

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-003

MICROBIOLOGY REVIEW

**MICROBIOLOGY TEAM LEADER REVIEW
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: June 12, 2006

SUBMISSION: NDA # 22-003

REVIEWER: Shukal Bala, Ph.D.
Microbiology Team Leader
Division of Special Pathogen and Immunologic Drug Products
Office of Antimicrobial Products

SUBJECT: Posaconazole

Introduction and Background:

The subject of this NDA is posaconazole (SCH 56592) a triazole with activity against *Candida albicans* and *Aspergillus fumigatus*. The preclinical studies supporting the activity of posaconazole were reviewed earlier

1. The clinical microbiologic studies for the prophylaxis of invasive fungal infections in high risk patients with prolonged neutropenia or who have undergone hematopoietic stem cell transplantation were reviewed by Dr Suvarna (for details see microbiology review dated May 15, 2006). This microbiology team leader review discusses essential microbiologic findings abstracted from Dr Suvarna, Dr Goodwin and Ms. Moore's reviews relevant to the labeling.

Comments:

1. Efficacy of posaconazole as a prophylactic agent was compared to fluconazole in studies C/I98-316 and PO1899 and itraconazole in study PO1899. Please note that
 - fluconazole is approved for the
 - treatment of oropharyngeal, esophageal and vaginal candidiasis, and
 - prophylaxis to decrease the incidence of Candidiasis in patients undergoing bone marrow transplantation; whereas
 - itraconazole is approved for the
 - treatment of Aspergillosis (pulmonary and extrapulmonary) in immunocompromised and nonimmunocompromised patients, and
 - empiric therapy in febrile neutropenic patients with suspected fungal infections

The results of the clinical studies show lower number of breakthrough infections in patients treated with posaconazole compared to fluconazole (Tables 1 and 2) in studies C/I98-316 and P01899 and same as itraconazole (Table 2) in study P01899 during the primary treatment phase in evaluable population. Please note treatment duration varied from 1 to ≥ 120 days (mean: 80 days ~ posaconazole and 77 days ~

fluconazole). However, similar observations were made in all treated subjects in both the studies while patients were on therapy (Tables 3 and 4). A majority of the breakthroughs were due to *Aspergillus* or *Candida* species in patients treated with posaconazole or comparators (for details see Microbiology review by Dr Suvama dated 5/15/06 and Medical officer review by Dr Maureen Tierney). There were fewer breakthroughs due to *Aspergillus* in patients administered posaconazole compared to fluconazole and same as subjects administered itraconazole. Overall, the numbers of breakthrough infections were small in all the groups.

Table 1: Pathogen group associated with proven (proven + probable) invasive fungal infections during the primary treatment phase (i.e., 16 weeks) in the evaluable population in randomized double-blind study C/198-316.

Species	Posaconazole	Fluconazole
<i>Aspergillus fumigatus</i>	0 (0)	2 (5)
<i>Aspergillus flavus</i>	0 (0)	2 (2)
<i>Aspergillus terreus</i>	0 (0)	0 (1)
<i>Aspergillus niger</i>	0 (0)	1 (1)
<i>Aspergillus species</i>	0 (4)	1 (8)
<i>Aspergillus</i> species Total	0 (4)	6 (17)
<i>Candida albicans</i>	0 (0)	0 (0)
<i>Candida glabrata</i>	2 (2)	1 (1)
<i>Candida krusei</i>	1 (1)	0 (0)
<i>Candida parapsilosis</i>	0 (0)	0 (0)
<i>Candida species</i>	0 (0)	0 (0)
<i>Candida</i> species Total	3 (3)	1 (1)
<i>Rhizomucor miehei</i>	0 (0)	1 (1)
<i>Pseudoallescheria boydii</i>	1 (1)	0 (0)
<i>Scedosporium prolificans</i>	1 (1)	0 (0)
<i>Trichosporon biegelii</i>	1 (1)	0 (0)
Other mold	0 (0)	1 (1)
Other fungal species Total	3 (3)	2 (2)
Total	6 (10)	9 (20)

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Table 2: Pathogen group associated with proven (proven + probable) invasive fungal infections during treatment (maximum period 12 weeks) in the evaluable populations in a randomized open label evaluator blinded study P01899

Species	Posaconazole	Fluconazole	Itraconazole
<i>Aspergillus fumigatus</i>	0 (0)	0 (1)	0 (1)
<i>Aspergillus flavus</i>	0 (0)	0 (2)	0 (0)
<i>Aspergillus</i> species	0 (2)	1 (11)	0 (4)
<i>Aspergillus</i> species Total	0 (2)	1 (14)	0 (5)
<i>Candida glabrata</i>	2 (2)	1 (1)	0 (0)
<i>Candida krusei</i> + <i>Candida parapsilosis</i>	0 (0)	1 (1)	0 (0)
<i>Candida tropicalis</i> + mold	1 (1)	0 (0)	0 (0)
<i>Candida</i> species + mold	0 (1)	0 (0)	0 (0)
<i>Candida</i> species Total	3 (4)	2 (2)	0 (0)
<i>Rhizomucor arrhizus</i>	0 (0)	1 (1)	0 (0)
<i>Pseudoallescheria boydii</i>	0 (0)	1 (1)	0 (0)
<i>Pneumocystis carinii</i>	1 (1)	0 (0)	0 (1)
Other fungal species Total	1 (1)	2 (2)	0 (1)
Total	4 (7)	5 (18)	0 (6)

Table 3: Pathogen group associated with proven (proven + probable) invasive fungal infections while on treatment in the all treated population in a randomized double-blind study C/198-316.

Species	Posaconazole	Fluconazole
<i>Aspergillus fumigatus</i>	0 (0)	3 (6)
<i>Aspergillus flavus</i>	0 (0)	2 (2)
<i>Aspergillus terreus</i>	0 (0)	0 (1)
<i>Aspergillus niger</i>	0 (0)	0 (0)
<i>Aspergillus</i> species	0 (3)	2 (8)
<i>Aspergillus</i> species Total	0 (3)	7 (17)
<i>Candida albicans</i>	1 (1)	1 (1)
<i>Candida glabrata</i>	0 (0)	1 (1)
<i>Candida krusei</i>	0 (0)	1 (1)
<i>Candida parapsilosis</i>	0 (0)	0 (0)
<i>Candida</i> species	0 (0)	0 (0)
<i>Candida</i> species Total	1 (1)	3 (3)
<i>Rhizomucor miehei</i>	0 (0)	1 (1)
<i>Pseudoallescheria boydii</i>	1 (1)	0 (0)
<i>Scedosporium prolificans</i>	0 (0)	0 (0)
<i>Trichosporon biegelii</i>	1 (1)	0 (0)
Other mold	1 (1)	1 (1)
Other fungal species Total	3 (3)	2 (2)
Total	4 (7)	12 (22)

Table 4: Pathogen group associated with proven (proven + probable) invasive fungal infections while on treatment in all treated populations in a randomized open label evaluator blinded study P01899

Species	Posaconazole	Fluconazole	Itraconazole
<i>Aspergillus fumigatus</i>	0 (0)	0 (1)	0 (1)
<i>Aspergillus flavus</i>	0 (0)	0 (2)	0 (0)
<i>Aspergillus</i> species	0 (2)	1 (12)	0 (4)
<i>Aspergillus</i> species Total	0 (2)	1 (15)	0 (5)
<i>Candida glabrata</i>	2 (2)	1 (1)	0 (0)
<i>Candida krusei</i> + <i>Candida parapsilosis</i>	0 (0)	1 (1)	0 (0)
<i>Candida tropicalis</i> + mold	1 (1)	0 (0)	0 (0)
<i>Candida</i> species + Mold	0 (1)	0 (0)	0 (0)
<i>Candida</i> species Total	3 (4)	2 (2)	0 (0)
<i>Rhizomucor arrhizus</i>	0 (0)	1 (1)	0 (0)
<i>Pseudoallescheria boydii</i>	0 (0)	1 (1)	0 (0)
<i>Pneumocystis carinii</i>	1 (1)	0 (0)	0 (1)
Other fungal species Total	1 (1)	2 (2)	0 (1)
Total	4 (7)	5 (19)	0 (6)

Similar observations were made at the follow up visits in both studies C/198-316 and P01899 (Tables 5 and 6), however the numbers were very small.

Table 5: Pathogen group associated with proven (proven + probable) invasive fungal infections during the post-treatment (follow-up) phase in the evaluable population in randomized double-blind study C/198-316.

Species	Posaconazole	Fluconazole
<i>A. fumigatus</i>	0 (0)	1 (4)
<i>Aspergillus</i> species	0 (2)	1 (4)
<i>Aspergillus</i> species Total	0 (2)	2 (8)
<i>Candida</i> species	0 (0)	1 (1)
Mold	0 (0)	0 (1)
Total	0 (2)	3 (10)

Table 6: Pathogen group associated with proven (proven + probable) invasive fungal infections during the post-treatment (follow-up) phase in the evaluable population in randomized double-blind study P01899.

Species	Posaconazole	Fluconazole	Itraconazole
<i>A. flavus</i>	0 (0)	1 (1)	0 (0)
<i>Aspergillus</i> species	0 (1)	0 (1)	1 (1)
<i>Aspergillus</i> species Total	0 (1)	1 (2)	1 (1)
<i>Kluyveromyces maxianus</i>	1 (1)	0 (0)	0 (0)
Total	1 (2)	1 (2)	1 (1)

- Based on Medical Officer's review of oropharyngeal candidiasis (OPC) indication posaconazole appears to be active against *C. albicans* (for details see review by Dr Regina Alivistos). The Microbiology review of the clinical studies in support of OPC indication is presently under review.

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X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Shukal Bala
6/21/2006 01:17:29 PM
MICROBIOLOGIST

Renata Albrecht
6/21/2006 06:54:41 PM
MEDICAL OFFICER

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGEN AND TRANSPLANT PRODUCTS

NDA #: 22-003

REVIEWER: Kalavati Suvarna

CORRESPONDENCE DATE: 12-21-05, 02-22-06, 03-01-06,
03-17-06

CDER RECEIPT DATE: 01-04-05, 02-22-06, 03-01-06, 03-17-06

REVIEW ASSIGN DATE: 01-04-05, 02-22-06, 03-02-06, 03-18-06

REVIEW COMPLETE DATE: 05-15-06

SPONSOR: Schering Corporation
2000 Galloping Hill Road,
Kenilworth, NJ 07033.

SUBMISSION REVIEWED: N-000 (original, BI, BM)

DRUG CATEGORY: Antifungal

INDICATION: Prophylaxis of invasive fungal infections

DOSAGE FORM: Oral Suspension

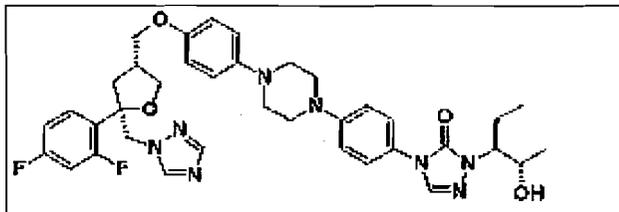
PRODUCT NAMES:

a. **PROPRIETARY:** Noxafil

b. **NONPROPRIETARY:** Posaconazole, SCH 56592.

c. **CHEMICAL:** 2,5-Anhydro-1,3,4-trideoxy-2-C-(2,4-difluorophenyl)-4-[[4-[4-[4-[1[(1S, 2S)-1-ethyl-2-hydroxypropyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazole-4-yl]phenyl]-1-piperazinyl]phenoxy]methyl]-1-(1*H*-1,2,4-triazol-1-yl)-D-*threo*-pentitol

STRUCTURAL FORMULA:



Molecular weight: 700.78

Empirical Formula: C₃₇H₄₂F₂N₈O₄

SUPPORTING DOCUMENTS: IND 51,662; _____

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1. EXECUTIVE SUMMARY

The sponsor is seeking approval of posaconazole (POS) oral suspension for the prophylaxis of invasive fungal infections (IFIs) in high-risk patients (≥ 13 years of age) with prolonged neutropenia or who have undergone hematopoietic stem cell transplantation. The sponsor has proposed a dose of 600 mg/day POS orally for the prophylaxis of IFIs. The duration of therapy will be based on recovery from neutropenia or immunosuppression.

Mechanism of action:

POS is a triazole anti-fungal compound that is chemically similar to the currently marketed triazole compounds fluconazole (FLZ), itraconazole (ITZ), and voriconazole (VRZ). The mechanism of action of POS against zygomycetes was examined in a study included in this submission and against *Candida* and *Aspergillus* species in the previous submission reviewed by Dr. Goodwin and Ms. Lynn Steele-Moore. The mechanism of action of POS is similar to other azoles in that it inhibits the lanosterol 14 α -demethylase enzyme (CYP51) involved in ergosterol biosynthesis.

Activity in vitro:

The *in vitro* activity of POS was measured against various fungal species according to the Clinical and Laboratory Standards Institute (CLSI) recommended methods (M27A2 and M38A). The *in vitro* activity of POS against yeasts and mold included in this submission were similar to that observed in studies reviewed previously.

Activity in vivo:

Drug resistance:

Candida albicans:

In drug resistance studies reviewed earlier by Dr. Goodwin and Ms Lynn Steele-Moore, prolonged exposure of *C. albicans* strain C43 to posaconazole did not alter the MICs following serial passages *in vitro*. Conversely, exposure of *C. albicans* to fluconazole resulted in changes to the fluconazole susceptibility indicated by the 16-60 fold rise in MICs in 5 of the 6 cultures. Please note that the clinical significance of these observations is not known.

In this submission, the mechanism of resistance to POS was characterized in two *Candida albicans* isolates with reduced susceptibility to azoles including POS. The mechanism of azole resistance in these isolates was due to mutations in the *ERG3* gene resulting in the inactivation of sterol $\Delta^{5,6}$ -desaturase enzyme.

In the clinical trial C/I98-316 conducted to evaluate the safety and efficacy of POS in the prophylaxis of invasive fungal infections, oral swish cultures were performed to study fungal colonization. *C. albicans* and *C. glabrata* isolates with reduced *in vitro* susceptibility (≥ 4 fold increase in MIC) to POS and other azoles were obtained after azole prophylaxis.

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Aspergillus fumigatus:

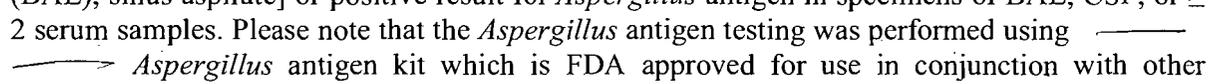
The sponsor has stated that spontaneous *A. fumigatus* laboratory mutants exhibiting a decrease in susceptibility to posaconazole arose at frequencies of 1 in 10^8 . The raw data supporting fluctuation in mutation frequency were not included for review. The laboratory mutants (POS MIC 1 to >8 $\mu\text{g/ml}$) were cross-resistant to itraconazole (MIC >16 $\mu\text{g/ml}$) and contained single amino acid substitution in the *CYP51A* gene. The clinical relevance of this finding is not known.

For a summary of *in vitro* studies evaluating cross-resistance between posaconazole and other azoles,

Drug combination:

A combination of posaconazole and amphotericin B or caspofungin was found to exhibit variable activity (antagonism, indifferent, additive or synergistic) against *A. fumigatus*, *A. flavus* and *C. albicans* *in vitro* and *in vivo*. In the absence of clinical relevance, the usefulness of including information on variable activity of drug combinations against *Aspergillus* and *Candida* in the label is not known.

Clinical microbiology:

Two studies (C/I98-316 and P01899) were included in this submission to support the prophylaxis indication. The IFI status in these studies was characterized using the EORTC - MSG standardized definitions. For proven infections, the microbiology criteria included positive culture from blood or a sterile site or histopathological evidence of hyphae from needle aspirations or biopsy samples. For probable infections, the microbiological criteria included positive culture from sites that may be colonized [for example, sputum, bronchoalveolar lavage (BAL), sinus aspirate] or positive result for *Aspergillus* antigen in specimens of BAL, CSF, or ≥ 2 serum samples. Please note that the *Aspergillus* antigen testing was performed using  *Aspergillus* antigen kit which is FDA approved for use in conjunction with other procedures such as microbiological culture or histological and radiological assessments using serum samples only. The cut-off for a positive test (an OD index of ≥ 0.5) using the FDA approved kit is lower than that used in European countries previously (OD cut-off for positive test ≥ 1.5). The lower cut-off has been stated to improve sensitivity with minimum effect on specificity. However, a recent study showed that the accuracy of the test improved with a higher threshold. It should be noted that the approved *Aspergillus* antigen test is not truly diagnostic but provides information on probability of IFIs. Positive results should be interpreted in conjunction with clinical and radiological findings as false-positive results due to presence of fungi other than *Aspergillus*, galactomannan from food, contamination from laboratory sources or administration of β -lactams are known to occur. Repeat testing of positive samples and testing of sequential serum samples for *Aspergillus* antigen is recommended by the manufacturer of the antigen detection kit. In addition to fungal culture and *Aspergillus* antigen detection, PCR testing using blood samples and *in vitro* susceptibility testing of breakthrough isolates and oral colonizers using CLSI recommended methods were performed in a central laboratory. The PCR testing was only performed for exploratory purposes and not used for diagnosis of fungal infection or fungal speciation. No correlation was observed between the PCR results and presence of galactomannan antigen or development of IFIs in the clinical studies.

Posaconazole
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In study C/I98-316, there were 20 FLZ treated patients and 10 POS treated patients who developed proven or probable IFIs during the primary treatment period (i.e., 16 weeks) in the evaluable population. In 9 patients (FLZ, n = 5; POS, n = 4) with probable infection, the diagnosis was made using *Aspergillus* antigen test. In 3 of the 9 patients, the diagnosis was based on a single test result using serum or BAL. As discussed previously, positive results should be interpreted in conjunction with clinical and radiological findings. Invasive fungal infections due to *Aspergillus* species (n = 17), *C. glabrata* (n = 1), *Rhizopus miehei* (n = 1) or unidentified mold were identified between 2 to 93 days after starting fluconazole prophylaxis. Similarly, invasive fungal infections due to *Aspergillus* species (n = 4), *C. glabrata* (n = 2), *C. krusei* (n = 1), *Pseudoallescheria boydii* (n = 1), *Scedosporium prolificans* (n = 1), *Trichosporon biegelii* (n = 1) were identified between 9 and 105 days after starting posaconazole prophylaxis. Limited *in vitro* susceptibility testing was performed on breakthrough isolates using CLSI recommended methods. The POS MICs against *Aspergillus* (n = 3) and *Candida* (n = 1) isolates were ≤ 0.125 $\mu\text{g/ml}$ while against 1 *Scedosporium* isolate, the POS MIC was 8 $\mu\text{g/ml}$.

In study P01899, 18 FLZ treated patients developed proven or probable IFIs during the oral treatment phase in the evaluable population. The majority of invasive fungal infections were due to *Aspergillus* species, *A. fumigatus* or *A. flavus* (n = 14). The remaining infections were due to *Candida* species other than *C. albicans* (n = 2), *Rhizopus arrhizus* (n = 1) or *Pseudoallescheria boydii* (n = 1). The IFIs were identified within 5 to 81 days of FLZ prophylaxis. There were 7 POS treated patients who developed proven or probable invasive fungal infections. The invasive fungal infections were due to *Aspergillus* species (n = 2), *C. glabrata* (n = 2), or mixed infections due to *Candida* species and mold (n = 2). One patient had infection due to *Pneumocystis carinii*. The invasive infections were identified on either the first day of treatment or 53 days after starting POS prophylaxis. None of the patients receiving ITZ prophylaxis developed a proven fungal infection during treatment. Six patients were identified as having probable fungal infections. Of the 6 patients, 4 had infections due to *Aspergillus* species, 1 due to *A. fumigatus* and 1 due to *Pneumocystis carinii*. Probable infections were diagnosed using the *Aspergillus* antigen test in 15 subjects (FLZ, n = 9; POS, n = 2; ITZ, n = 4). Few subjects had only one serum sample that was positive. As discussed previously, the results of the *Aspergillus* antigen test should be interpreted in conjunction with clinical and radiological findings. The baseline *in vitro* susceptibility testing was performed for 6 isolates (4 *Aspergillus* isolates and 2 *Candida* isolates). The POS MICs for all 6 isolates were ≤ 0.125 $\mu\text{g/ml}$.

Overall, the numbers of proven and probable breakthrough fungal infection were higher in FLZ and ITZ arms compared to the POS arm. Based on data from these two studies, posaconazole has the potential to prevent invasive fungal infections.

2. INTRODUCTION AND BACKGROUND

The subject of this NDA is posaconazole (POS), an azole antifungal agent for the prophylaxis of invasive fungal infections (IFIs) in high-risk patients (≥ 13 years of age) with prolonged neutropenia or who have undergone hematopoietic stem cell transplantation. The sponsor has proposed a dose of 600 mg/day POS orally (as divided doses with meals) for the prophylaxis of IFIs. The duration of therapy will be based on recovery from neutropenia or immunosuppression.

POS is a triazole anti-fungal compound. It belongs to the azole class of drugs which includes the currently marketed compounds fluconazole (FLZ), itraconazole (ITZ), and voriconazole (VRZ). In humans, the mean half-life of POS is 34.7 hours after administration of 400 mg oral suspension twice a day. POS is highly protein bound (97 to 99 %). A 2.6 to 4-fold increase in the relative bioavailability of POS is observed when a single dose of 400 mg POS is given with nonfat or high fat meal compared to fasting condition. In patients with refractory fungal infections, the mean area under the plasma concentration versus time curve (mean AUC) for POS is a third (8.6 $\mu\text{g}\cdot\text{hr}/\text{ml}$) of that observed in healthy volunteers (29.5 $\mu\text{g}\cdot\text{hr}/\text{ml}$). The mean maximum plasma drug concentration (mean C_{max}) for POS in healthy volunteers and patients is 2.9 and 0.9 $\mu\text{g}/\text{ml}$, respectively.

3. PRECLINICAL MICROBIOLOGY

For the preclinical microbiology information (mechanism of action, activity *in vitro* and *in vivo*, drug resistance, cross-resistance, and drug combinations) reviewed previously,

In this submission, the sponsor included some additional information in support of the mechanism of action, activity *in vitro*, and mechanism of resistance.

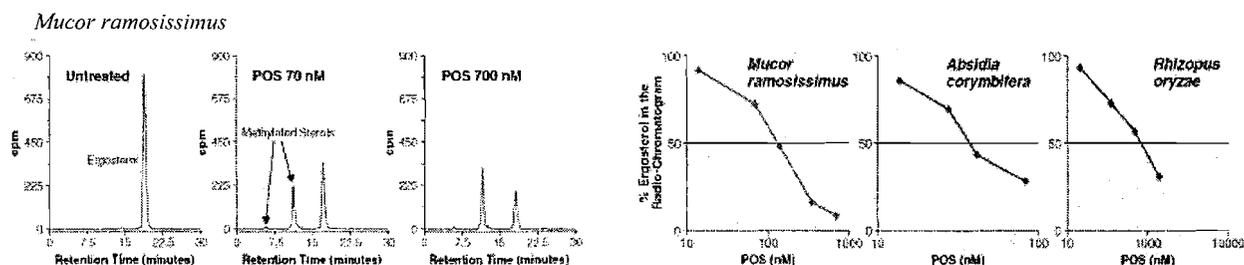
Mechanism of action:

The effect of posaconazole on sterol biosynthesis was examined in zygomycetes (study report D48627). The strains of *Absidia*, *Rhizopus* and *Rhizomucor* were labeled with [^{14}C]-acetate in the presence or absence of drug. The sterols were extracted and resolved by high performance liquid chromatography. The sterol peaks in the test samples were identified using gas chromatography and mass spectroscopy. Squalene, lanosterol, and ergosterol were used as standards. The relative amount of ergosterol in the sterol fraction was calculated by measuring the area of the peak corresponding to [^{14}C]-labeled ergosterol and expressing the value as a percentage of the total area in the radio-chromatogram. The amount of drug required to reduce the ergosterol peak by 50% (IC_{50}) was calculated. Exposure of *Absidia*, *Rhizopus* and *Rhizomucor* cells to posaconazole results in decrease of the ergosterol peak and increase in other peaks labeled as methylated sterols (Figure I). The inhibition of ergosterol synthesis was dependent on POS concentration. Please note that the chromatogram showing peak elution times for the standards were not shown for comparison. The findings in this study and those reported earlier

show that POS inhibits the synthesis of ergosterol in *Candida* species, *Aspergillus* species, and Zygomycetes.

Posaconazole
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Figure 1: Effect of posaconazole on sterol biosynthesis.



Activity in vitro:

In studies reviewed previously

, *in vitro* activity of POS was measured against various fungal species according to the Clinical and Laboratory Standards Institute (CLSI) recommended methods. *In vitro* activity was tested against 2,870 isolates of different *Aspergillus* spp., including *A. fumigatus*, *A. flavus*, *A. niger* and *A. terreus* (MIC₉₀ ≤ 1.0 µg/ml), 208 isolates of *Fusarium* spp. (MIC₉₀ 2 - 128 µg/ml), 50 isolates of *Coccidioides* spp (MIC₉₀ 1 µg/ml), 257 Zygomycetes (MIC₉₀ 0.25 - 16 µg/ml), 7370 isolates of *Candida albicans* (MIC₉₀ 0.063 µg/ml), 81 to 2106 isolates of *Candida* spp. other than *C. albicans* (MIC₉₀ 0.25 - 2 µg/ml), and 1219 *Cryptococcus* spp (MIC₉₀ 0.25 µg/ml) isolates. The *in vitro* activity of posaconazole against yeasts and mold included in this submission was similar to that observed in studies reviewed previously. Please note that the correlation between MIC and treatment outcome has not been established.

Drug Resistance:

The mechanism of resistance in two *C. albicans* clinical isolates (C410 and C655) with an MIC of > 8 µg/ml to various azoles was examined (study report D46055). Mutations in the *ERG11* (lanosterol 14α-demethylase) and *ERG3* (Δ^{5,6}-sterol desaturase) genes were determined by sequencing. Additionally, the sterols produced by these isolates were analyzed. An azole susceptible *C. albicans* isolate (C43) was used as control. The minimum inhibitory concentrations (MICs) of different azoles against the 3 isolates measured using the CLSI method M27-A is shown in Table 1. For isolate C410, no missense mutations were observed in the *ERG11* gene. For isolate C655, mutation in *ERG11* gene resulting in substitution of aspartic acid (D) at position 116 to glutamic acid (E) was observed. This mutation is also seen in azole susceptible isolate C43. Mutations resulting in introduction of a stop codon were observed in the *ERG3* gene of both C410 and C655 isolates but not in C43 isolate. The inactivation of sterol Δ^{5,6}-desaturase enzyme encoded by *ERG3* gene can prevent accumulation of methylated sterols and cause azole resistance. The major sterol identified in these isolates was stated to be ergosta-7, 22-dien-3-ol, an ergosterol precursor. However, data from the sterol analysis were not shown.

Table 1: The minimum inhibitory concentrations (MICs) of different azoles against *C. albicans* isolates

Organism	SPRI Strain #	MIC (µg/mL)				
		POS	ITZ	FLZ	VOR	AMB
<i>C. albicans</i>	C43	0.03	0.006	0.125	0.03	0.5
<i>C. albicans</i>	C665	>8	>8	>256	>16	2
<i>C. albicans</i>	C410	>8	>8	256	>16	4

4. CLINICAL MICROBIOLOGY

Two clinical studies (C/I98-316 and P01899) were included in this submission to support the prophylaxis indication. These studies are discussed in the following sections.

4.1. Study C/I98-316

This was a Phase 3, randomized, multi-center, double-blind, active control, parallel group, comparative study of POS versus FLZ in the prophylaxis of IFIs in high-risk subjects with graft versus host disease (GVHD) following allogeneic stem cell transplantation. Approximately 600 subjects from United States, Argentina, Australia, Austria, Brazil, Canada, The Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Mexico, The Netherlands, Peru, Poland, Portugal, Singapore, Saudi Arabia, South Africa, Spain, Sweden, and United Kingdom were enrolled. Protocol-eligible subjects were randomized to receive either 600 mg POS (200 mg TID), or 400 mg FLZ QD for 16 weeks or until an IFI occurred. Subjects with a history of proven or probable mold infection requiring secondary prophylaxis were excluded from study.

The primary efficacy endpoint of the study was the incidence of proven or probable IFIs within 16 weeks (112 days) of the first dose of treatment or 112 days from randomization if study drug was never taken (primary time period). For the purpose of this review, only treated patients were analyzed. Please note that the treatment duration varied from 1 to ≥ 120 days (mean duration in days = 80 for POS; 77 for FLZ). A clinical failure was defined as either the presence of a proven or probable IFI, or more than 5 days of empiric treatment with a systemic antifungal other than assigned study drug. Subjects not followed for the entire 16-week treatment phase were also considered as failures.

All subjects were followed one and two months after the 16-week treatment phase, including those subjects who developed an IFI during treatment. Subjects had periodic evaluations for the presence of fungal infection. These evaluations included signs and symptoms of infection, a physical examination, chest x-ray, chest CT scan, fungal cultures using blood, bronchoalveolar lavage (BAL), sputum, pleural fluid, or biopsy samples, if clinically indicated. Serial *Aspergillus* antigen testing and fungal PCR were also performed at a central laboratory.

Aspergillus antigen testing was performed by Dr. Paul Verweij (Netherlands) using serum, CSF, and BAL fluid. Circulating *Aspergillus* galactomannan was detected using *Aspergillus* enzyme immunoassay. Literature reports suggest that the threshold for a positive test using this kit was an optical density (OD) index of ≥ 1.5 while that of the FDA approved kit manufactured by _____ was ≥ 0.5 . Upon query regarding the differences in the two kits, the sponsor stated that _____ acquired _____ in 1999 and the two kits were the same. The kit is currently marketed as _____ *Aspergillus* antigen kit. Please note that the test kit manufactured by _____ is approved in the US for detection of antigen in serum samples only. The OD index cut-off for a positive test is ≥ 0.5 . The European Organization for Research and Treatment of Cancer (EUORTC), Invasive Fungal Infections Cooperative Group, and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG), have proposed galactomannan antigen positivity as a diagnostic criterion for invasive aspergillosis. Although galactomannan antigen detection test is FDA approved for the diagnosis of invasive aspergillosis, false positive reactions have been reported due to translocation of galactomannan antigen in food (Gangneux *et al.*, Lancet 2002,

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359:1251) and in patients receiving piperacillin/tazobactam (Adam *et al.*, Clin. Infect. Dis., 2004, 38: 917-920). Additionally, cross-reactivity due to presence of other fungi such as *Penicillium* species, *Rhodotorula* and *Paecilomyces* has been observed (Swanink *et al.*, Clin. Microbiol., 1997, 35:257-260). The usefulness of the assay for measuring drug efficacy is not known. The aspergillus antigen test results from the clinical studies were considered positive if the OD index was ≥ 0.5 despite the fact that these were multi-center trials and there were differences in European and US cut-off values for positive tests.

Fungal PCR was performed by Dr. Holger (Germany) using blood samples. Fungal PCR is an experimental method. It has not been integrated into the consensus EORTC/MSG criteria for diagnosis of probable/possible IFIs. The PCR data collected in these studies was not used for speciation of fungal isolates or adjudication of IFIs. Fungal DNA was extracted from patient's blood samples. The conserved region of the 18s rRNA gene of fungi was amplified by PCR. The PCR product was hybridized with the biotin labelled *Aspergillus fumigatus* or *Candida* spp. oligonucleotides and detected using an ELISA assay. The DSM-Strains (German Collection of microorganisms) of the medically important fungal species of *Aspergillus* (*A. fumigatus*, *A. flavus*, *A. niger*, *A. terreus*, *A. versicolor*) and *Candida* (*C. albicans*, *C. tropicalis*, *C. glabrata*, *C. krusei*, *C. parapsilosis*) were used as positive controls. The negative controls were not specified. A published report from Dr. Holger's laboratory reported a sensitivity of 100% (95% confidence interval [CI], 48 – 100%) and a specificity of 65% (95% CI, 53 – 75%) for the PCR assay in stem cell transplant patients.

Fungal susceptibility testing was done in four laboratories according to the region. However, all samples were retested in Dr. Rinaldi Laboratory (University of Texas, San Antonio). Susceptibility testing was performed according to the Clinical Laboratory Standards Institute (CLSI, previously known as National Committee for Clinical Laboratory Standards) methods. For the purpose of this review, susceptibility data collected in the central laboratory were used for analysis.

As mentioned above FDA analysis was performed on all treated patients. The modified intent-to-treat (MITT) and the evaluable subsets were also analyzed. The MITT subset was defined as subjects receiving at least one dose of study drug (capsules or suspension) and who met protocol specified criteria for acute/chronic GVHD at baseline or have sufficient levels of iatrogenic immunosuppression to consider them high-risk for IFI. The evaluable subset was defined as subjects from the MITT subset who met the entry criteria, received at least 80% of the assigned treatment based on the actual treatment duration, and did not receive concomitant medications or therapies that would confound the analysis of efficacy during the treatment phase. Figure 2 depicts the various study periods. Analysis was performed on the primary time period (i.e., 16 weeks) and post-treatment phase.

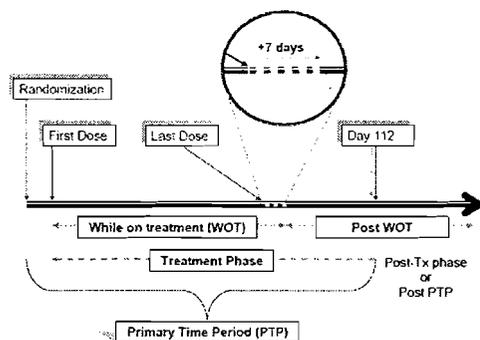


Figure 2: Study Period Diagram

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The number of patients randomized to the study and numbers in the different populations are shown in Table 2.

Table 2: The number of patients in each analysis population.

Populations (n)	Fluconazole Arm (n)	Posaconazole Arm (n)
All randomized (599)	298	301
All treated (579)	288	291
MITT (445)	234	211
Evaluable (384)	204	180

N = number of subjects

All subjects who were considered treatment failures (according to the investigator or the protocol definition of >5 days of systemic antifungal use) or who were classified by the investigator as having possible, probable, or proven IFI were referred to the Data Review Committee (DRC) for adjudication. The panel reviewed patient profiles (consisting of clinical, microbiological, and radiological data in the database) and narrative summaries (summarizing the chronology of the events, risk factors for IFI, diagnostic tests, and treatments captured in various modules of the clinical database) in order to characterize the IFI status using the EORTC - MSG standardized definitions (Tables 3 and 4).

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Table 3: EORTC - MSG standardized definitions for invasive fungal infections

EORTC ^a - MSG ^b FUNGAL CRITERIA ^c (SEPTEMBER 1998)	
PROVEN INVASIVE FUNGAL INFECTIONS	
<p>DEEP TISSUE INFECTIONS</p> <p>MOULD^d</p> <p>Histopathology showing hyphae or spherule (filamentous fungi without yeast forms) from a needle aspiration or biopsy with evidence of associated tissue damage (either microscopically or unequivocally by imaging).</p> <p style="text-align: center;">OR</p> <p>Positive culture obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection.</p>	<p>YEASTS^e</p> <p>Histopathology showing yeast cells and/or pseudohyphae from a needle aspiration or biopsy excluding mucous membranes.</p> <p style="text-align: center;">OR</p> <p>Positive culture obtained from a normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine, sputum and mucous membranes by a sterile procedure.</p> <p style="text-align: center;">OR</p> <p>Microscopy (India ink, mucicarmine stain) or antigen positivity for cryptococcus in CSF.</p>
<p>FUNGEMIA</p> <p>WOULDS^f</p> <p>Positive blood culture of fungi excluding <i>Aspergillus</i> spp. and <i>Penicillium</i> spp. other than <i>P. marneffei</i>, accompanied by temporarily related clinical signs and symptoms compatible with the relevant organism.</p>	<p>YEASTS^g</p> <p>Positive percutaneous blood culture of <i>Candida</i> and other yeasts in patients with temporarily related clinical signs and symptoms compatible with the relevant organism.</p>
<p>ENDEMIC FUNGAL INFECTIONS: histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis^h</p> <p>Either systemic or only confined to lungs, must be proven by culture from the site affected, in a host with symptoms attributed to the fungal infection. If cultures are negative or unobtainable, histopathological demonstration of the appropriate morphological forms must be combined with serological support.</p>	
<p>PROBABLE INVASIVE FUNGAL INFECTIONS</p> <p>Defined as at least one criterion from Post sector:</p> <p style="text-align: center;">AND</p> <p style="text-align: center;">one microbiological criterion</p> <p style="text-align: center;">AND</p> <p>one major (or two minor) clinical criteria from an abnormal site consistent with infection.</p>	
<p>POSSIBLEⁱ INVASIVE FUNGAL INFECTIONS</p> <p>Defined as at least one criterion from Post sector:</p> <p style="text-align: center;">AND</p> <p>one microbiological OR one major (or two minor) clinical criteria from an abnormal site consistent with infection.</p>	
<p>^a EORTC = European Organization for Research and Treatment of Cancer.</p> <p>^b Mycosis Study Group.</p> <p>^c Criteria have not yet been formally approved by the EORTC and MSG.</p> <p>^d Append identification at genus or species level if available.</p> <p>^e The POSSIBLE CATEGORY is NOT recommended for use in clinical trials on antifungal agents, but for use in studies on empirical treatment, epidemiological studies and studies on health economics when needed.</p>	

Table 4: Host factors, microbiological and clinical criteria for probable and possible invasive fungal infections.

CRITERIA FOR PROBABLE AND POSSIBLE INVASIVE FUNGAL INFECTIONS	CRITERIA FOR PROBABLE AND POSSIBLE INVASIVE FUNGAL INFECTIONS																																
<p style="text-align: center;">Host Factors</p> <ol style="list-style-type: none"> Neutropenia: PMN < 500/mm³ for more than 10 days. Persistent fever for > 96 hours refractory to appropriate broad spectrum antibacterial treatment. Body temperature either > 38°C or < 36°C AND any of the following predisposing conditions: <ol style="list-style-type: none"> Prolonged neutropenia (> 10 days) in the previous 60 days. Recent or current use of significant immunosuppressive agents in the previous 30 days. Invasive fungal infection in a previous episode. Co-existence of AIDS Signs and symptoms indicating GVHD Prolonged use of corticosteroids (> 3 weeks). 	<p style="text-align: center;">Clinical Criteria</p> <p style="text-align: center;">Should be related to the site of microbiological criteria and temporally related to current episode.</p> <table border="1" style="width: 100%;"> <thead> <tr> <th style="width: 50%;">MAJOR</th> <th style="width: 50%;">MINOR</th> </tr> </thead> </table>	MAJOR	MINOR																														
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<p style="text-align: center;">Microbiological Criteria</p> <ol style="list-style-type: none"> Positive culture of a mould (including <i>Aspergillus</i> spp., <i>Fusarium</i> spp., Zygomycetes, <i>Pseudoasarium</i> spp., <i>C. neoformans</i>) from sputum, BAL. Positive culture or cytology/direct microscopy for moulds from sinus aspirates. Positive cytology/direct microscopy for a mould or <i>Cryptococcus</i> from sputum, BAL. Positive aspergillus antigen in BAL, CSF or 22 blood samples. Positive cryptococcal antigen in blood Positive cytology/direct microscopy for fungal elements other than <i>Cryptococcus</i> in sterile body fluids. Two positive urine cultures of yeasts in the absence of urinary catheter. Candida casts in urine in the absence of urinary catheter Positive blood culture of <i>Candida</i> spp. Pulmonary abnormality and negative bacterial cultures of any possible bacteria from any specimen related to the lower respiratory tract infection including blood, sputum, BAL, etc. 	<table border="1" style="width: 100%;"> <tr> <td colspan="2" style="text-align: center;">Lower Respiratory System Infection</td> </tr> <tr> <td colspan="2">Any of the following: new infiltrate on CT imaging; halo sign; air-crescent sign or cavity within an area of consolidation.</td> </tr> <tr> <td style="width: 50%;"> <ol style="list-style-type: none"> Symptoms of LRTI (cough, chest pain, hemoptysis, dyspnea) Physical findings of pleural rub Any new infiltrate not fulfilling major criterion </td> <td style="width: 50%;"></td> </tr> <tr> <td colspan="2" style="text-align: center;">Sinonasal Infection</td> </tr> <tr> <td colspan="2">Suggestive radiological evidence of invasive infection in the sinuses (i.e. erosion of sinus walls or extension of infection to neighboring structures, extensive skull base destruction).</td> </tr> <tr> <td style="width: 50%;"> <ol style="list-style-type: none"> Upper respiratory symptoms (nasal discharge, stuffiness, etc.) Nose Ulceration or eschar of nasal mucosa or epistaxis Periorbital swelling Maxillary tenderness Black necrotic lesions or perforation of the hard-palate </td> <td style="width: 50%;"></td> </tr> <tr> <td colspan="2" style="text-align: center;">Central Nervous System Infection</td> </tr> <tr> <td colspan="2">Suggestive radiological evidence of CNS infection (i.e. meningitis extending from a perinasal, orbital or vertebral processes; intracerebral abscesses or infarcts).</td> </tr> <tr> <td colspan="2">(CSF negative for other pathogens by culture, microscopy and malignant cells)</td> </tr> <tr> <td style="width: 50%;"> <ol style="list-style-type: none"> Focal neurological symptoms and signs (including focal seizures, hemiparesis and cranial nerve palsies) Mental changes Meningeal irritation findings Abnormalities in CSF biochemistry and cell count </td> <td style="width: 50%;"></td> </tr> <tr> <td colspan="2" style="text-align: center;">Disseminated Fungal Infection</td> </tr> <tr> <td style="width: 50%;"> <ol style="list-style-type: none"> Papular or nodular skin lesions without any other explanation. Intraocular findings suggestive of hematogenous fungal chorioretinitis or endophthalmitis. </td> <td style="width: 50%;"></td> </tr> <tr> <td colspan="2" style="text-align: center;">Chronic Disseminated Candidiasis</td> </tr> <tr> <td colspan="2">Small, peripheral, target-like abscesses (Burr's eye) in liver and/or spleen demonstrated by CT, MRI or USS.</td> </tr> <tr> <td colspan="2" style="text-align: center;">Probable Candidemia</td> </tr> <tr> <td colspan="2">No prominent signs or symptoms of infection in patients with positive blood culture of <i>Candida</i>.</td> </tr> </table>	Lower Respiratory System Infection		Any of the following: new infiltrate on CT imaging; halo sign; air-crescent sign or cavity within an area of consolidation.		<ol style="list-style-type: none"> Symptoms of LRTI (cough, chest pain, hemoptysis, dyspnea) Physical findings of pleural rub Any new infiltrate not fulfilling major criterion 		Sinonasal Infection		Suggestive radiological evidence of invasive infection in the sinuses (i.e. erosion of sinus walls or extension of infection to neighboring structures, extensive skull base destruction).		<ol style="list-style-type: none"> Upper respiratory symptoms (nasal discharge, stuffiness, etc.) Nose Ulceration or eschar of nasal mucosa or epistaxis Periorbital swelling Maxillary tenderness Black necrotic lesions or perforation of the hard-palate 		Central Nervous System Infection		Suggestive radiological evidence of CNS infection (i.e. meningitis extending from a perinasal, orbital or vertebral processes; intracerebral abscesses or infarcts).		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The number of subjects with proven, probable, and possible invasive fungal infections in the different populations during the primary time period (i.e., end of 16 weeks) is shown in Table 5. As the primary endpoint of the study was incidence of proven or probable fungal infections at 16 weeks, only these infections are discussed in the following sections. In the evaluable populations, 20 FLZ treated patients developed proven or probable IFIs compared to 10 in the POS arm (Table 5). The results of *Aspergillus* antigen and PCR testing are shown in Table 6. As mentioned previously an OD index of ≥ 0.5 was considered as positive for aspergillus antigen. The antigen testing was done using serum samples for all patients except one patient where BAL fluid was tested. Five patients in the FLZ arm and 4 patients in the POS arm were considered to have probable infection based on *Aspergillus* antigen tests and clinical/radiological findings. It should be noted that 1 of 5 FLZ treated patients and 1 of 4 POS treated patients with probable infections had only one serum sample positive for aspergillus antigen (shaded rows, Table 6). In one POS treated patient, the aspergillus antigen test was positive using a single BAL sample (shown as bold, Table 6). According to the protocol, the microbiology criterion for probable IFIs is fulfilled if the aspergillus antigen test is positive using ≥ 2 serum samples or a single BAL/CSF sample. However, false-positive results have been known to occur due to inadequate sample storage, contaminating galactomannan from food or laboratory, administration of β -lactams, and other cross-reactive epitopes. Additionally, there are controversies regarding the correct threshold for a positive test as the accuracy of the test improves with a higher threshold (Rex, 2006, CID 42: 1428-1430; Pfeiffer *et al.*, 2006, CID 42: 1417-1427). Therefore, the results

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of the antigen tests should be interpreted with caution and only in conjunction with other diagnostic procedures such as microbiological culture or evidence from histological and radiological examinations. The PCR test was not used for diagnosis of fungal infections but for exploratory purposes. The results in Table 6 show that there was no correlation between a positive PCR result and occurrence of invasive fungal infections or positive culture.

In the fluconazole arm, the proven or probable invasive fungal infections were due to *Aspergillus* species (n = 17), *C. glabrata* (n = 1), *Rhizopus miehei* (n = 1) or unidentified mold (Tables 6 and 7). Invasive infections due to these pathogens were identified within 2 to 93 days after starting fluconazole prophylaxis (Table 6). In the posaconazole arm, the invasive fungal infections were due to *Aspergillus* species (n = 4), *C. glabrata* (n = 2), *C. krusei* (n = 1), *Pseudoallescheria boydii* (n = 1), *Scedosporium prolificans* (n = 1), and *Trichosporon biegelii* (n = 1). The invasive infections were identified between 9 and 105 days after starting posaconazole prophylaxis (Tables 6 and 7).

Limited *in vitro* susceptibility testing was performed on breakthrough isolates. For the purposes of this review, minimum inhibitory concentrations (MICs) reported by the central laboratory were used for analysis. The POS MICs against 3 *Aspergillus* isolates and 1 *Candida* isolate were ≤ 0.125 $\mu\text{g/ml}$. The POS MIC against 1 *Scedosporium* isolate was 8 $\mu\text{g/ml}$.

Table 5: The number of patients who developed proven, probable, or possible invasive fungal infections during primary time period (i.e. 16 weeks) in the different populations

<i>All randomized</i>		
IFIs	Fluconazole (n = 298)	Posaconazole (n = 301)
<i>Proven</i>	13	11
<i>Probable</i>	14	5
<i>Possible</i>	25	11
<i>Treated</i>		
IFIs	Fluconazole (n = 288)	Posaconazole (n = 291)
<i>Proven</i>	13	10
<i>Probable</i>	14	5
<i>Possible</i>	25	11
<i>MITT</i>		
IFIs	Fluconazole (n = 234)	Posaconazole (n = 211)
<i>Proven</i>	12	9
<i>Probable</i>	12	4
<i>Possible</i>	19	9
<i>Evaluable</i>		
IFIs	Fluconazole (n = 204)	Posaconazole (n = 180)
<i>Proven</i>	9	6
<i>Probable</i>	11	4
<i>Possible</i>	18	7

IFIs = invasive fungal infections.

Table 6. Pathogen identified as cause of invasive fungal infection during the primary treatment phase with fluconazole or posaconazole.

SubID	Treated	MITT	Evaluable	Pathogen (source**)	IFI	Treatment duration	Day of onset of IFI after first dose	MIC (µg/ml) ⁵	Aspergillus antigen result (day of result) ⁶	PCR result (day of result)
Fluconazole										
C012000006	yes	yes	yes	<i>Aspergillus flavus</i> (BAL fluid)	Proven	85	85	ND	Negative	Negative
C015000130	yes	yes	yes	<i>Aspergillus fumigatus</i> (Sputum)	Proven	115	93	ND	1 Positive (115)	Asp (50; 76; 100)
C016000083	yes	yes	yes	<i>Aspergillus niger</i> (Sphenoid sinus)	Proven	20	79	ND	Negative	Negative
C031000279	yes	yes	yes	<i>Aspergillus fumigatus</i> (BAL)	Proven	27	31	ND	1 Positive (28)	Can (-1) Asp (28)
C031000280	yes	yes	yes	<i>Aspergillus flavus</i> (Wound)	Proven	56	58	ND	3 Positive (43; 57; 63)	Asp (43)
C035000205	yes	yes	yes	Mold (Pleural fluid)	Proven	28	28	ND	Negative	Can (31; 33)
C035000220	yes	no	no	<i>Aspergillus flavus</i> (Pleural fluid)	Proven	26	84	FLZ = 64; POS = 0.06	1 Positive (78)	Asp (35; 78)
C046000260	yes	yes	no	<i>Candida krusei</i> (Blood)	Proven	36	36	FLZ = 32; POS = 0.125	Negative	Negative
C051000538	yes	yes	yes	<i>Aspergillus species</i> (bronchial washings)	Proven	14	17	ND	1 Positive (17)	Asp (-2)
1005000521	yes	yes	yes	<i>Candida glabrata</i> (esophageal biopsy)	Proven	28	31	ND	Negative	Asp (31)
1012000076	yes	yes	no	<i>Candida parapsilosis</i> (Blood)	Proven	7	30	ND	Negative	Can (-3; 10) Asp (47)
1044000600	yes	yes	no	<i>Candida albicans</i> (esophageal lesions)	Proven	2	2	ND	Negative	Negative
1045000440	yes	yes	yes	<i>Rhizomucor miehei</i> (Nasal biopsy)	Proven	60	61	ND	Negative	Asp (43)
C004000195	yes	yes	yes	<i>Aspergillus species</i>	Probable	14	18	ND	Negative	Negative
C012000014	yes	yes	yes	<i>Aspergillus fumigatus</i> (sputum and BAL)	Probable	37	37	ND	Negative	Asp (13)
C019000340	yes	yes	yes	<i>Aspergillus species</i>	Probable [#]	32	79	ND	3 Positive (72; 79; 82)	Negative
C025000034	yes	yes	yes	<i>Aspergillus species</i>	Probable ^d	57	28	ND	2 Positive (26; 28)	Negative
C046000259	yes	yes	yes	<i>Aspergillus species</i>	Probable ^d	39	38	ND	2 Positive (39)	Asp (39)
10020000868	yes	no	no	<i>Aspergillus species</i> (sputum)	Probable	113	35	FLZ = 256; POS = 0.03	2 Positive (15; 57)	Negative
1005000535	yes	yes	yes	<i>Aspergillus species</i>	Probable ^d	14	23	ND [†]	2 Positive (14; 27)	Can (-1) Asp (14; 21)
1011000740	yes	yes	yes	<i>Aspergillus species</i> (sputum)	Probable	11	14	ND	1 Positive (15)	Asp (15)
1012000071	yes	yes	yes	<i>Aspergillus species</i>	Probable ^d	45	80	ND	1 Positive (80) ^κ	Negative

^(a) the prefix number indicated number of serum samples tested; ^(b) minimum inhibitory concentration (MIC) reading after 48 hours of incubation; ND = not done; ^(c) = case report indicate multiple positive tests but results not given; Can = positive with *Candida* probe; Asp = positive with *Aspergillus* probe; ^(d) based on antigen assay; FLZ = fluconazole; POS = posaconazole; IFI = invasive fungal infections; ** source of culture

Table 6: Continued

SubID	Treated	MITT	Evaluable	Pathogen (source**)	IFI	Treatment duration	Day of onset of IFI after first dose	MIC ($\mu\text{g}/\text{ml}$) ^s	Aspergillus antigen result (day of result) [@]	PCR result (day of result)
Fluconazole										
I019000033	yes	yes	yes	<i>Aspergillus fumigatus</i> (BAL)	Probable	58	57	ND	2 Positive (43; 57)	Negative
I028000785	yes	no	no	<i>Aspergillus species</i> (sputum)	Probable	23	24	ND	Negative	Negative
I035000495	yes	yes	no	<i>Aspergillus species</i> (BAL)	Probable	6	57	ND	3 Pos (1; 16; 29)	Negative
I043000783	yes	yes	yes	<i>Aspergillus terreus</i> (lung biopsy)	Probable	80	45	ND	10 Positive (27 to 98)*	Asp (43)
I046000200	yes	yes	yes	<i>Aspergillus fumigatus</i> (BAL)	Probable	16	18	ND	2 Positive (19)*	Can (14)
Posaconazole										
C009000342	yes	yes	yes	<i>Candida krusei</i> (urine)	Proven	7	48	ND	1 Positive (42)	Asp (42)
C015000137	yes	yes	yes	<i>Pseudallescheria boydii</i> (multiple sites)	Proven	29	31	ND	Negative	Negative
C015000672	yes	yes	no	<i>Aspergillus fumigatus</i> + <i>Candida glabrata</i> (Bronchial washing)	Proven	2	18	ND	1 Positive (16)	Asp (-1; 16)
C020000120	yes	yes	no	Mold (lung biopsy)	Proven	4	9	ND	Negative	Asp (-2)
C025000022	yes	yes	yes	<i>Candida glabrata</i> (Blood)	Proven	33	75	ND	2 Positive (59; 70)	Negative
C025000030	yes	yes	yes	<i>Candida glabrata</i> (Blood)	Proven	17	14	FLZ = NA; POS = 8	Negative	ND
C035000217	no	no	no	<i>Candida species</i> (Blood)	Proven	.	20	ND	Negative	Can (7) Asp (7)
C043000516	yes	yes	no	Mold (lung biopsy)	Proven	4	104	FLZ = 64; POS = NA	Negative	Negative
I060000948	yes	no	no	<i>Aspergillus fumigatus</i> (Bronchial washing)	Proven	42	62	FLZ = NA; POS = NA	Negative	Negative
I066000618	yes	yes	yes	<i>Trichosporon hiegei</i> (Blood)	Proven	25	22	FLZ = 1.0; POS = 0.06	1 Positive (15)	Negative
I071000953	yes	yes	yes	<i>Scedosporium prolificans</i> (BAL)	Proven	14	80	ND	Negative	Asp (-1; 13)
C009000341	yes	yes	yes	<i>Aspergillus species</i>	Probable [#]	112	105	ND	3 positive (76, 105, 112)	Negative
C030000079	yes	yes	yes	<i>Aspergillus species</i>	Probable [#]	45	26	ND	1 Positive (14)	Asp (14)
I004000048	yes	yes	yes	<i>Aspergillus species</i>	Probable [#]	13	48	ND	5 Positive (35, 38, 43, 45, 49)	Asp (63; 72; 79)
I021000301	yes	no	no	<i>Aspergillus species</i> (histology lung biopsy)	Probable	66	78	ND	Negative	Asp (78)
I054000475	yes	yes	yes	<i>Aspergillus species</i>	Probable [#]	86	87	ND	1 Positive (NS)*	Asp (100; 136)

probable based on antigen test results; ** source of culture;

* 1 of positive result was using BAL sample;

[@] the prefix number indicated number of serum samples tested; \$ minimum inhibitory concentration (MIC) reading after 48 hours of incubation; ND = not done;

Can = positive with *Candida* probe; Asp = positive with *Aspergillus* probe; # based on antigen assay; FLZ = Fluconazole; POS = posaconazole; IFI = invasive fungal infections;

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Table 7: Pathogen group associated with proven and probable[^] IFIs during the primary time period (16 weeks) in the all treated and evaluable population.

Pathogen group	Fluconazole		Posaconazole	
	Treated	Evaluable	Treated	Evaluable
<i>Aspergillus fumigatus</i>	5	5	2	0
<i>Aspergillus flavus</i>	3	2	0	0
<i>Aspergillus terreus</i>	1	1	0	0
<i>Aspergillus niger</i>	1	1	0	0
<i>Aspergillus species</i>	11	8	5	4
<i>Candida albicans</i>	1	0	0	0
<i>Candida glabrata</i>	1	1	2	2
<i>Candida krusei</i>	1	0	1	1
<i>Candida parapsilosis</i>	1	0	0	0
<i>Rhizomucor miehei</i>	1	1	0	0
<i>Pseudoallescheria boydii</i>	0	0	1	1
<i>Scedosporium prolificans</i>	0	0	1	1
<i>Trichosporon biegelii</i>	0	0	1	1
Other mold	1	1	2	0
Total	27	20	15	10

[^]For probable IFIs, the species were isolated from sputum, BAL or biopsy samples.

Ten evaluable patients in the FLZ arm and 2 evaluable patients in the POS arm developed proven or probable invasive fungal infections during the post-therapy period i.e. after 16 weeks (Table 8). In the FLZ arm, the infections were due to *A. fumigatus* (n = 4), *Aspergillus* species (n = 4), *Candida* species (n = 1), and an unidentified mold in one patient. In the POS arm, the infections were due to *Aspergillus* species (n = 2). Overall, the activity of POS appears to be similar to FLZ for proven IFIs.

Table 8: Invasive fungal infections (IFIs) detected during post-treatment period in all treated patients. For probable IFIs, the species were isolated from sputum, BAL or biopsy samples.

SubID	MITT	Evaluable	Treatment	Pathogen	IFI	Treatment duration (days)	Day of onset of IFI after first dose
C012000002	no	no	Fluconazole	<i>Candida glabrata</i>	proven	116	143
C012000009	yes	no	Fluconazole	<i>Aspergillus fumigatus</i>	proven	47	120
C035000211	yes	yes	Fluconazole	<i>Aspergillus species</i>	proven	125	129
C042000497	no	no	Fluconazole	<i>Candida glabrata</i>	proven	114	172
C043000520	no	no	Fluconazole	<i>Candida glabrata</i>	proven	113	168
I015000807	yes	yes	Fluconazole	<i>Aspergillus fumigatus</i>	proven	114	113
I043000766	yes	yes	Fluconazole	<i>Candida species</i>	proven	112	135
C003000458	yes	no	Fluconazole	<i>Aspergillus species</i>	probable	1	144
C012000662	yes	yes	Fluconazole	<i>Aspergillus fumigatus</i>	probable	107	179
C043000517	yes	yes	Fluconazole	<i>Aspergillus species</i>	probable	110	132
C046000241	yes	yes	Fluconazole	Mold	probable	112	221
I020000009	yes	yes	Fluconazole	<i>Aspergillus species</i>	probable	113	145
I054000474	yes	yes	Fluconazole	<i>Aspergillus species</i>	probable	39	117
I066000617	yes	yes	Fluconazole	<i>Aspergillus fumigatus</i>	probable	112	161
I071000367	yes	yes	Fluconazole	<i>Aspergillus fumigatus</i>	probable	76	118
C017000639	no	no	Posaconazole	<i>Candida species</i>	proven	122	132
C035000207	no	no	Posaconazole	<i>Candida glabrata</i>	proven	138	165
C012000664	yes	yes	Posaconazole	<i>Aspergillus species</i>	probable	72	119
C050000419	yes	yes	Posaconazole	<i>Aspergillus species</i>	probable	114	173

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Oral swish cultures were collected during the study to evaluate fungal colonization. In subjects who received >14 days of antifungal therapy, the MICs of oral isolates of the same species obtained at baseline (defined as an isolate cultured before start of treatment or within 7 days of treatment start) and at end of treatment (EOT; defined as an isolate cultured less than 30 days before EOT or within 7 days post-EOT) were compared. The number of subjects for whom both pre- and post-treatment pathogen data were available for the FLZ and POS treatment arms were 24 and 21, respectively. In both groups, the principal pathogens were *C. albicans* and *C. glabrata* (Table 9). *C. krusei* was only detected in 4 subjects treated with FLZ. A ≥ 4 fold increase in POS MIC alone was observed in 4 *C. glabrata* isolates and 2 *C. albicans* isolates from POS treated patients compared to increases in FLZ MIC in 3 *C. glabrata* isolates and 4 *C. albicans* isolates from FLZ treated patients (Tables 9 and 10). Cross-resistance between POS and other azoles were observed in isolates from 4 subjects treated with FLZ and one subject treated with POS. The isolates exhibited a >4 fold decrease in susceptibility to all three azoles tested (POS, FLZ and ITZ) at EOT. Of the five EOT isolates, four were *C. glabrata* and one was *C. albicans*. The study suggests a potential for development of drug resistance in patients receiving POS prophylaxis and cross-resistance between azole drugs.

Table 9: Listing of susceptibilities for isolates that were the same at baseline and end of treatment (FLU = FLZ).

Site/Subject	Study Treatment	Pathogen	Source	POS BL MIC	POS EOT MIC	FLU BL MIC	FLU EOT MIC	ITR BL MIC	ITR EOT MIC	AMB BL MIC	AMB EOT MIC
C41163	FLU	Candida albicans	Mouth	0.0375	0.0675	4	5	0.0075	0.03	0.25	0.5
C41167	FLU	Candida albicans	Mouth	0.0075	0.0075	0.25	0.0625	0.0075	0.0075	0.125	0.125
C71462	FLU	Candida albicans	Mouth	0.0075	0.06	8	5	0.05	0.03	0.25	0.25
C251031	FLU	Candida albicans	Mouth	0.0375	0.0375	16	128	0.03	0.06	0.25	0.125
141042	FLU	Candida albicans	Mouth	0.0075	0.0075	0.0625	1	0.0075	0.06	0.25	0.25
141056	FLU	Candida albicans	Mouth	0.0075	0.0075	0.0625	0.0625	0.0075	0.0075	0.25	0.25
1411928	FLU	Candida albicans	Mouth	0.0075	16	0.0925	128	0.0075	16	0.125	0.5
1421668	FLU	Candida albicans	Mouth	0.0075	0.0075	0.0625	0.0625	0.0075	0.0075	0.25	0.125
1551601	FLU	Candida albicans	Mouth	0.0075	0.0075	0.0625	0.0625	0.0075	0.0075	0.125	0.125
1711354	FLU	Candida albicans	Mouth	0.0075	0.03	0.5	2	0.0075	0.03	0.25	0.25
1711955	FLU	Candida albicans	Mouth	0.03	0.03	8	4	0.05	0.125	0.25	0.25
C110002	FLU	Candida glabrata	Mouth	0.5	4	16	64	1	16	1	0.3
C151132	FLU	Candida glabrata	Mouth	0.125	0.5	8	8	0.25	1	0.25	0.25
C161092	FLU	Candida glabrata	Mouth	0.125	0.5	8	5	0.5	0.5	0.25	0.5
C421497	FLU	Candida glabrata	Mouth	0.5	2	16	32	1	8	0.25	0.5
1151807	FLU	Candida glabrata	Mouth	0.25	16	16	128	0.5	16	0.5	0.5
1231373	FLU	Candida glabrata	Mouth	15	4	128	128	4	15	0.25	0.25
1351491	FLU	Candida glabrata	Mouth	0.25	2	4	32	0.25	2	0.25	0.25
1131033	FLU	Candida krusei	Mouth	0.25	0.25	32	32	0.25	0.25	1	0.5
1431245	FLU	Candida krusei	Mouth	0.125	0.25	32	64	0.25	0.5	0.5	0.25
1431768	FLU	Candida krusei	Mouth	0.125	0.5	64	128	0.25	0.25	0.25	0.5
1541478	FLU	Candida krusei	Mouth	0.25	0.125	64	64	0.5	1	0.25	0.25
C251037	FLU	Saccharomyces cerevisiae	Mouth	0.03	0.06	0.5	0.5	0.03	0.06	0.25	0.25
1411628	FLU	Saccharomyces cerevisiae	Mouth	0.5	0.5	4	4	0.5	0.5	0.06	0.06
C41192	POS	Candida albicans	Mouth	0.03	0.03	0.5	1	0.06	0.06	0.125	0.125
C311252	POS	Candida albicans	Mouth	0.0075	0.0075	0.25	2	0.0075	0.06	0.125	0.25
1151340	POS	Candida albicans	Mouth	0.0075	0.03	0.0625	0.25	0.0075	0.0075	0.25	0.25
1211301	POS	Candida albicans	Mouth	0.0075	0.03	0.0625	0.25	0.0075	0.25	0.125	0.25
1251136	POS	Candida albicans	Mouth	0.0075	0.0075	0.25	0.0625	0.0075	0.0075	0.125	0.25

Table 10: Increase in MIC for Candida isolates in the posaconazole and fluconazole arms.

Fold increase in MIC	POS (n = 21)	FLZ (n = 24)
<i>C. albicans</i>		
≥ 4	2	4
> 4	-	3
<i>C. glabrata</i>		
≥ 4	4	3
>4	4	2

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Site/Subject	Study Treatment	Pathogen	Source	POS BL MIC	POS EOT MIC	FLU BL MIC	FLU EOT MIC	ITR BL MIC	ITR EOT MIC	AMB BL MIC	AMB EOT MIC
1221137	POS	Candida albicans	Mouth	0.03	0.03	2	4	0.05	0.25	0.25	0.25
1431664	POS	Candida albicans	Mouth	0.03	0.0075	0.0625	0.0625	0.0075	0.0075	0.125	0.125
1581641	POS	Candida albicans	Mouth	0.06	0.06	8	16	0.25	0.25	0.125	0.125
1611637	POS	Candida albicans	Mouth	0.03	0.0075	0.25	0.0625	0.05	0.0075	0.25	0.25
C41165	POS	Candida glabrata	Mouth	0.25	2	8	32	0.5	2	0.5	0.5
C71474	POS	Candida glabrata	Mouth	0.25	4	15	64	4	8	0.25	0.25
C161031	POS	Candida glabrata	Mouth	1	1	15	64	1	0.25	0.5	0.25
C251032	POS	Candida glabrata	Mouth	15	8	128	128	15	16	0.5	0.5
1321280	POS	Candida glabrata	Mouth	0.25	0.03	16	4	0.25	0.125	1	0.5
1431245	POS	Candida glabrata	Mouth	1	1	15	8	2	2	0.35	0.25
1431975	POS	Candida glabrata	Mouth	0.25	4	4	128	0.25	8	0.25	0.25
1431976	POS	Candida glabrata	Mouth	1	1	15	32	1	1	0.25	0.25
1651270	POS	Candida glabrata	Mouth	0.06	1	8	8	0.125	1	1	2
1711622	POS	Candida krusei	Mouth	0.125	0.125	32	32	0.25	0.25	0.125	0.125
C431512	POS	Saccharomyces cerevisiae	Mouth	1	4	8	32	0.5	4	0.06	0.125
1541621	POS	Saccharomyces cerevisiae	Mouth	0.5	0.5	8	4	0.5	0.5	0.06	0.015

AMB = amphotericin B; BL = baseline; EOT = end of treatment; FLU = fluconazole; ITR = itraconazole; MIC = minimum inhibitory concentration; POS = posaconazole.

Note: >4-fold increases in MIC are in bold text.

4.2. Study P01899

This was a Phase 3, randomized, evaluator-blinded, active control, parallel group, multi-center study. It was designed to assess the safety, tolerance, and efficacy of POS as a prophylactic agent against IFI in high-risk subjects with prolonged neutropenia. Subjects from United States, Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Colombia, Czech Republic, Denmark, Dominican Republic, Ecuador, El Salvador, France, Germany, Greece, Guatemala, Italy, Mexico, Netherlands, Panama, Peru, Poland, Portugal, Puerto Rico, Singapore, South Africa, Spain, Sweden, and United Kingdom were enrolled. Protocol-eligible subjects were randomized (1:1) to receive either 600 mg of POS (200 mg TID) or standard azole therapy (FLZ [400 mg QD] or ITZ [200 mg BID]). Treatment was continued until recovery from neutropenia or occurrence of an IFI for a maximal period of 12 weeks (84 calendar days) from randomization. Follow-up visits for all subjects (including those who discontinued treatment early for any reason) were to occur 30 days after the last dose of study drug or 100 days after randomization. All subjects had baseline and periodic evaluations for the presence of fungal infection as described in the previous study. As in the previous study, Dr. Rinaldi's Laboratory served as the central laboratory for fungal speciation and *in vitro* susceptibility testing while Dr. Holger's Laboratory performed the PCR testing. The *Aspergillus* galactomannan antigen testing was done by _____ (Belgium) using the FDA approved _____ *Aspergillus* antigen kit. A treatment failure was defined as the presence of a proven or probable IFI, ≥ 4 days of empiric parenteral (IV) antifungal treatment for a suspected IFI, >3 consecutive days or ≥ 10 cumulative days of IV alternative study medication during the treatment phase, or discontinuation due to an adverse event considered possibly or probably related to study drug. Subjects who withdrew from the study for any reason and were subsequently lost to follow-up during the treatment phase were also considered as treatment failures.

The number of subjects with proven, probable, and possible invasive fungal infections in the different populations during the oral treatment phase is shown in Table 11. The oral treatment duration varied from 1 to 151 days (mean treatment duration = 25 for POS; 21 for FLZ). The following discussion focuses on the primary endpoint of proven and probable infections during treatment. Proven breakthrough fungal infections were seen in 5 patients treated with FLZ and 4 patients treated with POS. No proven breakthrough fungal infections were observed in the ITZ arm. The number of probable breakthrough infections were higher in the FLZ treated patients (n = 14) compared to ITZ (n = 6) or POS (n = 3).

In the evaluable populations, 18 FLZ treated patients developed proven or probable invasive fungal infections during treatment (Table 11). In 10 patients, the diagnosis of probable infection was based on *Aspergillus* antigen or serology test results (the serology test was not specified and antibody titers were not shown) using serum samples. For 3 patients, the diagnosis was based on a single positive *Aspergillus* antigen test using serum samples. Repeat testing of the positive serum sample and testing of additional serum samples is recommended by the manufacturer of the kit. As discussed in the previous study, the results of the aspergillus antigen test should be interpreted with caution and in conjunction with other clinical and radiological findings. The PCR test was performed for exploratory reasons and not used in diagnosis of IFI. The results of the PCR test did not correlate with occurrence of invasive fungal infections or presence of galactomannan antigen (Table 12). As shown in Tables 12 and 13, the majority of proven or probable invasive fungal infections were due to *Aspergillus* species, *A. fumigatus* or *A. flavus* (n = 14), and the remaining infections were due to *Candida* species other than *C. albicans* (n = 2),

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Rhizopus arrhizus (n = 1) or *Pseudoallescheria boydii* (n = 1). Invasive infections due to these pathogens were identified within 5 to 81 days of initiating FLZ prophylaxis.

Table 11: The number of patients who developed proven, probable, or possible invasive fungal infections during treatment in the different populations.

<i>All randomized</i>			
IFIs	Fluconazole (n = 240)	Posaconazole (n = 304)	Itraconazole (n = 58)
Proven	5	4	0
Probable	14	3	6
Possible	46	59	8
<i>All treated and MITT</i>			
IFIs	Fluconazole (n = 238)	Posaconazole (n = 297)	Itraconazole (n = 54)
Proven	5	4	0
Probable	14	3	6
Possible	45	59	8
<i>Evaluable</i>			
IFIs	Fluconazole (n = 212)	Posaconazole (n = 265)	Itraconazole (n = 51)
Proven	5	4	0
Probable	13	3	6
Possible	41	55	8

IFIs = invasive fungal infections

Seven POS treated patients developed proven or probable invasive fungal infections during treatment. The invasive infections were identified on either the first day of treatment or 53 days after initiation of POS prophylaxis (Table 12). The *Aspergillus* antigen test results were used for diagnosis of probable infections in 2 out of 3 patients. In one patient, the result was based on testing of a single serum sample. As shown in Tables 12 and 13, the invasive fungal infections were due to *Aspergillus* species (n = 2), *C. glabrata* (n = 2), or mixed infections due to *Candida* species and mold (n = 2). One patient had infection due to *Pneumocystis carinii*.

None of the patients receiving ITZ prophylaxis developed a proven fungal infection during treatment. Six patients were identified as having probable fungal infections (Tables 11 and 12). The *Aspergillus* antigen test results were used for diagnosis of 4 out of 6 probable infections. In one patients, the results was based on one positive serum sample. Of the 6 patients, 4 had infections due to *Aspergillus* species, 1 due to *A. fumigatus* and 1 due to *Pneumocystis carinii* (Table 13).

During the post-treatment phase, 2 FLZ treated patients developed proven or probable IFI due to *A. flavus* or *Aspergillus* species. In the POS arm, 2 patients developed proven or probable IFIs due to *Kluyveromyces maxianus* or *Aspergillus* species. In the ITZ arm, 1 patient developed a proven infection due to *Aspergillus* species. Thus, there was no difference in the incidence of proven and probable IFIs between the treatment groups in the post-treatment phase.

The *in vitro* susceptibility testing was performed for 6 breakthrough isolates (4 *Aspergillus* isolates and 2 *Candida* isolates). The POS MICs for all 6 isolates were ≤ 0.125 $\mu\text{g/ml}$.

Overall, the activity of POS appears to be similar to FLZ for proven breakthrough infections. However, probable breakthrough infections in the POS arm were lower than that in the FLZ and ITZ arms.

Table 12: Pathogen identified as cause of invasive fungal infection during treatment with posaconazole, fluconazole or itraconazole

SubID	Treated	MITT	Evaluable	Pathogen (culture source)	IFI	Treatment duration	Day of onset of IFI after first dose	MIC at 48 hours (µg/ml)	Aspergillus antigen result (day)	PCR result (day)
Fluconazole										
0003001284	yes	yes	yes	<i>Aspergillus species</i> (small intestine)	Proven	52	52	ND	5 Positive (45-52)	Negative
0050001155	yes	yes	yes	<i>Rhizopus arrhizus</i> (Nasal tissue)	Proven	6	4	ND	Negative	Asp (1)
0057001498	yes	yes	yes	<i>Pseudallescheria boydii</i> (wound sample)	Proven	12	15	ND	Negative	Negative
0074001493	yes	yes	yes	<i>Candida glabrata</i> (blood)	Proven	27	28	ND	Negative	Negative
0148001248	yes	yes	yes	<i>Candida krusei</i> + <i>Candida parapsilosis</i> (blood)	Proven	12	10	ND	Negative	ND
0002001045	yes	yes	yes	<i>Aspergillus fumigatus</i> (BAL)	Probable	37	33	FLZ = >64 Posa = 0.125	Negative	Asp (2, 15)
0002001103	yes	yes	yes	<i>Aspergillus species</i> (NS)**	Probable	12	6	ND	4 Positive (8-14)	Negative
0002001211	yes	yes	yes	<i>Aspergillus species</i>	Probable ⁴	5	5	ND	4 Positive (1-14)	Negative
0002001307	yes	yes	yes	<i>Aspergillus species</i>	Probable ⁴	10	14	ND	6 Positive (14-38)	Asp (2)
0003001563	yes	yes	no	<i>Aspergillus species</i>	Probable ⁴	3	7	ND	6 Positive (10-30)	Negative
0008001352	yes	yes	yes	<i>Aspergillus species</i>	Probable ⁴	12	7	ND	1 Positive (7)	Negative
0041001215	yes	yes	yes	<i>Aspergillus species</i>	Probable ⁴	16	10	ND	2 Positive (13, 19)	ND
0041001242	yes	yes	yes	<i>Aspergillus flavus</i> (BAL)	Probable	18	11	FLZ = 64 Pos = 0.06	4 Positive (12-19)	ND
0041001461	yes	yes	yes	<i>Aspergillus species</i>	Probable ⁴	20	14	ND	2 Positive (10, 14)	Asp (1, 7)
0041001510	yes	yes	yes	<i>Aspergillus species</i>	Probable ⁴	10	10	ND	1 Positive (11)	Negative
0068001560	yes	yes	yes	<i>Aspergillus species</i>	Probable ⁴	12	12	ND	3 Positive (13-16)	Negative
0079001380	yes	yes	yes	<i>Aspergillus species</i>	Probable ⁴	82	81	ND	2 Positive (82, 112)	Asp (65)
0102001342	yes	yes	yes	<i>Aspergillus flavus</i> (BAL)	Probable	20	8	ND	6 Positive (10-52)	Negative
0139001081	yes	yes	yes	<i>Aspergillus species</i>	Probable ⁴	12	12	ND	1 Positive (14)	Asp (3, 16)

[#] probable based on antigen test results

⁽⁴⁾ the prefix number indicated number of serum samples tested; ⁵ minimum inhibitory concentration (MIC) reading after 48 hours of incubation; ND = not done;

Can = positive with *Candida* probe; Asp = positive with *Aspergillus* probe; ⁴ based on antigen assay; FLZ = fluconazole; POS = posaconazole; IFI = invasive fungal

infections; NS = not specified; ⁴probable infection based by serology

** diagnosis at autopsy

Shaded rows show patients with probable infection based on results from a single aspergillus antigen test.

Table 12: Continued

SubID	Treated	MITT	Evaluable	Pathogen (culture source)	IFI	Treatment duration	Day of onset of IFI after first dose	MIC (µg/ml)	Aspergillus antigen result (day)	PCR result (day)
<i>Posaconazole</i>										
0002001271	yes	yes	yes	<i>Pneumocystis carinii</i> (NS)**	Proven	45	50	ND	Negative	Negative
0015001415	yes	yes	yes	<i>Candida glabrata</i> (blood)	Proven	48	43	FLZ = 4 Pos = 0.125	Negative	Asp (42)
0041001329	yes	yes	yes	<i>Candida tropicalis</i> + mold (blood and BAL)	Proven	5	0	ND	Negative	Negative
0057001492	yes	yes	yes	<i>Candida glabrata</i> (blood)	Proven	12	7	FLZ = 8 Pos = 0.5	Negative	Can (7)
0010001371	yes	yes	yes	Mold + <i>Candida</i> species (BAL)	Probable [#]	9	10	FLZ = 4 Pos = 0.125	ND	ND
0015001239	yes	yes	yes	<i>Aspergillus</i> species	Probable [#]	54	53	ND	11 Positive (12, 92-99)	ND
0054001468	yes	yes	yes	<i>Aspergillus</i> species	Probable [#]	92	43	ND	1 Positive (43)	Asp (51, 71, 78)
<i>Itraconazole</i>										
0010001425	yes	yes	yes	<i>Aspergillus</i> species	Probable [#]	9	8	ND	2 Positive (3, 11)	Negative
0015001279	yes	yes	yes	<i>Aspergillus</i> species	Probable [#]	17	16	ND	2 Positive (17)	Asp (10)
0015001517	yes	yes	yes	<i>Aspergillus</i> species	Probable [#]	7	6	ND	16 Positive (8 to 22)	Negative
0084001179	yes	yes	yes	<i>Pneumocystis carinii</i> (BAL)	Probable	16	16	ND	Negative	Can (1), Asp (100)
0096001146	yes	yes	yes	<i>Aspergillus fumigatus</i> (NS)	Probable	19	18	FLZ = 64 Pos = 0.125	Negative	Asp (1)
0125001109	yes	yes	yes	<i>Aspergillus</i> species	Probable [#]	96	20	ND	1 Positive (21)	Asp (27, 39, 46)

probable based on antigen test results
 @ the prefix number indicated number of serum samples tested; ⁵ minimum inhibitory concentration (MIC) reading after 48 hours of incubation; ND = not done;
 Can = positive with *Candida* probe; Asp = positive with *Aspergillus* probe; [#] based on antigen assay; FLZ = fluconazole; POS = posaconazole; IFI = invasive fungal infections; NS = not specified; [^]probable infection based by serology
 ** diagnosis at autopsy
 Shaded rows show patients with probable infection based on results from a single aspergillus antigen test.

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Table 13: Pathogen group associated with proven and probable^ IFIs during treatment in the treated and evaluable population.

Pathogen group	Fluconazole		Posaconazole		Itraconazole	
	Treated	Evaluable	Treated	Evaluable	Treated	Evaluable
<i>Aspergillus fumigatus</i>	1	1	0	0	1	1
<i>Aspergillus flavus</i>	2	2	0	0	0	0
<i>Aspergillus species</i>	12	11	2	2	4	4
<i>Candida glabrata</i>	1	1	2	2	0	0
<i>Candida krusei</i> + <i>Candida parapsilosis</i>	1	1	0	0	0	0
<i>Candida tropicalis</i> + Mold	0	0	1	1	0	0
<i>Candida species</i> + Mold	0	0	1	1	0	0
<i>Rhizomucor arrhizus</i>	1	1	0	0	0	0
<i>Pseudoallescheria boydii</i>	1	1	0	0	0	0
<i>Pneumocystis carinii</i>	0	0	1	1	1	1
Total	19	18	7	7	6	6

^For probable IFIs, the species were isolated from BAL samples.

4.3. Interpretive criteria:

No interpretive criteria for *in vitro* susceptibility testing of fungi to POS have been proposed by the sponsor nor does the information provided by the sponsor support establishment of interpretive criteria.

5. CONCLUSIONS

The sponsor is seeking approval of POS for the prophylaxis of IFIs in high-risk patients (≥ 13 years of age) with prolonged neutropenia or who have undergone hematopoietic stem cell transplantation. The proposed dose is 600 mg/day POS orally (as divided doses with meals) until recovery from neutropenia or immunosuppression.

POS exhibits antifungal activity by inhibition of lanosterol 14 α -demethylase, an enzyme involved in ergosterol biosynthesis. This results in accumulation of methylated sterols. These studies were done using *Candida* species, *Aspergillus* species and Zygomycetes. The *in vitro* activity of POS against yeasts and mold was similar to that observed in studies reviewed previously

There are several mechanisms by which fungi develop resistance to azoles. These include target enzyme alterations, expression of efflux proteins, and development of compensatory pathways. Two *Candida* isolates with reduced susceptibility to azoles including posaconazole were shown to have mutations in the *ERG3* gene. The inactivation of sterol $\Delta^{5,6}$ -desaturase enzyme encoded by *ERG3* gene prevents accumulation of methylated sterols and cause azole resistance.

Two studies (C/198-316 and P01899) were included in this submission to support the prophylaxis indication. The IFI status in these studies was characterized using the EORTC - MSG standardized definitions. For proven infections, the microbiology criteria included positive culture from blood or a sterile site or histopathological evidence of hyphae from needle

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aspirations or biopsy samples. For probable infections, the microbiological criteria included positive culture from sites that may be colonized (for example, sputum, BAL fluid, sinus aspirate) or positive result for *Aspergillus* antigen in specimens of BAL, CSF, or ≥ 2 serum samples. The *Aspergillus* antigen testing was performed using the _____ *Aspergillus* antigen kit which is approved in the US for use with serum samples and in conjunction with other procedures such as microbiological culture or histological and radiological assessments. The cut-off for a positive test (an OD index of ≥ 0.5) using the FDA approved kit is lower than that used in European countries previously (OD cut-off for positive test ≥ 1.5). The lower cut-off has been stated to improve sensitivity with minimum effect on specificity. However, a recent study showed that the accuracy of the test improved with a higher threshold. Additional microbiological assessments included *in vitro* susceptibility testing of breakthrough isolates and oral colonizers using CLSI recommended methods and PCR testing in a central laboratory. The PCR testing was only performed for exploratory purposes and was not used for diagnosis of fungal infection or fungal speciation.

In study C/I98-316, there were 20 FLZ treated patients and 10 POS treated patients who developed proven or probable invasive fungal infections during the primary time period (16 weeks). In 9 patients (FLZ, n = 5; POS, n = 4) with probable infection, the diagnosis was made using *Aspergillus* antigen test. In 3 of the 9 patients, the diagnosis was based on a single test result using serum or BAL samples. It should be noted that the *Aspergillus* antigen test approved for use with serum samples in the US is not truly diagnostic but provides information on probability of IFIs. Positive results should be interpreted with caution in conjunction with clinical and radiological findings as false-positive results due to presence of fungi other than *Aspergillus*, galactomannan from food, contamination from laboratory sources or administration of β -lactams are known to occur. In the FLZ arm, the invasive fungal infections were due to *Aspergillus* species (n = 17), *C. glabrata* (n = 1), *Rhizopus miehei* (n = 1) or unidentified mold. Invasive infections due to these pathogens were identified between 2 and 93 days after starting fluconazole prophylaxis. In the POS arm, the invasive fungal infections were due to *Aspergillus* species (n = 4), *C. glabrata* (n = 2), *C. krusei* (n = 1), *Pseudoallescheria boydii* (n = 1), *Scedosporium prolificans* (n = 1), and *Trichosporon biegelii* (n = 1). The invasive infections were identified between 9 and 105 days after starting POS prophylaxis. Limited *in vitro* susceptibility testing was performed on breakthrough isolates. The POS MICs against *Aspergillus* (n = 3) and *Candida* (n = 1) isolates were ≤ 0.125 $\mu\text{g/ml}$ while POS MIC against 1 *Scedosporium* isolate was 8 $\mu\text{g/ml}$.

Oral swish cultures were performed to study fungal colonization in patients receiving prophylaxis. *Candida* isolates with reduced *in vitro* susceptibility to POS and/or other azoles were obtained after azole prophylaxis.

In study P01899, probable infections were diagnosed using the *Aspergillus* antigen test in 15 subjects (FLZ, n = 9; POS, n = 2; ITZ, n = 4). Few subjects had only one serum sample that was positive. As discussed previously, the results of the *Aspergillus* antigen test should be interpreted with caution in conjunction with clinical and radiological findings. There were 18 FLZ treated patients who developed proven or probable invasive fungal infections. The majority of invasive fungal infections were due to *Aspergillus* species, *A. fumigatus* or *A. flavus* (n = 14), and the

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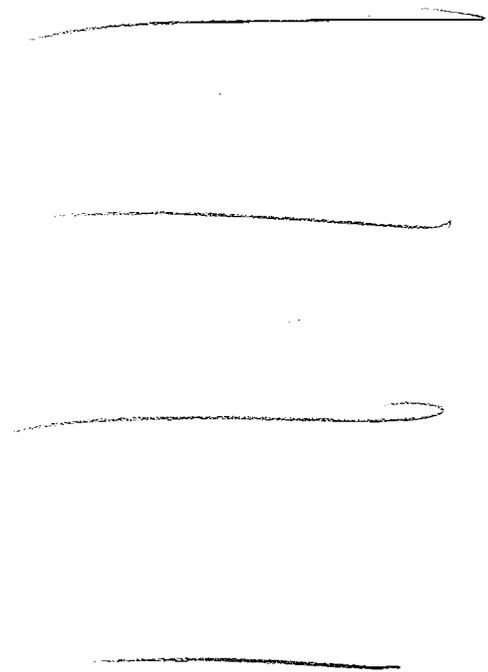
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remaining infections were due to *Candida* species other than *C. albicans* (n = 2), *Rhizopus arrhizus* (n = 1) or *Pseudoallescheria boydii* (n = 1). Invasive infections due to these pathogens were identified between 5 to 81 days after starting FLZ prophylaxis. There were 7 POS treated patients who developed proven or probable invasive fungal infections. The invasive fungal infections were due to *Aspergillus* species (n = 2), *C. glabrata* (n = 2), or mixed infections due to *Candida* species and mold (n = 2). One patient had infection due to *Pneumocystis carinii*. The invasive infections were identified on either the first day of treatment or 53 days after starting POS prophylaxis. None of the patients receiving ITZ prophylaxis developed a proven fungal infection during the treatment period. Six patients were identified as having probable fungal infections. Of the 6 patients, 4 had infections due to *Aspergillus* species, one due to *A. fumigatus* and another due to *Pneumocystis carinii*.

The *in vitro* susceptibility testing was performed for 6 breakthrough isolates (4 *Aspergillus* isolates and 2 *Candida* isolates). The POS MICs for all 6 isolates were $\leq 0.125 \mu\text{g/ml}$.

Although, a higher number of probable fungal infections were observed in FLZ and ITZ arms compared to POS arm, the numbers of proven breakthrough fungal infections were similar in the FLZ and POS arms. Overall, the activity of POS was similar to FLZ for proven IFIs in the two studies.

6. LABEL



2 Page(s) Withheld

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

2 § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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7. RECOMMENDATIONS

This NDA submission should be approved with respect to Microbiology.

Kalavati Suvarna
Microbiologist, HFD-590

CONCURRENCES:

Deputy Dir _____ Signature _____ Date _____

Micro TL _____ Signature _____ Date _____

CC:

Original IND

Division File

Review Micro

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/s/

Kalavati Suvarna
6/20/2006 03:17:04 PM
MICROBIOLOGIST

Shukal Bala
6/20/2006 03:55:54 PM
MICROBIOLOGIST