CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-027

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDAs/Serial Number:	22-027
Drug Name:	Noxafil™ (posaconazole) oral suspension
Indication(s):	Oropharyngeal Candidiasis
Applicant:	Schering-Plough Research Institute
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Keywords: clinical studies, NDA review, anti-fungal, oropharyngeal candidiasis, non-inferiority

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The efficacy of posaconazole oral suspension for the treatment of oropharyngeal candidiasis (OPC) in HIV positive patients was supported primarily by one controlled study. This study demonstrated that the efficacy (as assessed by the clinical response rate at the end therapy) of posaconazole is non-inferior to fluconazole assuming a non-inferiority margin of 15%. In addition, a multiple dose study of posaconazole oral capsule in HIV-positive subjects with OPC provided supportive efficacy data. Further, data on the effectiveness of posaconazole oral suspension in HIV-positive subjects with OPC refractory to treatment with fluconazole or itraconazole was provided in a non-comparative study. It is left to the medical division to determine whether the information from this study is sufficient to extend the indication to include a claim regarding the treatment of OPC refractory to treatment with fluconazole or itraconazole.

1.2 Brief Overview of Clinical Studies

One pivotal study, C/I97-331, has been submitted to provide support for the use of posaconazole oral suspension in the treatment of azole-susceptible OPC in HIV-positive patients. C/I97-331 was a Phase 3, randomized, comparative open-label (evaluator-blinded) study to evaluate the safety and efficacy of posaconazole versus fluconazole in OPC in HIV-positive patients. The study was conducted at sites in the United States and internationally. Subjects were randomized to receive either posaconazole oral suspension or fluconazole oral suspension in a 1:1 ratio. Both treatments were administered as a loading dose of 200 mg on day 1 followed by maintenance doses of 100 mg daily thereafter for 13 days. The primary efficacy endpoint was the clinical response based on signs and symptoms of oral mucositis at the end of therapy.

Supportive evidence was provided by Study C/I96-209, a Phase 2, randomized, double blind study to evaluate the safety, tolerability, and efficacy of multiple doses of posaconazole oral capsule versus fluconazole oral tablet in the treatment of OPC in HIV-positive patients. The study was conducted at sites in the United States and internationally. Subjects were randomized to receive one of 4 doses of posaconazole oral capsule or fluconazole oral tablet in a 1:1:1:1:1 ratio. All dose regimens of posaconazole oral capsules were administered as a loading dose of 400 mg on day 1. From day 2 to 14, posaconazole oral capsules were administered in 1 of 4 once a day regimens: 50 mg, 100 mg, 200 mg, or 400 mg. Fluconazole oral tablets were administered as a loading dose of 200 mg on day 1 followed by maintenance doses of 100 mg daily thereafter for 13 days. The primary efficacy endpoint was the clinical response based on signs and symptoms of oral mucositis at the end of therapy.

Also submitted was Study C/I97-330, a non-comparative study of HIV-positive subjects with OPC that was clinically refractory and/or microbiologically resistant to standard treatment

with fluconazole or itraconazole. Subjects were treated with posaconazole oral suspension 400 mg BID for 3 days followed by 400 mg once a day for 25 days with an option for further treatment during a 3 month maintenance period. After an amendment, subjects received 400 mg BID for 28 days. The primary endpoint was clinical response after 4 weeks.

1.3 Statistical Issues and Findings

OPC is an indication that would usually require 2 randomized controlled trials to determine efficacy. This submission contains only one randomized controlled trial using the formulation for which approval is being requested, posaconazole oral suspension. Supportive evidence is provided by the non-comparative study of posaconazole oral suspension in HIV-positive subjects with OPC that was clinically refractory and/or microbiologically resistant to standard treatment with fluconazole or itraconazole and the controlled multiple dose study of posaconazole oral capsule.

In study C/I97-331, the clinical success rate at the end of therapy (14 days) was 91.7% (155/169) for posaconazole oral suspension and 92.5% (148/160) for fluconazole. A 95% confidence interval about the difference between the success rates (posaconazole – fluconazole) was calculated to demonstrate the non-inferiority of posaconazole to fluconazole. The lower bound of this confidence interval was greater than the non-inferiority margin of -15%. Clinical response rates 4 weeks after treatment were similar between posaconazole (58%) and fluconazole (52.5%) but much lower than that observed at the end of therapy.

The 15% non-inferiority margin was proposed by the sponsor. The review team requested a justification of the non-inferiority margin on 4/24/06. The Applicant stated in their response dated 5/9/06 that a spontaneous cure rate with placebo of any magnitude would be unexpected particularly in HIV-infected patients with low CD_4 counts (<100). They also stated that the literature reports clinical success rates for fluconazole of 87% to 96%. Two studies of nystatin versus fluconazole were cited, one conducted in immunocompromised children with OPC and one in HIV-infected adults with OPC. In the study of immunocompromised children with OPC, the nystatin and fluconazole rates were 46% and 86%, respectively. In the study of HIV infected adults, the response rates were 52% for nystatin versus 87% for fluconazole and the 95% confidence interval for the difference in response rates (nystatin – fluconazole) was (-53%, -27%). Based on this, the non-inferiority margin that would retain 50% of this effect would correspond to a margin of -13.5%. The Applicant states that the 15% non-inferiority margin selected for Study C/I97-331 represents a small loss of efficacy that should still result in a treatment effect that is substantially higher than placebo. The Applicant's response does not discuss how their search of the literature was performed and if all applicable studies were reviewed. There is also no discussion of the constancy of the effect of the control by comparing the study design of the current study and the previous studies. The medical division, however, accepted the 15% non-inferiority margin to provide proof of the efficacy of posaconazole.

In study C/I96-209, the clinical success rate at the end of therapy (14 days) was 86.8% (79/91) for 100 mg posaconazole oral capsule and 89.2% (74/83) for fluconazole. The 95.2% confidence interval about the difference between the success rates was (-13.3, 8.5).

In study C/I97-331, the clinical success rate after 4 weeks of treatment was 74.2% (66/89).

2. INTRODUCTION

2.1 Overview

This is an NDA submission for posaconazole oral suspension. Posaconazole belongs to the triazole class of antifungal agents. The indication being sought by the applicant in this NDA is the treatment of oropharyngeal candidiasis (OPC), including infections refractory to itraconazole and fluconazole. The proposed therapeutic dose and regimen of posaconazole for OPC is a 200 mg oral suspension loading dose on the first day, followed by 100 mg oral suspension once daily thereafter for 13 days. The proposed therapeutic dose and regimen for refractory OPC is 400 mg twice a day for a duration of therapy based on the severity of the patient's underlying disease and clinical response.

[redacted] At the same time as the submission of the NDA for OPC, the applicant submitted NDA 22-003 for the indication of prophylaxis of fungal infections in patients who are at high risk of developing these infections. This NDA was approved on September 15, 2006.

The development program for OPC consisted of two randomized active controlled studies of HIV-infected subjects with azole-susceptible OPC (C/I96-209 and C/I97-331) and two non-comparative studies of HIV-infected subjects with azole-refractory OPC (C/I97-330 and P00298). Study C/I96-209 was a proof of concept dose ranging study of 4 doses of posaconazole oral capsules (50 mg, 100 mg, 200 mg, and 400 mg once daily all with a loading dose of 400 mg BID on Day 1) versus fluconazole. Study C/I97-331 was a phase 3 study of the safety and efficacy of posaconazole oral suspension versus fluconazole in the treatment of HIV-positive patients with OPC. Studies C/I97-330 and P00298 were open label studies of posaconazole oral suspension conducted in HIV-infected subjects with OPC who were clinically refractory and/or microbiologically resistant to treatment with fluconazole or itraconazole (azole-refractory OPC). Sixty of the 100 subjects in Study P00298 had been previously enrolled in Study C/I97-330.

Reviewer's Comment: *This review will focus on the pivotal OPC study, C/I97-331. Study C/I96-209 will be briefly discussed in this review since it provides supportive evidence of the*

efficacy of posaconazole in OPC in a randomized controlled study even though it used the oral capsule rather than the oral suspension of posaconazole. Also, the loading dose used with the oral capsule was higher than that used with the oral suspension. As for the studies of refractory OPC, the Medical Division imposed a requirement that the course of previous azole treatment for the current episode of OPC had to occur immediately before the initiation of treatment with posaconazole. Only subjects from Study C/I97-330 met this requirement. Therefore only Study C/I97-330 will be discussed in this review and just briefly since it was a non-comparative study. For a complete discussion of Studies C/I96-209 and C/I97-330, please refer to the Medical Officer review by Regina Alivisatos, M.D.

2.2 Data Sources

The data analyzed in this review comes from the Phase 3 study of the treatment of OPC, the multiple dose OPC study, and one study of refractory OPC submitted as the evidence to support the efficacy of posaconazole for the treatment of OPC. The study reports and datasets provided in the electronic submission were reviewed. These can be found in the

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study C/I97-331

3.1.1.1 Study Design

Study C/I97-331 was a Phase 3, open label, evaluator-blinded, randomized, multicenter study of posaconazole oral suspension versus fluconazole oral suspension in the treatment of HIV-positive subjects with OPC. The study was conducted at 44 centers in the United States and internationally from December 15, 1998 through October 27, 1999. The majority of the subjects were enrolled at the centers in South Africa (86), the United States (78), Chile (40), Thailand (34), and Mexico (32). The remaining countries enrolled 15 or few subjects. Subjects were randomized in a 1:1 ratio to receive either posaconazole oral suspension or fluconazole oral suspension. Therapy was to last for 14 days. Both treatments were administered as a loading dose of 200 mg on Day 1 followed by maintenance doses of 100 mg for the next 13 days. Due to the lack of an appropriately matched placebo suspension for fluconazole which would have allowed for a double dummy design, only the evaluators were blinded to the subject's assigned regimen.

Subjects 18 years or older were enrolled in the study if they were HIV-infected, had clinical evidence of pseudomenbranous OPC at the time of enrollment into the study, and had laboratory evidence of candidiasis documented by fungal stain or scraping positive for yeasts, hyphae or pseudohyphae that was consistent with *Candida* species and subsequently confirmed by a positive mycologic culture.

All subjects were seen at baseline, on study (day 8, Visit 2), end of treatment (study day 15, Visit 3), and followed for 1 month after treatment. Clinical evaluations included the assessment of mucositis by signs and or symptoms at each visit. The presence of plaques was graded according to the following scale:

- 0 None=absent
- 1 Minimal= 1 to 5 discrete plaques and/or one confluent plaque $\leq$ 3 cm in longest length
- 2 Diffuse= plaques that were more than minimal extent
- 3 Worse=plaques were clearly worse than on previous visit. (Applies only to Visits 2 and 3 in subjects with diffuse plaques on the previous visit.)

The severity of each symptom was graded according to the following scale:

- 0 None= symptom was not present
- 1 Mild= symptom was present but no or minimal interference was noted with eating
- 2 Moderate= symptom present which led to interference with eating many foods
- 3 Severe= symptom was very marked and the subject was unable to eat most foods.

Clinical response was evaluated according to the following definitions:

- Cure: Absence of plaques or ulcers and no or minimal symptoms
- Improvement: Partial resolution of pre-treatment signs and symptoms
- Clinical Failure: No improvement or worsening of signs or symptoms after at least 7 consecutive days of therapy. Evidence of *Candida* must be demonstrated by KOH, fungal, or Gram stain of persistent plaques.
- Relapse: Recurrence of signs or symptoms after initial improvement or cure at Visit 3
- Not assessed: Clinical assessment was not performed.

A successful clinical response included cure and improvement.

Quantitative mycological cultures were obtained using the oral swish technique. They were obtained at the end of treatment and in all subjects who relapsed at anytime and for treatment failures. Mycological response was evaluated according to the following definitions per the protocol:

- Eradication (Mycologic success): $\leq$ 20 CFU/mL *Candida* species
- Persistence (Mycologic failure): > 20 CFU/mL *Candida* species
- Relapse: $\leq$ 20 CFU/mL *Candida* species at Visit 3 and > 20 CFU/mL *Candida* species at Visit 4
- Superinfection: A *Candida* species present at Visit 3 but not at baseline
- New infection: A *Candida* species present for the first time at Visit 4
- Indeterminate: Extenuating circumstances preclude classification

Reviewer's Comments: *The Division requested that a cut off of anything greater than 0 CFU be used to define the evidence of Candida infection. This definition will be used for assessing mycological response in the analyses presented in this review.*

In the Applicant's analyses, subjects were treated as having a successful mycologic response if the Candida species(es) present at baseline was eradicated regardless of whether there was a superinfection or new infection observed. Subjects with superinfection or a new

Candida infection technically still have OPC and therefore should not be considered successfully treated for OPC. Therefore, these subjects will be treated as failures in the analyses presented in this review.

The primary objective of the study was to determine if posaconazole is at least as effective as fluconazole with the respect to clinical success after 14 days of treatment. Posaconazole was considered non-inferior to fluconazole if the lower limit of the two-sided 95% confidence interval based on the normal approximation to the binomial distribution for the difference between the clinical success rates (posaconazole - fluconazole) was at least -15%, the non-inferiority margin agreed to during protocol development (see Section 5.1 for a discussion of the selection of the non-inferiority margin). Assuming a clinical success rate of 85% for both treatment groups, a sample size of 120 patients per treatment groups was needed to demonstrate non-inferiority with 90% power.

The primary efficacy analysis was based on the MITT population. This population included all patients who received at least 1 dose of study medication and had a positive culture of a *Candida* species at baseline. A protocol evaluable population was also defined to provide supportive data to confirm the results of the MITT analysis. The protocol evaluable population consisted of patients who met key inclusion criteria; received at least 7 consecutive days of therapy and have a clinical assessment at Visit 3, unless declared a failure after 3 doses of study medication. The safety population consisted of all patients who received at least one dose of study treatment.

The primary efficacy endpoint is the proportion of subjects who were clinical successes (cured or improved) after 14 days of therapy. A two-sided 95% confidence interval calculated using the normal approximation to the binomial was used to estimate the difference in clinical success rates between the treatment groups. Non-inferiority of posaconazole to fluconazole will be concluded if the lower limit of the confidence interval is not less than -0.15. Secondary endpoints included clinical response 4 weeks after treatment and mycological response at each visit.

3.1.1.2 Patient Demographics

A total of 366 patients were randomized into the study, 182 patients were randomized to receive posaconazole and 184 to receive fluconazole. Of the patients randomized into the study, 178 and 172 patients received at least one dose of posaconazole and fluconazole, respectively. The MITT population included 329 patients (169 in the posaconazole group and 160 in the fluconazole group). The protocol evaluable population consisted of 143 posaconazole patients and 135 fluconazole patients. The most common reasons for exclusion from the protocol evaluable population were the subject did not have a positive baseline culture for *Candida* (9 posaconazole and 12 fluconazole) and noncompliance with protocol (7 each treatment group).

Table 1 summarizes the demographic and baseline characteristics of the MITT population. There were no significant differences across treatment groups. The study population was primarily male. Most of the patients were white or Hispanic. The mean age of the subjects

was 36 years for the posaconazole subjects and 37 years for the fluconazole subjects. With the exception of 1 fluconazole subject, all subjects were less than 65 years.

Table 1
Demographic and Baseline Characteristics (MITT)

	Treatment Group	
	posaconazole	**fluconazole**
# Patients	169	160
Gender		
Male	125 (74.0)	119 (74.4)
Female	44 (26.0)	41 (25.6)
Age mean (SD)	36.5 (8.0)	37.6 (9.2)
Median	35	36
Min, max	20, 61	19, 78
Race		
White	61 (36.1)	59 (36.9)
Black	41 (24.3)	30 (18.8)
Hispanic	49 (29.0)	51 (31.9)
Asian	16 (9.5)	15 (9.4)
Other	2 (1.2)	5 (3.1)
CD_4 Count mean (SD)	139.4 (173.4)	118.9 (143.4)
Median	83	71
Min, max	0, 935	0, 867
Region		
United States	35 (20.7)	26 (16.2)
Others	134 (79.3)	134 (83.8)

3.1.1.3 Efficacy Results

Table 2 summarizes the results of the primary endpoint, clinical response at the end of 14 days of therapy, for the MITT and protocol evaluable populations. For the MITT population, the success rate (cure plus improvement) was 91.7% for posaconazole and 92.5% for fluconazole. The lower limit of the 95% confidence interval about the difference in response rates is greater than the non-inferiority margin of –15%. The protocol evaluable results also support the claim of non-inferiority of posaconazole compared to fluconazole using a margin of -15%. Cure rates for the MITT population are 81.7% (138/169) for posaconazole and 82.5% (132/160) for fluconazole and the 95% confidence interval about the difference in cure rates is (-9.6, 5.6). Therefore, even if success was defined only using those who were considered clinical cures, posaconazole would be considered non-inferior to fluconazole using a non-inferiority margin of -15%.

Table 2
Clinical Response at End of 14 Days of Therapy

	posaconazole	fluconazole	Difference and 95% CI*
MITT	155/169 (91.7)	148/160 (92.5)	-0.8 (-7.2, 5.6)
Cure	138	132	
Improvement	17	16	
Protocol Evaluable	139/143 (97.2)	130/135 (96.3)	0.9 (-4.0, 5.8)
Cure	125	116	
Improvement	14	14	

*A difference (posaconazole- fluconazole) and 95% confidence interval is reported.

Reviewer's Comment: *The 95% confidence intervals reported in this review are slightly different than those reported in the Applicant's study report since a continuity correction is applied in the calculation of the confidence intervals presented in this review. The conclusions drawn, however, are the same.*

Table 3 summarizes the clinical response at the follow-up visit 4 weeks after therapy for the MITT and protocol evaluable populations. In the MITT population, clinical success (cure + improved) at follow-up was decreased from that seen at end of therapy, 58.0% (98/169) for posaconazole and 52.5% (84/160) for fluconazole. For those patients who were successfully treated at end of therapy in the MITT population, 29.0% (45/155) in the posaconazole group and 35.1% (52/148) in the fluconazole group relapsed at follow-up. Similar results are seen for the protocol evaluable population.

Table 3
Clinical Response at Follow-up

	MITT		Protocol Evaluable	
	posaconazole n=169	**fluconazole** n=160	**posaconazole** n=143	**fluconazole** n=135
Cure	95	81	83	72
Improved	3	3	3	3
Relapse	45	52	43	46
Indeterminate	12	12	10	9
Previous Failure	14	12	4	5

Mycologic response was a secondary endpoint. Table 4 summarizes mycologic response at end of therapy and at follow-up. The mycologic response rates were much lower than those seen for clinical response at both end of therapy and follow-up. At end of therapy, the mycologic eradication rates were similar between treatment groups. At follow-up, posaconazole has a slightly higher mycologic eradication rate than fluconazole. However, the rates for both treatments are extremely low and not significantly different. For those successfully eradicated at end of therapy, relapse rates were 55.7% (49/88) for posaconazole and 63.8% (51/80) for fluconazole in the MITT population and 58.2% (46/79) for posaconazole and 65.3% (47/72) for fluconazole in the protocol evaluable population.

Table 4
Mycologic Response

	MITT		Protocol Evaluable	
	posaconazole n=169	**fluconazole** n=160	**posaconazole** n=143	**fluconazole** n=135
End of Therapy				
Eradicated	88 (52.1)	80 (50.0)	79 (55.2)	72 (53.3)
Superinfection	18	19	14	17
Persistent	50	50	47	42
Presumed Persistent	3	4	1	2
Indeterminate	10	7	2	2
Difference and 95% CI*	2.1 (-9.3, 13.5)		1.9 (-10.5, 14.3)	
Follow-up				
Eradicated	25 (14.8)	13 (8.1)	23 (16.0)	13 (9.6)
New infection	3	3	2	3
Relapse	49	51	46	47
Indeterminate	11	13	8	9
Previous Failure	81	80	64	63
Difference and 95% CI*	6.7 (-0.7, 14.1)		6.4 (-2.1, 14.9)	

*A difference (posaconazole- fluconazole) in eradication rates and 95% confidence interval is reported.

Reviewer's Comment: *The rates at follow-up for both clinical response and mycologic response are slightly different from those presented by the Applicant in the study report. The conclusions drawn are similar with the exception of the Applicant's analysis of mycologic response at follow-up. In the MITT population, the Applicant is claiming a statistically significant difference favoring posaconazole (40.6% [41/101] posaconazole vs. 26.4% [24/91] fluconazole). The Applicant reported success rates based only on subjects who were successfully treated at end of therapy and had follow-up data, not the entire MITT population. In addition, in the analyses presented in Table 4, a successful mycologic response requires 0 CFU/mL of all Candida species with no superinfection at end of therapy and anything greater than 0 CFU/mL at follow-up is considered a relapse or new infection.*

3.1.2 Study C/I96-209

Study C/I96-209 was a multicenter, randomized, double blind, phase II study to evaluate the safety, tolerance, and efficacy of multiple doses of posaconazole oral capsule versus fluconazole in the treatment of OPC in HIV-positive patients. The study was conducted at 53 centers in the United States and internationally from April 17, 1997 through March 3, 1999. The majority of the sites enrolled 10 or fewer subjects. Subjects were randomized in a 1:1:1:1:1 ratio to receive either posaconazole oral capsule 400 mg BID on the first day followed by one of 4 doses once a day for 13 days: 50 mg, 100 mg, 200 mg, or 400 mg; or fluconazole oral tablets: 200 mg on the first day followed by 100 mg a day for 13 days. Two interim analyses were planned: the first after approximately 10 patients per dose group were enrolled and the second after approximately 50 patients per dose group were enrolled. The purpose of these interim analyses was to drop any inactive doses or any dose with

unacceptable toxicity. No unexpected safety or efficacy issues were observed at either interim analysis. Therefore, all doses of posaconazole were retained throughout the study.

A total of 486 subjects were randomized into the study, 469 subjects were treated with study medication, and 437 subjects were included in the MITT population (subjects who received study medication and had a positive culture for OPC at baseline). Table 5 summarizes the distribution of subjects by treatment group.

Table 5
Distribution of Subjects

	posaconazole 50 mg	posaconazole 100 mg	posaconazole 200 mg	posaconazole 400 mg	fluconazole
ITT	98	102	91	100	94
Treated	92	98	91	98	90
MITT	86	91	85	92	83

Table 6 summarizes the demographics of the MITT population. The 5 treatment groups were comparable with respect to age, sex, and race. The mean age was 37 years. Approximately 80% of the subjects were male. More than a third of the subjects were white, approximately a quarter of the subjects were black, and a fifth of the subjects were Hispanic.

Table 6
Demographics (MITT Population)

	posaconazole 50 mg	posaconazole 100 mg	posaconazole 200 mg	posaconazole 400 mg	fluconazole
# Patients	86	91	85	92	83
Gender					
Male	70 (81.4)	75 (82.4)	72 (84.7)	81 (89.1)	63 (75.9)
Female	16 (18.6)	16 (17.6)	13 (15.3)	10 (10.69)	20 (24.2)
Age mean (SD)	37.7 (8.7)	37.6 (9.2)	37.4 (8.7)	37.0 (8.6)	37.0 (8.2)
Median	37	38	37	36	37
Min, max	20, 65	18, 62	21, 58	21, 63	19, 59
Race					
White	32 (37.2)	45 (49.5)	38 (44.7)	43 (46.7)	36 (43.4)
Black	30 (34.9)	20 (22.0)	23 (27.1)	29 (31.5)	21 (25.3)
Hispanic	18 (20.9)	20 (22.0)	20 (23.5)	14 (15.2)	19 (22.9)
Asian	4 (4.7)	4 (4.4)	4 (4.7)	5 (5.4)	3 (3.6)
Other	2 (2.3)	2 (2.2)	0	1 (1.1)	4 (4.8)

The primary efficacy endpoint was the clinical response at the end of treatment. Clinical response was based on the signs and symptoms of mucositis and was defined as in Study C/I97-331. Pairwise comparisons of clinical response of each dose of posaconazole to fluconazole were summarized by using 95.2% confidence intervals (adjusted to maintain an experiment-wide error rate of 0.05 given the 2 interim analyses, each with a stopping rule of 0.001) about the difference in the success rates (posaconazole- fluconazole). A dose of posaconazole was to be considered efficacious if the lower limit of the confidence interval

was greater than -15%. Since the primary comparison pre-specified in the protocol was the comparison of the highest posaconazole dose to fluconazole, no additional adjustments for multiple comparisons were made.

Table 7 summarizes the results of clinical response at the end of therapy and at follow-up. Based on a non-inferiority margin of -15%, the 400 mg posaconazole capsule group was non-inferior to fluconazole (the primary comparison per the protocol) at the end of therapy. Using a similar non-inferiority margin, the 100 mg posaconazole capsule group was non-inferior to fluconazole as well. However, no dose response relationship was demonstrated. The 50 mg, 100 mg, and 400 mg posaconazole groups had similar clinical response rates at the end of therapy but the 200 mg posaconazole group had the lowest response rate of all treatment groups. The Applicant could find no explanation for the lower efficacy results for the 200 mg posaconazole group. Clinical success rates at follow-up were low for all treatment groups and ranged from 40% to 48%.

Table 7
Clinical Response at End of Therapy and Follow-up
MITT Population

	posaconazole 50 mg	**posaconazole 100 mg**	**posaconazole 200 mg**	**posaconazole 400 mg**	**fluconazole**
# Patients	86	91	85	92	83
End of Therapy					
Success	73 (84.9)	79 (86.8)	65 (76.5)	80 (87.0)	74 (89.2)
Cure	64	73	63	76	69
Improvement	9	6	2	4	5
Difference* (95.2% CI)	-4.3 (-15.7, 7.1)	-2.4 (-13.3, 8.5)	-12.7 (-25.2, -0.2)	-2.2 (-13.0, 8.6)	
Follow-up					
Success	35 (40.7)	41 (45.1)	35 (41.2)	45 (48.9)	39 (47.0)
Relapse	24	27	19	25	23
Previous Failure	13	12	20	12	9
Indeterminate	14	11	11	10	12

*A difference (posaconazole- fluconazole) in success rates and 95.2% confidence interval is reported.

Mycologic eradication rates at the end of therapy are presented in Table 8. As seen with clinical response, the 50 mg, 100 mg, and 400 mg posaconazole groups had similar eradication rates but the 200 mg posaconazole group had the lowest eradication rate of all treatment groups.

Table 8
Mycologic Eradication at End of Therapy
MITT Population

posaconazole 50 mg	**posaconazole 100 mg**	**posaconazole 200 mg**	**posaconazole 400 mg**	**fluconazole**
29/86 (33.7)	31/91 (34.1)	27/85 (31.8)	33/92 (35.9)	33/83 (39.7)

Reviewer's Comment: *The results presented in Table 8 are eradication only. The Applicant presented eradication rates with or without superinfection in the study report. For the posaconazole groups, the rates presented above are only slightly different from the Applicant's results because there were only 2 to 4 superinfections seen in any posaconazole group. The difference in the fluconazole results is larger because there were 9 superinfections in the fluconazole group. Thus, the Applicant reports an eradication rate of 50.6% for fluconazole.*

3.1.3 Study C/I97-330

Study C/I97-330 was a non-comparative multicenter study of posaconazole oral suspension in HIV-infected subjects with OPC that was refractory to standard treatment with oral fluconazole or itraconazole. Under the original protocol, subjects were treated with posaconazole oral suspension 400 mg BID for 3 days, followed by 400 mg QD for 25 days with an option for further treatment during a 3-month maintenance period. After 103 subjects were enrolled, the protocol was amended to simplify the dosing regimen and eliminate the maintenance period. Following the amendment, an additional 96 subjects were treated with posaconazole oral suspension 400 mg BID for 28 days. The protocol defined azole-refractory as a history of failure to improve or worsening of candidiasis after a standard course of therapy with fluconazole $\geq$100 mg/day for at least 10 consecutive days or itraconazole 200 mg/day for at least 10 consecutive days. Although not specified in the protocol, the medical division imposed an additional requirement that the course of previous azole treatment had to occur immediately before the initiation of posaconazole treatment. Therefore of the 199 subjects enrolled in the study, 96 subjects met the medical division's stricter definition for refractory OPC. The MITT population, which included subjects who had evidence of an azole-refractory *Candida* culture at baseline, included 89 subjects (45 treated under the original protocol and 44 treated under the amended protocol).

The primary efficacy parameter was the clinical success rate after 4 weeks of treatment in the MITT population. The clinical success rate was 74.2% (66/89, 50 cured and 16 improved). The 95% confidence interval about the clinical success rate is (64.5, 83.8). The clinical success rates were similar for subjects treated under the original protocol versus the amended protocol (73.3% and 75.0%, respectively). For further discussion of this study, please see the Medical Officer review.

3.2 Evaluation of Safety

In Study C/I97-331, a total of 114 patients (64%) in the posaconazole group and 117 patients (68%) in the fluconazole group had at least one treatment emergent clinical adverse event. Serious adverse events were reported in 17 (10%) posaconazole patients and 22 (13%) fluconazole patients. There were 5 deaths during the study, 4 patients from the posaconazole group and 1 patient from the fluconazole group. The 4 posaconazole deaths occurred between study day 3 and 31 and the fluconazole death occurred on study day 43.

For a detailed review of the safety data from all studies, please see the medical officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The following table summarizes the number of patients who had a successful clinical response at the end therapy for gender and race in Study C/I97-331. All but 1 fluconazole subject were in the age range of 18 to 65 years old so no subgroup analysis by age was performed. There are no significant treatment by subgroup interactions. The results by gender and by race are consistent with those of the overall population.

Table 9
Subgroup Analyses Clinical Response at End of Therapy
Study C/I97-331 MITT Population

	Treatment Group	
	posaconazole 100 mg oral suspension	**fluconazole**
Gender		
Male	116/125 (92.8)	110/119 (92.4)
Female	39/44 (88.6)	38/41 (92.7)
Race		
White	56/61 (91.8)	54/59 (91.5)
Black	37/41 (90.2)	29/30 (96.7)
Hispanic	44/49 (89.8)	47/51 (92.2)
Asian	16/16 (100.0)	15/15 (100.0)
Others	2/2 (100.0)	3/5 (60.0)

Table 10 summarizes the number of patients who had a successful clinical response at the end therapy for gender and race in Study C/I96-209 for the 100 mg capsule group and the control group. All subjects were between 18 and 65 years so no subgroup analysis by age was performed. As in Study C/I97-331, the results of Study C/I96-209 by gender and by race are consistent with those of the overall population.

Table 10
Subgroup Analyses Clinical Response at End of Therapy
Study C/I96-209 MITT Population

	Treatment Group	
	posaconazole 100 mg capsule	**fluconazole**
Gender		
Male	66/72 (91.7)	57/61 (93.4)
Female	13/15 (86.7)	17/19 (89.5)
Race		
White	43/45 (95.6)	31/36 (86.1)
Black	14/19 (73.7)	18/19 (94.7)
Hispanic	16/17 (94.1)	19/19 (100.0)
Asian	4/4 (100.0)	3/3 (100.0)
Others	2/2 (100.0)	3/3 (100.0)

4.2 Other Special/Subgroup Populations

Table 11 summarizes the number of patients who had a successful clinical response at the end therapy by baseline CD_4 count in Study C/I97-331. The results by baseline CD_4 count are consistent with those of the overall population.

Table 11
Subgroup Analyses Clinical Response at End of Therapy
Study C/I97-331 MITT Population

	Treatment Group	
	posaconazole 100 mg oral suspension	**fluconazole**
CD_4 Count		
≤100	87/95 (91.6)	92/97 (94.9)
>100	68/74 (91.9)	56/63 (88.9)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The results of the single comparative study (C/I97-331) submitted to support the use of posaconazole oral suspension for the treatment of OPC in HIV-positive patients suggest that posaconazole oral suspension is non-inferior (assuming a margin of 15%) to fluconazole as assessed by the clinical response at end of therapy for the MITT population. The 15% non-inferiority margin was proposed by the sponsor. The review team requested a justification of the non-inferiority margin on April 24, 2006. The Applicant stated in their response dated May 9, 2006 that a spontaneous cure rate with placebo of any magnitude would be unexpected particularly in HIV-infected patients with low CD_4 counts (<100). They also stated that the literature reports clinical success rates for fluconazole of 87% to 96%. Two studies of nystatin versus fluconazole were cited, one conducted in immunocompromised children with OPC and one in HIV-infected adults with OPC. In the study of immunocompromised children with OPC, the nystatin and fluconazole rates were 46% and 86%, respectively. In the study of HIV infected adults, the response rates were 52% for nystatin versus 87% for fluconazole and the 95% confidence interval for the difference in response rates (nystatin – fluconazole) was (-53%, -27%). Based on this, the non-inferiority margin that would retain 50% of this effect would correspond to a margin of -13.5%. The Applicant states that the 15% non-inferiority margin selected for the current study represents a small loss of efficacy that should still result in a treatment effect that is substantially higher than placebo. The Applicant's response does not discuss how their search of the literature was performed and if all applicable studies were reviewed. There is also no discussion of the constancy of the effect of the control by comparing the study design of the current study and the previous studies. The medical division, however, accepted the 15% non-inferiority margin to provide proof of the efficacy of posaconazole.

In study C/I97-331, there was a slight imbalance in the number of subjects who were randomized but did not receive study drug, 4 posaconazole subjects and 12 fluconazole subjects. These subjects were excluded from the MITT population. However, one subject from each group did not have a positive culture for *Candida* and would still be excluded from the MITT population. Since the study was open label, this could possibly bias the results. Therefore, a sensitivity analysis was performed by considering the remaining 3 posaconazole subjects as failures and 11 fluconazole subjects as successes to determine if there would be any impact on the study results. In the sensitivity analysis, the clinical success rate at end of therapy is 90.1% (155/172) for posaconazole and 93.0% (159/171) for fluconazole with a 95% confidence interval about the difference in clinical success rates of (-9.4%, 3.6%). A non-inferiority margin of 15% is still achieved therefore the impact of these 14 subjects who were randomized but did not receive study drug is minimal.

Additional evidence that posaconazole is effective in the treatment of OPC in HIV-positive patients comes from the multiple dose study of posaconazole capsule compared to fluconazole. Even though no dose response was demonstrated in the study, the Applicant assumed that a safe and efficacious dose of posaconazole might be a midpoint of the range of doses examined. Since the oral suspension formulation has a bioavailabilty 20-30% greater than the capsule form used in this study, the Applicant felt that 100 mg of the oral suspension would represent an exposure between the 100 mg and 200 mg capsule. This study only provides supportive evidence since the formulation and loading dose used in this study are different than the formulation and loading dose that is being requested for approval. In addition, the statistical analysis does not adjust for the eventual 100 mg comparison.

Information on posaconazole in the treatment of OPC in HIV-positive subjects who were refractory to standard treatment with fluconazole or itraconazole was provided in a noncomparative study of posaconazole oral suspension.

5.2 Conclusions and Recommendations

In a single Phase 3 comparative study of posaconazole oral suspension versus fluconazole in the treatment OPC in HIV-positive patients, posaconazole was shown to be non-inferior to fluconazole based on a non-inferiority margin of 15%. Supportive data was provided by a multiple dose study of posaconazole oral capsule in HIV-positive subjects with OPC. Further, data on the effectiveness of posaconazole oral suspension in HIV-positive subjects with OPC refractory to treatment with fluconazole or itraconazole was provided in a non-comparative study. It is left to the medical division to determine whether the information from this study is sufficient to extend the indication to include a claim regarding OPC refractory to treatment with fluconazole or itraconazole.

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