspergillosis
I004000049	158	Q1	Aspergillosis
I004000050	319	Q1	Candidiasis
I004000051	565	Q2	Aspergillosis
I004000052	681	Q2	Aspergillosis
I004000053	691	Q2	Other Fungi
I004000054	1562	Q3	Aspergillosis
I004000055	2080	Q4	Candidiasis

I004000056	2190	Q4	Other fungi
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Table 14. Incidence of Proven/Probable IFIs in Q1-Q2 vs. Q3-Q4 (Study C98316).

	Q1-Q2 (N=126)	Q3-Q4 (N=126)
C_{avg} (ng/mL)	21.5-915	915-3650
Incidence of Prove/Probable IFIs	4.76% (6/126)	2.38% (3/126)
Incidence of Aspergillosis	3.17% (4/126)	0.79% (1/126)

Further analysis, more importantly, showed that the incidence of Proven/Probable IFIs and Aspergillus infection in patients whose POS C_{avg} is ≤ 700 ng/mL were substantially higher compared with patients whose POS C_{avg} is > 700 ng/mL (Table 15). The results support the use of Clinical Failure for the recommendation of POS dose and validate the threshold plasma concentration of 700 ng/mL as C_{avg} in terms of the incidence of Proven/Probable IFIs.

Table 15. Incidence of Proven/Probable IFIs between those patients whose POS C_{avg} is ≤ 700 ng/mL and those patients whose POS C_{avg} is > 700 ng/mL (Study C98316).

C_{avg} (ng/mL)	≤ 700 ng/mL (N=92)	> 700 ng/mL (N=160)
Incidence of Prove/Probable IFIs	6.52% (6/92)	1.88% (3/160)
Incidence of Aspergillosis	4.35% (4/92)	0.63% (1/160)

In this analysis, 4 patients who had Proven/Probable IFIs were excluded because their plasma concentrations were measured only at more than 2 days after the last dose of POS. PK samples were collected at three days after the last dose of POS in 2 patients and at 14 days in 1 patient, and no information regarding PK sample day was provided in 1 patient. In the two patients whose PK samples were collected at three days after the last dose of POS, C_{avg} could be predicted using a mean $T_{1/2}$ (35 hours, range 20 to 66 hours). Based on the predicted C_{avg} values (approximately 54 ng/mL and 388 ng/mL), these two patients obviously belong to Q1. Including these two patients for the analysis, the incidence rate of Proven/Probable IFIs would be 7.5% (5/65) in Q1, 6.34% (8/126) in Q1-Q2, and 8.7% (8/92) in patients whose $C_{avg} \leq 700$ ng/mL, supporting the significant relationship between a higher incidence of Proven/Probable IFIs and lower plasma concentrations of POS.

The data obtained from Study P01899 also support the cutoff concentration of 700 ng/mL as C_{avg} to identify the patients who need an increase in POS dosage to attain a higher plasma concentration of POS. Compared with Study C98316, the plasma concentrations of POS were relatively lower in Study P01899 (See Table 5 on page 15). Table 16 shows POS C_{avg} in patients who had Proven/Probable IFIs and Table 17 shows that the incidence of Proven/Probable IFIs between those patients whose POS C_{avg} is ≤ 700 ng/mL and those patients whose POS C_{avg} is > 700 ng/mL. No incidence of Prove/Probable IFIs in patients who belong to Q4 and all Proven/Probable IFIs occurred for patients whose C_{avg} was ≤ 700 ng/mL. These results support again the use of Clinical Failure for the recommendation of POS dose and validate the threshold plasma concentration of 700 ng/mL as C_{avg} in terms of the incidence of Proven/Probable IFIs.

Table 16. POS C_{avg} in patients who had Proven/Probable IFIs (Study P01899)

Subject ID	C_{avg} (ng/mL)	Quartile	Pathogen
0054001468	254	Q1	Aspergillosis
0010001371	294	Q1	Other Fungi
0015001239	417	Q2	Aspergillosis
0015001415	491	Q3	Candidiasis
0057001492	606	Q3	Candidiasis
0002001271	629	Q3	Other Fungi

Table 17. Incidence of Proven/Probable IFIs between those patients whose POS C_{avg} is ≤ 700 ng/mL and those patients whose POS C_{avg} is > 700 ng/mL (Study P01899).

C_{avg} (ng/mL)	≤ 700 ng/mL (N=155)	> 700 ng/mL (N=60)
Incidence of Prove/Probable IFIs	3.87% (6/155)	0% (0/60)

Collectively, it is not appropriate to use Clinical Failure, instead of Proven/Probable IFIs, for the determination of the cutoff concentration of POS to identify the patients who needs an increase in the POS dosage. Additionally, the threshold concentration of 700 ng/mL as C_{avg} appears appropriate in terms of the incidence of Proven/Probable IFIs as well as in terms of Clinical Failure.

2.1.8. What will be the therapeutic advantage when POS dose is adjusted based on plasma concentrations of POS?

When dose is adjusted from 200 mg TID to 400 mg TID, based on the threshold C_{avg} of 700 ng/mL, the percent of patients whose C_{avg} is ≤ 700 ng/mL would be decreased from 37% (92/252) to 14% (35/252). The Clinical Failure rate for patients whose C_{avg} was ≤ 700 ng/mL (i.e., with 200 mg TID) would be reduced from 37% (34/92) to 25% (23/92) (Table 18).

According to the POS concentration-Clinical Failure relationship (See 2.1.2), in PK dataset from Study C98316, 37% total patients (92/252) has ≤ 700 ng/mL of C_{avg} which resulted in a Clinical Failure rate of $> 25\%$. When these patients receive 400 mg TID instead of 200 mg TID, plasma concentrations of POS is expected to be increased by at least 2 fold either under fasting conditions or when it given with food or a nutritional supplement (See 2.1.6). Accordingly, when dose is adjusted from 200 mg TID to 400 mg TID based on the threshold C_{avg} of 700 ng/mL, the percent of patients whose C_{avg} is ≤ 700 ng/mL can be decreased from 37% (92/252) to 14% (35/252) (Table 18).

The therapeutic advantage can also be found in terms of the incidence of Clinical Failure. In PK dataset of Study C98316, the incidence of Clinical Failure was significantly different for patients whose C_{avg} was > 700 ng/ml (18%; 29/160) from patients whose C_{avg} was ≤ 700 ng/mL (37%; 34/92). Based on these Clinical Failure rates, when dose adjusted from 200 mg TID to 400 mg TID, Clinical Failure rate for patients whose C_{avg} was ≤ 700 ng/mL (i.e., with 200 mg TID) can be reduced from 37% to 25% ($23 = 57 \times 0.18 + 35 \times 0.37$)/92).

Table 18. Percent of patients whose C_{avg} is ≤ 700 ng/mL and Clinical Failure rate as a function of POS dosing regimen

$C_{avg} \leq 700$ ng/mL	200 mg TID	400 mg TID (projection)
% of patients whose C_{avg} is ≤ 700 ng/mL	37% (92/252)	14% (35/252)
Clinical Failure rate in patients whose C_{avg} is ≤ 700 ng/mL	37% (34/92)	25% (23/92)

2.1.9. What dosage(s) are recommended based on the exposure-effectiveness relationship?

Based on the results of the above analyses, it is strongly recommended to determine POS dose according to its plasma concentration. The summary of dose recommendation based on the monitoring of POS plasma concentration is as follows.

Initial dose: 200 mg TID for all patients

Monitoring of plasma concentration(s) of POS on Day 2:

Plasma samples should be collected at 3 to 5 hours after any dose on Day 2.

- (a) If plasma concentration(s) of POS is ≤ 350 ng/mL, then give 400 mg TID
- (b) If plasma concentration(s) of POS is > 350 ng/mL, then give 200 mg TID

For patients whose plasma concentrations of POS cannot be high enough to ensure desirable clinical outcomes with 400 mg TID, other antifungal treatment for prophylaxis of IFIs may be needed. Thus, it is recommended to measure additional plasma concentrations of POS for patients who received 400 mg TID after Day 7 when plasma concentrations of POS reach steady state, and to switch to another antifungal treatment if C_{avg} after Day 7 is ≤ 700 ng/mL. Accordingly, the subsequent dose recommendation for patients who receive POS 400 mg TID is as follows.

Monitoring of plasma concentration(s) of POS after Day 7 for patients who received 400 mg TID:

- (a) If plasma concentration(s) of POS is > 700 ng/mL, then give 400 mg TID
- (b) If plasma concentration(s) of POS is ≤ 700 ng/mL, then switch to another antifungal drug

Figure 4 represents the scheme of dose recommendation of POS based on plasma concentrations of Posaconazole.

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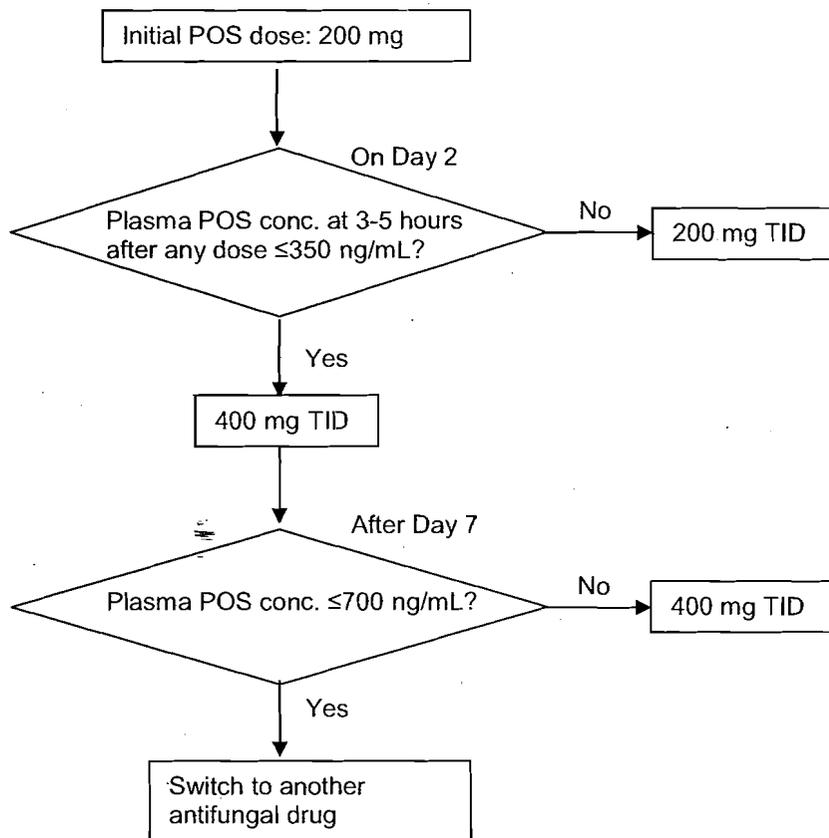


Figure 4. Dose recommendation of POS based on plasma concentrations of Posaconazole

2.1.10. What PK parameter was used for exposure-response relationship?

Individual subject's average concentration values (C_{avg}) were used to evaluate the exposure against response.

Since the elimination of POS is very slow (i.e., $T_{1/2}$: ~35 hours), the steady-state plasma concentration profile is relatively flat with minimal fluctuation over a dosing interval. Thus, individual average concentration values (C_{avg}) were used to evaluate the exposure against response. Figure 5 shows POS concentrations measured in all patients and patients who belonged in Q1 in Study C98316 as a function of time (days) after the beginning of POS treatment. The plasma concentrations of POS in patients who belong in Q1 were relatively low throughout the study period, indicating that C_{avg} in individual patient can be a PK parameter representing plasma exposure to POS.

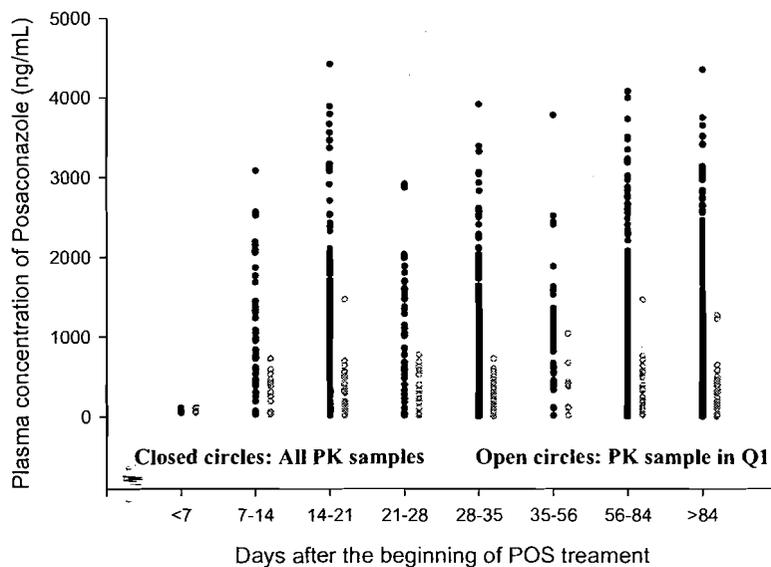


Figure 5. Plasma concentrations of POS (PK sample number=870) in all patients (n=252) as a function of time (days) after the beginning of POS treatment. (Study C98316)

2.2. Exposure-response relationship-Safety

2.2.1. What are the characteristics of the exposure-response relationship for safety?

The incidence rates of adverse events were not significantly dependent on plasma concentrations of POS.

The most common treatment-related (Possible and Probable) treatment-emergent adverse events were nausea, vomiting, diarrhea, hypokalemia, rash and elevations in hepatic enzymes (SGOT and SGPT increase). The relationship between these safety variables versus average plasma concentrations of POS (C_{avg}) were evaluated using a logistic regression analysis. In addition, the incidence rates of those adverse events were compared in 4 quartiles of C_{avg} . For these analyses, data from Study C98316 and P01899 were pooled. Plasma concentrations of POS were available from 450 patients of total 605 patients who received POS. The results are summarized in Table 19. Although the incidence of most treatment-related adverse events tends to be lower in the first quartile of C_{avg} compared with the fourth quartile of C_{avg} , the incidence rates of adverse events were not significantly dependent on plasma drug concentration.

Table 19. Incidence of treatment-emergent and drug-related (Possible and Probable) AEs (%) in the All Treated population in 4 quartiles of average plasma concentration POS (C_{avg}) (N=450; Studies C98-316 and P01988). Datasets from Study C98-316 and P01899 were pooled for these analyses.

	1 st Q (n=119)	2 nd Q (N=121)	3 rd Q (N=120)	4 th Q (N=120)	P value ^b
C_{avg} (ng/mL) ^a	205±105 [2.51-355]	498±77.1 [355-626]	835±138 [626-1118]	1751±538 [1118-3650]	
Diarrhea	3.36%	4.96%	8.33%	6.67%	0.4378
Nausea	7.56%	6.61%	10%	12.5%	0.3746
Vomiting	3.36%	4.96%	7.5%	6.67%	0.4639
Discontinuation	8.4%	7.44%	14.2%	17.5%	0.0595
Bilirubinemia	1.68%	3.31%	4.17%	3.33%	0.4787
SGOT increased	1.68%	2.48%	4.17%	3.33%	0.4016
SGPT increased	1.68%	3.31%	5%	3.33%	0.4911
Hepatic enz. increased	1.68%	3.31%	4.17%	3.33%	0.4787
Hypokalemia	0.84%	1.65%	4.17%	2.5%	0.4818
Rash	0.84%	1.65%	4.17%	3.33%	0.1739

^a: Mean±SD [range]

^b: Logistic regression for the relationship between the incidence of treatment-related adverse events and C_{avg}

2.2.2. Is there any expected safety issues when POS 400 mg TID is given to the patients whose steady-state C_{avg} is ≤ 700 ng/mL?

There would be expected to be no additional safety findings with 400 mg TID for those patients whose C_{avg} was ≤ 700 ng/mL (i.e., those who receive 200 mg TID initially). Based on the dose-proportional PK of POS, following 400 mg TID administration to patients whose C_{avg} was ≤ 700 ng/mL (i.e., those who receive 200 mg TID initially), C_{avg} would not be expected to be greater than 3650 ng/mL, which is the highest C_{avg} observed in patients treated with 200 mg TID in Study C98316.

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 § 552(b)(4) Trade Secret / Confidential

8 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

4.2. Population PK analysis

Objective of the analysis

To develop and validate a population pharmacokinetics model in the target population in order to find the influential covariates.

Methods

Design

This was a randomized, open-label, evaluator blinded, active-controlled, parallel-group, multicenter study. The study was designed to evaluate the safety and efficacy of posaconazole oral suspension compared with fluconazole or itraconazole in the prevention of invasive fungal infections in subjects with prolonged neutropenia due to remission induction chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes.

Data:

Pharmacokinetics

In the Posaconazole group (POS), 215 patients had at least one POS plasma concentration measurement. A total of 702 plasma POS samples were used in this analysis

Models

Pharmacokinetics

Structural Model

All patients with available pharmacokinetic data in the POS group were included. Time post dose was calculated using the time and date information of the sampling time. Dosing times were assumed to be the nominal dosing times planned in the clinical study protocol. The number of doses taken by each patient was calculated using the TID dosing regimen and the number of days each patient was on POS therapy. Advan's 2, 5, and 7 in NonMem were investigated. Advan 2 (Oral one compartment model) with microconstants (Trans 2) was used.

Covariate Model

Several subject covariates were available: gender, age, race, baseline body weight, the presence of mucositis at baseline, serum glutamic pyruvid transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), total bilirubin (BIL), gamma-

glutamyl transferase (GGT), presence of Neutropenia at baseline (NEU), occurrence of diarrhea (DIA), and the occurrence of vomiting (VOM). The effects of these covariates on the pharmacokinetic parameters of POS were investigated. In addition, the effect of intake of proton pump inhibitors (PPI) and H2 antagonists (H2A) on the PK of POS was investigated. Finally, the relationship between PK parameter estimates and the occurrence of IFIPP (Invasive Fungal Infection Proven or Probable) or IFIPPP (Invasive Fungal Infection Proved, Probable, or Possible) was investigated in a similar manner as categorical covariates. The bioavailability of POS has been shown to be significantly lower in fasting healthy volunteers relative to that in the fed state. However, no food intake data was available in this study and the effect of food on the plasma exposures of POS was not investigated.

Categorical covariates were investigated using the power model. For example, the effect of Race on V/F (V in NonMem) was incorporated into the model using the following equation:

$$V_i = TVV * \text{Theta}^{**\text{RACE}} * \exp(\text{eta})$$

where V_i is the individual predicted volume of distribution, TVV is the typical value of V (population mean value), and eta is a normally distributed value with a mean of zero (exponential or log-normal distribution of inter-subject variability in V). RACE is equal to 1 when individual is Caucasian and zero when the patient is non-Caucasian. As a result, the estimate of Theta represents the relationship between the mean estimates of V_i for Caucasians versus non-Caucasians.

Continuous covariates were introduced using the power model after correcting them with the mean value of that covariate. For example, the effect of age on the estimate of V_i was investigated using the following equation:

$$V_i = TVV * (\text{Age}/48.5)^{**\text{Theta}} * \exp(\text{eta})$$

where V_i is the individual predicted volume of distribution, TVV is the typical value of V (population mean value), and eta is a normally distributed value with a mean of zero (exponential or log-normal distribution of inter-subject variability in V), Age is the age for that patient, and 48.5 is the mean value of Age for the POS group (with PK data).

Covariates were investigated using a two-stage approach. First, a “Stepwise Forward Addition” was used and covariates with a change in the Objective function of ≥ 3.84 were incorporated one at a time. A second stage involved adding all the “significant” covariates from the first Stage (i.e., Stepwise Forward Addition) in one model (called Full Model) and then performing “Stepwise Backward Elimination”. Covariates that, when eliminated, caused a change greater than 10.88 in the Objective Function Value (OBJF) were kept in the model. The choice of the significant OBJF value was set a priori.

Covariates were assumed to affect V/F (apparent volume of distribution estimate, expressed as V in NonMem). Due to the nature of the data available, the model couldn't distinguish between the effect on V (true volume of distribution) and the effect on F

(bioavailability estimate). In other words, higher estimated V/F could mean higher volume of distribution estimate or a lower bioavailability estimate. Both will lead to lower exposures observed.

Since most of the data available in this study was at steady state conditions with no terminal phase defined, the typical value (population mean value) of half life was fixed at 35h [$k = 0.0198 \text{ h}^{-1}$]. Inter-subject variability of the k value was allowed assuming exponential (log-normal) distribution around the mean.

Inter-subject variability around the mean value of k_a and V was also assumed to have log-normal distribution. The same value of η was assumed for both V and k_a since the value of V in NonMem is actually V/F and the value of k_a is actually $k_a \cdot F$, the same η was used for both V and V/F.

Intra-subject (inter-occasion) variability was allowed and investigated with additive, proportional, and exponential models. An exponential model was then chosen based on the diagnostic plots. Model evaluation was performed using the OBJF value and diagnostics plots of Predicted versus Observed, Individual Predicted (ipred) Versus Observed, Residual, Weighted Residuals, and Predicted/Observed versus time plots.

The First Order Conditional Estimation method (FOCE, Method = 1 in NonMem) was used in the final model and covariate analysis. Initial parameter estimates for the FOCE method were used from successful NonMem runs with the First Order method (FO, Method = 0 in NonMem). Since plasma sampling in this study was sparse, T_{\max} estimation from observed data was deemed inappropriate. Additionally, data from all patients was analyzed simultaneously using NonMem regardless whether patients had extensive plasma sampling. Finally, in this clinical study, the number of breakthrough IFI infections was very low as a result of successful prophylaxis. Therefore a proper evaluation of the relationship between exposure response and AUC/MIC could not be conducted.

Software

The software used for the data formatting was Splus and for performing the population PK analysis, NONMEM was used.

Results and Discussion

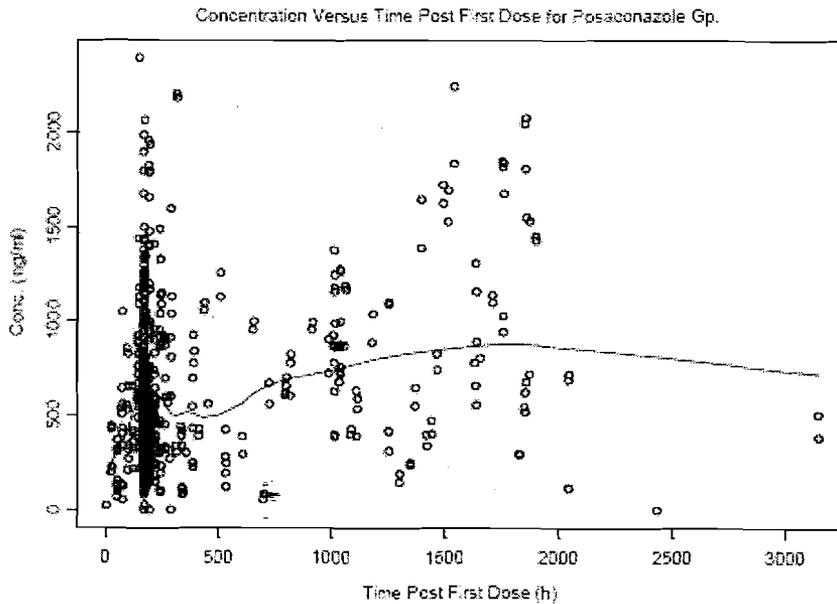
Data Integrity

All patients are included in the NonMem data sets Only 3 concentration time points were excluded as listed below:

- a. Patient 001125 at 195hr and 289hr time points only.
- b. Patient 001018 at 2431.33hr time point only.

The concentration-time profile for all subjects receiving posaconazole oral suspension 200 mg TID is given below:

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Model and Model Selection:

Final Model

Model description

Seven covariates were included in the "Full Model" following the Stepwise Forward Addition stage: DIA (Diarrhea), PPI (Intake of Proton Pump Inhibitors), IFIPP (Reported Invasive Fungal Infection, Proved or Probable), BIL (billirubin higher than twice the upper limit of normal), Baseline Body Weight, GGT liver enzymes higher than twice the upper limit of normal, and Race (Caucasian versus Non-Caucasian).

The Stepwise Backward Elimination Stage identified Baseline Body Weight and IFIPP as insignificant variables. The final model included five covariates as significant: DIA, PPI, BIL, GGT, and RACE (Caucasian versus Non-Caucasian).

The final estimated effects of the significant covariates on V/F estimate are included in Table 1. The model run numbers and comparisons of the OBJF values from each run of the Backward Elimination Stage are presented in Table 2.

Appears This Way
On Original

Table 1 Summary of Magnitude of Predicted Effects of Significant Covariates on V/F

Covariate	Estimated Effect on V/F (± Std. Error)	Estimated Effect on Exposure (Equals 1/Estimated Effect on V/F)
DIA	1.5 ± 0.20	0.667
PPI	1.43 ± 0.17	0.699
BIL	1.84 ± 0.33	0.544
GGT	1.17 ± 0.095	0.855
RACE (Caucasian vs. Non-Caucasian)	0.79 ± 0.065	1.266

Table 2. Model runs in the stepwise backward elimination stage

Model Runs in the Stepwise Backward Elimination Stage

Run #	Covariates	OBJF	Parameter	Value	Comments	OBJF Comparison	
131	DIA&PPI&FPP&GGT&BIL&WT&RACE	8350	ke	0.0196	Fixed ke to .0196. Eta(2) Related to ka and V.	BACKWARD ELIMINATION BASELINE	
			V	3380			
			ka	0.0428			
			Om1 CV%	60			
			Om2 CV%	39.1			
			EPS CV%	31.4			
			THETA4	1.6			DIA ON V/F
			THETA5	1.39			PPI ON V/F
			THETA6	1.21			IFIPP ON V/F
			THETA7	1.06			BILL ON V/F
			THETA8	0.39			WT (POWER) ON V/F
THETA9	1.2	GGT ON V/F					
THETA10	0.783	CAUCASIAN ON V/F					
132	DIA&PPI&FPP&GGT&BIL&WT&RACE	8425	ke		Fixed k to .0196. Eta(2) Related to ka and V.	75	
			V				
			ka				
			Om1 CV%				
			Om2 CV%				
			EPS CV%				
			THETA4	FIXED			DIA ON V/F
			THETA5				PPI ON V/F
			THETA6				IFIPP ON V/F
			THETA7				BILL ON V/F
			THETA8				WT (POWER) ON V/F
THETA9		GGT ON V/F					
THETA10		CAUCASIAN ON V/F					
133	DIA&PPI&FPP&GGT&BIL&WT&RACE	8360.4	ke		Fixed k to .0196. Eta(2) Related to ka and V.	30.4	
			V				
			ka				
			Om1 CV%				
			Om2 CV%				
			EPS CV%				
			THETA4				DIA ON V/F
			THETA5	FIXED			PPI ON V/F
			THETA6				IFIPP ON V/F
			THETA7				BILL ON V/F
			THETA8				WT (POWER) ON V/F
THETA9		GGT ON V/F					
THETA10		CAUCASIAN ON V/F					
134	DIA&PPI&FPP&GGT&BIL&WT&RACE	8351.2	ke		Fixed k to .0196. Eta(2) Related to ka and V.	1.2	
			V				
			ka				
			Om1 CV%				
			Om2 CV%				
			EPS CV%				
			THETA4				DIA ON V/F
			THETA5				PPI ON V/F
			THETA6	FIXED			IFIPP ON V/F
			THETA7				BILL ON V/F
			THETA8				WT (POWER) ON V/F
THETA9		GGT ON V/F					
THETA10		CAUCASIAN ON V/F					

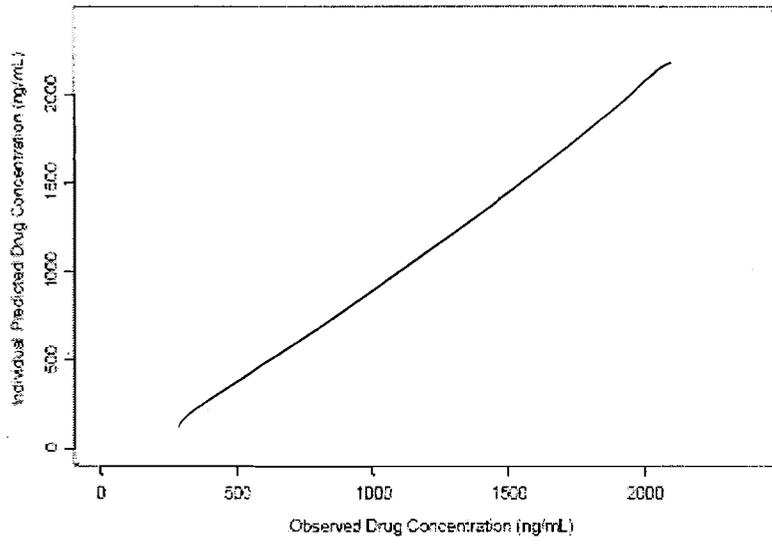
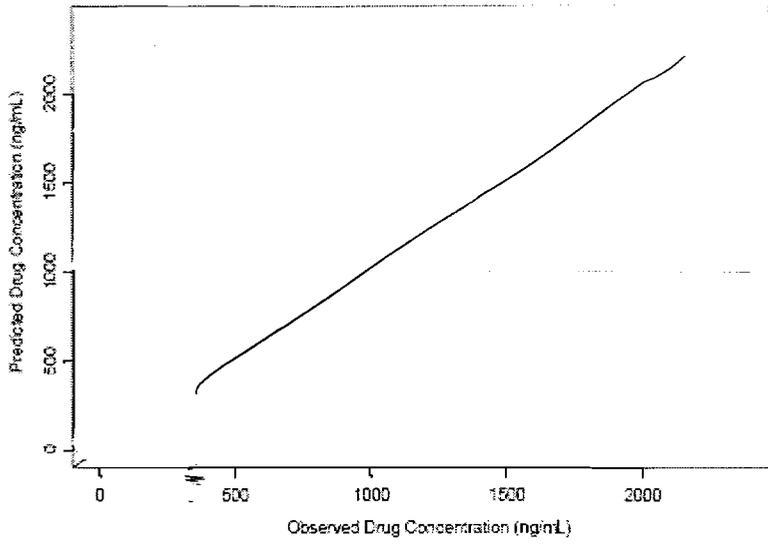
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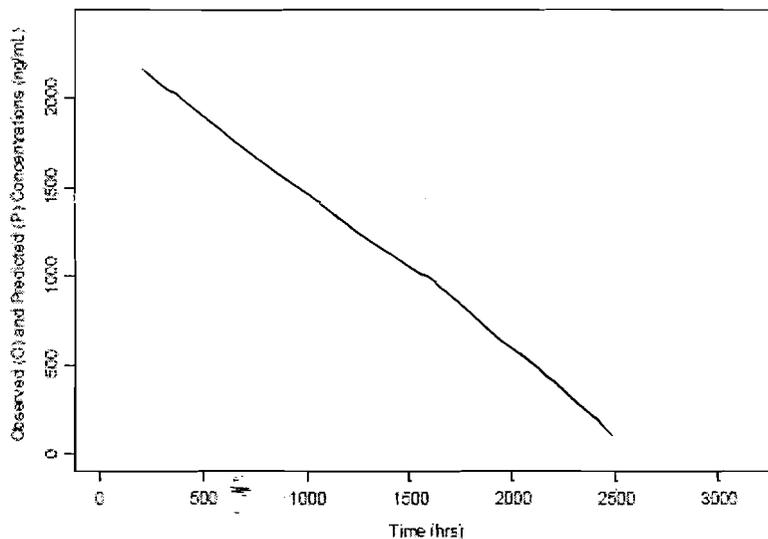
Run #	Covariates	OBJF	Parameter	Value	Comments	OBJF Comparison	
135	D:A&PPI&GGT&B:L&WT&RACE THIS IS A RUN WITHOUT IFPP. IT WILL SERVE AS BASE FOR NEXT RUNS.	8351.2	ke	0.0198	Fixed k to .0198. Eta(2) Related to ka and V.	New BASE	
			V	3420			
			ka	0.0431			
			Om1 CV%	49.1			
			Om2 CV%	38.1			
			EPS CV%	31.4			
			THETA4	1.5			DIA ON V/F
			THETA5	1.38			PP1 ON V/F
			THETA6	1.71			BILL ON V/F
			THETA7	0.395			WT (POWER) ON V/F
THETA8	1.19	GGT ON V/F					
THETA9	0.762	CAUCASIAN ON V/F					
136	D:A&PPI&GGT&B:L&WT&RACE THIS IS A RUN WITHOUT RACE. LOOKING FOR AN INCREASE IN OBJF BY MORE THAN 10.88 TO KEEP RACE IN THE EQUATION. race will be kept. Compared to Run 135	8401.9	ke	0.0198	Fixed k to .0198. Eta(2) Related to ka and V.	50.7	
			V	1750			
			ka	1.1600			
			Om1 CV%	56.2			
			Om2 CV%	35.8			
			EPS CV%	35.1			
			THETA4	1.53			DIA ON V/F
			THETA5	1.47			PP1 ON V/F
			THETA6	1.67			BILL ON V/F
			THETA7	0.391			WT (POWER) ON V/F
THETA8	1.15	GGT ON V/F					
THETA9	FIXED	CAUCASIAN ON V/F					
137	D:A&PPI&GGT&B:L&WT&RACE THIS IS A RUN WITHOUT GGT. LOOKING FOR AN INCREASE IN OBJF BY MORE THAN 10.88 TO KEEP GGT IN THE EQUATION. Compared to Run 135. GGT is significant and will not be removed.	8364.9	ke	0.0198	Fixed k to .0198. Eta(2) Related to ka and V.	13.7	
			V				
			ka				
			Om1 CV%				
			Om2 CV%				
			EPS CV%				
			THETA4				DIA ON V/F
			THETA5				PP1 ON V/F
			THETA6				BILL ON V/F
			THETA7				WT (POWER) ON V/F
THETA8	FIXED	GGT ON V/F					
THETA9		CAUCASIAN ON V/F					
138	D:A&PPI&GGT&B:L&WT&RACE THIS IS A RUN WITHOUT B:L. LOOKING FOR AN INCREASE IN OBJF BY MORE THAN 10.88 TO KEEP B:L IN THE EQUATION. Compared to Run 135. B:L is significant and wt not be removed.	8367.5	ke	0.0198	Fixed k to .0198. Eta(2) Related to ka and V.	16.3	
			V				
			ka				
			Om1 CV%				
			Om2 CV%				
			EPS CV%				
			THETA4				DIA ON V/F
			THETA5				PP1 ON V/F
			THETA6	FIXED			BILL ON V/F
			THETA7				WT (POWER) ON V/F
THETA8		GGT ON V/F					
THETA9		CAUCASIAN ON V/F					
139	D:A&PPI&GGT&B:L&WT&RACE THIS IS A RUN WITHOUT WT. LOOKING FOR AN INCREASE IN OBJF BY MORE THAN 10.88 TO KEEP WT IN THE EQUATION. WT SHOULD NOT BE INCLUDED IN THIS MODEL. Run is compared to Run 135. THIS MODEL RUN (139) IS THE FINAL MODEL WITH COVARATES	5360	ke	0.0198	Fixed k to .0198. Eta(2) Related to ka and V.	8.8	
			V	3290			
			ka	0.0398			
			Om1 CV%	47			
			Om2 CV%	38.5			
			EPS CV%	32.1			
			THETA4	1.50			DIA ON V/F
			THETA5	1.43			PP1 ON V/F
			THETA6	1.84			BILL ON V/F
			THETA7	FIXED			WT (POWER) ON V/F
THETA8	1.17	GGT ON V/F					
THETA9	0.787	CAUCASIAN ON V/F					

Goodness of fit

The diagnostic plots for the final model are given below:

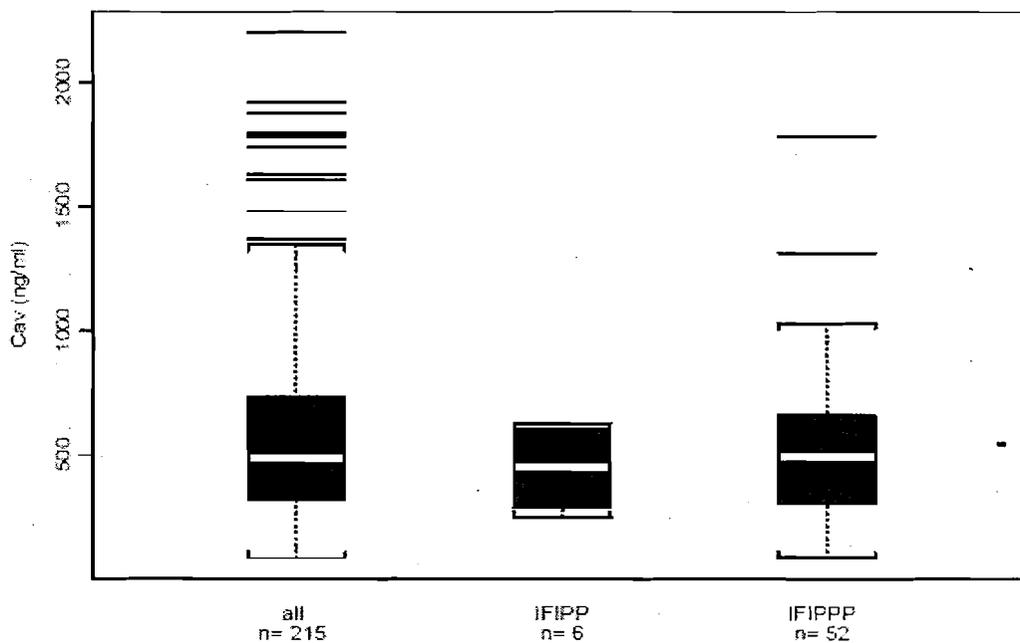
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Effect of Covariates on Average Concentrations

Subjects with IFIPP and IFIPPP have C_{av} values that are not different from the entire sampled population. This is demonstrated below.

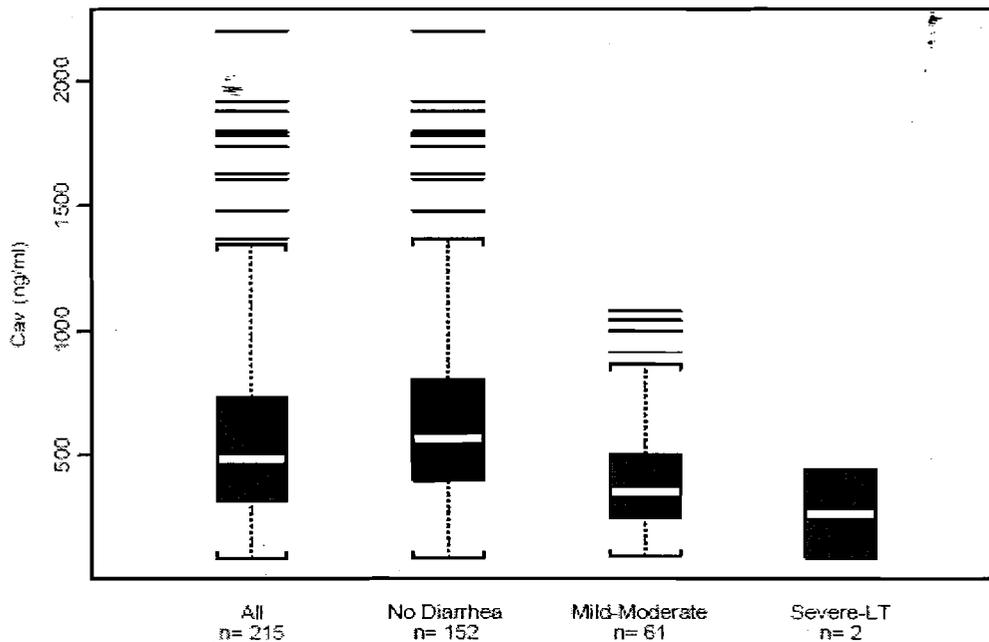


No association was found between C_{av} and gender ($P=0.2654$), baseline mucositis ($P=0.1002$), the presence of neutropenia ($P=0.7588$), occurrence of vomiting ($P=0.6842$), or H₂-receptor antagonist intake ($P=0.9129$).

Subjects with elevated GGT higher than twice the upper limit of normal (GGT $\geq 2 \times$ ULN) had C_{av} values that were lower than those with GGT $< 2 \times$ ULN

(P=0.0093). The difference between the mean C_{av} of these two groups is less than 30% and is not considered clinically relevant. A possible explanation for a lower C_{av} value in subjects with $GGT \geq 2 \times ULN$ could be that the subjects secreted comparatively less bile salts which are postulated to help solubilize POS in the GI tract. When all liver enzymes are taken into consideration, there was no difference in mean C_{av} values between subjects with any liver enzymes $\geq 2 \times ULN$ and subjects with liver enzymes $< 2 \times ULN$ (P=0.8196):

As expected for most orally administered drugs, C_{av} in subjects with recorded diarrhea was lower (P<0.0001) than those with no recorded diarrhea. The effect of diarrhea on C_{av} appeared to increase with its severity.



Caucasians had, on average, higher C_{av} values compared to non- Caucasians (P=0.0132).

Finally, subjects who received PPIs in the POS group had C_{av} values that were lower than subjects who had not received PPIs (P<0.0001). The ratio of C_{av} values (PPIs/no PPIs) was 0.71 (90% CI, 0.62-0.81).

In summary, C_{av} was found to be affected by four factors: diarrhea, $GGT \geq 2 \times ULN$, race and PPI intake. The table of subjects with IFIPP shows that none of these factors had a prevailing occurrence in these subjects is given below. Out of the 7 subjects with IFIPP, only 2 received a PPI, no subject had $GGT \geq 2 \times ULN$, and only 2 subjects had mild to moderate diarrhea. Five out of the 7 subjects with IFIPP were Caucasian. This leads to the conclusion that despite statistically significant differences in C_{av} values due to diarrhea, PPI intake, $GGT \geq 2 \times ULN$, and race, adequate plasma levels were attained in subjects for successful prophylaxis against IFIs.

Site No.	Subj. No.	Gender	Race	GGT	LIV	Diarrhea	PPINHIB
2	1271	M	Caucasian	0	0	0	0
10	1371	F	Asian	0	0	0	0
15	1239	M	Caucasian	0	1	1	0
15	1415	F	Caucasian	0	0	0	0
54	1468	F	Hispanic	0	0	1	0
57	1492	M	Caucasian	0	1	0	1
41	1329	F	Caucasian	0	0	0	1

no = 0, yes = 1.

F = female; GGT = gamma-glutamyl transpeptidase; IFI = invasive fungal infection; LIV = hepatic laboratory test; M = male; PPHIB = proton pump inhibitor; Site No. = site number; Subj. No. = subject number.

Reviewer's Comments

- The method and interpretation of population PK analyses to see the effect of covariates, e.g., patients demographic, on posaconazole PK seem appropriate from the perspective of Clinical Pharmacology and Biopharmaceutics.
- The sponsor has not performed the post hoc step in NONMEM to obtain estimates of the PK parameters such as AUC, CL, Vd etc.

Recommendations

Labeling

1. Please add a table to the clinical pharmacology section of the label to include the PK parameters such as steady state average concentrations, oral clearance, volume of distribution, AUC and elimination half-life of posaconazole.

4.2.1. POS PK in pediatric patients

In Studies P01899 and C98316, C_{avg} were available in 10 adolescents (13-17 years of age). The descriptive statistics of C_{avg} in adolescents are summarized in Table 1. Since these values were similar to patients ≥ 18 years of age. Thus, it appears appropriate to use the same dosing regimen for patients 13-17 years of age as adults (≥ 18 years of age).

Table 1. Steady-state average POS concentration in patients 13-17 years of age and adults (≥ 18 years of age) (Studies C98316 and P01899)

	N	Mean \pm SD	Median [Range]
13-17 years of age	10	760 \pm 404	682 [254-1370]

4.3 OCP Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics				
<i>New Drug Application Filing and Review Form</i>				
<i>General Information About the Submission</i>				
	Information		Information	
NDA Number	22-003	Brand Name	Noxafil	
OCP Division	DCP IV	Generic Name	Posaconazole	
Medical Division	DSPTP	Drug Class	Triazolol Antifungal	
OCP Reviewer	Seong H. Jang	Indication(s)	Prophylaxis of invasive fungal infections	
OCP Team Leader	Philip Colangelo	Dosage Form	Oral suspension (40 mg/mL)	
		Dosing Regimen	200 mg TID	
Date of Submission	12/22/05	Route of Administration	Oral	
Estimated Due Date of OCPB Review	05/22/05	Sponsor	Schering-Plough Corp	
PDUFA Due Date	06/22/06	Priority Classification	Priority (6 months)	
Division Due Date				
Advisory committee meeting	N/A			
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	2		
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 22-003

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Seong Jang
6/20/2006 04:12:08 PM
BIOPHARMACEUTICS

Phil Colangelo
6/20/2006 04:40:06 PM
BIOPHARMACEUTICS