CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205596Orig1s000

MEDICAL REVIEW(S)

Medical Officer Review - Addendum for NDA 205-596

Re: Use of In-line Filter with Posaconazole IV

The ONDQA review team, in consultation with the ONDQA precedence team (3/5/2014), recommend, that to ensure safety of IV posaconazole, the drug should be infused through an in-line filter. The ONDQA also recommends that the in-line filter should be co-packaged with the drug to ensure compliance with use of the filter. Data submitted with the original NDA suggest that posaconazole solution when diluted in 0.9% saline or 5% dextrose water (D5W) contained particles. The original label submitted with the NDA contained the following wording, (b) (4) The primary reviewer in ONDQA noted that the physical and chemical compatibility of Posaconazole Injection with common diluents (0.9% saline or D5W), IV bags, infusion sets as well in-line filter (Polyethersulfone (PES)) rated at 5 µm or smaller) and catheters (fluorinated ethylene-propylene (FEP)) were demonstrated for up to 120 minutes of infusion after 24 hour storage in admixture containers at room temperature and 5°C - see review (DARRTS, 2/20/2014) by Xuhong Li, Ph.D., ONDQA.

An in-line filter was included at the outset of the clinical study program in 2009 based on limited admixture compatibility data available at the time. Posaconazole Injection was infused with an in-line filter via central line over 90 minutes in the phase 3 pharmacokinetic/safety trial, P05520. The clinical protocol for Study P05520, required the use of a 0.22 µm in-line filter, and the hospitals/study sites provided the filters. In a teleconference on 3/11/14, Merck's stated that their recommendation for use of an in-line filter was included in the draft drug label for consistency with the clinical program though subsequent tests since 2009 did not demonstrate particles in the posaconazole admixture solution. Merck submitted new data on 2/28/2014 which they believe will demonstrate that there are no particles present in the admixture posaconazole solution; however, these data would need to be reviewed by the ONDQA review team.

The DAIP held three internal meetings (3/6/14, 3/11/14, 3/12/14) and two teleconferences with Merck (3/10/14/, 3/12/14) to discuss the safety implications for use of posaconazole IV with and without a co-packaged filter. The ONDQA review team, OAP senior management, clinical pharmacology review team, and pharmacists from drug shortage were variably involved in some of these meetings/teleconferences. At the most recent teleconference 3/12/14, Merck agreed to the use of an in-line filter but they did not agree to co-packaging of a filter with the drug. They believe that it is not feasible to co-package the drug with one type of in-line filter when hospitals use different brands of IV infusion sets which may not have compatible connections. Additionally, co-packaging with an in-line filter could take (b) (4). Following this

teleconference, the division held an internal meeting (3/12/14), to continue discussions with ONDQA reviewers regarding the options for safely administering posaconazole IV. The clinical review team, consulted with pharmacists in drug shortage and their opinion was that co-packaging the drug with a filter would not be practical; they advised that if a drug is labeled for use with a filter, the usual procedure is for a pharmacist to dilute the drug in the infusion solution (for example, normal saline or D5W) and to send the IV bag to the hospital floor accompanied with the appropriate size in-line filter. Prior to infusion, the in-line filter is connected to an infusion set by the nurse or it is also possible that that an infusion set that has the appropriate inline filter already attached would be used. Several examples were provided of drugs that are labeled (post market) for use with an in-line filter but without co-packaging of the filter. At the end of this meeting, the clinical review team and OAP concluded that labeling of posaconazole IV for use with an in-line filter (without co-packaging) would be appropriate. The ONDQA team will discuss this option with the ONDQA precedence team.

Medical Officer's Recommendation

I recommended labeling of posaconazole IV for administration with a 0.22 µM in-line filter as was used in the phase 3 pharmacokinetic/safety trial, P05520; however, I defer to the ONDQA review team for a final recommendation regarding the appropriate pore size of the in-line filter(s).

The final agreed label of posaconazole, Noxafil® is attached.

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

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/s/

ELIZABETH M OSHAUGHNESSY
03/13/2014

JOHN J ALEXANDER
03/13/2014

CLINICAL REVIEW

Application Type	New Drug Application
Application Number	205-596
Priority or Standard	Priority
Submit Date	Sept 12th, 2013
Received Date	Sept 13th, 2013
PDUFA Goal Date	Mar 13th, 2014
Division / Office	DAIP/ OAP
Reviewer Names	Elizabeth O'Shaughnessy, MD John Alexander, MD, MPH
Review Completion Date	Feb 12th, 2014
Established Name	Posaconazole
(Proposed) Trade Name	NOXAFIL®
Therapeutic Class	Triazole
Applicant	Merck
Formulation	IV solution
Dosing Regimen	300 mg IV BID x 1 day then 300 mg IV daily
Indication	Prophylaxis of Invasive Fungal Infection
Intended Populations	Neutropenic patients with hematological malignancies, and HSCT recipients.

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Medical Officer recommends that Posaconazole (POS) injection be approved for the prophylaxis of invasive *Aspergillus* and *Candida* infections in adults, 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. POS injection administered via intravenous infusion at a dose 300 mg PO BID on Day 1 and 300 mg daily thereafter was found to provide similar systemic exposures to that shown to be effective for prophylaxis using the posaconazole oral suspension. The safety profile of intravenous POS was similar to the marketed posaconazole oral suspension, NOXAFIL®. The duration of prophylaxis with POS injection will depend on the length of time a patient remains at risk for invasive fungal infection (IFI).

1.2 Risk Benefit Assessment

Patients with severe immunocompromise, such as patients with hematologic malignancies with prolonged neutropenia, or HSCT recipients with or without GVHD are at risk of life-threatening invasive fungal infections (IFI), such as *Aspergillus* pneumonia or candidemia.
The benefit of posaconazole oral suspension for prophylaxis of IFI in immunocompromised patients was previously demonstrated in two randomized controlled clinical trials[1,2] and it is FDA-approved for this indication. POS delayed-release tablet at dose of 300 mg PO BID on Day 1 and 300 mg daily was shown to provide similar drug exposure to posaconazole oral suspension in the target population of patients with hematologic malignancies with prolonged neutropenia at risk of IFI. POS tablet at dose of 300 mg PO BID on Day 1 and 300 mg daily was approved by the FDA on November 25th, 2013.

In this NDA submission, the pharmacokinetics, safety and tolerability of POS injection was evaluated in 72 healthy volunteers and 268 patients with hematologic malignancies at risk of IFI. POS injection was well tolerated when administered over 90 minutes via a central line, and it had an acceptable safety profile within the range of systemic exposures achieved in Study P05520. The safety data indicate that it has a similar safety profile to posaconazole oral suspension and POS delayed-release tablets. POS IV will be of benefit to patients who require antifungal prophylaxis but cannot take oral medications due to severe mucositis, nausea or vomiting.

[1] Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007; 356(4):348 -359.
[2] Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med. 2007; 356(4):335-347.

The survival rate at Day 65 (survival visit) was high at >90%. The incidence of breakthrough IFI in this trial was approximately 1% and was lower than previously reported in two randomized prophylaxis trials of posaconazole oral suspension.[1, 2]
There were two deaths in cohort 0 (subjects received 200mg IV single dose or placebo IV) and there was one death in the 200 mg IV multiple-dose, cohort 1. In the 300 mg multiple-dose cohorts, there were 19 (8%) deaths. The most common cause of death was sepsis/septic shock. One patient developed acute liver failure and died; POS IV could have contributed to the hepatic injury in this patient; however, it is more likely that death was due Gram-negative sepsis and progression of underlying acute myeloid leukemia.
The most common adverse reaction associated with POS IV was diarrhea. Other reported adverse reactions, associated with the azole class of antifungal drugs, included hepatotoxicity with elevation of hepatic transaminases and hyperbilirubinemia, and QTc interval prolongation. Six (2%) of the patients had hepatic function test results that met the criteria for Hy's Law during treatment with POS. The attribution of adverse reactions including hepatotoxicity was confounded by symptoms related to the patients' underlying hematologic malignancies and myelosuppressive drug regimens. There was one case of acute renal failure associated with Gram-negative sepsis. There was one case of asymptomatic QTc interval prolongation (QTc >500 msec) which led to discontinuation of study drug and resolved off study drug. There were no reports of adrenal insufficiency.
Overall, POS injection was well tolerated. Within the range of exposures that were observed in the open-label phase 3 trial (P05520), there does not appear to be an association of higher posaconazole concentration with a higher incidence of treatment-related adverse reactions following administration of POS IV. In summary, POS injection has an acceptable safety profile that is similar to the safety profile reported for posaconazole oral formulations, NOXAFIL®. The potential benefit of POS injection in preventing life-threatening invasive fungal infections outweighs the risk of adverse reactions in severely immunocompromised patients.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The medical officer does not recommend a postmarket risk evaluation and mitigation strategy (REMS).

1.4 Recommendations for Postmarket Requirements and Commitments

There are no new Postmarket Requirements (PMR) or Commitments (PMC) from a clinical perspective. The Division requested that the applicant conduct the following study, Study A, under NDA 205-053, therefore, there are no new studies requested for NDA 205-596. The PMR (Study A below) for NDA 205-053 will suffice for NDA 205-596:
Study A: A trial to evaluate the PK, safety, and tolerability of two new formulations of posaconazole (IV solution followed by sequential use of the new age-appropriate oral formulation) in immunocompromised pediatric patients with known or expected neutropenia between the ages of 2 to < 18 years of age.

Clinical Reviewer's Comment: *A safe and effective pediatric dosage regimen for the two new formulations of posaconazole can be determined in this study because the dosage regimen of POS Tablets was determined through a bridging to NOXAFIL Oral Suspension in adults (i.e., the attainment of pre-determined target PK exposure (i.e. Cmin) and safety/tolerability). The clinical pharmacology reviewers recommend that that the appropriate target PK exposure metric is the average steady-state Cmin of posaconazole, in lieu of steady-state Cavg.*

If Study A fails to find a safe and tolerable pediatric dosing regimen that will provide pediatric patients with the exposure greater than the pre-determined target PK exposure, then the following efficacy trial (Study B) with a safe and tolerable dosage regimen determined from Study A, but did not necessarily achieve the targeted POS PK exposure (steady-state Cmin) as that in adults, should be conducted:

Study B: A comparative, double-blind, randomized, multi-center study to evaluate the safety, efficacy, and tolerability of posaconazole [redacted] (b) (4) for the prophylaxis of invasive fungal infections (IFI) among in pediatric patients with known or expected neutropenia between the ages of 2 to <18 years.

The same PMR studies required in the approval letter for POS tablets (NDA 205-053) should be included as PMR for POS injection.

Clinical Reviewer's Comment: *A pediatric PK, safety, and tolerability study with the currently marketed posaconazole oral suspension, NOXAFIL® is ongoing and this study is part of the Pediatric Written Request Letter (2/28/2008) for NDA 22-003.*

2 Introduction and Regulatory Background

2.1 Product Information

Posaconazole (POS) (SCH 56592, MK-5592) is a triazole antifungal drug. POS was developed for the prevention and treatment of invasive fungal infections (IFI). POS, similar to other triazole drugs, blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of the enzyme lanosterol 14α-demethylase and accumulation of methylated sterol precursors. POS is active against a wide spectrum of yeasts and moulds that are pathogenic to humans.

The oral delayed-release tablet formulation was designed to overcome the limitations with poor gastrointestinal absorption of posaconazole oral suspension. The tablet combines posaconazole with a [redacted] (b) (4) [redacted] (b) (4) [redacted]

Posaconazole Injection, 18 mg posaconazole/mL is an intravenous (IV) formulation, providing a new dosage form in addition to the approved oral suspension and tablet formulations.

The drug product is to be diluted in 0.9% saline or 5% dextrose solution prior to administration by IV infusion. In this application, the indication sought for POS IV solution is the 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.

2.2 Tables of Currently Available Treatments for Proposed Indications

Posaconazole (NOXAFIL®) oral suspension was approved by the FDA in 2006 and POS Tablet was approved in 2013 for the 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 or those with hematologic malignancies with prolonged neutropenia from chemotherapy. POS tablets allow for once daily administration and are indicated for the same prophylaxis indication as POS oral suspension. POS is currently the only FDA-approved antifungal drug for the prophylaxis of invasive mould infection.

Fluconazole, DIFLUCAN®, is indicated to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy.

2.3 Availability of Proposed Active Ingredient in the United States

Posaconazole (NOXAFIL®) is marketed in the USA as an oral suspension formulation and a delayed-release tablet formulation.

2.4 Important Safety Issues with Consideration to Related Drugs

Triazole drugs such as fluconazole, itraconazole, voriconazole, and posaconazole are known to cause hepatotoxicity, QT interval prolongation which can lead to life-threatening ventricular arrhythmias, and potentially serious drug-drug interactions.
Hepatic adverse reactions e.g., mild to moderate elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALK-P), total bilirubin (tot. bili.), and/or clinical hepatitis have been reported in clinical trials of POS oral suspension.[1,2] Hepatic injury with hyperbilirubinemia and jaundice occur less commonly. Elevations in hepatic transaminases are generally reversible on discontinuation of therapy.
Triazoles are inhibitors of the CYP450 enzyme system. POS is an inhibitor of the CYP3A4 isoenzyme and is a known substrate for the energy-dependent efflux transporter P-gp. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by

POS, for example, nephrotoxicity and leukoencephalopathy (including isolated deaths) have been reported in clinical efficacy studies in patients with elevated cyclosporine concentrations. Compared to other triazoles such as itraconazole and voriconazole, other CYP isoenzymes (i.e., CYP1A2, CYP2C9, CYP2C19) are not affected by POS. Triazoles, including POS, may cause QTc interval prolongation which can potentially lead to life-threatening ventricular arrhythmias. Triazoles should not be coadministered with drugs known to prolong the QTc interval and metabolized through CYP3A4.[3] Concomitant administration of POS oral suspension with the CYP3A4 substrates, pimozide, and quinidine can result in increased plasma concentrations of these drugs, leading to QTc interval prolongation and rare occurrences of torsades de pointes have been reported.[3]

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Studies of POS IV were conducted under IND 75,061.

FDA Meetings / Correspondence

FDA meeting / Correspondence	Discussion/Agreements
February 11, 2009	Proposed clinical development program would include three healthy volunteer studies and one clinical study. Safety database minimum of 320 subjects.
October 23, 2009	FDA accepted the proposed target mean steady-state POS Cavg of 1,200 ng/mL with at least 90% of subjects between 500 ng/mL and 2,500 ng/mL.
February 14, 2012	Waiver for TQT study granted
December 7, 2012	Approved Pediatric Investigational Plan

2.6 Other Relevant Background Information

Not applicable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of the submission is satisfactory.

3.2 Compliance with Good Clinical Practices

The Applicant conducted the study in conformance with Good Clinical Practices.

[3] NOXAFIL® posaconazole oral suspension, USPI, rev. 6/2012

3.3 Financial Disclosures

See financial disclosure form in section 9.5.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to the review of chemistry manufacturing and controls by Mark Seggel, Ph.D.

4.2 Clinical Microbiology

Please refer to prior microbiology reviews for posaconazole oral suspension, NDA 22-003 and to the NOXAFIL® USPI.

4.3 Preclinical Pharmacology/Toxicology

There are no pertinent preclinical studies in NDA 205-596.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

POS is an antifungal triazole. POS, similar to other triazoles, inhibits lanosterol 14-alpha-demethylase, an enzyme that converts lanosterol to ergosterol, a vital component of the fungal cell membrane.

4.4.2 Pharmacodynamics

Please refer to the clinical pharmacology review by Seong Jang, Ph.D.

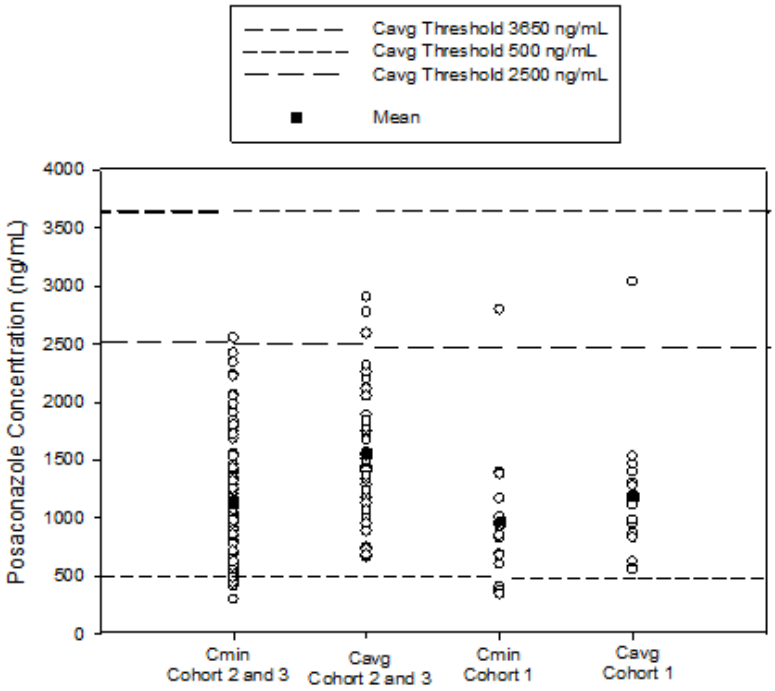
4.4.3 Pharmacokinetics

The Office of Clinical Pharmacology Division 4 reviewed the pharmacokinetic studies in this NDA. The development of POS IV solution is supported by the prior preclinical and clinical experience with the approved POS oral suspension. POS oral suspension has been evaluated in clinical trials in over 2,400 subjects.

A dose related increase in exposure was observed at steady state for both mean Cmax and AUC increasing 59% and 32% respectively when dosing increased from POS IV 200 mg to 300 mg. When administered at a 300 mg IV once daily dose (following 300 mg IV every 12 hours on Day1) to subjects at risk for IFIs, POS IV solution resulted in POS exposure in the target mean

steady-state POS Cavg of 1,200 ng/mL with at least 90% of subjects achieving exposures between 500 ng/mL and 2,500 ng/mL (predefined range). Such exposures have been previously proven to be efficacious and well tolerated. Serial PK analysis demonstrated that 94% of the subjects treated with POS 300 mg IV once daily attained steady state Cavg between 500-2500 ng/mL. POS exposure following IV infusion was generally higher than that following different regimens of POS oral suspension (with the recommendation of taking the suspension with food) but remained within the range of POS exposures previously studied.

Figure 1. All PK Cohorts (Cohorts 1, 2, and 3): Individual and mean steady state Cavg and Cmin for the 200-mg (Cohort 1) and 300-mg dose (Cohorts 2 and 3 combined) groups –Serial PK-evaluable Population on IV solution



Source: Figure 11-4, Clinical Study Report (CSR), page 114.

Table 1. Cohort 2 and 3: Posaconazole Steady-state Pharmacokinetic Parameters on Day 10/14 after 300 mg IV Solution Infusion Given Twice on Day 1 Followed by 300 mg Once Daily for 9 to 13 Additional Days, Serial PK Evaluable Population

Dose (mg)	Cohort	n	Cmax (ng/mL)	Tmax (hr)	AUC0-24 (hr.ng/mL)	Cavg (ng/mL)	Cmin (ng/mL)
300	2	19	2610 (39)	1.50 (0.98-4.00)	33800 (42)	1410 (42)	1046 (49)
	3	30	3696 (80)	1.52 (1.00-2.00)	37600 (31)	1566 (31)	1164 (40)
	2 3	49	3280 (74)	1.50 (0.98-4.00)	36100 (35)	1500 (35)	1090 (44)

Median (Min, Max) reported for Tmax
Cavg AUC(interval) at steady state/dosing interval
PK Parameters descriptive statistics are arithmetic means (arithmetic mean percent CV)
NA- Not Applicable
Source Data: [16.2.5.1.21]

Source: Table 11-6, Clinical Study Report (CSR), page 134.

Please refer to the clinical pharmacology review by Seong Jang, Ph.D. for a detailed review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

This clinical development program for POS IV solution was designed to bridge to the prior POS oral suspension clinical program. POS IV solution has been studied in 340 subjects, including 72 healthy volunteers enrolled in three Phase 1 studies (P04985, P06356 and P07783) and 268 patients who required antifungal prophylaxis and were enrolled in a pivotal Phase 1b/3 trial, P05520. POS IV solution has been developed to be administered via a central line based on local infusion-site reactions identified initially in preclinical studies and more definitively in the studies in healthy volunteers. Study P05520 is the focus of this clinical review.

Table 2. Overview of the Clinical Program for POS IV

Study	Short Protocol Titles	Study Design	POS Dose (mg)	Administration IV	No. of Subjects Treated	PK parameters
P04985	PK, safety & tolerability study in healthy volunteers (SD and MD)	XO	SD:200	Peripheral infusion	Active IV :9 Placebo:3	Single dose Cmax, AUC0-∞, and AUCtf

P06356	PK/safety & tolerability study in healthy adult volunteers (SD and MD)	Fixed Sequence	SD:300	Peripheral infusion over 30 mins	Active (IV POS): 45 Captisol® (cyclodextrin vehicle only): 9 Placebo (D5W): 18 MD: Active (IV POS): 5* Captisol® (cyclodextrin vehicle only): 9* Placebo(D5W): 4*	Single dose Cmax, AUC0-∞, and AUCtf Multiple dose AUC, Cavg and Cmax
P07783	Absolute bioavailability and MD, PK study in healthy volunteers (SD and MD)	XO	SD:300	Peripheral infusion over 30 mins	Active (POS): 13	Single dose Cmax, AUC0-∞, AUCtf
P05520	PK, safety & tolerability study in high risk subjects; IV solution followed by oral suspension	Parallel Group, High Risk Subjects	Cohort 0: 200 (SD) or placebo; Cohort 1: 200mg (MD); Cohorts 2 and 3: 300mg (MD)	Central line infusion of POS IV solution over 90 min 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: Active (POS):10 Placebo (D5W): 11 Cohort 1: POS 200 mg: 21 Cohort 2: POS 300 mg: 24 Cohort 3: POS 300 mg: 213	Multiple dose AUCτ, Cavg and Cmax

MD = Multiple Dose, SD = Single Dose, MD = multiple dose, XO = Cross-over Design; D5W = 5% dextrose in water.

5.2 Review Strategy

The safety and tolerability data in three Phase I studies (P04985, P06356 and P07783) and the pivotal Phase 1b/3 study, P05520, were reviewed. Study P055520 was a phase 1b/3, single-arm, uncontrolled, open-label, sequential- and parallel-group, global, multicenter, study of the pharmacokinetics, safety, and tolerability of POS IV solution used as prophylaxis in adult patients at high risk for invasive fungal infections (IFIs). Study P05520 was reviewed for safety and tolerability of POS IV in the target population of patients with hematologic malignancies at risk for IFI. The safety data for POS IV was compared to the known safety profile of oral formulations of POS (oral suspension and delayed-release tablets) and the triazole class of anti-fungal drugs in general.

5.3 Discussion of Individual Studies/Clinical Trials

The pivotal study, Study P05520, was an open-label, sequential- and parallel-group, multi-site study of the pharmacokinetics, safety, and tolerability of POS IV solution used as prophylaxis in subjects at high risk for IFIs to be conducted in conformance with Good Clinical Practices. P05520 was not designed as an efficacy study. The available PK and safety data from P05520

bridges to the existing data (including efficacy data) with the oral suspension. Subjects were to receive POS IV solution for a period of time followed by step down therapy with oral POS.
The clinical safety information in Study P05520 provided the support for the safety of POS IV in neutropenic subjects undergoing chemotherapy for leukemia and recipients of allogeneic hematopoietic stem cell transplant (HSCT) and patients with GVHD. A total of 268 subjects received at least one dose of study drug. Subjects were treated in 34 study centers (6 in the United States) in 12 countries.
The study consisted of four cohorts (Cohorts 0, 1, 2, and 3) treated in a sequential order. Cohort 0 was intended to assess the safety of a single 200 mg dose of POS IV solution (vs. placebo) in a small group of at least 20 subjects. Cohorts 1 and 2 were intended to obtain PK and safety at two different IV dosing regimens (200 mg or 300 mg) administered for 14 days in at least 15 subjects each, with the intent to select a final POS IV dose for evaluation in Cohort 3. Cohort 3 was intended to evaluate the safety and limited PK in a larger cohort of at least 200 subjects at the selected POS IV dose (300 mg). See Table 1.

Primary Objectives

Cohort 0: To determine the safety and tolerability of POS IV solution single dose administration via central line in a representative subject population.

Cohorts 1, 2, and 3: To characterize the PK of POS IV solution in a representative subject population.

Secondary Objectives
Cohort 0: To characterize POS exposures after single dose administration
Cohorts 1 and 2: To select the POS IV solution dose to be used in the broader patient population with hematologic malignancies in Cohort 3.
Cohort 3: To compare the POS exposures obtained with those achieved in previous POS pivotal trials for prophylaxis.
Cohorts 1, 2, and 3: To characterize POS exposures of POS IV solution and step-down to POS oral suspension therapy at steady state, to evaluate the safety and tolerability of POS IV solution in a representative population, and to compare the POS exposures obtained with the administration of the oral formulation versus the IV formulation at steady-state.
Cohort 3: To compare the POS exposures obtained with the administration of the IV solution with the POS oral formulation.

Per the clinical protocol, in Cohort 3, the following secondary endpoints were to be summarized using descriptive statistics for all subjects combined and by underlying disease:

(a) Clinical failure during the exposure phase as determined by incidence of IFIs, deaths, discontinuations, or use of systemic antifungals for empiric treatment of fungal infections for more than 4 days; and (b) Survival Assessment at Day 60 (at any day from Days 60 to 70).

A subject was counted as a clinical failure if they met one or more of the following criteria:

1. The subject was diagnosed by the investigator with probable or proven IFIs. There was no adjudication or review of IFI diagnosis.

2. The subject was confirmed to have died during the study (up to and including Day 70),

3. The subject discontinued study therapy for any reason,

4. The subject received systemic antifungals for empiric treatment of fungal infections for more than 4 days while the subject was receiving study treatment.

Three general amendments were subsequently finalized on Nov 24, 2009 (P05520AM1), March 22, 2011 (P05520AM2), and March 5, 2012 (P05520AM3). Pertinent changes in the protocol amendments included:

- P05520AM1 contained updated CMC information on the drug product formulation (IV solution for injection),
- P05520AM2 contained revised time points for the optional expanded PK sampling and the protocol was updated to include allogeneic hematopoietic stem cell transplant (HSCT) subjects in the pre-engraftment period (i.e. after they received their conditioning regimen for the transplant but while they were still neutropenic).
- In P05520AM3, the timing of the optional expanded pharmacokinetic (PK) sampling for Cohort 3 subjects was updated.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The indication is for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients who are at high risk of developing these infections due to being severely immunocompromised, such as HSCT recipients with graft versus host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy. In Study P05520 protocol, efficacy endpoints included a description of clinical failure, which was a composite endpoint based on the following: (a) incidence of IFIs, (b) the incidence of deaths, (c) the incidence of therapy discontinuations, and (d) the incidence of systemic antifungal use for empiric treatment of fungal infections for more than 4 days. See Section 7 for a review of the safety results for POS IV.

6.1.1 Methods

The study report and raw data in the study report for Study P05520 were reviewed to assess the safety profile of POS IV in relation to posaconazole systemic exposures in adult patients with hematologic malignancies at high risk for IFIs. Analyses of data in electronic study datasets were performed using JReview 9.26, Integrated Clinical Systems, Inc.

6.1.2 Demographics

In all cohorts combined, the total subject population had a mean age of 51 years (range: 18-82 years), almost all of the subjects were white (95%) and 55% of the population was male. Among the 279 treated subjects, 187 (67%) subjects had Acute Myeloid Leukemia (AML), 10 (4%) subjects had Myelodysplastic Syndromes (MDS), and 82 (29%) subjects were allogeneic HSCT recipients, as the primary diseases at enrollment. Only the 300-mg dose cohort enrolled patients with HSCT and GVHD per the protocol.

The demographic and baseline disease characteristics of the study population are summarized in the following table.

Table 3. Demographic and Baseline Characteristics for All Treated Subjects; N = 279

Characteristic		**Cohort 0: Placebo n (%)**	**Cohort 0: POS 200-mg Group n (%)**	**Cohort 1 POS 200-mg Group n (%)**	**Cohort 2: POS 300-mg Group n (%)**	**Cohort 3: POS 300-mg Group n (%)**
No. of subjects N/279(%)		11 (4)	10 (4)	21 (8)	24 (8)	213(75)
Sex	Male	5	5	13	13	117 (55)
	Female	6	5	8	11	96 (45)
Race	White	11 (100)	10 (100)	21	24	200 (94)
	Black	0	0	0	0	2
	Asian	0	0	0	0	3
	Multiracial	0	0	0	0	7
	Native American / or Alaskan native	0	0	0	0	1
Age (years)	Mean (SD)	60 (12)	59 (17)	49 (15)	52 (13)	51 (15)
	Range	34-76	18-75	18-75	19-82	18-82
Age (years) Group	18 to < 65yrs n=227(81%)	7	6	19	20	175
	65 yrs or older N=52(19%)	4	4	2	4	38
Weight (kg)	Median	74	79	81	75	78
	Range	61-90	47-113	56-97	57-102	46-148
Primary Diagnosis						
	Leukemia/AML	10	10	20	22	125
	MDS	1	0	1	2	6
	HSCT	0	0	0	0	82

Source: Adapted from study P005520, clinical study report, Table 10-9 p.120;
n=number of subjects; POS=posaconazole; SD=standard deviation.

Clinical Reviewer's Comment: *The study population is representative of adults with hematologic malignancies. Leukemia occurs more often in men than in women and is more common among white people. The demographics of patients in the 200mg and 300mg dose cohorts were similar with regard to other characteristics such as age and baseline weight. There were a limited number of elderly subjects in the trial, 52 (19%) were 65 years of age or older.*

6.1.3 Subject Disposition

In Study P05520, a total of 312 subjects were screened for eligibility, 287 patients were enrolled and 279 (97%) received at least one dose of IV posaconazole or placebo. This included 10 high-risk subjects who received a single 200 mg dose of POS IV solution, 21 high-risk subjects who received multiple dosing of 200 mg POS IV solution (following 200 mg twice on Day 1), and 237 high-risk subjects who received multiple dosing of 300 mg daily (following 300 mg twice on Day 1). Overall, 268 subjects have received POS IV solution in the pivotal Phase 1b/3 study for prophylaxis against IFI. One subject was not randomized, but was treated. Eleven (4%) subjects were treated with placebo IV in Cohort 0.

The distributions of reasons for early treatment discontinuation were due to adverse events (AEs) (16%), treatment failure (2%), subject did not wish to continue for any reason or subject withdrew consent (7%), non-compliance with protocol (1%), progression of disease under investigation (1%), and subject did not wish to continue for reasons related to assigned study treatment (<1%).

In the 300 mg dose group (Cohort 3), four subjects received the incorrect POS IV initial dose and maintenance doses at 250 mg rather than 300 mg (Subject Nos. 50/000315, 50/000659, 50/000663, and 50/000666) and 2 subjects received the incorrect POS IV initial dose and maintenance doses at 200 mg rather than 300 mg (Subject Nos. 27/000318 and 81/000326). None of the protocol deviations appeared to have a significant impact on the overall study conduct or study findings. Subject disposition for all dose cohorts are summarized in Table 4.

Table 4. Disposition of Study Subjects per Dose Group – Completed Treatment Phase -

REASONS FOR DROPOUT	Cohort 0 (n=21); Placebo (n=10); POS 200mg (n=11)	Cohort 1: POS 200 mg IV QD (n=21)	Cohort 2: POS 300mg IV QD (n=24)	Cohort 3: POS 300 mg IV QD (n=213)	Total No. of Subjects N=279
ADVERSE EVENT	1*	3	7	35 (16%)	46(16%)
NON-COMPLIANCE WITH PROTOCOL	-	1	-	3 (1%)	4
TREATMENT FAILURE	-	1	-	5 (2%)	6
SUBJECT WITHDREW CONSENT OR DID NOT WISH TO CONTINUE FOR ANY REASON	-	2	-	15 (7%)	17
PROGRESSION OF DISEASE	-	-	-	2(1%)	2
Total Subjects Discontinued	1(5%)	7 (33%)	7(29%)	60 (28%)	75 (27%)
Total Subjects Treated in Dose Group	21(100%)	21 (100%)	24 (100%)	213(100%)	279
Total Subjects Completed Treatment Phase	20(95%)	14(67%)	17(71%)	153 (72%)	184 (66%)

*The adverse event in cohort 0 occurred in the placebo group.

Clinical Reviewer's Comment: *Almost all subjects (99%) had treatment emergent adverse events (TEAE) during the trial, therefore a discontinuation rate of 15% due to adverse events is relatively low.*

6.1.4 Analysis of Primary Endpoint(s)

There was no primary efficacy endpoint in Study P05520.

6.1.5 Analysis of Secondary Endpoints(s)

Efficacy endpoints included a description of clinical failure, which was a composite endpoint based on the following: (a) incidence of invasive fungal infections (IFI), (b) the incidence of deaths, (c) the incidence of therapy discontinuations, and (d) the incidence of systemic antifungal use for empiric treatment of fungal infections for more than 4 days. A Day 65 survival assessment was performed, which included death at any time up through Day 65 + 5 day window.

Survival through Day 65

Nine of the 10 subjects (90%) in Cohort 0 treated with POS IV were alive at Day 65. Additionally, 10 of the 11 subjects (91%) in Cohort 0 treated with Placebo IV survived through Day 65. Twenty of the 21 subjects (95%) who were treated with multiple doses of 200 mg POS IV in Cohort 1 survived through Day 65. A total of 194 (92%) of subjects who received multiple doses of 300 mg POS IV in Cohorts 2 and 3 survived through Day 65. There were 22 (8%) deaths reported during Study P05520 and 19 (8%) deaths occurred in the 300-mg multiple dose groups (Cohorts 2 and 3). Deaths are discussed in more detail in Section 7.

Clinical Failures are summarized in the following tables. The results of "Overall Clinical Failure" count a subject only once, even though a single subject may be counted in multiple subcategories for reasons for clinical failure.

Table 5. Clinical Failure and Day 65 Survival in 200-mg Dose Group (Cohort 0 and 1)

	Cohort 0 (placebo IV), N=11	**Cohort 0 (200 mg IV) N=10**	**Cohort 1 (200 mg IV) N=21**	**Total No. Subjects**
Overall Clinical Failure	**2**	**1**	**7**	**10**
Deaths	1	1	1	3
Proven/ Probable IFI	0	0	1	1
Use of empiric therapy	0	0	0	0
Discontinued Antifungal Rx	1	0	7	8

In Cohort 1, the patient with proven or probable IFI discontinued therapy due to candidemia and subsequently died at Day 24; therefore this subject is counted in all three subcategories. In Cohort 0, the one treatment discontinuation (Subject No. 4/000002) was due to an adverse event. Among the seven discontinuations in Cohort 1, one subject, Subject No. 4/000113, was a failure of prophylactic treatment due to a breakthrough IFI. A brief case narrative is presented for this patient: Subject No. 4/000113, a 57 year-old white male subject with a history of AML, was diagnosed on Day 3 with candidemia (unresolved) which was treated with caspofungin and experienced anal pain which was treated with chlorhexidine. He received POS 200 mg IV BID Day 1, POS 200 mg IV QD on Day 2 to 5. The subject stopped study medication on Day 5 due to the candidemia. On Day 3, the POS concentration was 1,080ng/mL within the acceptable range. On Day 4, the subject was diagnosed with *Enterococcus faecium* bacteremia (unresolved) which was treated with vancomycin. The subject was found dead on Day 24. Macroscopic exam of autopsy showed a massive intrapulmonary hemorrhage, suspected bilateral pulmonary embolism, and disseminated aspergillosis.

Clinical Reviewer's Comment: *POS IV failed to prevent breakthrough candidemia in Subject No. 4/000113 and POS IV was discontinued on Day 5. The development of invasive aspergillosis complicated by pulmonary hemorrhage and death on Day 24 was unrelated to study drug.*

Table 6. Clinical Failure and Day 65 Survival in 300-mg Dose Cohort (Cohort 2 and 3)

	Cohort 2, n, (%), N=24	**Cohort 3, n, (%), N=213**	**Total, n, (%) N=237**
Overall Clinical Failure	**9 (38)**	**66 (31)**	**75 (32)**
Deaths	3 (12)	16 (7)	19 (8)
Proven/ Probable IFI	1 (4)	2 (1)	3 (1)
Use of empiric therapy	1 (4)	5 (2)	6 (3)
Discontinued Antifungal Rx	7 (29)	60 (28)	67 (28)

Among the 237 subjects in the POS 300 mg multiple dose group (Cohort 2 and 3 combined), 75 subjects (32%) had clinical failure. The clinical failure rates within Cohorts 2 and Cohort 3 were 38% and 31%, respectively.

Breakthrough Invasive Fungal Infections

In the 300-mg dose Cohort 2 & 3, three (1%) patients failed prophylaxis with POS IV and developed a proven or probable pulmonary mycosis. Six (3%) subjects received more than four days of systemic antifungals for empiric treatment of fungal infections.

Subject No. 7/000202 was a 20 year-old white male subject with a history of AML. On Day 1, he received POS 300 mg IV BID, then received POS 300 mg IV QD from Day 2 to 14. The Day 13 POS trough concentration was 1280 ng/mL, within the targeted range. He then transitioned to POS oral suspension 400 mg PO BID from Day 15 to 23. Probable pulmonary invasive fungal infection was diagnosed on Day 21. The subject discontinued from study due to the development of pulmonary mycosis on Day 24. The pulmonary mycosis was treated with caspofungin for four days followed by amphotericin B. On Day 29, the patient was a diagnosed with a proven invasive fungal infection based on histopathology of a bronchoalveolar lavage sample. On Day 39, the subject experienced hypotension, bacteremia, and renal failure. On Day 41, the patient improved and was discharged from the ICU.

Subject No. 9/000341 was a 30 year-old white male with a history of AML. He entered the study on Day 1 receiving POS 300 mg IV BID and then receiving POS 300 mg IV QD from Day 2 to 5, and POS oral suspension 200 mg TID from Day 6 to 14. He experienced mucositis on Day 1 and intermittent fever on Day 2, and was treated with amphotericin B, lidocaine, prednisolone and paracetamol, which were ongoing at the end of the study. He developed an IV catheter site

related reaction on Day 2 to 4. The subject received pentamidine for prophylaxis of pneumocystis pneumonia on Day 2. On Day 8, the POS trough concentration was 754 ng/mL, within the targeted range. On Day 11, computed tomography (CT) of the chest showed a new pulmonary nodular infiltrate with halo-sign consistent with invasive aspergillosis and POS IV was discontinued on Day 11. A bronchoscopy (Day 12) also revealed a positive galactomannan in bronchoalveolar lavage fluid; galactomannan index: 1.7 OD. The subject received amphotericin B for treatment of invasive fungal infection and ciprofloxacin, piperacillin/ tazobactam, and meropenem for prophylaxis of bacterial infection. POS was permanently discontinued on Day 14. On Day 42, the subject developed sepsis due to a multi-drug resistant *Pseudomonas aeruginosa* infection, which resulted in multi-organ failure and death on Day 44.

Subject No. 17/000339 was a 72 year-old white female with a history of AML. On Day 1, she received POS 300 mg IV BID, POS 300 mg IV QD treatment from Day 2 to 5, POS oral suspension 200 mg TID from Day 6 to 12, and POS 200 mg PO BID on Day 13. She experienced septicemia with *P. aeruginosa* infection on Day 9 for which she was treated with gentamicin and meropenem. On Day 13, she developed pulmonary mycosis. The POS trough concentration was 991ng/mL on Day 8 which was within the targeted range. The subject was treated with voriconazole, ondansetron, and morphine. The subject temporarily discontinued study drug as a result of fever then later discontinued on Day 13 due to pulmonary mycosis. The etiologic agent of pulmonary mycosis was not determined.

Cases of Possible Invasive Fungal Infection

Six of 237 (2.5%) subjects (3 females and 3 males) in the 300-mg cohort received empiric treatment of fungal infections for more than 4 days. They had abnormal radiographic findings but no mycological evidence of infection which is consistent with diagnosis of possible invasive fungal infection.**Error! Bookmark not defined.**

In the 300 mg IV dose groups, the majority (68%) of subjects did not meet any of the criteria for clinical failure. Among the 32% (75/237) of subjects that met the criteria for clinical failure, in most cases this was due to discontinuation of study therapy for reasons other than breakthrough fungal infection. Overall, the incidence of breakthrough IFI in this study was relatively low and similar to that previously reported for POS oral suspension.

Clinical Reviewer's Comment: *The breakthrough IFI rate (1%) for posaconazole IV was lower than that previously reported for posaconazole oral solution and POS delayed-release tablets. Six (2.5%) subjects received more than four days of systemic antifungals for empiric treatment of possible fungal infections. The breakthrough infection rate for the oral posaconazole solution prophylactic therapy was evaluated in two comparative, phase 3 trials[1,2] in patients with hematological malignancies, summarized in the NOXAFIL®, USPI. The breakthrough infection rate for IFI in those trials was 2 to 5%, similar to the breakthrough infection rate of 4.7% observed for POS delayed-release tablets. Both trials demonstrated substantially fewer breakthrough infections caused by Aspergillus species in patients receiving posaconazole prophylaxis when compared to patients receiving fluconazole or itraconazole.*

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

Not applicable.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Please refer to section 7.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

The safety database of 340 subjects included 72 subjects from three phase 1 studies and 268 subjects who received POS IV in Study P05520, the pivotal Phase 1b/3, open label, single-arm, non-comparative study for prophylaxis against IFI. Experience in healthy volunteers with multiple doses of POS IV solution was limited due to intolerance of POS IV infusion via a peripheral line and the maximum duration of treatment was four days.

The population in Study P05520 included 10 high risk patients who received a single 200-mg dose of POS IV, 21 high risk patients who received multiple doses of 200 mg POS IV (following 200 mg twice on Day 1), and 237 high-risk patients who received multiple doses of 300 mg POS IV daily (following 300 mg twice on Day 1) for a recommended minimum of 5 days and up to 28 days.

The majority (99%) of subjects in Study P05520 experienced a treatment emergent adverse reaction (TEAE). In cohort 1 (multiple doses of 200 mg IV), the most common adverse reaction (>25%) was nausea. Discontinuation of study drug due to an adverse experience occurred in 4 (19%) patients. In Cohorts 2 & 3 (multiple-doses of 300 mg IV), the most common TEAE was diarrhea and the most common TEAEs with an onset during the IV phase were diarrhea (32%), hypokalemia (22%) and pyrexia (21%).
Infusion site reactions (erythema, pain, thrombophlebitis) were common (6/9 [60%] subjects in one study) in healthy volunteers who received more than one dose of POS IV via the same peripheral IV catheter. Local intolerability was likely due to the irritation associated with the low pH of the infusion solution. Administration of POS IV as a single dose up to 300 mg and infused over 30 minutes via a peripheral line appeared to be generally well tolerated. The risk of

infusion site reactions including thrombophlebitis is not acceptable with multiple dosing via a peripheral IV catheter; therefore, POS IV should be administered by a central catheter. A single-dose may be infused through a peripheral IV catheter while insertion of a central line is pending. In Study P05520, patients received POS IV through a central line and there was a low incidence of infusion site reactions.

The survival rate in Study P05520 was high at 95% and 92% of patients in the 200-mg and the 300-mg dose groups, respectively. There were 22 deaths during the trial period. There were two deaths in Cohort 0. One death was reported in the 200-mg multiple dose cohort 1 and 19 (8%) deaths occurred in the 300-mg multiple-dose cohorts 2 & 3. The most common cause of death, reported in six subjects, was sepsis or septic shock. Other causes of death included progression of underlying hematologic malignancy (AML or MDS), multi-organ failure, renal failure, intestinal hemorrhage, subarachnoid hemorrhage, and acute respiratory distress syndrome (ARDS). There were no causes of death or SAEs leading to death considered to be directly related to POS in the 200-mg and 300-mg dose cohorts based on the review of the case narratives for each patient who died on study.

The study population was evaluated for safety issues associated with the triazole class of antifungal drugs including hepatotoxicity, QTc interval prolongation, adrenal insufficiency, and clinical drug-drug interactions. There was one subject (300-mg dose cohort) who met the protocol pre-specified criteria for significant QTc interval prolongation (QTc > 500 msec). The patient was asymptomatic, the study drug was discontinued and the event resolved.

One patient developed acute hepatic failure and POS IV probably contributed to the hepatic injury in this patient; however, it is likely that elevations in hepatic transaminases observed in this patient were also due to Gram-negative septic shock and progression of AML. Nine (4%) of the patients had hepatic function test results which met the criteria for Hy's Law at some point during POS treatment. However, three of the cases also had elevated alkaline phosphatase suggesting cholestasis. Hepatic transaminases and bilirubin levels improved after the study drug was stopped but the elevations in hepatic transaminases were ongoing beyond the end of all POS IV and oral treatment in six patients. Cases with elevated hepatic transaminases were difficult to evaluate for causality because they were confounded by concomitant administration of hepatotoxic myelosuppressive regimens, other concomitant medications, and development of GVHD.

The rates of treatment related adverse reactions in patients with high and low exposures to POS IV were compared and did not appear to be different. Within the range of drug exposures that were observed in P05520, there did not appear to be an association of higher POS concentration with a higher incidence of a treatment-related TEAE following administration of POS IV. The safety profile was similar among those subjects receiving POS IV solution in the 200-mg multiple-dose group (Cohort 1) as compared to those in the 300-mg group (Cohorts 2 and 3).

The frequency and nature of serious adverse events (SAEs) in subjects receiving POS IV solution (with step-down to POS oral suspension) in P05520 was similar to that seen in the previous prophylaxis studies with POS oral suspension. The frequency and nature of hepatic, cardiac, adrenal/metabolic, hypersensitivity, and gastrointestinal serious adverse reactions were

similar to the safety profile of posaconazole oral suspension and delayed release tablets. Changes in hepatic and renal function laboratory parameters were similar to the safety profile of posaconazole oral suspension and delayed release tablets.

The attribution of adverse reactions to POS IV was hampered by the fact the there was no comparative safety data and by adverse reactions related to the patients' underlying hematologic malignancies and concomitant myelosuppressive drug regimens.

In summary, POS IV administered via a central IV catheter was reasonably well tolerated and had a similar safety profile to the marketed posaconazole oral suspension. Based on the safety information provided in Study P05520 and the known safety profile of oral formulations of posaconazole, the potential benefit of POS IV in preventing life-threatening invasive fungal infection outweighs the risk of adverse reactions in immunocompromised patients with hematologic malignancies.

Treatment Emergent Adverse Reactions in 200-mg Dose Cohort

Adverse reactions reported in the 200-mg dose cohort are summarized in Table 6. All patients experienced at least one treatment-emergent adverse event and 19% experienced a serious adverse reaction

Table 7. Treatment Emergent Adverse Reactions in POS IV 200-mg Dose Cohort vs. Placebo

	Cohort 0: placebo IV	Cohort 0: POS 200 mg IV (SD)	Cohort 1: POS 200 mg IV (MD)
Treatment Emergent AE	11 (100)	10 (100)	20 (95)
Serious AE	2 (18)	2 (20)	4 (19)
Death	1 (9)	1 (10)	1 (5)
Severe/Life-threatening TEAE	7 (64)	5 (50)	11 (52)
Drug discontinuation due to AE	1 (9)	0	4 (19)

Source: Section 12.1.2.1.2 of Clinical study report, P05520; SD=single dose; MD=multiple dose

Treatment Emergent Adverse Reactions in 300-mg Dose Cohort

Adverse Reactions in patients who received the 300 mg IV dose are summarized in Table 7. The majority (99%) patients experienced at least one treatment-emergent adverse event and 30% experienced a serious adverse reaction.

Table 8. Treatment Emergent Adverse Reactions – 300 mg Dose vs. Placebo

	Cohort 0: placebo IV; N = 11 (100%)	Cohort 2 & 3: POS 300 mg IV; N = 237 (100%)
Treatment Emergent AE	11 (100)	235 (99)
Serious AE	2 (18)	71 (30)
Death	1 (9)	19 (8)
Severe/Life-threatening	7 (64)	123 (52)

TEAE		
Drug discontinuation due to AE	1 (9)	45 (19)

Source: Adapted from Table 12-34, Section 12.2 of the clinical study report, P05520

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

One open-label phase 3 trial, Study P05520, evaluated the PK, safety, and tolerability of POS IV in the intended population of neutropenic patients with hematological malignancies, post-HSCT and patients with GVHD.

7.1.2 Categorization of Adverse Events

Study P055520 used MedDRA version 15.1 for categorization of adverse events. Adverse events were summarized by MedDRA System Organ Class (SOC) and preferred term. Based on the verbatim description and preferred terms used to describe adverse reactions, the categorization of adverse events appears to be adequate.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable.

7.2 Adequacy of Safety Assessments

The safety assessments conducted during the trial period were adequate to make an evaluation of the safety profile of the study drug.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Extent of Exposure in the POS 200-mg IV multiple-dose group (Cohort 1)
The POS IV dosing regimen for the 21 subjects in Cohort 1 was POS 200 mg IV twice on Day 1, followed by 200 mg/day IV on Days 2 through 14. Subjects in Cohort 1 were to then receive 14 days of 400 mg POS orally twice daily. The mean duration of POS IV therapy was 12 days. A total of 17 (81%) subjects completed a full 14 days of treatment.

Extent of Exposure in the POS 300-mg IV multiple-dose, Cohorts 2 & 3
The POS IV dosing regimen for the subjects in Cohort 2 was POS 300 mg IV twice on Day 1, followed by 300 mg/day IV on Days 2 through 14. Subjects in Cohort 2 were to then receive 14 days of 400 mg POS oral suspension at 400 mg twice daily.

The POS dosing regimen for Cohort 3 subjects was POS 300 mg IV twice on Day 1, followed by 300 mg/day IV for at least 5 days, followed by POS oral suspension (either at 200 mg three times daily or 400 mg twice daily) to complete 28 days of treatment. In the 300-mg dose group the mean duration of therapy was 23 days. A total of 227 (96%) of subjects completed ≥ 5 days

which was the recommended minimum duration of exposure to POS IV and 24 (10%) subjects remained on the POS 300 mg IV for the maximum duration of 28 days. The extent of exposure to the POS 300 mg IV multiple dose in Cohorts 2 and 3 is summarized in Table 9.

Table 9. Extent of Exposure to Posaconazole 300 mg IV

Treatment Duration in Days[a]	**Cohorts 2 and 3 No. of Subjects N (%); All Treated Subjects (N=237)**
Received any Rx	237 (100)
≥1	237 (100)
≥2	237 (100)
≥3	234 (99)
5	227 (96)
6	141 (59)
≥8	130 (55)
≥15	67 (28)
≥22	24 (10)
28	12 (5)
Statistics[b]	
Mean	11.2 (SD = 7)
Median	9
Min, Max	2, 28

[a] Duration is based on treatment begin date and treatment end date and does not take into account possible dosing interruptions and subject noncompliance. [b] Statistics are exclusive of subjects not treated and subjects with an unknown duration.

Source: Adapted from Table 12-33, Section 12.2.1 of study report, P05520

Clinical Reviewer's Comment: *A total of 227 or 96% of patients completed the recommended minimum 5 days of IV prophylaxis which provided an adequate number of patients to assess the exposure response in relation to the safety of POS IV.*

7.2.2 Explorations for Dose Response

The exposure target was determined based upon the range of exposures achieved with POS oral suspension product in safety and efficacy trials, as well as the exposure-response relationship

found in earlier controlled studies.[1,2,3] Please refer to section 7.3.5 for a discussion of posaconazole exposures and safety of patients in the 200mg and 300mg Dose Cohorts. Please also refer to the clinical pharmacology reviews for posaconazole suspension (NDA 22-003) and posaconazole tablets (NDA 205-053) in DARRTS.

7.2.3 Special Animal and/or In Vitro Testing

See Pharmacology/Toxicology review by Owen McMaster, Ph.D.

7.2.4 Routine Clinical Testing

Not applicable.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to the clinical pharmacology review (10/17/13) by Seong Jang, Ph.D.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Triazole drugs are known to cause gastrointestinal adverse reactions, hepatotoxicity, QTc interval prolongation, adrenal suppression, and multiple potential drug-drug interactions. Triazole drugs inhibit P450 enzymes specifically CYP3A4 isoenzyme, which is the principle drug metabolizing enzyme in humans.[4] Concomitant use of the extended-spectrum triazoles with immunosuppressive drugs metabolized by the liver may cause severe hepatotoxicity, especially those metabolized by cytochrome P450 isoenzymes except for cytarabine or fludarabine.[5]

Triazole drugs including posaconazole interact with the calcineurin inhibitors to cause neurologic adverse reactions. Itraconazole and voriconazole interacts with vincristine to cause severe neurotoxicity.[6,7] Itraconazole has a potential negative inotropic effect and should be avoided in patients with a history of heart failure and with drugs that are potentially cardiotoxic (such as anthracyclines or high-dose cyclophosphamide).

Concomitant administration of extended-spectrum triazoles (posaconazole, voriconazole, itraconazole) with vincristine or high doses of cyclophosphamide should be avoided. Itraconazole interacts with cyclophosphamide to cause hepatic and renal toxicity.[8] Posaconazole

[4] Gubbins PO, Heldenbrand S. Clinically relevant drug interactions of current antifungal agents. Mycoses 2010; 53(2):95.
[5] Wingard, JR. Prophylaxis of invasive fungal infections in adults with hematologic malignancies. www.UpToDate.com Sept 2013
[6] Osato Y, et al. Retrospective Analysis of Neurotoxicity Induced by Vinca Alkaloids Combined with Azole AntiFungal Agents in Hematological Malignancies. Japanese Journal of Cancer and Chemotherapy OCT-2011; 38(10):1667-1672
[7] Takahashi N., et al. Itraconazole oral solution enhanced vincristine neurotoxicity in five patients with malignant lymphoma. Intern Med. 2008; 47(7):651-3
[8] Marr KA, Leisenring W, Crippa F, et al. Cyclophosphamide metabolism is affected by azole antifungals. Blood 2004;103(4):1557

is primarily metabolized by UDP glucuronidation, and is a substrate and inhibitor of p-glycoprotein; therefore, caution should be used with drugs metabolized by UDP glucuronidation, such as digoxin.

7.3 Major Safety Results

7.3.1 Deaths

There were 22 (7%) deaths reported during Study P05520. Two deaths occurred in subjects in Cohort 0, one subject received Placebo IV (6/000011) and one received POS 200mg IV (6/000005). Subject 4/000114 (Cohort 1: 200-mg multiple dose group), died of pulmonary embolism, pulmonary hemorrhage, and invasive aspergillosis.

A total of 19 (8%) deaths occurred in the 300-mg multiple dose groups (Cohorts 2 & 3). Three of 19 subjects had reported deaths after the Day 65 + 5 window (>70 days): Subject 23/000679 died on Day 72 due to a gastrointestinal bleed, Subject 27/000318 died on Day 125 due to progression of AML, and Subject 36/000305 died on Day 109 due to septic shock.

There were no deaths among the 72 healthy volunteer subjects receiving POS IV solution in the three Phase I POS IV studies.

Table 10. Deaths in Study Dose Cohorts – All treated subjects – Study P05520

Outcome	Cohort 0 - Placebo IV	Cohort 0 - POS IV	Cohort 1 - POS IV 200mg	Cohort 2 - POS IV 300mg	Cohort 3 POS IV 300mg	Total Subjects (n=279)
Deaths	1 (0.3%)	1 (0.3%)	1 (0.3%)	3 (1%)	16 (5.7%)	22 (7.3%)

Cause of Death Category

The most common cause of death was adverse events or progression of underlying hematologic malignancy.

Table 11. Cause of Death in 200-mg and 300-mg Dose Cohorts – All Treated Subjects; N=279

Cause Of Death MedDRA PT	Cohort 0 Placebo IV	Cohort 0 POS IV 200 mg	Cohort 1 POS IV 200 mg	Cohort 2 POS IV 300 mg	Cohort 3 POS IV 300 mg	Subjects Total, N=279
No. Subjects Survived	**10**	**9**	**20**	**21**	**198**	**258 (92%)**
Acute Hepatic Failure	0	0	0	0	1	1 (0.3%)
Acute Myeloid Leukemia	0	0	0	0	2 (1%)	2 (1%)
Acute Pulmonary Edema	0	0	0	0	1	1 (0.3%)
Acute Respiratory Distress Syndrome	0		0	0	1	1 (0.3%)
Bacterial Sepsis	0	0	0	1	0	1 (0.3%)
Disease Progression	0	0	0	0	1	1 (0.3%)
Hemorrhagic Enterocolitis	0	0	0	0	1	1 (0.3%)

Multi-Organ Failure	0	0	0	0	2 (1%)	2 (1%)
Pulmonary Embolism	0	0	1	0	0	1 (0.3%)
Renal Failure Acute	0	0	0	1	0	1 (0.3%)
Sepsis	0	1	0	1	2 (1%)	4 (1.3%)
Septic Shock	1	0	0	0	3 (1%)	4 (1.0%)
Subarachnoid Hem.	0	0	0	0	1	1 (0.3%)
Total No. Subjects	11 (4%)	10 (3%)	21 (7%)	24 (9%)	213 (76%)	279 (100%)

Source: Table 12-40, clinical study report, NDA 205-596; HEM. = hemorrhage;

Deaths in Cohorts 0 and 1 – 200 mg IV Dose

The causes of death for the three subjects who died in Cohorts 0 and 1 are discussed.

Subject 6/000005 (Cohort 0), a 53 year-old male with AML entered the study on Day 1 receiving POS 200 mg IV single dose via central line administration, followed by POS 400 mg PO BID treatment from Day 1 to 6. He received a single dose of POS 400 mg PO on Day 7. Later that day, he began taking POS 200 mg PO TID for IFI prophylaxis, and continued this until Day 12. On Day 18, the subject presented with respiratory insufficiency due to atypical pneumonia. On Day 23, sepsis was reported, and his condition deteriorated. The subject was intubated for progressive respiratory failure and he died on Day 34. No autopsy was performed.

Subject 6/000011 (Cohort 0), was a 54 year-old male with acute myeloid leukemia (AML) and HIV received placebo IV and POS 400 mg BID. On Day 16, the subject developed fever and presumed sepsis. The subject had elevated bilirubin levels (126 µmol/L, Grade 3) since Day 9, and bilirubin levels continued increase to Grade 4 hyperbilirubinemia which was life threatening and possibly related to placebo IV and oral posaconazole. On Day 16, the subject did not respond to treatment for presumed septic shock and died. No autopsy was performed.

Subject 4/000114 (Cohort 1), was a 57 year-old white male with stable AML, receiving cytarabine, amsacrin and clofarabine. The subject entered the study on Day 1 receiving POS 200 mg IV BID and then received POS 200 mg IV QD on Day 2 to 5. On Day 3, the subject was diagnosed with candidemia (unresolved) and experienced anal pain which were treated with caspofungin and chlorhexidine. On Day 4, he was diagnosed with *Enterococcus faecium* bacteremia (unresolved) treated with vancomycin. The subject stopped study drug on Day 5. The Day 3 POS concentration was 1080 ng/mL within the therapeutic range. The patient was found dead on Day 24 (21days after discontinuation of POS). Macroscopic exam at autopsy showed a massive intrapulmonary hemorrhage, suspected bilateral pulmonary embolism, and disseminated aspergillosis. The patient had elevated AST, ALT, GGT, and total bilirubin throughout the study from Day -1 until his death on Day 24.

Clinical Reviewer's Comment: *No deaths were related to adverse reactions to study drug in Cohorts 0 and 1.*

Immediate Causes of Death in Cohorts 2 and 3 - 300 mg IV Dose

Bacterial infections/sepsis accounted for 47% of the serious adverse reactions leading to death and 7 (37%) patients died of bacterial sepsis or septic shock. Other causes of death included progression of underlying hematologic malignancy (AML), (viral, bacterial, or fungal), multi-organ failure, ARDS, acute liver failure, and acute renal failure. Serious adverse reactions leading to death and the immediate causes of death in subjects who received POS 300 mg IV dose in cohorts 2 & 3 are summarized in Table 12.

Table 12. Cause of Death and Adverse Reactions leading to Death - 300 mg Dose Cohorts (2 & 3)

SUBJECT ID	Serious Adverse Event(s)	Days of Study Drug Rx	Day of onset (Days post end of Rx)	Immediate Cause of Death	Study Day of Death / (Days post end of Rx)
2/000310	*E. coli* bacteremia/ *C. difficile* colitis Multi-Organ Failure	28	56(28)	Multi-organ Failure	56 (28)
2/000320	Bacteremia and Meningoencephalitis due to*Enterococcus faecalis*/ Multi-Organ Failure	23	22	Multi-organ Failure	28 (5)
5/000303	Myelodysplastic Syndrome	23	29 (6)	Progression of AML	35 (12)
6/000205	*Enterococcus* sp. Bacteremia	28	32	Sepsis	34 (6)
6/000207	*E. Coli* Bacteremia / Acute Renal Failure (ARF)	6	3	ARF	8 (2)
6/000721	Subarachnoid Hemorrhage	22	21	Subarach. Hem.	30 (8)
8/000206	Sepsis / ARF / Subarachnoid Hem.	8	~ 6	Gram Neg. Sepsis	19 (11)
9/000341	Sepsis	14	42 (28)	Sepsis	44 (30)
9/000682	Sepsis	2	2	Sepsis	3 (1)
11/000712	AML/ GVHD/ Resp. Distress/ Veno-Occlusive Disease	9	8	Progression of Disease	9
23/000679	Intestinal Hemorrhage	3	52 (49)	Enterorrhagia due to colitis	72 (69)
27/000318	-	27	-	Progress. of AML	125 (98)
29/000356	Septic Shock	28	-	Septic Shock	42 (14)
29/000368	Bacterial Sepsis	14	12	Septic Shock	14
35/000311	Acute Pulmonary Edema	14	14	Acute Pulmonary Edema	15 (1)
36/000305	-	21	-	Likely Septic Shock	109 (88)
36/000390	Recurrence AML	18	18	AML	46 (28)
37/000652	Acute Hepatic Failure	28		Acute Hepatic Failure	40 (12)
38/000361	Acute Resp. Distress Syndrome (ARDS)	9	14 (5)	ARDS	21 (12)

(X) = for X days following the end of POS (IV and oral) treatment;

Deaths associated with Renal Failure or Hepatic Failure

POS, similar to other triazoles, can cause hepatotoxicity and POS IV solution contains SBECD which may accumulate in renal impairment; therefore, the two subjects who died of hepatic insufficiency or acute renal failure are discussed in more detail.

Subject 37/000652 was a 40 year-old white female who entered the study with acute lymphocytic leukemia (resolved) and following an allogeneic HSCT. On Day -1, the patient developed a severe Stage 3 GVHD-related skin rash. On Day 2, vancomycin-resistant *Enterococcus faecium* bacteremia was treated with linezolid. She received POS 300 mg IV BID on Day 1, POS 300 mg IV QD on Day 2 to 5, and POS 800 mg PO QD on Day 6 to 28. She developed renal dysfunction starting on Day 32 possibly due to hemorrhagic cystitis or tumor lysis syndrome. She again developed vancomycin-resistant *E. faecium* bacteremia on Day 35 to 36. The subject received metronidazole for *Clostridium difficile* colitis on Day 39. On Day 29, she developed elevated hepatic transaminases and total bilirubin and ALT (584 U/L) and total bilirubin (118 µmol/L) continued to rise and on Day 40 which was 12 days post end of the POS treatment, the patient died of severe liver failure.

Clinical Reviewer's Comment: *POS IV may have contributed to the hepatic insufficiency in Subject No. 37/000652 but there were other contributing factors to the development of hepatic insufficiency in this patient such as GVHD, bacterial sepsis, and medications such as cyclosporine, cefepime, paracetamol.*

Subject 6/000207 in Cohort 2, was a 73 year-old white female subject with AML, treated with cytarabine and mitoxantrone. She received POS 300 mg IV BID Day 1, and POS 300 mg IV QD Day 2 to 6. On an unknown date, the subject was diagnosed with progression of AML. On Day 3, she was neutropenic and she developed *Escherichia coli* sepsis, a fever of 38.6ºC and dyspnea. On Day 6, the subject developed acute renal failure (creatinine 361µmol/L) and also fulfilled the clinical laboratory criteria for Hy's Law (ALT 767 U/L; alkaline phosphatase 44U/L; total bilirubin 47µmol/L. POS was permanently stopped on Day 6 due to the elevated lab results and unfavorable prognosis of AML. The elevated levels were considered to be not related to study medication. The subject experienced "somnolence and circulatory insufficiency", and died on Day 8. No autopsy was performed. The cause of death was reported as acute renal failure due to *Escherichia coli* sepsis.

Clinical Reviewer's Comment: *SBECD is a known excipient in several marketed products, including one antifungal (IV voriconazole, VFEND®, voriconazole for injection). SBECD probably contributed to acute renal failure in this patient. ARF may have also been related to her underlying AML. This cyclodextrin is known to accumulate in subjects with renal dysfunction. Patients with moderate to severe renal impairment were excluded from Study P05520; therefore, no data are available for use of POS IV in patients with moderate to severe renal impairment. Therefore, it is recommended to avoid use of POS IV in patients with moderate to severe renal impairment. This recommendation is similar for IV voriconazole, recommends i.e., to avoid intravenous administration in patients with moderate to severe renal impairment (CrCL<50 ml/min). The total amount of the cyclodextrin in POS IV does not exceed the total amount of cyclodextrin in the IV formulation of voriconazole.*

Deaths due to Multi-Organ Failure

Subject 02/000310 (Cohort 3), a 71 year-old white female with AML was treated with daunorubicin, cytarabine, and tropisetron. She received POS 300 mg IV BID Day 1, POS 300 mg IV QD Day 2 to 5, POS 800 mg PO QD Day 6, POS 400 mg PO QD Day 8, POS 300 mg IV QD Day 9 to 22, and POS 800 mg PO QD Day 23 to 28. POS was interrupted on Day 28 for an unreported reason. She developed *E.coli* bacteremia Day 52. On Day 56, one month after POS was stopped; she died due to multi-organ failure which was unlikely to be due to POS.

Subject 2/000320, a 47 year-old female with AML, received POS 300 mg IV BID Day 1, POS 300 mg IV QD Day 2 to 5, POS 800 mg PO QD Day 6 to 8, and POS 300 mg IV QD Day 9 to 23. She was treated for *Enterobacter cloacae* sepsis on Day 6 to 28 and she developed bacteremia with *Enterococcus faecalis* on Day 19. On Day 22, the subject experienced life threatening *E. faecalis* meningo-encephalitis and was hospitalized on the same day. Blood culture and CSF from Day 21 grew *E. faecalis*. POS was discontinued on Day 23. Despite antibacterial treatment, the subject presented with worsening of *E. faecalis* meningo-encephalitis and multi-organ failure. The subject died on Day 28, after the life support measures were discontinued on the same day due to multi-organ failure. No autopsy was performed.

Clinical Reviewer's Comment: *The multi-organ failure in these two patients appeared to be related to bacterial sepsis and unrelated to POS. Overall, the serious adverse events of neutropenia, bacterial sepsis/septic shock, GVHD, and progression of hematologic malignancy are expected complications in neutropenic patients with hematologic malignancies or post-HSCT at risk of invasive infections. Based on the review of the case narratives for deaths there were no causes of death or SAEs leading to death considered to be directly related to POS in the 200 mg and 300 mg dose groups. In fact, a meta-analysis of studies of systemic antifungal prophylaxis with triazole drugs (fluconazole, itraconazole, posaconazole) has been shown to significantly decrease all-cause mortality in patients after chemotherapy.*[9,10]

7.3.2 Serious Adverse Events

Serious Adverse Events (SAEs) were reported for 64 of 237 (27%) subjects in the 300-mg dose group (Cohorts 2 and 3) in Study P05520. In 27 (11%) of these subjects, the onset of the reported SAEs was during the IV phase. SAEs that occurred with an onset during the IV phase reported by more than one subject were sepsis (3 subjects), renal failure acute (3 subjects), respiratory distress (2 subjects), respiratory failure (2 subjects), and subarachnoid hemorrhage (2 subjects).

In cohort 3, two subjects (1%) reported treatment-related SAEs with an onset during the IV phase: one subject (Subject No. 38/000361) developed hyperbilirubinemia, and one subject (Subject 8/000431) developed pulmonary mycosis.

[9] Robenshtok E, Gafter-Gvili A, Goldberg E, et al. Prophylaxis in cancer patients after chemotherapy or hematopoietic stem-cell transplantation: systematic review and meta-analysis. J Clin Oncol. 2007; 25(34):5471.
[10] Wingard JR, Prophylaxis of invasive fungal infections in adult hematopoietic cell transplant recipients. Source: www.uptodate.com (update from Feb. 17, 2013).

SAEs for all study cohorts are summarized in the following table. A patient may have experienced more than one SAE.

Table 13. Serious Adverse Events in Study Cohorts 0, 1, 2, and 3 – Study P05520

STUDY P05520 MedDRA Preferred Term	Cohort 0 - Placebo IV N=11	Cohort 0 - POS IV N=10	Cohort 1 - POS IV 200 mg N=21	Cohort 2 - POS IV 300 mg N=24	Cohort 3 POS IV 300 mg N=213
PYREXIA	0	0	0	0	5 (2.4%)
SEPSIS	0	1 (10%)	0	1 (4.2%)	4 (1.9%)
GRAFT VERSUS HOST DISEASE	0	0	0	0	3 (1.4%)
PNEUMONIA	0	0	0	0	3 (1.4%)
ACUTE MYELOID LEUKAEMIA RECURRENT	0	0	0	0	3 (1.4%)
RESPIRATORY DISTRESS	0	0	0	0	3 (1.4%)
ORAL HERPES	0	0	0	0	2 (0.9%)
RESPIRATORY FAILURE	0	1 (10%)	0	0	2 (0.9%)
FEBRILE NEUTROPENIA	0	0	0	0	2 (0.9%)
THROMBOCYTOPENIA	0	0	0	0	2 (0.9%)
CYTOMEGALOVIRUS INFECTION	0	0	0	0	2 (0.9%)
BRONCHOPNEUMONIA	0	0	0	0	2 (0.9%)
MULTI-ORGAN FAILURE	0	0	0	0	2 (0.9%)
VOMITING	0	0	0	1 (4.2%)	2 (0.9%)
SEPTIC SHOCK	1 (9.1%)	0	0	1 (4.2%)	2 (0.9%)
NAUSEA	0	0	0	1 (4.2%)	2 (0.9%)
HYPOTENSION	0	0	0	1 (4.2%)	1 (0.5%)
RENAL FAILURE	0	0	0	2 (8.3%)	1 (0.5%)
RENAL FAILURE ACUTE	0	0	0	2 (8.3%)	1 (0.5%)
SUBARACHNOID HAEMORRHAGE	0	0	0	1 (4.2%)	1 (0.5%)
BACTERIAL SEPSIS	0	0	0	1 (4.2%)	1 (0.5%)
NEUTROPENIC COLITIS	1 (9.1%)	0	0	0	1 (0.5%)
HYPERBILIRUBINAEMIA	1 (9.1%)	0	0	0	1 (0.5%)
ASPIRATION	0	0	0	1 (4.2%)	1 (0.5%)
PULMONARY HAEMORRHAGE	0	0	1 (4.8%)	1 (4.2%)	1 (0.5%)
ASPERGILLOSIS	0	0	1 (4.8%)	0	1 (0.5%)
Total no. of subjects	**3 (27%)**	**2 (20%)**	**2 (10%)**	**13 (54%)**	**51 (24%)**

Clinical Reviewer's Comment: *A similar rate of serious adverse events (SAE) were reported for 69 (33%) in the registration study for POS delayed-release 300mg tablets.*

Treatment Emergent Adverse Events

In the 300-mg IV group (Cohorts 2 and 3), almost all subjects reported at least one TEAE (235/237 subjects [99%]) with 90 subjects (38%) reporting a treatment-related TEAE during either the IV or oral phase, and 72 subjects (30%) experiencing at least one treatment-related TEAE during the IV phase. The most commonly reported treatment-related TEAE during the treatment phase (IV or Oral) were diarrhea (9%), nausea (8%), rash (6%), vomiting (5%), and

hypokalemia (5%). The most commonly reported treatment-related TEAE during the IV phase were diarrhea (8%), nausea (5%), rash (5%), vomiting (4%), and hypokalemia (4%).

In the 300-mg dose group (Cohorts 2 and 3), severe/life-threatening TEAE were reported in 123 subjects (52%), and study drug discontinuation due to an adverse experience occurred in 45 subjects (19%). The overall incidence of specific TEAE were all similar to those commonly reported with POS oral suspension.

In the 300-mg multiple dose groups (Cohorts 2 and 3), SAE were reported for 64 (27%) subjects. These SAE reflect the severity of illness in neutropenic patients with hematologic malignancies as well as the comorbidities commonly seen in the HSCT patient population. There were no adverse events leading to death considered directly related to study drug among any subject treated in the 300-mg dose group (Cohorts 2 and 3).

Infusion Site Reactions

In Study 4985, 12 healthy volunteers received POS IV as a single peripheral infusion over 90 minutes on Day 1. Nine subjects were treated with 200 mg POS IV and three subjects received dextrose IV placebo. Six out of 9 (60%) subjects treated with POS IV experienced post-infusion local reactions, manifested as erythema, induration, and tenderness at the IV catheter insertion site. The local infusion site reactions were reported between 5 and 22 hours post-infusion. Local intolerability was likely due to the irritation associated with the low pH of the infusion solution and it led to the early termination of this trial. The post-infusion local reactions resolved in all subjects. In a second healthy volunteer study, decreasing the time of infusion from 90 to 30 minutes lowered the rate of thrombophlebitis following single-dose infusions administered up to the 300 mg dose level. Infusion site reactions were experienced by 2 (22%) of 9 subjects following a single-dose 30 minute infusion containing only the vehicle solution and by 7 (16%) of 45 subjects following a single-dose infusion containing active posaconazole.

Clinical Reviewer's Comment: *The rate of local IV site reactions associated with infusion through peripheral IV lines was unacceptably high; therefore, POS IV should be infused through a central line over 90 minutes as was done in Study P05520. A single dose of POS IV appears relatively safe to be administered over 30 minutes through a peripheral line while insertion of a central IV catheter is pending.*

7.3.3 Dropouts and/or Discontinuations

Of the 72 healthy volunteers who received POS IV, two subjects (3%) discontinued treatment due to thrombophlebitis post infusion of multiple-doses of POS IV via a peripheral line. Twelve subjects discontinued treatment due to administrative reasons when the study was stopped because of an unacceptable rate of peripheral IV site reactions. Four (19%) subjects in the 200mg multiple dose group (Cohort 0 and 1) discontinued study drug due to hyperbilirubinemia, nausea, fatigue, or systemic candidiasis.

There were 42 of 237 (18%) subjects in the 300 mg multiple-dose group (Cohorts 2 and 3) who discontinued study drug due to an adverse reaction. Of these, 29 (12%) subjects discontinued study drug due to a TEAE with an onset during the IV phase. TEAE leading to discontinuation of

study drug with an onset during the IV phase reported by more than one subject included AML (3 subjects, 5/000418, 9/000228, and 11/000712), electrocardiogram QT prolonged (2 subjects, 40/000395 and 54/000680), and rash (2 subjects, 6/000335 and 88/000436).

The disposition of subjects who received at least one dose of POS 300-mg dose cohorts is summarized in Table 13.

Table 14. Discontinuations of Study Subjects per Dose Group – All Treated Subjects

Protocol No. P05520	Subject Status	Cohort 0 Placebo IV N=11	Cohort 0 POS IV 200mg SD N=10	Cohort 1 POS IV 200 mg MD N=21	Cohort 2 POS IV 300 mg MD N=24	Cohort 3 POS IV 300 mg MD N=213	No. of Subjects
	Completed Rx	10 (91%)	10 (100%)	14 (67%)	17 (71%)	153 (72%)	204 (73%)
	Adverse events	1 (9%)	0	3 (14%)	7 (29%)	35 (16%)	46 (16%)
	Reasons unrelated to study Rx*	0	0	1 (5%)	0	8 (4%)	9 (3%)
	Withdrew consent	0	0	1 (5%)	0	6 (3%)	7 (2%)
	Rx failure	0	0	1 (5%)	0	5 (2%)	6 (2%)
	Non-compliance	0	0	1 (5%)	0	3 (1%)	4 (1%)
	Progression of disease	0	0	0	0	2 (1%)	2 (1%)
	Reasons related to study Rx*	0	0	0	0	1 (0.5%)	1 (0.3%)
	No. of subjects	11	10	21	24	213	279

* for reasons unrelated to study assigned treatment. SD = single dose; MD = multiple dose

Clinical Reviewer's Comment: *The overall incidence of TEAEs leading to discontinuation of study drug was similar to the discontinuation rate (22%) reported in clinical trials with posaconazole delayed-release tablets.*

7.3.4 Significant Adverse Events

Hepatic Adverse Events

Of the 72 healthy volunteer subjects who received POS IV solution, one subject (6%) who was treated with a single 200 mg IV dose reported elevated hepatic transaminases. This was reported on Day 3 (ALT 253, AST 172 U/L) and resolved to normal ranges on Day 14. The $AUC_{0\text{-inf}}$ and Cmax of this subject were 26,402 ng-h/mL and 691 ng/mL, respectively; below the average values for these two parameters ($AUC_{0\text{-inf}}$ and Cmax of 28,100 ng-h/mL and 1,470 ng/mL, respectively) for the study.

In Cohort 0, Subject 6/000005 entered the study on Day 1, receiving open-label POS 200 mg IV single dose via central line administration, followed by POS 400 mg PO BID treatment from Day 1 to 6. He received a single dose of POS 400 mg PO on Day 7. Later that day he began taking POS 200 mg PO TID (marketed product, not study drug) for IFI prophylaxis, and continued this until Day 12. His liver function test enzymes AST, ALT and bilirubin levels and alkaline phosphatase were elevated at baseline. ALT continued to increase during treatment (ALT 8X ULN). Following discontinuation of study drug, on Day 14, transaminases (AST 11 U/L and ALT 40 U/L) decreased to below baseline levels, but an elevated bilirubin level was reported (296 μmol/L, Grade 4). The elevations of ALT and total bilirubin were probably related POS IV.

In Cohort 1, 200-mg IV multiple-dose group, one subject, Subject No. 4/000113 reported a TEAE of hyperbilirubinemia with an onset during the IV phase. One subject (Subject No. 6/000112) reported a TEAE of jaundice with an onset during the Oral phase of treatment.

In Cohorts 2 and 3, 300-mg IV dose group, and the most common adverse event was hyperbilirubinemia. The overall incidence of specific TEAEs related to hepatic function is summarized in the following table.

Table 15. Hepatic Adverse Reactions in Cohorts 2 and 3

	Cohort 2&3 IV plus Oral Phase (total) N=237	**Cohort 2&3 IV Phase 300 mg N=237**	**Cohort 2&3 Oral Phase 300 mg N=170**
Hyperbilirubinemia	4	4	0
Hepatic Fn. Abnormal	2	1	1
Acute Hepatic Failure	1	0	1
Drug Induced Liver Injury	1	1	0
Hepatotoxicity	1	0	1
Jaundice	1	1	0
Total	**10**	**7**	**3**

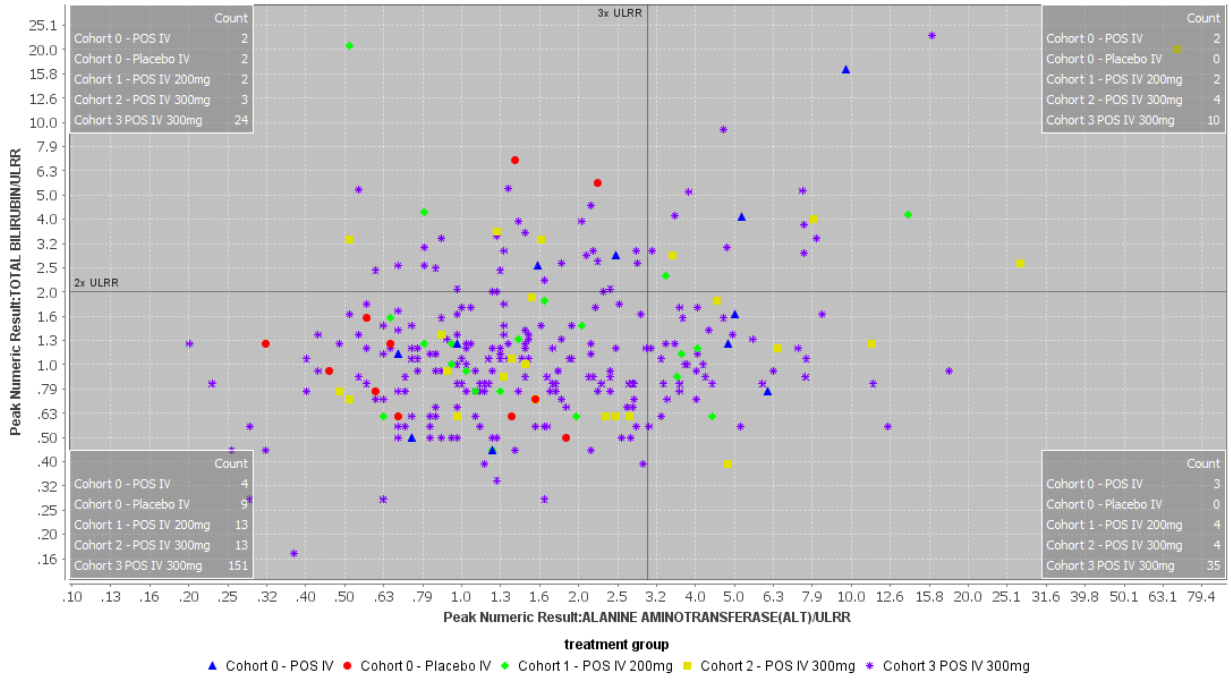
Cases with Elevated Transaminases and Hyperbilirubinemia - ALT ≥ 3X ULN and Total Bilirubin ≥ 2X ULN

Eighteen patients had hepatic transaminase elevations, ALT ≥ 3x upper limit of normal (ULN) and bilirubin levels ≥ 2x ULN at some point during the trial. The protocol pre-specified criteria for significant hepatic adverse effects were based on Hy's Law: ALT and/or AST ≥ 3X (ULN) with ALK-P ≤ 2X ULN and total bilirubin ≥ 2X ULN without evidence of biliary obstruction. Nine subjects (4/000221, 6/000207, 8/000206, 6/000734, 38/000361, 40/000358, 81/000694, 6/000008, 4/000110) fulfilled the criteria for Hy's Law. Three patients fulfilled the criteria for

Hy's Law after the study drug was stopped. Two subjects had an elevated ALT before POS IV was started. Two subjects (8/000206 and 38/00361) died. The other nine subjects did not meet the criteria for Hy's Law (Subjects 3/000669, 6/000218, 6/000349, 6/000005, 11/000380, 54/000680, 4/000113, 37/000660, 35/000340).

Patients who had elevated ALT ≥ 3X ULN or total bilirubin ≥ 2X ULN at any time during the trial are represented in the right upper quadrant of the graphic below. Patients are filtered by alkaline phosphatase ≤ 2x ULN.

Figure 2. Cases with ALT ≥ 3X ULN and Total Bilirubin ≥ 2X ULN and ALK-P ≤ 2X ULN



Nine subjects who fulfilled the criteria for Hy's Law are summarized in Table 16.

Table 16. Cases fulfilling criteria for Hy's Law – All Dose Cohorts

Cohort #	Subject ID	Gender / Age years	Max ALT U/L / Max. Tot. Bili. µmol/L	Day of Onset (days post end of Rx)	POS discontinued Y/N	Day of study: Resolved or Ongoing (days post end of Rx)
0	6/000008	M/70	183/49	Day 14 (8)	Y: Day 6	Day 14 (8): Ongoing
1	4/000110	M/45	488/75	Day 13 *Day -1: Elevated ALT at baseline*	N	Day 35 (7): Improved but Ongoing
2	4/000221	F/47	279/72	Day 14	N	Day 35 (7): Improved but Ongoing
2	6/000207	F/73	953/47	Day 6	Y: Day 6	Day 6: Ongoing
2	8/000206	F/51	2392/362	Day 8 *Day -4, Day 0: elevated transaminases at baseline*	Y: Day 9	Day 16 (7): Improved but ongoing
3	6/000734	M/29	262/94	Day 22	N	Day 35 (7): improved
3	38/000361	F/44	564/411	Day 15 (6)	Y: Day 9	Day 15: ongoing
3	40/000358	M/69	285/60	Day 10	Y: Day 10	Day 18 (8): improved
3	81/000694	M/25	134/93	Day 13 (8)	Y: Day 5	Day 16 (11): Resolved

(x) = days post end of POS treatment; Rx=treatment, D/C= discontinued; Y/N:=Yes/No; tot. bili= total bilirubin; inc.=increased; Normal ranges: ALT (6-35 U/L); Alkaline Phosphatase (35-130 U/L); Total Bilirubin (3-21 µmol/L).

Selected Case Narratives

Subject No. 6/000207 received POS 300 mg IV twice on Day 1 and POS 300 mg IV QD Day 2 to 6. She was diagnosed with progression of AML (treated with cytarabine and mitoxantrone) and developed *Escherichia coli* sepsis on Day 3. On Day 6, the subject developed acute renal failure and hepatic function tests fulfilled the laboratory criteria for Hy's Law. POS IV was stopped on Day 6 due to elevation of transaminases and creatinine, and poor disease prognosis.

She died on Day 8 of acute renal failure probably due to *E. coli* sepsis. The hepatotoxicity experienced by this patient cannot be attributed to POS IV alone because of other confounders such as sepsis and concomitant chemotherapeutic drugs but POS IV probably contributed to the liver and renal injury in this patient.

Subject No. 8/000206 with a history of AML, entered the study on Day 1 and received POS 300 mg IV BID then POS 300 mg IV QD from Day 2 to 8. She had an elevated AST and ALT at baseline. On Day 6, she developed pneumonia and Gram-negative sepsis due to *Enterobacter cloacae* and *E. coli*. POS was discontinued on Day 8 after a sudden increase in hepatic transaminases (SAE) and a general worsening of her overall condition. On Day 17, the subject experienced a subarachnoid hemorrhage and died on Day 19. Similar to subject 6/000207, hepatotoxicity cannot be attributed to POS IV alone but POS probably contributed to the liver injury in this patient.

Subject No. 40/000358 entered the study with stable acute myeloid leukemia (treated with daunorubicin and cytarabine). She received POS 300 mg IV BID Day 1, POS 300 mg IV QD Day 2 to 6, POS 600 mg PO QD Day 7 to 9, and POS 200 mg PO QD Day 10. Other medications included ceftazidime and paracetamol. On Day 10, the subject had increased AST and ALT levels, and both resolved on Day 13 and on Day 18, respectively. On Day 10, he experienced severe cholestasis (Tot. bili. 114.6µmol/L, ALK-P 304 U/L), which resolved Day 18 and POS was discontinued due to the adverse event of cholestasis. The subject experienced life threatening sepsis on Day 12. On Day 13, the subject had evidence of multiple organ failure: acute renal failure on CVHD (continuous veno-venous hemofiltration); respiratory failure, $Fi0_2$ at 50%; hepatic failure with increased cholestasis (no biliary obstruction on liver CT scan); cardiovascular failure which necessitated increased treatment with levophed and phenylephrine. On Day 14, he experienced supraventricular paroxysmal tachycardia (treated with amiodarone) and acute respiratory distress syndrome. The subject died on Day 21 from the acute respiratory distress syndrome after active treatments were stopped. No autopsy was performed. Severe sepsis probably led to multiorgan failure in this patient. POS probably contributed to the liver injury in this patient but there were other factors which contributed to hepatotoxicity including sepsis and concomitant medications.

Subject No. 81/000694, a 25 year old white male with a history of allogeneic HSCT, discontinued the study on Day 5 due to adverse event of hyperbilirubinemia, which was probably related to POS IV. The subject's total bilirubin started increasing on Day 2. The subject fulfilled the clinical laboratory criteria for Hy's Law at Day 13 (8 days after stopping POS).

Subject No. 38/000361 was a 44 year old white female who entered the study with leukemia treated with hydroxycarbamide, daunorubicin, methotrexate, allopurinol, cytarabine, platelets, and red blood cell transfusions. She received POS 300 mg IV BID on Day 1, POS 300 mg IV QD from Day 2 to 5, POS 600 mg PO QD from Day 6 to 7, and POS 300 mg IV QD from Day 8 to 9. Other medications included, piperacillin/tazobactam, paracetamol, dimenhydrinate, and metroclopramide. On Day 9, serum total bilirubin was elevated at 78 mmol/l with normal ALT and AST. POS was permanently discontinued on Day 9. On Day 12, she developed severe sepsis and acute renal failure and hypotension. Medications included sodium bicarbonate, IV fluids, phenylephrine, vasopressin, metronidazole, meropenem. On Day 14, the subject experienced supraventricular paroxysmal tachycardia treated with amiodarone and life threatening acute

respiratory distress syndrome. The subject died on Day 21 from the acute respiratory distress syndrome after active treatments were stopped. No autopsy was performed.

Clinical Reviewer's Comment: *Hyperbilirubinemia and elevated hepatic transaminases were probably associated with POS IV. There was no comparative safety data in this study; however, TEAEs related to hepatic function, were similar to those commonly reported with POS oral suspension. The hepatic adverse events which occurred during IV therapy are probably related to posaconazole but sepsis, progression of underlying hematologic disease, concomitant antibacterial drugs and chemotherapeutic regimens also contributed to the hepatic injury in these patients. The information in the current NOXAFIL label regarding hepatotoxicity appears adequate.*

Cardiac Adverse Reactions

Triazoles, including posaconazole, have been associated with prolongation of the QT interval and rare cases of torsades de pointes have been reported in patients taking posaconazole.[3] The protocol pre-specified criterion for QTc interval prolongation was QTc > 500 msec.

There were no cardiac adverse experiences reported among the 72 subjects receiving POS IV solution in the healthy volunteer studies.

200 mg IV Dose - Cohorts 0 and 1

No subjects in the 200-mg dose cohorts met the protocol pre-specified criteria for QTc interval prolongation. Two cardiac events were reported in this group. A TEAE of bradycardia with an onset during the IV phase was reported for one subject (Subject No. 8/000101). Tachycardia with an onset during the Oral phase was reported for one subject (Subject No. 6/000112). These cardiac events were not reported as SAE, and neither led to discontinuation of study drug.

300mg IV Dose - Cohorts 2 & 3

Cardiac TEAE were reported by 23 (11%) subjects and of these 21 subjects (9%) reported cardiac TEAE with an onset during the IV phase. Thirteen (5%) subjects experienced tachycardia and four subjects had an episode of QTc interval prolongation (QT_C > 500 msec). None of the six reports of cardiac TEAE with an onset during the oral phase were severe or life threatening.

Table 17. Cardiac Treatment-Emergent Adverse Events in Posaconazole 300-mg Dose Cohort; All Treated Subjects

Cardiac Disorders	IV Phase N=237	Severe or Life Threatening	Oral Phase N=170
Arrhythmia	1	0	0
Bradycardia	1	0	1
Cardiac failure	1	0	0
Congestive Cardiac failure	2	0	0
Tachycardia	13	0	5
ECG: QTc interval abnormal	0	0	1
ECG: QTc interval prolonged	4	1	1
Subjects reporting any cardiac adverse event	17 (7%)	-	6 (4%)

Source: Adapted from Table 2.7.4 of Clinical Summary Report, P05520;

In the 300-mg multiple-dose group (Cohorts 2 and 3) there was one subject who had at least one QTc interval measurement ≥ 500 msec during the treatment phase:

Subject No. 54/000680 is a 51 year-old white male who entered the study following HSCT. The subject's past cardiac history included aortic dilation (stable), atrial fibrillation (resolved), pericardial effusion (stable), and sinus bradycardia. His baseline QTc interval was 456 msec, uncorrected. On Day 5, he was noted to have a QTc interval ≥ 542 msec (Fridericia). POS IV was possibly related to the QT interval prolongation and POS was stopped for this reason on Day 5. The POS C_{min} level on Day 3 was 1050 ng/mL, within the targeted range. By Day 8, the QT_C interval had returned to baseline.

Clinical Reviewer's Comment: *An evaluation of effect on QT interval was not conducted for POS IV. However, results from a multiple time-matched ECG analyses in healthy volunteers did not show any increase in the mean QTc interval following administration of Posaconazole Oral Suspension up to 400 mg BID; these findings were discussed in the clinical pharmacology review for posaconazole oral suspension, NOXAFIL®, NDA 22-003, in 2006. The information in the current NOXAFIL label regarding QT interval prolongation appears adequate.*

Metabolic/Adrenal Adverse Reactions

No healthy volunteers developed metabolic or adrenal TEAE during the study period. In Cohort 1, serum electrolyte imbalances were reported: hypokalemia (3 subjects), hyperkalemia (1 subject), and hyponatremia (2 subjects).

In Cohorts 2 & 3, there were no reports of adrenal suppression. A total of 62 subjects (26%) reported a metabolic TEAE with an onset occurring during the IV phase. The most common metabolic TEAE was hypokalemia in 51 (22%) subjects and 9 (4%) were reported to be related to study drug. These events were not reported as SAE, and none of the serum electrolyte imbalances led to discontinuation of study drug.

Table 18. Metabolic/Adrenal Disorders - 300 mg Dose - Cohort 2 & 3

Endocrine Disorders, Preferred Term	Number of subjects n (%) of 300mg cohort IV phase, N=237	Severe, life-threatening	Oral Phase, n (%); N=170	Severe, life-threatening
Adrenal insufficiency	0	-	0	0
Hyperkalemia	4 (2)	1	6	1
Hypocalcemia	8 (3)	1	0	0
Hypokalemia	51 (22)	9 (4)	16 (9)	1
Blood Potassium decreased	3 (1)	0	1	0
Hyponatremia	5 (2)	0	1	0
All adverse Reactions	62 (26)	10 (4%)	22 (13)	2

Source: Adapted from Table 2.7.4 in clinical summary report, p. 129, Study P05520.

Clinical Reviewer's Comment: *Hypokalemia (~22%) was also the most commonly reported metabolic TEAE in clinical trials of POS oral suspension and POS delayed-release tablets. However, hypokalemia is a common problem in severely ill hospitalized patients and cannot be directly attributed in posaconazole in this non comparative trial.*

Hypersensitivity

There were no adverse experiences suggestive of hypersensitivity reported among the 72 subjects receiving POS IV in the healthy volunteer studies or in Cohorts 0 and 1 in Study P05520. Symptoms associated with possible hypersensitivity reactions for Cohorts 2 and 3 are summarized in the following table. Hypersensitivity TEAE were reported for 5 (2%) subjects. None of the events were severe or life-threatening.

Table 19. Hypersensitivity Treatment-Emergent Adverse Events; 300 mg IV Phase Cohort 2 and 3

MedDRA Body System/Organ Class	MedDRA Preferred Term	Subjects (N=237)
GENERAL DISORDERS	FACE OEDEMA	1 (<1%)
IMMUNE SYSTEM DISORDERS	DRUG HYPERSENSITIVITY	1 (<1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	DRUG ERUPTION	1 (<1%)
	URTICARIA	1 (<1%)

	SKIN REACTION	1 (<1%)
		5/237 (2%)

Clinical Reviewer's Comment: *Rash has been reported to be associated with posaconazole and other triazole drugs. Skin and subcutaneous disorders (rash and pruritus) occurred in 19% of posaconazole-treated patients, 18% of fluconazole-treated patients and 43% of itraconazole-treated patients in two phase 3 prophylaxis trials of posaconazole oral suspension. The current label with regard to hypersensitivity, as proposed by the sponsor, appears adequate based on the skin and hypersensitivity adverse reactions described in the study report for P05520.*

Gastrointestinal Adverse Reactions

During the POS IV phase, there were 157 subjects (66%) that reported TEAEs related to gastrointestinal disorders. The most commonly reported TEAE was diarrhea, reported in 75 subjects (32%).

Age

There were 53 (19%) subjects age 65 years and older in the treated (POS IV or placebo IV) study population. Fifteen (28%) subjects (Cohort 3:12 patients; Cohort 2: 3 patients) experienced 26 SAEs. Most of the SAEs were related to the patient's underlying hematologic malignancies and neutropenia and were unrelated to POS IV. There were four reports of bacterial sepsis which was also the most frequent TEAE in study population younger than 65 years of age. One patient developed a pulmonary IFI related to clinical failure of POS IV anti-fungal prophylaxis. SAEs are summarized in the following table.

Table 20. Serious Adverse Reactions in Patients ≥ 65 years of age (N=15)-300mg Dose Cohorts

Serious Adverse Events - MedDRA Preferred Term	No. of Serious Adverse Events*
ASPIRATION	2
ASTHENIA	1
BACTERIAL SEPSIS	1
CONSTIPATION	1
DIARRHEA HEMORRHAGIC	1
DYSPNEA	1
ESCHERICHIA COLI SEPSIS	1
FALL	1
GRAFT VERSUS HOST DISEASE	2
MULTI-ORGAN FAILURE	1
MYELODYSPLASTIC SYNDROME	1
NAUSEA	1
ORAL HERPES	1
PULMONARY HEMORRHAGE	1
PULMONARY MYCOSIS	1
RENAL FAILURE	1
RENAL FAILURE ACUTE	1
RESPIRATORY FAILURE	1
BACTERIAL SEPSIS	2
SPINAL COMPRESSION FRACTURE	1
SUBDURAL HEMORRHAGE	1
TRANSFUSION REACTION	1
VOMITING	1
No. of Serious Adverse Events	26

*there are more than one SAE per patient.

Gender

Male patients comprised 55% of the study population. Systemic exposures to POS IV were similar in male and female subjects. The overall proportion of TEAE was similar in males and female patients. Diarrhea, nausea, vomiting, and pyrexia were the most common side effects in both genders. There were no clinically significant differences in TEAE between male and female subjects. TEAE that occurred at a frequency of > 10% (MedDRA preferred terms) in the study and where there was ≥ 2% difference in the incidence between males and female subjects are summarized in Table 20.

Table 21. Adverse Reactions in Males and Females – Study P05520

Body System/Organ Class	TEAE: MedDRA Preferred Term	Female (N=124)	Male (N=152)	Subjects
BLOOD and LYMPHATIC DISORDERS	Anemia	16 (12.8%)	13 (8.6%)	29 (10.1%)
	Febrile Neutropenia	31 (24.8%)	53 (34.9%)	84 (29.3%)
	Thrombocytopenia	17 (13.6%)	13 (8.6%)	30 (10.5%)
GASTROINTESTINAL DISORDERS	Abdominal Pain / Abdominal Pain Upper	46 (32%)	43(28.3%)	89(31%)
	Constipation	21 (16.8%)	28 (18.4%)	49 (17.1%)
	Diarrhea	52 (41.6%)	69 (45.4%)	121 (42.2%)
	Nausea	56 (44.8%)	57 (37.5%)	113 (39.4%)
	Vomiting	35 (28.0%)	35 (23.0%)	70 (24.4%)
GENERAL DISORDERS /ADMINISTRATION SITE CONDITIONS	Catheter Site Erythema	11 (8.8%)	21 (13.8%)	32 (11.1%)
	Chills	18 (14.4%)	29 (19.1%)	47 (16.4%)
	Mucosal Inflammation	24 (19.2%)	29 (19.1%)	53 (18.5%)
	Pyrexia	45 (36.0%)	52 (34.2%)	97 (33.8%)
IMMUNE SYSTEM DISORDERS	GVHD	1 (0.8%)	6 (3.9%)	7 (2.4%)
	GVHD Skin	3 (2.4%)	8 (5.3%)	11 (3.8%)
INFECTIONS/ INFESTATIONS	Bacteremia	5 (4.0%)	7 (4.6%)	12 (4.2%)
	Bacterial Infection	1 (0.8%)	7 (4.6%)	8 (2.8%)
	Oral Herpes	6 (4.8%)	14 (9.2%)	20 (7%)
	Pseudomonas Infection	3 (2.4%)	0	3 (1%)
	Sepsis/Septic Shock	7 (5.6%)	11 (6.2%)	18 (6.2%)
	Staphylococcal Bacteremia	3 (2.4%)	10 (6.6%)	13 (4.5%)
	Staphylococcal Infection	5 (4.0%)	14 (9.2%)	19 (6.6%)
INJURY, POISONING / PROCEDURAL COMPLICATIONS	Allergic Transfusion Reaction	7 (5.6%)	5 (3.3%)	12 (4.2%)
	Fall	5 (4.0%)	1 (0.7%)	6 (2.1%)
	Transfusion Reaction	3 (2.4%)	9 (5.9%)	12 (4.2%)
INVESTIGATIONS	Alanine Aminotransferase Increased	4 (3.2%)	12 (7.9%)	16 (5.6%)
	Blood Bilirubin Increased	7 (5.6%)	6 (3.9%)	13 (4.5%)
METABOLISM/ NUTRITION DISORDERS	Decreased Appetite	19 (15.2%)	19 (12.5%)	38 (13.2%)
	Hypokalemia	36 (28.8%)	47 (30.9%)	83 (28.9%)
	Hypomagnesemia	14 (11.2%)	20 (13.2%)	34 (11.8%)
RESP. DISORDERS	Cough	25 (20.0%)	21 (13.8%)	46 (16%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Petechiae	16 (12.8%)	14 (9.2%)	30 (10.5%)
	Pruritus	17 (13.6%)	9 (5.9%)	26 (9.1%)
VASCULAR DISORDERS	Hypertension	11 (8.8%)	22 (14.5%)	33 (11.5%)

GVHD: graft versus host disease; CMV: cytomegalovirus; RESP= Respiratory

Race

Analyses of adverse reactions by race would not provide meaningful comparisons because less than 8% of patients in the trial were identified as non-white. The current posaconazole oral suspension, NOXAFIL® USPI label states that the pharmacokinetic profile of posaconazole is not significantly affected by race. No adjustment in the dosage of NOXAFIL is necessary based on race.

7.3.5 Submission Specific Primary Safety Concerns

Exposure Response Relationships (dose-response, concentration-response) for the Safety Profile of Posaconazole Injection

Within the range of exposures that were observed, there does not appear to be an association between higher posaconazole concentration and a higher incidence of a treatment-related TEAE following administration of POS IV. The mean C_{avg} (ng/mL) and range (ng/mL) was calculated in a limited number of patients, 16 subjects per quartile (Q) and are summarized below.

Table 22. Mean Cavg (ng/ML), Range (ng/mL) for each quartile

	Cavg Mean (ng/mL)	Cavg Range	No. of Subjects	No. (%) Subjects Reporting Any Adverse Event
Quartile 1	768 ng/mL	550 ng/mL to 1008 ng/mL	16	16 (100)
Quartile 2	12501 ng/mL	1048 ng/mL to 1394 ng/mL	16	16 (100)
Quartile 3	1528 ng/mL	1414 ng/mL to 1712 ng/mL	16	16 (100)
Quartile 4	2163 ng/mL	1721 ng/mL to 3034 ng/mL	16	16 (100)

Treatment Emergent Adverse Events By Quartiles (10% Incidence), All Treated Subjects, By Descending Frequency, Serial PK-Evaluable Population, Number (%) of Subjects

Treatment Emergent Adverse Events (≥10% incidence) which were possibly or probably associated with study drug are listed by descending frequency per quartile. TEAE considered unrelated to study drug are omitted. The most common TEAE reported for all quartiles was diarrhea in 32/48 (66%) patients. There was a lower incidence of diarrhea (38%) in patients with the highest exposure in Q4 compared to 56% in Q1, Q2, and Q3. Rash was more common in Q2. Catheter site erythema or pain or swelling was more common in Q4. Hypokalemia was more common in Q3.

Table 23. Treatment-related TEAE by quartile of Cavg values, all Cmin PK-evaluable subjects, POS Tablets - 200mg and 300mg cohorts combined

Treatment Emergent Adverse Events (TEAEs) Total No. of Subjects, N=48	**Quartile 1** N=16 (%) 550 to 1008 ng/mL	**Quartile 2** N=16(%) 1048 to 1394 ng/mL	**Quartile 3** N=16(%) 1414 to 1712 ng/mL	**Quartile 4** N=16(%) 1721 to 3034 ng/mL
Diarrhea	9 (56)	9 (56)	9 (56)	5 (38)

Nausea	7	6	6	1
Rash/rash maculopapular	3	8	4	6
Pyrexia	4	5	5	4
Hypokalemia	3	3	6	4
Vomiting	2	6	5	3
Headache	2	6	2	2
Catheter site erythema or pain or swelling	1	5	4	6
Hypophosphatemia	0	4	3	0
Hypomagnesemia	1	1	3	1
ALT increased or Hepatic enzyme increased	0	4	1	0
Bilirubin increased	1	2	0	0

Source: Section 12.4.8, clinical study report, NDA 205-596.

7.4 Supportive Safety Results

The safety of POS IV is supported by the known safety profile of posaconazole oral suspension, NOXAFIL®.[3]

7.4.1 Common Adverse Events

In the 200-mg dose cohort 1 (n=21), the most common TEAE (> 20% of subjects) included nausea, pyrexia, diarrhea, and febrile neutropenia.

In the 300-mg dose cohorts 2 & 3 (n=237), the most common TEAE (> 20% of subjects) included diarrhea (32%), pyrexia (25%), nausea (24%), and hypokalemia (23%). These TEAE were also commonly reported with posaconazole oral suspension and posaconazole delayed-release tablets USPI.

TEAEs occurring at a rate > 10% in the 300mg arm are outlined in the following table.

Table 24. Treatment Emergent Adverse Events - POS IV - 300mg Dose

MedDRA Preferred Term	Cohort 2 POS IV 300 mg	Cohort 3 POS IV 300 mg	Total Subjects
DIARRHEA	10 (41.7%)	83 (39%)	93 (32.4%)
PYREXIA	8 (33.3%)	65 (30.5%)	73 (25.4%)
NAUSEA	7 (29.2%)	63 (29.6%)	70 (24.4%)
HYPOKALEMIA	5 (20.8%)	62 (29.1%)	67 (23.3%)
RASH	8 (33.3%)	48 (22.5%)	56 (19.5%)
FEBRILE NEUTROPENIA	7 (29.2%)	47 (22.1%)	54 (18.8%)

HEADACHE	6 (25.0%)	43 (20.2%)	49 (17.1%)
VOMITING	5 (20.8%)	40 (18.8%)	45 (15.7%)
MUCOSAL INFLAMMATION	8 (33.3%)	36 (16.9%)	44 (15.3%)
ABDOMINAL PAIN	5 (20.8%)	36 (16.9%)	41 (14.3%)
EPISTAXIS	4 (16.7%)	36 (16.9%)	40 (13.9%)
CHILLS	4 (16.7%)	34 (16%)	38 (13.2%)
EDEMA PERIPHERAL	2 (8.3%)	33 (15.5%)	35 (12.2%)
CONSTIPATION	3 (12.5%)	28 (13.2%)	31 (10.8%)
COUGH	1 (4.2%)	30 (14.1%)	31 (10.8%)
HYPOMAGNESEMIA	3 (12.5%)	27 (12.7%)	30 (10.5%)
DECREASED APPETITE	3 (12.5%)	26 (12.2%)	29 (10.1%)
HYPERTENSION	1 (4.2%)	25 (11.7%)	26 (9.1%)
ABDOMINAL PAIN UPPER	4 (16.7%)	21 (9.9%)	25 (8.7%)
THROMBOCYTOPENIA	1 (4.2%)	24 (11.3%)	25 (8.7%)
DYSPNOEA	4 (16.7%)	20 (9.4%)	24 (8.4%)
FATIGUE	0	24 (11.3%)	24 (8.4%)
PETECHIAE	4 (16.7%)	20 (9.4%)	24 (8.4%)
ANEMIA	0	23 (10.8%)	23 (8.0%)

Healthy Volunteer Studies

Of the 72 healthy volunteers in the three studies who received at least one dose of POS IV solution, 19 (26%) subjects experienced at least one treatment-related TEAE. Most treatment-related TEAEs were mild and self-limiting. The most common treatment-related TEAE were infusion-site reactions (11 subjects [15%]), thrombophlebitis (5 subjects [7%]) and headache (3 subjects [4%]). Infusion site adverse reactions were associated with multiple infusions of POS IV through peripheral catheters. Multiple dosing via peripheral lines caused insertion site tenderness, erythema, and thrombophlebitis. TEAE that occurred in Studies 4985, 6356, 7783 are summarized in the following table.

Table 25. Treatment related TEAEs in Healthy Volunteers - Studies 4985, 6356, 7783

	POS IV 50 mg SD n=9	POS IV 100 mg SD n=9	POS IV 200 mg SD n=18	POS IV 250 mg SD n=9	POS IV 300 mg SD n=22	POS IV 100 mg MD n=5	All Combined n=72
SUBJECTS REPORTING ANY ADVERSE EXPERIENCE	1 (11)	0	4 (22)	3 (33)	7 (32)	4 (80)	19 (26)
GASTROINTESTINAL DISORDERS	0	0	0	0	1 (5)	0	1 (1)
NAUSEA	0	0	0	0	1 (5)	0	1 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (11)	0	4 (22)	2 (22)	3 (14)	4 (80)	14 (19)
INFUSION SITE PAIN	0	0	1 (6)	0	0	0	1 (1)
INFUSION SITE PARAESTHESIA	0	0	1 (6)	0	0	0	1 (1)
INFUSION SITE REACTION	1 (11)	0	1 (6)	2 (22)	3 (14)	4 (80)	11 (15)
MALAISE	0	0	0	0	0	1 (20)	1 (1)
OEDEMA PERIPHERAL	0	0	1 (6)	0	0	0	1 (1)
PYREXIA	0	0	0	0	0	1 (20)	1 (1)
INVESTIGATIONS	0	0	1 (6)	0	0	0	1 (1)
LIVER FUNCTION TEST ABNORMAL	0	0	1 (6)	0	0	0	1 (1)
NERVOUS SYSTEM DISORDERS	0	0	1 (6)	2 (22)	4 (18)	0	7 (10)
HEADACHE	0	0	1 (6)	1 (11)	1 (5)	0	3 (4)
MENTAL IMPAIRMENT	0	0	0	0	1 (5)	0	1 (1)
PARAESTHESIA	0	0	0	1 (11)	0	0	1 (1)
TENSION HEADACHE	0	0	0	0	2 (9)	0	2 (3)
VASCULAR DISORDERS	0	0	1 (6)	0	2 (9)	3 (60)	6 (8)
PHLEBITIS	0	0	0	0	1 (5)	0	1 (1)
THROMBOPHLEBITIS	0	0	1 (6)	0	1 (5)	3 (60)	5 (7)

SD: = Single dose; MD = Multiple dose; Column "POS IV 200mg SD": data are from P04985 and P06356; Column "POS IV 300mg SD": data are from P06356 and P07783. All other data are from P06356. Source: Section 5.3.5.3.1.10, page 55, Integrated Summary Safety (ISS), NDA 205-596.

7.4.2 Laboratory Findings

Toxicity Grade Shift Tables for Selected Serum Electrolytes – Study P05520

Changes from common toxicity criteria (CTC) Grade 0, 1, or 2 at Baseline to CTC Grade 3 or 4 are summarized in the following table. The most common grade change shift of this type occurred for serum potassium levels, hypokalemia was reported in 22 subjects (9%).

Table 26. Serum Electrolytes: Changes from CTC Grade 0, 1, or 2 at Baseline to CTC Grade 3 or 4 300 mg IV Dose, Cohort 2 and 3

Laboratory Parameters	Number of subjects, n/N (%) N= 27
Hyperkalemia	1/237 (0.4%)
Hypokalemia	22/237 (9%)
Hypernatremia	0/237
Hyponatremia	3/237 (1%)

Toxicity Grade Shift Tables – Hepatic Function Tests and Renal Function Tests
Changes from CTC Grade 0, 1, or 2 at baseline to CTC Grade 3 or 4 in patients treated with 300 mg IV Multiple-Dose (Cohort 3) are summarized in the following tables.

Table 27. Hepatic Enzymes: Changes from CTC Grade 0, 1, or 2 at Baseline to CTC Grade 3 or 4 - 300mg Dose IV - Cohort 3

Laboratory Parameters	Number of subjects, n/N (%) N= 213
Alanine aminotransferase (ALT)	12/213 (7%)
Aspartate aminotransferase (AST)	9/212 (4%)
Alkaline phosphatase	0/213
Total bilirubin	12/213 (6%)

ALT and AST
For hepatic function test laboratory parameters, the majority of subjects were Grade 0 or 1 at baseline, and they remained at Grade 0 or 1 throughout the study. The largest shifts that occurred were a four grade shift, from Grade 0 to Grade 4, for AST in 1 (0.5%) patient and a shift in from Grade 0 to 3 for ALT in 7 (3%) of patients. There was one patient in cohort 2 (POS 300 mg IV) who experienced a grade shift for ALT from Grade 1 to Grade 4.

Table 28. ALT: Toxicity Grade Shift Table - Alanine Aminotransferase (ALT) – 300 mg IV Multiple-Dose - Cohort 3

Cohort 3 POS IV 300mg – Multiple Dose						
ALANINE AMINOTRANSFERASE (ALT)		**Highest CTC Grade**				
		0	**1**	**2**	**3**	**Subjects**
Baseline high CTC grade	**0**	68 (31%)	76 (35%)	16 (7%)	7 (3%)	167 (76%)
	1	0	30 (14%)	3 (1%)	4 (2%)	37 (17%)
	2	0	0	6 (3%)	1 (< 1%)	7 (3%)
	3	0	0	0	2 (1%)	2 (1%)
	Subjects	68 (31%)	106 (48%)	25 (12%)	14 (6%)	213

Table 29. Toxicity Grade Shift Table – Aspartate Aminotransferase (AST) – 300 mg IV Multiple-Dose - Cohort 3

Cohort 3 POS IV 300mg – Multiple Dose							
ASPARTATE AMINOTRANSFERASE (AST)		**Highest CTC Grade**					
		0	**1**	**2**	**3**	**4**	**Subjects**
Baseline high CTC grade	**0**	93 (42%)	81 (37%)	5 (2%)	6 (3%)	1 (0.5%)	186 (85%)
	1		20 (9%)	2 (1%)	1 (0.5%)	0	23 (11%)
	2		0	2 (1%)	0	0	2 (1%)
	3	0	0	0	1 (0.5%)	0	1 (0.5%)
	Subjects	93 (42%)	101 (43%)	9 (41%)	8 (44%)	1 (0.5%)	212

Total Bilirubin

The majority (58%) of subjects' values for total bilirubin remained at Grade 0 throughout the study. Two (1%) subjects' values for total bilirubin shifted from Grade 0 to Grade 4 in the 300-mg multiple-dose cohort.

Table 30. Toxicity Grade Shift Table - Total Bilirubin – 300mg IV Multiple-Dose - Cohort 3

Cohort 3 POS IV 300mg							
TOTAL BILIRUBIN		**Highest CTC Grade**					
		0	**1**	**2**	**3**	**4**	**Subjects**
Baseline high CTC grade	**0**	128 (58%)	33 (15%)	17 (8%)	7 (3%)	2 (1%)	187 (85%)
	1	0	6 (3%)	10 (5%)	1 (0.5%)	0	17 (8%)
	2	0	0	5 (2%)	1 (0.5%)	1 (0.5%)	7 (3%)
	3	0	0	0	2 (1%)	0	2 (1%)
	Subjects	128 (58%)	39 (18%)	32 (15%)	11 (5%)	3 (1%)	213

Overall, ALT and AST and total bilirubin levels remained at a baseline toxicity Grade 0 or 1 for the majority of subjects. In the 300-mg multiple dose group, the number of subjects with baseline grade 0, 1 or 2 which shifted to grade 3 or 4 during the IV treatment phase of the study were: ALT: 12/213 (6%); AST: 9/212 (4%); total bilirubin: 12/213 (6%).

Serum Creatinine

The majority (79%) of subjects' values for serum creatinine remained at Grade 0 throughout the study. Two (1%) subject values for creatinine shifted from Grade 0 to Grade 3 in the multiple-dose 300mg IV, cohort 3.

Table 31. Toxicity Grade Shift Table - Creatinine Levels - 300mg Dose – Cohort 3

Cohort 3 POS IV 300mg						
		Highest CTC Grade				
CREATININE		**0**	**1**	**2**	**3**	**Subjects**
Baseline high CTC grade	**0**	174 (79%)	24 (11%)	8 (4%)	2 (1%)	208 (95%)
	1	0	5 (3%)	0	0	5 (2%)
	Subjects	174 (79%)	29 (13%)	8 (4%)	2 (1%)	213

7.4.3 Vital Signs

There were no concerning findings associated with study drug for body temperature, pulse rate, and blood pressure during study treatment in Cohort 1 (200 mg multiple dose) or Cohorts 2 and 3 (300 mg multiple dose) in Study P05520. See cardiac adverse effects, section 7.3.4.

7.4.4 Electrocardiograms (ECGs)

Azole antifungal drugs are associated with prolongation of the QTc interval which can potentially induce life-threatening ventricular arrhythmias. In the 300-mg multiple dose group (Cohorts 2 and 3) there was one subject who had at least one QTc interval measurement ≥500 msec during the treatment phase. The patient did not experience an arrhythmia and the QT_C interval prolongation resolved when POS was stopped.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

There are no issues with immunogenicity.

7.5 Other Safety Explorations

Not applicable

7.5.1 Dose Dependency for Adverse Events

Not applicable

7.5.2 Time Dependency for Adverse Events

Not applicable

7.5.3 Drug-Demographic Interactions

Not applicable

7.5.4 Drug-Disease Interactions

Not applicable

7.5.5 Drug-Drug Interactions

The drug interactions as described for POS oral suspension and POS delayed-release tablets are the same for POS IV, except for those that affect the absorption of POS by gastric pH and/or motility.

7.6 Additional Safety Evaluations

Not applicable

7.6.1 Human Carcinogenicity

No drug-related neoplasms were recorded in rats or mice treated with posaconazole for two years at doses higher than the clinical dose. Please refer to section 13, NONCLINICAL TOXICOLOGY in the posaconazole oral suspension, NOXAFIL® USPI.[3]

7.6.2 Human Reproduction and Pregnancy Data

No subject or female partner of a study subject had reported a new pregnancy at the time of data cut-off for Study P05520.
Please refer to section 8, USE IN SPECIAL POPULTIONS, in the posaconazole oral suspension, NOXAFIL® USPI. Posaconazole oral suspension is listed as, “Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. NOXAFIL should be used in pregnancy only if the potential benefit outweighs the potential risk to the fetus.”

7.6.3 Pediatrics and Assessment of Effects on Growth

There was no assessment of effects on growth. The study was conducted in adult patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no drug abuse potential for posaconazole.

7.7 Additional Submissions / Safety Issues

Not applicable.

8 Postmarketing Experience

There is no postmarket experience with posaconazole injection. Please refer to section 6, ADVERSE REACTIONS, for posaconazole oral suspension and delayed-release Tablets, NOXAFIL® USPI.[3] No clinically significant postmarket adverse reactions were identified for posaconazole oral suspension that have not previously been reported during clinical trials experience.

9 Appendices

9.1 Literature Review/References

See footnotes for literature references.

9.2 Labeling Recommendations

The main proposed change to the label from a clinical perspective is that the (b) (4)

9.3 Advisory Committee Meeting

An Advisory Committee meeting is not scheduled for this NDA.

9.4 Proposed Pediatric Study (ies) / Pediatric Review Committee (PeRC)

(b) (4)

In their pediatric plan, the sponsor proposed to conduct a study to evaluate the pharmacokinetics (PK), safety, and tolerability of two new formulations of posaconazole (IV solution followed by sequential use of the new age-appropriate oral formulation) in immunocompromised pediatric patients with known or expected neutropenia. The sponsor is requesting a waiver for pediatric patients < 2 years of age and a deferral for pediatric studies for pediatric patients > 2 to (b) (4) years of age. The adult studies for posaconazole oral suspension included patients 13 years and older. A meeting was held with the Pediatric Review Committee (PeRC) on January 29, 2014. The PeRC recommended that the same PMR for a pediatric study already addressed by PeRC for NDA 205-053 will suffice for NDA 205-596.

9.5 Clinical Investigator Financial Disclosure Review form.

Clinical Investigator Financial Disclosure
Review Template

Application Number: 205-596

Submission Date(s): 09/13/2013

Applicant: Merck

Product: Posaconazole Injection

Reviewer: Elizabeth O'Shaughnessy, MD

Date of Review: 02/11/2014

Covered Clinical Study (Name and/or Number): P05520

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 227		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: $2,012.00 Significant payments of other sorts: $36,000.00 (b) (6) Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3)		
Is an attachment provided with the	Yes ☒	No ☐ (Request explanation

reason:		from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[11] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Discussion: The applicant stated that they performed an internal search for proprietary or financial interests and significant payments of other sorts for all investigators. There were no significant financial interests or arrangements reported for 226 of 227 investigators who participated in the clinical trials of POS Injection or for the experts on the Data Monitoring Committee (DMC). Financial disclosure information was submitted for one sub-investigator: One of (b) (6) investigators at study Site (b) (6), (b) (6) was listed in the NDA under "Significant Payments of Other Sorts". A total of $38,012.00 ($36,000.00 payment made to a charity, (b) (6) and a payment was made to (b) (6) in the amount of $2,012.00 for honorarium, and was reported by the investigator on 01-24-2013.
Clinical Comment: The financial disclosure information is unlikely to impact on the results of the current trial as there were a total of five patients at risk of IFI (cohort 3) enrolled from site # (b) (6) by the principal investigator, (b) (6) Five patients accounted for (b) (6)% of the study population. Study P05520 was an open-label, single-arm, safety and PK study of posaconazole (POS) IV in the same target population (adults) as the posaconazole oral suspension and delayed-release tablets. Study P05520 was primarily designed as a safety study and there was no primary efficacy endpoint.

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

/s/

ELIZABETH M OSHAUGHNESSY
02/27/2014

JOHN J ALEXANDER
02/27/2014

CLINICAL FILING CHECKLIST FOR NDA 205596

NDA Number: 205596 **Applicant: Merck, Sharp & Dohme** **Stamp Date: 9/13/2013**

Drug Name: Posaconazole IV solution for injection **NDA Type: 505(b)1**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)1
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: P03536 Study Title: A Phase 1B Study of the Pharmacokinetics, Safety, and Tolerability of Intravenous Posaconazole (SCH 56592) in Patients with Neutropenia or Graft-Versus-Host Disease Sample Size: 75 Arms: five dose cohorts Location in submission:M5	X			The primary goal of this study was to evaluate the PK profiles of up to four different dosing regimens of POS IV in subjects with neutropenia or GVHD
EFFICACY					
14.	Do there appear to be the requisite number of adequate and			X	The submission

CLINICAL FILING CHECKLIST FOR NDA 205596

	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application? Pivotal Study #1: P05520: Pharmacokinetics, Safety, and Tolerability of Intravenous Posaconazole Solution Followed by Oral Posaconazole Suspension (SCH 56592) in Subjects at High Risk for Invasive Fungal Infections. Indication: 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 HSCT recipients with GVHD or those with hematologic malignancies with prolonged neutropenia from chemotherapy. Pivotal Study #2: NA Indication:				includes 4 clinical studies performed in support of the registration of the POS IV solution. Among these studies were 3 clinical studies of POS IV solution that enrolled 67 healthy volunteers (P04985, P06356, and P07783), and one clinical study (P05520) of POS IV solution in 250 patients at risk of developing IFI.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	See comment for Question #14.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			Foreign data is applicable - Invasive fungal disease in similar across hematological malignancy populations
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA 205596

	Content Parameter	Yes	No	NA	Comment
	efficacious?				
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			Foreign data is applicable - Invasive fungal disease in similar across hematological malignancy populations.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			Discussed with the clinical pharmacology reviewer.
CASE REPORT FORMS					

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 205596

	Content Parameter	Yes	No	NA	Comment
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____YES.____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

Elizabeth O'Shaughnessy 10/23/13

Reviewing Medical Officer Date

John Alexander

Clinical Team Leader Date

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

/s/

ELIZABETH M OSHAUGHNESSY
12/05/2013

JOHN J ALEXANDER
12/05/2013