CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-027

MICROBIOLOGY REVIEW(S)

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

DATE: October 18, 2006

SUBMISSION: NDA # 22-027

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 (POS) a triazole with activity against *Candida albicans* and *Aspergillus fumigatus*. The preclinical studies supporting the activity of POS were reviewed earlier (

The clinical microbiologic studies for the (1) prophylaxis of invasive fungal infections in high risk patients with prolonged neutropenia or who have undergone hematopoietic stem cell transplantation and (2) treatment of oropharyngeal candidiasis (OPC) including OPC refractory to itraconazole (ITZ) or fluconazole (FCZ) were reviewed by Dr Suvarna [for details see microbiology reviews dated May 15, 2006 (NDA 22-003) and July 31, 2006 (NDA 22-027), respectively]. The microbiology team leader review dated June 12, 2006 discusses essential microbiologic findings abstracted from Dr Suvarna, Dr Goodwin and Ms. Moore's reviews relevant to the labeling and review of prophylaxis of invasive fungal infections in high risk patients with prolonged neutropenia or who have undergone hematopoietic stem cell transplantation. This microbiology team leader review discusses essential microbiologic findings abstracted from Dr Suvarna's review dated July 31, 2006 relevant to labeling and approval of POS for the treatment of OPC including OPC refractory to FCZ or ITZ.

Comments:

1. Four clinical studies were conducted in patients with OPC (Studies C/I97-331 and C/I96-209) including OPC refractory to ITZ or FCZ (Studies C/I97-330 and P00298). Both FCZ and ITZ are approved for the treatment of OPC. The baseline pathogen identified in a majority of the patients enrolled in all the 4 studies was *C. albicans*. Mycological evaluations included microscopic examination of oral scrapings as well as speciation and quantitative cultures of oral swish samples in central laboratory. The sponsor proposed to use a threshold of $\leq$20 cfu/ml of *Candida* species for determining mycological success. The data supporting such a threshold were not available for review. In study C/I97-331 and C/I96-209 the data on mycological success based on both negative culture and $\leq$20 cfu/ml were available for review. Use of the negative culture criteria instead of a threshold of $\leq$20 cfu/ml resulted in 9

patients in the POS arm and 10 patients in the FCZ arm being classified as mycological failures in the microbiologically evaluable per protocol population. The favorable clinical response in this population included cure as well as improvement. Relapse was observed in 1/7 patients treated with POS and 4/10 patients treated with FCZ. Based on limited information in a small number of patients it was unclear if ≤20 cfu/ml would be a good predictor for clinical cure. Therefore, for the purpose of this review a favorable microbiologic response in patients with OPC is based on complete absence of *Candida* in culture. For patients with azole refractory OPC mycologic response based on negative culture for yeast was not available.

- Studies C/I97-331 and C/I96-209 show that
  - efficacy of POS to be similar to FCZ in HIV patients with OPC.
  - POS is active against *C. albicans* (223/241, 93%). However, the number patients with *Candida* species other than *C. albicans* as the sole baseline pathogen were very small to evaluate the activity of POS.
  - superinfections due to *Candida* species other than *C. albicans* were observed during treatment. In study C/I96-209, more superinfections were reported in the high dose (POS 400 ~ mg n=10) group compared to the lower dose groups (POS 50/100 mg ~ n=4; POS 200 mg ~ n= 6; FCZ ~ 100 mg n= 13). A majority of the superinfections were due to *Candida* species other than *C. albicans*.
  - the quantitative culture data were collected at both baseline and end of treatment visits in studies C/I97-331 and C/I96-209 in a subset of patients. There is a wide range of variation in the cfu/ml in individual patients.
    - The results from study C/I97-331 (n=97) in a subset of patients show about -2.5 to +1 log change in cfu/ml in patients in the POS arm compared to -3 to +1 log change in the FCZ arm (Table 1). Only 1 patient in POS arm and one FCZ arm failed treatment. The patient in the POS arm showed no change in cfu/ml at EOT; whereas the patient in the FCZ arm showed 1 log increase in cfu/ml compared to baseline.

Table 1: Median log change in cfu/ml at end of treatment compared to baseline in patients showing favorable or unfavorable response at end of treatment visit in study C/I97-331

Group	Clinical success	Clinical failure
Posaconazole	-2.5 to +1 (n=47)	0 (n=1)
Fluconazole	-3 to +1 (n=48)	+1 (n=1)

- The results from study C/I106/209 show that median log change in cfu/ml was higher in patients treated with POS (50, 100 mg or 200 mg) and FCZ (100 mg) in patients with favorable response compared to patients failing treatment at the same dose (Table 2). There was no difference in median cfu/ml in patients showing favorable or unfavorable response treated with 400 mg dose.

- These results of quantitative culture should be interpreted with caution because of a wide range of variability and the small number of patients failing treatment in different treatment groups (Tables 1, 2 and 3). A wide variation in cfu/ml could be due to the immunocompromised status in HIV patients, other associated disorders associated with the disease, colonization of yeast and others.

Table 2: Median and range of log change in cfu/ml at end of treatment compared to baseline in patients showing favorable or unfavorable response at end of treatment visit in study C/I96-209

Treatment Group	Clinical Success			Clinical Failure		
	Log Change in CFU/ml			Log Change in CFU/ml		
	Median	Range	N	Median	Range	N
POS						
50 mg	-0.42	-2.89 to +0.49	45	0	-1.69 to +0.95	7
100 mg	-0.71	-2.69 to +0.78	38	-0.31	-2.31 to 0	8
200 mg	-1.09	-2.98 to +0.30	33	-0.04	-1.21 to +0.43	6
400 mg	-0.76	-2.69 to +0.46	42	-0.87	-2.14 to +1.18	7
FCZ						
100 mg	-1.65	-2.91 to +0.48	21	-0.16	-0.22 to +0.69	3

Table 3: Variability in cfu/ml at different visits in patients showing favorable or unfavorable clinical response in study C/I96-209

CFU/ml	POS 100 mg		FCZ 100 mg	
	Clinical success (n=38)	Clinical failure (n=8)	Clinical success (n=21)	Clinical failure (n=3)
Baseline	3430 (90 – 100,000)	5001 (310 – 15,700)	2660 (10 – 32,000)	1520 (50 – 8,500)
EOT	555 (10 – 10,000)	3001 (70 – 5,001)	195 (3 – 24,300)	600 (250 - 9,100)
Log change: Median (Range)	-0.71 (-2.69 to +0.78)	-0.31 (-2.31 to 0)	-1.65 (-2.91 to +0.48)	-0.16 (-2.14 to +1.18)

- Studies C/I97-330 and P00298 were to measure the efficacy of POS in HIV subjects with OPC refractory or resistant to FCZ or ITZ.
  - In study C/I97-330, clinical success was observed in 66 of the 89 patients (74%) with refractory OPC. A majority of the patients had a 2 log reduction in cfu. Complete absence of yeast was not documented.
  - In study P00298 none of the patients were evaluated to be refractory by the Medical Officer.

2. *C. albicans* was identified as a sole pathogen in a majority of the patients at baseline. Number of patients with *Candida* species other than *C. albicans* was very small. As discussed in the microbiology team leader review dated June 12, 2006 [redacted] should not be described in the label.

3. The sponsor has proposed to describe in the label that [redacted]

4

5.

6. No additional changes are recommended at this time in the Microbiology section of the label.

The Label (Microbiology section):

(Deletions to sponsor's proposal are striked out and the additions are double underlined)

RECOMMENDATIONS:

The NDA submission should be approved.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Shukal Bala
10/18/2006 01:39:08 PM
MICROBIOLOGIST

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGEN AND TRANSPLANT PRODUCTS

NDA #: 22-027

REVIEWER: Kalavati Suvarna
CORRESPONDENCE DATE: 12-21-05, 02-23-06, 03-08-06, 03-17-06, 05-16-06, 05-26-06
CDER RECEIPT DATE: 01-04-05, 02-24-06, 03-09-06, 03-17-06, 05-17-06, 05-30-06
REVIEW ASSIGN DATE: 01-04-05, 02-24-06, 03-12-06, 03-18-06, 05-19-06, 06-12-06
REVIEW COMPLETE DATE: 07-31-06

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

SUBMISSION REVIEWED: N-000 (original, MA, BM, BL)

DRUG CATEGORY: Antifungal

INDICATION: Treatment of oropharyngeal candidiasis, including OPC refractory to itraconazole or fluconazole

DOSAGE FORM: Oral Suspension

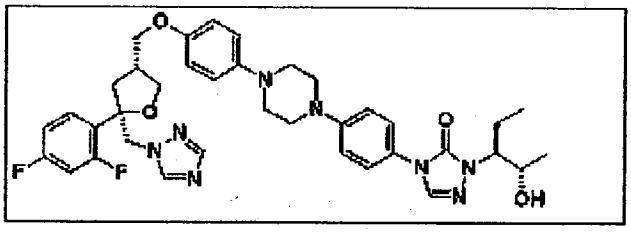
PRODUCT NAMES:

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-4*H*-1,2,4-triazole-4-yl]phenyl]-1-piperazinyl]phenoxy]methyl]-1-(*1H*-1,2,4-triazol-1-yl)-D-*threo*-pentitol

STRUCTURAL FORMULA:



Molecular weight: 700.78
Empirical Formula: $C_{37}H_{42}F_2N_8O_4$

SUPPORTING DOCUMENTS: IND 51,662; ——— NDA 22-003.

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1. EXECUTIVE SUMMARY

The sponsor is seeking approval of posaconazole (POS) oral suspension for the treatment of oropharyngeal candidiasis (OPC), including OPC refractory to itraconazole (ITZ) or fluconazole (FLZ). For OPC, a loading dose of 200 mg on the first day followed by 100 mg once daily for 13 days was proposed. For refractory OPC, a 400 mg dose twice a day was proposed. The duration of therapy will depend on the severity of the patient's underlying disease and clinical response.

POS is a triazole anti-fungal compound that is chemically similar to the currently marketed azoles, FLZ, ITZ, and voriconazole (VRZ). 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. No new preclinical microbiology information was included in this submission. Data reviewed previously suggests that POS was active *in vitro* against *Candida albicans*. Additionally, POS was effective in reducing the fungal burden in the tissues of normal and/or immunocompromised mice infected with *C. albicans* (For the review of preclinical microbiology, please see microbiology review for NDA 22-003 dated 5-15-06).

Four clinical studies were included in support of the proposed indication. Mycological evaluations included microscopic examination of oral scrapings and quantitative culture of oral swish samples. Speciation of isolates cultured from oral swish samples and *in vitro* susceptibility testing using the Clinical Laboratory Standards Institute (CLSI) methods were performed in central laboratories. In the pivotal study C/I 97-331, the safety and efficacy of POS oral suspension (100 mg for 14 days) was compared to FLZ (100 mg for 14 days) in the treatment of azole-susceptible OPC in HIV-infected subjects. In the MITT population, a successful clinical outcome was observed in 92% of patients treated with POS compared to 93% treated with FLZ. Mycological outcome was based on quantitative culture of oral swish samples. The sponsor proposed to use a threshold of ≤ 20 CFU/ml of *Candida* species in oral swish samples for determining mycological success. The mycological response data in this study were presented not only as CFU/ml of *Candida* in oral swish samples but also as absence of yeast in culture. Please note that the basis for the threshold of ≤ 20 CFU/ml of *Candida* species in oral swish samples is unclear. Therefore, mycological response based on presence or absence of yeast in culture was analyzed. The percentage of patients showing mycological eradication in the POS and FLZ arms was 53% and 50%, respectively. Use of the FDA criteria of negative yeast culture compared to sponsor's criteria of ≤ 20 CFU/ml resulted in 9 patients in the POS arm and 10 patients in the FLZ arm being classified as mycological failures. The clinical response in these patients was cure or improvement. Majority of patients in the study had *C. albicans* as the baseline isolate. The POS MIC_{90} for baseline *C. albicans* was 0.06 μg/ml. Very few patients had *Candida* species other than *C. albicans* as sole baseline pathogen. These species were mainly present as mixed infections. Eleven patients in the POS arm had super-infections with a *Candida* species other than that observed at baseline. The super-infections were mainly due to *Candida* species other than *C. albicans* and mixed infection of *Candida* species. The POS MICs for isolates causing super-infections were low (≤ 0.5 μg/ml). The POS MIC_{90} of baseline *Candida* isolates obtained from patients with a clinical and mycological success was 0.06 μg/ml. Clinical relapse was observed in 30% patients treated with POS compared to 34% patients treated with FLZ at 1 month post-treatment. Similarly, mycological relapse was observed in 32% of patients

treated with POS compared to 35% treated with FLZ. An increase in POS and FLZ MICs at follow-up was observed in *C. albicans* isolates from two patients with clinical relapse after POS therapy.

Study C/I 96-209 was a dose-ranging comparative study using an oral capsule formulation rather than proposed oral suspension. This study was considered supportive of the indication. The patient population and comparator were same as study C/I97-331. No dose response was observed in this study. The sponsor has stated that this was due to the high loading dose of POS used in the study and long half-life of the drug. A successful clinical response was observed in 90% of POS treated patients compared to 94% treated with FLZ. Super-infection due to *C. glabrata*, *C. krusei*, and *C. tropicalis* was observed in 4 of 83 patients treated with 100 mg POS. The POS MIC of these isolates ranged from 0.06 to 1 μg/ml. The POS MIC for isolates from patients with a successful clinical outcome overlapped with those of isolates from patients with clinical failure. Relapse was observed in 40% patients treated with POS 100 mg compared to 36% patients treated with FLZ 100 mg. The median day of relapse in the POS and FLZ arms were 41 and 22 days, respectively. The results of study C/I96-209 were consistent with the pivotal study C/I97-331.

Overall, the two studies show that the efficacy of POS is similar to FLZ for the treatment of OPC, and that POS has activity against *C. albicans* (successful clinical outcome in 223/241, 93%). Although, 72% (13/18) patients with *C. glabrata* and 100% (8/8) patients with *C. krusei* had a successful clinical outcome, these pathogens were present as mixed infections. The number of patients with *Candida* species other than *C. albicans* as the sole baseline pathogen was low. Super-infections due to these two pathogens were observed during treatment.

Two open-label studies (C/I 97-330 and P00298) were conducted in HIV infected subjects with azole refractory OPC and/or EC. [redacted] There were 199 OPC subjects enrolled in C/I97-330 (60 of these subjects were subsequently enrolled in P00298) and 40 POS-naïve OPC subjects enrolled in P00298. Study C/I 97-330 was the pivotal study in HIV infected subjects with OPC refractory to FLZ or ITZ therapy or OPC due to FLZ or ITZ resistant *Candida* (resistant definition based on CLSI criteria). The study evaluated the proposed dose (400 mg BID) after 4 weeks of treatment. Patients were allowed to continue with a maintenance phase of 400 mg BID for 3 months. The mycological success in this study was based on a threshold of ≤ 20 CFU/ml of *Candida* species in oral swish samples. As mentioned previously, the basis for this threshold is unclear. The medical officer determined that 89 patients enrolled in study C/I97-330 had refractory OPC. A successful clinical outcome was observed in 66 (74%) patients. Majority of these patients had a 2 log reduction in fungal burden. Data on absence of yeast in culture were not collected. For patients enrolled in study P00298, the 400 mg BID dose was evaluated after 3 months of treatment. Patients were allowed to continue with POS treatment for up to 12 months. None of the patients enrolled in study P000298 were considered to have refractory OPC. Most patients had *C. albicans* as the baseline pathogen. *C. glabrata* and *C. krusei* were observed as mixed infection at baseline. With a 400 mg BID POS dose, a successful clinical outcome was observed in 83% (117/142) patients with *C. albicans*, 74% (23/31) patients with *C. glabrata*, and 67% (6/9) patients with *C. krusei*. The activity of POS against *Candida* species other than *C. albicans* should be interpreted with caution as the study

did not measure eradication of yeast at the end of 4 weeks or 3 months of therapy. Relapse rates could not be determined as majority of patients continued onto maintenance phase or discontinued from study. The baseline POS MICs for patients with successful clinical outcome overlapped with that for isolates from patients with clinical failure. The number of patients with high baseline POS MICs was low. There was a positive correlation between POS and ITZ MICs of baseline isolates, suggesting cross-resistance between the two azoles. Increase in POS MIC was observed in isolates from two patients at 4 weeks of POS therapy.

The effectiveness of POS was evaluated in patients with OPC due to isolates with high FLZ (≥ 64 µg/ml) and ITZ (≥ 1 µg/ml) MIC values (resistant according to CLSI criteria). Over 50% of the baseline isolates in studies C/I97-330 and P000298 had high FLZ and/or ITZ MIC values (resistant category). Please note that although the CLSI document describes FLZ and ITZ interpretative criteria, this information has not been reviewed by the Agency and the FLZ and ITZ labels do not describe the breakpoints or interpretive criteria.

In summary, the studies suggest that POS is effective for treatment of OPC, including OPC refractory to FLZ or ITZ. The baseline pathogen was *C. albicans* in a majority of patients. Mycological success should be based on absence of yeast in culture. A study evaluating asymptomatic oral carriage of *Candida albicans* in HIV infected patients showed that the concentration of yeast in oral rinse for patients with OPC was similar to those without OPC and varied from 10 to 3000 CFU/ml. Although, yeast carriage over time is useful to predict onset of clinical disease, its usefulness to predict efficacy is not known.

2. INTRODUCTION AND BACKGROUND

The subject of this NDA is posaconazole (POS), an azole antifungal agent for the treatment of oropharyngeal candidiasis (OPC), including OPC refractory to itraconazole (ITZ) and fluconazole (FLZ). For treatment of OPC, a loading dose of 200 mg oral suspension on the first day followed by 100 mg once daily for 13 days was proposed. For treatment of refractory OPC, a 400 mg dose twice a day was proposed. The duration of therapy for refractory OPC will be based on the severity of the patient's underlying disease and clinical response.

POS is chemically similar to the currently marketed triazole compounds FLZ, 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 was observed when a single dose of 400 mg POS was given with nonfat or high fat meal compared to fasting conditions. In patients with refractory fungal infections, the mean area under the plasma concentration versus time curve (AUC) for POS was a third (8.6 µl/ml) of that observed in healthy volunteers (29.5 µl /ml). The mean maximum plasma drug concentrations (C_{max}) for POS in healthy volunteers and patients were 2.9 and 0.9 µg/ml, respectively.

3. PRECLINICAL MICROBIOLOGY

No new preclinical microbiology information was included in this submission. For a review of the preclinical microbiology information (mechanism of action, activity *in vitro* and *in vivo*, drug

resistance, cross-resistance, and drug combination), please see microbiology review [redacted] NDA 22-003 dated 5-15-06).

4. CLINICAL MICROBIOLOGY

The sponsor submitted four studies in support of the OPC indication. These include:

(1) The pivotal randomized, active-controlled, phase III clinical study (C/I97-331) in HIV infected subjects with azole-susceptible OPC.

(2) A phase II dose ranging study (C/I96-209) using the capsule rather than the proposed oral suspension formulation of POS.

(3) An open label clinical study C/I97-330 in HIV infected subjects with OPC refractory to FLZ or ITZ therapy and/or OPC due to FLZ or ITZ resistant *Candida* [resistant definition based on Clinical Laboratory Standards Institute (CLSI) criteria].

(4) An open label maintenance study P00298 in HIV infected subjects with OPC refractory to FLZ or ITZ therapy and/or OPC due to FLZ or ITZ resistant *Candida* [resistant definitions based on CLSI criteria].

4.1. Description of the clinical studies:

4.1.1. Study C/I97-331:

This was a Phase III, multi-center, randomized, evaluator-blinded trial conducted to compare the safety and efficacy of POS with FLZ for the treatment of OPC in HIV-infected patients. Patients who were HIV seropositive (documented by Western blot or other approved confirmatory test) with pseudomembranous OPC ($\geq$ 2 discrete pseudomembranous plaques or a single confluent plaque $\geq$ 3 cm) were enrolled. Patients with oral scrapings positive for yeasts, hyphae or pseudohyphae, consistent with *Candida* species and subsequently confirmed by a positive mycological culture were included. Patients taking systemic antifungals within 1 week prior to enrollment or topical antifungals within 2 days of enrollment were excluded. Additionally, patients with history of treatment failure with FLZ (100 mg/day for 2 weeks in the last 3 months) and prior use of POS in the preceding 3 months were excluded. Patients were randomized (1:1 ratio) to either POS or FLZ oral suspension (200 mg given on Day 1, followed by 100 mg once daily for the next 13 days). The primary endpoint of the study was clinical response after 14 days of treatment. The secondary endpoints were mycological response at 14 days and 4 weeks after the last dose.

The investigator examined the oral cavity for signs and symptoms and categorized the clinical response to treatment. For mycological evaluation, specimens obtained by scraping or swabbing oropharynx lesions were used for wet mount preparation with 10% KOH, and stained with chlorazol black E or gram stain at the local laboratory. In addition, quantitative cultures were performed using oral swish technique at the local laboratory. If both fungal microscopic examination and quantitative culture were performed at the same time, the swish samples for quantitative culture were taken before the scraping was obtained for fungal microscopic exam. In addition, identification of species and susceptibility testing was performed at the central

laboratory ([redacted] using the CLSI broth microdilution method for antifungal drug susceptibility testing of *Candida* (M27-T method). For amphotericin, endpoint for MIC reading was no growth while that for azoles was 80% reduction in growth.

Clinical response was evaluated according to the following definitions:
Cure: Absence of plaques or ulcers and minimal or no symptoms
Improvement: Partial resolution of pre-treatment signs and symptoms of OPC
Clinical Failure: No improvement or worsening of signs or symptoms after at least 7 consecutive days of therapy. Evidence of *Candida* in persistent plaques was demonstrated by KOH, fungal or gram stain.
Relapse: Recurrence of signs or symptoms after initial improvement or cure at EOT in patients who received ≥ 80% of study drug dose.
Not Assessed: Clinical assessment was not performed.
A successful clinical response was defined as clinical cure or improvement at EOT.

Mycological response at EOT was determined based on quantitative mycological culture results and according to the following definitions:
Eradication (Mycological success): ≤ 20 CFU/ml *Candida* species
Persistence (Mycological failure): > 20 CFU/ml *Candida* species
Relapse: ≤ 20 CFU/ml *Candida* species at EOT and >20 CFU/ml at follow-up.
Super-infection: A *Candida* species present during treatment but not at baseline.
New Infection: A *Candida* species present for the first time at follow-up.
Indeterminant: Cannot be classified into one of the other groups.

The sponsor provided a reference (Graybill *et al.*, Am. J. Med., 1998, 104: 33-39) to support the threshold of ≤ 20 CFU/ml for defining mycological response in patients with OPC. However, the basis for using the cut-off of ≤ 20 CFU/ml in patients with OPC is unclear as no data to support this threshold were included in the publication nor was any additional information included in the NDA. In the study by Graybill *et al.*(1994), it should be noted that mycological response based both on absence of yeast in culture (45/59; 76%) and ≤ 20 CFU/ml of yeast in oral swish samples (52/59; 88%) were included. The correlation between the mycological response using either of the two methods and clinical response was not shown. As the sponsor had collected information on negative yeast cultures, a re-analysis of data based on negative cultures was requested. For the purpose of this review, eradication defined as absence of yeast in culture was used for analysis. In addition, patients with super-infections were considered as mycological failures.

The modified intent-to-treat (MITT) population included all randomized patients who received at least one dose of study drug and had a positive culture for *Candida* species at baseline. The protocol evaluable subjects included all treated patients who met the inclusion criteria and received at least 7 consecutive days of study drug. Patients who received at least 3 days of treatment prior to discontinuation were considered as failures due to an adverse event or efficacy.

The MITT subset included 169 and 160 subjects, in the POS and FLZ arms, respectively. A majority of patients in the study were immunocompromised as indicated by the low CD4 cell counts. The median baseline CD4 cell counts per mm^3 was 80 (range: 0 to 937) in the POS

group, and 65 (range: 0 to 867) in FLZ group. The median (range) baseline yeast cell counts in oral swish samples in the POS arm was 1194 (20 to > 29300) CFU/ml, and in the FLZ arm was 1725 (30 to < 26000) CFU/ml. Majority of patients in both treatment groups (POS, n = 142 and FLZ, n = 139) had *C. albicans* as the baseline isolate. The remaining patients (POS, n = 27 and FLZ, n = 21) had infections due to *Candida* species other than *C. albicans* or an unidentified *Candida* species or mixed infections (Table 1). A successful clinical outcome was observed in 92% patients treated with POS compared to 93% patients treated with FLZ (Table 1). The mycological eradication rates in the POS and FLZ arms were 53% and 50%, respectively. The overall therapeutic responses in the POS and FLZ arms were 50% and 48%, respectively.

The per protocol evaluable population included 143 and 135 subjects, in the POS and FLZ arms, respectively. Similar trend was observed in the evaluable population. There were 25 patients (POS, n = 11; FLZ, n = 14) who eradicated the baseline pathogen but had super-infections due to a *Candida* species not present at baseline. All subjects with super-infections had a successful clinical response (Table 2). However, these subjects were considered as mycological failures.

Table 1: Clinical success and mycological eradication rates by baseline pathogens in patients treated with POS or FLZ in study C/I 97-331.

Baseline pathogen	MITT						Evaluable					
	POS			FLZ			POS			FLZ		
	Clinical success	Mycological eradication	Therapeutic response	Clinical success	Mycological eradication	Therapeutic response	Clinical success	Mycological eradication	Therapeutic response	Clinical success	Mycological eradication	Therapeutic response
C. albicans	132/142 (93%)	79/142 (56%)	76/142 (54%)	128/139 (92%)	72/139 (52%)	68/139 (49%)	118/120 (98%)	71/120 (59%)	69/120 (58%)	113/118 (96%)	65/118 (55%)	62/118 (53%)
C. albicans + C. glabrata	9/11 (82%)	3/11 (27%)	3/11 (27%)	7/7	2/7	2/7	8/9 (89%)	3/9 (33%)	3/9 (33%)	5/5	1/5	1/7
C. albicans + C. krusei	4/4	2/4	2/4	5/5	3/5	3/5	4/4	2/4	2/4	4/4	3/4	3/4
C. albicans + C. nodaensis	1/1	1/1	1/1	0/0	0/0	0/0	1/1	1/1	1/1	0/0	0/0	0/0
C. albicans + Candida species	1/1	0/1	0/1	0/0	0/0	0/0	1/1	0/1	0/0	0/0	0/0	0/0
C. albicans + C. tropicalis	2/2	0/2	0/2	3/3	0/3	0/3	2/2	0/2	0.2	3/3	0/3	0/3
C. albicans + non-Candida species	2/2	2/2	2/2	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
C. dubliniensis + non-Candida species	0/0	0/0	0/0	0/1	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0
C. glabrata	0/0	0/0	0/0	1/1	0/1	0/1	0/0	0/0	0/0	1/1	0/1	0/1
C. glabrata + C. dubliniensis	0/1	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
C. glabrata + Candida species	1/1	0/1	0/1	0/0	0/0	0/0	1/1	0/1	0/1	0/0	0/0	0/0
C. glabrata + C. tropicalis	0/1	0/1	0/1	0/0	0/0	0/0	0/1	0/1	0/1	0/0	0/0	0/0
C. krusei	1/1	0/1	0/1	1/1	1/1	1/1	1/1	0/1	0/1	1/1	1/1	1/1
C. krusei + non-Candida species	0/0	0/0	0/0	1/1	1/1	1/1	0/0	0/0	0/0	1/1	1/1	1/1
Candida species	2/2	1/2	1/2	1/1	0/1	0/1	2/2	1/2	1/2	1/1	0/1	0/1
Total	**155/169 (92%)**	**88/169 (52%)**	**85/169 (50%)**	**148/160 (93%)**	**80/160 (50%)**	**76/160 (48%)**	**139/143 (90%)**	**79/143 (55%)**	**77/143 (54%)**	**130/135 (96%)**	**72/135 (53%)**	**69/135 (51%)**

POS = posaconazole
FLZ = fluconazole
Clinical success = cure + improved
Mycological eradication = absence of *Candida* in culture.
Therapeutic response = clinical success + mycological eradication

Table 2: Pathogenic species associated with super-infection in study C/I 97-331.

Treatment group	Species (n)	CFU/ml	POS MIC (µg/ml)	Clinical response
POS (n = 11)				
	Candida albicans + *Candida glabrata* (1)	2000	0.5	Cure
	Candida dubliniensis (2)	710, >5000	< 0.015	Cure
	Candida glabrata (1)	110	< 0.5	Cure
	Candida glabrata (1)	5000	0.5	Improvement
	Candida guilliermondii (1)	200	0.06	Cure
	Candida krusei (1)	40	0.25	Cure
	Candida krusei + non *Candida* species (2)	30 - >5000	0.25	Cure
	Candida magnoliae (1)	>5000	0.125	Cure
	Candida parapsilosis (1)	650	0.03	Cure
FLZ (n = 14)				
	Candida dubliniensis (3)	30 - >5000	NA	Cure
	Candida glabrata (5)	1110 - >5000	NA	Cure
	Candida glabrata + non *Candida* species (1)	>3000	NA	Cure
	Candida krusei (2)	>5000	NA	Cure
	Candida species (2)	>5000	NA	Cure
	Candida tropicalis (1)	>10,000	NA	Cure

n = number of patients with isolate; CFU = colony forming units of *Candida* species;
POS = posaconazole; FLZ = fluconazole; NA = not applicable

Use of the FDA criteria of negative yeast culture compared to sponsor's criteria of ≤ 20 CFU/ml resulted in 9 patients in the POS arm and 10 patients in the FLZ arm being classified as mycological failures in the MITT population. The clinical response in these patients was cure or improvement (Table 3). Follow-up information was not available for 2 of the 9 patients treated with POS. Relapse was observed in 1/7 POS treated patients and 4/10 patients treated with FLZ (Table 3). Based on the limited data, it is not clear if ≤ 20 CFU/ml would be a good predictor for clinical cure.

Information on log change in CFU/ml at EOT was available for 97 (POS = 48/169; FLZ = 49/160) patients. The log change in CFU/ml in oral swish samples of patients with clinical cure ranged from -2.5 log to +1 log in the POS arm and from – 3 log to +1 log in the FLZ arm. One patient with clinical failure in each of POS and FLZ arm showed no change in CFU, and a 1 log increase in CFU at EOT, respectively.

Table 3. Mycological outcomes of MITT patients treated with POS or FLZ using sponsor's criteria of ≤ 20 CFU/ml and FDA criteria of absence of yeast in culture.

Subject ID	Evaluable	Baseline Pathogen (CFU/ml)	End of therapy Pathogen (CFU/ml)	Clinical response	Mycological success based on ≤ 20 CFU/ml	Mycological success based on absence of yeast in culture	Clinical relapse at follow-up
POS							
C013000061	Yes	*Candida albicans* (330)	*Candida albicans* (10)	Cure	Eradication	Persistence	Cure
C012000136	Yes	*Candida albicans* (1360)	*Candida albicans* (10)	Cure	Eradication	Persistence	Cure
I014000133	Yes	*Candida albicans* (460)	*Candida albicans* (10)	Cure	Eradication	Persistence	Cure
I039000430	Yes	*Candida albicans* (328)	*Candida albicans* (20)	Improvement	Eradication	Persistence	Improvement
I039000433	Yes	*Candida albicans* (3170)	*Candida albicans* (10)	Cure	Eradication	Persistence	Relapse
I039000441	Yes	*Candida albicans* (240)	*Candida albicans* (10)	Cure	Eradication	Persistence	Not available
I033000463	Yes	*Candida albicans* (>3000)	*Candida albicans* (10)	Cure	Eradication	Persistence	Not available
I033000465	Yes	*Candida albicans* (> 3000)	*Candida albicans* (10)	Cure	Eradication	Persistence	Cure
I015000593	Yes	*Candida albicans* (< 3810)	*Candida albicans* (< 10)	Cure	Eradication	Persistence	Cure
FLZ							
C003000049	Yes	*Candida albicans* (>5000)	*Candida albicans* (10)	Improvement	Eradication	Persistence	Relapse
C013000063	Yes	*Candida albicans* (> 5000)	*Candida albicans* (10)	Cure	Eradication	Persistence	Cure
C008000073	Yes	*Candida albicans* (> 5000)	*Candida albicans* (20)	Cure	Eradication	Persistence	Relapse
I037000013	Yes	*Candida albicans* (2600)	*Candida albicans* (10)	Cure	Eradication	Persistence	Cure
I020000170	No	*Candida albicans* (< 760) and *Candida krusei* (40)	*Candida albicans* (< 20)	Cure	Eradication	Persistence	Relapse
I020000174	Yes	*Candida albicans* (>3000)	*Candida albicans* (10)	Cure	Eradication	Persistence	Cure
I019000206	Yes	*Candida albicans* (180)	*Candida albicans* (20)	Cure	Eradication	Persistence	Cure
I015000590	Yes	*Candida albicans* (< 12800)	*Candida albicans* (< 20)	Cure	Eradication	Persistence	Relapse
I017000603	Yes	*Candida albicans* (> 5000)	*Candida albicans* 20)	Cure	Eradication	Persistence	Cure
I016000664	Yes	*Candida albicans* (< 470)	*Candida albicans* (< 10)	Cure	Eradication	Persistence	Cure

The POS and FLZ MICs were determined for baseline isolates in the two treatment groups. The POS MIC_{90} for *C. albicans* in both treatment groups was 0.06 µg/ml (Table 4). The FLZ MIC_{90}s for *C. albicans* in the POS and FLZ arms were 8 and 4 µg/ml, respectively. The baseline POS and FLZ MICs for other *Candida* species were comparable in the two arms. The POS MIC_{90} of baseline *Candida* isolates obtained from patients with a clinical and mycological success was 0.06 µg/ml (Figures 1 and 2).

Table 4. Baseline MIC of *Candida* isolates in study C/I 97-331.

***Candida* species**	**n**	**POS arm**		**n**	**FLZ arm**	
		POS MIC_{90} (range)	**FLZ MIC_{90} (range)**		**POS MIC_{90} (range)**	**FLZ MIC_{90} (range)**
C. albicans	161	0.06 (0.015 – 16)	8 (0.12 - 64)	156	0.06 (0.015 – 8)	4 (0.12 – 64)
C. dubliniensis	1	0.015	0.125	1	0.015	16
C. glabrata	14	4 (0.125 – 4)	32 (8 – 64)	8	1 (0.015 – 8)	64 (4 – 64)
C. krusei	5	0.25 (0.015 – 0.25)	64 (8 – 64)	7	0.25 (0.125 – 0.5)	64 (32 – 64)
C. nodaensis	1	0.03	64	0	-	-
C. tropicalis	3	(0.03 – 8)	(0.12 – 64)	3	8	64
Candida species	5	(0.015 – 8)	(0.25 - 64)	1	0.5	8

Some patients had mixed infections at baseline.

Figure 1: Relationship between baseline posaconazole MIC (BPOSMIC1) of *Candida* isolates and clinical outcome (ceotsf) at EOT for patients with OPC from study C/I97-331.

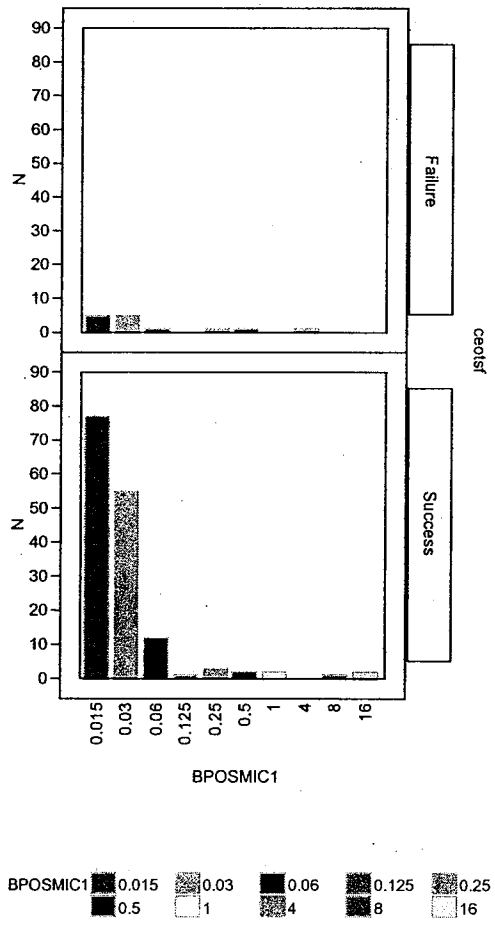
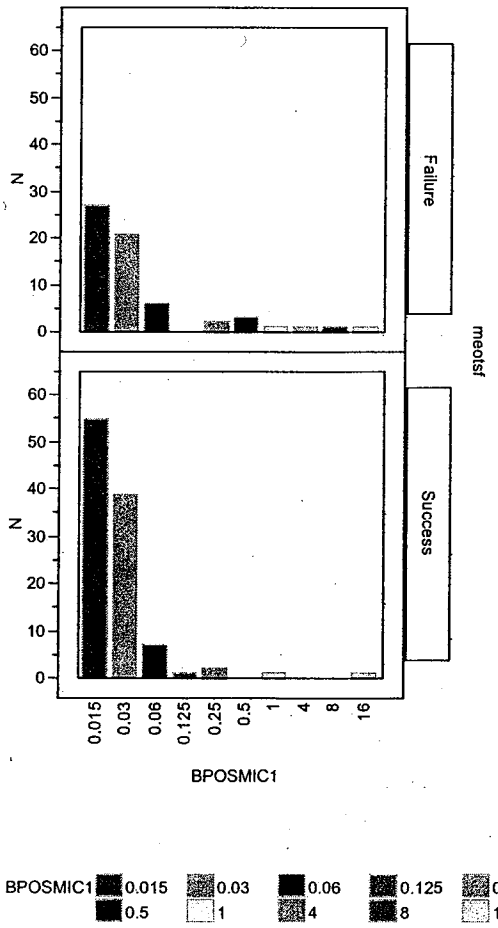


Figure 2: Relationship between baseline posaconazole MIC (BPOSMIC1) of *Candida* isolates and mycological outcome (meotsf) at EOT for patients with OPC from study C/I97-331.



A follow-up evaluation was performed 4 weeks after discontinuation of therapy in the per protocol evaluable population. The percentage of patients that showed a sustained clinical response at 4 weeks after discontinuation of therapy in the POS and FLZ arms were 60% and 56%, respectively (Table 5).

The percentage of patients with sustained mycological eradication at 4 weeks after discontinuation of therapy in the POS and FLZ arms were 16% and 10%, respectively. The percentages of patients with clinical relapse were similar in the POS (30%) and FLZ (34%) arms. Similarly, patients that had a mycological relapse was slightly lower in the POS arm (32%) compared to FLZ arm (35%).

Table 5: Clinical and mycological responses by baseline pathogen at follow-up visit (4 weeks after discontinuation of therapy).

Baseline pathogen	**Evaluable population**							
	POS				**FLZ**			
	Clinical success	**Mycological eradication**	**Clinical relapse**	**Mycological relapse**	**Clinical success**	**Mycological eradication**	**Clinical relapse**	**Mycological relapse**
C. albicans	69/120 (58%)	18/120 (15%)	40/120 (33%)	43/120 (36%)	66/118 (56%)	12/118 (10%)	40/118 (34%)	43/118 (36%)
C. albicans + C. glabrata	7/9	2/9	1/9	1/9	3/5	0/5	2/5	1/5
C. albicans + C. krusei	3/4	1/4	1/4	1/4	4/4	1/4	0/4	2/4
C. albicans + C. nodaensis	0/1	0/1	1/1	1/1	0/0	0/0	0/0	0/0
C. albicans + Candida species	1/1	0/1	0/1	0/1	0/0	0/0	0/0	0/0
C. albicans + C. tropicalis	2/2	0/2	0/2	0/2	1/3	0/3	1/3	0/3
C. albicans + non-Candida species	1/1	1/1	0/1	0/1	1/1	0/1	0/1	1/1
C. glabrata	0/0	0/0	0/0	0/0	0/1	0/1	1/1	0/1
C. glabrata + Candida species	0/1	0/1	0/1	0/1	0/0	0/0	0/0	0/0
C. glabrata + C. tropicalis	0/1	0/1	0/1	0/1	0/0	0/0	0/0	0/0
C. krusei	1/1	0/1	0/1	0/1	0/1	0/1	1/1	0/1
krusei + non-Candida species	0/0	0/0	0/0	0/0	0/1	0/1	1/1	0/1
Candida species	2/2	1/2	0/2	0/2	**0/1**	0/1	0/1	0/1
Total	**86/143 (60%)**	**23/143 (16%)**	**43/143 (30%)**	**46/143 (32%)**	**75/135 (56%)**	**13/135 (10%)**	**46/135 (34%)**	**47/135 (35%)**

POS = posaconazole
FLZ = fluconazole
Clinical success = cure + improved
Mycological eradication = absence of *Candida* in culture.

Of the patients who had clinical relapse, 3 *C. albicans* isolates from 2 patients treated with POS and 1 patient treated with FLZ showed an increase in POS MIC and FLZ MIC at follow-up (Table 6). There was no change in POS MIC of the remaining isolates except few isolates (POS, n = 3) with a 4 to 64 fold decrease in POS MIC.

Table 6: Changes in POS MIC in 3 patients who relapsed.

SubID	**Treatment group**	**Treatment duration**	**Baseline CD4 cell count/mm^3**	**Pathogen**	**Baseline CFU/ml**	**Baseline FLZ MIC**	**Baseline POS MIC**	**Follow-up CFU/ml**	**Follow-up FLZ MIC**	**Follow-up POS MIC**
I97331-19-000163	POS	14	27	*C. albicans*	7850	0.5	**0.015**	>17,000	>64.0	**>8.0**
I97331-14-000649*	POS	15	32	*C. albicans*	6240	8.0	**0.015**	60	>64.0	**4.0**
C97331-18-000170	FLZ	14	7	*C. albicans*	>5000	8.0	0.125	2500	>64.0	>8.0

* patient had mixed infection with *C. tropicalis* at follow-up visit
POS treated patients shown in bold

Overall, the study shows that the efficacy of POS is similar to FLZ against OPC. The majority of patients had *C. albicans* as the sole pathogen at baseline. The number of patients with *Candida* species

other than *C. albicans* was low. Based on the limited data on log change in CFU of *Candida* species in oral swish samples of 97 patients, it is not clear how log change in CFU correlates with clinical cure. The relationship between number of yeast and clinical disease could not be established. As *Candida* is part of the normal oral flora, oral swish samples may not be useful for documentation of OPC infection. Use of the FDA criteria of negative yeast culture compared to sponsor's criteria of ≤ 20 CFU/ml resulted in 9 patients in the POS arm and 10 patients in the FLZ arm being classified as mycological failures. The clinical response in these patients was cure or improvement. The POS MIC_{90} of baseline *Candida* isolates obtained from patients with a clinical and mycological success was 0.06 µg/ml. Increase in POS MIC was identified in *C. albicans* isolates from two patients who relapsed after POS therapy and 1 patient after FLZ therapy. These patients were also severely immunocompromised.

4.1.2. Study C/I96-209:

This was a phase II randomized (5 arm), active control, parallel group, multi-center, double blind study conducted to compare the safety and efficacy of different doses of POS capsule formulation with FLZ for the treatment of OPC in HIV infected patients. The documentation of HIV infection and OPC were same as in the study C/I97-331. Please note that this study used the capsule formulation of POS as opposed to the proposed oral suspension. Therefore, data from this study were considered as supportive for efficacy. Patients taking systemic antifungal within 14 days prior to enrollment or topical antifungals within 1 day of enrollment were excluded. Additionally, patients with primary HIV seroconversion – related mucosal candidiasis, systemic candidiasis, forms of OPC other than pseudomembranous (unless accompanied by pseudomembranous OPC), documented or suspected fungal esophagitis were excluded. Patients received a loading dose of 400 mg POS capsule BID on day 1, followed by one of the following 4 QD maintenance regimens: 50, 100, 200, or 400 mg for 13 days. Subjects randomized to FLZ received 200 mg on the first day followed by 100 mg QD for 13 days. The primary efficacy endpoint was the clinical response at EOT. Clinical response at follow-up (28 days after EOT) was used to determine if the clinical response was sustained. The secondary endpoint was mycological response at EOT. The definitions of clinical and mycological response were same as in study C/I97-331. As in study C/I97-331, data on absence of yeast in culture were available and used for efficacy analysis by the FDA.

The diagnostic methods used for mycological evaluations were same as in study C/I97-331. Speciation and susceptibility testing were performed at three different central laboratories based on location of the clinical sites (for sites in US, Canada and Mexico, [redacted] for sites in Argentina and Chile, [redacted] for sites in Europe, [redacted]). All laboratories followed the CLSI M27-A method for *in vitro* susceptibility testing of yeasts.

For the purpose of this review, mycological response based on absence or presence of yeast in culture was analyzed. The evaluable population consisted of the 409 patients who satisfied all inclusion/exclusion criteria, received at least 10 days of study drug, had a clinical assessment at EOT and no systemic or oral topical antifungal during study period. No dose response was observed in this study. The reason for absence of dose response is unclear. The sponsor has stated that the absence of a dose response may be due to high loading dose used in the study and the long half-life of the drug. Please note that the bioavailability of the capsule is 10% lower than that of the oral suspension.

Majority of patients had *C. albicans* as the baseline isolate; few patients had *Candida* species other than *C. albicans* (Tables 7 and 8). The clinical success in the 100 mg (proposed dose) POS group (90%) and FLZ group (94%) were similar. The overall (clinical + mycological) success with 100 mg POS was 41% compared to 54% in FLZ group (Table 7). The clinical success rates were similar to that seen in study C/I97-331. As in study C/I97-331, POS was shown to be active against *C. albicans* in this study.

There was wide variation in the level of yeast carriage in individual patients (Table 9). Several factors such as immune status, smoking, diet, and use of dentures affect carriage of yeasts. In addition, high carriage of yeasts in HIV infected patients without OPC is common. The reduction in median CFU/ml at end of therapy was greater in patients with successful clinical outcome compared to those who failed after POS or FLZ therapy. However, the range of log change in CFU of *Candida* species in oral swish samples appear to be similar in POS treated patients with clinical success and failure with few outliers (Table 10 and Figure 3). The number of patients with no change or increase in log CFU/ml at end of therapy was small. The relationship between number of yeast and clinical disease could not be established. As *Candida* is part of the normal oral flora, oral swish samples may not be useful for documentation of OPC infection.

Table 7: Clinical and mycological response of evaluable patients by baseline pathogen in the dose ranging study C/I 96-209.

Pathogen	50 mg POS			100 mg POS			200 mg POS			400 mg POS			FLU		
	Clinical success	Mycological eradication	Overall response	Clinical success	Mycological eradication	Overall response	Clinical success	Mycological eradication	Overall response	Clinical success	Mycological eradication	Overall response	Clinical success	Mycological eradication	Overall response
C. albicans	61/73	28/73	27/73	65/71	31/71	31/71	58/74	30/74	28/74	69/75	35/75	33/75	59/64	38/64	38/64
C. albicans + *C. dubliniensis*	0/0	0/0	0/0	0/0	0/0	0/0	1/1	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0
C. albicans + *C. glabrata*	0/1	0/1	0/1	2/3	0/3	0/3	1/2	0/2	0/2	4/5	0/5	0/5	3/3	0/3	0/3
C. albicans + *C. glabrata* + *C. tropicalis*	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	1/1	0/1	0/1	0/0	0/0	0/0
C. albicans + *C. krusei*	1/1	0/1	0/1	3/3	1/3	1/3	0/0	0/0	0/0	2/2	1/2	1/2	0/0	0/0	0/0
C. albicans + *C. pseudotropicalis*	0/0	0/0	0/0	1/1	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
C. albicans + *C. tropicalis*	1/1	1/1	1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/1	0/1	1/1	0/1	0/1
C. albicans + unidentified yeast	0/0	0/0	0/0	1/1	1/1	1/1	0/0	0/0	0/0	0/0	0/0	0/0	2/2	1/2	1/2
C. dubliniensis	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	1/1	1/1	1/1
C. glabrata	2/2	0/2	0/2	1/1	0/1	0/1	1/1	0/1	0/1	1/1	0/1	0/1	3/3	0/3	0/3
C. glabrata + *C. krusei*	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1	0/1	0/1	0/0	0/0	0/0
C. glabrata + *C. tropicalis*	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	1/2	0/2	0/2	0/0	0/0	0/0
C. lipolytica	0/0	0/0	0/0	0/0	0/0	0/0	1/1	0/1	0/1	0/0	0/0	0/0	0/0	0/0	0/0
C. tropicalis	3/3	2/3	2/3	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	1/1	1/1	1/1
C. tropicalis + unidentified yeast	0/0	0/0	0/0	0/1	1/1	1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Unidentified yeast	0/0	0/0	0/0	2/2	0/2	0/2	1/1	0/1	0/1	0/0	0/0	0/0	2/2	0/2	0/2
Total	**68/81 (84%)**	**31/81 (38%)**	**30/81 (37%)**	**75/83 (90%)**	**34/83 (41%)**	**34/83 (41%)**	**63/80 (79%)**	**30/80 (38%)**	**28/80 (35%)**	**78/88 (89%)**	**36/88 (41%)**	**34/88 (38%)**	**72/77 (94%)**	**41/77 (53%)**	**41/77 (53%)**

Mycological eradication = absence of yeast in culture.
Clinical success = cure + improved

Table 8: Clinical and mycological response of evaluable patients by baseline pathogen irrespective of mixed infections in the dose ranging study C/I 96-209.

Pathogen*	50 mg POS			100 mg POS			200 mg POS			400 mg POS			FLU		
	Clinical success	Mycological eradication	Overall response	Clinical success	Mycological eradication	Overall response	Clinical success	Mycological eradication	Overall response	Clinical success	Mycological eradication	Overall response	Clinical success	Mycological eradication	Overall response
C. albicans	63/75	29/75	28/75	**72/78**	**33/78**	**33/78**	60/76	30/76	28/76	76/84	36/84	36/84	**65/69**	**39/69**	**39/69**
C. dubliniensis	0/0	0/0	0/0	**0/0**	**0/0**	**0/0**	1/1	0/1	0/1	0/0	0/0	0/0	**1/1**	**1/1**	**1/1**
C. glabrata	2/3	0/3	0/3	**3/4**	**0/4**	**0/4**	2/3	0/3	0/3	7/10	0/10	0/10	**6/6**	**0/6**	**0/6**
C. krusei	1/1	0/1	0/1	**3/3**	**1/3**	**1/3**	0/0	0/0	0/0	2/3	1/3	1/3	**0/0**	**0/0**	**0/0**
C. lipolytica	0/0	0/0	0/0	**0/0**	**0/0**	**0/0**	1/1	0/1	0/1	0/0	0/0	0/0	**0/0**	**0/0**	**0/0**
C. pseudotropicalis	0/0	0/0	0/0	**1/1**	**0/1**	**0/1**	0/0	0/0	0/0	0/0	0/0	0/0	**0/0**	**0/0**	**0/0**
C. tropicalis	4/4	3/4	3/4	**0/1**	**1/1**	**1/1**	0/0	0/0	0/0	2/4	0/4	0/4	**2/2**	**1/2**	**1/2**

*some patients had more than one Candida species at baseline; Mycological eradication = absence of yeast in culture; Clinical success = cure + improved;

Table 9: Median CFU/ml at baseline at end of therapy by clinical outcome for the different treatment groups.

Treatment group	Clinical success			Clinical failure		
	N	Median baseline CFU/ml (range)	Median end of therapy CFU/ml (range)	N	Median baseline CFU/ml (range)	Median end of therapy CFU/ml (range)
POS 50 mg	68	3001 (10 – 18200)	640 (1 – 17900)	13	5001 (260 – 30001)	4000 (100 – 12000)
POS 100 mg	75	3430 (90 – 100000)	555 (10 – 10000)	8	5001 (310 – 15700)	3001 (70 – 5001)
POS 200 mg	63	2760 (10 – 24000)	270 (2 – 10800)	17	1645 (250 – 10001)	1770 (200 – 8000)
POS 400 mg	78	2715 (10 – 29000)	580 (10 – 10800)	10	4400 (120 – 9600)	1510 (10 – 5001)
FLZ 100 mg	72	2660 (10 – 32000)	195 (3 – 24300)	5	1520 (50 – 8500)	600 (250 – 9100)

Please note that CFU/ml with a greater than sign were converted to next integer for the purposes of this analysis
N = number of subjects

Table 10: Relationship of log change in CFU of *Candida* species in oral swish samples to clinical outcome.

Treatment group	Log change in CFU/ml (range)	
	Clinical Success	Clinical Failure
POS 50 mg	-2.89 to +0.49 log (n = 68)	-1.69 to +0.95 log (n = 13)
POS 100mg	**-2.69 to +0.78 log (n = 75)**	**-2.31 log to no change (n = 8)**
POS 200 mg	-2.98 to +0.30 log (n = 63)	-1.21 to +0.43 log (n = 17)
POS 400 mg	-2.69 to +0.46 log (n = 78)	-2.14 to +1.18 log (n =10)
FLZ 100mg	**-2.91 to +0.48 log (n = 72)**	**-0.22 to +0.69 log (n = 5)**

n = number of patients with clinical outcome. Please note that some of the patients did not have an entry for CFU/ml at end of therapy.

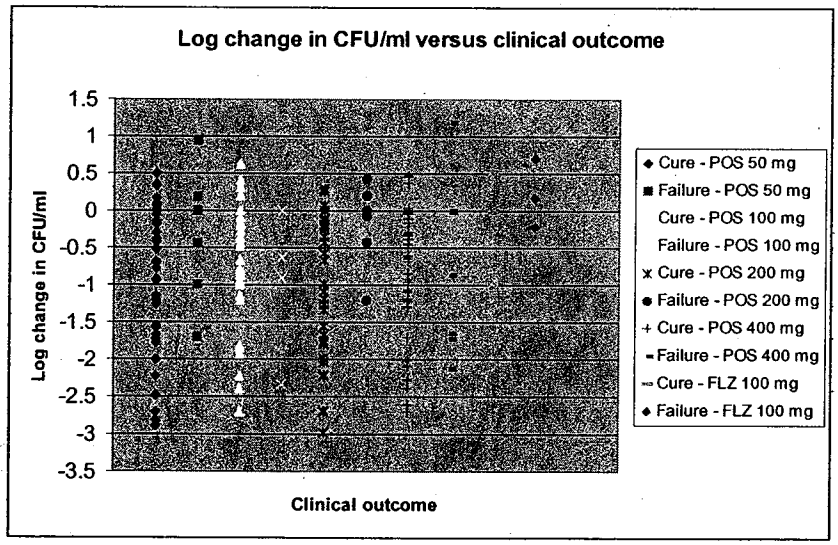


Figure 3: Log change in CFU/ml versus clinical outcome for the different treatment groups. Only patients with complete information were analyzed.

For the purposes of this review, super-infections were considered as mycological failures. As with study C/I97-331, super-infections were observed in the POS and FLZ arms (Table 11). The super-infections were due to *Candida* species other than *C. albicans*. The POS MICs of isolates causing super-infection varied from <0.015 to 8 µg/ml. The FLZ MICs of isolates causing super-infection varied from <0.125 to 128 µg/ml. There appears to be a trend towards increase in super-infections with increasing dose of POS.

The baseline MICs of *C. albicans* isolates from patients with a successful clinical response overlapped with those for isolates in patients with clinical failure (Table 12). However, the

number of isolates with high MICs was too small to determine the correlation between MIC and clinical outcome.

Table 11: Patients who eradicated baseline pathogen but developed super-infection at EOT

SubID	Clinical response at EOT	Pathogen causing super-infection (POS MIC)
POS 50 mg		
4000008	Cure	*C. krusei* (<0.03 µg/ml)
7000004	Failure	*C. glabrata* (0.5 µg/ml)
17000005	Cure	*Candida glabrata* (1 µg/ml) + *Candida tropicalis* (<0.015 µg/ml)
36000002	Cure	*C. glabrata* (0.5 µg/ml)
POS 100 mg		
3000010	**Cure**	***Candida tropicalis* (0.06 µg/ml)**
24000006	**Cure**	***Candida glabrata* (1.0 µg/ml)**
27000002	**Improvement**	***Candida glabrata* (0.25 µg/ml)**
32000010	**Cure**	***Candida glabrata* (0.25 µg/ml)**
POS 200 mg		
1000005	Cure	*Candida glabrata* (2.0 µg/ml)
4000006	Cure	*Candida tropicalis* (0.03 µg/ml)
18000015	Failure	*Candida krusei* (0.06 µg/ml)
23000007	Cure	*Candida dubliniensis* (<0.015 µg/ml)
31000003	Improvement	*Candida glabrata* (8.0 µg/ml)
32000009	Cure	*Candida glabrata* (<0.015 µg/ml)
POS 400 mg		
2000001	Cure	*Candida tropicalis* (0.25 µg/ml)
21000001	Failure	*Candida albicans* (0.06 µg/ml)
24000005	Cure	*Candida glabrata* (0.5 µg/ml)
27000001	Failure	*Candida dubliniensis* (<0.015 µg/ml)
34000017	Failure	*Candida tropicalis* (0.125 µg/ml)
36000013	Cure	*Candida tropicalis* (0.06 µg/ml)
38000006	Cure	*Candida glabrata* (0.03 µg/ml)
41000004	Cure	*Candida albicans* (0.015 µg/ml)
41000020	Cure	*Candida guilliermondii* (0.015 µg/ml)
41000023	Cure	*Candida glabrata* (1.0 µg/ml)
FLZ 100 mg	**Clinical response at EOT**	**Pathogen causing super-infection (FLZ MIC)**
3000012	**Cure**	***Candida albicans* (0.5 µg/ml) + *Candida glabrata* (32.0 µg/ml)**
11000004	**Cure**	***Candida glabrata* (4.0 µg/ml)**
11000015	**Cure**	***Candida glabrata* (32.0 µg/ml)**
23000007	**Cure**	***Candida dubliniensis* (<0.125 µg/ml)**
26000006	**Cure**	***Candida krusei* (128.0 µg/ml)**
31000004	**Cure**	***Candida parapsilosis* (ND)**
32000001	**Cure**	***Candida glabrata* (0.5 µg/ml)**
34000001	**Cure**	***Candida tropicalis* (>64.0 µg/ml)**
34000003	**Improvement**	***Candida tropicalis* (>64.0 µg/ml)**
34000018	**Cure**	***Candida krusei* (32.0 µg/ml)**
36000007	**Cure**	***Candida albicans* (0.25 µg/ml)**
40000003	**Improvement**	***Candida krusei* (32.0 µg/ml)**
46000009	**Improvement**	***Candida glabrata* (2.0 µg/ml)**

Rows shown in bold indicated proposed dose of POS and approved dose of FLZ

Table 12: Relationship of baseline MIC values of isolates with clinical outcome in study C/I96-209.

Pathogen	50 mg POS				100 mg POS				200 mg POS				400 mg POS			
	Clinical Success		Clinical Failure		Clinical Success		Clinical Failure		Clinical Success		Clinical Failure		Clinical Success		Clinical Failure	
	n	Baseline MIC_{90} (range) in µg/ml	n	Baseline MIC_{90} (range) in µg/ml	n	Baseline MIC_{90} (range) in µg/ml	n	Baseline MIC_{90} (range) in µg/ml	n	Baseline MIC_{90} (range) in µg/ml	n	Baseline MIC_{90} (range) in µg/ml	n	Baseline MIC_{90} (range) in µg/ml	n	Baseline MIC_{90} (range) in µg/ml
C. albicans	63	0.125 (0.015 – 8)	12	0.25 (0.015 - 0.25)	72	0.125 (0.015 – 12)	6	0.25 (0.06 – 4)	60	0.06 (0.015 – 4)	16	0.125 (0.015 -0.25)	76	0.06 (0.015 - >8)	8	0.06 (0.015 - >4)
C. dubliniensis	-	-	-	-	-	-	-	-	1	- (0.015)	-	-	-	-	-	-
C. glabrata	2	- (4)	1	- (0.5)	2	- (0.015 - 0.5)	1	- (0.5)	2	- (0.25 – 0.5)	1	- (0.5)	5	- (0.06 – 16)	1	- (0.25)
C. krusei	1	- (1)	-	-	3	- (0.06 – 0.3)	-	-	-	-	-	-	1	- (0.25)	1	- (0.125)
C. lipolytica	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
C. pseudotropicalis	-	-	-	-	1	(0.12)	-	-	-	-	-	-	2	- (>8)	2	- (1 - >4)
C. tropicalis	3	- (0.06 - >8)	-	-	-	-	1	- (0.06)	-	-	-	-	-	-	-	-

The percentage of patients with clinical relapse at follow-up in 100 mg POS and FLZ groups were 40% and 36%, respectively (Table 13). Relapse occurred between days 7 and 64 (median - 41 days) after discontinuation of POS (100 mg) therapy compared to 16 to 71 days (median - 22 days) after discontinuation of FLZ therapy.

Table 13: Patient with clinical relapse in the different treatment groups.

Treatment Group	Baseline Pathogen (n)	Relapse n/N (%)	Median day of relapse after discontinuation of therapy (range)
POS 50 mg	*C. albicans* (22); *C. glabrata* (1)	23/57 (40%)	30 (9 – 70)
POS 100 mg	***C. albicans* (24);** ***C. albicans* + *C. glabrata* (1);** ***C. albicans* + *C. krusei* (2)**	**27/67(40%)**	**41 (7 – 64)**
POS 200mg	*C. albicans* (17); *C. albicans* + *C. glabrata* (1); *C. glabrata* (1)	19/54 (35%)	42 (15 – 50)
POS 400 mg	*C. albicans* (18); *C. albicans* + *C. glabrata* (2); *C. albicans* + *C. krusei* (2); *C. glabrata* (1)	23/69 (33%)	39 (19 – 46)
FLZ 100 mg	***C. albicans* (18);** ***C. albicans* + *C. glabrata* (2);** ***C. glabrata* (1)** **Unidentified yeast (1)**	**22/61 (36%)**	**22 (16 – 71)**

n = number of subjects with pathogen;
Rows shown in bold indicated proposed dose of POS and approved dose of FLZ

The results of study C/I96-209 are consistent with that seen in study C/I97-331.

4.1.3. Study C/I97-330:

This was a Phase III, non-comparative, open-label, multi-center study of POS in HIV-infected subjects with OPC and/or EC unresponsive to standard treatment with oral FLZ or ITZ or with isolates resistant to FLZ or ITZ based on CLSI criteria (isolates were considered resistant to FLZ if MIC was $\geq$ 64 µg/ml and resistant to ITZ if MIC was $\geq$ 1 µg/ml). Refractory disease was defined as history of failure to standard course of therapy with FLZ $\geq$100 mg/day or ITZ 200 mg/day for at least 10 consecutive days. Patients using any systemic or oral antifungal therapy within 1 week prior to enrollment into the study or topical antifungals within 2 days of enrollment were excluded. Patients received POS oral suspension, 400 mg BID for 3 days, followed by 400 mg daily (QD) for 25 days. If at day 14, the subject was not responding to treatment, the investigator had the option to increase the POS dose to 400 mg BID. The treatment phase (25 days) was followed by a maintenance phase in which patients received 400 mg BID POS thrice weekly for 12 weeks. The protocol was amended on February 25, 1999. The amended protocol consisted of only the treatment phase (28 days; POS 400 mg BID). Thus, the total duration of treatment for patients enrolled in the study varied depending on whether they were part of the original or amended protocol (Table 14). All patients were to receive a clinical evaluation at 1 month post-treatment. However, the study was terminated and subjects were allowed to rollover to a new study (Protocol No. P00298, please see section 4.1.4) with a 12 month maintenance phase. Therefore, analysis for relapse rates in these patients could not be performed. As the acute treatment period for the original and amended protocols lasted from

days 1 through 29, this period of 4 weeks was the focus of the analyses performed by the sponsor and FDA.

The primary study objective was to assess the clinical response of refractory OPC following treatment with POS oral suspension at 4 weeks. Secondary objectives included: a) mycological response at 4 weeks; and b) *in vitro* susceptibility to POS before and after therapy.

Oral scrapings were examined for the presence of *Candida* in persistent plaques by KOH, fungal or Gram stain. In addition, quantitative cultures were performed using oral swish cultures. If both microscopic examination and quantitative culture were performed, the swish samples for quantitative culture were taken before the scraping was obtained for fungal microscopic exam. The speciation and susceptibility testing were performed at three different central laboratories (

However, only data confirmed at Laboratory were provided in the datasets. The definitions of clinical response and mycological response at EOT were same as in study C/I97-331. Please note that mycological success was based on ≤ 20 CFU/ml of *Candida* in quantitative oral swish cultures. Data on negative cultures for yeast were not available for this study.

The MITT population included all patients with a refractory OPC who received one dose of study drug and had a baseline *Candida* culture performed. The evaluable population included patients who met the inclusion/exclusion criteria, received at least 14 days of study drug and had an EOT evaluation. There were 199 patients enrolled in this study. Of the 199 patients, 176 were part of the MITT population and 158 were evaluable. The breakdown of the patients in the different populations and their baseline characteristics are shown in Table 14. Majority of patients in the study had low CD4 cell counts at baseline.

Table 14: Treatment duration and baseline CD4 cell counts of patients enrolled in study C/I 97-330.

Characteristics	**MITT (n = 176)**		**Evaluable (n = 158)**	
	Original Protocol	**Amended Protocol**	**Original Protocol**	**Amended Protocol**
Number of patients	89	87	81	77
Median treatment duration (range) in days	90 (1 - 197)	28 (2 – 41)	104 (4 – 197)	29 (12 - 41)
Baseline CD4 cells/mm^3- median (range)	12 (1 - 492)	10 (1 – 271)	12.5 (1 - 492)	10 (1 - 271)
C. albicans	64	58	61	53
C. dublinensis	0	1	0	0
C. glabrata	4	3	4	3
C. krusei	2	1	2	1
C. tropicalis	1	1	1	1
C. albicans + C. glabrata	11	18	7	14
C. albicans + C. krusei	2	4	1	4
C. albicans + C. norvegensis	0	1	0	1
C. albicans + C. tropicalis	1	0	1	0
C. dublinensis + C. glabrata	1	0	1	0
C. glabrata + C. krusei	1	0	1	0
glabrata + C. tropicalis	1	0	1	0
. glabrata + C. inconspicua + C. tropicalis	1	0	1	0

The medical officer independently identified patients that had refractory OPC based on failure to respond to standard FLZ or ITZ therapy immediately prior to initiation of POS rather than a history of failure to standard FLZ or ITZ therapy. For the purpose of this review, patients classified by the medical officer as refractory were analyzed (Table 15). Additionally, all patients with baseline isolates classified as resistant to FLZ and/or ITZ based on CLSI criteria were analyzed (Table 16).

Of the 176 MITT patients, 89 were considered as having refractory OPC by the medical officer. The clinical and mycological response in these 89 patients was analyzed (Table 15). The baseline pathogen in these patients were *C. albicans* (n = 60), *C. dublinensis* (n = 1), *C. glabrata* (n = 3), *C. tropicalis* (n = 1), and mixed infections due to *Candida* species (n = 22). Over 50% of the isolates had high FLZ (MIC ≥ 64 µg/ml; n = 15), high FLZ plus ITZ (FLZ MIC ≥ 64 µg/ml + ITZ MIC ≥ 1 µg/ml; n = 37) or high ITZ (MIC ≥ 1 µg/ml; n = 2) MIC values. The baseline CFU/ml in these 89 patients varied from 40 to 20,800 with the median baseline CFU/ml varying from 2962 to > 4000. Thus, majority of patients had a 2 log reduction in fungal burden. A successful clinical outcome was observed in 74% (66/89) patients. Mycological success based on ≤ 20 CFU/ml was observed in 33% (29/89) patients.

Table 15: Clinical and mycological response of 89 patients with refractory OPC in study C/I97-330 by baseline pathogen.

Species	N	Median baseline CFU/ml (range)	Clinical success	Mycological success
***C. albicans* – all**	**60**	**2962 (40 - 20800)**	**49/60 (82%)**	**23/60 (38%)**
– FLZ (≥ 64 µg/ml) + ITZ (≥ 1 µg/ml)	17	3350 (40 - >5000)	14/17 (82%)	5/17 (29%)
– FLZ (≥ 64 µg/ml)	11	1670 (60 - >5000)	11/11 (100%)	4/11 (100%)
– ITZ (≥ 1 µg/ml)	2	11010 (1220 - 20800)	2/2	0/2
***C. dublinensis* – all**	**1**	**- (290)**	**0/1**	**0/1**
***C. glabrata* – all**	**3**	**>4000 (>3000 - >5000)**	**1/3**	**1/3**
– FLZ (≥ 64 µg/ml) + ITZ (≥ 1 µg/ml)	2	>3000 (>3000)	1/2	0/2
***C. krusei* - all**	**2**	**4000 (3000 - 5000)**	**2/2**	**1/2**
– FLZ (≥ 64 µg/ml) + ITZ (≥ 1 µg/ml)	1	- (>5000)	1/1	1/1
– FLZ (≥ 64 µg/ml)	1	- (>5000)	1/1	0/1
***C. tropicalis*- all**	**1**	**- (>5000)**	**1/1**	**1/1**
– FLZ (≥ 64 µg/ml)	1	- (>5000)	1/1	1/1
***C. albicans* + *C. glabrata* - all**	**16**	**4251 (490 - >5000)**	**9/16 (56%)**	**3/16 (19%)**
– FLZ (≥ 64 µg/ml) + ITZ (≥ 1 µg/ml)	13	3500 (490 - > 5000)	8/13 (62%)	3/13 (23%)
– FLZ (≥ 64 µg/ml)	1	- (>5000)	0/1	0/1
***C. albicans* + *C. krusei* - all**	**4**	**4000 (560-7000)**	**2/4**	**0/4**
- (FLZ≥ 64 µg/ml + ITZ ≥ 1 µg/ml)	1	- (>5000)	0/1	0/1
– FLZ (≥ 64 µg/ml)	1	- (>3000)	1/1	0/1
***C. albicans* + *C. tropicalis* - all**	**1**	**- (12200)**	**1/1**	**0/1**
***C. glabrata* + *C. tropicalis* -all**	**1**	**- (>5000)**	**1/1**	**0/1**
– FLZ (≥ 64 µg/ml) + ITZ (≥ 1 µg/ml)	1	- (>5000)	1/1	0/1
Total	**89**		**66/89 (74%)**	**29/89 (33%)**

Clinical success = cure + improved
Mycological success = ≤20 CFU/ml of Candida species in oral swish samples.

As data on FLZ and ITZ MICs for isolates from all patients defined as refractory by medical officer plus those with history of failure to FLZ or ITZ therapy were available, an attempt was made to evaluate the clinical and mycological responses based on *in vitro* susceptibility of the

baseline isolate to FLZ and/or ITZ on all MITT patients (n = 176). The sponsor categorized isolates with FLZ MIC ≥ 32 µg/ml and ITZ MIC ≥ 1 µg/ml as resistant, irrespective of clinical refractoriness. The CLSI has a cut-off of ≥ 64 µg/ml for FLZ resistance with the caveat that this cut-off should not be used for *Candida* species intrinsically resistant to FLZ. For the purpose of this review, an analysis of isolates resistant to FLZ and ITZ was performed using the CLSI cut-off. Please note that although the CLSI document describes FLZ and ITZ interpretative criteria, the information has not been reviewed by the Agency and the FLZ and ITZ labels do not describe the breakpoints or interpretive criteria.

In vitro susceptibility data were available for 215 baseline isolates from 176 patients. Over 50% of the isolates had high FLZ (MIC ≥ 64 µg/ml; n = 41), high FLZ plus ITZ (FLZ MIC≥ 64 µg/ml + ITZ MIC ≥ 1 µg/ml; n = 61) or high ITZ (MIC ≥ 1 µg/ml; n = 14) MIC values (Table 16). The activity of POS against isolates that had high FLZ and/or ITZ MICs was similar to that seen with isolates having low FLZ and/or ITZ MIC values. Successful clinical outcome by species was as follows: *C. albicans* (76%, 121/159), *C. glabrata* (67%, 26/39), *C. krusei* (60%, 6/10). The number of isolates for other *Candida* species was low. Please note that the mycological success shown in Table 16 is based on the sponsor's criteria of ≤20 CFU/ml of *Candida* species in quantitative cultures. Although, this information is useful it is unclear if reduction in colony counts to ≤20 CFU/ml represents a true eradication. As mentioned previously, data on absence of yeast in culture were not collected.

Table 16: Clinical and mycological success at EOT in all patients with OPC with or without EC from study C/I97-330 by baseline species irrespective of single or mixed *Candida* infections[#].

Baseline Species*	MITT		Evaluable	
	Clinical success (%)	Mycological success[&] (%)	Clinical success (%)	Mycological success[&] (%)
C. albicans (FLZ MIC <64 µg/ml and ITZ <1 µg/ml)	58/78 (74%)	25/78 (32%)	55/66 (83%)	25/66 (38%)
C. albicans (FLZ MIC ≥ 64 µg/ml)	26/35 (74%)	9/35 (26%)	25/33 (76%)	9/33 (27%)
C. albicans (ITZ MIC ≥ 1 µg/ml)	7/7 (100%)	1/7 (14%)	7/7 (100%)	1/7 (17%)
C. albicans (FLZ MIC ≥64 µg/ml and ITZ ≥1 µg/ml)	30/39 (77%)	8/39 (21%)	30/36 (83%)	8/36 (22%)
***C. albicans* (all)**	**121/159 (76%)**	**43/159 (27%)**	**117/142 (83%)**	**43/142 (30%)**
C. glabrata (FLZ MIC <64 µg/ml and ITZ <1 µg/ml)	8/13 (62%)	2/13 (15%)	8/12 (67%)	2/12 (17%)
C. glabrata (FLZ MIC ≥ 64 µg/ml)	1/1	0/1	1/1	0/1
C. glabrata (ITZ MIC ≥ 1 µg/ml)	5/7 (71%)	0/7 (0%)	3/3 (100%)	0/3 (0%)
C. glabrata (FLZ MIC ≥64 µg/ml and ITZ ≥1 µg/ml)	12/18 (67%)	2/18 (11%)	11/15 (73%)	2/15 (13%)
***C. glabrata* (all)**	**26/39 (67%)**	**4/39 (8%)**	**23/31 (74%)**	**4/31 (13%)**
C. krusei (FLZ MIC <64 µg/ml and ITZ <1 µg/ml)	1/2	0/2	1/2	0/2
C. krusei (FLZ MIC ≥ 64 µg/ml)	2/4 (50%)	0/4 (0%)	2/4 (50%)	0/4 (0%)
C. krusei (FLZ MIC ≥64 µg/ml and ITZ ≥1 µg/ml)	3/4 (75%)	1/4 (25%)	3/3 (10%)	1/3 (33%)
***C. krusei* (all)**	**6/10 (60%)**	**1/10 (10%)**	**6/9 (67%)**	**1/9 (11%)**
C. dublinensis (FLZ MIC <64 µg/ml and ITZ <1 µg/ml)	1/2	0/2	1/1	0/1
***C. dubliniensis* (all)**	**1/2**	**0/2**	**1/1**	**0/1**
C. tropicalis (FLZ MIC <64 µg/ml and ITZ <1 µg/ml)	2/3	0/3	2/3	0/3
***C. tropicalis* (all)**	**2/3**	**0/3**	**2/3**	**0/3**
C. inconspicua (FLZ MIC <64 µg/ml and ITZ <1 µg/ml)	1/1	0/1	1/1	0/1
***C. inconspicua* (all)**	**1/1**	**1/1**	**1/1**	**1/1**
rvegensis (FLZ MIC ≥ 64 µg/ml)	1/1	1/1	1/1	1/1
***C. norvegensis* (all)**	**1/1**	**1/1**	**1/1**	**1/1**
Total	**158/215 (73%)**	**50/215 (23%)**	**151/188 (80%)**	**50/188 (27%)**

*Species were categorized based on interpretive criteria used by CLSI. However, these criteria do not apply for strains known to be intrinsically resistant to fluconazole such as *C. krusei* and *C. norvegensis*. Please note that the data supporting the interpretive criteria have note been reviewed by the FDA and the FLZ and ITZ labels do not include any information on breakpoints. Patients may have more than one *Candida* species at baseline.

[#] The analysis is based on dataset OPC330.xpt provided by the sponsor.

[&]Mycological success was based on ≤ 20 CFU/ml of *Candida* species in quantitative culture.

There was overlap in the baseline POS MIC for patients with clinical or mycological success versus clinical or mycological failure (Figures 4 and 5). The number of isolates with high POS MIC (≥ 2 µg/ml) was low.

Figure 4: Relationship between baseline posaconazole MIC of *Candida* isolates and clinical outcome at 4 weeks for patients with OPC from study C/I97-330. Median MIC of isolates from patients with successful outcome = median MIC of isolates from patients who failed = 0.25 µg/ml

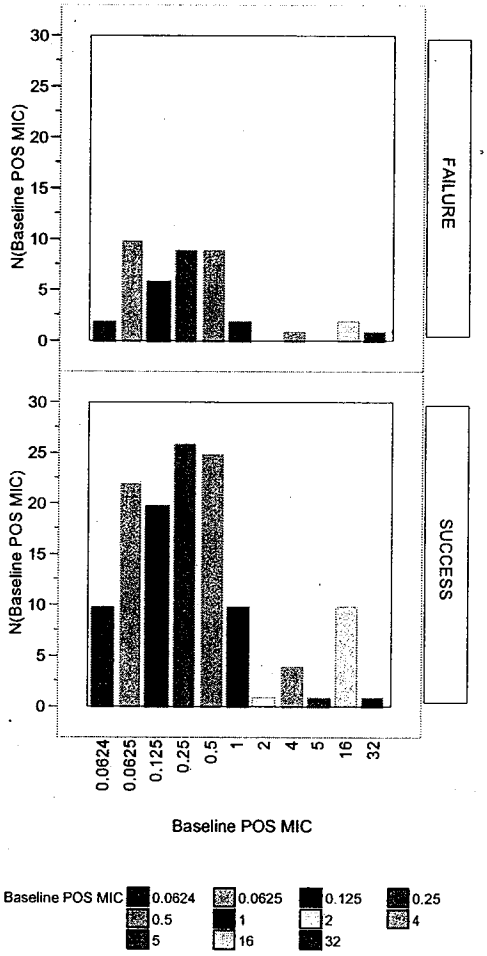
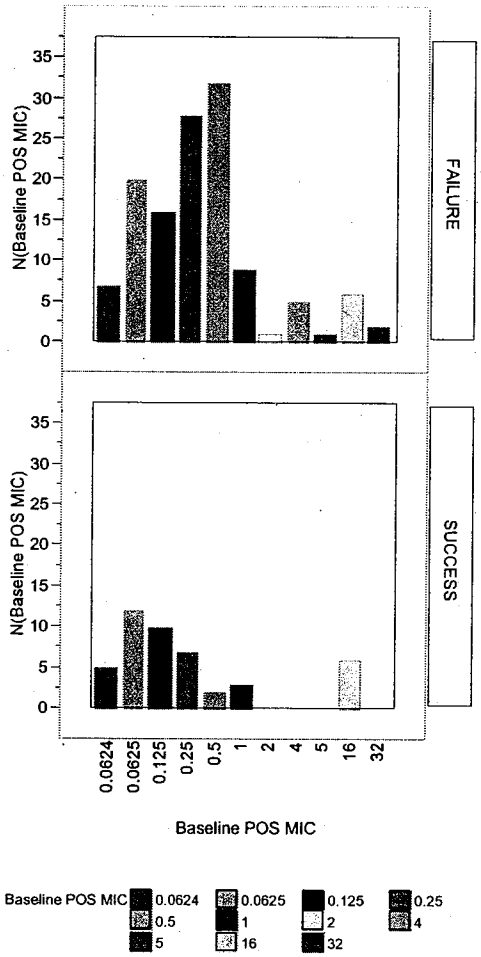
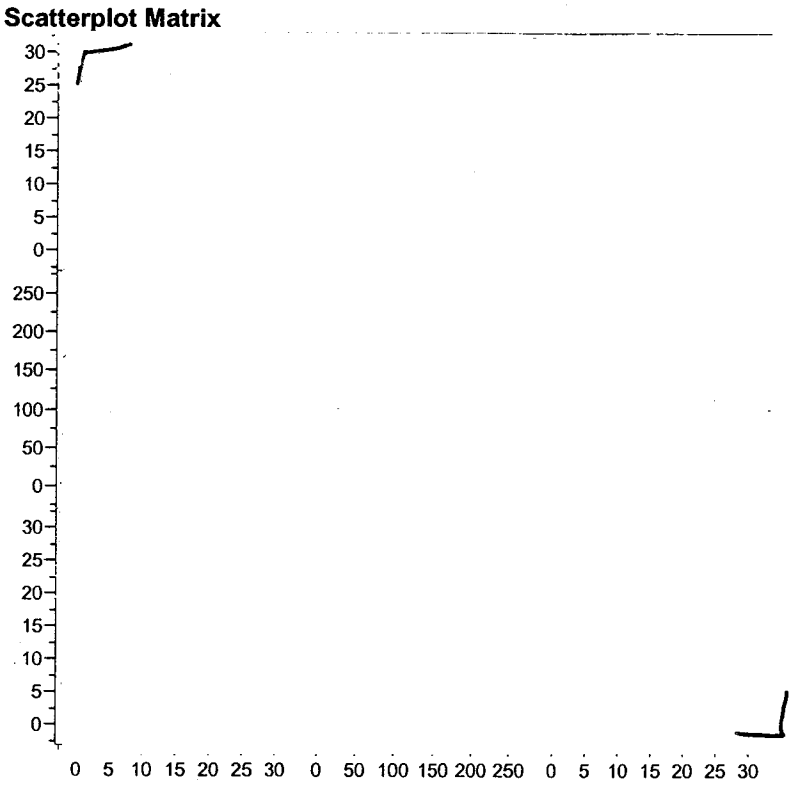


Figure 5: Relationship between baseline posaconazole MIC of *Candida* isolates and mycological outcome at 4 weeks for patients with OPC from study C/I97-330. Please note mycological success is based on ≤20 CFU/ml of *Candida* species in quantitative cultures. Median MIC for isolates from patients with a successful mycological outcome = 0.125 µg/ml; Median MIC for isolates from patients who failed mycologically = 0.25 µg/ml.



A scattergram of POS MIC versus FLZ or ITZ MICs of baseline isolates was plotted (Figure 6). The POS MICs correlated positively with ITZ MIC (r = 0.84), suggesting cross-resistance between the two azoles. The correlation between POS and FLZ MICs of baseline isolates was low (r = 0.43).

Figure 6: Scattergram of posaconazole (POS) MIC versus fluconazole (FLZ) and itraconazole (ITZ) MICs of baseline isolates.



Increase (>32 fold) in POS MIC was observed in isolates from 2 patients during POS therapy (Table 17). However, both patients had a successful clinical outcome but were mycological failures.

Table 17: Changes in posaconazole susceptibility of *Candida* isolates from study C/I97-330.

Patient ID	Pathogen	Baseline POSMIC (µg/ml)	POS MIC at 4 weeks (µg/ml)	Clinical outcome at 4 weeks	Mycological outcome at 4 weeks
C97330-3-000005	*Candida albicans*	0.125	>8.0	Cure	Persistence
I97330-11-000005	*Candida glabrata*	0.5	>16.0	Improvement	Persistence

POS = posaconazole

Relapse rates could not be analyzed as majority of patients continued onto the maintenance phase with study drug or were discontinued from the study.

4.1.4. Study P00298

This was a Phase III, noncomparative, open-label, multi-center study of POS in HIV-infected patients with OPC and/or EC refractory to other azole antifungal agents. Patients (1) who were previously treated with POS in study C/I97-330 and who had incomplete resolution of disease or relapse, or (2) whose condition failed to improve or worsened after a standard course of therapy with FLZ or ITZ within 3 months prior to enrollment were included. There was no requirement

for a washout period after terminating therapy with a systemic antifungal agent. During the treatment phase, subjects received 400 mg BID POS oral suspension for up to 3 months in contrast to 25 - 28 days in the study C/I97-330.

Clinical and mycological evaluations and response definitions were same as in study C/I97-330. laboratory served as the central laboratory for fungal culture, speciation and susceptibility testing. The primary efficacy endpoint was clinical response (cure or improved) at the end of the 3 month acute treatment period. Subjects with a clinical response of cure were observed for up to 1 month during an untreated follow-up period. Subjects who relapsed during follow-up or who showed improvement at the end of the treatment phase were eligible for the maintenance phase, continuing treatment with POS 400 mg BID for up to 12 months. The maintenance phase in this study was longer compared to study C/I97-330 (3 months).

The MITT subset included all treated subjects with a positive culture for *Candida* and evidence of clinical or mycological resistance to *Candida* at baseline. The evaluable subset included all treated subjects who satisfied all key inclusion/exclusion criteria and received at least 60 days of study medication with no more than 7 consecutive days missed. The study included 60 patients who rolled-over from study C/I97-330 (POS treated) and 40 posaconazole naïve patients (POS naïve). The study was considered supportive as majority of the patients in this study rolled-over from study C/I97-330. Of the 60 POS treated patients rolled over from C/I97-330, 58 were included in the MITT population and 49 were evaluable. Of the 40 posaconazole naïve patients, 32 were included in the MITT population and 26 were evaluable. The treatment duration, baseline CD4 counts, and baseline *Candida* CFU/ml in the POS treated and POS naïve patients, in the MITT and evaluable populations are shown in Table 18. The Medical officer determined that none of the subjects had refractory OPC in this study.

Table 18: Baseline characteristics of patients in study P000298.

Baseline characteristics	**MITT (n = 90)**		**Evaluable (n = 75)**	
	POS treated (n = 58)	**POS naïve (n = 32)**	**POS treated (n = 49)**	**POS naïve (n = 26)**
Median treatment duration in days (range)	129 (8 - 708)	84.5 (1 - 486)	154 (8 – 708)	87 (1 – 486)
Median CD4 cells/mm^3 (range)	36 (4 – 68)	5.5 (0 - 72)	36 (4 – 68)	5.5 (0 - 41)
Median *Candida* CFU/ml (range)	1100 (40 - 100,000)	1000 (70 – 100,000)	1140 (40 – 18,000)	1810 (70 – 100,000)

The analysis of clinical and mycological response by baseline pathogen was performed using the "OPC298.xpt"dataset provided by the sponsor. Of the MITT patients, the baseline *Candida* species was not identified in 11 POS treated patients and 6 POS naïve patients (Table 19). *C. albicans* was the most common pathogen identified at baseline (34/58 in POS treated group and 11/32 in POS naïve group). The baseline pathogens in the remaining patients were *C. glabrata* (n = 3), *C. parapsilosis* (n = 2), *C. tropicalis* (n = 1), mixed infections due to multiple *Candida* species or *C. albicans* + *Saccharomyces* (n = 22). Most patients in the POS naïve population had baseline isolates with high FLZ (≥ 64 µg/ml) and/or ITZ (≥ 1 µg/ml) MICs (Table 20). Clinical success in POS treated and POS naïve groups were 84% and 81%, respectively (Table 19). Mycological evaluations were not mandatory for patients who responded clinically. Mycological responders had ≤ 20 CFU/ml of baseline *Candida* species in the oral swish samples.

Mycological response was observed in 7% patients in the POS treated group and 16% in the POS naïve group. The evaluable population showed similar results. Data on absence of yeast in culture were not collected.

Of the 34 patients with baseline *C. albicans*, 6 patients relapsed (Table 19). Majority of patients did not have a follow-up visit as they continued onto maintenance phase or discontinued.

Table 19: The clinical and mycological response of patients enrolled in study P000298 by baseline pathogen.

Species	MITT				Evaluable			
	POS treated		POS naive		POS treated		POS naive	
	Clinical success*	Mycological responder#	Clinical success*	Mycological responder#	Clinical success*	Mycological responder#	Clinical success*	Mycological responder#
C. albicans	30/34 (6R)	4/34	10/11	3/11	29/40 (6R)	3/40	8/9	3/9
C. albicans + *C. glabrata*	8/9	0/9	4/6	0/6	7/8	0/8	2/4	0/4
C. albicans + *C. krusei*	0/0	0/0	1/1	0/1	0/0	0/0	1/1	0/1
C. albicans + *C. tropicalis*	0/0	0/0	1/1	1/1	0/0	0/0	1/1	1/1
C. albicans + *Saccharomyces cerevisiae*	2/2	0/2	0/1	0/1	2/2	0/2	0/1	0/1
C. glabrata	1/1	0/1	2/2	1/2	1/1	0/1	2/2	1/2
C. glabrata + *C. krusei*	1/1	0/1			1/1	0/1		
C. albicans + *C. glabrata* + *C. krusei*	0/0	0/0	1/1	0/1	0/0	0/0	0/0	0/0
C. dublinensis + *C. glabrata*	0/0	0/0	1/1	0/1	0/0	0/0	1/1	0/0
C. parapsilosis	0/0	0/0	1/1	0/1	0/0	0/0	1/1	0/1
C. tropicalis	0/0	0/0	0/1	0/1	0/0	0/0	0/1	0/1
Unidentified *Candida*	7/11	0/11	5/6	0/6	5/6	0/6	5/6	0/6
Total	**49/58 (84%)**	**4/58 (7%)**	**26/32 (81%)**	**5/32 (16%)**	**45/58 (78%)**	**3/58 (5%)**	**19/26 (73%)**	**5/26 (19%)**

* clinical success = cure and improved. The number followed by letter R in the parenthesis indicates the number of patients who relapsed clinically at follow-up.

Mycological responder had ≤ 20 CFU/ml of baseline *Candida* species.

Note: The majority of MITT subjects were not assessed for clinical relapse at follow-up Month 1 because they either did not have the follow-up visit, going immediately into maintenance or discontinuing during acute treatment, or they were already treatment failures. Cultures at the end of acute treatment were not mandated for subjects who were clinical responders.

Majority of the patients had isolates with low baseline POS MIC. The number of isolates with high MIC (≥ 2 µg/ml) was too low to determine the correlation between clinical outcome and baseline POS MIC (Figure 7).

Table 20: Clinical and mycological outcome of POS naïve patients stratified by FLZ and ITZ MICs of baseline pathogen.

Pathogen (MIC µg/ml)	**MITT**			**Evaluable**		
	n	**Clinical outcome**	**Mycological outcome**	**n**	**Clinical outcome**	**Mycological outcome**
***C. albicans* -all**	**11**	**10/11 (91%)**	**3/11 (27%)**	**9**	**8/9 (89%)**	**3/9 (33%)**
- FLZ (≥ 64 µg/ml) + ITZ (≥ 1 µg/ml)	6	5/6	0/6	5	4/5	0/5
- ITZ (≥ 1 µg/ml)	1	0/1	0/1	0	0	0
- FLZ (≥ 64 µg/ml)	2	2/2	1/2	2	2/2	1/2
***C. glabrata* -all**	**2**	**2/2**	**1/2**	**2**	**2/2**	**1/2**
- FLZ (≥ 64 µg/ml) + ITZ (≥ 1 µg/ml)	2	2/2	1/2	2	2/2	1/2
***C. tropicalis* -all**	**1**	**0/1**	**0/1**	**1**	**0/1**	**0/1**
***C. parapsilosis* -all**	**1**	**1/1**	**0/1**	**1**	**1/1**	**0/1**
***C. albicans* + *C. glabrata* -all**	**6**	**4/6**	**0/6**	**4**	**2/4**	**0/4**
- FLZ (≥ 64 µg/ml) + ITZ (≥ 1 µg/ml)	4	4/4	0/4	2	2/2	0/2
- ITZ (≥ 1 µg/ml)	1	1/1	0/1	1	1/1	0/1
***C. albicans* + *C. krusei* -all**	**1**	**1/1**	**0/1**	**1**	**1/1**	**0/1**
***C. albicans* + *C. tropicalis*-all**	**1**	**1/1**	**1/1**	**1**	**1/1**	**1/1**
- FLZ (≥ 64 µg/ml) + ITZ (≥ 1 µg/ml)	1	1/1	0/1	1	1/1	0/1
***C. albicans* + *Saccharomyces*-all**	**1**	**0/1**	**0/1**	**1**	**0/1**	**0/1**
- FLZ (≥ 64 µg/ml) + ITZ (≥ 1 µg/ml)	1	0/1	0/1	1	0/1	0/1
***C. albicans* + *C. glabrata* + *C. krusei*- all**	**1**	**1/1**	**0/1**	**0**	**0/0**	**0/0**
- FLZ (≥ 64 µg/ml) + ITZ (≥ 1 µg/ml)	1	1/1	0/1	0	0/0	0/0
***C. dublinensis* + *C. glabrata* -all**	**1**	**1/1**	**0/1**	**1**	**1/1**	**0/1**
- FLZ (≥ 64 µg/ml) + ITZ (≥ 1 µg/ml)	1	1/1	0/1	1	1/1	0/1
Unidentified *Candida*	**6**	**5/6**	**0/6**	**5**	**5/5**	**0/5**
Total	**32**	**26/32 (81%)**	**5/32 (16%)**	**26**	**21/26 (81%)**	**5/26 (19%)**

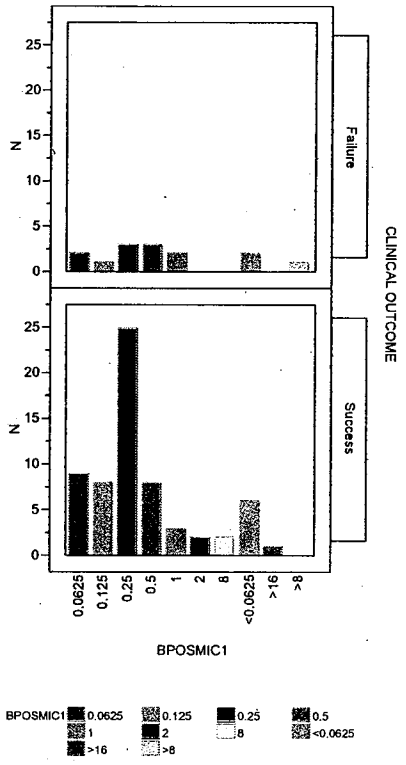


Figure 7: Relationship between POS MIC and clinical outcome in study P00298 at 3 month after POS therapy

Based on data from study C/I97-330, clinical success was observed in 74% (66/89) patients with refractory OPC after 1 month of POS treatment. For studies C/I97-330 and P00289, the clinical success in patients with isolates having high FLZ (≥ 64 mg/ml) and/or ITZ (≥ 1 μg/ml) MICs were similar to those with susceptible *Candida* isolates. However, please note that studies C/I97-330 and P00289 had limitations in that mycological success was based on quantitative culture of ≤20 CFU/ml of baseline *Candida* species and it is unclear if this represents true eradication (absence of yeast).

5. CONCLUSIONS

The subject of this NDA is POS, an azole antifungal agent for the treatment of OPC, including infections refractory to ITZ and/or FLZ. For treatment of OPC, a loading dose of 200 mg oral suspension on the first day followed by 100 mg once daily for 13 days was proposed. For refractory OPC, a 400 mg dose twice a day was proposed. The duration of therapy for refractory OPC will be based on the severity of the patient's underlying disease and clinical response.

No new preclinical information was included in this submission. For a summary of preclinical microbiology, please see microbiology review [redacted] NDA 22-003 dated 5-15-06.

The sponsor submitted 4 studies in HIV infected patients with OPC: 2 studies (C/97-331 and C/I96-209) enrolled patients with azole susceptible OPC while 2 others (C/I97-330 and P000298) enrolled patients with OPC refractory to FLZ or ITZ. POS loading dose of 200 mg followed by 100 mg QD for 13 days was evaluated. Study C/I96-209 was a phase II dose ranging study using the capsule rather than the proposed oral suspension formulation of POS. The POS loading dose was high (400 BID) followed by 4 different POS regimens (50 mg. 100 mg, 200 mg and 400 mg) for 13 days. Please note that this study was considered supportive for the indication. Fluconazole was the comparator in both studies. The primary endpoint in both studies was clinical success at 14 days (EOT). In the pivotal study C/I97-331, a successful clinical outcome was observed in 92% of patients treated with POS compared to 93% patients treated with FLZ. Mycological response data based on absence of yeast in quantitative culture and ≤ 20 CFU/ml of *Candida* species in oral swish samples were available. It is unclear if ≤ 20 CFU/ml of *Candida* species in oral swish samples represents true eradication. Hence, a conservative approach of absence of yeast in culture was used to determine mycological success. The percentage of patients showing mycological eradication in the POS and FLZ arms was 53% and 50%, respectively. Use of the conservative approach resulted in 9 POS treated patients and 10 FLZ treated patients being converted to mycological failures. All these patients had a clinically successful outcome. The log change in CFU/ml in oral swish samples of patients with clinical cure ranged from -2.5 log to +1 log in the POS arm (n = 47) and from – 3 log to +1 log in the FLZ arm (n = 48). One patient with clinical failure in each of POS and FLZ arm showed no change in CFU, and a 1 log increase in CFU at EOT, respectively. Based on limited data, it is unclear how log change in CFU correlates with clinical cure. Majority of patients in the study had *C. albicans* as the baseline isolate. The POS MIC_{90} for baseline *C. albicans* was 0.06 μg/ml. Eleven patients in the POS arm had super-infections with a *Candida* species other than that observed at baseline. The POS MIC for isolates causing super-infections was low (≤ 0.5 μg/ml). The POS MIC_{90} of isolates from patients with clinical and mycological success was 0.06 μg/ml.

Clinical relapse was observed in 30% patients treated with POS compared to 34% patients treated with FLZ at 1 month post-treatment. Similarly, mycological relapse was observed in 32% of patients treated with POS compared to 35% patients treated with FLZ. *C. albicans* isolates from 2 patients with clinical relapse after POS therapy showed an increase in POS and FLZ MICs at follow-up.

Study C/I96-209 was a dose ranging study with the capsule formulation. No dose response was observed in this study. The sponsor has stated that this was due to the high loading dose of POS used in the study and long half-life of the drug. A successful clinical response was observed in 90% of POS treated patients compared to 94% treated with FLZ. Asymptomatic carriage of yeasts is common in HIV infected patients. A greater reduction in medium cfu/ml was noted in patients with clinical success compared to those who failed in all treatment groups. However, the ranges of log change in CFU of *Candida* species in oral swish samples overlapped in patients with clinical success and clinical failure except for few outliers. The number of patients with no change or increase in CFU/ml was too small. The relationship between number of yeasts in oral swish sample and clinical disease could not be established. As many factors affect oral carriage of yeast and *Candida* is part of the normal oral flora, oral swish samples may not be useful to document OPC infections. Super-infection was observed in 4 patients treated with 100 mg POS. The POS MIC of these isolates ranged from 0.06 to 1 µg/ml. The POS MIC for isolates from patients with a successful clinical outcome overlapped with those of isolates from patients with clinical failure. Relapse was observed in 40% patients treated with POS 100 mg compared to 36% patients treated with FLZ 100 mg. The median (range) day of relapse in the POS and FLZ arms were 41 (7 to 64), and 22 (16 to 71) days, respectively. The results of study C/I96-209 were consistent with the pivotal study C/I97-331. Overall, the two studies show that the efficacy of POS is similar to FLZ and that POS has activity against *C. albicans* (Table 21). The number of patients with *Candida* species other than *C. albicans* as sole pathogen was low. Irrespective of mixed infection, the percentage of patients with *C. glabrata* (17%, 3/18) or *C. krusei* (38%, 3/8) with successful overall outcome was low.

Table 21: Pooled results for overall response stratified by baseline pathogen irrespective of mixed infection in OPC studies C/I97-331 and C/I96-209.

Pathogen	POS			FLU		
	Study C/I97-331	Study C/I96-209	Both studies	Study C/I97-331	Study C/I96-209	Both studies
	Overall response at 14 days	Overall response at 14 days	Overall response at 14 days	Overall response at 14 days	Overall response at 14 days	Overall response at 14 days
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
C. albicans	84/163 (52%)[a]	33/78 (42%)[a]	**117/241 (49%)**	88/155 (48%)[a]	39/69 (56%)[a]	**127/224 (57%)**
C. dublinensis	0/1	0/0	**0/1**	0/1	1/1	**1/2**
C. glabrata	3/14 (21%)*	0/4[#]	**3/18 (17%)**	2/8 (25%)[#]	0/6[&]	**2/14 (15%)**
C. krusei	2/5 (40%)[#]	1/3*	**3/8 (38%)**	5/7 (71%)[#]	0/0*	**5/7 (71%)**
C. lipolytica	0/0	0/0	**0/0**	0/0	0/0	**0/0**
C. nodaensis	1/1	0/0	**1/1**	0/0	0/0	**0/0**
C. pseudotropicalis	0/0	0/1	**0/1**	0/0	0/0	**0/0**
C. tropicalis	0/3	1/1	**1/4**	1/4	1/2	**2/6 (33%)**

Overall response = clinical cure or improved and mycological eradication
* all patients with mixed infections
[#] only 1 patients with single infection rest were mixed infection
[&] 3 patients with single infection and 3 with mixed infection
[a] includes patients with mixed infection

Study C/I97-330 was the pivotal study for refractory OPC indication. The study was open label study in HIV infected subjects with OPC refractory to FLZ or ITZ therapy or OPC due to FLZ or ITZ resistant *Candida* [resistant definition based on CLSI criteria]. Patients received 400 mg POS BID for 3 days followed by 400 mg QD or BID for 25 days (original protocol) or 400 mg POS BID for 28 days (amended protocol). After this period of acute treatment, patients could continue therapy (maintenance phase) for up to 3 months. This protocol was later terminated and patients rolled over to another open label study P00298. Please note that 60 of the 100 patients enrolled in study P00298 were previously enrolled in study C/I97-330 and the study did not have a consistent end of therapy evaluation. Therefore, this study was considered supportive. The mycological success in these studies was based on a threshold of $\leq$ 20 CFU/ml of *Candida* species in oral swish samples. The basis for this threshold is unclear. A study evaluating asymptomatic oral carriage of *Candida albicans* in HIV infected patients showed that the concentration of yeast in rinse for patients with OPC was similar to those without OPC and varied from 10 to 3000 CFU/ml (Fong *et al.*, 1997, Clin Invest Med 20: 85-90). Oral carriage of *Candida* was associated with low CD4 cell counts. In another study (Vargas and Joly 2002, J. Clin. Micro 40: 341-350), intensity of carriage increased with progression from asymptomatic carriage to oral thrush. Although, yeast carriage over time is useful to predict onset of clinical disease, its usefulness to predict efficacy is not known. The medical officer determined that 89 patients enrolled in study C/I97-330 had refractory OPC. A successful clinical outcome was observed in 66 (74%) patients. A majority of patients had *C. albicans* followed by *C. glabrata* and *C. krusei* as the baseline pathogen (Table 22). However, it should be noted that most patients with *C. glabrata* and *C. krusei* had mixed infections. A 2 log reduction in fungal burden was observed in majority of patients. None of the patients enrolled in study P000298 were considered to have refractory OPC. The POS MIC for patients with a successful clinical outcome overlapped with that of isolates from patients with clinical failure in studies C/I97-330 and P000298. However, there was a positive correlation between POS MIC and ITZ MIC of baseline isolates, suggesting cross-resistance between the two azoles. Increase in POS MIC was observed in isolates from 2 patients at 4 weeks of POS therapy. Relapse rates could not be determined as majority of patients continued onto maintenance phase or discontinued from study.

Over 50% of the isolates in studies C/I97-330 and P000298 had high FLZ ($\geq$ 64 µg/ml) and/or ITZ ($\geq$1 µg/ml) MIC values (resistant according to CLSI criteria). The sponsor attempted to evaluate the efficacy of POS in patients with isolates categorized as resistant to FLZ and/or ITZ based on CLSI criteria. Please note that although the CLSI document describes FLZ and ITZ interpretative criteria, the information has not been reviewed by the Agency and the FLZ and ITZ labels do not describe the breakpoints or interpretive criteria.

Table 22: Clinical response by baseline pathogen irrespective of mixed infections for refractory OPC studies C/I97-330 and P00298

Pathogen	Study C/I97-330	Study P00298
	Clinical response at 4 weeks	Clinical response at 3 months
	n/N (%)	n/N (%)
C. albicans	117/142 (83%)	12/16 (75%)
C. dublinensis	1/1	1/1
C. glabrata	23/31 (74%)	5/7 (71%)
C. krusei	6/9 (67%)	1/1
C. inconspicua	1/1	0/0
C. norvegensis	1/1	0/0
C. parapsilosis	0/0	1/1
C. tropicalis	2/3	1/2

Overall, the studies suggest that POS is effective for treatment of OPC, including OPC refractory to FLZ or ITZ.

6. LABEL

6.1. Sponsor's version of the label

2 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

7. RECOMMENDATIONS

This NDA submission is approvable with respect to Microbiology pending an accepted version of the label.

Kalavati Suvarna
Microbiologist, HFD-590

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