CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205053Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 205-053	Submission Date(s): 01/25/2013
Drug	Posaconazole
Trade Name	Noxafil® Tablets
OCP Reviewers	Seong H, Jang, Ph.D.
OCP Team Leader	Phil Colangelo, Pharm.D., Ph.D.
OCP Division	DCP4
OND division	DAIP
Sponsor	Merck
Relevant IND(s)	IND (b) (4)
Submission Type; Code	Original; 1S
Formulation; Strength(s)	Oral Tablets; 100 mg
Indication	Prophylaxis of invasive *Aspergillosis* and *Candida* infections in patients 13 years of age and older
Dosage and Administration	Loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression.

Table of Contents

1. Executive Summary

Posaconazole (also known as SCH056592, MK-5592 and Noxafil®; hereafter referred to as POS), is a triazole antifungal agent with activity against both pathogenic yeasts and molds. POS was developed initially as an oral suspension and subsequently approved for the prevention of invasive fungal infections (IFI) in immunocompromised patients, specifically neutropenic patients under treatment for acute myelogenous leukemia (AML) or myelodysplasia (MDS), as well as hematopoietic stem-cell transplant (HSCT) patients with graft-versus-host disease (GVHD). The limitations of POS Oral Suspension are the need to administer multiple times a day and to take with food (preferably a high fat meal) or nutritional supplement to ensure adequate oral absorption and systemic PK exposure. The recommended dosing for prophylaxis is 200 mg POS Oral Suspension three times a day, with each dose to be taken with a high fat meal. Patients requiring antifungal prophylaxis include those with chemotherapy-induced side effects, namely severe nausea or vomiting, or GVHD complications of severe mucositis or diarrhea. Concomitant with these side effects, it may be difficult to ensure adequate food intake to optimize POS exposure. It is important to attain adequate exposure throughout the full course of antifungal prophylaxis to achieve optimal outcomes. Therefore, the sponsor developed a new solid oral tablet formulation of POS (hereafter referred to as POS Tablets) that can be taken once daily (b) (4), to reach the previously established POS systemic plasma exposure associated with adequate antifungal prophylaxis. (b) (4)

The clinical program for POS Tablets was designed to demonstrate comparable systemic PK exposure and safety among similar patient populations for which the POS Oral Suspension has already been approved (see above). The exposure target was based upon the range of exposures achieved and the exposure-response relationship established in earlier controlled studies of POS Oral Suspension. In this current NDA submission, the Phase 1B/3 study (Study P05615) showed that the proposed dose of POS Tablets (i.e., 300 mg QD following a loading dose of 300 mg BID on the first day) provided POS exposure within the pre-defined target exposure range, without safety problems, in patients with AML and in HSCT recipients (see **1.3** on pg. 3), indicating that the proposed dose of POS Tablets is acceptable for the prophylaxis of invasive fungal infections.

(b) (4) With the currently available information in this NDA, the Clinical Pharmacology team recommends that POS Tablets be given with food. Based on previous studies of the oral suspension, it is expected that food intake would also increase the systemic bioavailability of POS from the tablet formulation. (b) (4)

1.1. Recommendation

The Office of Clinical Pharmacology Division 4 has reviewed NDA 205-053 for POS Tablets. From a Clinical Pharmacology perspective, it is acceptable to support the approval of POS Tablets for prophylaxis of invasive *Aspergillosis* and *Candida* infections in patients 13 years of age and older.

1.2. Phase 4 Commitments

No Phase 4 commitments are recommended. (b) (4)

1.3. Summary of Important Clinical Pharmacology findings

Rationale for Development of POS Tablets

In order to overcome the limitations of POS Oral Suspension [i.e., the need to administer POS Oral Suspension multiple times a day and to take with food (preferably a high fat meal) or nutritional supplement to ensure adequate systemic PK exposure], the sponsor has developed a POS oral tablet formulation designed to release POS in the small intestine, thus maximizing systemic absorption. Specifically, the POS Tablets combine POS with a pH-sensitive (b) (4) ; this approach limits POS absorption in the stomach and maximizes its release in the small intestines.

Proposed Dose Justification: Bridging to POS Oral Suspension

The proposed dosing regimen of POS Tablets for the prophylaxis of invasive fungal infections is a loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day thereafter. This dosing regimen was evaluated in a Phase 1B/3 study (Study P05615) designed to demonstrate that this tablet dosage regimen will provide POS exposure within the pre-defined target exposure range. The exposure target was determined based upon the range of exposures achieved with the oral suspension product in safety and efficacy trials, as well as the exposure-response relationship found in earlier controlled studies of POS Oral Suspension (see **2.2.2**), i.e.,

- C_{min} at steady-state levels ≥500 ng/mL or AUC ≥12,000 hr•ng/mL in at least 90% of subjects (in the serial PK-evaluable dosing cohort)
- Mean C_{min} steady-state level ≤2,500 ng/mL or AUC ≤59,000 hr•ng/mL (in the serial PK-evaluable dosing cohort)
- No subject with a mean steady-state plasma concentration >3,750 ng/mL or with a steady-state AUC >90,000 hr•ng/mL (in the serial PK-evaluable dosing cohort)

In general, the steady state POS C_{min} following administration of POS Tablets 300 mg QD fell within the pre-defined target exposure (Table 1). The steady state POS C_{min} was ≥500 ng/mL in 94.6% of patients (176 out of 186 patients treated with 300 mg QD dose of POS Tablets). The mean C_{min} at steady-state in 186 patients treated with 300 mg QD dose of POS Tablets was ≤2,500 ng/mL (i.e., 1716 ng/mL). Although there were 6 patients with a steady state POS C_{min} >3750 ng/mL, no substantial safety issues were found in these patients (see **2.2.4.4**). Accordingly, the proposed dose of POS Tablets (i.e., 300 mg QD following a loading dose of 300 mg BID on the first day) is acceptable to the Clinical Pharmacology review team for the prophylaxis of invasive fungal infections.

Table 1. Steady-state C_{min} POS plasma concentrations (ng/mL) (Study P05615)

N	Mean	SD	Min	5th	10th	25th	Median	75th	90th	95th	Max
186	1716	1091	210	479	676	1105	1530	2060	2850	3220	9135

No. of Patients with average C_{min} <500 ng/mL: 10 (5.4%)
No. of Patients with average C_{min} >3750 ng/mL: 6 (3.2%)

Absorption and Food Effect

After administration of single and multiple doses of POS Tablets, peak plasma concentrations were attained at a median T_{max} of 4 to 5 hours both in patients and in healthy volunteers. Following a dose of 300 mg of the to-be-marketed formulation of POS Tablets (i.e., Tablet D), maximum concentrations were 614 and 2764 ng/mL after single dosing (fasted) and at steady state (fed), respectively (Study P07783). The absolute bioavailability (F) of POS Tablet D was calculated to be on average 0.54 at the clinically relevant dose of 300 mg relative to the (b) (4) IV solution (Study P07783).

No PK study was conducted to evaluate the effect of food on the systemic bioavailability of Tablet D. A PK study (Study P04975) conducted with earlier formulations (Tablet A and Tablet B) showed that no substantial food effect on the bioavailability of Tablet A and Tablet B. However, it is not reasonable to extrapolate the effect of food intake on the bioavailability of Tablet A and Tablet B to Tablet D. The composition of Tablet D is not comparable to that of Tablet A and Tablet B, and the difference in composition resulted in a substantial difference in the systemic bioavailability between Tablets A and B *vs.* Tablet D. In addition, in Study P05615 (a pivotal clinical trial), food intake data were not collected for the subjects. It is not acceptable to conclude that POS Tablets were in fact given without regard to food intake in Study P05615 merely because the study protocol indicated that the drug was to be taken without regard to food. With the currently available data, the Clinical Pharmacology review team is recommending that POS Tablets should be given with food because it is expected that food intake would increase the systemic bioavailability of POS from the tablet formulation (see **2.5.3** for further discussion).

Distribution, Metabolism and Excretion

No additional studies were conducted with POS Tablets, as the data obtained with POS Oral Suspension are considered appropriate to characterize POS distribution, metabolism and excretion from POS Tablets.

Drug-Drug Interactions: Effect of medications that affect the gastric pH and gastric motility

There is no clinically meaningful effect of gastric pH or gastric motility on the PK of POS after co-administration of POS tablets with the drugs listed in Table 2 below. However, POS exposure is substantially reduced by these same drugs after co-administration of POS Oral Suspension.

Table 2. Mean (%CV) pharmacokinetic parameters of POS following single 400 mg dose of POS Tablets alone or with concomitant medications that effect gastric pH or motility to healthy volunteers (Study P07764)

Treatment	**C_{max} (ng/ml)**	**T_{max}[a] (hr)**	**$AUC_{0-\infty}$ (hr·ng/ml)**	**$t_{½}$ (hr)**	**CL/F (L/hr)**
POS Alone	1090 (43)	4 (2-8)	42406 (49)	27.3 (37)	12.2 (64)
POS + Mylanta	1112 (36)	4.8 (3-12)	42468 (39)	27.7 (29)	11.1 (47)
POS + Ranitidine	1094 (37)	4 (3-5)	39287 (37)	26.9 (35)	11.7 (40)
POS + Esomeprazole	1104 (35)	4.5 (3-24)	41574 (43)	28.0 (30)	11.3 (42)
POS+ Metoclopramide	935 (44)	4 (2-6)	38513 (43)	29.0 (38)	12.9 (59)

[a]: Median (range)

_____.

Seong H. Jang, Ph.D.
Clinical Pharmacology Reviewer
OTS/OCP/DCP 4

Concurrence _____.

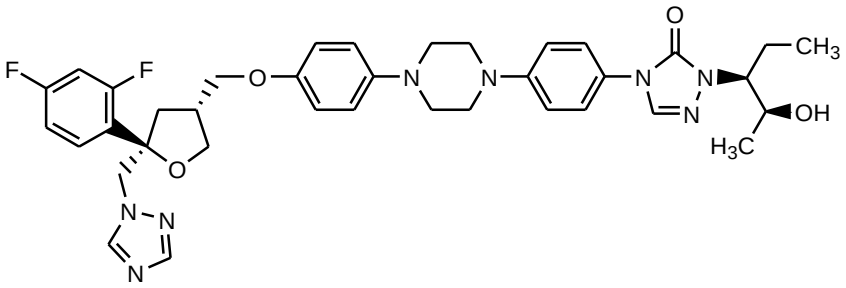
Phil Colangelo, Pharm.D., Ph.D.
Clinical Pharmacology Team Leader
OTS/OCP/DCP 4

2. Question-Based Review

2.1. General attributes of the drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

NOXAFIL® (posaconazole, POS) is a triazole antifungal agent available as a tablet or suspension for oral administration. POS is designated chemically as 4-[4-[4-[4-[[(3R,5R)-5- (2,4-difluorophenyl)tetrahydro-5- (1H-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1S,2S)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one with an empirical formula of $C_{37}H_{42}F_2N_8O_4$ and a molecular weight of 700.8. The chemical structure is:



POS is a white powder with a low aqueous solubility.

POS Tablet is a yellow, coated, capsule-shaped tablet containing 100 mg of POS. Each tablet contains the inactive ingredients: hypromellose acetate succinate, microcrystalline cellulose, hydroxypropylcellulose, silicon dioxide, croscarmellose sodium, magnesium stearate, and Opadry® II Yellow (consists of the following ingredients: polyvinyl alcohol partially hydrolyzed, Macrogol/PEG 3350, titanium dioxide, talc, and iron oxide yellow).

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

POS blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14α-demethylase responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane. The resulting accumulation of methylated sterol precursors and depletion of ergosterol within the cell membrane weakens the structure and function of the fungal cell membrane. This process may be responsible for the antifungal activity of posaconazole.

The proposed indications of POS Tablets are prophylaxis of invasive Aspergillus and Candida infections in patients, 13 years of age and older, who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The proposed dose of POS Tablets is summarized in Table 3. POS Tablets should be swallowed whole, and not be divided, crushed, or chewed. (b) (4) . The Clinical Pharmacology review team will recommend that POS Tablets should be given with food because it is expected that food intake would increase the systemic bioavailability of POS from the tablet formulation, as was observed with the oral suspension.

Table 3. Proposed dosage and administration for Noxafil Tablets

Indication	Dose and Duration of Therapy
Prophylaxis of Invasive Fungal Infections	Loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The POS Tablet formulation has been studied in six clinical studies in healthy volunteers and one pivotal clinical study in patients (Table 4). A total of 334 subjects treated with POS Tablets were enrolled in these studies to support the registration of POS Tablets: 104 healthy volunteers in Studies P04975, P05637, P07764, P07691, and P07783; 230 patients at risk of developing IFI (invasive fungal infections) in Study P05615.

Table 4. Overview of the clinical program with the POS Tablets

Study	**Short Protocol Titles**	**Study Design**	**POS Dose (mg)**	**Formulation and Food Intake (fasted if not specified)**	**No. of Subjects Treated with Active Drug**
P04975	PK & food effect study in healthy adult volunteers (SD)	XO (4-way, 2-part)	100	Tablet A, Tablet B, Capsule, OS (Fasted & fed)	16
P05637	PK study in healthy adult volunteers (SD and MD)	Parallel / fixed sequence	200, 400	200 BID 200 QD 400 QD Tablet C-green MD: without regard to food	19
P07691	Relative bioavailability study in healthy adult volunteers (SD)	XO	100	Tablet C-green Tablet D-yellow OS	23
P07764	DDI study with drugs impacting gastric pH or gastric motility in healthy adult volunteers (SD)	XO	400	Tablet D-green	21
P07783	Absolute bioavailability and MD PK study in healthy adult volunteers (SD and MD)	XO	300	Tablet D-yellow IV solution MD 300 QD with Tablet D-yellow MD: breakfast one hour after drug intake	13 SD 12 MD
P05615	Dose finding and confirmation study in adult patients receiving prophylaxis (MD)	Fixed sequence	200, 300	Tablet C-green Tablet D-green Without regard to food	20 (200 mg); 210 (300 mg)

XO: Crossover study

There was an up to 40% difference in the bioavailability of POS between the to-be-marketed formulation (Tablet D) and early development formulations (Tablet A, Tablet B, and Tablet C) (Table 5 and see **2.5.2** for details). Thus, the Clinical Pharmacology of POS Tablets was reviewed mainly based on the studies conducted with Tablet D.

Table 5. Comparison of dose normalized $AUC_{0-\infty}$ [geometric means (% CV)] between single dose studies performed with POS Tablets formulations.

Dose[a]	Treatment	$AUC_{0-\infty}$	$AUC_{0-\infty}$ normalized to 100 mg	Study Number
100 mg	Tablet A	11394 (24%)	11394	P04975
	Tablet B	11429 (23%)	11429	P04975
	Tablet C	9188 (33%)	9188	P07691
	Tablet D	8321 (36%)	8321	P07691
200 mg	Tablet C	23374 (25%)	11687	P05637
300 mg	Tablet D	21399 (49%)	7133	P07783
400 mg	Tablet C	44137 (36%)	11034	P05637
	Tablet D	37709 (55%)	9427	P07764

[a]: dose was given in 100 mg tablets

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The clinical program for POS Tablets was designed to demonstrate comparable systemic PK exposure and safety among similar patient populations for which the POS Oral Suspension has already been approved. Thus, the endpoint of clinical studies was whether the proposed dosing regimen of POS Tablets will provide POS exposure within the pre-defined target exposure range, which was determined based on an exposure-response (E-R) relationship established with POS Oral Suspension.

In clinical trials of the POS Oral Suspension, a clear E-R relationship was identified, with higher exposures associated with a higher likelihood of clinical response. In particular, efficacy for prophylaxis and salvage treatment with POS Oral Suspension was greater in POS-treated subjects than in control subjects when POS exposures were within the second or higher quartiles (Figures 1 and 2). Importantly, this effect was seen not only in the pivotal Phase 3 prophylaxis studies (P01899 and C/I98-316) but also in patients with aspergillosis enrolled in the refractory IFI study (P00041). The corresponding data are summarized in Table 6.

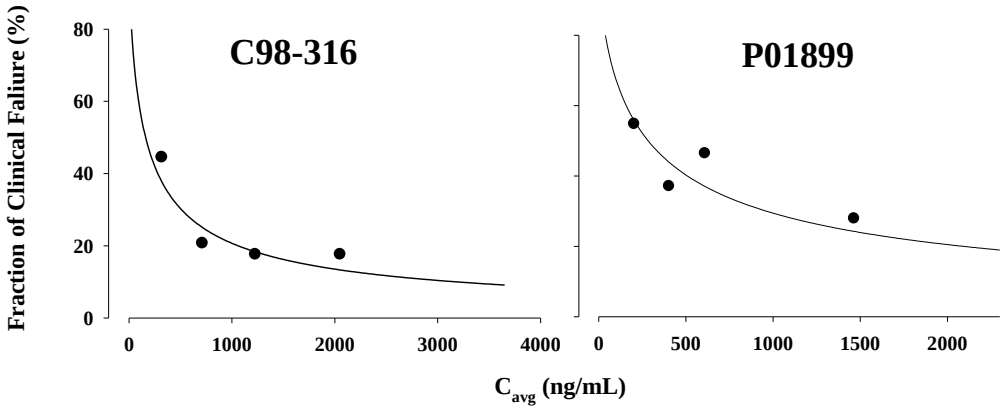


Figure 1. POS exposure-response relationship for the prophylaxis of IFIs in patients with GVHD (N=252) (Study C98316) and patients with AML/MDS (Study P01899) following administration of **POS Oral Suspension**. Logistic regression was performed using natural log of average concentrations per patient ($\log(C_{avg})$) 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 quartiles of C_{avg} (closed circles) are plotted to assess the goodness-of-fit.

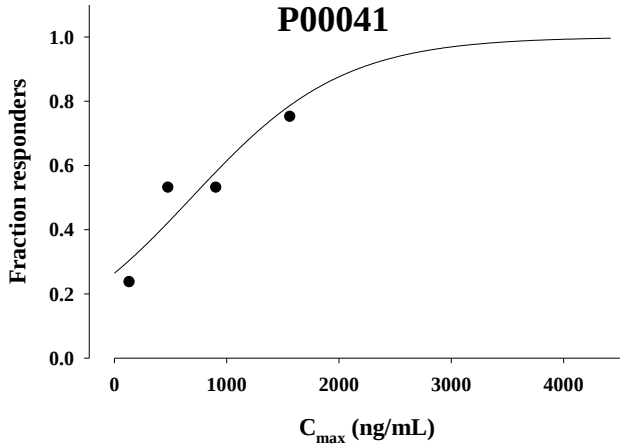


Figure 2. POS E-R relationship for the treatment of Aspergillosis in patients with *Aspergillus* infection (Study P00041; n=67) following administration of **POS Oral Suspension**. Logistic regression was performed using concentrations as a continuous variable and the clinical response as a binary variable (yes or no). The line represents the regression fit. Subsequent to the logistic regression, the response rates in each of 4 concentration quartiles (symbols) are plotted to assess the goodness-of-fit.

Table 6. POS Oral Suspension exposure response analysis in clinical treatment and prophylaxis trials

	Study P00041[a] (Treatment of refractory aspergillosis)		**Study P01899[b] (Prophylaxis in AML/MDS)**		**Study C98-316[b] (Prophylaxis in GVHD)**	
	C_{max} Range (ng/mL)	Response (%)	C_{avg} Range (ng/mL)	Response (%)	C_{avg} Range (ng/mL)	Response (%)
Q1	55-277	24	90-322	45.3	22-557	55.6
Q2	290-544	53	322-490	63.0	557-915	79.4
Q3	550-861	53	490-734	53.7	915-1563	82.5
Q4	877-2010	71	734-2200	72.2	1563-3650	82.5

[a]:Trial for salvage treatment of IFI
[b]: Prophylaxis trial
AML=acute myelogenous leukemia, MDS=myelodysplastic syndromes, GVHD=graft versus host disease

This exposure response relationship for POS Oral Suspension supported the exposure target for the registration of POS Tablet. The primary intent of the pivotal clinical study in patients (Study P05615) was to fully characterize the pharmacokinetics (PK) and assess safety of POS Tablets in neutropenic patients with acute myelogenous leukemia (AML) or myelodysplasia (MDS), and in patients who had undergone a HSCT and were under treatment for GVHD. Study P05615 was designed as a bridging study to the POS Oral Suspension clinical program. The exposure target for POS Tablets in Study P05615 was to be within the range of POS exposures previously studied and demonstrated to be safe and effective in the prophylaxis and salvage treatment setting with POS Oral Suspension.

The exposure target range for POS Tablets was set (by the sponsor) as follows:
• C_{avg} at steady-state levels ≥500 ng/mL or AUC ≥12,000 hr•ng/mL in at least 90% of subjects (in the serial PK-evaluable dosing cohort)
• Mean C_{avg} steady-state level ≤2,500 ng/mL or AUC ≤59,000 hr•ng/mL (in the serial PK-evaluable dosing cohort)
• No subject with a mean steady-state plasma concentration >3,750 ng/mL or with a steady-state AUC >90,000 hr•ng/mL (in the serial PK-evaluable dosing cohort)

However, C_{avg} at steady-state is not appropriate to bridge from POS Oral Suspension to POS Tablets because the bridging should be based on steady-state C_{min} measured for POS Tablets (see below). This issue was discussed with the sponsor in a previous meeting.

Steady-State C_{min} vs. Steady-State C_{avg} for POS Oral Suspension and POS Tablets
In the E-R analyses with data obtained from POS Oral Suspension, average values of POS concentrations (C_{avg}) measured in each patient were used by the FDA for the exposure of POS. In the Phase 3 studies with POS Oral Suspension, however, only one POS concentration was determined in the majority of patients. In those patients, C_{avg} was equal to the value of one POS concentration (mainly measured as a trough concentration). In patients who had two to three POS concentrations, C_{avg} was the average value of the POS concentrations determined in each patient. This method to determine C_{avg} in each patient who had limited POS concentrations in the Phase 3 study was accepted by the Clinical Pharmacology reviewer because the concentration-time profile of POS following administration of POS Oral Suspension at TID dosing at steady

state was considered to be nearly constant as observed during a constant IV infusion. The relatively constant POS concentrations at steady state were expected from a long elimination half-life of POS (i.e., ~35 hours) compared to the dosing interval (i.e., 8 hours) following administration of POS Oral Suspension 200 mg TID. In fact, relatively constant POS concentrations following administration of POS Oral Suspension 400 mg BID had been observed in a previous study.

However, the flat concentration profile does not hold true for POS Tablets. The elimination half-life of POS Tablets is 26 hours following a dose regimen of 300 mg QD and does not appear long compared to the dosing interval (i.e., every 24 hours). Thus, unlike following administration of POS Oral Suspension 200 mg TID, the concentration-time profile of POS following administration of POS Tablets 300 mg QD is not nearly constant (See Figure 4 in **2.2.5.1**).

The sponsor used a time-averaged concentration ("C_{avg}"=AUC/24 hour) for the analysis of PK data obtained from Phase 1B in Study P05615 where a full concentration-time profile was obtained from each patient. Note that "C_{avg}" (time-averaged concentration) is substantially different from C_{avg} (average value of measured concentrations) if the concentration-time profile is not nearly constant during dosing interval, whereas "C_{avg}" would be similar to C_{avg} and C_{min} if concentration-time profile is nearly constant during dosing interval. Then, in patients with one concentration (i.e., C_{min}) in Study P05615, the predicted "C_{avg}" was estimated from the relationship between "C_{avg}" and trough POS concentration (C_{min}) (i.e., "C_{avg}" = $214 + 1.07 \cdot C_{min}$), which was obtained from Phase 1B in Study P05615. Thus, C_{avg} for the E-R analyses in the studies with POS Oral Suspension is not comparable to "C_{avg}" obtained from Study P05615. Accordingly, bridging "C_{avg}" in Study P05615 to C_{avg} in Studies with POS Oral Suspension is not appropriate. It is not known whether the antifungal efficacy of POS is related to time above minimum effective concentration (i.e., 500 ng/mL). Thus, using a more conservative approach, bridging POS Tablets exposure to POS Oral Suspension should be based on C_{min} instead of "C_{avg}". Given this, the exposure target range for the use of POS Tablets in patients should be set as follows:

- C_{min} at steady-state levels ≥500 ng/mL or AUC ≥12,000 hr•ng/mL in at least 90% of subjects (in the serial PK-evaluable dosing cohort)
- Mean C_{min} steady-state level ≤2,500 ng/mL or AUC ≤59,000 hr•ng/mL (in the serial PK-evaluable dosing cohort)
- No subject with a mean steady-state plasma concentration >3,750 ng/mL or with a steady-state AUC >90,000 hr•ng/mL (in the serial PK-evaluable dosing cohort)

2.2.3. Are the active moieties in plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

POS was the active moiety measured in human plasma in clinical pharmacology studies, biopharmaceutical studies, and clinical studies. There is no evidence that any POS metabolites are pharmacologically active. Because POS plasma protein binding is not concentration-dependent, total drug concentration (bound plus free) of POS was measured in human plasma.

2.2.4. Exposure-response

2.2.4.1. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to onset and offset of the desirable pharmacological response or clinical endpoint.

Because efficacy was not one of the objectives for Study P05615, no formal E-R analyses were conducted on the POS Tablet data. See **2.2.2** for the E-R relationship for efficacy following POS Oral Suspension.

2.2.4.2. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to onset and offset of the desirable pharmacological response or clinical endpoint.

The E-R analyses for safety of POS Oral Suspension (Studies P01899 and C/I98-316) indicated that there was no correlation of POS exposure and safety (i.e., similar incidence of adverse events at different POS exposure).

The E-R relationships for safety of POS Tablets were evaluated with the data from Study P05615. This assessment was performed using all subjects for whom steady-state concentrations had been determined, and combined the C_{min} PK-evaluable population for both the 200 mg and 300 mg dosing cohorts. For this analysis, subjects were included according to C_{avg}, and the incidence of reported treatment-related Treatment-Emergent Adverse Events (TEAEs) was evaluated by quartile of exposure. A total of 205 subjects were included in the analysis of the incidence of AEs by quartile of exposure. Table 7 summarizes the incidence of treatment-related TEAEs by quartile of exposure. Table 8 summarizes the most common treatment-related TEAEs ($\geq$2% incidence) for the four quartiles by descending frequency. Within the range of exposures that have been observed in this study, there does not appear to be an association of higher POS concentration with a higher incidence of a treatment-related TEAE following administration of POS Tablets.

Table 7. Summary of all treatment-related TEAEs by quartile of C_{avg} values, all C_{min} PK-evaluable subjects, POS Tablets - 200 mg and 300 mg cohorts combined

	Cavg Mean (ng/mL)	Cavg Range	No. of Subjects	No. of Subjects Reporting Any Adverse Event

Quartile 1	860 ng/mL	442 ng/mL to 1223 ng/mL	51	29 (57)
Quartile 2	1481 ng/mL	1240 ng/mL to 1710 ng/mL	51	19 (37)
Quartile 3	1979 ng/mL	1719 ng/mL to 2291 ng/mL	51	16 (31)
Quartile 4	3194 ng/mL	2304 ng/mL to 9523 ng/mL	52	20 (38)

Table 8. Summary of treatment-related TEAEs by quartile of C_{avg} values, all C_{min} PK-evaluable subjects, POS Tablets - 200 mg and 300 mg cohorts combined. Adverse Events are presented in decreasing frequency based upon the treatment group 'PK Evaluable Subjects'.

Mean C_{avg} (ng/ML) Range (ng/mL) Number of Subjects	Quartile 1 860 442 -1223 n=51	Quartile 2 1481 1240 - 1710 n=51	Quartile 3 1979 1719 - 2291 n=51	Quartile 4 3194 2304 - 9523 n=52
Nausea	5 (10)[a]	5 (10)	3 (6)	7 (13)
Diarrhoea	6 (12)	3 (6)	6 (12)	2 (4)
Abdominal Pain	4 (8)	3 (6)	2 (4)	1 (2)
Vomiting	3 (6)	3 (6)	0	4 (8)
Alanine Aminotransferase Increased	2 (4)	2 (4)	4 (8)	1 (2)
Hypokalaemia	3 (6)	0	3 (6)	2 (4)
Rash	5 (10)	1 (2)	1 (2)	1 (2)
Aspartate Aminotransferase Increased	0	2 (4)	3 (6)	2 (4)
Abdominal Pain Upper	2 (4)	1 (2)	1 (2)	2 (4)
Dyspepsia	1 (2)	2 (4)	3 (6)	0
Hypophosphataemia	3 (6)	1 (2)	1 (2)	1 (2)
Liver Function Test Abnormal	2 (4)	2 (4)	0	1 (2)
Decreased Appetite	1 (2)	2 (4)	0	1 (2)
Flatulence	1 (2)	1 (2)	2 (4)	0
Hypomagnesaemia	2 (4)	1 (2)	0	1 (2)

[a]: number and incidence (%)

2.2.4.3. Does this drug prolong the QT or QTc interval?

The evaluation of effect on QT and QT prolongation was not conducted following the administration of POS Tablets. Results from a multiple time-matched ECG analysis in healthy volunteers did not show any increase in the mean of the QTc interval following administration of POS Oral Suspension (up to 400 mg BID; see Clinical Pharmacology Review 2006).

2.2.4.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration response, and are there any unresolved dosing or administration issues?

Yes, the dosing regimen selected by the sponsor is consistent with the known relationship between dose-concentration response. There is no unresolved dosing or administration issue.

The dose that was evaluated in Part 2 of Study P05615 was determined in Part 1 of the study. In Part 1, two sequential and escalating dosing cohorts (200 mg QD and 300 mg QD, after BID on Day 1 only) were evaluated with serial PK sampling to fully characterize the PK profile of POS. The PK parameters of POS on Day 8 following administration of POS Tablets 200 mg QD and 300 mg QD to patients undergoing chemotherapy for AML or MDS are summarized in Table 9.

Table 9. Mean (%CV) of PK parameters in serial PK-evaluable subjects on Day 8 following multiple dosing of POS Tablets (200 mg QD and 300 mg QD)

Dose	N	C_{max} (ng/mL)	T_{max}[a] (hr)	AUC_{0-24} (ng·hr/mL)	C_{avg} (ng/mL)	C_{min} (ng/mL)	CL/F (L/hr)
200 mg	18	1310 (47)	4 (2.0-8.1)	23500 (49)	981 (48)	812 (55)	10.9 (53)
300 mg	33	1930 (32)	2.2 (1.3-8.1)	34300 (36)	1440 (36)	1190 (47)	10.1 (43)

[a]: Median (range)

Based on steady-state (on Day 8) data from these serial PK-evaluable patients, 6 of 18 (i.e., 33%) patients receiving POS Tablets 200 mg QD attained C_{min} < 500 ng/mL, whereas 3 of 33 (9%) patients receiving POS Tablets 300 mg QD attained C_{min} < 500 ng/mL. Accordingly, 300 mg QD (after BID on Day 1 only) was determined to proceed to Part 2 of the study.

The distribution of steady state POS C_{min} following administration of POS Tablets 300 mg QD is shown in Figure 3 and Table 10 (Study P05615). In general, the steady state POS C_{min} ranged within the pre-defined target exposure (see **2.2.2**). The steady state POS C_{min} was ≥500 ng/mL in 94.6% (176 out of 186 patients) of patients treated with 300 mg QD dose of POS Tablets. The mean C_{min} at steady-state in 186 patients treated with 300 mg QD dose of POS Tablets was ≤2,500 ng/mL (i.e., 1716 ng/mL). Although, there were 6 patients with a steady state POS C_{min} >3750 ng/mL, no substantial safety issues were found in these patients (see detailed narratives for these 6 patients in Table 11. Accordingly, the proposed dose of POS Tablets (i.e., 300 mg QD with a loading dose of 300 mg BID on the first day) is acceptable for the prophylaxis of invasive fungal infections from the perspective of the Clinical Pharmacology review team.

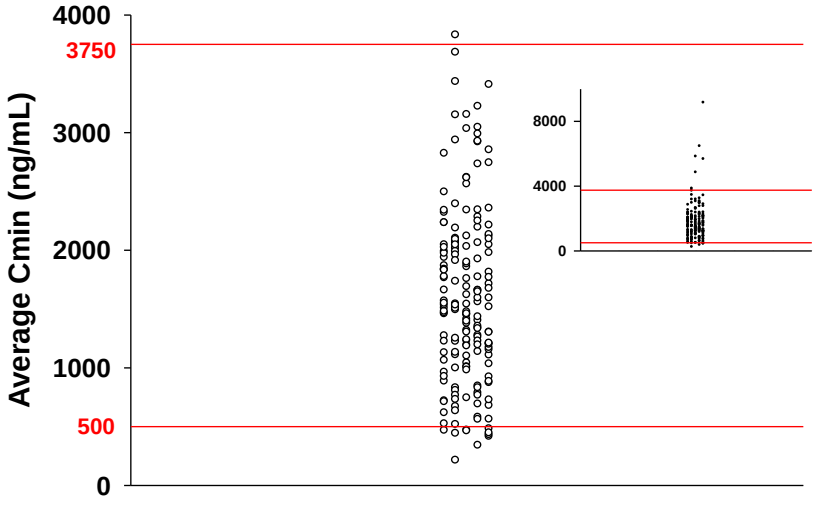


Figure 3. Distribution of steady state POS C_{min} (Study P05615)

Table 10. Steady-state C_{min} POS plasma concentrations (ng/mL) (Study P05615)

N	Mean	SD	Min	5th	10th	25th	Median	75th	90th	95th	Max
186	1716	1091	210	479	676	1105	1530	2060	2850	3220	9135

No. of Patients with average C_{min} <500 ng/mL: 10 (5.4%)
No. of Patients with average C_{min} >3750 ng/mL: 6 (3.2%)

Table 11. Individual PK parameters of subjects with average C_{min} ≥3750 ng/mL (All C_{min} PK-evaluable subjects, POS Tablets - 300 mg Cohort)

Subject Number	Treatment Duration (days)	Avg C_{min} (ng/mL)	Predicted C_{avg} (ng/mL)	Primary Disease	Comments
21/000110	28	3830	4120	HSCT	• Subject with acute Grade 1 GVHD. • No treatment-related TEAEs reported. • The subject completed treatment.
29/000128	28	5800	6130	HSCT	• Subject with chronic extensive GVHD of skin, liver, and mucosa. • Treatment-related TEAEs (all mild or moderate intensity) included the following: abdominal pain, decreased magnesium, decreased potassium, decreased calcium, decreased phosphorus, decreased heart rate, increased alkaline phosphatase, and supraventricular extrasystoles (study medication not discontinued). No treatment given for these mild or moderate AEs. • The subject completed treatment.
36/000182	29	6445	6790	HSCT	• Subject with chronic limited GVHD. • Treatment -related TEAEs included the following: mild and moderate increased ALT (Baseline 54 U/L, Peak 213 U/L), mild AST increased (Baseline 19

					U/L, Peak 38 U/L), and mild alkaline phosphatase (Baseline 110 U/L, Peak 137 U/L). • Improvement of ALT seen while continuing study medication. • The subject completed treatment.
36/000196	8	4820	5130	HSCT	• Subject with chronic limited GVHD. • Subject experienced one treatment-related TEAE of severe increased blood pressure (BP) to 170/110 (baseline 120/70) without associated symptoms on Day 8. Normal ECG. New concomitant medication of oral contraceptives. • The subject discontinued study treatment on Day 8. • Antihypertensive therapy was given on Day 8 with improvement in BP. • No other treatment-related TEAEs or cardiovascular events reported.
36/000199	28	9130	9520	HSCT	• No treatment-related TEAEs reported. • The subject completed treatment.
13/000217	28	5640	5970	HSCT	• Subject with intermittent skin GVHD. • Treatment-related TEAE of mild, intermittent nausea reported on Day 12 and was ongoing. • The subject completed treatment.

ALT=alanine aminotransferase; AML=acute myelogenous leukemia; BP=blood pressure; ECG=electrocardiogram; GVHD=graft-versus-host disease; HSCT=hematopoietic stem cell transplant; Predicted Cavg= predicted average concentration from Cmin; TEAEs=treatment-emergent adverse events.

2.2.5. What are the PK characteristics of the drug and its major metabolite?

Overall, the single-dose PK of POS following administration of POS Tablets was linear at doses ranging from 100 mg to 300 mg. The general POS PK characteristics following POS Tablets administration are similar to those following POS Oral Suspension except the absorption process. The detailed PK characteristics of POS following administration of POS Tablets are provided below.

2.2.5.1. What are the single and multiple dose PK parameters?

The PK parameters of POS following single and multiple oral administration of Tablet D (the final to-be-marketed formulation) are listed in Tables 12 and 13, respectively. The mean concentration-time profile of POS following multiple oral administration of the to-be-marketed Tablet D was described in Figure 4.

Table 12. Mean (% CV) PK parameters of POS following single dose administration of POS Tablets

Study	Dose (mg)	N	$AUC_{0-\infty}$ (ng·hr/mL)	C_{max} (ng/mL)	T_{max}[a] (h)	$t_{1/2}$ (h)	CL/F (L/h)
P07691	100	22	8786.2 (33)	287 (40)	5 (3-12)	27 (27)	12.7 (37)
P07783	300	13	23647 (48)	614 (38)	5 (3-6)	28 (26)	15.4 (46)

[a]: Median (range)

Table 13. Mean (% CV) PK parameters of POS following multiple dose administration of POS Tablets (Study P07783)

Dose (mg)	AUC_{τ}[†]	C_{max} (ng/mL)	C_{avg} (ng/mL)	C_{min} (ng/mL)	T_{max}[a] (h)	$t_{1/2}$ (h)	Cl/F (L/h)
300*	51618 (25.4)	2764 (20.6)	2151 (25.4)	1785 (28.5)	4 (3-6)	31 (39.6)	7.5 (25.6)

[a]: Median (range)
[*]: Multiple doses of 3x100 mg POS Tablet D-yellow, twice daily on Day 1 and once daily on Days 2 to 8

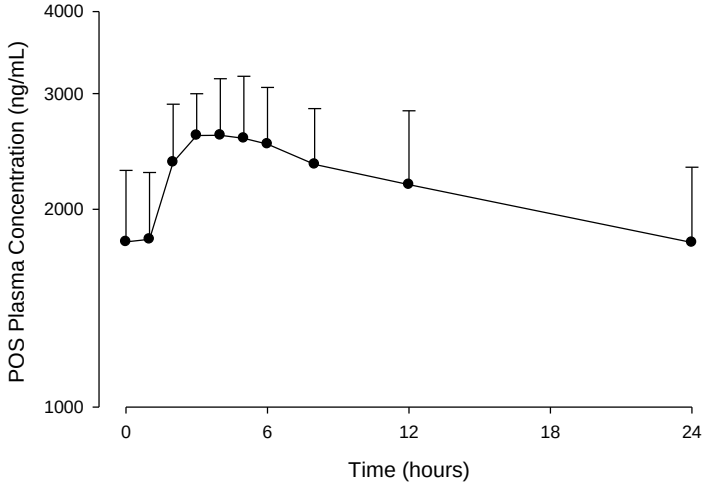


Figure 4. The mean concentration-time profile of POS following multiple oral administration of the to-be-marketed Tablet D (on Day 8, Study P07783)

POS concentration steady state was reached by Day 6 of 300 mg daily doses. The mean trough concentration on Day 6, 7 and 8 ranged from 1646 ng/mL to 1749 ng/mL (Table 14). The mean ratio [90% CI] of the pairwise comparisons between Days 6, 7 and 8 were 1.05 [0.93, 1.19] and 0.98 [0.92, 1.05].

Table 14. Assessment of time to reach steady state using posaconazole plasma trough concentrations

Study Day Comparison	LS Mean For Pair-wise Difference	90% CI For Pair-wise Difference
(Day 7+Day 8)/2 *vs.* Day 6	1.05	(0.93, 1.19)
Day 8 *vs.* Day 7	0.98	(0.92, 1.05)

2.2.5.2. How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Patients have approximately 25% lower exposure as compared to healthy volunteers after multiple dosing of POS Tablets. Factors associated with the underlying acute illness may have had an impact on POS absorption and steady state exposure.

One patient study was performed using the POS Tablets (Study P05615) in which 200 and 300 mg doses were investigated. Comparison of the exposure and CL/F and $t_{1/2}$ based on multiple dose data are shown in Tables 15 and 16.

Table 15. Mean values of selected PK parameters after administration of POS Tablets to healthy volunteers (HV) and patients

Steady state exposure	C_{max} (ng/mL)	T_{max}[a] (h)	C_{avg}[b] (ng/mL)
200 mg HV (Study 05637)	1800	5	1310
200 mg patients	1310	4	981
300 mg HV (Study 07783)	2764	4	2151
300 mg patients	2090	4	1580

[a]: Median
[b]:Cavg = AUCτ/τ;

Table 16. Mean (% CV) PK parameters after multiple dose administration of POS Tablets to healthy volunteers and patients

	CL/F (L/h)	$T_{1/2}$ (h)	V/F (L)
Healthy volunteers	7.5 (58)	31 (36)	327 (57.3)
Patients	9.8 (48)	32 (49)	Na

Na: Not analyzed

The mean C_{avg} at steady state in patients was 981 ng/mL and 1580 ng/mL for 200 mg and 300 mg dose, respectively. The exposures that were reported in this study are approximately 25% lower than that seen with POS Tablets in studies performed in healthy volunteers. In Study P05637, when healthy volunteers were given a dose of 200 mg QD to steady state, the healthy volunteer population achieved a C_{avg} of 1310 ng/mL. For the 300 mg dose level, mean steady state C_{avg} obtained in healthy volunteers was 2151 ng/mL (Study P07783).

For both the patient study and the healthy volunteer study, the time to maximal concentration (T_{max}) was similar. Half-life is comparable between healthy volunteers and patients after multiple dosing. Apparent clearance is somewhat higher in patients as compared to healthy volunteers. This is most likely the effect of bioavailability differences between healthy volunteers and patients. In patients, it is likely that factors associated with the underlying acute illness may have had an impact on POS absorption and steady state exposure. For POS Tablets, the differences in exposure between healthy volunteers and patients are much less than the exposure differences reported for POS Oral Suspension for these populations [see Clinical Pharmacology review for POS Oral Suspension (May, 2006)].

2.2.5.3. What are the characteristics of drug absorption?

After administration of POS Tablets, peak plasma concentrations were attained at a median T_{max} of 4 to 5 hours both in patients and in healthy volunteers, after both single and multiple dosing. For 300 mg dose POS Tablet D (the final to-be-marketed formulation), maximum concentrations were 614 and 2764 ng/mL after single dosing (fasted) and at steady state (fed), respectively (Study P07783).

The absolute bioavailability of POS Tablet D was calculated to be on average 0.54 at the clinically relevant dose of 300 mg relative to the (b) (4) IV solution (Study P07783). Mean plasma concentration-time profiles and pharmacokinetic parameters following a single-dose administration of POS Tablet D (Treatment A: 3 x 100 mg tablet) and POS IV solution (Treatment B: 300 mg) are presented in Figure 5 and Table 17, respectively. The individual absolute bioavailability estimates in that study ranged from 0.26 to 0.77. Variability (expressed as %CV) of the $AUC_{0-\infty}$ was 48% for POS Tablets and 32% for the POS IV solution.

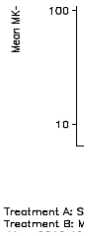


Figure 5. Mean plasma concentration-time profiles following a single-dose administration of POS Tablet D (Treatment A: 3 x 100 mg tablet) and POS IV solution (Treatment B: 300 mg)

Table 17. Summary of POS PK parameters [Geometric Mean (% CV)] following a single-dose administration of POS Tablet D (Treatment A: 3 x 100 mg tablet) and POS IV solution (Treatment B: 300 mg)

Parameter (unit)	Treatment A (N=13)	Treatment B (n=13)
C_{max} (ng/mL)	572 (41.9)	4172 (22.3)
T_{max} (hr)[a]	5.00 (2.98 – 6.00)	0.5 (0.25 – 0.5)
$T_{1/2}$ (hr)	27.4 (23.3)	27.9 (25.4)
AUC_{0-t} (ng·hr/mL)	20606 (49.2)	40767 (36.0)
$AUC_{0-\infty}$ (ng·hr/mL)	21399 (49.0)	42044 (36.9)
V_z/F (V for IV) (L)	554.1 (33.0)	287.1 (23.6)
CL/F (CL for IV) (L/hr)	14.0 (49.0)	7.1 (37.0)

[a]: Median (range)

No PK study was conducted to evaluate the effect of food on the systemic bioavailability of Tablet D (i.e., to-be-marketed formulation). It is not reasonable to extrapolate the results of Study P04975 (i.e., the effect of food intake on the bioavailability of Tablets A and B to Tablet D) because the composition of Tablet D is not comparable to that of Tablet A and Tablet B, and the composition difference resulted in a substantial difference in the absorption between Tablets A and B *vs.* Tablet D (see Table 26 in **2.5.2.1**)**.** See **2.5.3** for further discussion regarding the effect of food intake on the bioavailability of POS Tablets).

2.2.5.4. What are the characteristics of drug distribution?

POS is highly protein bound (>98%), predominantly to albumin. After administration of the POS Tablets, POS has a mean apparent volume of distribution of 394 L (CV, 42%), ranging between 294-583 L among the studies in healthy volunteers. From the absolute bioavailability study (Study P07783), it was concluded that volume of distribution (after intravenous administration) was 287 L, indicating that POS may be distributed into tissues.

2.2.5.5. Does the mass balance study suggest renal or hepatic as the major route of elimination?

No formal radiolabelled mass-balance studies have been conducted with POS Tablets as data obtained with the oral suspension are considered appropriate.

Following administration of POS Oral Suspension, POS is predominantly excreted in the feces (77% of the radiolabeled dose) with the major component eliminated as parent drug (66% of the radiolabeled dose). Renal clearance is a minor elimination pathway, with 14% of the radiolabeled dose excreted in urine (<0.2% of the radiolabeled dose is parent drug) [Clinical Pharmacology Review of POS Oral Suspension (May, 2006)].

2.2.5.6. What are the characteristics of drug metabolism?

No additional metabolism studies with POS Tablets have been performed as the data obtained with POS Oral Suspension are considered appropriate. POS does not have any major circulating oxidative metabolites and its concentrations are unlikely to be altered by inhibitors of CYP450 enzymes. Of the circulating metabolites, the majority are glucuronide conjugates of POS with only minor amounts of metabolites formed by CYP450. The primary metabolic pathways for POS include direct glucuronidation, oxidation, cleavage (N- and O-dealkylation), and conjugation (glucuronidation and sulfonation) of oxidative metabolites or cleavage products. CYP3A4 (and possibly CYP1A1 and 3A5), UGT1A4, and P-glycoprotein (PGP) are enzymes and transporters that play a role in the elimination of POS. Furthermore, POS is a strong inhibitor for CYP3A4, and also inhibits PGP and UGT1A1. Induction of glucuronidation decreases POS exposure. The excreted metabolites in urine and feces account for approximately 17% of the administered radiolabeled dose. See the Clinical Pharmacology Review of POS Oral Suspension (May, 2006) for the further information.

2.2.5.7. What are the characteristics of drug excretion?

POS is eliminated with a mean half-life ($t_{½}$) ranging between 26 and 31 hours and a mean apparent clearance ranging from 7.5 to 11 L/hr following administration of POS Tablets. See **2.2.5.5** for the renal elimination routes of POS following administration of POS Oral Suspension.

2.2.5.8. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The POS Tablets exhibited linear pharmacokinetics in healthy volunteers after multiple once-daily dosing between 200 mg and 300 mg in terms of AUC and C_{max}, but there was a less than dose proportional increase between once-daily dosing of 300 and 400 mg (Table 18). No doses above 400 mg QD have been investigated with the POS Tablets.

Table 18. Treatment effect on pharmacokinetic parameters following multiple dose oral administration of POS Tablets – Composite PK analysis

Parameter	Treatment	N[a]	Dose-normalized comparison vs. 300 mg QD		
			GMR	90% CI	p-Value[b]
$AUC_{0\text{-}24hr}$ (ng·hr/ml)	Tablet C 200 mg BID	8	0.936	0.470-1.865	0.8717
	Tablet C 200 mg QD	8	1.001	0.503-1.993	0.9982
	Tablet C 400 mg QD	8	0.772	0.410-1.452	0.4898
	Tablet D 300 mg QD	11			
C_{max} (ng/ml)	Tablet C 200 mg BID	8	0.821	0.437-1.542	0.5967
	Tablet C 200 mg QD	8	1.035	0.550-1.945	0.9274
	Tablet C 400 mg QD	8	0.742	0.416-1.324	0.3868
	Tablet D 300 mg QD	11			

[a]:Number of observations, some subjects from crossover studies had more than one observation
[b]:p-Value is for the hypothesis testing whether the true GMR is 1 for the corresponding comparisons

The data indicate that steady state POS exposure is dose proportional between 200 mg QD and 300 mg QD as the geometric mean ratios (GMRs) for all three dose normalized parameters are

essentially 1. It should be noted that because different doses and formulations have been used in the different studies, it is difficult to discriminate between effects of dose, study and tablet formulation on the exposure after administration of POS Tablets.

2.2.5.9. How do the PK parameters change with time following chronic dosing?

After multiple dosing of POS Tablets in healthy volunteers the CL/F is somewhat lower as compared to CL/F after single dosing (7.5 versus 15.4 L/h, for multiple and single dosing, respectively) and half-life is somewhat longer (31 hours after multiple dosing and 26 hours after single dosing). This results in a greater accumulation than that predicted from single-dose data.

POS is metabolized only to a limited extent. POS is a strong inhibitor for CYP3A4, and also inhibits P-glycoprotein (PGP) and UGT1A1, systems that are involved in the metabolism and elimination of POS from the body. As it cannot be excluded that POS is able to at least partly inhibit its own metabolism/elimination, this might be a possible explanation for the effect of multiple dosing on the apparent clearance.

In summary, the data indicate a small decrease in apparent clearance upon multiple dosing of POS Tablets, for which no single clear explanation exists. Multiple doses of POS result in greater than expected exposures based on single dose data. However, these exposures will be beneficial in terms of attaining the exposure greater than needed for efficacy and remain within the exposure ranges observed previously that were shown to be safe (See **2.2.4.2**).

2.2.5.10. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Based on the composite PK analysis, the multiple-dose PK data in healthy volunteers showed higher variability compared to single dose data with a % CV of 46.5% and 42.2%, respectively for $AUC_{0\text{-}24hr}$ and C_{max}. The variability of steady state pharmacokinetics in patients was moderate to high with % CV of 46.8% for $AUC_{0\text{-}24hr}$ and 42.2% for C_{max}, which was very similar to the variability in healthy subjects at steady state.

As there was only one study (Study P04975) containing data with repeated measurements, the within-subject variability was not very well characterized.

2.3. Intrinsic Factors

The effects of intrinsic factors on the exposure and exposure-response relationship for POS following the administration of POS Tablets are anticipated to be similar to those for POS Oral Suspension and were not evaluated further in this NDA. Please see the previous Clinical Pharmacology Review (May, 2006) for the further information regarding POS Oral Suspension.

2.4. Extrinsic factors

The effects of extrinsic factors on the exposure and exposure-response relationship for POS Oral Suspension are anticipated to be similar to those for POS Tablets with the exception of

interaction of POS Tablets with antacids, proton pump inhibitors, gastric motility drugs, and H2 acid blocking agents (see below). Briefly, POS is an inhibitor of the cytochrome P450 enzyme CYP3A4 at clinically relevant concentrations and, thus, possesses the potential for drug interactions with concomitantly administered drugs metabolized by CYP3A4. In vivo, POS does not significantly inhibit other human CYP450 enzymes, including CYP1A2, CYP2E1, CYP2C8/9 and CYP2D6. POS does not have any major circulating metabolites and its concentrations are unlikely to be altered by inhibitors and/or inducers of CYP450 enzymes. While most POS is excreted unchanged via the biliary tract, a minor route of metabolism of POS is via UDP -glucuronosyltransferase (Phase 2 enzymes); therefore, inhibitors or inducers of this clearance system may affect POS's plasma concentrations. POS is a substrate and inhibitor of the transporter PGP, so inhibitors or inducers of the PGP system may affect POS plasma concentrations. Please see the Clinical Pharmacology Review of POS Oral Suspension (May, 2006) for the further information.

In this NDA, a drug interaction study with POS Tablets was conducted to evaluate the effect of concomitant medications that affect the gastric pH and gastric motility on the pharmacokinetics (PK) of POS (Study P07764).

Study 07764: Effect of medications that affect the gastric pH and gastric motility: There is no clinically meaningful effect of gastric pH or gastric motility on the PK of POS after co-administration of POS Tablets with each of these drugs affecting the gastric pH or gastric motility, whereas POS exposure after administration of POS Oral Suspension is substantially reduced by these drugs.

A summary of pharmacokinetic parameters following single-dose administration of 4 X 100 mg POS Tablets alone (Treatment A) or with concomitant medications including the antacid Mylanta® (Treatment B), ranitidine (Treatment C), esomeprazole (Treatment D), or metoclopramide (Treatment E) is presented in Table 19. Mean plasma concentration-time profiles of POS are presented in Figure 6. The comparisons of $AUC_{0\text{-last}}$ and C_{max} between treatment groups are summarized in Tables 20-23.

Table 19. Mean (%CV) of the PK parameters of POS following single-dose administration of 400 mg POS Tablets alone with concomitant medications to healthy volunteers

Treatment	C_{max} (ng/mL)	T_{max}[a] (hr)	$AUC_{0\text{-last}}$ (hr·ng/mL)	$AUC_{0\text{-}\infty}$ (hr·ng/mL)	$t_{½}$ (hr)	CL/F (L/hr)	Vz/F (L)
POS Alone	1090 (43)	4 (2-8)	40967 (47)	42406 (49)	27.3 (37)	12.2 (64)	435.2 (51)
POS + Mylanta®	1112 (36)	4.8 (3-12)	41247 (39)	42468 (39)	27.7 (29)	11.1 (47)	419.0 (36)
POS + Ranitidine	1094 (37)	4 (3-5)	38046 (35)	39287 (37)	26.9 (35)	11.7 (40)	428.1 (35)
POS + Esomeprazole	1104 (35)	4.5 (3-24)	40083 (40)	41574 (43)	28.0 (30)	11.3 (42)	431.7 (34)
POS + Metoclopramide	935 (44)	4 (2-6)	36975 (40)	38513 (43)	29.0 (38)	12.9 (59)	498.1 (49)

[a]: Median (min-max)

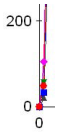


Figure 6. Arithmetic mean POS plasma concentration-time profiles following single-dose administration of 400 mg POS Tablets Alone or with concomitant medications to healthy volunteers (N = 20 for Treatment A, C, D, and E; N = 21 for Treatment B) (Inset is Semi-Log Scale)

Table 20. Summary of POS pharmacokinetic parameters for comparison of a single 400 mg dose of POS Tablets with a single 400 mg dose of POS Tablets + 20 mL of **Mylanta®** ultimate strength liquid in healthy subjects

PK parameter	Treatment A[a]			Treatment B[b]			Treatment (A/B)		rMSE[d]
	N	GM[e]	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0\text{-last}}$[c]	20	36892	(30370, 44813)	21	38394	(31697, 46507)	1.04	(0.9, 1.2)	0.271
C_{max}[c]	20	982	(815, 1184)	21	1045	(871, 1255)	1.06	(0.9, 1.26)	0.314

[a]Treatment A: A single 400 mg of POS Tablets
[b]Treatment B: A single 400 mg dose of POS Tablets + 20 mL of Mylanta ultimate strength liquid
[c]: Back-transformed least-squares mean and CI from mixed effects model performed on natural log-transformed values.
[d]rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effect model.
rMSE*100% approximates the within-subject % CV on the raw scale.
[e]GM: geometric mean

Table 21. Summary of POS pharmacokinetic parameters for comparison of a single 400 mg dose of POS Tablets with a single 400 mg dose of POS Tablets + morning dose of 150 mg **ranitidine** tablets BID in healthy subjects

PK parameter	Treatment A[a]			Treatment C[b]			Treatment (A/B)		rMSE[d]
	N	GM[e]	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0\text{-last}}$[c]	20	36892	(30370, 44813)	20	35963	(29606, 43684)	0.97	(0.84, 1.12)	0.271
C_{max}[c]	20	982	(815, 1184)	20	1022	(848, 1231)	1.04	(0.88, 1.23)	0.314

[a]Treatment A: A single 400 mg of POS Tablets
[b]Treatment C: A single 400 mg dose of POS Tablets + morning dose of 150 mg ranitidine tablet BID
[c]: Back-transformed least-squares mean and CI from mixed effects model performed on natural log-transformed values.
[d]rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effect model.
rMSE*100% approximates the within-subject % CV on the raw scale.
[e]GM: geometric mean

Table 22. Summary of POS pharmacokinetic parameters for comparison of a single 400 mg dose of POS Tablets with a single 400 mg dose of POS Tablets + **esomeprazole** 40 mg QAM x 5 days (Day -4 to 1) in healthy subjects

PK parameter	Treatment A[a]			Treatment D[b]			Treatment (A/B)		rMSE[d]
	N	GM[e]	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0\text{-last}}$[c]	20	36892	(30370, 44813)	20	37534	(30905, 45586)	1.02	(0.88, 1.17)	0.271
C_{max}[c]	20	982	(815, 1184)	20	1033	(857, 1245)	1.05	(0.89, 1.24)	0.314

[a]Treatment A: A single 400 mg of POS Tablets
[b]Treatment D: A single 400 mg dose of POS Tablets + esomeprazole 40 mg QAM x 5 days (Day -4 to 1)
[c]: Back-transformed least-squares mean and CI from mixed effects model performed on natural log-transformed values.
[d]rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effect model.
rMSE*100% approximates the within-subject % CV on the raw scale.
[e]GM: geometric mean

Table 23. Summary of POS pharmacokinetic parameters for comparison of a single 400 mg dose of POS Tablets with a single 400 mg dose of POS Tablets + **metoclopramide** 15 mg Four Times Daily During 2 Days (Day -1 and 1)

PK parameter	Treatment A[a]			Treatment E[b]			Treatment (A/B)		rMSE[d]
	N	GM[e]	95% CI	N	GM	95% CI	GMR	90% CI	
$AUC_{0\text{-last}}$[c]	20	36892	(30370, 44813)	20	34150	(28113, 41483)	0.93	(0.8, 1.07)	0.271
C_{max}[c]	20	982	(815, 1184)	20	847	(703, 1021)	0.86	(0.73, 1.02)	0.314

[a]Treatment A: A single 400 mg of POS Tablets
[b]Treatment E: A single 400 mg dose of POS Tablets + metoclopramide 15 mg Four Times Daily During 2 Days (Day -1 and 1)
[c]: Back-transformed least-squares mean and CI from mixed effects model performed on natural log-transformed values.
[d]rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effect model.
rMSE*100% approximates the within-subject % CV on the raw scale.
[e]GM: geometric mean

2.5. General Biopharmaceutics

2.5.1. Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

POS is a Biopharmaceutics Classification System (BCS) Class 2 (low solubility-high permeability). See Clinical Pharmacology Review of POS Oral Suspension (May, 2006) for further information.

2.5.2. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The to-be-marketed formulation (Tablet D) was used in the pivotal clinical trial (Study P05615). As part of the early formulation development of POS tablets, three tablet formulations (Tablet A, Tablet B, and Tablet C) were evaluated. An overview of the composition of the three tablet formulations and the to-be-marketed formulation (Tablet D) is summarized in Table 24.

Table 24. Description of the composition of POS Tablet formulations.

Component	Function	Tablet A mg/tablet	Tablet B mg/tablet	Tablet C[a] mg/tablet	Tablet D[b] mg/tablet
(b) (4)					
Posaconazole Micronized	(b) (4)	100.0	100.0	100.0	100.0
Hypromellose Acetate Succinate[c], NF/Ph, Eur				(b) (4)	(b) (4)
(b) (4)					
Cellulose Microcrystalline, NF/Ph, Eur					
(b) (4)					
Hydroxypropyl Cellulose					
Silicon Dioxide, NF/Ph, Eur					
(b) (4)					
Croscarmellose Sodium, NF/Ph, Eur					
Magnesium Stearate, NF/Ph, Eur					
(b) (4)					
Opadry® II (b) (4)					
(b) (4)					

[a]: Tablet C is the film coated tablet with green color for cosmetic purposes only.
[b]: Tablet D is the film coated tablet with either yellow or green color for cosmetic purposes only.
[c] (b) (4).
[d]: (b) (4).

2.5.2.1. What data support or do not support a waiver of *in vivo* BE data?

Because the to-be-marketed formulation (Tablet D) was used in the pivotal clinical trial (Study P05615), an *in vivo* BE study was not needed. However, three clinical pharmacology studies were conducted in order to evaluate the relative and absolute bioavailability of POS administered as different tablets and dosage forms and/or the effect of food on the pharmacokinetics of POS.

The biopharmaceutical studies included:
• P04975 – 4 different POS formulations were evaluated in this single-dose relative bioavailability study: Tablet A, Tablet B, oral suspension, and capsule. A food effect was also evaluated in this study.
• P07691 – 3 different POS formulations were evaluated in this single dose relative bioavailability study: Tablet D, Tablet C, and oral suspension.
• P07783 – 2 different POS formulations were evaluated in this absolute bioavailability study: Tablet D versus an (b) (4) IV solution.

Study P07691 showed that following a single dose administration of POS 100 mg in the fasted state in healthy adults, the AUCs and C_{max} of Tablet D were slightly lower compared to Tablet C (12% and 14% lower respectively for $AUC_{0-\infty}$ and C_{max}, Table 25)

Table 25. Relative bioavailability of POS following oral administration of Tablet D and Tablet C (Study P07691).

		AUC_{0-last} (ng.hr/mL)	$AUC_{0-\infty}$ (ng.hr/mL)	C_{max} (ng/mL)
Tablet C (n=23)	GM	9208	8775	309.8
	90% CI	(8214, 10322)	(7804, 9867)	(271.2, 353.9)
Tablet D (n=23)	GM	8236	7723	265.3
	90% CI	(7253, 9352)	(6733, 8860)	(229.5, 306.7)
Ratio Tablet /Tablet C	GMR	0.894	0.880	0.856
	90% CI	(0.821, 0.975)	(0.799, 0.970)	(0.748, 0.980)

No single study was conducted to compare all 4 tablet formulations. A cross-study comparison using an ANOVA between the prototype tablet formulations (i.e., Tablet A, Tablet B and Tablet C) and the to-be-marketed tablet formulation (Tablet D) showed that the mean $AUC_{0-\infty}$ and C_{max} estimates following administration of Tablets A and B were approximately 43% and 25% greater, respectively, compared with Tablet D when all were given in the fasted state (Table 26).

Table 26. Effect of formulation on pharmacokinetic parameters following single dose oral administration of POS

Parameter	Formulation	N[a]	Comparison vs. Tablet D		
			GMR	90% CI	p-Value[b]
$AUC_{0-\infty}$ (ng·hr/ml)	Tablet A	16	1.430	1.196-1.710	0.0012
	Tablet B	16	1.435	1.200-1.715	0.0011
	Tablet C	41	1.067	0.935-1.218	0.4155
	Tablet D	55			
C_{max} (ng/ml)	Tablet A	16	1.271	1.003-1.612	0.0961
	Tablet B	16	1.257	0.991-1.594	0.1127
	Tablet C	42	1.128	0.996-1.277	0.1104
	Tablet D	55			

[a]: Number of observations, some subjects from crossover studies had more than one observation
[b]: p-Value is for the hypothesis testing whether the true GMR is 1 for the corresponding comparisons

2.5.2.2. What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

Not applicable.

2.5.2.3. If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Not applicable.

2.5.3. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

(b) (4)

With the currently available data submitted with the POS Tablets NDA, the Clinical Pharmacology review team will recommend that POS Tablets should be given with food because it is expected that food intake would increase the systemic bioavailability of POS from the tablet formulation, as was observed with the oral suspension.

The effect of food on the BA of POS was evaluated with Tablet A and Tablet B (Study P04975). There was no substantial food effect on the bioavailability of Tablet A and Tablet B (Table 27). Only C_{max} values after administration of POS Tablet A were slightly lower in fed as compared to fasted conditions. However, a PK study to evaluate the effect of food on the systemic bioavailability of Tablet D (i.e., to-be marketed formulation) was not conducted. It is not

reasonable to extrapolate the results of Study P04975 to Tablet D because the composition of Tablet D is not comparable to that of Tablet A and Tablet B, which resulted in a substantial difference in the systemic bioavailability between Tablets A and B *vs.* Tablet D (see Table 26 in **2.5.2.1**).

Table 27. Statistical summary of pharmacokinetic parameters after single dose administration of POS (100 mg) Tablet A and Tablet B under fed and fasted conditions (Study P04975).

Pharmacokinetic Parameters	**Fasted**			**Fed**			**Ratio (Fed/Fasted)**	
	N	**GM[a]**	**95 % CI**	**N**	**GM[a]**	**95 % CI**	**GMR[b]**	**90 % CI**
Tablet A								
$AUC_{0\text{-last}}$ (ng.hr/mL)	16	11001.30	(9588.70, 12622.01)	15	11251.2	(9799.25, 12918.29)	1.02	(0.92, 1.13)
$AUC_{0\text{-}\infty}$ (ng.hr/mL)	16	11295.02	(9857.29, 12942.46)	15	11504.9	(10048.97, 13171.92)	1.02	(0.92, 1.13)
C_{max} (ng/mL)	16	372.34	(323.30, 428.83)	15	316.11	(273.48, 365.38)	0.85	(0.75, 0.96)
Tablet B								
$AUC_{0\text{-last}}$ (ng.hr/mL)	16	10780.92	(9583.00, 12128.60)	15	11651.9	(10113.72, 13424.11)	1.08	(0.98, 1.19)
$AUC_{0\text{-}\infty}$ (ng.hr/mL)	16	11046.72	(9838.34, 12403.51)	15	11967.7	(10380.51, 13797.75)	1.08	(0.98, 1.19)
C_{max} (ng/mL)	16	349.76	(311.11, 393.21)	15	329.86	(279.56, 389.21)	0.94	(0.83, 1.07)

[a]: Geometric mean computed from least squares estimate from a linear mixed effect model performed on the natural-log transformed values.;
[b]: GMR: geometric mean ratio

In Study P05615 (a pivotal clinical trial), food intake data were not collected for the subjects. Thus, the Clinical Pharmacology review team cannot verify that POS Tablets were in fact given without regard to food intake in Study P05615 merely because the study protocol indicated that the drug was to be taken without regard to food.

The results of Study P07691 which showed comparable estimates for posaconazole AUC and C_{max} between Tablet D (100 mg) in the fasted state and POS Oral Suspension (100 mg) after a high fat meal (Table 28) (b) (4)

The recommended daily dose of POS Tablets is 300 mg (i.e., 300 mg QD), whereas the recommended daily dose of the oral suspension is 600 mg (i.e., 200 mg TID). Thus, the results of Study P07691 may be interpreted to indicate that the AUC and C_{max} of posaconazole following the administration of POS Tablets 300 mg QD in the fasted state might be 50% lower compared with that following the administration of POS Oral Suspension 200 mg TID with a high fat meal.

Table 28. Summary of the mean (%CV) results of the comparative bioavailability studies of POS (100 mg) Tablet D (fasted) and oral suspension (fed) (Study 07691).

Dosage Form	**N**	**C_{max} (ng/mL)**	**T_{max} (hr)[a]**	**$AUC_{0\text{-last}}$ (ng·hr/mL)**	**$AUC_{0\text{-}\infty}$ (ng·hr/mL)**	**$T_{1/2}$ (hr)**
Tablet D (fasted)	22	288 (40)	5 (3-12)	8327 (34)	8786 (33)	27.0 (27)
Oral suspension (fed)	23	249 (25)	5 (4-12)	8018 (32)	8482 (31)	26.2 (26)

[a]: Median (range)

2.5.4. When would a fed BE study be appropriate, and was one conducted?

Not Applicable.

2.5.5. If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

One strength formulation (100 mg Tablet) was developed.

2.5.6. If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of a PK-PD relationship?

See Table 25 in **2.5.3**.

2.5.7. If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either *in vitro* or *in vivo* data to evaluate BE?

Not applicable.

2.5.8. What other significant, unresolved issues related to *in vitro* dissolution or *in vivo* BA and BE need to be addressed?

Not applicable.

2.6. Analytical Section

2.6.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

POS was the active moiety measured in human plasma in clinical pharmacology studies, biopharmaceutical studies, and clinical studies.

2.6.2. Which metabolites have been selected for analysis and why?

There is no evidence that any POS metabolites are pharmacologically/microbiologically active, and therefore no metabolites were analyzed.

2.6.3. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Because posaconazole plasma protein binding is not concentration-dependent, total drug concentration (bound plus free) of posaconazole was measured in human plasma.

2.6.4. What bioanalytical methods are used to assess concentrations?

Two analytical methods were used for quantification of POS in human plasma; these methods were validated for specificity, sensitivity, and reproducibility. Each of the bioanalytical methods utilized was based on a (b) (4) of the analytes from the biological matrix followed by liquid chromatography (LC) coupled with tandem mass spectrometric detection (MS/MS). The LC-MS/MS method in plasma was developed and utilized at Merck Research Laboratories (formerly Schering Plough Research Laboratories, Summit, NJ) (DM 27496) and subsequently transferred to (b) (4)). A summary of these methods is listed in Table 29.

Table 29. Validation summary for assays used to determine POS concentrations in human plasma

Study No.	Matrix	Analytical Method	Analytical Laboratory[a]	Internal Standard	Regression, weighting[b]	Range (ng/mL) [LLOQ]	Accuracy[c] (% bias)[d]	Precision[c] (%CV)	Clinical Studies Supported by Method
DM 27496	plasma	LC-MS/MS	Merck (SPRI)	$^{15}N_2$-^{13}C-SCH 56592	quadratic, 1/conc^2	5.00 to 5000 [5.00]	2.3 to 8.7	-4.6 to 0.7	P04975, P05615, P05637
DM 27904	plasma	HPLC UV 262 nm	(b) (4)	$^{15}N_2$-13C-SCH 56592	quadratic, 1/conc^2	5.00 to 5000 [5.00]	4.6 to 5.7	-4.5 to 2.4	P05615, P07691, P07764, P07783

[a]: (b) (4) SPRI = Schering-Plough Research Institute, Summit, New Jersey.
[b]: conc = concentration.
[c]: Precision or accuracy data for QC samples at 4 concentrations including one at the LLOQ.
[d]: % bias = ([mean of measured values-nominal]÷nominal)x100.

2.6.4.1. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The LLOQ of the LC-MS/MS assay was established at approximately 5.00 ng/mL of plasma (linear concentration ranges 5.00 to 5,000 ng/mL). A calibration curve was generated using a quadratic regression with 1/concentration^2 weighting.

2.6.4.2. What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The LLOQ and ULOQ for LC/MS/MS in the plasma assay were 5 ng/mL and 5000 ng/mL, respectively. The same assay range was validated for both methods.

2.6.4.3. What are the accuracy, precision, and selectivity at these limits?

Accuracy (%bias) and precision (CV) of the methods were assessed in three analytical runs using quality control (QC) samples at four concentrations (n=5 or 6 per concentration) spanning the calibration range, including one at the lower limit of quantitation (LLOQ). For an acceptable run,

- at least two-thirds of all QC samples in each run and 50% of the QC samples at each concentration level had individual %bias within ±15% (±20% at the LLOQ).
- the within-run and between-run CV was ±15% of the nominal concentration at each QC level (±20% at the LLOQ).

Each validation run contained a calibration curve of nine or ten nonzero standards that were processed and analyzed at least in duplicate. In an acceptable run,

- at least two-thirds of the individual calibration standards had %bias within ±15% of their nominal values (±20% at the LLOQ).
- at least one of the two calibration standards at both the LLOQ and the upper limit of quantitation must meet this criterion.
- the calibration curve had an r value ≥0.99 or r^2 value ≥0.98.

All analytical methods met the requirements for specificity, sensitivity, accuracy, and precision (Table 26).

2.6.4.4. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Analyte stability (in matrix and extract) at room temperature and stability in the matrix after storage at -20°C, after at least five freeze/thaw cycles, and after dilution was demonstrated for POS (Table 30).

Table 30. Stability of POS in analyzed matrix and extract

	Matrix Storage		**Extract Storage**	**Matrix**	
Analyte	RT[a]	-20°C	RT	F/T[b]	Dilution Integrity
Plasma					
POS	24 hr	349 days	237 hr	5	10-fold

[a]: RT = room temperature.
[b]: F/T = number of freeze/thaw cycles.

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

/s/

SEONG H JANG
10/17/2013

PHILIP M COLANGELO
10/17/2013

BIOPHARMACEUTICS REVIEW

Office of New Drug Quality Assessment

Application No.:	NDA 205053	**Reviewer:** Mark R. Seggel	
Submission Date:	25-JAN-2013		
Division:	DAIP	**Team Leader:** Angelica Dorantes, Ph.D.	
Applicant:	Merck Sharp & Dohme Corp.	**Acting Supervisor:** Rik Lostritto, Ph.D.	
Trade Name:	Noxafil	**Date Assigned:**	04-FEB-2013
Generic Name:	posaconazole	**Date of Review:**	22-AUG-2013; revised 27-SEP-2013
Indication:	Prevention and treatment of invasive fungal infections	**Type of Submission:**	505(b)(1)
Formulation / strengths	Delayed-release tablet, 100 mg	**GRMP Goal:**	21-OCT-2013
Route of Administration	Oral	**PDUFA Goal:**	25-NOV-2013

SUMMARY OFBIOPHARMACEUTICS FINDINGS:

Submission: Posaconazole is a synthetic, small molecule inhibitor of the fungal enzyme lanosterol 14α-demethylase. Posaconazole is a weakly basic compound and has extremely low solubility (b) (4) (b) (4) in an aqueous solution with pH higher than 4, but is relatively soluble (b) (4) in an aqueous solution with pH (b) (4)

Noxafil (posaconazole) oral suspension, 40 mg / mL was approved under NDA 22-003 on 15-SEP-2006 for the prophylaxis of invasive fungal infections. Additional indications have since been added. The use of the oral suspension, especially in the very sick, is complicated in that it must be taken with a meal. The package insert states, "Each dose of NOXAFIL should be administered with a full meal or with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale) in patients who cannot eat a full meal." (b) (4)

The solubility of posaconazole in the low pH environment of the stomach leads to the dissolution of posaconazole oral suspension, followed by "a relatively uncontrolled and unpredictable" precipitation upon reaching neutral pH in the small intestine in the fasting state. This results in low and variable absorption of the posaconazole oral suspension formulation. Incomplete solubilization of posaconazole in the stomach could also result in the observed positive food effect, most likely due to enhanced solubilization and/or reduced precipitation of posaconazole oral suspension in the presence of food.

The delayed-release tablet described in NDA 205053 was developed to overcome these limitations of posaconazole oral suspension. The tablet consists of (b) (4) a non-functional film coating. By limiting the dissolution of posaconazole in the acidic stomach environment, the uncontrolled precipitation in the small intestine is eliminated. Solubility in the more neutral pH environment of the intestine is enhanced by dissolution of amorphous posaconazole to form a supersaturated solution.

The Applicant concludes that, "posaconazole tablets has been shown to be safe and well tolerated, to provide optimal pharmacokinetic exposures, can be administered once daily after twice daily dosing on the 1st day [redacted] the labeling will indicate that the delayed-release tablets are to be taken with food.

Review: This review focuses on the Biopharmaceutics evaluation and acceptability of:

1. Proposed dissolution method and acceptance criteria.
2. In vitro alcohol dose dumping studies.

1. Dissolution Method and Acceptance Criteria

Dissolution method: The originally proposed dissolution method consisted of an acid stage and a buffer stage, as is typical for a delayed-release dosage form. A [redacted]-rpm paddle speed was specified. However, the acid stage sample was collected at [redacted] rather than after two hours, as specified in USP<711>, Delayed-Release Dosage Forms. The pH was changed by the addition of buffer after [redacted]. The Applicant was advised to follow the procedure described for Delayed-Release Dosage Forms in USP<711>. While the Applicant described logistical concerns, they ultimately developed a dissolution test method in accordance with USP<711>, using Apparatus II, paddles at 75 rpm. Because of the low solubility of posaconazole, polysorbate 80 is included in the buffer stage dissolution medium.

Acceptance Criteria: The [redacted] acceptance criteria are consistent with USP<711> - acid stage: NMT [redacted]% at 2 hours; buffer stage Q= [redacted]% at [redacted] after pH change as generally recommendation by USP<711>). The data obtained at release and on stability indicate that the drug product does not release posaconazole. Posaconazole is rapidly dissolved upon change in pH; complete dissolution is achieved within [redacted] minutes of addition of the buffer (i.e., the [redacted] minute pull time).

2. In Vitro Alcohol Dose Dumping

As a modified release formulation, the Applicant was also asked to evaluate the potential for alcohol dose dumping. In vitro dissolution profiles were obtained in 0.1 N HCl containing 0, 5, 10, 20 and 40% v/v ethanol. After 120 minutes, the most dissolved, approximately 26%, was observed in the medium containing 20% ethanol. Interestingly, only about 15% was dissolved in the medium containing 40% ethanol. Overall, the study results indicate that there is not dose dumping in the initial dissolution phase, but the dissolution rate slowly increases with alcohol (probably due to an increase in the solubility of posaconazole). In conclusion, the study results indicate that there is low potential for a significant in vivo alcohol dose dumping effect.

RECOMMENDATION:

***Dissolution Method*:** Based on the evaluation of the provided data the following proposed dissolution method is acceptable.

Apparatus	USP Type-II, Paddle
Medium	Acid Stage: 0.01 N HCl Buffer: 0.2 M phosphate buffer with 1.46% polysorbate 80 Buffer Stage: pH 6.8, 50 mM phosphate with 0.37% polysorbate 80
Volume	Acid Stage: 750 mL Buffer: 250 mL Buffer Stage: 1000 mL
Paddle Rotation Speed	75 rpm
Temperature	37.0°C ± 0.5°C

Acceptance Criteria: The Applicant agreed to implement FDA's recommended buffer stage acceptance criterion of Q = (b)(4)% at 145 minutes (5 minutes for pH change plus 20 minutes after pH change)**.** The following acceptance criteria are acceptable for the dissolution test for batch release and on stability.

Acceptance Criteria	• Acid Stage: Meets USP <711> criteria for Delayed Release Dosage Form (no individual value exceeds (b)(4)% dissolved at 120 minutes at Level 1). • Buffer Stage: Q = (b)(4)% at 145 minutes [continuous testing] (120 minutes acid stage + 5 minutes for pH change + 20 minutes after pH change).

OVERALL RECOMMENDATION:

The dissolution test method and acceptance criteria, as revised, will ensure adequate and consistent product performance across batches. It is therefore recommended from the Biopharmaceutics perspective that NDA 205053 for Noxafil (posaconazole) Delayed-Release Tablets be approved.

Signature
Mark R. Seggel
Reviewer
Office of New Drug Quality Assessment

Signature
Angelica Dorantes, Ph.D.
Biopharmaceutics Team leader
Office of New Drug Quality Assessment

cc: R.Lostritto, R.Madurawe, D.Matecka, N.Bhandari, A.Rodgers

BIOPHARMACEUTICS ASSESSMENT

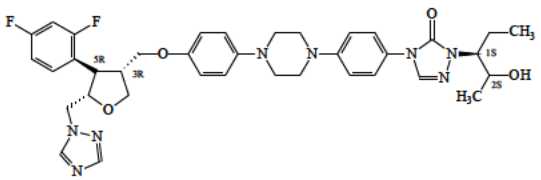
Review Notes

Submissions with Relevant Biopharmaceutics Information

Submission(s) Reviewed (eCTD)	Document Date
Original (0000)	25-JAN-2013
Amendment (0003); acknowledge delayed-release dosage form, labeling	30-APR-2013
Amendment (0006); primary stability data update	15-MAY-2013
Amendment (0009); in vitro alcohol dose dumping study	13-JUN-2013
Amendment (0010); response to information request	27-JUN-2013
Amendment (0012); updated Module 3	26-JUL-2013
Amendment (0015); dissolution test and acceptance criteria	10-SEP-2013
Amendment (0016); dissolution acceptance criteria	27-SEP-2013

S - Drug Substance

Structure of posaconazole:



Molecular Formula: $C_{37}H_{42}F_2N_8O_4$
Molecular Weight: 700.78
CAS: 171228-49-2

Table 1. Summary Physico-Chemical Data for Posaconazole

Description	White powder
Thermal Analysis	(b) (4)
UV Properties	See Table S.1.3.3
(b) (4)	(b) (4)

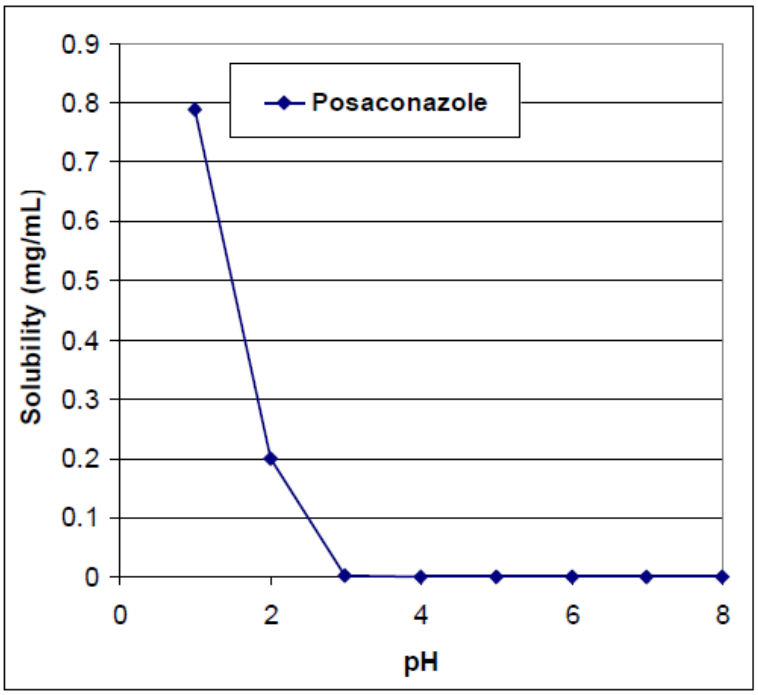
(b) (4) The drug product is designed to stabilize posaconazole in an amorphous form. See Chemistry Review for NDA 205053 for details.

Table S.1.3.2. Solubility of Posaconazole in Various Aqueous and Non-Aqueous Media

Medium	Solubility (mg/mL) [a]
Deionized Water	<0.001 (insoluble) [c]
0.1N HCl	0.79 (very slightly soluble)
pH 3 Buffer	0.003 (insoluble)
pH 5 Buffer	<0.001 (insoluble)
pH 7 Buffer	<0.001 (insoluble)
0.1N NaOH	0.001 (insoluble)
Ethanol	4.5
Methanol	12.5
Acetone	24.4
Acetonitrile	10.4
Hexanes	<0.001 (insoluble)
PEG 300: Water, 50:50	0.11
PEG 400: Water, 50:50	0.08
Propylene Glycol: Water, 40:60	0.02
PEG 400	23
Miglyol 812	0.40
Corn Oil	0.10
Intralipid 20 (Fat Emulsion)	0.2
2-hydroxypropyl-β-cyclodextrin, 10% w/v in Water	1.1
2-hydroxypropyl-β-cyclodextrin, 45% w/v in Water	26
2.4% w/w Polysorbate 80 in Water [b]	0.085

a: Determined at either ambient laboratory temperature (approximately 23 C) or 25 C.
b: Polysorbate 80 concentration equivalent to that in the drug product concentrate during microfluidization.
c. Solubility classification.

Figure 1. Solubility Profile of Posaconazole in Aqueous Solution at Different pH.



P - DRUG PRODUCT

Description and Composition of the Drug Product:

Formulation Development Summary: The drug product was designed to disintegrate in the low pH of the stomach and to release Posaconazole for absorption in the neutral pH of the small intestine. A pH sensitive (b) (4) was chosen based on the targeted product profile. (b) (4) dissolves to release the drug substance at around pH 6 and above. All clinical formulations discussed below were manufactured (b) (4)

(b) (4)

DISSOLUTION TEST METHOD

The originally proposed regulatory dissolution method and the revised regulatory method are compared in Table 4. The development of these methods is described in the following sections. This is followed by the supporting data.

Table 4. Proposed and Revised Regulatory Dissolution Methods

		Revised (Regulatory) Method	Original Optimized Method (Proposed Regulatory Test)
Paddle Speed		75 rpm	(b) (4)
Acid Stage Dissolution Media		750 mL 0.01 N HCl	
Buffer used to convert acid media into pH 6.8		250 mL of 0.2M Phosphate buffer with 1.46% Tween 80	
Final buffer stage media	Buffer Composition	pH 6.8, 50 mM Phosphate	
	Polysorbate 80	0.37%	
pH change duration		5 minutes immediately after 120-minute acid stage sample pull	
Acid Stage		120 minutes	
Acid Stage Time Point		120 minutes	
Buffer Stage Time point (minutes)	Profile Pull	135, 140, 155, 170 (10, 15, 30, 45 minutes after buffer addition and pH change)	
	Commercial Product Single Time Pull	(b) (4) **145 minutes**	

Dissolution Method Development:

Development of the optimized dissolution method initially proposed as the regulatory test is documented in eCTD Sequence 0000, Section 3.3, Dissolution Report. The final proposed regulatory method is described in eCTD Sequence 0010, Sections 1.11.1 and 3.2.P.5.

- ***Initial Formulation Screening:*** Initial formulation screening was conducted using USP Apparatus II (paddle) at (b) (4)

- ***Early Tablet (b) (4) Screening Method:*** Dissolution profiles of two tablet formulations (A, (b) (4) formulation, and B, (b) (4) formulation), (b) (4) (b) (4) were obtained in pH 6.8 phosphate buffer. Dissolution was slow or incomplete. Precipitation of posaconazole was observed.

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Reviewer's Comments: *A buffer stage acceptance criterion of Q = (b) (4)% at (b) (4) minutes (continuous testing), which the clinical and FSS batches meet, is consistent with the Applicant's stated development goal of achieving (b) (4)% dissolution of posaconazole within (b) (4) minutes at pH 6.8 (see 2.3.P and 3.2.P.2.2).* (b) (4) *drug dissolution at (b) (4) minutes.*

(b) (4) *Based on internal discussions of the potential risk (minimal) a delayed-release product dissolving completely at 145 minutes versus one completely dissolving in (b) (4) minutes, it was determined that we could accept a buffer stage acceptance criterion of Q= (b) (4)% at 145 minutes (5 minutes for pH change plus 20 minutes after pH change). Note that although dissolution profile data have not previously been obtained at 145 minutes, this time point is reasonable based on the data obtained at (b) (4) (b) (4) minutes.*

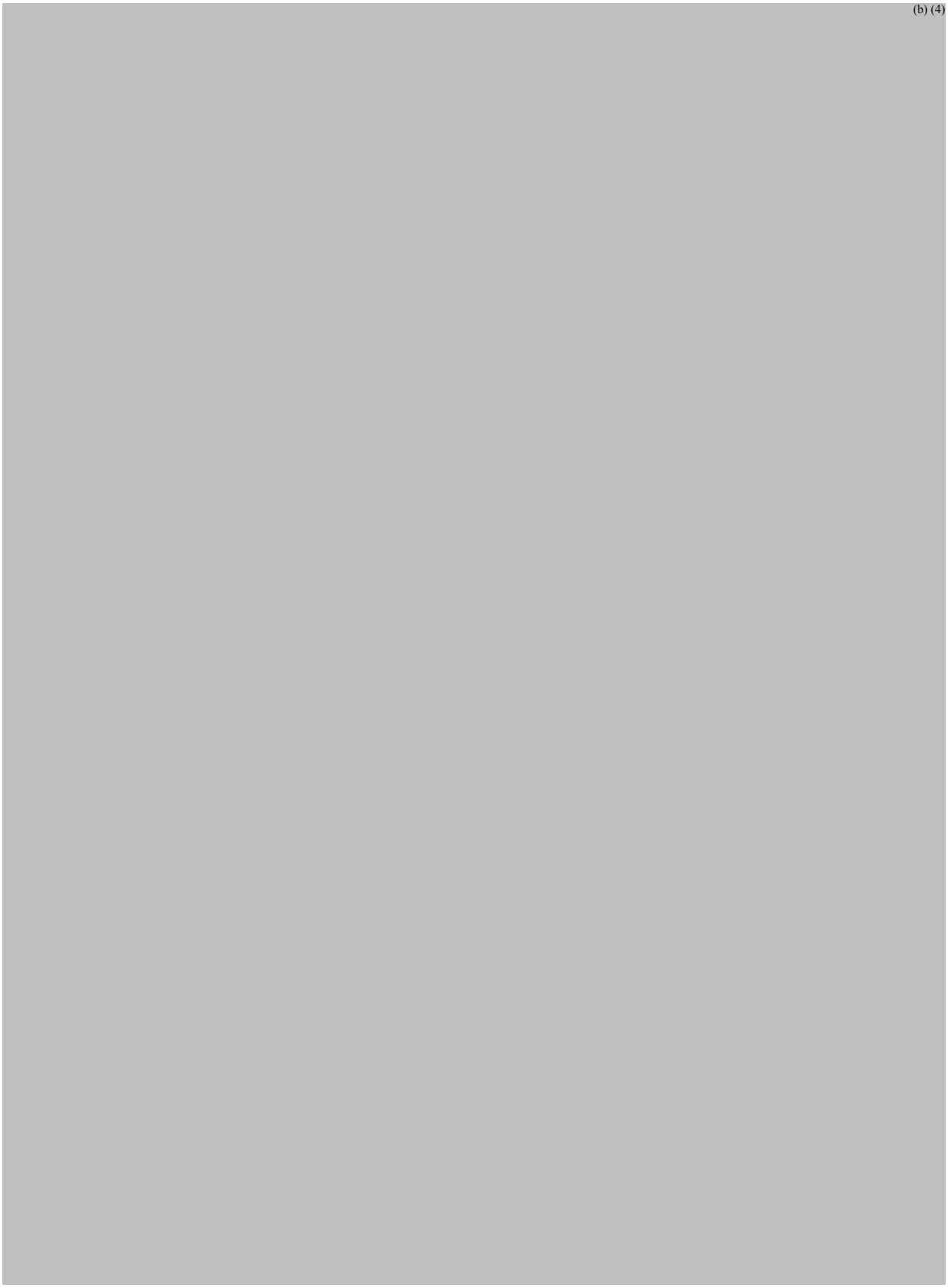
Applicant's Response: On September 27, 2013, Merck accepted FDA's proposed buffer stage acceptance criterion of Q = (b) (4)% at 145 minutes [continuous testing, i.e., 5 minutes for pH change plus 20 minutes].

Reviewer's Overall Assessment : SATISFACTORY

Although it appears that a tighter buffer stage acceptance criterion is feasible, the data are limited. An acceptance criterion of Q = (b) (4)% at (b) (4) minutes continuous testing is sufficiently discriminating to ensure consistent quality and bioavailability, as measured by in vitro performance, as they relate to the safety and efficacy of posaconazole delayed-release tablets.

SUPPORTING DISSOLUTION DATA:

(b) (4)



2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

IN VITRO ALCOHOL DOSE DUMPING STUDY:

The April 9, 2013 request for a study to evaluate in vitro alcohol induced dose dumping was addressed in the June 13, 2013 submission (eCTD sequence 0009).

Alcohol Dose Dumping - In Vitro Testing Parameters

Apparatus: USP II (paddle)
Rotation Speed: 100 RPM
Dissolution Media:
0.1N HCl containing: (v/v)
- 0% ethanol
- 5% ethanol
- 10% ethanol
- 20% ethanol
- 40% ethanol

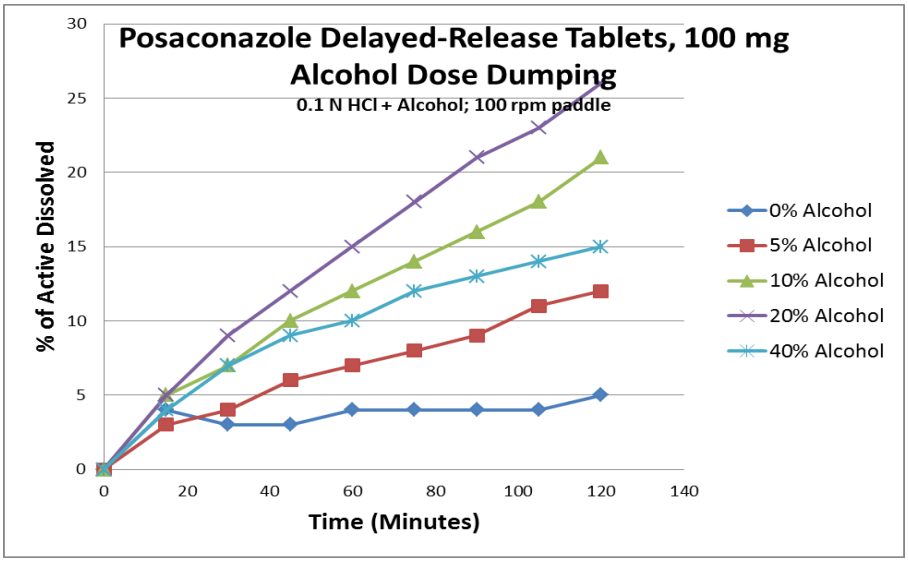
Dissolution Volume: 900 mL
Medium Temperature: 37° ± 0.5°C
Sampling Volume: 10 mL per pull

(b) (4)

Sampling Time: 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2 hrs
Replicates: n=12

Similarity f2 Calculation Results

Dissolution Condition	f2 Value
5% Alcohol	67
10% Alcohol	50
20% Alcohol	43
40% Alcohol	56



Dissolution Profiles: 0% Alcohol								
	Time Point (Minute)							
Vessel	15	30	45	60	75	90	105	120
1	4	3	3	3	4	4	4	4
2	5	3	3	4	4	4	4	4
3	3	3	3	3	3	4	4	4
4	4	3	3	3	4	4	4	4
5	3	3	3	3	3	4	4	4
6	3	2	3	3	4	4	4	5
7	5	4	4	5	5	5	6	6
8	7	4	4	4	4	4	4	5
9	5	3	3	3	4	4	4	4
10	4	4	3	4	4	4	4	5
11	5	5	5	5	8	6	6	6
12	3	4	4	4	4	4	4	5
Avg	4	3	3	4	4	4	4	5
%RSD	30	26	22	19	32	16	19	16

Dissolution Profiles: 5% Alcohol								
	Time Point (Minutes)							
Vessel	15	30	45	60	75	90	105	120
1	3	5	7	8	10	11	13	15
2	3	4	5	7	8	9	10	11
3	3	4	6	7	8	9	10	11
4	3	4	5	6	7	8	9	11
5	3	5	6	8	9	10	12	13
6	3	5	6	8	9	10	11	13
7	3	4	5	6	8	9	10	11
8	3	5	6	7	8	10	11	12
9	3	4	6	7	8	9	11	12
10	3	4	5	7	8	9	10	11
11	3	5	6	7	8	10	11	12
12	3	4	6	7	8	9	10	11
Avg	3	4	6	7	8	9	11	12
%RSD	0	13	10	10	9	9	10	10

Dissolution Profile: 10% Alcohol								
	Time Points (Minutes)							
Vessel	15	30	45	60	75	90	105	120
1	4	7	10	12	14	16	18	20
2	4	7	10	12	14	16	18	20
3	5	8	11	13	16	18	21	24
4	5	7	10	12	15	17	19	22

5	5	8	10	13	15	17	19	21
6	5	8	10	12	14	17	19	21
7	5	7	9	12	14	16	18	20
8	4	6	9	11	13	15	17	19
9	4	7	9	11	13	15	17	19
10	5	7	10	12	14	16	18	21
11	4	7	9	11	13	15	17	19
12	5	7	10	12	15	17	19	21
Avg	5	7	10	12	14	16	18	21
%RSD	10	8	6	6	7	6	6	7

Dissolution Profile: 20% Alcohol								
	Time Points (Minutes)							
Vessel	15	30	45	60	75	90	105	120
1	7	12	15	19	22	26	30	35
2	5	8	11	14	16	18	21	23
3	4	8	11	14	17	20	23	25
4	6	10	14	17	20	23	26	30
5	4	8	10	12	15	17	19	21
6	6	9	13	16	18	21	24	27
7	5	9	12	15	17	20	23	25
8	5	9	12	15	17	20	23	25
9	6	10	13	17	20	23	26	29
10	4	7	10	13	16	18	20	22
11	6	10	13	17	20	23	26	29
12	4	8	10	13	16	18	20	22
Avg	5	9	12	15	18	21	23	26
%RSD	21	15	14	14	12	13	14	16

Dissolution Profile: 40% Alcohol								
	Time Point (Minutes)							
Vessel	15	30	45	60	75	90	105	120
1	4	7	9	10	12	13	14	15
2	4	7	9	10	11	12	13	14
3	4	7	9	10	12	13	14	15
4	4	7	8	10	11	13	14	15
5	4	7	9	10	12	13	14	15
6	4	7	9	10	12	13	14	15
7	4	7	9	10	12	13	14	15
8	4	7	9	10	12	13	14	15
9	4	7	9	10	12	13	14	15
10	4	7	9	10	12	13	14	15
11	4	7	9	10	12	13	14	15
12	4	7	9	10	12	13	14	15
Avg	4	7	9	10	12	13	14	15
%RSD	0	0	3	0	3	2	2	2

<u>Reviewer's Assessment</u>: SATISFACTORY

After 120 minutes, approximately 26% was observed in the medium containing 20% ethanol. Interestingly, only about 15% was dissolved in the medium containing 40% ethanol. Overall, the results indicate that there is not dose dumping in the initial dissolution phase, but the percentage of drug dissolved slowly increases with alcohol (probably due to an increase in the solubility of posaconazole). In conclusion, the results indicate that there is low potential for an in vivo alcohol dose dumping effect.

- **Analytical Procedure**:

(b) (4)

[redacted]

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

<u>Reviewer's Assessment</u>: SATISFACTORY

The analytical procedure has been adequately described and validated. Based on these results, the procedure appears to be suitable for the analysis of posaconazole delayed-release tablet dissolution samples.

INFORMATION REQUESTS SENT TO THE APPLICANT

- **Information Request 09-APR-2013 (74-Day Letter/Filing Communication)**

Biopharmaceutics

3. The proposed regulatory dissolution test is not acceptable. Posaconazole delayed-release tablets should be tested in accordance with USP<711>, Dissolution, Delayed-Release Dosage Forms. Please note that the acid stage is 2 hours long. (b) (4) Develop a discriminatory dissolution method in accordance with the USP dissolution monograph. Deviations from the USP method should be justified with supporting data. The dissolution report should include individual (n=12) and mean data, %RSD, and profiles.

4. As a delayed-release product, the potential impact of alcohol induced dose dumping should be evaluated. Please conduct an in vitro alcohol dose dumping study in 0.1 N HCl dissolution media containing 0%, 5%, 10%, 20% and 40% alcohol. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile. The shape of the dissolution profiles should be compared to determine if the delayed release characteristics are maintained. The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference). The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided to FDA for review and comments.

5. As a delayed-release product, the correct established name for the drug product is 'posaconazole delayed-release tablets'. This should be reflected in all product labeling.

6. Confirm that the dissolution data reported in P.2.3 Manufacturing Process Development were obtained using the originally proposed regulatory method. If not, the specific methods should be indicated. Where only mean values (or plots of mean values) are reported, please provide individual values and %RSD along with the mean results.

- **Information Request 06-JUN-2013 (response by 27-JUN-2013 requested.)**

1. We reiterate that the proposed regulatory dissolution test is not acceptable. Posaconazole delayed-release tablets should be tested in accordance with USP<711>, Dissolution, Delayed-Release Dosage Forms. The acid stage is 2 hours long and buffer should be added immediately after removal of the sample aliquots. You have not provided any scientific evidence that the dissolution test for posaconazole delayed-release tablets cannot be performed in accordance with USP<711>, Dissolution, Delayed-Release Dosage Forms. Please revise the dissolution test accordingly.

    - Paddle speed (75 rpm (b) (4)) should be re-evaluated in the context of the revised dissolution procedure.

    - Note that the USP recommended acid stage medium consists of 0.1 N HCl. Please provide your rationale for the use of 0.01 N HCl rather than 0.1 N HCl.

    - (b) (4)

2. (b) (4)

(b) (4)

- **Information Request 28-AUG-2013 (response by 09-SEP-2013 requested)**

Your proposed acceptance criterion of Q = (b) (4)% at (b) (4) for the buffer stage is not supported by the provided dissolution data and is not acceptable. It is recommended that you implement an acceptance criterion of Q (b) (4)% (b) (4) for the buffer stage. Provide the revised specification table for your drug product with the updated acceptance criteria for the dissolution test.

- **Information Request …?-2013 (response by 27-SEP-2013 requested)**

1. (b) (4)

(b) (4)

Therefore, we continue to recommend an acceptance criterion of Q = (b) (4)% at (b) (4) . Nevertheless, we are willing to accept a buffer stage acceptance criterion of Q= (b) (4)% at 145 minutes (5 minutes for pH change plus 20 minutes after pH change). If you agree with our recommendation, implement this dissolution criterion and provide the revised specifications table for your drug product with this update. Note that if additional dissolution data from other clinical/ pharmacokinetics batches become available, testing at a later time point could be reconsidered.

Additionally, we note that Stage 2 testing of 20 – 30% of batches is not inconsistent with regulatory expectations.

###

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

/s/

MARK R SEGGEL
09/30/2013

ANGELICA DORANTES
09/30/2013

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

NDA/BLA Number	**205-053**	**Brand Name**	**Noxafil®**
OCP Division (I, II, III, IV, V)	**DCP4**	**Generic Name**	**Posaconazole**
Medical Division	**DAIP**	**Drug Class**	**Triazole antigunfal**
OCP Reviewer	**Seong Jang, PhD**	**Indication(s)**	**Prophylaxis of invasive *Aspergillosis* and *Candida* infections in patients, 13 years of age and older**
OCP Team Leader	**Phil Colangelo, PhD**	**Dosage Form**	**Oral Tablets**
Pharmacometrics Reviewer	**NA**	**Dosing Regimen**	**Loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day thereafter. Duration of therapy is based on recovery from neutropenia or immnusuppression**
Date of Submission	**January 25, 2013**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**TBD**	**Sponsor**	**Merck**
Medical Division Due Date	**TBD**	**Priority Classification**	**TBD**
PDUFA Due Date	**TBD**	**AC Meeting (if applicable)**	**TBD**

Clinical Pharmacology and Biopharmaceutics Information

	"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:	**X**			
multiple dose:	**X**			
PATIENTS -				
single dose:				
multiple dose:	**X**			
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**			
In-vivo effects of primary drug:				
In-vitro:				

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	**X**			
Phase 3:	**X**			**Not randomized controlled study**
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	**X**			**Pop PK study**
Data rich:	**X**			
Data sparse:	**X**			
II. Biopharmaceutics				
Absolute bioavailability	**X**			
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**			
Bioequivalence studies -				
traditional design; single / multi dose:	**X**			**The to-be-marketed formulation has been used in clinical development (Phase 3 study)**
replicate design; single / multi dose:				
Food-drug interaction studies	**X**			
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
TOTAL NUMBER OF STUDIES				

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	**The to-be-marketed formulation has been used in clinical development (Phase 3 study)**
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			Conducted previously with oral suspension
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			Conducted previously with oral suspension
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes, the resubmission is fileable from a clinical pharmacology perspective.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Please provide the food intake data in individual patients in Study P05615. If the sponsor submitted the data, please inform the location of data.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

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

/s/

SEONG H JANG
03/05/2013

PHILIP M COLANGELO
03/08/2013