CLINICAL REVIEW

Application Type	New Drug Application
Application Number	205-053
Priority or Standard	Standard
Submit Date	Jan 25th, 2013
Received Date	Jan 25th, 2013
PDUFA Goal Date	Nov 25th, 2013
Division / Office	DAIP/ OAP
Reviewer Names	Elizabeth O'Shaughnessy, MD John Alexander, MD, MPH
Review Completion Date	October 8th, 2013
Established Name	Posaconazole
(Proposed) Trade Name	NOXAFIL®
Therapeutic Class	Triazole
Applicant	Merck
Formulation	100mg Tablet
Dosing Regimen	300mg PO BID x 1 day then 300mg PO daily
Indication	Prophylaxis of Invasive Fungal Infection
Intended Populations	Neutropenic Patients with Hematological Malignancies, and HSCT.

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 delayed-release tablet (POS tablet) be approved 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 with graft versus host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy. POS tablet administered at a dose of 300 mg PO BID on Day 1 and 300 mg daily thereafter was found to provide similar exposure to that shown to be effective for prophylaxis using the posaconazole oral suspension. The safety profile of POS tablet was similar to the marketed posaconazole oral suspension, NOXAFIL®. The duration of POS tablet therapy 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 has been demonstrated in two randomized controlled clinical trials[1,2] and it is FDA-approved for this indication. POS 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 based on the results of five pharmacokinetic (PK) and bioavailability studies and one open-label trial, PK, safety and tolerability trial, Study P05615, in the target population of patients with hematologic malignancies with prolonged neutropenia at risk of IFI.

In Study P05615, the safety and tolerability of POS tablets was evaluated in 230 patients with hematologic malignancies at risk of IFI and the safety data indicate that it had a similar safety profile to posaconazole oral suspension. POS tablets taken without regard to food intake were well tolerated, and had an acceptable safety profile within the range of systemic exposures that were studied. The survival rate at Day 65 (survival visit) was high at > 90%. The incidence of breakthrough IFI in this trial was approximately 5% and was similar to that previously reported in two randomized prophylaxis trials of posaconazole oral suspension.[1, 2]
There were two deaths in the 200 mg dose cohort. In the 300 mg dose cohort, there were 20 (9%) deaths, 18 subjects died within the study period and two died beyond the survival visit on Day 65 (> Day 70). The most common causes of death were infections, including sepsis and septic shock. There was one patient who died from multi-organ failure, including renal failure, and the

[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.

immediate cause of death was reported as hepatic insufficiency. POS tablet might have contributed to the hepatic injury in this patient however it is more likely that death was due to complications post HSCT, including CMV reactivation and hepatotoxic effects associated with myelosuppressive drugs.
The most common adverse reactions associated with POS tablets were diarrhea and nausea. Other adverse reactions also associated with the azole class of antifungal drugs, included hepatotoxicity with elevation of hepatic transaminases and hyperbilirubinemia, QTc interval prolongation, adrenal insufficiency, and drug-drug interactions. Five (2%) subjects developed hepatic treatment emergent adverse reactions (TEAEs) that were probably related to study drug and led to discontinuation of study drug. Two (<1%) of the patients had hepatic function test results that met the criteria for Hy's Law during treatment with POS tablet, study drug was discontinued and hepatic enzymes and bilirubin levels returned to the normal ranges or had improved before the end of the study period. The attribution of adverse reactions to POS tablets was confounded by symptoms related to the patients' underlying hematologic malignancies and myelosuppressive drug regimens. There were two (<1%) cases of renal failure associated with drug interactions with POS tablets and a calcineurin inhibitor (cyclosporine) leading to death. There was one case of asymptomatic QTc interval prolongation (QTc >500 msec) which led to discontinuation of study drug. Adrenal insufficiency was reported in one patient post-HSCT with gastric GVHD, and POS tablets were continued.
Posaconazole oral suspension is dosed three times per day and has poor gastrointestinal absorption. POS tablets are dosed once daily (after an initial loading dose on day 1) which should help compliance among patients. Since tablets may be taken without regard to food they may be beneficial to patients who are too ill to eat food.
Overall, POS tablets were well tolerated. Within the range of exposures that were observed in the phase 3 trial, 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 tablets. In summary, POS tablets have an acceptable safety profile that is similar to the safety profile reported for posaconazole oral suspension formulation, NOXAFIL®. The potential benefit of POS tablets 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

The Division requests that the applicant conduct:
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 1 to <18 years.

Clinical Reviewer's Comment: *A safe and effective pediatric dosage regimen of 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 (new IV and oral formulations) for the prophylaxis of invasive fungal infections (IFI) among in pediatric patients with known or expected neutropenia between the ages of (b) (4) to <18 years.

Clinical Reviewer's Comment: *I recommend that the applicant discuss the PK results from Study A with the Division before proceeding with Study B. A pediatric PK, safety, and tolerability study with 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

The oral tablet formulation was designed to overcome the limitations with poor gastrointestinal absorption of posaconazole oral suspension. The oral tablet releases posaconazole in the small intestine, thus maximizing systemic absorption. (b) (4)

(b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Posaconazole (NOXAFIL®) is marketed as an oral suspension and was approved by the FDA in 2006. Posaconazole oral suspension is approved 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. Posaconazole is currently the only FDA-approved antifungal drug for the prophylaxis of invasive mold 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 in an oral suspension 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, QTc 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, total bilirubin, and/or clinical hepatitis have been reported in clinical trials of posaconazole 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 including posaconazole are inhibitors of CYP450 enzyme system. Posaconazole 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 posaconazole, 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 (mainly itraconazole and voriconazole), other CYP isoenzymes (i.e., CYP1A2, CYP2C9, CYP2C19) are not affected by posaconazole. Triazoles, including posaconazole, have been associated with 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 posaconazole oral suspension with the CYP3A4 substrates, pimozide, and quinidine can result in increased plasma concentrations of these drugs, leading to QTc 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 tablets were conducted under IND 51,316. On March 25th 2010, the applicant submitted a briefing document to FDA to discuss the clinical development program for POS tablets which involved the use of PK bridging studies to register POS tablets for the same prophylaxis indication as posaconazole oral suspension. At a meeting held on April 28, 2010, the Applicant proposed two Phase 1, PK trials in healthy volunteers, (P04975 and P05637), and a PK, safety and tolerability trial (P05615) in the target population of neutropenic patients with hematologic malignancies at risk of IFI.

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

The Division agreed with the bridging strategy, however, the clinical pharmacology reviewers recommended three additional Phase 1 studies which included a relative bioavailability (BA) study to compare the POS tablets relative to the posaconazole oral suspension, an absolute BA study, and a PK study to evaluate the effects of drugs that increase the pH of the stomach on the systemic absorption of POS tablets.
A teleconference was held with the Applicant on January 27th, 2012 and it was agreed that the available data supporting the dose of POS tablets, 300 mg PO twice daily dosing on Day 1 and 300 mg PO daily, were sufficient for submission of an NDA.

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.

3.3 Financial Disclosures

There were no significant financial arrangements reported for investigators participating in the clinical trials of POS tablets.

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 205-053.

4.4 Clinical Pharmacology

The Office of Clinical Pharmacology Division 4 reviewed the pharmacokinetic studies in this NDA. The Division recommends approval of POS tablets for prophylaxis of invasive *Aspergillosis* and *Candida* infections. Study P05615 was designed as a bridging study to the POS Oral Suspension clinical program. The exposure target for POS Tablets in Study P05615 was to be within the range of POS exposures previously studied and demonstrated to be safe and effective in the prophylaxis and salvage treatment setting with POS Oral Suspension. When POS tablets were administered to 50 PK-evaluable subjects with neutropenia and hematologic malignancies or HSCT, a 300 mg dose of POS tablet taken without regard to food intake resulted in mean Cavg at steady state of 1580 ng/mL. Overall, 90% of subjects treated with the 300-mg QD dose of POS tablet attained Cavg between 500 ng/mL and 2500 ng/mL, and, thus, the pre-defined exposure target range was achieved at the 300 mg dose level. The clinical pharmacology reviewer used a more conservative approach to review the PK results bridging POS tablet exposure to posaconazole oral suspension based on Cmin instead of "Cavg". Given this, the exposure target range for the use of POS Tablets in patients was set as:

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

Please refer to the review by Seong Jang, Ph.D. for an assessment of the PK, food- effect studies and bioavailability studies in healthy volunteers.

During the review of this NDA, the Division asked the sponsor to conduct an additional food-effect PK study in order to confirm the sponsor's proposal that POS tablet may be given without food. The applicant completed the food-effect study toward the end of the review cycle for NDA 205-053 and they plan to submit the final clinical study report as a labeling supplement after the Division of Anti-infective Products (DAIP) takes an action on this NDA.

4.4.1 Mechanism of Action

Posaconazole is a broad spectrum antifungal triazole. Posaconazole, 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

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

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1. Overview of the Clinical Program for POS Tablets

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

MD= Multiple Dose, OS=Oral Suspension SD=Single Dose, XO=Cross-over Design

5.2 Review Strategy

Study P05615 was a phase 3, single-arm, uncontrolled, open-label, multicenter, global study of the PK, safety and tolerability of POS tablets used as prophylaxis in adult patients with

hematologic malignancies at high risk for IFIs. A total of 235 subjects were enrolled. Subjects were treated in 42 study centers (7 in the United States) in 15 countries. This study was reviewed for safety and tolerability of POS tablets in the target population of patients with hematologic malignancies at risk for IFI. The safety information for POS tablets was compared to the safety profile of posaconazole oral suspension and the triazole class of anti-fungal drugs in general.

5.3 Discussion of Individual Studies/Clinical Trials

The clinical safety information in Study P05615 provided the support for the safety of POS tablets in neutropenic subjects undergoing chemotherapy for AML or MDS and subjects who were recipients of allogeneic hematopoietic stem cell transplant (HSCT) and patients with GVHD.

The objectives of Study P05615, were: first, to fully characterize the PK and assess safety of POS tablets when given without regard to food in small cohorts of neutropenic subjects (with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS); and second, to confirm the PK and further assess the safety profile of the tablet formulation when given without regard to food intake in a broader population of immunocompromised patients with hematological malignancies representative of patients who would benefit from antifungal prophylaxis. There was no primary efficacy endpoint in the study. Survival outcome at Day 65 was a secondary efficacy endpoint. All subjects were evaluated for safety. Study P05615 was conducted in two parts:

Part 1
Part 1 enrolled neutropenic subjects undergoing chemotherapy for AML or MDS. The treatment duration was up to 28 days, with a minimum duration of therapy of 8 days and a maximum duration of 28±1 days. Two sequential and escalating dosing cohorts were evaluated with serial PK sampling to characterize the PK profile of POS tablets. A full PK assessment was to be done on Days 1 and 8. Sparse PK sampling (trough, C_{min}) was performed on all subjects. The cohorts were to be evaluated for safety information. The dose selection and decision to proceed to Part 2 were based on the POS tablet exposures achieved and the safety observed among the Part 1 subjects.

An independent DSMB reviewed the data from Parts 1A (200 mg dose) and 1B (300 mg dose) to support dose selection for the Phase 3 component of the study. Part 2 (Phase 3) of the current study further evaluated the selected 300 mg dose when given to a larger target patient population to further evaluate the PK and safety of the selected dose.

Part 2 (Phase 3)
Part 2 enrolled two patient populations, neutropenic subjects undergoing chemotherapy for AML or MDS and subjects who were recipients of allogeneic hematopoietic stem cell transplant (HSCT). The duration of study drug therapy was 28±1 days. All subjects received 300 mg PO BID on Day 1, followed by 300 mg PO QD thereafter. In Part 2, sparse PK sampling (trough, C_{min}) was performed on all subjects. A subset of approximately 30 HSCT patients were evaluated with serial PK sampling to fully characterize the PK profile of POS tablet.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

There was no primary efficacy endpoint in Study P05615. The results for the secondary efficacy endpoint, clinical failure and survival at Day 65, is discussed in this section. See Section 7 for a review of the safety results for POS tablets.

6.1.1 Methods

The study report and raw data in the study report for Study P05615 were reviewed to assess the safety profile of POS tablets in relation to posaconazole systemic exposures in adult patients with hematologic malignancies at high risk for IFIs. Analyses were performed using JReview 9.26, (b) (4)

6.1.2 Demographics

200-mg Dose Cohort: A majority of the 20 treated subjects in the 200-mg cohort were males (60%), white (95%), not Hispanic or Latino (65%), with a mean age of 51 years (range=30-69 years) and a mean body mass index (BMI) of 27 kg/m^2. The cohort included 13 (65%) subjects with AML (new diagnosis), 4 (20%) subjects with AML (first relapse), and 3 (15%) subjects with MDS.

300-mg Dose Cohort: A majority of the 210 treated subjects were males (62%), white (93%), not Hispanic or Latino (84%), with a mean age of 51 years (range=19-78 years) and a mean body mass index (BMI) of 26 kg/m^2. The cohort included 97 (46%) subjects with AML (new diagnosis), 16 (8%) subjects with AML (first relapse), 6 (3%) subjects with MDS, and 91 (43%) subjects with HSCT, as the primary diseases at study entry. Only the 300-mg dose cohort enrolled patients with HSCT and GVHD per the protocol.

Table 2. Demographic and Baseline Disease Characteristics for All Treated Subjects

Characteristic		POS 200-mg Group (N=20) n (%)	POS 300-mg Group (N=210) n (%)
Sex	Male	12 (60)	131 (62)
	Female	8 (40)	79 (38)
Race	White	19 (95)	196 (93)
	Black		2 (1)
	Asian	1 (5)	2 (1)
	Multiracial	0	6 (3)
	Native Hawaiian/ other pacific Islander	0	4 (2)
Age (years)	Mean	51	51
	Range (min, max.)	30-69	19-78
Age (years) Group	18 - <65y	17 (85)	175 (83)
	> 65y	3 (15)	35 (17)
Weight (kg)	Median	77	75
	Range	54-99	45-172
Primary Diagnosis	AML (new diagnosis)[a]	13 (65)	97 (46)
	AML (relapse)	4 (20)	16 (8)
	MDS	3 (15)	6 (3)
	HSCT	0	91(43)

n=number of subjects; POS=posaconazole; SD=standard deviation.
[a] Subject 13/000052 enrolled into the study with neutropenia following chemotherapy for mastocytosis. As the chemotherapy and anticipated duration of neutropenia for this disorder was similar to that given for AML, this subject was included in the AML (New Diagnosis) group.
Source: Table adapted from source data in study report, for Study P05615.

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 200-mg and 300-mg dose cohorts were similar for other characteristics such as age and baseline weight. There were a limited number of elderly subjects in the trial, 38 (18%) were 65 years of age or older.*

6.1.3 Subject Disposition

A total of 230 subjects received at least one dose of POS tablets, 20 subjects were treated with 200 mg (Part 1A), and 210 subjects were treated with 300 mg (Part 1B, n=34; Part 2, n=176). Of the 235 subjects who were enrolled, five subjects did not receive study treatment after an additional evaluation of the eligibility criteria was conducted.

The majority of subjects (179, 78%) completed 28 days of treatment. The main reasons for early treatment discontinuation were adverse events (AEs) (15% of patients), treatment failure (3%), protocol non-compliance (3%) and withdrawal of consent (1%). Subject disposition for the 200-mg and 300-mg Dose Cohorts are summarized in Table 3.

Table 3. Disposition of Study Subjects per Dose Group – All Treated Subjects

REASONS FOR DROPOUT	POS 200 mg QD	POS 300 mg QD	Total No. of Subjects
ADVERSE EVENT	2 (10%)	32 (15%)	34 (15%)
NON-COMPLIANCE WITH PROTOCOL	1 (5%)	7 (3%)	8 (3%)
TREATMENT FAILURE	1 (5%)	6 (3%)	7 (3%)
SUBJECT WITHDREW CONSENT	0 (0%)	2 (1%)	2 (1%)
Total Subjects Discontinued	**4 (20%)**	**47 (22%)**	**51 (22%)**
Total Subjects Treated in Dose Group	**20 (100%)**	**210 (100%)**	**230(100%)**
Total Subjects Completed Treatment Phase	**16 (80%)**	**163 (78%)**	**179 (78%)**

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 P05615.

6.1.5 Analysis of Secondary Endpoints(s)

Clinical Failure and Day 65 Survival in 200-mg Dose Cohort

There were two (10%) deaths reported during the study period in the 200-mg Cohort. Breakthrough IFIs (proven or probable[4]) as determined by the investigator, were reported for two (10%) subjects treated with POS tablets. One subject died within seven days of their last treatment, and one subject died seven days after the last treatment with POS tablets. Both subjects died of disseminated mold infections. Brief case narratives are presented for both patients:

Subject No. 11/000002 was a 57-year-old white male with AML diagnosed with disseminated aspergillosis, who had an abnormal radiograph and positive blood culture for *Aspergillus fumigatus* on Day 20. On Day 21 the patient was diagnosed with fungal pneumonia and was switched to alternative antifungal treatment. He received POS tablets, 200 mg a day from Day 2 to 23. The patient was profoundly neutropenic and thrombocytopenic from Day -15 to Day 37. Study treatment was discontinued on Study Day 23 and the patient died from disseminated aspergillosis on Study Day 37. On Day 8, the subject's posaconazole concentration (C_{max}) peaked

[4] De Pauw B, Walsh TJ, Donnelly JP, *e t al* . European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008; **46**: 1813 – 1821.

at 1,200 ng/mL. The C_{min} value at steady state (Day 8) was 668 ng/mL. At Day 23, the subject's C_{min} POS concentration was 261 ng/mL.

Subject No. 11/000003 was of 53-year-old white male with MDS diagnosed with disseminated fusariosis (lung, sinus, and blood). He had an abnormal radiograph and positive blood culture on Day 16 and was treated with another triazole drug. The patient complained of mild facial pain beginning on Day 6. The patient was neutropenic from Day -1 to Day 30. He received POS tablets (200 mg) from the Day 1 to Day 29. On Day 29, the patient developed pneumonia, severe renal failure, and septic shock. The subject was discontinued from study treatment on Study Day 29 and died on Study Day 30. On Day 8, the subject's POS concentration (C_{max}) peaked at 1,020 ng/mL. The C_{min} value at steady state was 335 ng/mL. At Day 29, the C_{min} for POS concentration was 162 ng/mL.

Clinical Reviewer's Comment: *Both subjects were profoundly neutropenic and died of disseminated mold infections. The minimum POS concentrations at steady state for subject 11/000002 and subject 11/000003 were 668 ng/mL and 335 ng/mL (low), respectively and C_{min} was even lower in the last week of the study treatment at 261 ng/mL and 162 ng/mL, respectively. The profound neutropenia and low concentration of posaconazole below the threshold concentration of C_{avg} 500 ng/mL contributed to the failure of anti-fungal prophylaxis and the development of breakthrough invasive fungal infection in at least one of the patients, Subject No. 11/000002 and probably in both patients. Subject No. 11/000003 complained of facial pain on Day 6 of therapy which raises a concern that he might have had an ongoing Fusarium infection in the sinus prior to starting prophylaxis with POS tablets. These two patients would not be expected to survive without recovery of their neutrophil counts.*

Clinical Failure and Day 65 Survival in 300-mg Dose Cohort

In the 300-mg Cohort, there was one (<1%) patient treated with POS tablets who failed prophylaxis and developed a probable IFI as determined by the investigator. There were an additional nine cases of possible IFI who were analyzed as clinical failures which resulted in a breakthrough fungal infection rate of 10/210 (4.7%).

Subject No. 34/000171 with AML was diagnosed with a fungal infection involving the pleura on Day 8. The patient appeared to be colonized with Candida as *Candida glabrata* was isolated from feces on Day 7. This subject was discontinued from POS tablets on Study Day 10 and an alternative anti-fungal drug was used. The patient was alive at the Day 65 survival visit. The fungal infection was considered ongoing at the time of reporting. The posaconazole concentration was above the pre-defined cut-off, C_{avg} 500 ng/mL: on Day 8, Cavg was 2530 ng/mL and on Day 11 (1 day after the subject received the last dose), the posaconazole concentration was 2930 ng/mL.

Cases of Possible Invasive Fungal Infection

Nine subjects in the 300-mg Cohort had abnormal radiographic findings but no mycological evidence of infection which is consistent with diagnosis of possible invasive fungal infection.[4]

Deaths

The majority of the deaths occurred in Part 2 of the trial; 18 (9%) of the treated subjects were not alive at Day 65. Two additional subjects in the 300-mg dose cohort died after the survival visit on Day 65 (>70 days). Deaths are discussed in more detail in Section 7.

Clinical Reviewer's Comment: *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 in Study P05615. Both trials demonstrated substantially fewer breakthrough infections caused by Aspergillus species in patients receiving posaconazole prophylaxis when compared to patients receiving fluconazole or itraconazole. Deaths are described in more detail in Section 7.*

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

Study P05615 was a single-arm study and therefore there are no comparative safety data for POS tablets. The safety database included 230 patients who received at least one dose of POS tablets. The most common adverse reactions (>25%) were diarrhea and nausea. Other adverse reactions included elevation of hepatic transaminases, QTc interval prolongation, and drug-drug interactions, all of which are known adverse reactions associated with triazole antifungal drugs.

The survival rate was high at 90% and 91% of subjects in the 200-mg and the 300-mg dosing cohorts, respectively, at the survival visit on Day 65. There were 20 deaths during the trial period, two in the 200-mg dose cohort and 18 (9%) in the 300-mg dose cohort. Two deaths, in the 300-mg dose cohort, occurred beyond the survival visit on Day 65 (> Day 70). The patients died from progression of their underlying hematologic malignancy, sepsis, fungal pneumonia, viral hepatitis, cardiac disorders, and complications post HSCT due to graft-versus-host disease. The most common causes of death were due to infections (including sepsis and septic shock), reported in eight subjects. Two cases of renal failure associated with drug-drug interactions with a calcineurin inhibitor resulted in death. There were three additional cases of renal toxicity in patients who survived, which were also due to drug-drug interactions with posaconazole and calcineurin inhibitors. Elevation of creatinine levels resolved in two cases, when the dose of the calcineurin inhibitor was reduced; these two patients remained on posaconazole while the dose of cyclosporine was reduced. There was one patient, post HSCT, who died from multi-organ failure including renal failure, and the immediate cause of death was reported as hepatic insufficiency. POS tablets might have contributed to the hepatic injury in this patient; however, it is more likely that death was due to complications post HSCT, including CMV reactivation, and hepatotoxic effects associated with myelosuppressive drugs. Adrenal insufficiency was reported in one patient post HSCT, probably due to severe illness due to GVHD and treatment with POS tablets was continued.

The 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.

Elevation of hepatic transaminases and hyperbilirubinemia were reversible in most cases. Five subjects (2%) had hepatic TEAEs that were considered related to study drug and led to discontinuation of study drug. Two (<1%) of the patients had hepatic function test results meeting the criteria for Hy's Law during their treatment. Hepatic transaminases and bilirubin levels returned to normal ranges in one patient and had improved in the other patient before the end of the study period. Many of the cases with elevated hepatic transaminases were confounded by adverse reactions associated with myelosuppressive regimens for treatment of leukemia or HSCT and GVHD.

The attribution of adverse reactions to POS tablets was confounded 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. The adverse reactions in patients with high and low exposures to POS tablets were compared and did not appear to be different. Within the range of exposures that have been observed in this study, 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 Tablets.

In summary, POS tablets were reasonably well tolerated and had a similar safety profile to the marketed posaconazole oral suspension. Based on the safety information provided in Study P05615 and the known safety profile of posaconazole, the potential benefit of POS tablets 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 4. Most of the adverse reactions were infections, pneumonia and septic shock. One patient had a breakthrough fungal pneumonia on POS tablet prophylaxis.

Table 4. Treatment Emergent Adverse Reactions in 200-mg Dose Cohort

Protocol No. P05615

System Organ Class Preferred Term	Number of Subjects (n,%) All Treated Subjects 200 mg n=20
Subjects Reporting Any Adverse Event	2 (10)
Infections And Infestations	2 (10)
Pneumonia	1 (5)
Pneumonia Fungal	1 (5)
Septic Shock	1 (5)
Nervous System Disorders	1 (5)
Sinus Headache	1 (5)

n=number of subjects; POS=posaconazole.
Source Data: Section 14.6.1.16.

Source: Section 14.6 of the study report, P05615

Treatment Emergent Adverse Reactions in 300-mg Dose Cohort

The majority of subjects (99%) experienced at least one TEAE. The overall survival at Day 65 was high at 91%. SAEs were reported for 69 (33%) subjects. There were 20 deaths in the trial; 18 (9%) subjects had died by Day 65, and the remaining 2 subjects died after the survival visit Day 65. Adverse Reactions in the 300-mg dose cohort are summarized in Table 5.

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Table 5. Treatment Emergent Adverse Reactions – 300-mg Dose Cohort

Protocol No. P05615

	Number of Subjects (n,%) All Treated Subjects POS Tablet 300 mg Cohort n=210
Treatment-Emergent Adverse Events	207 (99)
Treatment-Related Treatment-Emergent Adverse Events	84 (40)
Serious Adverse Events	69 (33)
Deaths	20 (10)
Severe/Life-Threatening Treatment Emergent Adverse Events	111 (53)
Study Drug Discontinuation Due to an Adverse Event	38 (18)

n=number of subjects; POS=posaconazole.

Note: Deaths are also included in serious adverse event count.

Source Data: Section 14.7.1.1.

Source: Section 14.7 of the study report, P05615

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

One phase 3 trial, Study P05615, evaluated the PK, safety, and tolerability of POS tablet in the intended population of neutropenic patients with hematological malignancies, post-HSCT and patients with GVHD.

7.1.2 Categorization of Adverse Events

Study P05615 use MedDRA version 15.0 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.

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

Extent of Exposure

In the 300-mg dose cohort (Parts 1B and 2 combined; n=210), the mean duration of therapy was 23 days.

A total of 193 (92%) of subjects completed ≥ 8 days which was the recommended minimum duration of exposure to POS tablets and 151 (72%) subjects remained on the 300-mg dose of POS tablets for the maximum duration of 28 days. There were 21 (10%) subjects that received a 300-mg dose of POS tablets on Day 29 which was allowed in the protocol because the final treatment visit was to be on Day 28 (+/- 1 day). Of these 21 subjects, 17 received a total of 29 days of dosing.

Table 6. Extent of Exposure to Posaconazole Tablets – 300-mg Dose Cohort

Treatment Duration in Days[a]	**No. of Subjects N (%); All Treated Subjects (N=210)**
Received any Rx	210 (100)
≥1	210 (100)
≥2	207 (99)
≥3	205 (98)
≥8	193 (92)
≥14	178 (85)
≥21	151(72)
> 28	21 (10)
Statistics[b]	
Mean	23 (SD = 8)
Median	28
Min, Max	1, 30

[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 12-26, Section 14.2.2.13.1. of study report, P05615

Clinical Reviewer's Comment: *A total of 151 or 72% of patients completed 28 days of prophylaxis which provided an adequate number of patients to assess the exposure response in relation to the safety of POS tablet.*

7.2.2 Explorations for Dose Response

The exposure target was determined based upon the range of exposures achieved with the oral suspension product in safety and efficacy trials, as well as the exposure-response relationship found in earlier controlled studies of POS Oral Suspension.[1,2,3] Please refer to section 7.3.5 for a discussion of posaconazole exposures and safety of patients in the 200-mg and 300-mg Dose Cohorts. Please also refer to the clinical pharmacology review (10/ 17/ 2013) by Dr. Seong Jang.

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 isoenzymes, which is the principle drug metabolizing enzyme in humans.[5] 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.[6]

Triazole drugs including posaconazole interact with the calcineurin inhibitors to cause neurologic adverse reactions. Itraconazole and voriconazole interacts with vincristine to cause severe neurotoxicity.[7,8] Itraconazole has a potential negative inotropic effect and should be

[5] Gubbins PO, Heldenbrand S. Clinically relevant drug interactions of current antifungal agents. Mycoses. 2010;53(2):95.
[6] Wingard, JR. Prophylaxis of invasive fungal infections in adults with hematologic malignancies. www.UpToDate.com Sept 2013
[7] 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
[8] Takahashi N., et al. Itraconazole oral solution enhanced vincristine neurotoxicity in five patients with malignant lymphoma. Intern Med. 2008;47(7):651-3

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.[9] Posaconazole 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 2 (10%) deaths in the 200-mg dose cohort. There were 20 (9%) deaths reported during the study period in the 300-mg cohort. By Day 65, 18 (6%) subjects had died, and the remaining two subjects died after the Day 65 visit.

Table 7. Deaths in Study Dose Cohorts – All treated subjects – Study P05615

Survival Status	POS 200 mg QD, n=20	POS 300 mg QD, n=210
Alive	18 (90%)	191 (91%)
Dead	2 (10%)	18 (9%)
Subjects - Total	20 (100%)	210 (100%)

Cause of Death Category

The two patients who died in the 200-mg dose group died of fungal pneumonia and sepsis. In the 300-mg dose cohort, (eight subjects died due to adverse events, five due to progression of disease and two were listed as "other"). The most common causes of death were infection-like causes (including sepsis and septic shock) reported in eight subjects. Two cases were associated with drug-drug interactions with calcineurin inhibitors leading to renal failure as an AE leading to death. The categories for cause of death in both dose cohorts are summarized in Table 8.

[9] Marr KA, Leisenring W, Crippa F, et al. Cyclophosphamide metabolism is affected by azole antifungals. Blood. 2004;103(4):1557

Table 8. Cause of Death in 200mg and 300mg Dose Cohorts

Cause of Death Category	POS 200 mg QD; N=20	POS 300 mg QD N=210
Missing	0	1 (0.4%)
Adverse Event	0	14 (6.1%)
Disease Related Complications	2 (0.9%)	0
Other	0	1 (0.4%)
Progression of Disease	0	5 (2.2%)

Immediate Causes of Death

Patients died from progression of disease, sepsis, (viral, bacterial, or fungal) pneumonia, viral hepatitis, cardiac disorders, and graft-versus-host disease. The majority of adverse reactions were related to the underlying disease and opportunistic infections due to profound neutropenia. Serious adverse events in the 22 patients who died included sepsis, pneumonia, organ failure, and GVHD. Eight patients died of bacterial or viral infections. Subject no. 26/000157 in the 300-mg dose cohort died of multi-organ failure including hepatic insufficiency and this case is discussed in more detail in the section, "Serious Adverse Events in Patients Who Died". The immediate causes of death in each of the dose cohorts are summarized in the Table 9.

Table 9. Immediate Cause of Death in 200-mg and 300-mg Dose Cohorts

EXACT CAUSE OF DEATH DESCRIPTION	POS 200 mg QD; N=20	POS 300 mg QD; N=210
WORSENING COPD	0	1 (0.4%)
CARDIAC ARREST	0	2 (0.9%)
CARDIOPULMONARY ARREST	0	1 (0.4%)
CARDIOVASCULAR INSUFFICIENCY	0	1 (0.4%)
T CELL PROLYMPHOCYTIC LEUKAEMIA	0	1 (0.4%)
GVH DISEASE	0	2 (0.8%)
HEPATIC INSUFFICIENCY	0	1 (0.4%)
PATCHY INFILTRATES PNEUMONIA*	1 (0.4%)	0
PNEUMONIA BILATERAL*	1 (0.4%)	0
PROGRESSION OF AML	0	1 (0.4%)
PROGRESSIVE LEUKEMIA	0	1 (0.4%)
PSEUDOMONAS AERUGINOSA SEPTICEMIA	0	1 (0.4%)
RELAPSE OF SEPTIC SHOCK	0	1 (0.4%)
RHYTHMOGENIC HEART FAILURE	0	1 (0.4%)
SEPSIS	0	3 (1.3%)
SEPTIC SHOCK	0	1 (0.4%)
VIRAL HEPATITIS	0	1 (0.4%)
WORSENING RSV PNEUMONIA	0	1 (0.4%)

*fungal pneumonia

Clinical Reviewer's Comment:
The adverse events of neutropenia, bacterial sepsis, bacterial pneumonia, transplant failure, GVHD, and progression of disease are expected complications in patients with hematologic malignancies with neutropenia or post-HSCT. There were no causes of death or AEs leading to death considered to be directly related to study drug in the 200-mg and 300-mg dose cohorts. POS tablet may have contributed to the hepatic insufficiency in Subject No. 29/000157 but there were several other contributing factors to the patient's multi-organ failure. 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.[10,11]

Subject No. 26/000157, with multi-organ failure and an immediate cause of death due to hepatic insufficiency was further evaluated. This was a 22-year-old white male who received an allogeneic bone marrow transplant on Day -20 for which he received a myelosuppressive regimen that included busulfan, thiotepa, cyclophosphamide, and alemtuzumab. He had a recent medical history of elevated hepatic transaminases, increased alkaline phosphatase, increased AST; hypocalcemia (resolved), hypokalemia (resolved), and hypomagnesemia (stable). The subject entered the study on Day 1 and received POS 300 mg PO BID followed by POS 300 mg PO daily from Day 2 to 28. Hepatic transaminases and total bilirubin were normal at study entry. Total bilirubin levels were mildly elevated 24 µmol/L on Day -7 (prior to study entry) and was 26 µmol/L on Day 3 of treatment with POS but remained ≤ 2X ULN. On (b) (6), the subject presented with cytomegalovirus (CMV) reactivation and was hospitalized. On an unknown date, he experienced severe anasarca, severe renal failure, hyperbilirubinemia and multi-organ failure. He received foscarnet and gancyclovir and he had deterioration of renal function. His clinical status worsened during his hospitalization from (b) (6).

The following graphical patient profile for Subject No. 26/000157 summarizes the results of the patient's liver function and renal function tests throughout the trial. Two laboratory values for the same test are provided on some study days e.g., SGPT on Day 2 was 15 U/L and 8 U/L. On Day 2, serum creatinine was 97µmol/L and 100µmol/L.

[10] 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. Source:

[11] Wingard JR, Prophylaxis of invasive fungal infections in adult hematopoietic cell transplant recipients. Source: www.uptodate.com (update from Feb. 17, 2013).

Figure 1. Graphical Patient Profile - Subject No. 26/000157

Survival status: 1= alive; 2=dead.
Source: Patient profile was constructed using JReview9.2 with raw data from electronic datasets, NDA 205-053.

Clinical Reviewer's Comment: *The patient completed 28 days of POS tablets. CMV reactivation and nephrotoxicity associated with foscarnet and gancycolvir were probably associated with the patient's worsening renal function. These adverse reactions are likely to be complications post-HSCT and are unlikely to be due to POS tablets. The case narrative for this patient states that he died on Day 43. The death report states the cause of death due to multi-organ failure, anasarca, renal failure, and hyperbilirubinaemia; though the study report lists hepatic insufficiency as the immediate cause of death. No autopsy was performed.*

7.3.2 Nonfatal Serious Adverse Events

Serious Adverse Events

Serious Adverse Events (SAE) were reported for 69 (33%) of the 300-mg cohort subjects. For the 300-mg cohort, the most common SAE terms reported were 11 (5%) subjects with febrile neutropenia, 5 (2%) subjects with sepsis, and 4 (2%) subjects with diarrhea.

Serious adverse events occurring at a rate of ≥ 1% of subjects are summarized in the following table. Neutropenia, sepsis, cytomegalovirus infection, diarrhea, and elevated serum creatinine

were the most common serious adverse events reported. Febrile neutropenia and sepsis (*Klebsiella spp., Pseudomonas spp.* infections) were related to the underlying myelosuppressive drugs and the underlying hematological malignancy and not to POS tablets. CMV infections (2 patients) were opportunistic infections post-HSCT.

Table 10. Serious Adverse Events in the 200-mg and 300-mg Dose Cohorts

Serious Adverse Events	POS 200 mg QD N=20	POS 300 mg QD N=210
FEBRILE NEUTROPENIA	2 (10%)	9 (4.2%)
SEPSIS	1 (5%)	5 (2.4%)
CYTOMEGALOVIRUS INFECTION	0 (0%)	3 (1.4%)
DIARRHEA	0 (0%)	3 (1.4%)
BLOOD CREATININE INCREASED	0 (0%)	3 (1.4%)
SEPTIC SHOCK	1 (5%)	2 (1%)
PNEUMONIA	1 (5%)	2 (1%)
PSEUDOMONAL SEPSIS	0	2 (1%)
RENAL FAILURE	1 (5%)	1 (0.5%)
HYPOTENSION	1 (5%)	1 0.5%)
PYREXIA	0	2 (1%)
MULTI-ORGAN FAILURE	0	2 (0.9%)
LIVER FUNCTION TEST ABNORMAL	0	2 (1%)
RESPIRATORY FAILURE	0	2 (1%)
DRUG INTERACTION	0	2 (1%)
DEHYDRATION	1 (5%)	1 (0.5%)
BLOOD BILIRUBIN INCREASED	0	2 (1%)
RESPIRATORY DISTRESS	0	2 (1%)
CYTOMEGALOVIRUS VIREMIA	0	2 (1%)
KLEBSIELLA INFECTION	0	2 (1%)
Total number of subjects.	8/20(40%)	50/210 (24%)

Serious Adverse Events -Related to Study Drug

Seven subjects, one patient in the 200-mg dose cohort and six patients in the 300-mg dose cohort experienced serious adverse reactions considered to be related to posaconazole. Four patients experienced hepatotoxicity and three patients experienced renal toxicity.

200-mg Dose Cohort

Subject No. 11/000007, a 30-year-old male with AML, experienced renal failure with an increase in serum creatinine to 344 µmol/L (3.9 mg/dL) on Day 14, which peaked at 667 µmol/L (7.5 mg/dL) on Day 15. Study drug was discontinued following the Day 14 dose. On Study Day -5, and Day 1, creatinine levels were normal ranging from 61 to 70 µmol/L (0.7- 0.8 mg/dL) and blood pressure was normal at study entry 121/76 at screening and 105/59 on Day 1. He had raised diastolic blood pressure on day 15 through 23, maximum BP: 137/94. The patient developed thrombocytopenia and was treated with IV platelet transfusions, Day 8-14. The subject received concomitant medications including vancomycin which was also discontinued following the occurrence of renal failure. Other medications included ciprofloxacin, filgrastim for neutropenia (Day 6 to 15), metoclopramide, and ondansetron for vomiting. Hepatic function tests remained within normal levels. Vital signs remained normal throughout the study period.

The renal failure was treated with furosemide and his creatinine level decreased to 141 µmol/L (1.5 mg/dL) on Day 29, but was still approximately twice the patient's baseline level. Creatinine levels continued to decrease and on Day 34, serum creatinine was in the normal range (114 µmol/L or 1.3 mg/dL) but still above patient's baseline creatinine level 61 to 70 µmol/L (0.7-0.8 mg/dL).

The following graphical patient profile for Subject No. 11/000007 summarizes the results of the patient's liver function and renal function tests throughout the trial. Different values for normal ranges (highlighted in blue) for serum creatinine were provided in the datasets, therefore two sets of laboratory values are provided for serum creatinine.

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Figure 2 Graphical Patient Profile - Subject No 11/000007

Status code: 1= alive; 2 = Dead. Different values for normal ranges (highlighted in blue) for creatinine were provided in the datasets. A normal creatinine result is approximately 0.7 to 1.3 mg/dL (63-114 µmol/L) for men and 0.6 to 1.1 mg/dL for women, approx. 53-97µmol/L. Source: Patient profile was constructed using JReview 9.2 from electronic datasets, NDA 205-053.

Clinical Reviewer's Comment: *The occurrence of reversible acute renal failure in this patient was probably related to underlying illness, and concomitant drugs such as vancomycin and ciprofloxacin.*

300-mg Dose Cohort

In the 300-mg dose cohort, 6 (3%) subjects experienced serious adverse events that appeared to be associated with posaconazole. Two (1%) subjects (26/000140 and 26/000177) experienced renal toxicity with increases in serum creatinine related to drug-drug interactions with cyclosporine, two (1%) subjects (2/000152 and 2/000179) had abnormal hepatic function tests,

one (<1%) subject (50/000072) developed hepatotoxicity, and one (<1%) patient (29/000104) developed renal failure while on POS tablet prophylaxis.

Subject No. 2/000152: A 43-year-old white male with a diagnosis of AML entered the trial at 12 days post allogeneic HSCT. He developed worsening hepatic function tests on Day 20 which improved but was ongoing at the end of the study. POS tablet was permanently discontinued on Day 23. He was hospitalized on (b) (6) with thrombocytopenic purpura (TTP) treated with plasma infusion. The patient experienced elevated transaminases and mild elevation of total bilirubin during treatment with POS tablets. AST was normal at baseline, became elevated from Day 15 to Day 30 and returned to normal on Day 36. The peak AST level was 68 U/mL. ALT was normal at baseline, became elevated at day 28 through day 30 and returned to normal at Day 36. The peak ALT level was 99 U/ML *(approximately 2.5x ULN)*. Total bilirubin levels were mildly elevated at 19 µmol/L on Day 24 and returned to normal on Day 29. During the time of elevation of liver function tests the posaconazole trough concentration peaked at 1420 ng/mL on Day 24.

The following graphical patient profile summarizes the results of the patient's (Subject No. 2/000152) liver function and renal function tests throughout the trial.

Figure 3. Graphical Patient Profile - Subject No. 2/000152

Status code: 1= alive; 2 = Dead. Source: Patient profile was constructed using JReview9.2 with raw data from electronic datasets, NDA 205-053.

Clinical Reviewer's Comment: *Elevated hepatic transaminases were transiently elevated and probably associated with POS tablets, transaminases returned to normal when the study drug was stopped. Thrombocytopenic purpura (TTP) is likely to be related to complications post HSCT.*

Subject Nos. 2/000179 and 50/000072 are discussed in the section on hepatic adverse reactions.

Subject No. 26/000140: This 60-year-old white female, post HSCT (Day -17), experienced adverse reactions associated with a drug interaction between POS tablets and cyclosporine. CMV reactivation was diagnosed on Day 3 and was treated with intravenous gancyclovir and it resolved on Day 10. At the onset of study therapy, the subject's creatinine level was within normal limits. From Day 3 through Day 28, the patient had elevated creatinine levels which peaked at 240 µmol/L (2.7 mg/dL) on Day 28. On (b) (6) creatinine levels were elevated at 2.3 mg/dL and the patient was hospitalized. She was treated with intravenous hydration and the dose of cyclosporine was reduced. The subject was discharged on (b) (6) with a creatinine of 1.6 mg/dL. The posaconazole trough concentration peaked at 2770 ng/mL on Day 21. On Day 66, the subject was reported to be recovered and her creatinine level was 123 µmol/L (1.4 mg/dL).

The following graphical patient profile summarizes the results of the patients liver function and renal function tests throughout the trial.

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Source: Patient profile was constructed using JReview9.2 from electronic datasets, NDA 205-053.

Clinical Reviewer's Comment: *Multiple factors could have contributed to renal toxicity in this patient. A drug-drug interaction between cyclosporine and posaconazole was the most likely contributing factor to renal toxicity. Concomitant administration of posaconazole (and other triazole drugs) with calcineurin inhibitors, cyclosporine or tacrolimus, increases the blood trough concentration of the calcineurin inhibitor. Both CMV reactivation and treatment with IV gancyclovir (nephrotoxic) probably also contributed to the renal toxicity. Elevated creatinine was noted on Day 3, the same day that CMV reactivation was diagnosed and treatment with gancyclovir began.*

Subject No. 26/000177: This was a 20-year-old white male who received an allogeneic HSCT (Day -21) and was receiving cyclosporine for treatment of graft-versus-host disease. He was treated with cyclosporine, methylprednisolone, and mycophenolic acid. The subject received cyclosporine IV from Day -14 to 8 for graft-versus-host-disease prophylaxis. Creatinine levels were raised to 2.7 mg/dL and the patient was treated with hydration with normal saline and a reduced dose of cyclosporine. The patient also had rhinorrhagia and life-threatening thrombocytopenia which improved on Day 19. Creatinine peaked on Day 7 at 256 µmol/L(2.9 mg/dL). He was discharged on (b) (6) and re-hospitalized on (b) (6) with creatinine levels of

2.7 mg/dL, total bilirubin 2.96 mg/dL and elevated lactate dehydrogenase LDH 783 U/L and hyperphosphatemia (resolved on Day 16). POS tablets were permanently discontinued on Day 16. The patient's elevated creatinine levels decreased to 1.4 mg/dL (122 µmol/L) by Day 28. The posaconazole trough concentration peaked at 1410 ng/mL on Day 3.

The following graphical patient profile summarizes the results of the patient's liver function and renal function tests throughout the trial.

Figure 5. Graphical Patient Profile – Subject No. 26/000177

(b) (6)

Source: Patient profile was constructed using JReview9.2 with raw data from electronic datasets, NDA 205-053.

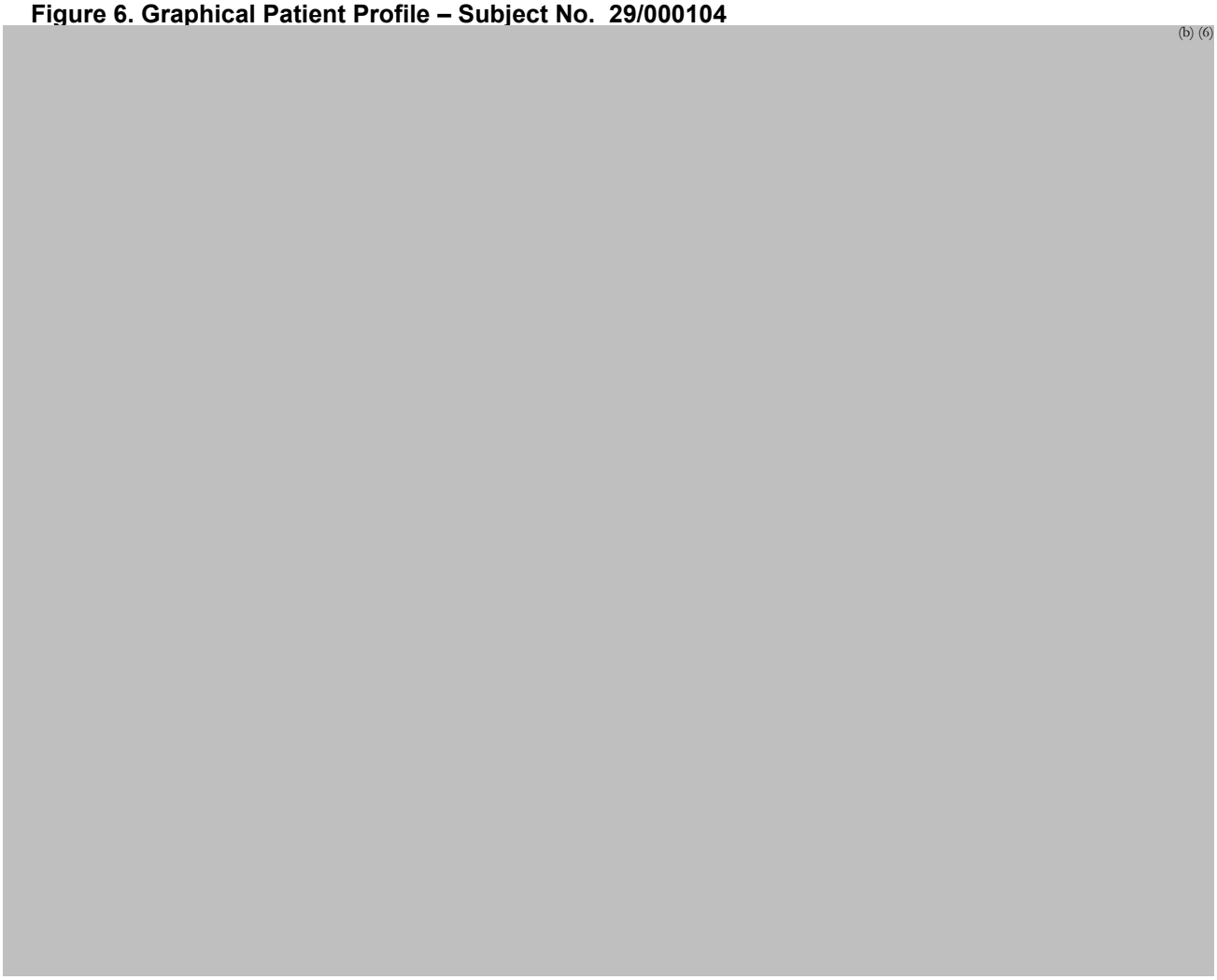
Clinical Reviewer's Comment: *A drug-drug interaction between cyclosporine and posaconazole was the most likely contributing factor to renal toxicity.*

Subject No. 29/000104: This was a 56-year-old multiracial male who had an allogeneic bone marrow transplant and was treated with tacrolimus and prednisone for GVHD starting on Day -11 and ongoing through the trial. He received CMV treatment with valgancyclovir. On Day 28 the patient was diagnosed with renal failure, serum urea was 94 mg/dL, serum creatinine was

elevated 4.6 mg/dL, uric acid was 9.3 mg/dL and the calculated creatinine clearance was 14. Valgancyclovir was discontinued on Day 30 and the renal failure resolved. The posaconazole trough concentration peaked at 1590 ng/mL at Day 28 (EOT).

The following graphical patient profile summarizes the results of the patient's liver function and renal function tests throughout the trial.

Figure 6. Graphical Patient Profile – Subject No. 29/000104



Source: Patient profile was constructed using JReview9.2 with raw data from electronic datasets, NDA 205-053.

Clinical Reviewer's Comment: *There were three cases of renal toxicity and all were due to drug-drug interactions with posaconazole and a calcineurin inhibitors (cyclosporine or tacrolimus). All patients survived. Elevation of creatinine levels resolved, in all cases, when the dose of the calcineurin inhibitor was reduced. Two patients remained on posaconazole while the dose of cyclosporine was reduced. Other contributory factors to the renal toxicity were the use of gancyclovir or valgancyclovir (nephrotoxic), for treatment of CMV infection. Drug-drug interactions with calcineurin inhibitors are known adverse reactions associated with triazoles as described in the posaconazole suspension, NOXAFIL® USPI.*

7.3.3 Dropouts and/or Discontinuations

The majority of subjects (179, 78%) completed 28 days of study treatment. The reasons for early treatment discontinuation were: adverse events (15%), treatment failure (3%), protocol non-compliance (3%) and withdrew consent (1%). Five patients never received POS tablets. Three were not eligible once the inclusion criteria for these patients were reviewed, one patient withdrew consent and one patient had an adverse event prior to dosing with posaconazole.

Disposition of subjects who received at least one dose of POS in the 200-mg and the 300-mg dose cohorts is summarized in Table 11.

Table 11. Disposition of Study Subjects per Dose Group – All Treated Subjects

REASONS FOR DROPOUT	POS 200 mg QD (N=20)	POS 300 mg QD (N=210)	No. of Subjects - both dose categories
ADVERSE EVENT	2 (10%)	32 (15%)	34 (15%)
NON-COMPLIANCE WITH PROTOCOL	1 (5%)	7 (3%)	8 (3%)
TREATMENT FAILURE	1 (5%)	6 (3%)	7 (3%)
SUBJECT WITHDREW CONSENT	0 (0%)	2 (1%)	2 (1%)
Subjects Who Discontinued	**4 (20%)**	**47 (22%)**	**51 (22%)**
Subjects Who Completed Treatment Phase	**16 (80%)**	**163 (78%)**	**179 (78%)**

7.3.4 Significant Adverse Events

Adverse Reactions of Special Interest

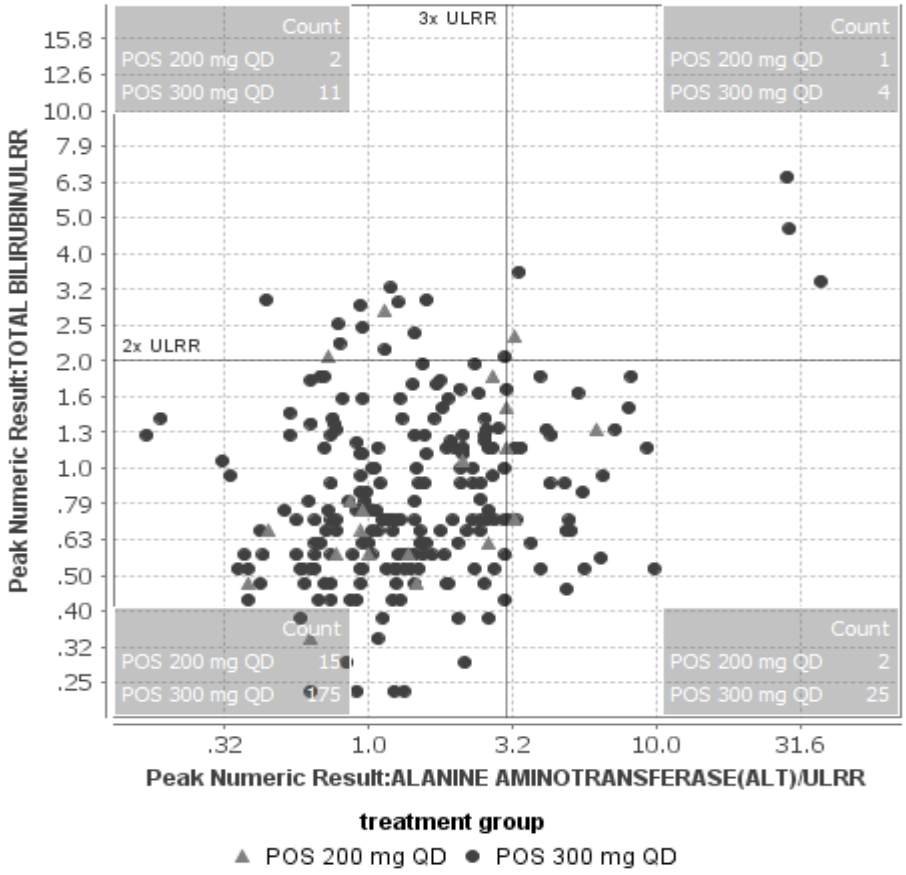
Hepatic Adverse Events

Nineteen (9%) patients experienced hepatic adverse events (MedDRA preferred terms: liver function test abnormality, elevated hepatic enzymes, or hepatotoxicity). Five patients had hepatic transaminase elevations, ALT ≥ 3x ULN and bilirubin levels ≥ 2x ULN.

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

Patients who developed elevated ALT ≥ 3X ULN and total bilirubin ≥ 2X ULN at any time during the trial are represented in the right upper quadrant of the graphic below. Five cases (11/000006, 81/000167, 2/000179, 22/000193, 50/00072) are described. The protocol pre-specified criteria for significant hepatic adverse effects (Hy's Law: ALT and/or AST ≥ 3X upper limit of normal (ULN) with ALK-P ≤ 2X ULN and total bilirubin ≥ 2X ULN without evidence of biliary obstruction. Two of the cases in the 300-mg dose cohort fulfilled the criteria for Hy's Law.

Figure 7. Cases with ALT ≥ 3X ULN and Total Bilirubin ≥ 2X ULN



Case Narratives

200-mg Dose Cohort

One subject in the 200 mg dose cohort had elevated hepatic transaminases during treatment with POS tablets. Subject No. 11/000006, a 38-year-old male, diagnosed with leukemia, experienced an episode of hyperbilirubinemia (≥2 x ULN) and increase in transaminases (ALT ≥ 3 x ULN) while on POS tablets. The event was of moderate intensity, began on Day 8, fluctuated and was ongoing. No action was taken with POS tablets. The results did not fulfill the criteria for Hy's Law because alkaline phosphatase levels were elevated suggesting cholestasis. The hepatic adverse event did not lead to discontinuation of the POS tablets.

The following patient profile summarizes liver function tests and adverse events that occurred throughout the study for patient, Subject No. 11/000006.

Figure 8. Graphical Patient Profile - Subject No. 11/000006

Source: Patient profile was constructed using JReview9.2 with raw data from electronic datasets, NDA 205-053.

Clinical Reviewers Comment: *The subject did not fulfill the criteria for Hy's Law because alkaline phosphatase levels were also elevated, suggesting cholestasis. The hepatic adverse event did not lead to discontinuation of the POS tablets.*

300-mg Dose Cohort

Subject No. 81-000167, a 31-year-old white female, entered the study with new diagnosis of unstable acute promyelocytic leukemia (APML). Baseline hepatic enzymes were in the normal range, ALT 31 U/L and AST 22 U/L. Total bilirubin was normal at 7 µmoL and was also normal on Day 14. On Day 21, total bilirubin was elevated at 85 µmol/L but there were no results for ALT and AST on Day 21. On Day 28 (EOT), AST was 49 U/L, ALT was 149 U/L and total bilirubin had decreased to 23 µmol/L. On Day 36, AST was 63 U/L, ALT was 137 U/L and total bilirubin was 16 µmol/L. There are no data on whether the ALT levels returned to baseline beyond Day 36. The concentration of POS peaked at 2850 ng/mL. The subject completed a 28-day course of POS tablets.

The following graphical patient profile summarizes liver function tests throughout the study for patient, Subject No. 81/000167. Different values for normal ranges (highlighted in blue) for ALT and total bilirubin were provided in the datasets indicating the tests might have been performed at different laboratories.

Figure 9. Graphical Patient Profile - Subject No. 81- 000167

Source: Patient profile was constructed using JReview9.2 with raw data from electronic datasets, NDA 205-053. Different values for normal ranges (highlighted in blue) for ALT and total bilirubin were provided in the datasets indicating the tests may have been performed at different laboratories.

Clinical Reviewers Comment: *This patient experienced an episode of hyperbilirubinemia during the study which resolved while remaining on study drug and was unlikely to have been caused by POS tablets. The hepatic function results did not meet criteria for Hy's Law.*

Hy's Law

The protocol pre-specified criteria for significant hepatic adverse effects (Hy's Law: ALT and/or AST ≥ 3X upper limit of normal (ULN) with ALK-P ≤ 2X ULN and total bilirubin ≥ 2X ULN without evidence of biliary obstruction). No subjects in the 200-mg cohort met the protocol pre-specified criteria for significant hepatic adverse effects (Hy's Law). There were three 300-mg cohort subjects that met the protocol pre-specified criteria for Hy's Law. Three of the patients had a diagnosis of acute myelocytic leukemia, AML. Subject Nos. 50/000072 and 2/000179 had unstable AML and were receiving chemotherapy. Subject No. 22/000193 had a history of treatment for hepatitis B virus infection with entecavir prior to study entry. POS tablets were discontinued during the first week of treatment in the three subjects because of concern with liver toxicity manifested by elevations in hepatic transaminases and total bilirubin levels.

Subject No. 50/000072 was a 51-year-old white male with newly diagnosed unstable AML, who developed neutropenia following chemotherapy. On (b) (6) the subject was transferred to the intensive care unit due to respiratory failure. On Day 9, he experienced a SAE of hepatotoxicity and study treatment with POS tablets was discontinued. The posaconazole trough concentration peaked at 783 ng/mL on Day 9. Hepatic transaminases peaked on Days 9-12 and then declined thereafter as follows: ALT levels at baseline were normal. On Day 9, ALT level peaked at 1583 U/L; ALT levels continued to decrease from Day 12, (841 U/L) Day 23, 96 U/L and had returned to baseline at Day 33. Total bilirubin levels were normal at baseline and peaked at Day 12, 70 µmol/L, and returned to normal at Day 33, 21µmol/L.

The following graphical patient profile for Subject No. 50/000072 summarizes the results of the patient's liver function and renal function tests throughout the trial. Different values for normal ranges (highlighted in blue) for serum ALT, AST, total bilirubin and creatinine levels were provided in the datasets indicating the tests may have been performed at different laboratories. Therefore, two sets of laboratory values for these parameters are provided in the graphical patient profile.

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Figure 10 Graphical Patient Profile - Subject No 50/000072

Source: Patient profile was constructed using JReview9.2 with raw data from electronic datasets, NDA 205-053. Different values for normal ranges (highlighted in blue) for ALT, AST and total bilirubin and creatinine were provided in the datasets indicating the tests may have been performed at different laboratories.

Clinical Reviewer's Comment: *The patient's hepatic function tests results fulfilled the criteria for Hy's Law. The elevated transaminases and bilirubin had returned to normal range by study Day 18. Hepatotoxicity cannot be attributed to POS tablets alone as the patient received treatment with multiple concomitant medications, all of which could cause hepatotoxicity; these included paracetamol, teicoplanin, piperacillin/tazobactam, and anidulafungin.*

Subject No. 2/000179, a 53-year-old white female, entered the study with a new diagnosis unstable AML and pancytopenia post AML chemotherapy. She was treated with ciprofloxacin (Day -5 to Day 2) and vancomycin (Day -1 through Day 8) for febrile neutropenia and received valacyclovir for treatment of herpes simplex virus infection (Day 2 through Day 8). Hepatic transaminases and bilirubin level began to increase on Day 6 and POS tablets were held following the Day 6 dosing. Despite discontinuation of POS tablets, hepatic transaminases rose

to higher than 10X ULN, the peak ALT was 958 U/L (Day 14) and the peak AST was 315 U/L (Day 9). The peak total bilirubin was 137 µmol/L on Day 9. Vancomycin and valacyclovir were discontinued on Day 8; however, ALT and bilirubin levels continued to rise. POS tablet treatment was discontinued on Day 9. There is no information for hepatic function tests beyond Day 14. It was reported that she recovered from worsening hepatotoxicity on Day 25. Posaconazole trough concentration peaked on Day 3 at 1,020 ng/mL.

The following graphical patient profile for Subject No. 50/000072 summarizes the results of the patient's liver function and renal function tests throughout the trial. Different values for normal ranges (highlighted in blue) for serum ALT, AST, total bilirubin and creatinine levels were provided in the datasets indicating the tests may have been performed at different laboratories. Therefore, two sets of laboratory values are provided in the graphical patient profile.

Figure 11. Graphical Patient Profile - Subject No. 2/000179

Source: Patient profile was constructed using JReview9.2 with raw data from electronic datasets, NDA 205-053. Different values for normal ranges (highlighted in blue) for ALT, AST and total bilirubin and creatinine were provided in the datasets indicating the tests may have been performed at different laboratories.

Clinical Reviewer's Comment: *This patient's hepatic function test results fulfilled the criteria for Hy's Law. Hepatic transaminases and total bilirubin continued to rise after the POS tablets were stopped but it is likely that the worsening liver function was probably due to POS tablets and side-effects of the chemotherapy regimen for AML. It is not reported if her hepatic function tests returned to baseline because the results at Day 25 are not available and the patient was withdrawn from the study. Posaconazole levels were within the expected range, Cavg > 500 ng/mL.*

Subject No. 22/000193, a 38-year-old white female with history of acute myelocytic leukemia underwent a HSCT on Day -211 and had a history of treatment for hepatitis B infection. She was hepatitis B surface antigen HBsAg (+) and became HBsAg (−) following treatment with entecavir. On study Day 1, she received POS tablets from Day 2 to 5. She developed jaundice on study Day 5, and POS tablets were discontinued on the same day. Concomitant medications included folinic acid, tacrolimus, mycophenolic acid, and ursodeoxycholic acid (Day 5 to continuing) and methylprednisolone (Day 5 to 22) for GVHD. On Day - 6, transaminase levels and total bilirubin levels were normal and on Day 1, baseline hepatic transaminase levels were elevated: serum ALT was 850 U/L, AST was 472 U/L, total bilirubin was 16 µmol/L, and alkaline phosphatase was 30 U/L. On Day 5, it was discovered that the patient had elevated transaminases and jaundice before taking posaconazole. POS tablets were discontinued on Day 5. On Day 7, the total bilirubin level was 98 µmol/L and the ALT levels peaked at 1,149 U/L. A liver biopsy on Day 18 was negative for GVHD. She was discharged on (b) (6) with improved, declining transaminases levels and total bilirubin levels, and no jaundice. It was reported that she recovered from jaundice and elevated bilirubin on Day 78.

Clinical Reviewer's Comment: *The patient's baseline hepatic transaminase levels were elevated. This patient's hepatic function test results fulfilled the criteria for Hy's Law and were probably due to hepatitis secondary to Hepatitis B virus infection and side-effects of myelosuppressive drugs. POS tablets probably exacerbated the patient's underlying hepatitis.*

The following graphical patient profile for Subject No. 22/000193 summarizes the results of the patient's liver function and renal function tests throughout the trial. Different values for normal ranges (highlighted in blue) for serum ALT, AST, total bilirubin and creatinine levels were provided in the datasets indicating the tests may have been performed at different laboratories. Therefore, two sets of laboratory values are provided in the graphical patient profile.

Figure 12. Graphical Patient Profile - Subject No. 22/000193

Source: Patient profile was constructed using JReview9.2 with raw data from electronic datasets, NDA 205-053. Different values for normal ranges (highlighted in blue) for ALT, AST and total bilirubin and creatinine were provided in the datasets indicating the tests may have been performed at different laboratories.

Cardiac Adverse Effects

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.

200-mg Dose Cohort

No subjects in the 200-mg dose cohort met the protocol pre-specified criteria for QTc interval prolongation.

300-mg Dose Cohort

Cardiac TEAEs were reported by 11 (5%) subjects, 3 subjects had congestive cardiac failure (Subject Nos. 10/000043, 13/000080, and 80/000149). One subject experienced bradycardia, two had QTc interval prolongation and eight had cardiac failure. Four (2%) of these subjects experienced severe or life-threatening cardiac TEAEs (Subject Nos. 9/000209, 13/000059, 13/000080, and 17/000170).

Two cardiac events (Subject No. 13/000080 and Subject No. 17/000170) were reported as SAEs, led to drug discontinuation and death. Subject 13/000080 died from "rhythmogenic cardiac failure" and Subject No. 17/000170 had myocardial ischemia, pulmonary edema, and cardiac failure.

Table 12. Treatment-Emergent Adverse Events in Posaconazole – 300-mg Dose Cohort; All Treated Subjects (N=210)

Cardiac Disorders	No. of Subjects
Bradycardia	1
Cardiac failure	3
Congestive cardiac failure	3
Cardiopulmonary failure	1
Left ventricular failure	1
ECG: QTc interval prolonged	2
Subjects reporting any adverse event	11 (5%)

Source: Adapted from Table 12-41, of Study Report, P05615

Cardiac Adverse Events Probably Related to Posaconazole

Two subjects (Subject Nos. 4/000041 and 24/000108) had cardiac treatment-emergent adverse events that were probably or possibly related to study therapy. All patients were asymptomatic and one patient (24/000108) was discontinued from therapy.

Subject No. 24/000108, a 47-year-old white female with newly diagnosed unstable AML, received POS tablets from Days 2 to 7. The subject experienced ECG QTc prolongation > 500 msec and moderate sinus bradycardia diagnosed on ECG that began on Day 7 and ended on Day 10. Both of these events were probably related to POS tablets and treatment was discontinued on

Day 7. The QT/QTcB/QTcF on ECG (Day8) was 509 msec/437 msec/460 msec, respectively, with a ventricular rate of 44. Posaconazole trough concentration peaked at 811 ng/mL on Day 3.

Subject No. 4/000041, a 36-year-old white male with AML completed 14 days of POS tablets. He experienced asymptomatic bradycardia that began one day post treatment on Day 15 and ended on Day 16 (1 day duration). The posaconazole concentration (Cmax) peaked at 1890 ng/mL on Day 8.

Subject No. 9/000209, a 64-year-old male with AML, and a history of coronary artery disease was reported to have three episodes of QTc interval prolongation diagnosed on ECG between Day 21 and Day 31. On Day 1 prior to study therapy, the following QT readings were recorded: QT/QTcB/QTcF values of 385 msec/441 msec/421 msec. The QTc interval prolongation was never more than 448 msec and the ECG readings did not fulfill the predefined criteria for QTc interval prolongation. The posaconazole trough concentration peaked at 1690 ng/mL on Day 22. The subject completed 28 days of study therapy.

Clinical Reviewer's Comment: *An evaluation of effect on QT interval was not conducted for POS tablets. 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.*

Metabolic/Adrenal Disorders - 300-mg Dose Cohort

Metabolic TEAEs were the second most common TEAE of special interest reported for subjects in the study. Hypokalemia was commonly reported in 46/210 (22%) of subjects. These events were not reported as SAEs, and none led to discontinuation of study drug. The most common (≥ 5%) adrenal or metabolic TEAEs were hypokalemia (46 [22%] subjects) and hypocalcemia (13 [6%] subjects).

Table 13. Metabolic/Adrenal Disorders - 300 mg Dose Cohort

Endocrine Disorders, Preferred term	Number of subjects n, % of 300-mg cohort	Severe, life-threatening
Adrenal insufficiency	1 (<1)	1
Hyperkalemia	1 (<1)	0
Hypocalcemia	13 (6)	1
Hypokalemia	54 (22)	8
Hyponatremia	4 (2)	2
All adverse Reactions	66 (31)	12 (6%)

Source: Adapted from Table 12-43 in study report, P05615.

One subject was reported to have a TEAE of adrenal insufficiency, Subject No. 4/000202, a 31-year-old white female, with a history of recurrent T-Cell lymphoma, who underwent a HSCT with subsequent gastric GVHD. The subject also had a history of CMV viremia treated with valacyclovir and gancyclovir. She was treated with methotrexate and cyclosporine for gastric GVHD. She received an IV bolus of methylprednisolone on Day -6 with subsequent oral prednisone taper from Day -6 through Day 12. Prednisone was discontinued after Day 12. On (b) (6), she experienced an SAE of loss of consciousness and was hospitalized. On Day 21, she underwent ACTH testing with evidence of adrenal insufficiency and was resumed on a maintenance dose of corticosteroids (hydrocortisone 30 mg daily from Day 23 continuing through the end of the study period). The event of adrenal insufficiency was reported as ongoing at the end of the study. No action was taken with regard to POS tablets. Her sodium level at baseline was within normal limits (137 mmol/L) but fell to 130 mmol/L on Day 22. On Day 27, sodium returned to normal (138 mmol/L) and remained stable through the last visit on Day 35. The subject's posaconazole trough concentration peaked at 1320 ng/mL on Day 16.

Hypersensitivity

Symptoms associated with possible hypersensitivity reactions are summarized in the following table. Hypersensitivity TEAEs were reported for 17 (8%) subjects.

Table 14. Hypersensitivity Treatment-Emergent Adverse Events - 300-mg Dose Cohort

Decoded MedDRA Body system/Organ class	Decoded MedDRA preferred term	POS 300 mg QD
GENERAL DISORDERS	FACE OEDEMA	1 (0.5%)
	DRUG HYPERSENSITIVITY	2 (1%)
IMMUNE SYSTEM DISORDERS	BRONCHOSPASM	3 (1%)
	DRUG ERUPTION	1 (0.5%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	RED MAN SYNDROME	1 (0.5%)
	SKIN EXFOLIATION	1 (0.5%)
	SKIN REACTION	1 (0.5%)
	TOXIC SKIN ERUPTION	1 (0.5%)
	URTICARIA	6 (3%)
	Subjects	17/210 (8%)

Two (Subject Nos. 41/000122 and 48/000143) experienced severe hypersensitivity TEAEs. The hypersensitivity reaction experienced by Subject No. 41/000122, reported as a SAE, was related to vancomycin and not to POS tablets and is not further discussed. Subject No. 48/000143 completed 24 days of POS tablets treatment. This patient developed urticaria on study Day 2 which lasted 24 hours. Hepatic enzymes and serum creatinine were within the normal ranges throughout the trial. The patient had an average C_{min} value > 3650 ng/mL and < 3750 ng/mL concentration of posaconazole during the trial.

Seven patients developed urticaria, in the 300-mg dose group and two patients experienced other skin disorders, skin exfoliation, and "toxic skin eruption". Two patients discontinued posaconazole and one of them withdrew consent. These cases are summarized in Table 15.

Table 15. Hypersensitivity - Dermatologic Manifestations - POS Tablet - 300-mg Dose Cohort

Subject No.	Type of Skin Reaction / Study Day Start	POS Discontinued *(yes/no)*	Length of POS treatment
48/000143	Urticaria / Day 2	No	POS x 24 days
2/000039	Urticaria / Day 9	No	Withdrew consent, Day 12
50/000094	Toxic Skin Eruption / Day 17	No	POS x 23 days
31/000093	Urticaria / Day 1	No	POS x 21 days
34/000130	Urticaria / Day 5	No	POS x 21 days
48/000116	Urticaria / Day 2	No	POS x 20 days
48/000143	Urticaria / Day 1	No	POS x 24 days
64/000226	Urticaria / Day 9	No	POS x 27 days
4/000041	Skin Exfoliation / Day 12	No	POS x 14 days

Three subjects, Subject Nos. 2/000039, 50/000094, and 4/000041 had a TEAE possibly related to study drug that included urticaria, a toxic skin eruption, and skin exfoliation, respectively.

Subject No. 2/000039, a 70-year-old white male with diabetes mellitus and a new diagnosis of AML, developed staphylococcal bacteremia on Day 2, and a transfusion reaction on Day 4 of the trial. He experienced hives, described as mild intensity, on the upper torso that began on Day 9 and ended on Day 10 (1 day duration). No action was taken with regard to POS tablets. The subject was treated with 50 mg of diphenhydramine PRN. The subject's posaconazole concentration peaked at 937 ng/mL on Day 2.

Subject No. 50/000094, a 26-year-old white male with a new diagnosis of AML and a history of lymphadenopathy and an erythematous rash, developed a new skin rash described as a toxic skin eruption from Day 17 to Day 22. No action was taken with regard to POS tablets. The posaconazole concentration peaked at 1230 ng/mL on Day 23.

Subject No. 4/000041, a 36-year old male, developed skin exfoliation on Day 12 and POS was stopped on Day 14. He was considered to have completed study therapy and POS study therapy was discontinued on Day 14 upon resolution of neutropenia following chemotherapy for AML. On Day 7, he had pruritus and a generalized rash; skin exfoliation began on Day 12. No location for desquamation was provided and no comment was provided regarding the etiology of the desquamation. The onset of skin exfoliation was temporally related to the resolution of neutropenia and the discontinuation of antibiotic therapy for fever and prophylaxis of fever. The

pruritis resolved on Day 10 and the rash resolved on Day 22 (8 days post-treatment with POS tablets) after treatment with diphenhydramine, glaxal base, and hydrocortisone. On Day 15 (1 day post-treatment with POS tablets) to ongoing, increased ALT and AST levels were reported of severe intensity and were considered possibly related to POS tablets. He also experienced asymptomatic bradycardia which is discussed in the section on Cardiac Effects. The posaconazole concentration peaked at 1890 ng/mL on Day 8.

Clinical Reviewer's Comment: *The two patients who experienced a toxic skin eruption and skin exfoliation were further evaluated by the reviewer to assess if they could have been associated with severe drug reactions. Subject No. 50/000094 developed what was described as a toxic skin eruption. The rash was described as being mild in intensity and the fact that posaconazole was continued suggests that it was not a severe skin reaction such as toxic epidermal necrolysis (TEN). Subject No. 2/000039 developed urticaria which was possibly related to POS tablets; however, urticaria resolved in 24 hours while on POS tablets. Subject No. 4/000041, had additional probable causes for his rash i.e., imipenem and/or piperacillin/tazobactam. Skin exfoliation may have been a sequel to the rash which began Day 7. The other five patients who experienced urticaria continued POS tablets; therefore it was unlikely that it was the cause of urticaria in these patients. Rash has been reported to be associated with posaconazole; 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 for posaconazole oral suspension.*

The current label for posaconazole oral suspension, NOXAFIL® and the label proposed by the sponsor includes rash in the Adverse Reactions section which is adequate based on the skin rashes described in the study report for P05615.

Gastrointestinal Adverse Reactions

Gastrointestinal (GI) disorders were reported for 148 subjects and 18 subjects experienced severe gastrointestinal adverse events. The most commonly reported gastrointestinal AEs in ≥ 10% of subjects included diarrhea (29%), nausea (27%), vomiting (13%), abdominal pain (11%), and constipation (10%). The most frequently reported treatment emergent adverse reactions (>25%) were diarrhea and nausea. In the 200-mg dose cohort, 20 subjects (100%) had a GI TEAE. The GI TEAEs in 5 subjects (25%) were probably related to study drug. Study drug discontinuation due to a GI adverse reaction occurred with 1 subject (5%) in the 200-mg cohort.

In the 300-mg dose cohort, 148 subjects (70%) had a GI TEAE, of which GI TEAEs in 54 subjects (26%) were judged to be related to study drug. Study drug discontinuation due to a GI reaction occurred with 10 subjects (5%) in the 300-mg cohort.

Age

In the 200-mg cohort (n=20), the small number of subjects in the age group of ≥65 years of age (n=3) compared to the age group of < 65 years of age (n=17) did not allow for a meaningful interpretation of TEAEs by age group.

In the 300-mg cohort (n=210), there were 35 subjects ≥ 65 years of age compared to 175 subjects in the age group of < 65 years of age. TEAEs and serious adverse events were similar in the group age ≥ 65 years of age and in younger patients. Febrile neutropenia (associated with underlying immunocompromise) and dehydration were the most common (≥ 3%) SAEs in patients ≥ 65 years of age. Febrile neutropenia was the most common (≥ 3%) SAE in patients < 65 years of age (n=175). Serious adverse reactions in patients ≥ 65 years of age are summarized in Table 16.

Table 16. Serious Adverse Reactions in Patients ≥ 65 years of age –300-mg Dose Cohort

Serious Adverse Reactions	POS 300 mg QD
FEBRILE NEUTROPENIA	3 (9%)
DEHYDRATION	1 (3%)
DIZZINESS	0
ANAEMIA	0
ACUTE MYELOID LEUKAEMIA	1 (3%)
ALLERGIC TRANSFUSION REACTION	1 (3%)
ASTHENIA	1 (3%)
BLOOD CREATININE INCREASED	1 (3%)
CARDIAC ARREST	1 (3%)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	1 (3%)
DIARRHEA	1 (3%)
KLEBSIELLA INFECTION	1 (3%)
POLYCYTHAEMIA VERA	1 (3%)
RENAL FAILURE ACUTE	1 (3%)
SEPSIS	1 (3%)
SPLENIC HAEMORRHAGE	1 (3%)
STAPHYLOCOCCAL SEPSIS	1 (3%)
STREPTOCOCCAL SEPSIS	1 (3%)
Total	18/35 (51%)

Gender

Male patients comprised 62% of the study population. Similar exposures for POS tablets were observed in male and female subjects. The overall proportion of TEAEs was higher in males than in female patients, 61% in male patients and 37% in female patients. Adverse Reactions in males and females are summarized in the following table.

Adverse reactions (MedDRA Preferred terms) where there was ≥ 2% difference in the incidence between males and female subjects are summarized in Table 17. Diarrhea, fever, and nausea were the most common side effects in both genders.

Table 17. Adverse Reactions in Males and Females by MedDRA Preferred Term

Decoded MedDRA Preferred Term	Female	Male
CATHETER SITE ERYTHEMA	4 (2%)	19 (8%)
CHEST PAIN	9 (4%)	3 (1%)
CHILLS	8 (3%)	20 (9%)
COUGH	18 (8%)	31 (13%)
DIARRHEA	34 (14%)	50 (21%)
DRY SKIN	1 (0.4%)	8 (3%)
DYSPNEA	8 (3%)	13 (6%)
EPISTAXIS	18 (8%)	24 (10%)
ERYTHEMA	6 (3%)	11 (5%)
FATIGUE	4 (2%)	14 (6%)
FEBRILE NEUTROPENIA	24 (10%)	36 (15%)
HAEMATURIA	2 (1%)	6 (3%)
HEADACHE	12 (5%)	27 (11%)
HERPES SIMPLEX	3 (1%)	7 (3%)
HYPERTENSION	10 (4%)	17 (7%)
HYPOKALAEMIA	23 (10%)	34 (14%)
HYPOTENSION	8 (3%)	12 (5%)
INSOMNIA	6 (3%)	19 (8%)
NAUSEA	33 (14%)	47 (20%)
OEDEMA PERIPHERAL	14 (6%)	24 (10%)
PETECHIAE	9 (4%)	14 (6%)
PNEUMONIA	2 (1%)	8 (3%)
PYREXIA	29 (12%)	51 (22%)
RASH	18 (8%)	29 (12%)
RENAL FAILURE	0 (0%)	7 (3%)
THROMBOCYTOPENIA	18 (8%)	26 (11%)

Race

Since less than 6% of patients in the trial were identified as non-white, analyses of adverse reactions by race would not provide meaningful comparisons. 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 Tablets

- *Excerpts from Clinical Pharmacology review by Seong Jang, Ph.D.*

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

The exposure-response relationships for safety of POS tablets were evaluated with the data from Study P05615. The exposure target was determined based upon the range of exposures achieved with the oral suspension product in safety and efficacy trials, as well as the exposure-response relationship found in earlier controlled studies of POS Oral Suspension.

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

The assessment of exposure-response relationships was performed using all subjects for whom steady-state concentrations had been determined, and combined the C_{min} PK-evaluable population for both the 200-mg and 300-mg dosing cohorts. For this analysis, subjects were included according to C_{avg}, and the incidence of reported treatment-related Treatment-Emergent Adverse Events (TEAEs) was evaluated by quartile of exposure. A total of 205 subjects were included in the analysis of the incidence of AEs by quartile of exposure. Table 18 summarizes the incidence of treatment-related TEAEs by quartile of exposure. Table 19 summarizes the most common treatment-related TEAEs (≥2% incidence) for the four quartiles by descending frequency. Within the range of exposures that have been observed in this study, there does not appear to be an association of higher posaconazole concentration with a higher incidence of a treatment-related TEAE following administration of POS Tablets.

Table 18. TEAEs by quartile of Cavg values, all Cmin PK-evaluable subjects, POS Tablets – 200-mg and 300-mg Dose Cohorts Combined

	Cavg Mean (ng/mL)	Cavg Range	No. of Subjects	No. (%) Subjects Reporting Any Adverse Event
Quartile 1	860 ng/mL	442 ng/mL to 1223 ng/mL	51	29 (57)
Quartile 2	1481 ng/mL	1240 ng/mL to 1710 ng/mL	51	19 (37)
Quartile 3	1979 ng/mL	1719 ng/mL to 2291 ng/mL	51	16 (31)
Quartile 4	3194 ng/mL	2304 ng/mL to 9523 ng/mL	52	20 (38)

Table 19. Treatment-related TEAEs by quartile of Cavg values, all Cmin PK-evaluable subjects, POS Tablets - 200-mg and 300-mg cohorts combined

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

[a]: number and incidence (%); Adverse Events are presented in decreasing frequency based upon the treatment group 'PK Evaluable Subjects'.

Subjects with Low Posaconazole Exposures (200-mg Cohort)

Three subjects in the 200-mg cohort had low exposures to posaconazole (Cavg levels <500 ng/mL) as shown in Table 20. All three subjects completed treatment with POS tablets. Treatment related adverse reactions (diarrhea and rash) were reported for one subject, Subject No. 2/000013.

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Table 20. Subjects with Low Posaconazole Exposures (200-mg Cohort)

Protocol No P05615

Subject Number	Treatment Duration (days)	Avg Cmin (ng/mL)	Cavg (ng/mL)	Primary Disease	Comments
11/000001	27	352	378	Leukemia	• No treatment-related TEAEs reported. • No IFI was reported. • The subject completed treatment.
10/000009	20	334	392	Leukemia	• No treatment-related TEAEs reported. • No IFI was reported. • The subject completed treatment.
2/000013	18	377	406	Leukemia	• Three treatment-related TEAEs reported: rash, Days 3 to 13, mild in severity; diarrhoea, Days 3 to 13, mild in severity; and tachycardia, Days 4 to 6, mild in severity. • No IFI was reported. • The subject completed treatment.

IFI=invasive fungal infection; Cavg=AUCtf/tf; TEAEs=treatment-emergent adverse events.

Source data: Section 14.4.10, [16.1.9.10.5], [16.2.1.4.1], [16.2.1.7.1], and [16.2.1.9.5].

Source: Adapted from Table 12-61, study report, P05615

Subjects with High Posaconazole Exposures (300-mg Cohort)

There were no subjects in the 300-mg Cohort with POS Cavg levels in the range of lower exposure of <500 ng/mL. Seven subjects in the 300-mg cohort had predicted Cavg (pCavg) ≥3750 ng/mL and there were an additional two subjects with pCavg levels between 3650 ng/mL and 3750 ng/mL. Six subjects completed from 22 to 29 days of treatment with POS tablets. One subject discontinued treatment on Day 8. Treatment-related adverse reactions for these subjects are summarized in Table 21.

Table 21. Subjects with High Posaconazole Exposures (300-mg Cohort)

Protocol No P05615

Subject Number	Treatment Duration (days)	Avg Cmin (ng/mL)	Predicted Cavg (ng/mL)	Primary Disease	Comments
21/000141	22	3410	3690	AML	• Treatment-related TEAEs of diarrhoea and vomiting (both mild). Treament was given for the mild vomiting, and no treatment was given for the diarrhoea. After study treatment was completed, a treatment-related TEAE of moderate increased AST was reported (Baseline, 22 U/L; Peak, 124 U/L. • The subject completed treatment.
39/000075	28	3430	3720	HSCT	• No treatment-related TEAEs reported. • .The subject completed treatment.
21/000110	28	3830	4120	HSCT	• Subject with acute Grade 1 GVHD. • No treatment-related TEAEs reported. • The subject completed treatment.
29/000128	28	5800	6130	HSCT	• Subject with chronic extensive GVHD of skin, liver, and mucosa. • Treatment-related TEAEs (all mild or moderate intensity) included the following: abdominal pain, decreased magnesium, decreased potassium, decreased calcium, decreased phosphorus, decreased heart rate, increased alkaline phosphatase, and supraventricular extrasystoles (study medication not discontinued). No treatment given for these mild or moderate AEs. • The subject completed treatment.

Subject Number	Treatment Duration (days)	Avg Cmin (ng/mL)	Predicted Cavg (ng/mL)	Primary Disease	Comments
48/000143	24	3680	3970	AML (first relapse)	• Subject with AML with neutropenia. • No treatment-related TEAEs reported. • The subject completed treatment.
36/000182	29	6450	6790	HSCT	• Subject with chronic limited GVHD. • Treatment -related TEAEs included the following: mild and moderate increased ALT (Baseline 54 U/L, Peak 213 U/L), mild AST increased (Baseline 19 U/L, Peak 38 U/L), and mild alkaline phosphatase (Baseline 110 U/L, Peak 137 U/L). • Improvement of ALT seen while continuing study medication. • The subject completed treatment.
36/000196	8	4820	5130	HSCT	• Subject with chronic limited GVHD. • Subject experienced one treatment-related TEAE of severe increased blood pressure (BP) to 170/110 (baseline 120/70) without associated symptoms on Day 8. Normal ECG. New concomitant medication of oral contraceptives. • The subject discontinued study treatment on Day 8. • Antihypertensive therapy was given on Day 8 with improvement in BP. • No other treatment-related TEAEs or cardiovascular events reported.
36/000199	28	9140	9520	HSCT	• No treatment-related TEAEs reported. • The subject completed treatment.
13/000217	28	5640	5970	HSCT	• Subject with intermittent skin GVHD. • Treatment-related TEAE of mild, intermittent nausea reported on Day 12 and was ongoing. • The subject completed treatment.

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

Source data: Section 14.4.11, [16.1.9.10.5], [16.2.2.4.1], [16.2.2.7.1], [16.2.2.9.4], and [16.2.2.9.5].

Source: Adapted from Table 12-60, study report, P05615

Clinical Reviewer's Comment: *The clinical reviewer agrees with the clinical pharmacology reviewer conclusions that within the range of exposures that have been observed in this study, there does not appear to be an association of higher posaconazole concentration with a higher*

incidence of a treatment-related TEAE following administration of POS tablets. The exposure-response analyses for safety of posaconazole oral suspension (Studies P01899 and C/I98-316) also indicated that there was no correlation between exposure and safety - see clinical pharmacology review by Seong Jang, Ph.D.

7.4 Supportive Safety Results

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

7.4.1 Common Adverse Events

In the 200-mg dose group, the most common TEAEs (40% of subjects) included diarrhea and vomiting. In the 300-mg dose cohort, the most common TEAEs (≥ 20% of subjects) included diarrhea (29%), pyrexia (28%), nausea (27%), hypokalemia (22%), and febrile neutropenia (20%). These TEAEs were also commonly reported with posaconazole oral suspension and are described in the posaconazole oral suspension USPI. Many of the common adverse events were related to underlying hematological malignancy for example, thrombocytopenia and febrile neutropenia.

Treatment-emergent adverse events (TEAE) occurring at a rate ≥ 5% in the 300-mg arm are outlined in the following table. Diarrhea, nausea, and fever were the most common TEAEs occurring in more than >25% of patients in the 300-mg dose cohort.

Table 22. Treatment Emergent Adverse Events - POS Tablets - 200-mg and 300-mg Dose Cohorts

TREATMENT EMERGENT ADVERSE EVENTS (TEAE)	POS 200 mg QD N=20	POS 300 mg QD N=210
DIARRHEA	8 (40%)	61 (29%)
PYREXIA	6 (30%)	59 (28%)
NAUSEA	4 (20%)	56 (26%)
HYPOKALAEMIA	4 (20%)	46 (22%)
FEBRILE NEUTROPENIA	7 (35%)	42 (20%)
COUGH	7 (35%)	35 (16%)
RASH	5 (25%)	34 (16%)
EPISTAXIS	6 (30%)	30 (14%)

THROMBOCYTOPENIA	7 (35%)	29 (14%)
VOMITING	8 (40%)	28 (13%)
OEDEMA PERIPHERAL	2 (10%)	33 (15%)
MUCOSAL INFLAMMATION	6 (30%)	29 (13%)
HEADACHE	4 (20%)	30 (14%)
ABDOMINAL PAIN	6 (30%)	23 (11%)
ANAEMIA	6 (30%)	22 (10%)
CHILLS	6 (30%)	22 (10%)
CONSTIPATION	7 (35%)	20 (9%)
ASTHENIA	6 (30%)	20 (9%)
HYPERTENSION	3 (15%)	23 (11%)
HYPOMAGNESAEMIA	2 (10%)	20 (9%)
CATHETER SITE ERYTHEMA	2 (10%)	20 (9%)
PETECHIAE	2 (10%)	19 (9%)
DECREASED APPETITE	4 (20%)	17 (8%)
HYPOPHOSPHATEMIA	4 (20%)	17 (8%)
NEUTROPENIA	4 (20%)	15 (7%)
DYSPNEA	2 (10%)	17 (8%)
INSOMNIA	3 (15%)	15 (7%)
HYPOTENSION	4 (20%)	13 (6%)
ALANINE AMINOTRANSFERASE INCREASED	2 (10%)	15 (7%)
PRURITUS	1 (5%)	16 (8%)
FATIGUE	2 (10%)	14 (7%)
TACHYCARDIA	2 (10%)	13 (6%)
ABDOMINAL PAIN UPPER	1 (5%)	14 (7%)
DYSPEPSIA	2 (10%)	13 (6%)
HYPOCALCEMIA	1 (5%)	13 (6%)

DIZZINESS	1 (5%)	13 (6%)
PAIN IN EXTREMITY	4 (20%)	10 (5%)
ANXIETY	0	14 (7%)
BACK PAIN	0	13 (6%)
ERYTHEMA	1 (5%)	12 (6%)
HAEMORRHOIDS	2 (10%)	11 (5%)
ASPARTATE AMINOTRANSFERASE INCREASED	0	12 (6%)
DYSURIA	1 (5%)	11 (5%)
OROPHARYNGEAL PAIN	0 (0%)	12 (6%)
CHEST PAIN	3 (15%)	8 (4%)
MOUTH HEMORRHAGE	2 (10%)	8 (4%)
DRY MOUTH	0	10 (5%)
CMV INFECTION	0 (4%)	10 (5%)

7.4.2 Laboratory Findings

Laboratory Investigations

Change from Baseline by Visit for Selected Chemistry Laboratory Parameters – 300-mg Dose Cohort

The on-treatment mean creatinine, AST, ALT, ALK-P, and total bilirubin concentrations and the changes from baseline are summarized in Table 23. Mean creatinine levels had incremental increases and decreases during treatment and were declining after the end of treatment. Mean ALT levels increased between Days 3 to 14, had incremental increases and decrease to the end of treatment, and were declining to follow-up. Mean AST levels increased incrementally between Days 3 to 8 and returned to baseline level by follow-up. Mean ALK-P levels increased between Days 3 to 21 and had incremental increases and decreases to follow-up. Mean total bilirubin levels had incremental increases and decreases during treatment and returned to baseline level by follow-up.

Table 23. Mean Concentration and Change from Baseline by Visit for Selected Chemistry Laboratory Parameters, POS Tablet - 300-mg Cohort

Protocol No. P05615

Visit	Number of Subjects, All Treated Subjects 300 mg Cohort														
	Creatinine (µmol/L)			AST (U/L)			ALT (U/L)			ALK-P (U/L)			Total Bilirubin (µmol/L)		
	n	Mean Creatinine Con	Chg from BL	n	Mean AST Con	Chg from BL	n	Mean ALT Con	Chg from BL	n	Mean ALK-P Con	Chg from BL	n	Mean TBILI Con	Chg from BL
Baseline	209	74.8	-------	208	25.8	-------	209	35.3	-------	209	78.3	-------	209	12.7	-------
Day 1	7	88.4	10.1	6	18.8	-3.2	7	24.4	-0.3	7	79.1	7.1	7	17.0	1.3
Day 3	205	79.6	4.7	197	26.6	0.5	199	36.4	0.8	204	78.6	-0.2	200	13.5	0.8
Day 8	197	79.6	4.2	192	38.7	12.3	196	57.7	21.7	197	87.0	8.0	196	15.5	3.0
Day 14	184	78.6	2.9	180	32.7	8.3	182	55.8	22.9	184	101.1	21.7	184	14.3	2.0
Day 21	162	83.7	7.7	159	31.0	6.0	162	46.3	14.4	162	102.8	24.1	162	13.0	1.0
Day 28	137	89.6	12.3	134	30.1	4.0	135	41.3	7.4	136	98.5	16.4	136	11.8	0.1
Endpoint	209	84.2	9.4	208	34.2	8.3	208	56.3	20.9	209	104.2	25.8	208	13.9	1.2
FW	165	82.6	7.2	159	25.9	-1.3	161	40.4	3.6	164	97.0	19.3	162	12.2	-0.2

ALK-P=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BL=baseline; Chg=change; Con=concentration; Endpoint= last non-missing measurement up to the last day of study treatment + 6 days; FW=follow-up; n=number of subjects.

Note: Only subjects with Baseline and at least one value post baseline are included. The maximum value is presented for each time interval.

Source Data: Section 14.8.6.5.

The following are normal ranges in serum for some of the laboratory tests submitted in the NDA. ALT: 6-43 U/L; AST: 11-36 U/L; Total bilirubin: 3-21 µmol/L; alkaline phosphatase: 44 to 147 IU/L;; Potassium: 3.4 mmol/L to 5.4 mmol/L; Sodium: 135-145 mmol/L. Note: Two sets of normal ranges for ALT, AST and total bilirubin, and creatinine were provided in the datasets indicating the tests may have been performed at different laboratories.

Source: Adapted from Table 12-51 of clinical study report, P05615.

Toxicity Grade Shift Tables for Selected Serum Electrolytes

Changes from common toxicity criteria (CTC) Grade 0, 1, or 2 at Baseline to CTC Grade 3 or 4

Changes from CTC Grade 0, 1, or 2 at baseline to CTC Grade 3 or 4 for selected serum electrolytes are summarized in Table 24. The most common grade change shift of this type occurred for hypokalemia in 26 (12%) subjects.

Table 24. Serum Electrolytes: Changes from CTC Grade 0, 1, or 2 at Baseline to CTC Grade 3 or 4 - 300-mg Dose Cohort

Laboratory Parameters - Chemistry	**Number of subjects, n/N%** **N= 210**
Hyperkalemia	6/209 (3)
Hypokalemia	26/209 (12)
Hypernatremia	0/209
Hyponatremia	6 /209(3)

N=number of subjects with a baseline value and at least one other value obtained during the treatment phase for each laboratory parameter.

Clinical Reviewer's Comment: *Hypokalemia is listed as an adverse reaction in the posaconazole oral suspension, NOXAFIL® USPI.*

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 at any point during the course of the study for ALK-P, ALT, AST, and total bilirubin concentrations are summarized in Table 25. A change from CTC Grade 0, 1, or 2 at Baseline to CTC Grade 3 or 4 occurred most frequently for ALT levels, occurring in 5% of subjects in the 300-mg dose cohort.

Table 25. Hepatic Enzymes: Changes from CTC Grade 0, 1, or 2 at Baseline to CTC Grade 3 or 4 - 300-mg Dose Cohort

Laboratory Parameters	Number of subjects, n/N(%) N= 210
Alanine aminotransferase	11/210 (5%)
Aspartate aminotransferase	4/210 (2%)
Alkaline phosphatase	1/210 (0.5%)
Total bilirubin	5/210 (2%)

AST, ALT, and Total Bilirubin

200-mg Dose Cohort

For liver function test laboratory parameters, the majority of subjects' baseline values were Grade 0, and the majority of subjects' values remained at Grade 0 throughout the study. The largest shift that occurred was a three grade shift, from Grade 0 to Grade 3, for ALK-P in 1 subject (5%). Overall, in the 200-mg dose group, the following subjects with baseline grade 0, 1 or 2 shifted to grade 3 or 4 during the treatment phase of the study: ALT: 1/20 (5%); AST: 0/20 (0%); total bilirubin: 0/20 (0%); alkaline phosphatase (ALK-P): 1/20 (5%); and hypokalemia: 5/20 (25%).

300-mg Dose Cohort

ALT and AST and total bilirubin levels remained at a baseline toxicity Grade 0 for the majority of subjects.

Table 26. Toxicity Grade Shift Table - 300-mg Dose Cohort - Alanine Aminotransferase (ALT)

Lab Parameter Description	Baseline CTC grade	0	1	2	3	4	Subjects
Alanine Aminotransferase (ALT) Highest CTC Grade	0	67(31%)	76(35%)	9(4%)	6(3%)	1(0.5%)	159(74%)
	1	0	37(17%)	6(3%)	3(1%)	1(0.5%)	47(22%)
	2	0	0	0	1(0.5%)	0	1(0.5%)
	3	0	0	0	21	0	2(1%)
	4	0	0	0	0	1(0.5%)	1(0.5%)
	Subjects	72(33%)	113(53%	15(7%)	12(6%)	3(1%)	210(100%)

Table 27. Toxicity Grade Shift Table – Aspartate Aminotransferase (AST) - 300-mg Dose Cohort

Lab Parameter Description	Baseline high CTC grade	0	1	2	3	4	Subjects
Aspartate Aminotransferase (AST) Highest CTC Grade	0	98(46%)	74(34%	7(3%)	2(1%)	1 (0.5%)	182 (85%)
	1	0	22(10%)	2(1%)	1(0.5%)	0	25 (12%)
	2	0	0	2(1%)	0	0	2 (1%)
	3	0	0	0	1(0.5%)	0	1 (0.5%)
	Subject	102(48%	97(45%)	11(5%)	4(2%)	1(0.5%)	210 (100%)

Total Bilirubin

The majority (62%) of subjects' values for total bilirubin remained at Grade 0 throughout the study. Four (2%) subjects' values for total bilirubin shifted from Grade 0 to Grade 4 in the 300-mg dose cohort.

Table 28. Toxicity Grade Shift Table - Total Bilirubin – 300-mg Dose Cohort

Lab Parameter	Baseline CTC Grade	0	1	2	3	Subjects
Total Bilirubin Highest CTC Grade	0	133 (62%)	34 (16%)	13 (6%)	4 (2%)	184 (86%)
	1	0	10 (4%)	7 (3%)	1 (0.5%)	18 (8%)
	2	0	0	8 (4%)	0	8 (4%)
	Subjects	138 (64%)	44 (20%)	28 (13%)	5 (2%)	210 (100%)

Overall, the largest shifts that occurred for ALT and AST were four grade shifts, from Grade 0 to Grade 4 in one subject. The largest shifts that occurred for ALKP and total bilirubin were three grade shifts, from Grade 0 to Grade 3; 1 subject ALK-P and 4 (2%) subjects for total bilirubin. Overall, the following subjects with baseline grade 0, 1 or 2 shifted to grade 3 or 4 during the treatment phase of the study in the 300-mg dose group: ALT: 11/210 (5%); AST: 4/210 (0%); total bilirubin: 5/210 (2%); Alkaline phosphatase (ALK-P): 1/210 (0.5%); and hypokalemia: 26/210 (12%).

Serum Creatinine

The majority (92%) of subjects' values for serum creatinine remained at Grade 0 throughout the study. One (0.5%) subject values for creatinine shifted from Grade 0 to Grade 4 in the 300mg Dose Cohort.

Table 29. Toxicity Grade Shift Table - Creatinine Levels - 300-mg Dose Cohort

Lab Parameter	Baseline CTC Grade	0	1	2	3	Subjects
Creatinine Highest CTC Grade	0	197 (92%)	44 (21%)	6 (3%)	1 (0.5%)	197 (92%)
	1	10 (5%)	12 (6%)	3 (2%)	0	12 (6%)
	2	1 (0.5%)	1 (0.5%)	1 (0.5%)	0	1 (0.5%)
	Subjects	208 (97%)	57 (27%)	10 (5%)	1 (0.5%)	210 (100%)

7.4.3 Vital Signs

Vital signs, including temperature, pulse, and blood pressure, were to be taken for all subjects at baseline (Day -7 to Day -1), Day 1, Day 2, Day 3, Day 8 (±1 day), Day 14 (±1 day), Day 21 (±1 day), Day 28 (±1 day) or EOT and at follow-up visit 1 (+7 days post completion of therapy). In the 200-mg and 300-mg dose cohorts, there were no concerning findings of vital signs (pulse rate, and blood pressure) during study treatment. Fever was reported as an adverse event in 6 (30%) and 59 (38%) subjects in the 200-mg and 300-mg dose cohorts, respectively. The patients developed neutropenic fever which was related to bacterial, viral, and a few cases of breakthrough invasive fungal infections. One patient, Subject No. 36/000196, a 40-year-old female post-HSCT in the 300-mg dose cohort, experienced a hypertensive episode on Day 8 and discontinued study treatment on Day 8.

7.4.4 Electrocardiograms (ECGs)

Azole antifungal drugs are associated with prolongation of the QTc interval which can potentially induce life-threatening ventricular arrhythmias. Subject No. 10/00062, in the 300-mg dose cohort, had at least one QTc interval measurement ≥500 msec on Day 8 during the treatment phase, and he remained asymptomatic. Subject No. 10/00062 was a 66-year-old female subject with a medical history of hypertension and left bundle branch block (LBBB) on EKG. She had an episode of QTc interval prolongation noted on EKG on Day 8 but was asymptomatic. Pretreatment (Day 1) ECG showed heart rate of 77 without LBBB, QT of 369 msec/ QTcB of

418 msec/ QTcF of 401 msec. On Day 8, ECG showed a heart rate of 102 with LBBB, QT of 420 msec/ QTcB of 549 msec/ QTcF of 502 msec. On Day 16, ECG showed a heart rate of 111 with LBBB and QT of 364 msec/ QTcB of 494 msec/ and QTcF of 464 msec.
At the last day of study drug (Day 29), the ECG showed a heart rate of 111 with LBBB, QT of 367 msec/ QTcB of 500 msec/ QTc F of 451 msec and subject remained asymptomatic. POS tablets were not discontinued, and the subject completed a 29-day course of study therapy. The subject's POS trough concentration peaked at 2070 ng/mL on Day 14.

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

Not applicable

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 2 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 P05615.
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 delayed-release tablets. Please refer to section 6, ADVERSE REACTIONS, in the posaconazole oral suspension, 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 clinical study (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)

The posaconazole tablet is not suitable for young children because they are unable to consistently swallow tablets or capsules. The formulation of the tablet also does not permit the tablet to be crushed or split; therefore, weight-based dosing is not possible. The sponsor plans to try to develop an age-appropriate oral powder formulation that corresponds to the properties of the table (b) (4)

In their pediatric plan, the sponsor proposes 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 < 13 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 October 2, 2013. The PeRC recommended that a waiver be granted for patients < 1 year old instead of two years old because cases of hematological malignancies do occur in children between the ages of 1 to 2 years of age. The PeRC also recommended that an efficacy study be requested if a pediatric dose cannot be determined in the PK study proposed by the sponsor.

Clinical Reviewer's Comment: *The applicant's plans 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 proposes enrolling pediatric patients ≥ 2 years of age but PeRC recommends that the sponsor include children ≥1 years of age which will improve enrollment and capture the youngest children with hematologic malignancies. If a pediatric dose cannot be determined then an efficacy study would be required to evaluate the safety, efficacy, and tolerability of orally administered posaconazole for the prophylaxis of invasive fungal infections (IFI) among pediatric patients with known or expected neutropenia.*

If a new age appropriate powder formulation can be developed, the current Pediatric Written Request for posaconazole oral suspension (NDA 22-003, 22-027) may need to be amended so that the new posaconazole powder formulation could be used.

Pediatric Written Request NDA 22-003

Requested studies were listed in the original Pediatric Written Request letter for NDA 22-003 dated, 2/28/2008:

Invasive Fungal Infections

Study 1: A multi-center, open-label, sequential multiple-dose escalation study to evaluate the pharmacokinetics (PK), safety, and tolerability of posaconazole following oral administration in immunocompromised pediatric patients ≥2 to <17 years of age with known or expected neutropenia.

Study 2A: A multi-center study to evaluate the safety, efficacy, and tolerability of orally administered posaconazole for the prophylaxis of invasive fungal infections (IFI) among children ≥2 to <17 years of age with known or expected neutropenia.

OR

If Study 1 fails to find a fixed dose to be used in study 2A, then study 2B will be conducted instead of study 2A

Study 2B: A comparative, double-blind, randomized, multi-center study to evaluate the safety, efficacy, and tolerability of orally administered posaconazole for the prophylaxis of invasive fungal infections (IFI) among pediatric patients with known or expected neutropenia.

Oropharyngeal Candidiasis

Study 3: A dose finding pharmacokinetic modeling and simulation study for the treatment of oropharyngeal candidiasis in immunocompromised pediatric patients ≥2 to <17 years of age.

Study 4: A pharmacokinetic and treatment study of oropharyngeal candidiasis in pediatric patients aged 2 to ≤17 years.

Study 5: An open-label pharmacokinetic and treatment study of oropharyngeal candidiasis in pediatric patients aged 0 to < 2years old.

***Clinical Reviewer's Comments**:*

1. *Study P03579 is currently in progress to address study 1 in the pediatric written request for NDA 22-003. Study P03579 is a multi-center, open-label, sequential multiple-dose escalation study to evaluate the pharmacokinetics (PK), safety, and tolerability of posaconazole oral suspension following administration in immunocompromised pediatric patients ≥2 to <17 years of age with known or expected neutropenia. The study has experienced slow recruitment over the past 4.5 years despite efforts by the sponsor to enhance enrollment and for this reason, an extension was recently granted for completion of pediatric studies for posaconazole oral suspension, NDA 22003. In 2013, extensions for submission of final reports were granted for the two PREA commitments related to prophylaxis of invasive Aspergillus and Candida infections (proposed completion date December 31, 2018) and the treatment of oropharyngeal candidiasis in pediatric patients (proposed completion date March 31, 2019).*

2. *The reviewer recommends that a waiver be granted to conduct a treatment study of posaconazole suspension for oropharyngeal candidiasis in pediatric patients, aged 0 to < 17 years old as currently outlined in the PWR letter, 2/28/2008. The reasons for this recommendation include the impracticality with regard to enrollment of pediatric patients at risk of oropharyngeal candidiasis such as children and adolescents with HIV/AIDS in the USA, the unfavorable risk/benefit ratio, particularly in immunocompetent infants with oral thrush, often a self-limiting infection which can be treated with topical nystatin if necessary, and the potential for increasing triazole resistance in Candida species due to increased use of posaconazole in the community.*

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/s/

ELIZABETH M OSHAUGHNESSY
11/06/2013

JOHN J ALEXANDER
11/07/2013