CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 205-596	Submission Date(s): 09/13/2013
Drug	Posaconazole
Trade Name	Noxafil® injection
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 75,061
Submission Type; Code	Original; 1S; Priority Review
Formulation; Strength(s)	IV Solution; 18 mg/mL (16.7 mL vial: 300 mg in a vial)
Indication	Prophylaxis of invasive *Aspergillosis* and *Candida* infections in patients 18 years of age and older
Dosage and Administration	Loading dose of 300 mg (300 mg IV solution) twice a day on the first day, then 300 mg (300 mg IV solution) once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression.

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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 approved for the prevention of invasive fungal infections (IFIs) 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 recommended dosing for prophylaxis is 200 mg Noxafil oral suspension three times a day (TID), with each dose to be taken with a (b) (4) meal. Recently, a new solid oral tablet formulation of POS (Noxafil delayed-release tablets) was developed and approved for the same indication as Noxafil oral suspension (with the exception of treatment of oropharyngeal candidiasis). Noxafil delayed-release tablets provide POS exposure above the threshold concentration in more patients (i.e., >90%) compared with Noxafil oral suspension. The recommended dose of Noxafil delayed-release tablets is 300 mg (3 x 100 mg delayed release tablets) twice a day (BID) on the first day, and 300 mg once a day (QD) starting on the second day. Noxafil delayed release tablets should be taken with food.

Although POS oral formulations (i.e., Noxafil delayed release tablets and oral suspension), are effective to prevent IFIs, the use of oral POS is however limited by the lack of an intravenous formulation for patients who are unable to take an oral medication. To meet the needs of these patient populations, the sponsor developed an intravenous formulation of POS (hereafter referred to as Noxafil injection) for the same indications currently approved for the oral suspension (with the exception of treatment of oropharyngeal candidiasis) and Noxafil delayed-release tablets in patients 18 years of age and older. The proposed dosage regimen for Noxafil injection is 300 mg BID on Day 1, followed by 300 mg QD given as a 90 minute infusion via a central venous line.

The clinical program for Noxafil injection was designed to demonstrate comparable systemic PK exposure and safety among similar patient populations for which Noxafil oral suspension has already been approved. The exposure target was based upon the range of exposures achieved and the exposure-response relationship established in earlier controlled studies of Noxafil oral suspension. In this current NDA submission, the Phase 1B/3 study (Study P05520) showed that the proposed dose of Noxafil injection (i.e., 300 mg BID on the first day, then 300 mg QD thereafter by a slow 90 minute infusion via a central venous line) 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 Noxafil injection is acceptable for the prophylaxis of invasive fungal infections.

1.1. Recommendation

The Office of Clinical Pharmacology Division 4 has reviewed NDA 205-596 for Noxafil injection. From a Clinical Pharmacology perspective, the review of the data submitted in this NDA supports the approval of Noxafil injection for prophylaxis of invasive *Aspergillosis* and *Candida* infections in patients 18 years of age and older.

1.2. Phase 4 Commitments

No Phase 4 commitments are recommended.

1.3. Summary of Important Clinical Pharmacology findings

Proposed Dose Justification: Bridging to Noxafil oral suspension

The proposed dosing regimen of Noxafil injection for the prophylaxis of invasive fungal infections is a loading dose of 300 mg BID on the first day, then 300 mg QD thereafter. This dosing regimen was evaluated in a Phase 1B/3 study (Study P05520) designed to demonstrate that this dosing 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 Noxafil oral suspension (see **2.2.2**), i.e.,

- Mean steady-state C_{min} of approximately 1,200 ng/mL, with at least 90% of the subjects between 500 ng/mL and 2,500 ng/mL.
- No subject with C_{min} at steady-state above 3,650 ng/mL.
- No subject with C_{min} at steady-state below 200 ng/mL.

In general, the steady state POS C_{min} following administration of Noxafil injection 300 mg QD fell within the pre-defined target exposure (Table 1). The steady state POS C_{min} was ≥500 ng/mL in 92.7% of patients (190 out of 205 patients treated with 300 mg QD Noxafil injection); 7.3% (15/205) of patients had steady-state POS C_{min} <500 ng/mL. The mean C_{min} at steady-state in 205 patients treated with 300 mg QD Noxafil injection was ≤2,500 ng/mL (i.e., 1085 ng/mL). There was no patient with a steady state C_{min} above 3,650 ng/mL. There was one patient with a steady state POS C_{min} <200 ng/mL. Accordingly, the proposed dose of Noxafil injection (i.e., a loading dose of 300 mg BID on the first day, then 300 mg QD thereafter) is acceptable to the Clinical Pharmacology review team for the prophylaxis of invasive fungal infections.

Table 1. Distribution of POS C_{min} (ng/mL) measured at the earliest Day (i.e., after Day 3) in each patient after administration of 300 mg BID Noxafil injection on Day 1, followed by a maintenance dose of 300 mg Noxafil injection QD to high-risk subjects (C_{min} PK-evaluable population in Cohorts 2 and 3 in Study P05520). Data are expressed as C_{min} values at each percentile.

N	Mean	SD	Min	5th[a]	10th[a]	25th[a]	Median	75th[a]	90th[a]	95th[a]	Max[a]
205	1085	446	180	412	544	777	1050	1340	1720	1920	2330

No. of Patients with average C_{min} <500 ng/mL: 15 (7.3%)
[a]: Percentiles

Infusion via Central Venous line

Noxafil injection has been developed to be administered via a central venous line based on local infusion-site reactions identified initially in preclinical studies and more definitively in the first clinical study in healthy volunteers (Study P04985). Infusion through a peripheral venous line over 30 min has been evaluated only as a single dose in healthy volunteers. Multiple dosing via peripheral venous line resulted in infusion site AEs. In Study P05520 Noxafil injection was

administered via a central venous line by slow intravenous infusion over 90 minutes. Accordingly, the labeling will recommend that Noxafil injection is to be given in the same manner as was done in Study P05520. If a central venous catheter is not available, Noxafil injection may be administered through a peripheral venous catheter by slow intravenous infusion over 30 minutes only as a single dose. Intravenous bolus administration of Noxafil injection has not been evaluated.

Distribution, Metabolism and Excretion
No additional studies were conducted with Noxafil injection, as the data obtained with Noxafil oral suspension are considered appropriate to characterize POS distribution, metabolism and excretion from Noxafil injection.

Effect of Intrinsic Factors
No additional studies to evaluate the effect of intrinsic factors were conducted with Noxafil injection. However, similar to Noxafil oral suspension and Noxafil delayed Release tablets, intrinsic factors such as age, race, weight, gender and hepatic impairment would also not significantly affect the pharmacokinetics of POS following administration of Noxafil injection and no dose adjustments are considered necessary. No clinically relevant differences in exposure were observed between the subpopulations (AML or HSCT) receiving Noxafil injection.

Renal Impairment: Noxafil injection contains the excipient sulfobutyl ether beta-cyclodextrin (SBECD), and plasma levels of this cyclodextrin are known to accumulate in subjects with renal impairment. Therefore, patients with moderate to severe renal impairment (CrCL <50 mL/min) were excluded from the Phase 1b/3 Study (Study P05520) and no data are available for use of Noxafil injection in patients with moderate to severe renal impairment. Therefore, it is recommended to avoid use of Noxafil injection in patients with moderate to severe renal impairment. This recommendation mirrors that for IV voriconazole (Vfend®), which also contains SBECD, and the approved Vfend® for injection labeling recommends to avoid intravenous administration in patients with moderate to severe renal impairment (CrCL<50 ml/min). The total amount of the SBECD in Noxafil injection does not exceed that in the IV formulation of voriconazole. .

Effect of Extrinsic Factors
The drug interactions as described for Noxafil oral suspension and POS oral tablets are considered relevant to Noxafil injection, except for those drugs that affect the absorption of POS (via alterations in gastric pH and motility). No additional studies to evaluate the effect of extrinsic factors were conducted with Noxafil injection.

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Concurrence _____.

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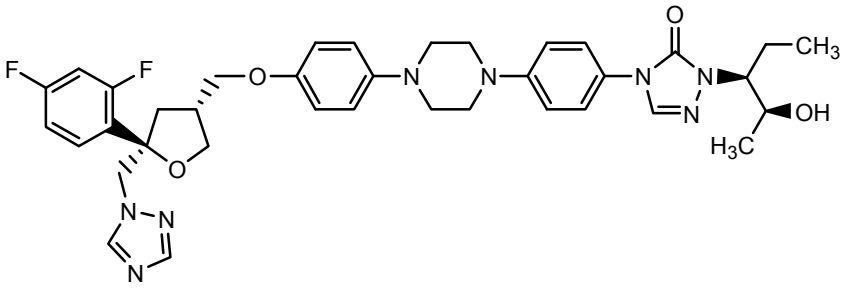
2. Question-Based Review

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.

NOXAFIL injection is available, as a clear colorless to yellow liquid essentially free of foreign matter, in 20 mL Type I glass vials closed with bromobutyl rubber stopper and aluminum seal containing 16.7 mL of solution (18 mg of posaconazole per mL), the equivalent of 300 mg dose strength. Each vial contains 300 mg of posaconazole and the following inactive ingredients: Betadex Sulfobutyl Ether Sodium (SBECD), edetate disodium, hydrochloric acid, sodium hydroxide, and water for injection

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 indication of Noxafil injection is prophylaxis of invasive Aspergillus and Candida infections in patients, 18 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 dosage regimen for Noxafil injection is summarized in Table 2. Noxafil injection should be administered via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC), by slow intravenous (IV) infusion over approximately 90 minutes. If a central venous catheter is not available, a single infusion may be administered through a peripheral venous catheter by slow IV infusion over 30 minutes. Noxafil injection is not for IV bolus administration.

Table 2. Proposed dosage and administration for Noxafil Tablets

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

Reviewer's comments: Infusion through a peripheral venous line over 30 min has been evaluated only as a single dose in healthy volunteers. Multiple dosing via peripheral venous line resulted in infusion site AEs. Thus, we recommend revising the labeling as follows.

*"Noxafil Injection should be administered via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC), by slow intravenous infusion over approximately 90 minutes. If a central venous catheter is not available, Noxafil injection may be administered through a peripheral venous catheter by slow intravenous infusion over 30 minutes only as a single dose in advance of central venous line placement or to bridge the period during which a central venous line is replaced or is in use for other intravenous treatment. When multiple dosing is required, the infusion should be done via a central venous line. Do not give Noxafil Injection as an intravenous bolus injection.***"**

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?

Noxafil injection has been studied in three clinical studies in healthy volunteers and one pivotal clinical study in patients (Table 3). A total of 340 subjects treated with Noxafil injection were enrolled in these studies: 72 healthy volunteers in 3 Phase 1 Studies P04985, P06356, and P07783; 268 patients who required antifungal prophylaxis (hereafter also referred to interchangeably as "high-risk subjects") in a pivotal Phase 1b/3 study (Study P05520).

Table 3. Overview of the clinical program with the Noxafil injection

Study	Short Protocol Titles	Study Design/ Population	POS Dose (mg)	Administration IV	No. of Subjects Treated with Active Drug
P04985	PK, safety & tolerability in healthy volunteers (SD and MD)	XO Healthy volunteers	SD: 200	Peripheral infusion over 90 minutes	9
P06356	PK, safety & tolerability in healthy volunteers (SD and MD)	Fixed sequence Healthy volunteers	SD: 0 (vehicle IV solution only), 50, 100, 200, 250 and 300 MD: 100 bid on day 1, QD on days 2-10	Peripheral infusion over 30 minutes	SD: 45 Captisol® (cyclodextrin vehicle only): 9 MD: 5 Captisol® (cyclodextrin vehicle only): 9
P07783	Absolute bioavailability and MD PK study in healthy volunteers (SD)	XO Healthy volunteers	SD: 300	Peripheral infusion over 30 minutes	13
P05520	PK, safety & tolerability in high risk subjects; IV solution followed by oral suspension	Parallel group High risk subjects	**Cohort 0:** 200 (SD) or placebo **Cohorts 1 and 2:** 200 and 300 mg BID on Day 1, followed by 200 mg or 300 mg QD on Days 2-14 **Cohort 3:** 300 mg BID on Day 1 followed by 300 mg QD for a minimum of 5 days **All cohorts:** step down to POS oral suspension	Central line infusion of Noxafil injection for 1 day (Cohort 0), 14 days (Cohorts 1 and 2), or at least 5 days (Cohort 3), followed by POS oral suspension 400 mg BID (Cohorts 0-3) or 200 mg TID (Cohort 3 only)	**Cohort 0:**10 **Cohort 1:** POS 200 mg :21 **Cohort 2:** POS 300 mg: 24 **Cohort 3:** POS 300 mg: 213

XO = Crossover study; SD = single dose; MD = multiple dose; POS= posaconazole;

Noxafil injection has been developed to be administered via a central venous line based on local infusion-site reactions identified initially in preclinical studies and more definitively in the first clinical study in healthy volunteers (Study P04985). As central line administration would not be deemed acceptable in healthy volunteer studies (Studies P06356 and P07783). Central line administration was given in the pivotal study in high-risk subjects (Study P0552). Since the peripheral infusion caused local infusion-site reactions (including thrombophlebitis) after multiple dosing or infusion over 90 minutes, some studies (P04985 and P06356) were terminated early. A single infusion via a peripheral vein over 30 minutes was supported by the results of Studies P06356

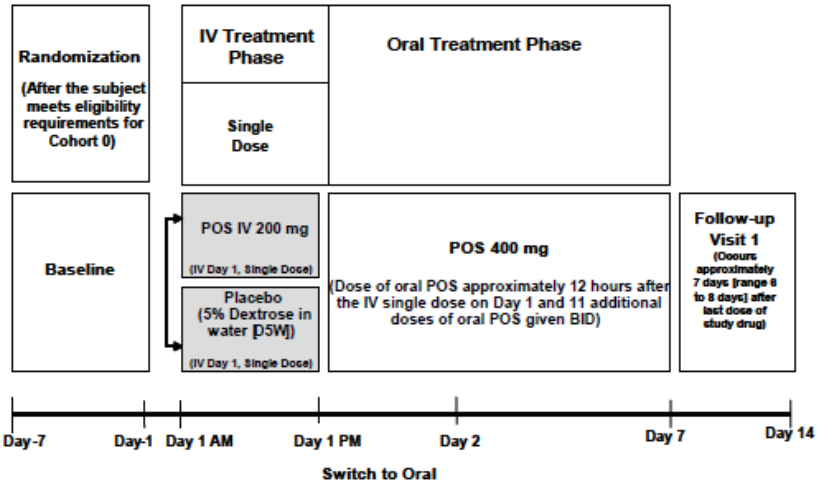
and P07783. It should be noted that multiple dosing via a peripheral vein has not been evaluated either in healthy volunteers or in high-risk subjects.

Study P05520: Study Design

Study P05520 was an open-label, sequential- and parallel-group, multi-site study of the pharmacokinetics, safety, and tolerability of Noxafil injection used as prophylaxis in subjects at high risk for invasive fungal infections (IFIs). The study consisted of 4 sequentially-performed cohorts in Phase 1b (Cohorts 0, 1, and 2) and Phase 3 (Cohort 3). Overall, the study enrolled 279 high-risk subjects, including 268 receiving at least 1 dose of Noxafil injection. In all subjects, Noxafil injection was administered via a central line as a 90-minute infusion.

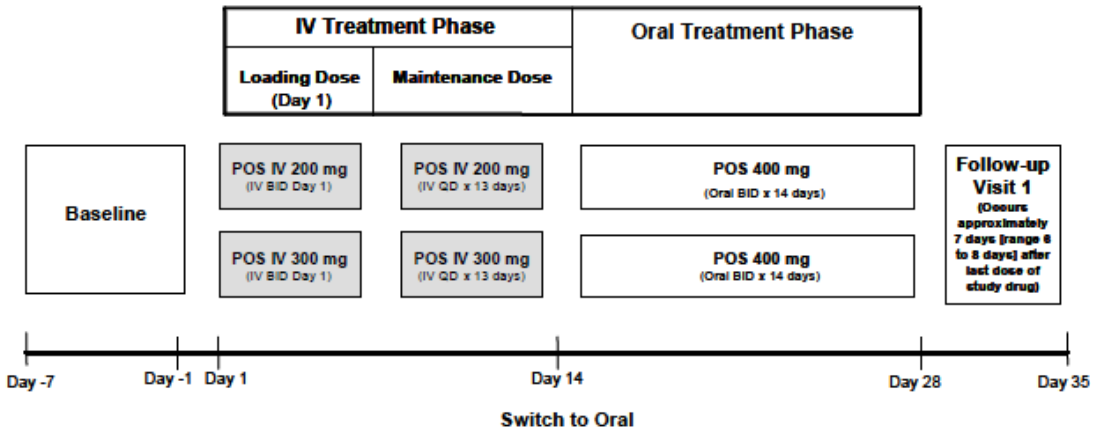
In Cohort 0, subjects were randomized to receive either a single dose of Noxafil injection or a single IV dose of placebo (5% dextrose in water [D5W]) on Day 1. A total of 21 subjects were enrolled in Cohort 0 (10 on IV POS solution, 11 on placebo). Blood samples for the determination of plasma POS concentrations were drawn at selected time points.

Graphical Depiction of Study Design for Cohort 0:



In Cohorts 1 and 2, two escalating dosing regimens were tested in order to obtain detailed PK and safety information during treatment with Noxafil injection for 14 days followed by 14 days therapy with Noxafil oral suspension. In Cohort 1, 21 subjects were treated with Noxafil injection, and, in Cohort 2, 24 subjects were treated with Noxafil injection. In both cohorts, blood samples for the determination of plasma POS concentrations were drawn at selected time points.

Graphical Depiction of Study Design for Cohorts 1 and 2:



In Cohort 3, Noxafil injection was given for at least 5 days followed by Noxafil oral suspension to complete 28 days of treatment to enable evaluation of the selected dose in a broader population. In Cohort 3, a total of 213 subjects were treated with Noxafil injection. Approximately 40 Cohort 3 subjects at selected sites were to receive a minimum of 10 days of therapy with Noxafil injection as part of an expanded PK sampling group.

After the IV therapy portion of the trial was completed, Cohort 3 subjects were randomized to receive POS oral suspension either as 200 mg TID or 400 mg BID. On Day 6, if the subject was able to tolerate oral medication, the subject had the option to begin treatment with a Noxafil oral suspension dosing regimen as per randomized treatment assignment which was to be continued for up to 23 more days (28 days total treatment). The investigator may have switched the subject back to Noxafil injection if the subject was unable to tolerate oral suspension. If, in the opinion of the investigator, he/she felt that the subject would NOT be able to tolerate oral dosing on Day 6, the subject would continue on Noxafil injection therapy until he/she was able to tolerate oral medications. Plasma trough sampling was obtained from all Cohort 3 subjects during IV and oral therapy phases.

All subjects with PK data were to be included in the PK analysis at the corresponding time point(s). For each cohort, the PK Evaluable Set was to include those subjects who met inclusion and exclusion criteria, had complied with protocol procedures (included collection of specified PK and dosing parameters), had no major protocol violations, and had documented adherence to dosing and PK regimens till sampling. There were two PK populations that were evaluated: (1) the Serial PK-evaluable Population, for which full PK profiles were evaluated and (2) the C_{min} PK-evaluable Population, for which only C_{min} was evaluated.

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 Noxafil injection was designed to demonstrate comparable systemic PK exposure and safety among similar patient populations for which the Noxafil oral suspension has already been approved. Thus, the endpoint of clinical studies was whether the proposed dosing

regimen of Noxafil injection will provide POS exposure within the pre-defined target exposure range, which was determined based on an exposure-response (E-R) relationship established with Noxafil oral suspension. The same approach was used for the development of POS delayed-release tablets (see Clinical Pharmacology Review of NDA 205-503, October 2013).

The exposure response relationship for Noxafil oral suspension was used to support the exposure target for the registration of Noxafil injection. The primary intent of the pivotal clinical study in patients (Study P05520) was to fully characterize the pharmacokinetics (PK) and assess safety of Noxafil injection in high risk subjects. Study P05520 was designed as a bridging study to the Noxafil oral suspension clinical program. The exposure target for Noxafil injection in Study P05520 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 Noxafil oral suspension.

The exposure target range for Noxafil injection was set (by the sponsor) as follows:
• Mean steady-state C_{avg} (AUC_{0-24} divided by 24 hr) of approximately 1,200 ng/mL (or AUC_{0-24} of 28,800 ng•hr/mL), with at least 90% of the subjects between 500 ng/mL (or AUC_{0-24} of 12,000 ng•hr/mL) and 2,500 ng/mL (or AUC_{0-24} of 60,000 ng•hr/mL).
• No subject with mean C_{avg} at steady-state above 3,650 ng/mL (or AUC_{0-24} above 87,600 ng•hr/mL).
• No subject with mean C_{avg} at steady-state below 200 ng/mL (or AUC_{0-24} below 4,800 ng•hr/mL).

However, C_{avg} at steady-state is not appropriate to bridge from Noxafil oral suspension to Noxafil injection because the bridging should be based on steady-state C_{min} measured for Noxafil injection, as applied for POS delayed-release tablets (see Clinical Pharmacology Review of NDA 205-503, October 2013 for the rationale of using steady-state C_{min} instead of C_{avg} to bridge Noxafil oral suspension to Noxafil injection). Accordingly, the exposure target range for the use of Noxafil injection in patients should be set as follows:

• Mean steady-state mean C_{min} of approximately 1,200 ng/mL, with at least 90% of the subjects between 500 ng/mL and 2,500 ng/mL.
• No subject with mean C_{min} at steady-state above 3,650 ng/mL.
• No subject with mean C_{min} at steady-state below 200 ng/mL.

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 P05520, no formal E-R analyses were conducted on the Noxafil injection data. See Clinical Pharmacology Review of NDA 205-503, October 2013, for the E-R relationship for efficacy following Noxafil 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 Noxafil oral suspension (Studies P01899 and C/I98-316) and POS delayed-release tablets (Study P05615) 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 Noxafil injection were evaluated with the data from Study P05520. This assessment was performed using all subjects for whom steady-state concentrations had been determined, and combined the Serial PK-evaluable population for both the 200 mg and 300 mg dose groups. For this analysis, subjects were included according to the calculated C_{avg}, which was performed by the Sponsor, and the incidence of reported treatment-emergent adverse events (TEAEs) was evaluated by quartile of exposure. A total of 64 subjects were included in the analysis of the incidence of AEs by quartile of exposure.

Table 4 summarizes the incidence of TEAEs by quartile of exposure. 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 Noxafil injection.

Table 4. Summary of all TEAEs by quartile of C_{avg} values in all subjects of Serial PK-evaluable population. Noxafil injection 200 mg and 300 mg dose group combined (Cohorts 1, 2, and 3)

	Cavg Mean (ng/mL)	Cavg Range	No. of Subjects	No. of Subjects Reporting Any TEAEs
Quartile 1	768 ng/mL	550 ng/mL to 1008 ng/mL	16	2 (13)
Quartile 2	1250 ng/mL	1048 ng/mL to 1394 ng/mL	16	6 (38)
Quartile 3	1528 ng/mL	1414 ng/mL to 1712 ng/mL	16	4 (25)
Quartile 4	2163 ng/mL	1721 ng/mL to 3034 ng/mL	16	4 (25)

n=number of subjects; C_{avg}= time-averaged concentration (i.e., AUC_{0-24}/24 hr)

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 Noxafil injection. 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 Noxafil 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 Cohort 3 of Study P05520 was determined in Cohorts 1 and 2 of the study. In Cohorts 1 and 2, 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 14 following administration of Noxafil injection 200 mg QD and 300 mg QD to high risk subjects are summarized in Table 5.

Table 5. Study P05520: Mean (%CV) of PK parameters in serial PK-evaluable patients on Day 14 following multiple dosing of Noxafil injection (200 mg QD and 300 mg QD)

Cohort	Dose (mg)	N	C_{max} (ng/mL)	T_{max}[a] (hr)	AUC_{0-24} (ng·hr/mL)	C_{avg} (ng/mL)	C_{min} (ng/mL)	CL (L/hr)
1	200	15	1950 (50)	1.00 (1.0-4.02)	28200 (51)	1180 (51)	958 (63)	8.51 (42)
2	300	19	2610 (39)	1.5 (0.98-4.00)	33800 (42)	1410 (42)	1046 (49)	10.6 (45)

[a]: Median (range)

Based on steady-state (on Day 14) data from these serial PK-evaluable patients, 3 of 15 (i.e., 20%) patients receiving Noxafil injection 200 mg QD (Cohort 1) attained C_{min} < 500 ng/mL (380, 399, and 439 ng/mL), whereas 4 of 19 (21%) patients receiving Noxafil injection 300 mg QD (Cohort 2) attained C_{min} < 500 ng/mL (i.e., 410, 438, 486, and 498 ng/mL). Although the number of patients in Cohort 1 and Cohort 2 were limited, 300 mg QD appeared to provide higher POS exposure in terms of AUC_{0-24} without noticeable increase in the incidence of AEs. Thus, 300 mg QD (after BID on Day 1 only) was determined to proceed to Cohort 3 of the study.

The evaluation of C_{min} following 300 mg QD dosing was based on the data from Cohorts 2 and 3 (both 300 mg QD dosing following BID dosing on Day 1 only) in both the serial PK evaluable population and the C_{min} PK evaluable population.

C_{min} in Serial PK-evaluable population: 300 mg QD (Study P05520: Cohorts 2 and 3)
Overall, 49 subjects, including 19 subjects in Cohort 2 and 30 subjects in Cohort 3, were classified as the Serial PK-evaluable population for the 300 mg dose-group. Based on the steady state data from 49 serial PK evaluable subjects receiving 300 mg Noxafil injection QD (after BID dosing on Day 1), five subjects (10%) attained steady state C_{min} values below 500 ng/mL. Forty-four subjects (90%) attained steady state C_{min} values between 500 and 2500 ng/mL. No subject's C_{min} value was above 2500 ng/mL (Table 6).

Table 6. Study P05520: Cohorts 2 & 3 (Serial PK Evaluable Populations): Frequency Distribution of Steady-State C_{min} on Day 10 or 14 after 300 mg BID Noxafil Injection on Day 1, followed by 300 mg QD for 9 or 13 additional Days

Number of Subjects	PK C_{min} Criteria	Percentage (%)
5	<500 ng/mL and ≥200 ng/mL	10
44	between 500 and 2500 ng/mL	90
0	>2500 but ≤ 3650 ng/mL	0
0	>3650 ng/mL	0

Steady-state C_{min} in C_{min} PK-evaluable population: 300 mg QD (Study P05520: Cohorts 2 and 3)
In Cohort 2, subjects received a BID dose of 300 mg Noxafil injection on Day 1 followed by a maintenance dose of 300 mg Noxafil injection QD for 13 days and C_{min} were obtained at Days 3, 6, 12, and 13. In Cohort 3, subjects received a BID dose of 300 mg Noxafil injection on Day 1 followed 300 mg Noxafil injection QD for at least 5 days and C_{min} were obtained at Days 3, 6, and 8. For a conservative evaluation of C_{min}, the distribution of C_{min} measured at the earliest Day (i.e., after Day 3) in each patient ($C_{min,afterD3}$) was analyzed from the combined data of Cohorts 2 and 3. In general, there was no substantial difference in C_{min} values after Day 3. The number of patients in the combined C_{min} PK-evaluable population was 205. The first C_{min} was obtained on Day 3 in 192 patients. In 13 patients, the first C_{min} was obtained on Day 6. The distribution of $C_{min,afterD3}$ following administration of Noxafil injection 300 mg QD is shown in Figure 1 and Table 7. In general, the $C_{min,afterD3}$ ranged within the pre-defined target exposure (see **2.2.2**). The $C_{min,afterD3}$ was ≥500 ng/mL in 92.7% (190 out of 205 patients) of patients treated with 300 mg QD dose of Noxafil injection. The mean $C_{min,afterD3}$ in 205 patients treated with 300 mg QD dose of Noxafil injection was ≤2,500 ng/mL (i.e., 1085 ng/mL). No patients had $C_{min,afterD3}$ > 3650 ng/mL. Only one patient had $C_{min,afterD3}$ < 200 ng/mL. Accordingly, the proposed dose of Noxafil injection (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.

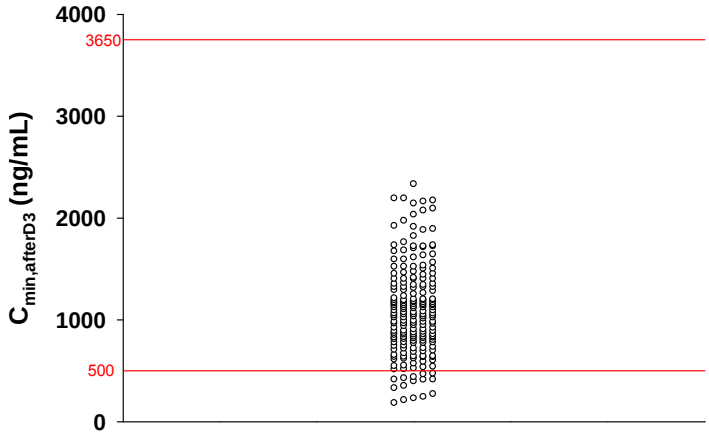


Figure 1. Distribution of C_{min} measured at the earliest Day (i.e., after Day 3) in each patient ($C_{min,afterD3}$) after administration of a BID dose 300 mg Noxafil injection on Day 1 followed by a maintenance dose of 300 mg Noxafil injection QD to high-risk subjects (C_{min} PK-evaluable population in Cohorts 2 and 3 in Study P05520).

Table 7. Distribution of POS C_{min} (ng/mL) measured at the earliest Day (i.e., after Day 3) in each patient after administration of 300 mg BID Noxafil injection on Day 1, followed by a maintenance dose of 300 mg Noxafil injection QD to high-risk subjects (C_{min} PK-evaluable population in Cohorts 2 and 3 in Study P05520). Data are expressed as C_{min} values at each percentile.

N	Mean	SD	Min	5th[a]	10th[a]	25th[a]	Median	75th[a]	90th[a]	95th[a]	Max[a]
205	1085	446	180	412	544	777	1050	1340	1720	1920	2330

No. of Patients with average C_{min} <500 ng/mL: 15 (7.3%)
[a]: Percentiles

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

Three clinical pharmacology studies in healthy volunteers have been performed with Noxafil injection (Studies P04985, P06356, and P07783).

Study P04985 was designed to evaluate the PK of Noxafil injection when administered as single and multiple doses via peripheral venous line over 90 minutes. However, this study was terminated early due to local infusion-site reactions observed following single-dose infusion of POS IV 200 mg.

Study P06356 was designed to evaluate PK of Noxafil injection as single and multiple doses via peripheral venous line over 30 minutes. However, Part 2 (i.e., multiple dose ascending) of Study P06356 was also prematurely terminated due to local infusion-site AEs.

Study P07783 was designed to estimate the absolute bioavailability of POS oral tablets. In this Study, Noxafil injection was given as a single dose of 300 mg (30 minutes infusion via peripheral venous line). Study P07783 was reviewed when the study report was submitted for

NDA 205-053 (Noxafil delayed-release Tablets). Consequently, the PK parameters from healthy volunteers mainly consist of those obtained following single dose administration.

The multiple dose PK parameters of Noxafil injection were obtained only from high-risk subjects in Study P05520. In Study P05520, Noxafil injection was given by slow infusion over 90 minutes via central venous line to avoid infusion-site AEs). The detailed PK characteristics of POS following administration of Noxafil injection are provided below.

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

Single Dose PK Parameters

Table 8 summarizes the PK parameters of POS following single administration of Noxafil injection in healthy volunteers. Overall, following administration of single IV doses from 50 to 200 mg of Noxafil injection, POS exhibits more than dose-proportional increases in exposure , and POS exposure increased in a dose-proportional manner after single IV doses from 200 to 300 mg in healthy volunteers.

Table 8. Summary of POS Pharmacokinetic Parameters for Noxafil Injection in Healthy Volunteers, presented as mean (%CV)

Study No. (Infusion Time)	**Posaconazole IV Solution Dose (mg)**	**n**	**t½ (hr)**	**T_{max}[a] (hr)**	**C_{max} (ng/mL)**	**$AUC_{0-\infty}$ (ng·hr/mL)**	**V_z (L)**	**CL (L/hr)**
P04985 (90 min)	200	9	24.3 (22)	1.00 (1.00-4.00)	1470 (24)	28100 (26)	254 (17)	7.46 (20)
P06356 (30 min)	50	9	18.7 (34)	0.6 (0.5- 0.7)	313 (30)	4890 (30)	294 (39)	10.9 (25)
	100	9	19.6 (16)	0.5 (0.5- 0.5)	1330 (27)	11200 (26)	262 (22)	9.40 (23)
	200	9	23.6 (23)	0.5 (0.5-24)[b]	2250 (29)	35400 (50)	226 (38)	6.54 (32)
	250	9	26.0 (23)	0.5 (0.5-0.5)	2260 (26)	41500 (41)	245 (33)	6.68 (29)
	300	9	24.6 (20)	0.5 (0.5-1.0)	2840 (30)	46400 (26)	236 (17)	6.90 (27)
P07783 (30 min)	300	13	28.8 (28)	0.5 (0.25-0.5)	4258 (19)	44380 (32)	295 (25)	7.61(41)

[a]:Median (range)

Multiple Dose PK Parameters

Table 9 summarizes the PK parameters of POS from Study P05520 following 200 mg and 300 mg BID Noxafil injection on Day 1, and 200 mg and 300 mg QD thereafter, respectively (infusion over 90 minutes via central venous line) in patients at high risk for IFI.

Table 9. Posaconazole steady-state mean (CV%) PK Parameters after 200 mg and 300 mg BID Noxafil Injection on Day 1 followed, by 200 mg and 300 mg QD, respectively, in high risk patients (Study P05520; Serial PK-evaluable population)

Dose (mg)	Day	n	C_{max} (ng/mL)	T_{max}[a] (hr)	AUC_{0-24} (ng·hr/mL)	C_{avg}[b] (ng/mL)	C_{min} (ng/mL)
200	14	15	1950 (50)	1.00 (1.0 – 4.02)	28200 (51)	1180 (51)	958 (63)
300	10/14	49	3280 (74)	1.5 (0.98 – 4.00)	36100 (35)	1500 (35)	1090 (44)

[a]:Median (range)
[b]: Cavg=time-averaged concentration (i.e., AUC_{0-24} at steady state/24 hr)

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

One study was performed using Noxafil injection in high risk subjects (Study P05520) in which single and multiple doses of 200 mg and multiple doses of 300 mg were investigated. In healthy volunteers, only single dose data were included. It should be noted that healthy volunteers were dosed peripherally, whereas high risk subjects were dosed via a central line. Moreover, infusion durations differed between the studies: P06356 and P07783, 30 minutes infusion duration; P04985 and P05520, 90 minutes infusion duration.

In Table 10, exposure is compared between healthy volunteers and high risk subjects dosed with 200 and 300 mg doses in different dose regimens. When comparing the steady state exposure in high risk subjects with healthy volunteers, assuming AUC_{inf} after single dose administration should be similar to AUC_{τ} at steady state after multiple dose with linear PK, the exposure in high risk subjects and healthy volunteers is similar for the 200 mg dose level but approximately 20% lower in high risk subjects than in healthy volunteers for the 300 mg dose level.

Table 10. Exposure after administration of Noxafil injection to healthy volunteers and high-risk subjects

Noxafil injection dose, population & regimen	Infusion Time (minutes)	Mean AUC_{inf} for Healthy volunteers; Mean AUC_{τ} for High-risk subjects
200 mg, healthy volunteers, single dose[a]	90/30	28100
200 mg, high risk subjects, multiple dose[b]	90	28200
300 mg, healthy volunteers, single dose[c]	30	44501
300 mg, high risk subjects, multiple dose[b]	90	36100

[a]: Studies P04985 and P06356; [b]: Study P05520; [c]: Studies P06356 and P07783

2.2.5.3. What are the characteristics of drug absorption?

Not Applicable for IV solution.

2.2.5.4. What are the characteristics of drug distribution?

POS is highly protein bound (>98%), predominantly to albumin. The mean volume of distribution of POS after IV solution administration was 261 L and ranged from 226-295 L between studies and dose levels, indicating that POS may be distributed into tissues following Noxafil injection administration.

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 Noxafil injection.

2.2.5.6. What are the characteristics of drug metabolism?

No additional metabolism studies with Noxafil injection have been performed as the data obtained with Noxafil 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 Noxafil 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 ($t_{½}$) of 27 hours and a mean total body clearance (CL) of 7.3 L/hr following a 300 mg dose of Noxafil injection, ranging from 7.5 to 11 L/hr following administration of Noxafil injection.

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

Following administration of Noxafil injection, POS exhibited greater than dose proportional increase in exposure in healthy volunteers after single dosing of 50 to 200 mg and dose proportional increase in exposure between 200 and 300 mg (Table 8). POS exhibited slightly less than dose proportional exposure after multiple once daily dosing of Noxafil injection in high risk subjects between 200 mg and 300 mg in terms of AUC and C_{max} (Table 9), but this is considered not clinically relevant. No doses above 300 mg QD have been investigated with Noxafil injection.

In Table 11, the clearance (CL), volume of distribution (V), and half-lives (t1/2) in healthy subjects are summarized as a function of dose. The CL at higher doses of Noxafil injection was

somewhat lower as compared to lower doses (7.3 versus 10.9 L/h, respectively for 300 mg and 50 mg dose level) and $t_{1/2}$ was somewhat shorter (27 hours at the 300 mg dose and 19 hours for the 50 mg dose). For the volume of distribution, the relation with dose is less clear.

Table 11. Mean clearance, volume of distribution and half-life as a function of dose of Noxafil injection in the 3 Phase 1 studies (Studies P04985, P06356, and P07783)

Single Dose (n)	Clearance (L/h)	Volume (L)	half-life (h)
50 mg (9)	10.9	294	19
100 mg (9)	9.4	262	20
200 mg[a] (18)	7.0	240	24
250 mg (9)	6.7	245	26
300 mg[b] (22)	7.3	270	27

[a]: mean of Studies P06356 and P04985; [b]: mean of Studies P06356 and P07783

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

Limited data are available to evaluate time dependency of POS pharmacokinetics, as multiple dose data in healthy volunteers were not obtained. Although single and multiple dose pharmacokinetics were obtained in high risk subjects, single dose data were collected on a BID dosing regimen only. Based on the C_{min} data that were collected in high-risk subjects (Study P05520) on Days 3, 6, and 8, steady state appears to be obtained after Day 3 (after BID dosing on Day 1 only; Table 12).

Table 12. Mean (%CV) of C_{min} values following IV solution 300 mg dosing (BID on Day 1 followed by QD dosing) for at Least 5 Days (C_{min} PK-Evaluable Population in Cohort 3: Study P05520)

Day	N	C_{min} (ng/mL)	% C_{min} <500 ng/mL
3	169	1073 (42)	7
6	108	1320 (44)	6
8	56	1297 (44)	5

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?

The total variability for single dose POS C_{max} and AUC_{inf} is moderate with CV% of 35.6% and 28.2%, respectively. The between-study variability for AUC_{inf} is quite low (8.3%) indicating consistency between the studies, whereas the between-study variability for C_{max} is relatively larger (21.5%). The within-subject variability could not be estimated from the composite PK analysis, because of lack of data on repeat dosing.

Based on the composite PK analysis, the total variability of steady state pharmacokinetics in high risk subjects was moderate to high with a CV% of 39.7% for $AUC_{0\text{-}24hr}$ and 44.9% for C_{max}, which was slightly higher than the variability in healthy subjects.

2.3. Intrinsic Factors

As for Noxafil oral suspension [Clinical Pharmacology Review (May, 2006)], intrinsic factors of age, race, weight, gender and hepatic impairment do not significantly affect the pharmacokinetics of POS following Noxafil injection and no dose adjustments are considered necessary.

However, due to the cyclodextrin excipient, it is recommended to avoid the use of Noxafil injection in patients with creatinine clearance <50 mL/min. No clinically relevant differences in exposure were observed between the subpopulations (AML or HSCT) receiving Noxafil injection (see Table 17 below).

Age

Table 13 shows the results of the composite PK analyses on the effect of age on POS IV single dose pharmacokinetics in healthy volunteers and multiple dose pharmacokinetics in high risk subjects. The age ranged from 19 to 65 years in healthy volunteers and from 18 to 75 years in high risk subjects following administration of Noxafil injection. In both populations, there was no statistically significant relationship between age and AUC, but there was a (marginally) statistically significant relationship between age and C_{max} which was not considered to be clinically relevant. For every 10 year increase in age, C_{max} would be expected to increase by 7.2% in healthy volunteers and 6.2% in high risk subjects. Overall, age does not appear to have a clinically relevant effect on exposure following administration of Noxafil injection.

Table 13. Effect of age on PK parameters following single and multiple dose administration of Noxafil injection in healthy volunteers and high risk subjects

Parameter	N[a]	Slope	90% CI for Slope	p- Value[b]	Change in Age(years)	Fold-Change in PK	90% CI for Fold-Change
Single dose in healthy volunteers							
Cmax (ng/ml) [c]	58	0.007	0.002, 0.012	0.0344	10	1.072	1.016, 1.131
$AUC_{0-\infty}$ (ng*hr/ml)	67	0.003	-.002, 0.007	0.3259	10	1.027	0.982,1.074
Multiple dose in high risk subjects							
Cmax (ng/ml)	64	-.006	-.013, -.000	0.0992	10	0.938	0.880, 1.000
AUC_{0-24hr} (ng*hr/ml)	64	-.002	-.007, 0.004	0.6452	10	0.984	0.930, 1.042

[a]: Number of subjects
[b]: p-Value is for the hypothesis testing whether the true slope=0 between corresponding PK parameters and age
[c]: C_{max} for the nine subjects in P04985 were excluded due to different IV infusion time

As no subjects <18 years of age have been dosed with Noxafil injection, there are no pediatric PK data to be included for this formulation. The Sponsor proposes that the use of Noxafil injection is limited to adults (≥18 years of age).

Gender

Table 14 shows the results of the composite PK analyses on the effect of gender on POS single dose pharmacokinetics in healthy volunteers and multiple dose pharmacokinetics in high risk subjects following administration of Noxafil injection. Ratios of geometric means for female *vs.* male are shown, and their 90% confidence intervals for the ratios and p-values. In high risk subjects, both C_{max} and $AUC_{0-\infty}$ were higher for females compared to males. This effect was not, or to a lesser extent, observed in healthy volunteers. According to the composite PK analysis in high risk subjects, gender may have an effect on exposure following administration of Noxafil injection. However, this was not consistently present in the healthy volunteers, and has not been previously described for other POS formulations. In addition, the magnitude of effect on AUC is small compared with C_{max}. Of note, the frequency of adverse effects was similar between male and female high risk subjects. Therefore, this gender difference following Noxafil injection administration is considered as an isolated finding with limited clinical relevance.

Table 14. Effect of gender on PK parameters following single and multiple dose administration of Noxafil injection in healthy volunteers and high-risk subjects

Parameter	**Gender**	**N**	**Comparison vs. White**		
			GMR	**90% CI**	**p-Value[a]**
Single dose in healthy volunteers					
C_{max} (ng/ml)[b]	Female	25	1.026	0.896, 1.176	0.7487
	Male	33			
$AUC_{0-\infty}$ (ng·hr/ml)	Female	26	1.125	0.993, 1.275	0.1199
	White	55			
Multiple dose in high-risk subjects					
C_{max} (ng/ml)	Female	24	1.459	1.196, 1.779	0.0024
	Male	40			
AUC_{0-24} (ng·hr/ml)	Female	24	1.225	0.993, 1.275	0.061
	White	40			

[a]: p-Value is for the hypothesis testing whether the true GMR is 1 for the corresponding comparisons
[b]: C_{max} for the nine subjects in P04985 were excluded due to different IV infusion time

Race

Table 15 shows the results of the composite PK analyses on the effect of race on POS single dose pharmacokinetics in healthy volunteers following administration of Noxafil injection. For high risk subjects, race was not included in the analysis since there were only two categories (White and Hispanic) with only 2 Hispanics out of 65 high risk subjects. In the healthy volunteer data, only four subjects fall into the category of 'Other' including one Asian, two Hispanic and one multiracial subject. Hence, this 'Other' group was not reported due to the very small sample size. The geometric mean ratios of Black/White are shown, as are 90% confidence intervals for the ratios and p-values. $AUC_{0-\infty}$ for Black healthy volunteers is slightly higher compared to White healthy volunteers following administration of Noxafil injection, however, the amount of data is limited, the magnitude of this difference is considered not clinically relevant and this result is not statistically significant, indicating that race does not have a clinically relevant effect on exposure following administration of Noxafil injection.

Table 15. Effect of race on PK parameters following single dose administration of Noxafil injection in healthy volunteers

Parameter	Race	N	Comparison vs. White		
			GMR	90% CI	p-Value[a]
C_{max} (ng/ml)[b]	Black	8	1.004	0.811, 1.244	0.9734
	White	47			
$AUC_{0-\infty}$ (ng·hr/ml)	Black	8	1.179	0.967, 1.438	0.1697
	White	55			

[a]: p-Value is for the hypothesis testing whether the true GMR is 1 for the corresponding comparisons
[b]: C_{max} for the nine subjects in P04985 were excluded due to different IV infusion time

Weight

Table 16 shows the results of the composite PK analyses on the effect of weight on single dose POS pharmacokinetics in healthy volunteers and multiple dose pharmacokinetics in high risk subjects following administration of Noxafil injection. The weight ranged from 54.3 to 108.6 kg in healthy volunteer studies and from 56 kg to 126 kg in high risk subjects.

In healthy volunteers (after single dose), there was a statistically significant negative relationship between weight and $AUC_{0-\infty}$ but not for C_{max}. For every 10 kg increase in weight, $AUC_{0-\infty}$ would be expected to decrease by 12.3%. This effect was not seen in high risk subjects. In high risk subjects, for every 10 kg increase in weight, AUC_{0-24} would be expected to decrease by 1.8% and C_{max} would be expected to decrease by 5.8%.

An additional analysis was conducted to better understand the relation between gender, weight, and exposure. When gender was taken out of the model, for every 10 kg increase in weight, AUC_{0-24} and C_{max} would be expected to decrease by 4.2% (p=0.25) and 10% (p=0.02), respectively). This indicates that gender may partly account for the weight effect in high risk subjects. On average, males were heavier than females (males: 80.8 ± 11.0 kg vs. females: 71.7 ± 15.0 kg).

Table 16. Effect of weight on PK parameters following single and multiple dose administration of Noxafil injection in healthy volunteers and high risk subjects

Parameter	N[a]	Slope	90% CI for Slope	p- Value[b]	Change in Age(years)	Fold-Change in PK	90% CI for Fold-Change
Single dose in healthy volunteers							
C_{max} (ng/ml)[c]	58	-0.005	-.011, 0.002	0.2234	10	0.953	0.894, 1.017
$AUC_{0-\infty}$ (ng·hr/ml)	67	-0.013	-.019, -.007	0.0004	10	0.877	0.827, 0.929
Multiple dose in high risk subjects							
C_{max} (ng/ml)	64	-0.006	-.013, 0.001	0.1734	10	0.942	0.876, 1.013
AUC_{0-24} (ng·hr/ml)	64	-0.002	-.008, 0.005	0.6340	10	0.982	0.920, 1.047

[a]: Number of subjects
[b]: p-Value is for the hypothesis testing whether the true slope=0 between corresponding PK parameters and age
[c]: C_{max} for the nine subjects in P04985 were excluded due to different IV infusion time

Renal Impairment

Noxafil injection contains the excipient SBECD, and plasma levels of this cyclodextrin are known to accumulate in subjects with renal dysfunction. Therefore, patients with moderate to severe renal impairment were excluded from Study P05520 and no data are available for use of Noxafil injection in patients with moderate to severe renal impairment. Therefore, it is recommended to avoid use of Noxafil injection in patients with moderate to severe renal impairment. This recommendation mirrors that for IV voriconazole (Vfend®), which also contains SBECD, and the approved Vfend® for injection labeling recommends to avoid intravenous administration in patients with moderate to severe renal impairment (CrCL<50 ml/min). The total amount of the SBECD in Noxafil injection does not exceed that in the IV formulation of voriconazole.

No additional renal impairment studies have been performed for Noxafil injection because the data available for the Noxafil oral suspension are considered applicable to Noxafil injection as well.

Hepatic Impairment

No additional hepatic impairment studies have been performed for Noxafil injection because the data available for the Noxafil oral suspension are considered applicable to Noxafil injection as well.

Patient Population

Table 17 shows the results of the composite PK analyses on the effect of patient population on multiple dose pharmacokinetics in study P05520. Ratios of geometric means for AML vs. HSCT are shown, as are 90% confidence intervals for the ratios and p-values for the comparison. There is a slightly lower C_{avg}, AUC_{0-24} and C_{max} in AML subjects compared to HSCT subjects, but this difference is only statistically significant for C_{max}. However, these differences are not considered clinically relevant.

Table 17. Effect of patient population on PK parameters following multiple dose administration of Noxafil injection (Study P05520)

Parameter	Patient population	N[a]	Comparison vs. BMT (HSCT)		
			GMR	90% CI	p-Value[b]
C_{max} (ng/ml)	AML	34	0.742	0.601, 0.917	0.0219
	BMT (HSCT)	30			
AUC_{0-24} (ng*hr/ml)	AML	34	0.844	0.698, 1.019	0.1381
	BMT (HSCT)	30			
C_{avg} (ng/ml)	AML	34	0.844	0.698, 1.019	0.1381
	BMT (HSCT)	30			

[a]: Number of subjects; GMR: geometric mean ratio

[b]: p-Value is for the hypothesis testing whether the true GMR is 1

2.4. Extrinsic factors

The drug interactions as described for Noxafil oral suspension and POS oral tablets are considered relevant to Noxafil injection, except for those that affect the absorption of POS (via gastric pH and motility). No additional studies to evaluate the effect of extrinsic factors were conducted with Noxafil injection. Please see the previous Clinical Pharmacology Reviews (May, 2006 and September, 2013) for the further information regarding Noxafil oral suspension and Noxafil delayed-release tablets.

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 solid phase extraction 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 18.

Table 18. 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	P04985
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	P05520, P06356, P07783

(b) (4) SPRI = Schering-Plough Research Institute, Summit, New Jersey.

: 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.

The reviewer finds that all analytical methods met the requirements for specificity, sensitivity, accuracy, and precision.

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 19).

Table 19. Stability of compounds in Plasma and Extracts

Analyte	Storage Temperature			Extract Storage		Stability	
	RT[a] (hr)	-20°C (days)	-80°C (days)	RT (hr)	4°C (hr)	F/T[b] (cycles)	Dilution Integrity
Posaconazole (Whole Blood)	5	124	ND	48	ND	5	10-fold
Posaconazole (Plasma)	24	349	ND	120	237	5	10-fold

a: RT = Room Temperature
b: F/T = Freeze/thaw
ND = Not determined;

3. Labeling Recommendation

34 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SEONG H JANG
02/19/2014

PHILIP M COLANGELO
02/19/2014

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

NDA/BLA Number	**205-596**	**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, (b) (4) of age and older**
OCP Team Leader	**Phil Colangelo, PhD**	**Dosage Form**	**IV Solution**
Pharmacometrics Reviewer	**NA**	**Dosing Regimen**	**Loading dose of 300 mg (300 mg IV solution) twice a day on the first day, then 300 mg (300 mg IV Solution) once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression.**
Date of Submission	**September 13, 2013**	**Route of Administration**	**IV**
Estimated Due Date of OCP Review	**January 13, 2014**	**Sponsor**	**Merck**
Medical Division Due Date	**February 13,2014**	**Priority Classification**	**Priority**
PDUFA Due Date	**March 13, 2014**	**AC Meeting (if applicable)**	**Not Applicable**

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**	**1**		
multiple dose:	**X**	**1**		
PATIENTS -				
single dose:				
multiple dose:	**X**	**1**		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	**X**	**1**		**Not randomized controlled study**
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	**X**	**1**		**Pop PK study**
Data rich:	**X**			
Data sparse:	**X**			
II. Biopharmaceutics				
Absolute bioavailability	**X**	**1**		
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
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		***4***		

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	IV formulation
2	Has the applicant provided metabolism and drug-drug interaction information?		X		Done with oral formulations
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			
	General				

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST FOR NDA/BLA SUBMISSIONS

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 submission 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.

Seong H. Jang, Ph.D.

Reviewing Clinical Pharmacologist Date

Phil Colangelo, Pharm.D., Ph.D.

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
11/04/2013

PHILIP M COLANGELO
11/04/2013