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APPLICATION NUMBER:

22-027

MEDICAL REVIEW(S)

NDA 22-027
Posaconazole
Medical Officer's Review of
Oropharyngeal and
Refractory Oropharyngeal Candidiasis

Application Type	**NDA 22-027**
Submission Number	**000**
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Reviewer Name	**Regina Alivisatos, MD**
Review Completion Date	
Established Name	**Posaconazole**
(Proposed) Trade Name	**Noxafil®**
Therapeutic Class	**Antifungal Agent**
Applicant	**Schering-Plough Research Institute**
Priority Designation	**S**
Formulation	**Oral Suspension**
Dosing Regimen	**100 mg PO QD and 400 mg PO BID**
Indication	**OPC and Refractory OPC**
Intended Population	**Adults**

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1. EXECUTIVE SUMMARY

Recommendation on Regulatory Action

An approval is recommended for the following proposed Indication:

NOXAFIL (posaconazole) is indicated for the treatment of oropharyngeal candidiasis, including infections refractory to itraconazole and fluconazole.

Summary of Clinical Findings

Brief Overview of Clinical Program

In support of the OPC indication, the Applicant submitted 2 randomized controlled double or evaluator blinded comparative studies of the efficacy of posaconazole versus a fluconazole comparator. One study (C196-209) was a dose finding study and was considered supportive for the OPC indication.

In addition, the sponsor submitted the results from 2 open label studies of posaconazole in HIV infected adults with azole refractory OPC. One study (P00298) was primarily a maintenance therapy study and was considered supportive for the refractory indication.

Efficacy

The applicant submitted 2 randomized, active-controlled, clinical studies in HIV-infected subjects with azole-susceptible OPC in support of the OPC indication. The approved dose of oral fluconazole was used as the active control in both studies.

Posaconazole was administered as an oral capsule in C/I96-209 and as an oral suspension in C/I97-331. The difference in the bioavailability between the suspension and capsule is approximately 10%, and the posaconazole clinical response rates were similar (86.8% in C/I96-209 (capsules) versus 91.7% in C/I97-331 (oral suspension). In study 331 the requested posaconazole dose of 100 mg for 14 days found to be non-inferior to the approved comparator fluconazole 100 mg QD for 14 days regimen for both the primary efficacy parameter of clinical response at the EOT/TOC visit but also for the secondary parameters of clinical response or relapse rate 2 weeks post treatment as well as for mycologic response at both visits. In addition to the differences in bioavailibity there may have been a topical antifungal effect on the OPC from the oral suspension.

The primary efficacy parameter in both OPC studies was the clinical success rate (defined as cure or improvement) at the conclusion of 14 days of treatment in the Modified Intent-to-Treat (MITT) subset (all randomized subjects who had a positive *Candida* culture at Baseline and took at least one dose of study drug). Additional analyses were performed in a protocol evaluable (PE) as well as an ITT/All treated population.

In the dose-finding Phase II study, C/I96-209, 469 subjects were treated with a loading dose of posaconazole of 400 mg twice daily (BID) for 1 day, followed by 50 mg, 100 mg, 200 mg, or 400 mg once daily (QD) for 13 days, or fluconazole 200 mg QD for 1 day, followed by 100 mg QD for 13 days (14 days total).

A successful clinical response (cured and improved) was achieved by 87% of subjects in the 400 mg POSA group; 76.5% in the 200 mg group; 86.8% in the 100 mg group (requested dose); 84.9% in the 50 mg group; and 89.2% in the fluconazole group for the modified ITT subjects. No statistical conclusions could be drawn from this study because of the lack of a dose response and the aberrant results achieved on the 200 mg arm. Clinical Response at follow-up revealed relapse rates that decreased as the dose increased. The relapse rate for the fluconazole treated subjects was 36% as compared to the 41% relapse rate for the 100 mg posaconazole treated subjects (requested dose).

Success and Relapse Rates MITT and PP
OPC C/I96-209

		SCH 56592			
	50 mg	**100 mg**	**200 mg**	**400 mg**	**FLZ**
MITT	N = 86	N = 91	N = 85	N = 92	N = 83
Success Rate (a)	**73 (84.9%)**	**79 (86.8%)**	**65 (76.5%)**	**80 (87.0%)**	**74 (89.2%)**
Cure	64 (74.4%)	73 (80.2%)	63 (74.1%)	76 (82.6%)	69 (83.1%)
Improvement	9 (10.5%)	6 (6.6%)	2 (2.4%)	4 (4.3%)	5 (6.0%)
FDA 95.2% CI cures only with CCF	- 21.25, 4.82	-15.65, 9.85	- 22.63, 4.60	- 12.94, 11.90	
MITT F/U	N = 59	N = 68	N = 54	N = 70	N = 62
Relapse Rate	24 (40.7%)	27 (39.7%)	19 (35.2%)	25(35.7%)	23 (37.1%)
PP	N = 81	N = 83	N = 80	N = 88	N = 77
Success Rate (a)	**68 (84.0%)**	**75 (90.4%)**	**63 (78.8%)**	**78 (88.6%)**	**72 (93.5%)**
Cure	59 (72.8%)	70 (84.3%)	61 (76.3%)	75 (85.2%)	67 (87.0%)
Improvement	9 (11.1%)	5 (6.0%)	2 (2.5%)	3 (3.4%)	5 (6.5%)
FDA 95.2% CI cures only with CCF	- 27.8, - 0.54	- 14.86, 9.51	- 24.12, 2.59	- 13.65, 10.08	
PP F/U	N = 57	N = 66	N = 53	N = 68	N = 61
Relapse Rate	23 (40.4%)	27 (40.9%)	19 (35.8%)	23 (33.8%)	22 (36.1%)

Modified Intent-to-Treat (MITT) subset (all randomized subjects who had a positive *Candida* culture at Baseline and took at least one dose of study drug
Protocol Evaluable Subjects (PE or PP): All treated subjects who met key inclusion criteria and received at least 7 consecutive days of study medication for the treatment of oral candidiasis. Patients must have a clinical assessment at Visit 3, or must have at least 3 days of treatment and discontinued prior to Visit 3 either as a treatment failure or an adverse event.
Relapse: Recurrence of signs or symptoms after initial improvement or cure at Visit 3 (and having taken ≥80% of doses)
CCF: Continuity Correction Factor

Mycological response by patient was a secondary efficacy variable. Eradication of infection in the modified ITT group occurred in 40.2% of subjects in the 400 mg POSA group; 35.3% of subjects in the 200 mg group; 37.4% of subjects in the 100 mg group; 36% of subjects in the 50 mg group; and 50.6% of subjects in the fluconazole group. The

results obtained in the FLU treated subjects were consistent with those obtained in study 331 but the results obtained in the POSA treated subjects at any dose were lower than those obtained for the FLU patients as well as compared to those obtained from the POSA arm of study 331.

The success rate for the 200 mg dose of SCH 56592, which was the lowest of all treatment groups and was not clinically equivalent to fluconazole in any population, was considered anomalous and review of several study parameters including demographics, CD4 count, and severity of OPC did not reveal an explanation for the lower efficacy in this group.

No dose response relationship was demonstrated in this study. This may have been due to use of the same high loading dose (400 mg) of POSA each group and to the long half-life of the drug.

The results of this study supported the use of the 100 mg dose of the POSA suspension the treatment of OPC in HIV-positive subjects.

In the Phase-3 study, C/I97-331, 350 subjects were treated with posaconazole or fluconazole oral suspension (100 mg BID for 1 day followed by 100 mg QD for 13 days).

The clinical response rate achieved with POSA was non-inferior to that achieved with FLU after 14 days of treatment in both the MITT (91.7% vs. 92.5%, respectively) and protocol evaluable subsets (97.2% vs. 96.3%, respectively). These success rates for POSA versus FLU were consistent with those achieved in the ITT (89.0% vs. 86.4%, respectively) and All-Treated (91.0% vs. 92.4%, respectively) subsets for both treatments. Non-inferiority was also shown when only cures were assessed as successes.

Clinical Response at the EOT and Follow-up
MITT and PE per FDA criteria

	Posaconazole	**Fluconazole**	
MITT	N= 171	N = 160	
Success	156 (91.2%)	148 (92.5%)	- 7.76, 5.22
Failure All	15 (8.7%)	12 (7.5%)	
Cure	139 (81.3%)	132 (82.5%)	- 10.12, 7.69
Improved	17 (9.9%)	16 (10%)	
MITT F/U	N= 144	N = 136	-5.59, 18.17
Clinical Relapse	46 (32%)	52 (38.3%)	
MITT F/U	N = 95	N = 82	
Mycologic Relapse	61 (64.2%)	64 (78%)	
PE	N= 143	N = 135	
Success	139 (97.2%)	130 (96.3%)	- 3.99, 5.8
Failure All	4 (2.8%)	5 (3.7%)	
Cure	125 (87.4%)	116 (85.9%)	- 7.23, 10.2
Improved	14 (9.8%)	14 (10.4%)	
PE F/U	N= 129	N = 121	- 7.99, 17.36
Clinical Relapse	43 (33.3%)	46 (38%)	
PE F/U	N = 85	N = 75	

Relapse	55 (64.7%)	59 (76.6%)

Modified Intent-to-Treat (MITT) subset (all randomized subjects who had a positive *Candida* culture at Baseline and took at least one dose of study drug
Protocol Evaluable Subjects (PE or PP): All treated subjects who met key inclusion criteria and received at least 7 consecutive days of study medication for the treatment of oral candidiasis. Patients must have a clinical assessment at Visit 3, or must have at least 3 days of treatment and discontinued prior to Visit 3 either as a treatment failure or an adverse event.
Relapse: Recurrence of signs or symptoms after initial improvement or cure at Visit 3 (and having taken ≥80% of doses)
CCF: Continuity Correction Factor

Clinical response rates 4 weeks after the cessation of treatment were similar between posaconazole- and fluconazole-treated subjects (68.5%, 98/143 versus 61.8%, 84/136, respectively).

As per the sponsor, subjects treated with posaconazole had a greater sustained mycological success rate 4 weeks following cessation of treatment than did subjects treated with fluconazole (POSA 40.6%, 41/101 versus FLU 26.4%, 24/91, respectively; P=0.0376); however this was a secondary endpoint, not applied in all subjects. When mycologic response by pathogen was assessed using the Agency standard of 0 CFU/mL in the ITT population sustained eradication rates for FLU had a greater decrease from test of cure to post treatment follow-up than the eradication rates for POSA. Mycologic eradication for FLU decreased from approximately 63% to 16%, while the eradication rates for POSA dropped from 64% to 31%.

Comment: It should be noted that mycologic assessment was NOT preformed routinely in all subjects and these conclusions were drawn only from the subset of subjects in whom culture was performed.

Study 331 demonstrated that posaconazole was non-inferior to fluconazole in the treatment of HIV-infected subjects with azole susceptible OPC. Clinical relapse rates were similar between the treatment arms. Study 209 provided supportive evidence for these conclusions.

Azole refractory OPC:

In support of the efficacy of posaconazole in azole-refractory OPC, the applicant submitted 2 open label non-comparative trials of posaconazole in the treatment of patients with refractory candidiasis in immunosuppressed HIV-infected subjects. There were 239 unique subjects enrolled in these trials. In the agency analyses, study P00298 was considered supportive of study C/I97-330 because 60% of the subjects were roll-overs from study C97-330 and because subjects did not have a primary endpoint similar to that used for study C/I97-330.

The primary efficacy parameter was the clinical success rate (cure or improvement) after 4 weeks (C/I97-330) or 3 months (P00298) of treatment among subjects in the MITT subset. This visit occurred at the end of the acute treatment phase. All patients had this visit either on the last day of treatment (amended) or after 4 weeks of treatment (original) thus providing the ability to assess all subjects at one similar timepoint (snapshot).

Subjects in C/I97-330 were treated with posaconazole 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 (original protocol, 800 QD 3 x week) or posaconazole 400 mg BID for 28 days (amended protocol). The higher posaconazole doses were chosen in order to be consistent with the rest of the Applicant's clinical program for the treatment of refractory IFIs. The change in regimen was done for convenience purposes and in order to be consistent with the broader development program.

In the Applicant's analysis, among subjects in the MITT subset there was a 75% (132/176) clinical success rate (cure or improved) and a 36.5% (46/126) mycological response rate after 4 weeks of posaconazole treatment (NOTE: limited number of subjects were re-cultured).

Clinical success rates ranged from 71% to 100%, inclusive, for all azole-resistant *Candida* species identified at baseline. *Candida albicans* was the primary isolate followed by *Candida glabrata.*

Clinical success rates were similar for subjects in the original versus the amended protocols after 4 weeks of posaconazole treatment (MITT 75.3%, 67/89 and 74.7%, 65/87, respectively).

Clinical relapse rates in at Week 4 of Follow-up (defined as 23 through 37 days after the last dose of study drug) were 32.8%, 22/67 for those treated under the original protocol and 24.6%, 16/65 for those treated under the amended protocol suggesting more sustained efficacy with the 800-mg daily dosing regimen compared to the 400-mg daily dosing or maintenance 800-mg/day intermittent (three times weekly) dosing regimens. A relapse was defined as the presence of greater than 20 CFU/mL of the same *Candida* species at a post-treatment follow-up visit as was present at Baseline.

This study supported the use of posaconazole 400 mg BID for 28 days in HIV infected subjects with OPC refractory to fluconazole or itraconazole. Inadequate documentation was provided regarding mycologic eradication rates in this study.

In P00298 100 HIV-infected subjects with OPC and/or EC were treated with posaconazole 400 mg BID for up to 15 months, including a 3-month acute treatment period followed by a 12-month maintenance period. Sixty of these subjects had previously participated in C/I97-330. Because of the large number of subjects that were re-enrolled in this study, the lack of a consistent TOC evaluation timepoint and the differences in the inclusion criteria it was determined that this study would be considered supportive only.

Among subjects in the MITT subset, an 85.6% (77/90) clinical success rate (cure or improved) was achieved after 3 months of posaconazole treatment. The majority of subjects were immediately enrolled in a12-month maintenance period or were retreated under the same protocol if they relapsed after treatment cessation.

Among the 239 unique subjects treated with posaconazole in the two azole-refractory OPC studies, 69%, (165/239) of subjects took posaconazole for up to 3 months, 14% (34/239) took posaconazole for 3 to <6 months, 9% (22/239) took posaconazole for 6 to <12 months, and 6% (15/239) took posaconazole for at least 12 months. The mean exposure to posaconazole based on the actual days dosed was 102 days (range of 1 to 544 days). The mean duration of treatment, inclusive of gaps or stops in treatment was 154 days. Sixty-seven percent (67%, 10/15) of subjects treated with posaconazole for at least 12 months had continued clinical success (cure or improvement) at the last assessment. The majority of *Candida* isolates tested remained susceptible to posaconazole.

For the Agency analyses, a dataset of 239 unique subjects with refractory OPC supplied by the applicant, (199 subjects from study C/I97-330 and 40 from P0298) was used. In order for a subject to be included in the Agency population, they had to meet the following inclusion requirement per the original protocols:

- History of failure to improve or worsening of candidiasis after a standard course of therapy with FLZ ≥100 mg/day for at least 10 consecutive days, or ITZ 200 mg/day for at least 10 consecutive days for oral candidiasis or ≥3 weeks for esophageal candidiasis.

Comment: The sponsor did not specify that the course of previous azole treatment had to occur immediately before the initiation of POSA but this is a regulatory requirement that has been applied to other antifungal applications in order to differentiate true refractory diease from relapse or recurrence.

87 subjects were excluded from the refractory population because they either did not receive any previous AF treatment and/or they did not receive either ITR or FLU and/or the duration of previous azole treatment did not meet the protocol specified duration of 10 days or was unknown (N = 11, C1/003: 9 days, C2:005 unknown, C2/009: 3 days, C30/003: 8 days, C200018: 4days, I2/002 and I2/0004 unknown, I12/007: 7 days, I19/003: 4 days, I19/004: 8 days, I19/006: 9 days). 7 subjects were excluded because the prior azole treatment was discontinued > 14 days before initiation of POSA treatment, raising concerns of recurrence as opposed to refractory disease.

19 subjects were excluded because documentation of the dose used during the previous treatment course was not provided (19 from study 0298).

In total 143 subjects were excluded. For the Agency analyses 96 treated subjects were qualified to be included in the rOPC category. All of these subjects were from study C/I97-330, 89 were included in the MITT population and 81 in the evaluable.

Comment: In study P0298 the previous fluconazole or itraconazole course could have been many months earlier, thus no subjects from this trial were included in the Agency dataset.

Clinical and Mycologic efficacy by patient were assessed at the end of the acute treatment phase; all patients had this visit either on the last day of treatment or the end of the acute treatment or on the day before start of maintenance). This timepoint provided a snapshot of efficacy for all subjects and this assessment was the protocol defined primary endpoint.

Patients were assessed at other timepoints including at a follow-up visit (range 23 – 37 days) 4 weeks after the last dose unless lost to follow-up, and at the EOT visit defined as the last clinical response on or before the stop of treatment +7 days thus occurring at different timepoints depending upon when the last dose of therapy occurred for a given subject. The value of the EOT asessement was in that it was performed 7 days off of treatment and provided an initial assessment of relapse.

Mycologic efficacy by patient was assessed only at the week 4 visit and not all subjects received such an assessment. In this analysis if a subject did not have an EOT culture, they were presumed to have a persistent pathogen.

Only the primary endpoint and the EOT visit are reported because 65% of subjects did not have a follow-up visit at 23- 37 days post-treatment thus leaving little value to this assessment.

Table 4
Clinical and Mycologic Response by Patient
Refractory OPC
Agency Population

	MITT N= 89		**EE N = 81**	
Clinical Response	**Week 4 Last day of treatment N (%)**	**EOT 7 days after the last day of treatment N (%)**	**Week 4 Last day of treatment N (%)**	**EOT 7 days after the last day of treatment N (%)**
Cure	50 (56.1)	51 (57.3)	50 (61.7)	47 (58)
Improved	16 (17.9)	19 (21.3)	16 (19.7)	16 (19.7)
Failed	22 (24.7)	7 (7.8)	15 (18.5)	7 (8.6)
Unknown or No f/u	1 (1.1)	1 (1.1)	NA	NA
Relapse	NA	11 (12.3)	NA	11 (13.5)
Mycologic response				
Responder	28 (31.4)		28 (34.5)	
Non-responder	31(34.8)		31 (38.2)	
No culture	7 (7.8)		7 (8.6)	
?	23 (25.8)		15 (18.5)	

Relapse was defined as the presence of > 20 CFU/mL of the same *Candida* species at a post-treatment follow-up visit as was present at Baseline
Responder=Mycological success, ≤20 CFU/mL for all *Candida* species present at Baseline
Non-Responder=Mycological failure, >20 CFU/mL *Candida* species
Not Assessed=Subject was not cultured.

When the Agency Clinical Response Rate was compared to the Applicant's, higher combined responses were obtained in the Agency population (Agency 80.8% cured and improved as compared to 75.3% Applicant for the MITT). In the Applicant's analysis,

51.2% (102/199) subjects were considered cured as compared to 56.1% (50/89) in the agency analysis. Relapse rates were also similar in both analyses and increased over time as subjects discontinued treatment.

As noted in the Applicant's analysis, mycologic cultures were not required in subjects who were clinical responders or for those continuing onto maintenance If only those subjects who had a mycologic assessment are included, mycologic response rate at week 4 was 31.4% in the MITT and 34.5% in the EE population and was lower than that attained in the Applicant's analysis (36.5%). The value of this analysis is unclear as few patients had a culture performed.

There were 52/89 (58.4%) refractory MITT patients with baseline isolates considered resistant because of high MIC values and thus considered more difficult to treat (49/81 (60.5%) evaluable). Of the 52 MITT subjects 15 had a baseline isolate considered resistant to fluconazole, 35 to both fluconazole and itraconazole and 2 resistant to itraconazole alone. There were 50 subjects with baseline FLU resistance and 37 with baseline ITR resistance.

These 52 MITT subjects had 69 isolates at baseline including 46 *Candida albicans* (30 alone, 14 with *Candida glabrata*, 2 with *Candida krusei),* 17 *Candida glabrata* (2 alone, 14 with *Candida albicans* and 1 with *Candida tropicalis*), 4 *Candida krusei* (2 alone and 2 with *Candida albicans*) and 2 *Candida tropicalis* (1 alone and 1 with *Candida glabrata*). In total there were 46 isolates of *Candida albicans*, 17 *Candida glabrata*, 3 *Candida krusei,* and 2 *Candida tropicalis.*

For the EE population 49 subjects had 62 isolates including 43 *Candida albicans,* 15 *Candida glabrata,* 2 *Candida krusei,* and 2 *Candida tropicalis.*

Of the MITT subjects with *Candida albicans* at baseline, 39 had an MIC of 64 mcg/mL, (considered to represent isolates that are more difficult to treat). 23 of these subjects were cured (50%), 9 improved (19.5%), 6 (13%) failed and 1 did not have an outcome assessment.

There were 3 subjects with *Candida albicans* and a baseline MIC of 32 mcg/mL (1 cure, 1 improved and 1 failure) and 4 subjects with baseline MICs of 8 mcg/mL (2 failures and 2 improved).

In conclusion POSA demonstrated acceptable efficacy in a subpopulation of highly immunosuppressed HIV-infected subjects with refractory OPC. Large numbers of these subjects had *Candida albicans* isolates at baseline that had high fluconazole and/or itraconazole MICs. Comparable clinical efficacy was also demonstrated in these subjects, however not all subjects had mycologic evaluations off treatment and a much smaller percentage had documented eradication.

The results of the two studies supported the efficacy of posaconazole in the treatment of HIV-infected subjects with azole-refractory OPC.

Safety:

The most common adverse events observed in the total original NDA dataset were gastrointestinal in origin (nausea, vomiting, diarrhea, and abdominal pain) and headache. Analyses of safety data based on age, sex, and race revealed no significant trends related to these demographic characteristics although there did appear to be a question of a higher incidence of AEs in the Asian population possibly due to differences in metabolism of the compound. Long-term administration of posaconazole (> 1 year) demonstrated no evidence of late-appearing adverse effects or worsening of effects over time.

An association between posaconazole and QTc prolongation or negative inotropic effects could not be ruled out as one case of Torsade de pointes was reported. Mild to moderate, transient increases in transaminases were noted as were 7 cases of hepatic failure one of which was attributable to posaconazole in the rIFI population. There were multiple confounding factors in this case and a definitive attribution could not be made. There were no cases of hepatic failure in subjects with OPC or refractory OPC. Generally subjects with baseline abnormal hepatic function appeared to have more frequent worsening of hepatic function as compared to those subjects with normal baseline function.

No specific adverse effect was identified from detailed evaluation of other types of adverse events of interest, including neurologic events, calcium homeostasis, steroidogenesis, and hypersensitivity. As with other azoles, posaconazole was associated with visual changes and/or rash in few subjects.

Posaconazole may affect the pharmacokinetics of other drugs such as cyclosporine and tacrolimus that are metabolized through the CYP3A4 enzyme system and these drugs should be monitored at the initiation of posaconazole therapy, as clinically indicated during posaconazole therapy, and at the end of therapy.

Excerpts _____ for OPC and rOPC are summarized below:

The safety for the OPC and rOPC indications was assessed in 4 studies (2 controlled, C/196-209 & C/197-331 N =557 patients and two uncontrolled studies in refractory OPC/EC, studies C/197-330 & P00298, N = 239 patients).

NOTE: Subjects in the controlled OPC pool received POS doses of 50 – 400 mg PO QD or fluconazole 100 mg QD. Subjects in the rOPC studies received 800 mg PO QD.

A similar percentage of posaconazole and fluconazole treated subjects with OPC reported an AE (356/557 (64%) POS and 175/262 (67%) FLU). The types of AEs were similar for subjects treated with posaconazole ≤ 400 mg/day and fluconazole 100 mg/day.

The most commonly reported AEs were diarrhea (reported for 10% of subjects on posaconazole and 13% of subjects on fluconazole), nausea (9% and 11%), headache (8% and 9%), fever (6% and 8%) and vomiting (7% each). Both azoles were associated with neutropenia (4% POS vs. 3% FLU) and neither was associated with tachycardia or other rhythm disturbances in the controlled OPC population. Hepatic events also occurred with a similar frequency between the treatment arms. The incidence of treatment-related AEs was similar between the POS and FLU treatment arms (POS 150/557 (27%) and FLU 70/262 (27%) whereas a higher percentage 135/239 (56.4%) of refractory OPC POS-treated subjects reported such events.

In the Controlled OPC pool, the most commonly reported **treatment related** AEs were nausea (reported for 5% of subjects on posaconazole and 7% of subjects on fluconazole), diarrhea (3% and 5%, respectively), and vomiting (4% and 2%, respectively).

As expected, in the Refractory OPC Pool which was compromised of primarily end stage HIV patients, AEs were reported for 221/239 (92%) of subjects. The most common AEs were fever (34%), diarrhea (29%), nausea (29%), vomiting (28%), and coughing (25%).

Neutropenia was reported more frequently in the refractory OPC POS-treated population (16%) refractory POS vs. 4% controlled OPC POS vs. 3% FLU). The increased incidence in the refractory population may be due in part to the more severe underlying disease in these subjects and the multiple drugs they were taking for HIV suppression, however a concomitant effect of POS could not be ruled out because of the lack of comparative data in this population. The most commonly reported treatment related AEs in the refractory pool were diarrhea (11%), nausea (8%), neutropenia (8%), headache (8%) and vomiting (7%).

Treatment Related, Adverse Events (Any Grade):
Greater Than or Equal to 2% (OPC Pool)

Number (%) of Subjects

Adverse Event	Controlled OPC Pool POS n=557		FLZ n=262		Refractory OPC Pool POS n=239
Subjects Reporting any AE	**150**	**(27)**	**70**	**(27)**	**135 (56)**
Body As A Whole - General Disorders					
Anorexia	6	(1)	1	(<1)	7 (3)
Asthenia	4	(1)	2	(1)	6 (3)
Dizziness	9	(2)	5	(2)	8 (3)
Fatigue	8	(1)	5	(2)	7 (3)
Fever	10	(2)	1	(<1)	6 (3)
Headache	16	(3)	5	(2)	18 (8)
Central and Periph Nerv System					
Somnolence	4	(1)	5	(2)	3 (1)
Disorders of Blood and Lymphatic System					
Anemia	2	(<1)	0		6 (3)
Neutropenia	10	(2)	4	(2)	20 (8)
Gastro-Intestinal System Disorders					
Abdominal Pain	10	(2)	8	(3)	12 (5)
Diarrhea	19	(3)	13	(5)	26 (11)
Flatulence	6	(1)	0		11 (5)
Mouth Dry	7	(1)	6	(2)	5 (2)
Nausea	27	(5)	18	(7)	20 (8)
Vomiting	20	(4)	4	(2)	16 (7)
Liver and Biliary System Disorders					
Hepatic Enzymes Increased	1	(<1)	0		5 (2)
Hepatic Function Abnormal	3	(1)	4	(2)	0
Metabolic and Nutritional Disorders					
Phosphatase Alkaline Increased	3	(1)	3	(1)	5 (2)
Musculo-Skeletal System Disorders					
Myalgia	1	(<1)	0		4 (2)
Platelet, Bleeding and Clotting Disorders					
Thrombocytopenia	3	(1)	0		4 (2)
Psychiatric Disorders					
Insomnia	3	(1)	0		6 (3)
Skin and Subcutaneous Tissue Disorders					
Pruritus	6	(1)	2	(1)	5 (2)
Rash	8	(1)	4	(2)	10 (4)

In the Phase II comparative study of posaconazole vs. fluconazole, (96-209) SAEs were reported for 51/379 (13%) of subjects on posaconazole and 16/90 (18%) of subjects on fluconazole. The most commonly reported SAE was fever (3% with POS; 6% with FLZ). The SAEs included 2 sudden deaths on the fluconazole arm as compared to none on the posaconazole arm.

In the Phase III OPC study (97-331), 17/178 (10%) of POS- treated subjects reported a SAE compared to 22/172 (13%) for FLU-treated subjects. Respiratory insufficiency was reported for 2 posaconazole treated subjects (1%); all other SAEs were reported in one posaconazole treated subject each There were no treatment-related SAEs reported for subjects treated with posaconazole. Two subjects (1%) on fluconazole had treatment related SAEs (1 subject with increased SGPT and 1 subject with gastroenteritis, vomiting, diarrhea, and dehydration).

In the Refractory OPC Pool which was comprised of a much iller patient population, SAEs were reported for 55% (132/239) of subjects. The most commonly reported SAEs were fever and neutropenia, reported for 13% and 10% of subjects, respectively. Treatment related SAEs were reported for 14% (34/239) of subjects and included neutropenia and abdominal pain reported for 5% and 2% of subjects, respectively. Posaconazole was discontinued in two subjects (I97330/04-002 and P00298/11-002) who developed neutropenia that was considered serious and treatment-related. All other treatment-related SAEs were reported for ≤1% of subjects on posaconazole.

In conclusion SAEs were reported at a similar rate in posaconazole and fluconazole treated subjects in the controlled OPC studies. Additionally the type of events reported was similar. The frequency of SAEs increased in the more seriously ill patient populations with and refractory candidiasis. An unexpected event was worsening of neutropenia in subjects with refractory HIV disease. All subjects with this event were from the same center and were suffering from cryptococcal meningitis. A relationship between POS-treatment and exacerbation of underlying neutropenia could not be ruled out.

In the Controlled OPC Pool, 9% (50/557) of subjects on posaconazole and 5% (14/262) of subjects on fluconazole reported AEs that led to discontinuation or death. The difference between the two treatment pools resulted from a greater proportion of posaconazole subjects with GI disorders (3% for posaconazole and 1% for fluconazole) and liver and biliary disorders (6% for posaconazole and 0% for fluconazole).

In the Refractory OPC Pool, 34% (81/239) of subjects had AEs that led to discontinuation or death. The most commonly reported of these AEs were AIDS (7%), respiratory insufficiency (3%), neutropenia, pneumonia, and sepsis (2% each).

There was no evidence of a dose-related increase in the number or types of adverse events that led to discontinuation or death in either OPC pool.

In the Controlled OPC Pool, 18/557 (3%) of posaconazole-treated subjects and 5/ 262 (2%) of fluconazole –treated subjects died. Deaths were primarily attributed to progression or complications of underlying HIV disease as confirmed by a review of the patient narratives and CRF. Although the number of deaths on the POS treatment arm was higher than that on the fluconazole arm, there did not appear to be any predominant cause of death other than progression of underlying disease or complications of the underlying disease. There was 1 case of sudden death in a fluconazole-treated patient where fluconazole could not be ruled out as a contributing cause although death occurred 3 weeks after the end of treatment.

In the Refractory OPC Pool, population of highly immunosuppressed and often terminally ill patients, 53/239 (22%) of subjects died. Deaths were primarily attributed to AEs considered unlikely related to posaconazole or to progression or complications of underlying HIV disease. One death was considered due to an AE related to treatment, 1 death was thought to be related to treatment and 2 deaths were of unknown cause.

There were 2 cases of worsening neutropenia and death while on treatment. The contributory effects of POS-treatment on the WBC count and the effects on mortality could not be ruled out.

Summary of Deaths (OPC Pool)

	Number (%) of Subjects		
	Controlled OPC Pool		Refractory OPC Pool
Cause of Death	POS n=557	FLZ n=262	POS n=239
Total Number of Deaths	**18 (3)**	**5 (2)**	**53 (22)**
Adverse Event	**1 (<1)**	**0**	**29 (12)**
Related	0	0	1 (<1)
Unrelated	1 (<1)	0	27 (11)
Unknown/Not Specified	0	0	1 (<1)
Progression or Complication of Underlying Disease	**13 (2)**	**3 (1)**	**21 (9)**
Complications Related to Disease Under Investigation	**1 (<1)**	**0**	**1 (<1)**
Progression of Disease Under Investigation	**0**	**1 (<1)**	**0**
Other[a]	**3 (1)**	**0**	**2 (1)**
Unknown[b]	0	1 (<1)	0

a: AIDS wasting syndrome (I97-331/6-0077); acute respiratory failure (I97-331/16-256); suicide (C/I97-331/16-663) in the Controlled OPC Pool; and unspecified other cause of death (P00298/01-007 and P00298/02-/002) in the Refractory OPC Pool.
b: C96-209/32-001 in the Controlled OPC Pool.

The overall proportions of subjects with Grade 3 or Grade 4 AEs were similar for subjects treated with POS and FLU in the controlled OPC studies where POS doses were ≤ 400 mg QD. Grade 3 AEs were reported in 56/577 (10%) of POS treated controlled OPC subjects as compared to 28/262 (11%) of FLU-treated subjects. Grade 4 AEs were reported for 21/557 (4%) subjects on POS and 8 /262 (3%) subjects on FLU.

Events that occurred more than once included neutropenia (7 Grade 3 reports and 0 Grade 4 reports), nausea (4 Grade 3 reports and 0 grade 4 reports), headache (3 grade 3 and 0 Grade 4 reports), pneumonia (4 grade 3 and 0 Grade 4 reports), diarrhea, vomiting, and abdominal pain (2 Grade 3 reports each and 1 Grade 4 report for diarrhea). Other events including bilirubinemia and increased hepatic enzymes were reported for 1% of posaconazole-treated subjects and ≤1% of subjects on fluconazole. Grade 4 anemia and respiratory insufficiency were reported for 1% of subjects on posaconazole and for no subject on fluconazole. Grade 3 events in FLU-treated subjects included anemia (3 Grade 3 reports), neutropenia (2 Grade 3 reports), abdominal pain (2 reports), diarrhea (3 reports), vomiting (2 reports), tuberculosis (4 reports), and dehydration (3 reports).

Treatment related Grade 3 events were reported for 19% (45/239) of subjects, and treatment related Grade 4 events were reported for 5% (12/239) of subjects. Treatment related Grade 3 events reported for more than one subject were neutropenia (n=10 (4%); flatulence (n=3); anemia, aggravated anemia, abdominal pain, asthenia, diarrhea, nausea, vomiting, and thrombocytopenia (n=2 for each). As per the applicant, "Generally, the neutropenia was associated with co-administration of other bone marrow suppressing drugs and the presence of advanced HIV disease."

Treatment-related Grade 4 AEs included neutropenia (n=6 (3%), sudden death, cardiac failure, cerebrovascular accident, leukopenia, increased hepatic enzymes, hypokalemia, acute renal failure, respiratory disorder (each reported for 1 subject).

There was no evidence of a dose-related increase in the number or types of Grade 3 or Grade 4 AEs for subjects in the Controlled OPC pool. Grade 3 AEs were reported for 10% (38/368), 12% (11/91), and 7% (7/98) of subjects treated with ≤100 mg/day, 200 mg/day, and 400 mg/day, respectively; Grade 4 AEs were reported for 4% (16/368), 3% (3/91), and 2% (2/98) of subjects in the 3 dose groups, respectively.

In the Refractory OPC Pool, Grade 3 AEs were reported for 43% (39/90) of subjects treated with <800 mg/day and for 66% (99/149) of subjects treated with 800 mg/day. Grade 3 anemia (7% vs. 3%), asthenia (7% vs. 1%), nausea (5% vs .0), vomiting (8% vs. 1%), oral candidiasis (5% vs. 1%), weight decrease, fever (7% vs. 3%) were reported more often for subjects treated with 800 mg/day (5% to 8%) than for subjects treated with <800 mg/day (≤2%). Treatment-related Grade 3 AEs were reported for 14% (13/90) of subject treated with <800 mg/day and 21% (32/149) of subjects treated with 800 mg/day.

Grade 4 AEs were reported for 20% (18/90) of subjects treated with <800 mg/day and for 28% (42/149) of subjects treated with 800 mg/day.

Treatment-related Grade 4 AEs were reported for 10% (9/90) of subjects treated with <800 mg/day and for 2% (3/149) of subjects treated with 800 mg/day. Treatment-related Grade 4 neutropenia was reported more often for subjects treated with <800 mg/day (6%, 5/90) than for subjects treated with 800 mg/day (1%, 1/149).

The potential for a dose related increase in AEs appears to exist although many of the reported AEs appeared related to the underlying disease.

In the Controlled OPC Pool, the proportions of subjects with Grade 3 or Grade 4 AEs during the first 7 days of treatment were similar for POS and FLU: 5% (28/557) for POS subjects and 3% (8/262) for FLU subjects.

In the Refractory OPC Pool, 11% (26/239) of subjects reported Grade 3/4 AEs during the first 7 days of treatment. Neutropenia, reported for 2% (5/239) of subjects, was the most commonly reported Grade 3 or Grade 4 AE in the Refractory OPC Pool. All other Grade 3 or Grade 4 AEs during the first 7 days of treatment were reported for ≤1% of POS subjects.

In the Refractory OPC Pool, 32% (77/239) of subjects had Grade 3 or Grade 4 AEs during the first 30 days of treatment. The most commonly reported Grade 3 or Grade 4 AE for subjects in the Refractory OPC Pool was neutropenia (reported for 6% [14/239] of subjects).

With regards to the frequency of reporting events over time, 46% of subjects reported AEs during the first 3 months of treatment, 35/110 (32%) during the 3 – 6 month period, 21/55 (38%) during the 6 – 9 months period, 11/40 (28%) within the 9- 12 month period and then the percentage increased again to 17 of 31 subjects (55%) reporting an AE after 12 months. Events that occurred after a year could have reflected progression of the underlying HIV disease. Neutropenia was spread out across the reporting periods.

Hepatic AEs occurred with a similar frequency between posaconazole and fluconazole treated subjects in the controlled OPC pool (posaconazole 31/557 (6%) and fluconazole 13/262 (5%). The events were treatment-related in 3% of posaconazole and fluconazole treated subjects. The most common hepatic AEs were bilirubinemia (1% for both groups), and abnormal hepatic function, increased SGOT, and increased SGPT, each reported by 1% of posaconazole treated subjects and by 2% of fluconazole treated subjects. Increased alkaline phosphatase was reported for 1% of subjects in the posaconazole group and 3% of the subjects in the fluconazole group. Grade 3 hepatic AEs were reported for 1% of posaconazole and fluconazole treated subjects and a single POS-treated subject had a Grade 4 AE. Six subjects (1%) discontinued posaconazole treatment due to hepatic adverse events but no hepatic adverse events resulted in death. For three of these subjects, the hepatic events that resulted in discontinuation were treatment related (one event of hepatic enzymes increased and 2 episodes of hepatitis). One fluconazole treated subject discontinued due to increased alkaline phosphatase.

Serious hepatic adverse events were reported for 2% of posaconazole-treated subjects (n=4) and 1% of fluconazole-treated subjects (n=1) in the controlled OPC group of study 331. There were no treatment related hepatic SAEs in the posaconazole group.

In the Phase II study C96209 2%, (6/379) of POS treated subjects and 2% of FLU treated subjects (2/90) had serious hepatic AEs reported. 10 of 557 OPC subjects (1.7%) had serious hepatic AEs. The serious hepatic AEs included 4 reports of hepatic function abnormal (1%) POS, 2 reports of increased SGOT (1%) as well as 1 report each of bilirubinemia, hepatic enzymes increased, hepatitis, cholestatic hepatitis and SGPT increased in the POS treated subjects as compared to none of the fluconazole treated subjects. The 2 events in the fluconazole treated subjects were one episode each of hepatic cirrhosis and hepatic disorder NOS. As in the Phase I population, it appeared as if the hepatic events most often occurred a few days after the start of treatment or even at the EOT and slowly resolved over the ensuing weeks. Overall, the safety profile of low dose posaconazole (up to 400 mg/day) was comparable to that of fluconazole with regard to hepatic safety.

In the refractory OPC pool (N = 239) hepatic AEs were reported in 40/239 (17%) of subjects, and were treatment related in 15/239 (6%) of subjects. The most commonly reported hepatic AEs were bilirubinemia, increased hepatic enzymes, increased SGOT, increased SGPT, and hepatomegaly, each reported in 6 – 8 (3%) of subjects, and hepatitis and jaundice reported in 4 -5 (2%) subjects. All other hepatic AEs were reported for ≤ 1% of subjects. Increased alkaline phosphatase was reported in 8 (3%) subjects. Grade 3 events were reported in 14/239 (6%) of subjects and Grade 4 events were reported in 3/239 (1%) subjects. Two percent of subjects had treatment related Grade 3 or Grade 4

hepatic AEs. One subject (P00298-03/101) had a Grade 4 hepatic AE (hepatic enzymes increased) that was considered possibly related to treatment.

Six refractory OPC subjects (3%) discontinued/died due to hepatic events; for three subjects (1%), the events were treatment related. One subject (C97330/16-001) died due to hepatic failure 77 days after discontinuing treatment with posaconazole; the hepatic failure was considered by the investigator to be unlikely related to posaconazole and the MO agreed.

In both the controlled and refractory populations, liver abnormalities appeared to occur more frequently in subjects with pre-existing liver disease. LFT increases occurred after the first week of treatment in both groups.

Cardiovascular system AEs: Five of 557 posaconazole treated subjects (1%) and one of 262 fluconazole treated subjects in the controlled OPC pool (<1%) reported general cardiovascular disorders. None of the events was considered treatment related on either arm. Hypotension was reported for three posaconazole-treated subjects, for two of these subjects the events were considered severe (Grade 3). Circulatory failure (Grade 4) was reported for one posaconazole treated subject. The fluconazole-treated subject reported hypertension. No posaconazole treated subject in the Controlled OPC Pool reported hypertension. Two subjects reported palpitations and one each reported AV block, cardiac arrest, and extrasystoles.

Heart rate and rhythm disorders were reported for 2% (9/557) of posaconazole-treated subjects and no fluconazole treated subject. The adverse event of "ECG abnormal" was reported in four posaconazole treated subjects (1%) and "QT/QTc prolongation" was reported for one posaconazole treated subject (96209/08/001), all of which were mild or moderate in severity, and all cases of abnormal ECG were considered treatment related. Two subjects reported palpitations and one each reported AV block, cardiac arrest, and extrasystoles. One subject had a cardiac arrest (Grade 4) in the posaconazole treated group, considered unlikely related to treatment. Additional terms that might be indicative of cardiac disease such as edema, leg edema, and peripheral edema were reported in less than 1% for both posaconazole and fluconazole; none was considered a Grade 3 or 4 event and none was considered to be treatment-related. The preferred terms of syncope, sudden death, and death were also examined as potential markers for arrhythmia. Death was reported for one posaconazole-treated subject and syncope was reported for one fluconazole treated subject. Two fluconazole-treated subjects from Study C/I96-209 had SAE reports of "sudden death" (C96209-12/04 and I96209-40/03); Neither of these events was considered by the investigator to be treatment related.

In the Refractory OPC Pool, AEs in the general cardiovascular disorders category were reported for 15% (35/239) of the subjects, and treatment-related events were reported for 3% (7/239) of subjects. The most common AEs were hypertension (3%, n = 6), hypotension (3%, n = 8), and cardiac failure (2%n = 5). Two events each of cardiac failure aggravated, ejection fraction decreased, and aggravated hypertension as well as one event of mitral insufficiency were considered treatment related. Hypotension, cardiac

failure, and hypertension were reported as Grade 3 events in ≤ 1% of subjects (3, 1, and 1). Six subjects (3%) reported eight Grade 4 general cardiovascular disorders, which included cardiac failure (n = 3, 1%), cardiorespiratory arrest (n = 2, 1%), hypotension (1), circulatory failure (1), and myocardial infarction (1).

Heart rate and rhythm disorders were noted in 5% (11/239) of subjects. The most common event was tachycardia (n = 7, 3%). All other events were noted in <1% of subjects. One subject reported Grade 3 bradycardia (considered treatment related) and one subject each reported Grade 4 arrhythmia and Grade 4 cardiac arrest (both considered unlikely related to treatment). Other events that may indicate a cardiac etiology, such as edema (n = 8), leg edema (n = 16), and peripheral edema (n = 4) occurred in 3%, 7%, and 2%, respectively. Sudden death, death, and syncope were reported in one subject each.

There was one subject with QT prolongation who discontinued treatment for this event considered related to treatment. A narrative for this subject with confounding factors such as hypokalemia is supplied below:

A 45-year-old HIV (+) male subject with a history of weight loss, sinus bradycardia (ventricular rate of 53 beats per minute [bpm] on 03 APR 2000), a Baseline QTc of 0.424 seconds on 03 APR 2000, lymphadenopathy, thrombocytopenia, anemia, hypokalemia, oral hairy leukoplakia, esophageal stricture with diverticula, and IV drug abuse on methadone maintenance, initiated POS 400 mg PO BID on 03 APR 2000 for OPC). On 17 APR 2000 the subject was noted to have a QTc prolongation of 0.46 seconds and a heart rate of 62 bpm. On 25 APR 2000 the subject's QTc was 0.425 seconds. The subject was also noted to have a relapse of oral candidiasis. The study drug was discontinued after the 17 APR 2000 doses for QTc prolongation bradycardia. The subject was hospitalized for oral candidiasis, and treated with amphotericin B and intravenous fluids. No treatment was required for the bradycardia or the QTc prolongation. The subject's heart rate improved to 76 bpm on 24 APR 2000, but was 62 bpm 1 week later. The investigator considered the worsening QTc prolongation to be related, the sinus bradycardia to be probably related and the OPC to be unrelated to study medication.

EKG assessment in the OPC pool was based only on study C96-209 where ECGs were recorded at baseline and Day 8 during the study and at the EOT and the post treatment follow-up visit, if the prior visit's ECG was abnormal. In the remaining OPC studies, ECGs were obtained only at baseline. Analysis of the maximum change from baseline in QTcF interval during the treatment phase showed virtually no change from the mean or median baseline values with either posaconazole ≤ 400 mg/day or fluconazole 100 mg/day administered for 14 days. The maximum change from baseline was 89 msec in the posaconazole group and 80 msec in the fluconazole group. There were no subjects with QTcF intervals of greater than or equal to 500 msec during the treatment phase. One percent (1%) of subjects in both the posaconazole and fluconazole groups had changes from baseline QTcF intervals of at least 60 msec during the treatment phase (2/308 posaconazole vs. 1/76 FLU). Additionally, there were 6 posaconazole treated males with QTc (6/273) ≥ 450 msec including 1 subject where this value represented a change of at least 60 msec from baseline. No females had QTc intervals of 470 msec or greater on the posaconazole arm. One subject on the fluconazole arm (male) had similar changes.

Based on the review of the data, it appeared as if posaconazole may have some potential for cardiotoxicity including rate and rhythm disturbances such as QT prolongation and

torsades de pointes in the appropriate clinical settings and appropriate cautionary labeling should be applied until future comparative studies can further delineate the frequency of such events in a severely ill population.

In the controlled OPC pool which provided the only source of comparative data albeit at a lesser dose, similar proportions of posaconazole and fluconazole treated subjects experienced neurologic AEs: autonomic nervous system disorders (1%),central and/or peripheral nervous system disorders (6% POS -7% FLU), and psychiatric disorders (3% POS-4% FLU).

The most commonly reported neurologic AE was somnolence (2% with both posaconazole and fluconazole). Anxiety was reported for 2% of fluconazole-treated subjects and <1% of POS treated subjects. Hot flushes and paresthesias were reported with similar frequencies on both treatment arms. Insomnia was the most frequently reported AE in POS treated subjects (8, 1%) vs. 3 (1%) FLU. There were few treatment-related neurologic events (14 reports POS vs. 11 FLU), the most common of which included somnolence (1% posaconazole, 2% fluconazole), paresthesia (1% posaconazole, 1% fluconazole), and insomnia (1% posaconazole, 0 fluconazole); There were two subjects with Grade 4 neurologic adverse events reported with both treatments (cryptococcal meningitis and suicide attempt in the posaconazole group and convulsions and sensory disturbance in the fluconazole group).

In the Refractory OPC Pool 1% of subjects reported AEs that were classified as autonomic nervous system disorders, 35% had AEs classified as central or peripheral nervous system disorders, and 36% had AEs classified as psychiatric disorders. The most commonly reported neurologic AEs were insomnia (16%, 39 reports), anxiety (9%, 22 reports), depression (8%, 20 reports); hypoesthesia (13 reports), neuropathy (11 reports), somnolence (11 reports) and paresthesia (12 reports) (5% each); worsened depression and confusion (4%, 9 reports each); convulsions, abnormal gait and amnesia (3% each); and abnormal dreaming, sleep disorder, ataxia, encephalopathy, altered mental status, neuralgia, speech disorder and tremor (2% each). Most of these events were considered unlikely to be related to treatment, and 26 were Grade 3 or Grade 4. The Grade 3 events that were reported by more than one subject were convulsions (n=4), encephalopathy (n=3), depression (n=3), confusion (n=2), altered mental status (n=2), and neuropathy (n=2). Reports of Grade 4 events included coma (n=3) and cerebral hemorrhage, cerebrovascular accident NOS, confusion, and consciousness decreased (1 subject each). The MO reviewed all the CRFs of subjects with SAEs (31 subjects (13%) experienced SAEs classified as central or peripheral nervous system disorders and 12 subjects (5%) experienced SAEs that were classified as psychiatric disorders) or Grade 3 or 4 events and concurred that such events appeared not to be causally related to posaconazole. There were other etiologies to explain these events including the onset of convulsions during posaconazole and fluconazole treatments including pre-existing CNS infections and cerebrovascular accidents.

To conclude, a trend in neurologic adverse events was not seen in the NDA database. Events such as somnolence, insomnia, and hot flushes appeared to be related to azole

treatment as these AEs are consistently found throughout the indications as well as in the comparative FLU population. The most frequent neurologic AEs included insomnia, depression, anxiety, altered mental status, confusion, tremor, hypoesthesia, somnolence, agitation, paresthesia, coma, and convulsions.

There were no serious neurological complications that could be attributed to the administration of posaconazole.

The proportions of subjects with potentially clinically significant hematologic abnormalities, defined as CTC Grade shifts from 0, 1, or 2 at baseline to 3 or 4 at the worst value during the treatment period in the Controlled OPC Pool were similar for posaconazole and fluconazole. The most common clinically significant hematologic abnormalities in the posaconazole and fluconazole treatment pools (posaconazole and fluconazole) were decreases in neutrophil count (reported for 10% and 7% of subjects on posaconazole and fluconazole, respectively) and decreases in leukocyte count (7% and 5% respectively).

In the Refractory OPC Pool, the most commonly reported clinically significant abnormalities for hematology were decreases in leukocytes (21%), neutrophils (18%), hematocrit (10%), and hemoglobin (9%). The greater proportion of subjects with clinically significant changes in neutrophil counts in the Refractory OPC Pool occurred in the setting of more severe HIV disease and use of concomitant medications that may result in bone marrow suppression and that confounded attribution.

Table 33
Number (%) of Subjects With Shifts in Hematology Laboratory Values from CTC Grade 0, 1, or 2 at Baseline to Grade 3 or 4 at the Worst Value During Treatment (OPC Pool)

	Number (%) of Subjects		
	Controlled OPC Pool		Refractory OPC Pool
	POS	FLZ	POS
Laboratory Parameter	n=557	n=262	n=239
Hemoglobin	9/517 (2)	3/242 (1)	20/219 (9)
Hematocrit	11/510 (2)	2/238 (1)	21/218 (10)
Leukocyte Count	36/518 (7)	13/242 (5)	45/219 (21)
Platelet Count	1/501 (<1)	2/238 (1)	3/203 (1)
Neutrophil Count	47/448 (10)	12/171 (7)	38/211 (18)

OPC = oropharyngeal candidiasis; POS = posaconazole; FLZ = fluconazole.

Of the 11 subjects who reported neutropenia as a treatment related SAE, 2 discontinued from the study (I97-330/04-002 and P00298/11-002). Most subjects with treatment related SAEs of neutropenia had a history of neutropenia and were taking multiple concomitant antiretroviral medications; however, the possibility that posaconazole may have exacerbated these subjects' neutropenia cannot be ruled out.

Two posaconazole-treated subjects had developed AEs associated with elevated creatinine levels. Subject C97330-09/001 was discontinued from the study because of

Grade 4 acute renal failure. The investigator considered the acute renal failure to be possibly related to study drug.

Subject C97330-09/001 with an elevated baseline serum creatinine of 309 mmol/L (reference range: 40 to 110 mmol/L) had serum creatinine values of 327 mmol/L and 460 mmol/L on Days 9 and 22, respectively. The subject was discontinued from the study on Day 22 because of acute renal failure. Two days later, serum creatinine was 530 µmol/L. No renal abnormalities were recorded on the subject's medical history. Concomitant antiretroviral medications were stavudine, norvir, saquinavir, and lamivudine.

Subject C97331-06/042 was discontinued from the study because of multiple persistently abnormal laboratory results, which were reported as adverse events (increased hepatic enzymes, hyperuricemia, albuminuria, and anemia). Renal insufficiency was also reported at this time, considered possibly related to study drug.

Recommendations:

An approval is recommended for the requested OPC and refractory OPC indication. The proposed dose for OPC 100 mg BID for 1 day followed by 100 mg QD for 13 days and for refractory OPC is 400 mg BID [redacted]

2. Methods

A. Materials Reviewed: NDA Electronic submission

CDROM submitted January 20, 2005

B. Historical Perspective and State of Armamentarium for the Indication:

Oropharyngeal candidiasis (OPC) has become increasingly frequent in the last decades because of the increasing number of immunosuppressed patients primarily due to HIV/AIDS and because of the progress made in transplant medicine and cancer chemotherapy. A large number of all fungal infections are caused by *Candida* species and OPC is the most common manifestation of *Candida* species infections. OPC is an opportunistic infection in HIV-infected patients and is often the first sign of HIV infection. The incidence of OPC increases as the CD4 count falls. These infections are caused primarily by *Candida albicans,* although other *Candida* species, such as *Candida glabrata* and *Candida krusei,* are becoming more frequent and are less susceptible to available azole antifungal agents. OPC infections are often repetitive and recurrent in HIV infected subjects and are associated with oral pain and difficulty swallowing. Eating is also impaired leading to significant weight loss.

As per current guidance (IDSA, CID 2004:38; 1/15) therapeutic options include topical azole agents, oral azoles, or oral polyenes (such as nystatin and/or oral amphotericin B). For refractory or recurrent infections, orally administered azoles or intravenous amphotericin B or caspofungin are recommended.

Generally most HIV and cancer patients with uncomplicated OPC who are treated with topical therapies, such as nystatin or clotrimazole troches have an initial response but tend to relapse more quickly than patients treated with fluconazole and resistance may develop to either regimen .(Multicenter Study group, J of the Acquired Immunod s 1993; 6)

Of the azole antifungals, fluconazole is superior to ketoconazole and itraconazole solution is comparable to fluconazole in terms of efficacy. There have been reports of clinical failures due to the development of resistance following repeated courses of therapy or prolonged suppressive therapy with these agents in HIV infected patients. The incidence of refractory disease or the development of resistant isolates appears to be independent of the use of suppressive or episodic treatment. Advanced immunosuppression, the number of prior OPC episodes and the duration of fluconazole therapy are independent risk factors for the development of fluconazole resistance. The clinical significance of resistant isolates is not clear. (Clinical Microbiology reviews, Oct. 2001, Rex et al Vol. 14; 4).

Susceptibility testing for yeasts passed through a number of phases and the NCCLS issued an approved guidance the M27-A in 1997 that specifies methods for such testing. Of note are such issues as the relevance of 24 versus 48 hour susceptibility assessments because interpretive breakpoints were initially established only after 48 hours of incubation. Current thought is that a 24 hour reading may be more clinically relevant because of the "trailing growth" phenomenon. Isolates exhibiting this behavior apparently appear susceptible at 24 hours and resistant at 48. Researchers have concluded that such isolates should be categorized as susceptible. Another issue that can affect testing results is the PH. The M27-A method includes interpretive breakpoints for itraconazole, fluconazole and ketoconazole versus *Candida albicans.* Specifically for fluconazole, these breakpoints were based on an analysis of treatment outcomes in both mucosal and invasive disease and include the description of a novel endpoint the s-DD (susceptibility is dose dependent). For fluconazole the S-DD range includes MICs of 16 – 32 mcg/mL. Isolates with MICs above this range are classified as resistant. The S-DD breakpoint concept emphasizes the importance of achieving maximal blood and tissue FLU levels for isolates with higher MICs. Maximal dose in this context is 400 mg/day in an average 70 Kg adult. Others have reported that fluconazole isolates with MICs > 8 mcg/mL are unlikely to be responsive to 100 mg FLU/day. Generally it appears as if the literature supports the use of increasing doses of fluconazole when MICs increase. This data is supported by PK data that have shown that for FLU the best predictor of response is the AUC/MIC ratio.

Similar breakpoints exist for ITR. These interpretive breakpoints were generated from subjects with mucosal infection. Isolates with MICs of > 0.5 mcg/mL are classified as resistant, those with MICs < 0.125 as sensitive and those in between as S-DD. Up to 80% of patients with fluconazole-refractory infections will respond to itraconazole solution. However, all OPC patients with fluconazole-refractory disease who responded to itraconazole treatment and entered a 6-week, treatment-free, follow-up phase (n=22) relapsed within 1 month following treatment cessation; the median time to relapse was 14 days (Saag et all, AIDS RES. Hum. Retroviruses15:1413-1417).

This open-label, multicenter trial evaluated the efficacy and safety of a new oral solution formulation of itraconazole in HIV+/AIDS patients with fluconazole-refractory oropharyngeal candidiasis. Seventy-four HIV+/AIDS patients with mycologically confirmed oropharyngeal candidiasis who failed fluconazole therapy (200 mg/day) were treated with 100 mg of itraconazole oral solution administered twice daily (200 mg/day) for 14 days. Patients who demonstrated an incomplete response to treatment were treated for an additional 14 days (28 days total). Clinical responders were eligible for participation in a separate 6-month maintenance protocol. If they declined further treatment, responders were monitored for 6 weeks post treatment. The primary efficacy parameter was clinical response (i.e., no lesions or symptoms) at end of treatment. Fungal cultures were performed at baseline and at the end of treatment. Among the 74 patients who had mycologically confirmed, fluconazole-unresponsive, oropharyngeal candidiasis at baseline, 41 (55%) achieved a clinical response by day 28. The median time to response was 7 days (range, 7 to 28 days). Candida albicans was the most common pathogen isolated, either alone (62%) or in combination with another Candida species (31%). All 22 patients who entered the optional, off-therapy, 6-week follow-up phase relapsed; mean time to relapse was 13 days. Itraconazole oral solution was well-tolerated; adverse events were predominantly gastrointestinal disturbances. This trial demonstrates that itraconazole oral solution is a useful therapy in the treatment of HIV-infected patients with fluconazole-refractory oropharyngeal candidiasis.

There does not appear to be a firm definition of refractory OPC although usually this entity appears in HIV infected subjects who are not on HAART with low CD4 counts and who have previously received azole treatment, usually fluconazole. Often subjects with refractory disease respond to higher doses of FLU than the approved 100 mg QD dose. Other authors have defined refractory disease as that which is unresponsive to 200 mg PO of fluconazole QD for 7 – 14 days and others as that that is unresponsive to 400 mg PO QD for 7 – 14 days.

A review of Mucosal Candidiasis in HIV-infected patients (Vazquez, HIV Clinical Trials, VOl1.1, July-August 2000) divided antifungal resistance into 2 categories, clinical and in vitro. Clinical resistance signifies failure of the antifungal to eradicate the infection in the absence of in vitro resistance and in vitro resistance can be divided in to primary (innate or intrinsic) and secondary (acquired) resistance. Clinical resistance can be due to low serum or tissue drug levels, non-adherence, drug-drug interactions and advanced AIDS. As noted above, the author reiterates the issues associated with antifungal susceptibility testing and the conflicting results from studies where HIV patients with both high and low MICs were successfully or unsuccessfully treated. The author concluded that the appropriate nomenclature for non-responsive OPC in HIV subjects with a number of risk factors including low CD4 counts, greater number of previous episodes of OPC, longer median duration of previous antifungal treatment (all) and longer duration of previous systemic azole treatment is azole-refractory OPC as opposed to resistant OPC.

State of Armamentarium for Indication(s)

Antifungal products that are approved for the treatment of OPC include ketoconazole, fluconazole, and itraconazole. Voriconazole, caspofungin (AP September 2002), and amphotericin B (IV) are indicated for EC but not for OPC. At present no antifungal has received the indication of "refractory OP candidiasis"

Pertinent excerpts from the labels that provide clinical information are copied below:

Sporanox® (itraconazole)

Indication and Usage Section:
SPORANOX® (itraconazole) Oral Solution is also indicated for the treatment of oropharyngeal and esophageal candidiasis.

Oropharyngeal Candidiasis: Two randomized, controlled studies for the treatment of oropharyngeal candidiasis have been conducted (total n=344). In one trial, clinical response to either 7 or 14 days of itraconazole oral solution, 200 mg/day, was similar to fluconazole tablets and averaged 84% across all arms. Clinical response in this study was defined as cured or improved (only minimal signs and symptoms with no visible lesions). Approximately 5% of subjects were lost to follow-up before any evaluations could be performed. Response to 14 days therapy of itraconazole oral solution was associated with a lower relapse rate than 7 days of itraconazole therapy. In another trial, the clinical response rate (defined as cured or improved) for itraconazole oral solution was similar to clotrimazole troches and averaged approximately 71% across both arms, with approximately 3% of subjects lost to follow-up before any evaluations could be performed. Ninety-two percent of the patients in these studies were HIV seropositive.
In an uncontrolled, open-label study of selected patients clinically unresponsive to fluconazole tablets (n=74, all patients HIV seropositive), patients were treated with itraconazole oral solution 100 mg b.i.d. (Clinically unresponsive to fluconazole in this study was defined as having received a dose of fluconazole tablets at least 200 mg/day for a minimum of 14 days.) Treatment duration was 14-28 days based on response. Approximately 55% of patients had complete resolution of oral lesions. Of patients who responded and then entered a follow-up phase (n=22), all relapsed within 1 month (median 14 days) when treatment was discontinued. Although baseline endoscopies had not been performed, several patients in this study developed symptoms of esophageal candidiasis while receiving therapy with itraconazole oral solution. Itraconazole oral solution has not been directly compared to other agents in a controlled trial of similar patients.

Diflucan® (fluconazole)
Indications and Usage Section states:
DIFLUCAN (fluconazole) is indicated for the treatment of Oropharyngeal and esophageal candidiasis.

The recommended dosage of DIFLUCAN for oropharyngeal candidiasis is 200 mg on the first day, followed by 100 mg once daily. Clinical evidence of oropharyngeal candidiasis generally resolves within several days, but treatment should be continued for at least 2 weeks to decrease the likelihood of relapse.

NIZORAL® (ketoconazole) Tablets are indicated for the treatment of the following systemic fungal infections: candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. NIZORAL® Tablets should not be used for fungal meningitis because it penetrates poorly into the cerebral-spinal fluid.

C. Important Milestones in Product Development

The original IND [redacted] study the tablet formulation of POSA was submitted on August 16, 1996, followed by IND 51,662 to study the oral suspension on October 4,

1996. The OPC (309 and 331) studies appear to have commenced in 1997 but no records of the original protocol submissions and FDA comments could be located.

The Applicant submitted the initial protocol for study C97-330 on December 9, 1997 (IND 51,662 (015) and for I97-330 on April 14, 1998 (034). Protocol C97-330 was amended on April 1, 1999 (073) and both were amended on July 7, 1999 (097).

Study C97-330 was originally designed as a 4 week trial of posaconazole in HIV infected subjects with OPC/EC at an initial dose of 400 mg bid x 3 days followed by 400 mg qd x 2 weeks with further adjustment of the dose depending upon response. After the start of the study the applicant designed and submitted study 298, a long term safety study where subjects with OPC/EC received 400 mg bid of posaconazole for up to 12 months. Clinical response was to be assessed in all C/I97-330 subjects at a 1 month visit (EOT), after which subjects might have continued in 330 maintenance (Original protocol) or enrolled in 298 (Amended protocol), with or without a hiatus. Off treatment 30 day follow-up assessments, if done at all, were performed at variable times.

Records of discussion between the applicant and the Agency date back to a 9/5/97 teleconference where the key point was:

- The proposed open label study would not result in a fluconazole-resistant claim in the INDICATIONS section of the label but that the data could be used in the OPC clinical studies section with wording similar to that in the itraconazole label.

The Agency provided comments on both protocols on May 10, 1999 and the applicant responded to the Agency comments on July 7, 1999. There was also a teleconference between the Agency and SPRI on May 24, 1999. The minutes for all the meetings were provided by the Applicant.

[redacted]. With regards to refractory OPC the following points were discussed:

- The Agency requested that the applicant clarify the inclusion criterion that specified that patient must have clinical evidence of oral/esophageal candidiasis.

- The Agency recommended a combined clinical and mycological endpoint and an agreement was reached with the Agency in the May 24, 1999 teleconference to only utilize a clinical endpoint but that the mycological data must be collected.

- The Applicant proposed to compare results of this trial with the historical efficacy seen in an open label study of itraconazole in azole-refractory patients.

The Applicant submitted the following statement on 1/17/2005:
The literature reports that up to 80% of patients with fluconazole-refractory infections will respond to itraconazole solution (Pappas PG et al, IDSA Guidelines for Treatment of Candidiasis, Clinical Infectious Diseases; 2004; 38:161-189).

- The Applicant defined relapse as the emergence of the same species of *Candida* during the post treatment period after eradication and re-infection as the emergence of a new *Candida* species during the post-treatment period.

- In the original protocol, the Applicant elected to utilize the quantitation of yeast per ml of a swish and spit specimen as a method to assess for eradication or persistence in final specimens. Specifically, < 20 yeast/mL would be indicative of eradication (Graybill et al AM J Med 1998:104:33- 39)

- The Agency recommended that the following definitions of mycologic response be used:

  Mycologic response at the EOT = eradication or NO growth
  Mycologic treatment failure = any growth at the EOT
  Mycologic response at the EOS= < 20 CFU/mL at the EOS visit
  Mycologic failure at the EOS = ≥ 20 CFU yeast/mL at the EOS visit

Note: The sponsor elected NOT to utilize the Agency definitions of mycologic response but rather to base the primary efficacy endpoint on clinical outcome only.

- The Agency requested that all isolates be tested for sensitivity versus fluconazole and itraconazole. Also requested were the baseline CD4 count, the number of previous episodes of oral candidiasis patients experienced prior to posaconazole treatment and information regarding antiretroviral treatment at baseline.

The Agency agreed that the sponsor has adequate data to review for this indication in a Presubmission meeting on October 25, 2005. Also discussed was the
The applicant was informed that
. The safety from the OPC/rOPC studies was previously reviewed

D. Proposed Indication: (copied from Applicant's proposed label 12/21/05)

NOXAFIL (posaconazole) is indicated for the treatment of oropharyngeal candidiasis, including infections refractory to itraconazole and fluconazole.

3. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Microbiology

See FDA Microbiology review. Posaconazole which like other azoles acts by blocking ergosterol biosynthesis by inhibiting the enzyme lanosterol 14(-demthylase (CYP51), has antifungal activity against susceptible and resistant strains of moulds and yeasts (e.g. *Candida albicans*, non-albicans *Candida*, and *Cryptococcus*). Its activity was superior to

fluconazole and voriconazole in its ability to inhibit CYP51 in *Candida albicans* and superior to voriconazole and itraconazole against the same enzyme in *A. fumigatus*.

As azole resistance is an issue in the clinical setting, an assessment by the applicant revealed that in *Candida albicans*, multiple amino acid substitutions in CYP51 were required to confer major reductions in susceptibility to posaconazole, leading the Applicant to postulate that development of resistance to posaconazole may be slower than for other azoles. A second mechanism of resistance is due to increased expression of efflux pumps resulting in decreased intracellular concentration of the drugs. Similar to other azoles, posaconazole is a substrate for some of the *Candida albicans* multi-drug efflux transporter pumps (ABC-family) but, unlike fluconazole and voriconazole, posaconazole is not a substrate for the major facilitator pumps. A third mechanism of resistance was identified in clinical *Candida albicans* isolates that exhibited decreased susceptibility to all azoles but did not have amino acid substitutions in CYP51 or increased expression of the efflux pump genes. These isolates had nonsense mutations in the *ERG3* gene resulting in a non-functional $\Delta_{5,6}$-sterol desaturase enzyme, thereby abrogating the toxicity of the methylated sterol intermediates. This mechanism of resistance was rarely observed.

B. Pharmacokinetics and Pharmacodynamics

For further detailed information, Please refer to the BP review.

4. Description of Clinical Data and Sources

A. Overall Data:

The Applicant submitted 2 randomized controlled double or evaluator blinded comparative studies of the efficacy of posaconazole versus a fluconazole comparator. One study (C196-209) was a dose finding study that is considered supportive for the OPC indication.

In addition, the sponsor submitted the results from 2 open label studies of posaconazole in HIV infected adults with azole refractory OPC.

B. Table Listing the Clinical Trials

Table 1
List of Clinical Trials

Study Number Study Center(s) Study Dates Study Status	Design, Objective(s), and Control(s)	Diagnosis and Criteria for Inclusion	Test Product, Regimen, and Duration of Treatment	Criteria for Evaluation	No. of Subjects Age Range Sex (no. M/F)
Azole-susceptible Oropharyngeal Candidiasis					
C/I96-209	Phase-2, Randomized, active controlled, double blind	HIV-infected adults	POS 400 mg BID on Day 1	Clinical response,	485/469

53 centers (USA/International) APR 1997-MAR 1999 Completed	dose-finding study with fluconazole as the active comparator	(≥18 years) with OPC (≥2 discrete pseudomembranous plaques or a single confluent plaque ≥3 cm, and positive *Candida* culture)	followed by one of the following regimens on Days 2-14: POS 50 mg QD (n=98); POS 100 mg QD (n=102); POS 200 mg QD (n=91), or POS 400 mg QD (n=100); administered as oral capsules vs. FLU 200 mg QD on Day 1 and FLU 100 mg QD on Days 2-14 (n=94)	mycological response, AEs, laboratory assessments, ECGs, vital signs	18-65 398 M/87 F
C/I97-331 47 centers (USA/International) DEC 1998-OCT 1999 Completed	Phase-3, Randomized, active controlled, evaluator blind, efficacy and safety study with fluconazole as the active comparator	HIV-infected adults (≥18 years) with OPC (clinical evidence of pseudomembranous OPC confirmed with positive *Candida* culture)	POS 100 mg BID on Day 1, followed by POS 100 mg QD on Days 2-14 administered as an oral suspension (n=182) vs. FLU 200 mg on Day 1, followed by 100 mg QD on Days 2-14 (n=184)	Clinical response, mycological response, AEs, laboratory assessments, ECGs, vital signs	366/350 19-78 276 M/90 F
Azole refractory OPC					
C/I97-330 30 centers (USA/International) MAR 1998-SEP 2000 Completed	Phase-3, open label, uncontrolled efficacy safety study	HIV-infected adults (>18 years) with OPC and/or EC refractory to standard course of therapy with azole antifungals (FLZ or ITZ), and expected survival of ³6 months	Amended: POS 400 mg BID for 28 days; administered as oral suspension (Amended Protocol; n=96) POS 400 mg BID x 3 days, then 400 mg QD x 25 days, followed by 400 mg BID three times weekly x 3 months, administered as oral suspension (Original Protocol; n=103)	Clinical response, mycological response AEs, labs	-/199/115 20-69 174 M/25 F EC= 43
P00298 19 centers (USA/International) MAR 1999-JAN 2003 Completed	Phase-3, open label uncontrolled efficacy and safety study	HIV-infected adults (³18 years) with OPC and/or EC refractory to standard course of therapy with azole antifungals (FLZ or ITZ), and expected survival of ³6 months (subjects previously enrolled in C/I97-330 and treatment-naive)	POS 400 mg BID for up to 15 months; administered as oral suspension (Treatment Phase of up to 3 months, with 1-month follow-up for subjects with clinical cure, followed by Maintenance Phase of up to 12 months for subjects who relapsed in follow-up or showed improvement after Treatment Phase)	Clinical response, mycological response AEs, labs, neuro exams	-/100/65 25-61 84 M/16 F EC = 11

C. Post-marketing Experience

This drug is not marketed in the US at present.

5. Clinical Review Methods

A. How the Review was conducted including overview of materials reviewed and methods used to evaluate data quality and integrity

A random sample of CRFs of cases were reviewed. Additionally the jump datasets were reviewed for accuracy in the transcription of data. With regard to rOPC, a separate

dataset was requested. Each study was reviewed separately and then combined into an integrated efficacy summary.

B. Were Trials Conducted in Accordance with Accepted Ethical Standards

It appeared as if the trial (s) were conducted ethically and after IRB approval. In all CRFs reviewed the consent forms were signed.

C. Evaluation of Financial Disclosure

There was no conflict of interest with regards to the indication under review,

6. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The applicant submitted 2 randomized, active-controlled, clinical studies in HIV-infected subjects with azole-susceptible OPC in support of the OPC indication. The approved dose of oral fluconazole was used as the active control in both studies.

Posaconazole was administered as an oral capsule in C/I96-209 and as an oral suspension in C/I97-331. The difference in the bioavailability between the suspension and capsule is approximately 10%, and the posaconazole clinical response rates were similar (86.8% in C/I96-209 (capsules) versus 91.7% in C/I97-331 (oral suspension). In study 331 the requested posaconazole dose of 100 mg for 14 days found to be non-inferior to the approved comparator fluconazole 100 mg QD for 14 days regimen for both the primary efficacy parameter of clinical response at the EOT/TOC visit but also for the secondary parameters of clinical response or relapse rate 2 weeks post treatment as well as for mycologic response at both visits. In addition to the differences in bioavailibity, there may have been a topical antifungal effect on the OPC from the oral suspension.

The primary efficacy parameter in the both OPC studies was the clinical success rate (defined as cure or improvement) at the conclusion of 14 days of treatment in the Modified Intent-to-Treat (MITT) subset (all randomized subjects who had a positive *Candida* culture at Baseline and took at least one dose of study drug). Additional analyses were performed in a protocol evaluable (PE) as well as an ITT/All treated population.

In the dose-finding Phase-2 study, C/I96-209, 469 subjects were treated with a loading dose of posaconazole pf 400 mg twice daily (BID) for 1 day, followed by 50 mg, 100 mg, 200 mg, or 400 mg once daily (QD) for 13 days, or fluconazole 200 mg QD for 1 day, followed by 100 mg QD for 13 days.

A successful clinical response (cured and improved) was achieved by 87% of subjects in the 400 mg POSA group; 76.5% in the 200 mg group; 86.8% in the 100 mg group (requested dose); 84.9% in the 50 mg group; and 89.2% in the fluconazole group for the

modified ITT subjects. No statistical conclusions could be drawn from this study because of the lack of a dose response and the aberrant results achieved on the 200 mg arm. Clinical Response at follow-up revealed relapse rates that decreased as the dose increased. Of note was the 36% relapse rate for the FLU treated subjects as compared to the 41% relapse rate for the 100 mg posaconazole treated subjects (requested dose).

Table 2
Success and Relapse Rates MITT and PP
OPC C/I96-209

		Posaconazole			
	50 mg	**100 mg**	**200 mg**	**400 mg**	**FLZ**
MITT	N = 86	N = 91	N = 85	N = 92	N = 83
Success Rate (a)	**73 (84.9%)**	**79 (86.8%)**	**65 (76.5%)**	**80 (87.0%)**	**74 (89.2%)**
Cure	64 (74.4%)	73 (80.2%)	63 (74.1%)	76 (82.6%)	69 (83.1%)
Improvement	9 (10.5%)	6 (6.6%)	2 (2.4%)	4 (4.3%)	5 (6.0%)
FDA 95.2% CI cures only with CCF	- 21.25, 4.82	-15.65, 9.85	- 22.63, 4.60	- 12.94, 11.90	
MITT F/U	N = 59	N = 68	N = 54	N = 70	N = 62
Relapse Rate	24 (40.7%)	27 (39.7%)	19 (35.2%)	25(35.7%)	23 (37.1%)
PP	N = 81	N = 83	N = 80	N = 88	N = 77
Success Rate (a)	**68 (84.0%)**	**75 (90.4%)**	**63 (78.8%)**	**78 (88.6%)**	**72 (93.5%)**
Cure	59 (72.8%)	70 (84.3%)	61 (76.3%)	75 (85.2%)	67 (87.0%)
Improvement	9 (11.1%)	5 (6.0%)	2 (2.5%)	3 (3.4%)	5 (6.5%)
FDA 95.2% CI cures only with CCF	- 27.8, - 0.54	- 14.86, 9.51	- 24.12, 2.59	- 13.65, 10.08	
PP F/U	N = 57	N = 66	N = 53	N = 68	N = 61
Relapse Rate	23 (40.4%)	27 (40.9%)	19 (35.8%)	23 (33.8%)	22 (36.1%)

Modified Intent-to-Treat (MITT) subset (all randomized subjects who had a positive *Candida* culture at Baseline and took at least one dose of study drug

Protocol Evaluable Subjects (PE or PP): All treated subjects who met key inclusion criteria and received at least 7 consecutive days of study medication for the treatment of oral candidiasis. Patients must have a clinical assessment at Visit 3, or must have at least 3 days of treatment and discontinued prior to Visit 3 either as a treatment failure or an adverse event.

Relapse: Recurrence of signs or symptoms after initial improvement or cure at Visit 3 (and having taken ≥80% of doses)

CCF: Continuity Correction Factor

Mycological response was a secondary efficacy variable. Eradication of infection in the modified ITT group occurred in 40.2% of subjects in the 400 mg POSA group; 35.3% of subjects in the 200 mg group; 37.4% of subjects in the 100 mg group; 36.0% of subjects in the 50 mg group; and 50.6% of subjects in the fluconazole group. The results obtained in the FLU treated subjects were consistent with those obtained in study 331 but the results obtained in the POSA treated subjects at any dose were lower than those obtained for the FLU patients as well as compared to those obtained from the POSA arm of study 331.

The success rate for the 200 mg dose of POSA, which was the lowest of all treatment groups and was not non-inferior to fluconazole in any population, was considered

anomalous and review of several study parameters including demographics, CD4 count, and severity of OPC did not reveal an explanation for the lower efficacy in this group.

No dose response relationship was demonstrated in this study. This may have been due to use of the same high loading dose (400 mg) of POSA each group and to the long half-life of the drug.

The results of this study supported the use of the 100 mg dose of the POSA suspension the treatment of OPC in HIV-positive subjects.

In the Phase-3 study, C/I97-331, 350 subjects were treated with posaconazole or fluconazole oral suspension (100 mg BID for 1 day followed by 100 mg QD for 13 days).

The clinical response rate achieved with POSA was non-inferior to that achieved with FLU after 14 days of treatment in both the MITT (91.7% vs. 92.5%, respectively) and protocol evaluable subsets (97.2% vs. 96.3%, respectively). This success rate for POSA versus FLU was consistent with that achieved in the ITT (89% vs. 86.4%, respectively) and all-treated (91% vs. 92.4%, respectively) subsets for both treatments. NI was also shown when only cures were assessed as successes.

Table 3
Clinical Response at the EOT and Follow-up
MITT and PE per FDA criteria

MITT	N= 171	N = 160	
Success	156 (91.2%)	148 (92.5%)	- 7.76, 5.22
Failure All	15 (8.7%)	12 (7.5%)	
Cure	139 (81.3%)	132 (82.5%)	- 10.12, 7.69
Improved	17 (9.9%)	16 (10%)	
MITT F/U	N= 144	N = 136	-5.59, 18.17
Clinical Relapse	46 (32%)	52 (38.3%)	
MITT F/U	N = 95	N = 82	
Mycologic Relapse	61 (64.2%)	64 (78%)	
PE	N= 143	N = 135	
Success	139 (97.2%)	130 (96.3%)	- 3.99, 5.8
Failure All	4 (2.8%)	5 (3.7%)	
Cure	125 (87.4%)	116 (85.9%)	- 7.23, 10.2
Improved	14 (9.8%)	14 (10.4%)	
PE F/U	N= 129	N = 121	- 7.99, 17.36
Clinical Relapse	43 (33.3%)	46 (38%)	
PE F/U	N = 85	N = 75	
Relapse	55 (64.7%)	59 (76.6%)	

Modified Intent-to-Treat (MITT) subset (all randomized subjects who had a positive *Candida* culture at Baseline and took at least one dose of study drug

Protocol Evaluable Subjects (PE or PP): All treated subjects who met key inclusion criteria and received at least 7 consecutive days of study medication for the treatment of oral candidiasis. Patients must have a clinical assessment at Visit 3, or must have at least 3 days of treatment and discontinued prior to Visit 3 either as a treatment failure or an adverse event.

Relapse: Recurrence of signs or symptoms after initial improvement or cure at Visit 3 (and having taken ≥80% of doses)

CCF: Continuity Correction Factor

FDA criteria Mycologic response at the EOT = eradication or NO growth, Mycologic treatment failure = any growth at the EOT, Mycologic response at the EOS= < 20 CFU/mL at the EOS visit, Mycologic failure at the EOS = ≥ 20 CFU yeast/mL at the EOS visit

Clinical response rates 4 weeks after the cessation of treatment were similar between posaconazole- and fluconazole-treated subjects (68.5%, 98/143 versus 61.8%, 84/136, respectively).

Study 331 demonstrated that posaconazole is non-inferior to fluconazole in the treatment of HIV-infected subjects with azole susceptible OPC. In addition, posaconazole appeared to be associated with fewer mycological relapses following cessation of treatment. Clinical relapse rates were similar between the treatment arms. Study 209 provided supportive evidence for these conclusions.

Azole refractory OPC:

In support of the efficacy of posaconazole in azole-refractory OPC, the applicant submitted 2 open label non-comparative trials of posaconazole in the treatment of patients with refractory candidiasis in immunosuppressed HIV-infected subjects. There were 239 unique subjects enrolled in these trials. In the agency analyses, study P00298 was considered supportive of study C/I97-330 because 60% of the subjects were roll-overs from study C.97-330 and because subjects did not have a primary endpoint similar to that used for study C/I97-330.

The primary efficacy parameter was the clinical success rate (cure or improvement) after 4 weeks (C/I97-330) or 3 months (P00298) of treatment among subjects in the MITT subset. This visit occurred at the end of the acute treatment phase. All patients had this visit either on the last day of treatment (amended) or after 4 weeks of treatment (original) thus providing the ability to assess all subjects at one similar timepoint (snapshot).

Subjects in C/I97-330 were treated with posaconazole 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 (original protocol, 800 QD 3 x week) or posaconazole 400 mg BID for 28 days (amended protocol). The higher posaconazole doses were chosen in order to be consistent with the rest of the Applicant's clinical program for the treatment of refractory IFIs. The change in regimen was done for convenience purposes and in order to be consistent with the broader development program.

In the Applicant's analysis, among subjects in the MITT subset, there was a 75% (132/176) clinical success rate (cure or improved) and a 36.5% (46/126) mycological response rate after 4 weeks of posaconazole treatment.

Clinical success rates ranged from 71% to 100%, inclusive, for all azole-resistant *Candida* species identified at baseline. *Candida albicans* was the primary isolate followed by *Candida glabrata.*

Clinical success rates were similar for subjects in the original versus the amended protocols after 4 weeks of posaconazole treatment (MITT 75.3%, 67/89 and 74.7%, 65/87, respectively).

Clinical relapse rates in at Week 4 of Follow-up (defined as 23 through 37 days after the last dose of study drug) were 32.8%, 22/67 for those treated under the original protocol and 24.6%, 16/65 for those treated under the amended protocol suggesting more sustained efficacy with the 800-mg daily dosing regimen compared to the 400-mg daily dosing or maintenance 800-mg/day intermittent (three times weekly) dosing regimens. A relapse was defined as the presence of greater than 20 CFU/mL of the same *Candida* species at a post-treatment follow-up visit as was present at Baseline.

This study supported the use of posaconazole 400 mg BID for 28 days in HIV infected subjects with OPC refractory to fluconazole or itraconazole. Inadequate documentation was provided regarding mycologic eradication rates in this study.

In P00298, 100 HIV-infected subjects with OPC and/or EC were treated with posaconazole 400 mg BID for up to 15 months, including a 3-month acute treatment period followed by a 12-month maintenance period. Sixty of these subjects had previously participated in C/I97-330. Because of the large number of subjects that were re-enrolled in this study, the lack of a consistent TOC evaluation timepoint and the differences in the inclusion criteria, it was determined that this study would be considered supportive.

Among subjects in the MITT subset, an 85.6% (77/90) clinical success rate (cure or improved) was achieved after 3 months of posaconazole treatment. The majority of subjects were immediately enrolled in a12-month maintenance period or were retreated under the same protocol if they relapsed after treatment cessation.

Among the 239 unique subjects treated with posaconazole in the two azole-refractory OPC studies, 69%, (165/239) of subjects took posaconazole for up to 3 months, 14% (34/239) took posaconazole for 3 to <6 months, 9% (22/239) took posaconazole for 6 to <12 months, and 6% (15/239) took posaconazole for at least 12 months. The mean exposure to posaconazole based on the actual days dosed was 102 days (range of 1 to 544 days). The mean duration of treatment, inclusive of gaps or stops in treatment was 154 days. Sixty-seven percent (67%, 10/15) of subjects treated with posaconazole for at least 12 months had continued clinical success (cure or improvement) at the last assessment. The majority of *Candida* isolates tested remained susceptible to posaconazole.

For the agency analyses, a dataset of 239 unique subjects with refractory OPC supplied by the applicant, (199 subjects from study C/I97-330 and 40 from P0298) was used. In order for a subject to be included in the Agency population, they had to meet the following inclusion requirement per the original protocols:

- History of failure to improve or worsening of candidiasis after a standard course of therapy with FLZ ≥100 mg/day for at least 10 consecutive days, or ITZ 200

mg/day for at least 10 consecutive days for oral candidiasis or ≥3 weeks for esophageal candidiasis.

Comment: The sponsor did not specify that the course of previous azole treatment had to occur immediately before the initiation of POSA but this is a regulatory requirement that has been applied to other antifungal applications in order to differentiate true refractory diease from relapse or recurrence.

87 subjects were excluded from the refractory population because they either did not receive any previous AF treatment and/or they did not receive either ITR or FLU and/or the duration of previous azole treatment did not meet the protocol specified duration of 10 days or was unknown (N = 11, C1/003: 9 days, C2:005 unknown, C2/009: 3 days, C30/003: 8 days, C200018: 4days, I2/002 and I2/0004 unknown, I12/007: 7 days, I19/003: 4 days, I19/004: 8 days, I19/006: 9 days). 7 subjects were excluded because the prior azole treatment was discontinued > 14 days before initiation of POSA treatment, raising concerns of recurrence as opposed to refractory disease.

19 subjects were excluded because documentation of the dose used during the previous treatment course was not provided (19 from study 0298).

In total, 143 subjects were excluded. For the Agency analyses 96 treated subjects were qualified to be included in the rOPC category. All of these subjects were from study C/I97-330, 89 were included in the MITT population and 81 in the evaluable.

Comment: In study P0298 the previous fluconazole or itraconazole course could have been many months earlier, thus no subjects from this trial were included in the Agency dataset.

Clinical and Mycologic efficacy by patient were assessed at the end of the acute treatment phase; all patients had this visit either on the last day of treatment or the end of the acute treatment or on the day before start of maintenance). This timepoint provided a snapshot of efficacy for all subjects and this assessment was the protocol defined primary endpoint.

Patients were assessed at other timepoints including at a follow-up visit (range 23 – 37 days) 4 weeks after the last dose unless lost to follow-up, and at the EOT visit defined as the last clinical response on or before the stop of treatment +7 days thus occurring at different timepoints depending upon when the last dose of therapy occurred for a given subject. The value of the EOT asessement was in that it was performed 7 days off of treatment and provided an initial assessment of relapse.

Ex for F/U visit: For an Original protocol subject receiving 30 days of acute treatment followed by 60 days of maintenance therapy, this visit could occur 113-127 days from study drug initiation. For an Amended protocol subject receiving 28 days of acute treatment, this visit could occur 51-65 days from study drug initiation.

Mycologic efficacy by patient was assessed only at the week 4 visit and not all subjects received such an assessment. In this analysis if a subject did not have an EOT culture, they were presumed to have a persistent pathogen.

Only the primary endpoint and the EOT visit are reported because: 65% of subjects did not have a follow-up visit at 23- 37 days post-treatment thus leaving little value to this assessment.

Table 4
Clinical and Mycologic Response by Patient
Refractory OPC
Agency Population

	MITT N= 89		EE N = 81	
Clinical Response	**Week 4 Last day of treatment N (%)**	**EOT 7 days after the last day of treatment N (%)**	**Week 4 Last day of treatment N (%)**	**EOT 7 days after the last day of treatment N (%)**
Cure	50 (56.1)	51 (57.3)	50 (61.7)	47 (58)
Improved	16 (17.9)	19 (21.3)	16 (19.7)	16 (19.7)
Failed	22 (24.7)	7 (7.8)	15 (18.5)	7 (8.6)
Unknown or No f/u	1 (1.1)	1 (1.1)	NA	NA
Relapse	NA	11 (12.3)	NA	11 (13.5)
Mycologic response				
Responder	28 (31.4)		28 (34.5)	
Non-responder	31(34.8)		31 (38.2)	
No culture	7 (7.8)		7 (8.6)	
?	23 (25.8)		15 (18.5)	

Relapse was defined as the presence of > 20 CFU/mL of the same *Candida* species at a post-treatment follow-up visit as was present at Baseline
Responder=Mycological success, ≤20 CFU/mL for all *Candida* species present at Baseline
Non-Responder=Mycological failure, >20 CFU/mL *Candida* species
Not Assessed=Subject was not cultured.

When the Agency Clinical Response Rate was compared to the Applicant's, higher combined responses were obtained in the Agency population (Agency 80.8% cured and improved as compared to 75.3% Applicant for the MITT). In the Applicant's analysis, 51.2% (102/199) subjects were considered cured as compared to 56.1% (50/89) in the agency analysis. Relapse rates were also similar in both analyses and increased over time as subjects discontinued treatment.

As noted in the Applicant's analysis, mycologic cultures were not required in subjects who were clinical responders or for those continuing onto maintenance If only those subjects who had a mycologic assessment are included, mycologic response rate at week 4 was 31.4% in the MITT and 34.5% in the EE population and was lower than that attained in the Applicant's analysis (36.5%). As noted previously the value of this analysis is questionable as cultures were obtained in few patients

There were 52/89 (58.4%) refractory MITT patients with baseline isolates considered resistant because of high MIC values and thus considered more difficult to treat (49/81

(60.5%) evaluable). Of the 52 MITT subjects 15 had a baseline isolate considered resistant to fluconazole, 35 to both fluconazole and itraconazole and 2 resistant to itraconazole alone. There were 50 subjects with baseline FLU resistance and 37 with baseline ITR resistance.

These 52 MITT subjects had 69 isolates at baseline including 46 *Candida albicans* (30 alone, 14 with *Candida glabrata*, 2 with *Candida krusei),* 17 *Candida glabrata* (2 alone, 14 with *Candida albicans* and 1 with *Candida tropicalis*), 4 *Candida krusei* (2 alone and 2 with *Candida albicans*) and 2 *Candida tropicalis* (1 alone and 1 with *Candida glabrata*). In total there were 46 isolates of *Candida albicans*, 17 *Candida glabrata*, 3 *Candida krusei,* and 2 *Candida tropicalis*.

For the EE population 49 subjects had 62 isolates including 43 *Candida albicans,* 15 *Candida glabrata,* 2 *Candida krusei,* and 2 *Candida tropicalis.*

Of the MITT subjects with *Candida albicans* at baseline, 39 had an MIC of 64 mcg/mL, (considered to represent isolates that are more difficult to treat). 23 of these subjects were cured (50%), 9 improved (19.5%), 6 (13%) failed and 1 did not have an outcome assessment.

There were 3 subjects with *Candida albicans* and a baseline MIC of 32 mcg/mL (1 cure, 1 improved and 1 failure) and 4 subjects with baseline MICs of 8 mcg/mL (2 failures and 2 improved).

In conclusion POSA demonstrated acceptable efficacy in a subpopulation of highly immunosuppressed HIV-infected subjects with refractory OPC. Large numbers of these subjects had *Candida albicans* isolates at baseline that had high fluconazole and/or itraconazole MICs. Comparable clinical efficacy was also demonstrated in these subjects, however not all subjects had mycologic evaluations off treatment and a much smaller percentage had documented eradication.

The results of the two studies supported the efficacy of posaconazole is in the treatment of HIV-infected subjects with azole-refractory OPC.

B. Detailed Review of Trials

Study C/I96-209

Title: A Multicenter, Randomized, Double-Blind, Phase 2 Study to Evaluate the Safety, Tolerance and Efficacy of Multiple Doses of Posaconazole versus Fluconazole in the Treatment of Oropharyngeal Candidiasis (OPC) in HIV Positive Patients (Protocol Nos. C/I96-209)

53 sites in USA, Canada, Mexico, Austria, Belgium, France, Germany, Argentina, Chile, Guatemala, Panama, Dominican Republic, Venezuela, South Africa, Australia, Israel, and Thailand.

Randomized (5-arm), active-control, parallel-group, multicenter, double blind study conducted to evaluate the safety and efficacy of four different dose levels of POSA as compared to fluconazole in the treatment of azole-susceptible OPC in HIV-positive subjects. Subjects were treated with POSA capsules 400 mg BID for 1 day, followed by 50 mg, 100 mg, 200 mg, or 400 mg QD for 13 days, or with fluconazole 200 mg QD for 1 day followed by 100 mg QD for 13 days. The primary objective of this study was to demonstrate the clinical efficacy of the highest dose of posaconazole. Secondary objectives included safety, dose selection, mycological efficacy, and population pharmacokinetics.

Comment: *This study utilized the capsule formulation as opposed to the oral suspension used in study 331. Issues associated with the use of the capsule include its lesser bioavailability as well the loss of a direct antifungal effect on OPC lesions as compared to the suspension. This trial was considered supportive of 331 and primarily served to verify the reproducibility of the results of that trial.*

The primary efficacy analysis was the clinical success rate, defined as the number of subjects with a cure (absence of pseudomembranous plaques and no, or minimal, symptoms) or improvement (partial resolution of pretreatment signs and symptoms) after 14 days of treatment in the MITT subset.

The MITT subset consisted of all randomized subjects with a positive *Candida* culture at Visit 1 (Baseline) who had taken at least one dose of study drug. The Per protocol population (PP or PE) was a subpopulation of the MITT population and included those who satisfied all inclusion/exclusion criteria, and:

- Had a minimum of 10 and no more than 14 consecutive days of treatment with the assigned study drug, unless early treatment failure occurs. In the event of a treatment failure, a minimum of 3 consecutive days of treatment was required for a subject to be in the per-protocol population.

- Had no systemic or oral topical antifungal treatment during the study, including the period between the post-treatment and follow-up visits, except for treatment of a failure or relapse.

- Had a clinical assessment at the end of treatment, or earlier if the subject discontinues).

- The assessment visit must have been performed between 0 and 3 days after the end of treatment.

The Agency efficacy conclusions were mainly based on the data from the MITT subjects.

Five hundred one subjects were enrolled and 485 subjects were randomized. Sixteen of the 501 enrolled subjects were not randomized because they did not meet protocol

eligibility. These included 9 subjects who did not meet the inclusion criteria, and 7 subjects who met the exclusion criteria.

A total of 469 subjects were treated with study medication and included in the all-treated subjects' subset; 437 subjects were included in the MITT subset; and 409 subjects were included in the PP subjects' subset.

There were 48 protocol deviations among the 485 randomized subjects. Twelve (25%) of these subjects were not confirmed as receiving study medication and 36 (75%) did not meet the entrance criteria. Four of the latter 36 subjects also did not receive study medication.

Twenty-four of the 36 subjects (66.6%) who did not meet the entrance criteria did not have a positive mycology result at Visit 1. All 48 subjects who were protocol deviations were not included in the modified ITT subset of subjects. Therefore, the total number of subjects in the modified ITT subset was 437.

Nineteen subjects had variations from the protocol that the Sponsor's medical staff felt was clinically minor and would not affect the interpretation of the results of the study. The project physician approved the continuation of these subjects in the study.

These variations from the protocol included a change in concomitant medications (10 subjects), abnormal laboratory results (8 subjects), and an insufficient wash-out time for concomitant medications (1 subject).

One subject inadvertently entered the study twice at two different sites. Subject I96-209-42/008, — , born — , entered the study on May 14, 1998 and received 13 days treatment with 400 mg SCH 56592 (5/14/98 to 5/26/98) before being discontinued from the study due to elevated transaminases (transient hepatitis) on 5/28/98. Liver function tests were >3 X ULN. This subject completed the TOC where he was considered a cure; there was no follow-up visit. Subsequently, subject I96-209-41/020, — ,orn ' — entered this study on November 11, 1998 and received 14 days of treatment with 100 mg SCH 56592 (11/11/98 to 11/24/98). This subject completed all 4 visits (including follow-up) and was considered a cure. The study monitor discovered and confirmed with the investigators that subject — is the same person and had entered the study twice, at two different sites. The Sponsor's project physician allowed both treatment cycles into the database.

Comment: *The MO reviewed the reason for exemption of all the above patients and agreed with the subjects' inclusion into the study. The inclusion of one posaconazole subjects twice on different treatment arms should have been determined not acceptable, however the exclusion of this patient will not alter the results for this supportive trial.*

Table 5
Study Populations C/I97-209

ITT Subjects	POSA				
	50 mg	**100 mg**	**200 mg**	**400 mg**	**FLU**

	98	102	91	100	94
All Treated Subjects	92	98	91	98	90
Modified ITT Subjects	86	91	85	92	83
Per-protocol Subjects	81	83	80	88	77

Comment: *A large number of subjects, approximately 25 – 33% across the treatment arms discontinued treatment early. The most frequent reasons for discontinuation were treatment failure and adverse events. The frequency of these events was comparable across the treatment arms. A large number of patients were also lost to follow-up including 10% of subjects on the fluconazole treatment arm. The CRFs for these subjects were reviewed and additional analyses were performed on the all treated population where all of these subjects were assessed as failures. These changes did not alter the results of the study.*

Table 6
Disposition of Patients
C/I97-209

	Posaconazole				**Fluconazole**
	50 mg (n=92)	**100 mg (n=98)**	**200 mg (n=91)**	**400 mg (n=98)**	**100 mg (n=90)**
Completed Treatment	62 (67%)	69 (70%)	58 (64%)	74 (76%)	66 (73%)
Discontinued Treatment (a)	30 (33%)	29 (30%)	33 (36%)	24 (24%)	24 (27%)
adverse events b, c	10 (11%)	6 (6%)	6 (7%)	6 (6%)	4 (4%)
death	2 (2%)	1 (1%)	3 (3%)	1 (1%)	1 (1%)
treatment failure	9 (10%)	9 (9%)	8 (9%)	9 (9%)	5 (6%)
lost to follow-up	4 (4%)	7 (7%)	5 (5%)	5 (5%)	9 (10%)
noncompliance with protocol	4 (4%)	2 (2%)	5 (5%)	1 (1%)	3 (3%)
did not meet protocol eligibility	1 (1%)	4 (4%)	4 (4%)	2 (2%)	2 (2%)
administrative	0	0	2 (2%)	0	0
Entered Follow-Up	64 (70%)	71 (72%)	57 (63%)	74 (76%)	68 (76%)
Completed Follow-Up	60 (94%)	70 (99%)	56 (98%)	74 (100%)	67 (99%)
Discontinued Follow-Up	4 (6%)	1 (1%)	1 (2%)	0	1 (1%)
adverse event	1 (2%)	0	0	0	0
treatment failure	3 (5%)	1 (1%)	1 (2%)	0	1 (1%)

a: Percentages of subjects discontinuing for each individual reason was based on the total number of subjects discontinuing.
b: Follow-up clinical response not available or subject clinically relapsed.
c: 32 subjects (total) discontinued treatment due to an AE, as captured on the final status CRF page. This total differs from the 28 subjects listed in **Section 16.2.2.** as discontinued due to an AE, as captured on the AE CRF page

There were 48 protocol deviations among the 485 randomized subjects. Twelve of these subjects did not receive study medication and 36 did not meet the inclusion/exclusion criteria. Four of the latter 36 subjects also did not receive study medication. Sixteen with protocol deviations did not receive study medication; 469 subjects were treated with study medication.

Twenty-four of the 36 subjects who did not meet the inclusion criteria did not have a positive mycology result at Visit 1. All 48 subjects who were protocol deviations were not included in the MITT subset of subjects. Therefore, the total number of subjects in the MITT subset was 437.

Demographics:

The 5 treatment groups were comparable with respect to age, sex, race, and weight. Baseline CD4 counts were also similar across the treatment arms. The mean # of previous episodes of OPC during the previous year was approximately 2 in all treatment groups.

Table 7
Demographics C/I97-209

All Treated	**Posaconazole**				**Fluconazole**
	50 mg (n=92)	**100 mg (n=98)**	**200 mg (n=91)**	**400 mg (n=98)**	**100 mg (n=90)**
Age (y)					
mean ±sd	38.0±9.1	38.0±9.1	37.0±8.7	37.2±8.4	37.8±8.7
median	37.0	38.5	36.0	36.5	37.5
min-max	20-65	18-62	21-58	21-63	19-61
Sex [no.(%) subjects]					
female	18 (19.5%)	17(17.3%)	16(17.5%)	11(11.2%)	21(23.3%)
male	74 (80.4%)	81(82.6%)	75(82.4%)	87(88.7%)	69(76.6%)
Race (no.(%) subjects)					
Asian	4 (4.3%)	4(4%)	4(4.3%)	5(5.1%)	3(3.3%)
Black	32 (34.7%)	22(22.4%)	23(25.2%)	30(30.6%)	23(25.5%)
Caucasian	35 (38.0%)	50(51.0%)	42(46.1%)	45(45.9%)	41(45.5%)
Hispanic	19 (20.6%)	20(20.4%)	22(24.1%)	16(16.3%)	19(21.1%)
other	2 (2.1%)	2(2.0%)	0(0%)	2(2%)	4(4.4%)
Weight (kg)					
mean ±sd	64.5±14.7	66.7±15.1	63.6±13.7	64.9±12.8	62.7±14.9
median	64.0	65.0	61.0	65.0	60.0
# of episodes of OPC in previous year					
n	n = 92	n = 98	n = 90	n = 98	n = 88
mean ±sd	2.1±3.1	2.1±2.3	2.1±2.5	2.5±3.2	1.9±2.0
median	1	1	1	2	1
min-max	0-24	0-12	0-12	0-24	0-12
CD4 count (cells/mm 3)					
n	n = 92	n = 98	n = 91	n = 97	n = 89
mean ±sd	140±181	130±156	153±194	159±200	122±169
median	55	68	82	82	54
min-max	2-794	1-690	5-998	0-1110	0-1050
Fungal Microscopic Exam					

KOH	88	93	89	89	85
Gram Stain	3	5	2	7	4
Biancofluor	1	0	0	1	0
Missing	0	0	0	1	1

Comment: *The patients in this study were demographically similar to the patients in study 331. Subjects were predominantly middle-aged males with a broad race distribution. The degree of immunosuppression varied but generally subjects had CD4 counts < 200. Demographics were similar in the MITT and PP population.*
NOTE: For further study details, see Appendix A.

Efficacy Analyses:

Clinical Response at the TOC (Day 15) and at Follow-Up (Day 42):

As per the applicant, "Across all posaconazole treatment groups, clinical success was achieved in 77-90% of the subjects, and in the fluconazole treatment group, clinical success was achieved in 89-94% of the subjects. The 400 mg and 100 mg doses of posaconazole were non-inferior to the comparator in both the MITT and per-protocol subjects.

The 50 mg dose of POSA was also equivalent to fluconazole by the same criteria in the MITT subjects only."

The clinical success rate for the 200 mg dose of POSA which was the lowest of all treatment groups and was not clinically equivalent to fluconazole in any data set, was considered anomalous by the applicant.

Comment: *Notable in the analysis of clinical success was the lack of a dose response across the posaconazole treatment groups. Additionally the results of the 200 mg group appeared aberrant. An explanation of these results was not found despite additional analyses by CD4, number of previous episodes of OPC, pathogen etc. Clinical success rates were comparable between the 100 mg and 400 mg dose groups and the comparator fluconazole. Because of these issues, it was determined that statistical conclusions could not be drawn from this Phase II supportive study although 95.2% CIS are provided. Clinical success rates were comparable between the posaconazole 100 mg and posaconazole 400 mg treatment arms and the fluconazole comparator arm for both the MITT and PP populations although the fluconazole rates were numerically superior.*

Table 8
Clinical Success Rates at the EOT
MITT/PP Populations C/I97-209

		POSA			
	50 mg	**100 mg**	**200 mg**	**400 mg**	**FLZ**
MITT	N = 86	N = 91	N = 85	N = 92	N = 83
Success Rate (a)	**73 (84.9%)**	**79 (86.8%)**	**65 (76.5%)**	**80 (87.0%)**	**74 (89.2%)**
Cure	64 (74.4%)	73 (80.2%)	63 (74.1%)	76 (82.6%)	69 (83.1%)
Improvement	9 (10.5%)	6 (6.6%)	2 (2.4%)	4 (4.3%)	5 (6.0%)

FDA 95.2% CI cures only with CCF	- 21.25, 4.82	-15.65, 9.85	- 22.63, 4.60	- 12.94, 11.90	
PP	N = 81	N = 83	N = 80	N = 88	N = 77
Success Rate (a)	**68 (84.0%)**	**75 (90.4%)**	**63 (78.8%)**	**78 (88.6%)**	**72 (93.5%)**
Cure	59 (72.8%)	70 (84.3%)	61 (76.3%)	75 (85.2%)	67 (87.0%)
Improvement	9 (11.1%)	5 (6.0%)	2 (2.5%)	3 (3.4%)	5 (6.5%)
FDA 95.2% CI cures only with CCF	- 27.8, - 0.54	- 14.86, 9.51	- 24.12, 2.59	- 13.65, 10.08	

Clinical Response at follow-up revealed relapse rates that decreased as the dose increased from the 50 up to the 400 mg dose groups. Of note was the 36% relapse rate for the FLU treated subjects as compared to the 41% relapse rate for the 100 mg posaconazole treated subjects (requested dose).

Table 9
Relapse Rates at Follow-up
MITT/PP Populations C/I97-209

		POSA			
	50 mg	**100 mg**	**200 mg**	**400 mg**	**FLZ**
MITT	N = 59	N = 68	N = 54	N = 70	N = 62
Relapse Rate	24 (40.7%)	27 (39.7%)	19 (35.2%)	25(35.7%)	23 (37.1%)
PP	N = 57	N = 66	N = 53	N = 68	N = 61
Relapse Rate	23 (40.4%)	**27 (40.9%)**	19 (35.8%)	23 (33.8%)	22 (36.1%)

Analyses of Mycologic Response:

As per the applicant, "Analysis of mycological response for the MITT subset of subjects did not demonstrate equivalence between any POSA dose and fluconazole. No statistically significant difference between fluconazole and the 50 mg, 100 mg, and 400 mg doses of POSA was demonstrated at the ≥ 0.05 level of significance. However, the fluconazole group had a significantly better response compared to the 200 mg POSA group."

The mycologic eradication rate for the FLU treated subjects was consistent with that attained on the fluconazole treatment arm in study 331 and ranged from 50 – 53%. The posaconazole treatment arm eradication rates were much lower than those attained in study 331 and ranged from 37.4 - 41% for the MITT and PP populations at the 100 mg dose and 40.- 42% for the 400 mg dose group. . This difference was not explainable as the pathogen most commonly isolated was Candida albicans (see by Pathogen analysis).

Table 10
Mycologic Eradication Rates by Patient at the EOT
MITT/PP Populations C/I97-209

		SCH 56592			
	50 mg	100 mg	200 mg	400 mg	FLZ
MITT	N = 86	N = 91	N = 85	N = 92	N = 83
Eradication	31 (36.0%)	34 (37.4%)	30 (35.3%)	37 (40.2%)	42 (50.6%)
95.2% CI (applicant)	- 30.6, 1.55	-29.04, 4,47	- 32.54, 1.05	-26.36, 5.59	

PP	N = 81	N = 83	N = 80	N = 88	N = 77
Eradication	31 (28.3%)	34 (41%)	30 (37.5%)	37 (42%)	41 (53.2%)
95.2% CI (applicant)	-31.75, 1.8	-9.04, 4.47	-32.54, 1.05	-27.7, 5.34	

Mycologic Response by Pathogen at TOC (MITT):

When mycologic response was assessed by pathogen at the TOC/EOT visit the Candida albicans eradication rate for fluconazole was numerically superior to the rates achieved with all posaconazole doses and echoed the mycologic response by patient rate indicative of the fact that most patients had only one type of pathogen isolated.

Table 11
Mycologic Eradication Rates by Pathogen at the EOT
MITTC/I97-209

Mycological Response	**POSA 50 mg**	**POSA 100 mg**	**POSA 200 mg**	**POSA 400 mg**	**FLZ 100 mg**
		Candida. albicans			
# Isolated	N = 81	**N = 87**	N = 81	N = 87	**N = 74**
# Eradicated	30 (37.0%)	**33 (37.9%)**	31 (38.3%)	41 (47.1%)	**43 (58.1%)**
		Candida glabrata			
# Isolated	N = 3	N = 4	N = 3	N = 9	N = 6
# Eradicated	0	2 (50%)	0	2 (22%)	0
		Other Candida Species			
# Isolated	N = 4	N = 5	N = 1	N = 7	N = 4
# Eradicated	3 (75%)	3 (60%)	0	3 (42.9%)	3 (75%)
		Non-Candida Species			
# Isolated	N = 0	N = 4	N = 1	N = 0	N = 4
# Eradicated	0	2 (50%)	0	0	3 (75%)

Therapeutic Response:

At the Reviewer's request, the Applicant submitted additional analyses of mycologic response by patient based on FDA criteria where eradication was = to 0 CFU/ML.

Table 12
Therapeutic response
All Treated Population CI97-209 per Protocol and per FDA

Criteria for Therapeutic Success	**POSA 50mg n/N (%)**	**POSA 100mg n/N (%)**	**POSA 200mg n/N (%)**	**POSA 400mg n/N (%)**	**FLU 100mg n/N (%)**
Protocol Defined Cure					
<=20CFU/ mL	25/92 (27)	28/98 (29)	25/91 (27)	32/98 (33)	31/90 (34)
95.2 % CI for the difference (pos-flu):	(-20.77, 6.23)	(-19.27, 7.56)	(-20.53, 6.58)	(-15.42, 11.84)	
FDA Defined Cure					
0 CFU/ml	19/92 (21)	24/98 (24)	23/91 (25)	27/98 (28)	23/90 (26)

95.2 % CI for the difference (pos-flu):	(-17.24, 7.44)	(-13.57, 11.44)	(-13.08, 12.52)	(-10.74, 14.73)

Conclusions:

No statistical conclusions could be drawn from this Phase II study.

A successful clinical response (cured and improved) , the primary efficacy variable, was achieved by 87% of subjects in the 400 mg POSA group; 76.5% in the 200 mg group; 86.8% in the 100 mg group(requested dose); 84.9% in the 50 mg group; and 89.2% in the fluconazole group for the MITT subjects.

Mycological response was the secondary efficacy variable. Eradication of infection in the MITT group occurred in 40.2% of subjects in the 400 mg POSA group; 35.3% of subjects in the 200 mg group; 37.4% of subjects in the 100 mg group; 36% of subjects in the 50 mg group; and 50.6% of subjects in the fluconazole group. The results obtained in the FLU treated subjects were consistent with those obtained in study 331 but the results obtained in the POSA treated subjects at any dose were much lower than those obtained for the FLU patients as well as compared to those obtained from the POSA arm of study 331.

The success rate for the 200 mg dose of POSA, the lowest of all treatment groups and not clinically equivalent to fluconazole in any data set, was considered anomalous. Despite a careful review of several study parameters including demographics, CD4 count, and severity of OPC, no explanation was found for the lower efficacy in this group.

No dose response relationship was demonstrated in this study. As per the applicant, this may have been due to use of the same high loading dose (400 mg) of POSA in each group and to the long half-life of the drug.

This study used the capsule formulation of POSA. The bioavailability of the oral suspension formulation is approximately 10% greater than the capsule form. A dose of 100 mg of the oral suspension POSA would therefore represent an exposure between the 100 mg and 200 mg dose. The difference in the formulations provides a plausible explanation for the differences in efficacy as compared to study 331.

The results of this study supported the use of the 100 mg dose of POSA for the treatment of OPC in HIV-positive subjects but could not be used to support labeling

Study C/I97-331

Title: Randomized, Controlled Trial of Posaconazole Oral Suspension versus Fluconazole Suspension in the Treatment of Oropharyngeal Candidiasis (OPC) in HIV-Positive Patients

Summary: Randomized, evaluator-blinded, multicenter study designed to compare the efficacy, safety, and tolerance of posaconazole versus fluconazole in the treatment of HIV-positive subjects with OPC. Subjects were randomized to receive an oral suspension of posaconazole or fluconazole 100 mg BID on Day 1 followed by 100 mg QD for 13 days. There were 36 study sites in Latin and Central America, the USA, Canada and Europe.

Comment: The oral suspension was used in this study as opposed to the capsule that was used in the Phase II dose response study.

There were two phases to the study, the Treatment Phase and the Follow-up Phase. The Treatment Phase was from days 1 – 14. Subjects were followed for 1 month after the Treatment Phase. If subjects discontinued the study early, the reason for and date of discontinuation were obtained, and all procedures and evaluations scheduled for the EOT visit (V3) were completed at the time of study discontinuation. Data on compliance, AEs, concomitant medication, clinical exam, and laboratory and mycologic findings were also obtained from these subjects at the time of study discontinuation.

All subjects underwent periodic assessments for the presence of OPC. These evaluations included a vital signs assessment (blood pressure and pulse), concomitant medication(s), urinalysis, CBC, blood chemistry, and mycologic culture. Other evaluations performed during the study included a complete physical exam at Visit 1, determination of plasma POSA concentrations from blood samples collected at Visit 3, and a review of AEs that occurred at any time during this study.

A successful clinical response was defined as clinical cure or improvement at Visit 3.

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, modified from an ACTG Protocol:

- 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. (Applied 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(s) present, which led to interference with eating many foods
- 3: Severe = Symptom(s) were very marked. 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 of candidiasis
- 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 (and having taken ≥80% of doses)
- Not Assessed: Clinical assessment was not performed

***Comment**: In the Agency sensitivity analyses any subject who was classified as improved was reassessed by the MO and reclassified as a cure or a failure. The need for additional therapy within the study period was the determining factor.*

Mycological response was a secondary efficacy endpoint and was determined based on quantitative mycological culture results. The major endpoint for determining mycologic efficacy was the end of treatment (Visit 3). Quantitative culture was performed in all subjects who relapsed at anytime and for treatment failures.

Mycological response was initially evaluated 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 Visit 3 and >20 CFU/mL at Visit 4
- Superinfection: A *Candida* species present at Visit 3 (end of treatment), but not at baseline
- New Infection: A *Candida* species present for the first time at Visit 4
- Indeterminant: Extenuating circumstances preclude classification

***Comment**: It was requested that the sponsor re-define eradication at Visit 3 as the complete absence of yeast on culture. These analyses were provided by the applicant although the reassessment led to the exclusion of only 2 subjects from the MITT analysis.*

The Division also requested that "therapeutic response" be utilized as the primary endpoint. A successful therapeutic response was that where the subjects were both clinical cures and had mycologic eradication. Any other combination would constitute a therapeutic failure. The Applicant did not originally provide these analyses however they were requested from the Applicant at the time of NDA submission.

The primary efficacy endpoint was the clinical success rate, defined as the number of subjects with a cure (absence of plaques or ulcers and no or minimal, symptoms) or improvement (partial resolution of pre-treatment signs and symptoms of candidiasis) after 14 days of treatment in the MITT population.

The MITT subset consisted of all randomized subjects who had a positive *Candida* culture at Baseline and took at least one dose of study drug. Secondary endpoints included a comparison of clinical success rates after 7 days of treatment with POSA versus that achieved after 14 days of fluconazole, clinical and mycological relapse rates 4 weeks after the last dose of study drug, and mycological response rates by visit.

Other datasets analyzed were:

- **Randomized, Not Treated Subjects (ITT):** All randomized subjects who either received or did not receive treatment. These subjects were included in the Intent-To-Treat (ITT) population.

- **All Treated Subjects:** All randomized subjects who received at least one dose of study medication. All summaries of safety data were based on this subset of subjects.

- **Protocol Evaluable Subjects (PE or PP):** All treated subjects who met key inclusion criteria and received at least 7 consecutive days of study medication for the treatment of oral candidiasis. Patients must have a clinical assessment at Visit 3, or must have at least 3 days of treatment and discontinued prior to Visit 3 either as a treatment failure or an adverse event.

A total of 366 subjects were randomized in the study; 182 subjects were randomized to receive posaconazole and 184 to receive fluconazole. 350 subjects received at least one dose of posaconazole or fluconazole. The majority of subjects in both treatment groups received treatment for 11 to 14 days. There were 329 subjects in the original MITT subset: 169 subjects treated with posaconazole and 160 subjects treated with fluconazole (MITT Adjusted per FDA definitions 171, 160).

Thirty six (36) posaconazole randomized subjects (19.7%) and 44 of 184 fluconazole randomized subjects (23.9%) did not complete the study. Four of these subjects on the POSA arm and 12 on the fluconazole arm did not receive treatment because they either did not have a positive baseline mycologic assessment (2 POSA and 4 FLU) or because they did not follow-up subsequent to randomization (2 POSA, 8 FLU). In total 13 subjects on the posaconazole arm and 24 on the fluconazole arm were excluded from the MITT populations.

Table 13
Study Populations
Study C/I97-331

Subset of Subjects	Posaconazole 100 mg	Fluconazole 100 mg
All Randomized IITT)	182	184
Randomized but not treated	4	12
All treated	178	172
All Treated but not meeting protocol requirements	9	12
Modified intent-to-treat	169	160

MITT but did not meet PE criteria	26	25
Protocol evaluable	143	135

Intent-to-treat (ITT) subset=all randomized population
All treated subset=subjects who were randomized and received at least one dose of study drug
Modified Intent-to-treat (MITT) subset=subjects who were randomized, received at least one dose of study drug, and had a positive culture for *Candida* at Baseline
Protocol evaluable subset=population that met key study inclusion criteria and received at least 7 consecutive days of study medication for oral candidiasis.

Comment: The 9 POSA and 12 FLU subjects that did not meet protocol requirement were reviewed. All of these subjects had negative baseline cultures.

Comment: *Reviewed listing E-4-2 (page 747 of 331A) and there is concordance in numbers. Also provided were revised analyses per Agency request regarding the definition of mycologic eradication. In the Agency population, eradication was defined as the complete absence of yeast cells in the V3 TOC cultures.* ***The reassessment of the data led to minimal changes in the datasets. Specifically only*** *2 additional subjects were included in the MITT population on the posaconazole arm and none on the fluconazole arm MITT 171 POSA, 160 FLU). The other populations did not change.*

Table 14
Number of subjects in various populations subsets for each study Arm by SPRI or FDA criteria

Population subsets	Protocol specified criteria		FDA-criteria	
	POS	FLU	POS	FLU
All-treated	178	172	178	172
MITT	169	160	171	160
Protocol evaluable	143	135	143	135

Twenty one posaconazole treated subjects (12%) and 19 fluconazole-treated subjects (11%) discontinued treatment.

Comment: *The most common reasons for discontinuation included the occurrence of AEs (4% POSA versus 3% FLU), non-compliance, treatment failure, and loss to follow-up. There were 12 POSA subjects who discontinued for these reasons (6.7%) as compared to 10 of 172 fluconazole treated subjects (5.8%). The primary difference between the treatment arms seemed to be "noncompliance" with more posaconazole-treated subjects non-compliant to treatment. Additional analyses where these subjects were assessed as failures did not alter the outcome. Similar numbers of subjects continued the study through follow-up.*

Table 15
Disposition of Patients
Study C/I97-331

Status	Posaconazole (n=178)	Fluconazole (n=172)

Number (%) of Subjects Who Completed Treatment	**157 (88)**	**153 (89)**
(%) of Subjects Who Discontinued Treatment	**21 (12)**	**19 (11)**
Adverse event	7 (4)	6 (3)
Treatment failure	3 (2)	3 (2)
Lost to follow-up	3 (2)	4 (2)
Subject decided not to continue treatment	1 (<1)	0
Noncompliance	5 (3)	3 (2)
Did not meet protocol eligibility	2 (1)	3 (2)
Completed Follow-Up	**150 (84)**	**141 (82)**
Discontinued Follow-Up	**28 (16)**	**31 (18)**
Did not enter follow-up	16 (9)	14 (8)
Adverse event	3 (2)	4 (2)
Relapse/recurrence	2 (1)	5 (3)
Lost to follow-up	3 (2)	6 (3)
Noncompliance with protocol	3 (2)	1 (<1)
Failed to meet study entry criteria	1 (<1)	1 (<1)

EFFICACY

Demographic and Other Baseline Characteristics

***Comment**: The POSA and FLU treatment arms were comparable for demographic and other baseline characteristics, including age, sex, and race, and fungal microscopic exam findings. The subjects were primarily younger men and with a broad racial distribution.*

Table 16
Demographics MITT C/I97-331

Demographic Characteristic	Posaconazole 100 mg (n=178)	Fluconazole 100 mg (n=172)
Age (yr)		
Mean ±sd	36.4.±7.8	37.6±9.1
Median	35.0	36.0
Minimum-maximum	20-61	19-78
Sex, number.(%) subjects		
Female	47 (26)	41 (24)
Male	131 (74)	131 (76)
Race, number.(%) subjects		
Asian	17 (10)	16 (9)
Black	42 (24)	33 (19)
Caucasian	66 (37)	67 (39)
Hispanic	51 (29)	51 (30)
Other	2 (1)	5 (3)
CD4 count		
n	178	170
Mean ±sd	137±170.5	132±160.7
Median	81	78.5
Minimum-maximum	0-935	0-867
Fungal Microscopic Exam:		

KOH	103 (58)	98 (57)
Gram Stain	2 (1)	1 (<1)
Fungal Stain	72 (40)	73 (42)
Missing	1 (<1)	0 (0)

a: Other=Mixed, Middle Eastern, Puerto Rican, and Native American Indian.

***Comment**: CD4 counts were similar for the subpopulations of the all treated population (MITT and PE). CD4 counts in the fluconazole treated subjects were somewhat lower in both populations (MITT POSA mean CD4 82 versus 71 FLU and PE POSA 80 versus 65 FLU). It is unlikely that these small differences would have had any effect on outcome. CD4 counts in this study were much higher than those seen in the refractory OPC population and indicate that this population was immunocompetent enough to be cured.*

Duration of Treatment:

Sixty seven percent of the POSA subjects as compared to 77% of the fluconazole subjects received between 1 – 14 days of treatment. Interestingly, a larger percentage (25%) of POSA treated subjects received ≥15 days of treatment as compared to 16% of the fluconazole subjects. In order to assess if this difference was due to a larger number of later cures on the POSA arm, the applicant was requested to provide additional analyses by duration of treatment.

Table 17
All Treated Population per Agency Criteria
Duration of Treatment

Length of Exposure (Days)	Posaconazole 100 mg (n=178)	Fluconazole 100 mg (n=172)
1-3	2 (1)	2 (1)
4-6	4 (2)	2 (1)
7-10	8 (4)	6 (3)
11-14	119 (67)	133 (77)
≥15	45 (25)	28 (16)
Missing	0 (0)	1 (<1)

Efficacy Analyses

Primary Endpoint: Clinical Response

The clinical response rate achieved with POSA was non-inferior to that achieved with FLU after 14 days of treatment in both the MITT (91.7% vs. 92.5%, respectively) and protocol evaluable subsets (97.2% vs. 96.3%, respectively). This success rate for POSA versus FLU was consistent with that achieved in the ITT (89.0% vs. 86.4%, respectively) and all-treated (91.0% vs. 92.4%, respectively) populations for both treatment arms. A by center analysis can be found in APPENDIX A. There was consistency in the results across the centers.

Table 18
Clinical Response at the EOT
All Populations per FDA criteria C/I97-331

	POSA	FLU	95% CI per MO with CCF
All Treated	N= 178	N = 172	
Success	162 (91%)	159 (92.4%)	-7.7, 4.9
Failure All	16 (9%)	13 (7.5%)	
Cure	145 (81.4%)	141 (82%)	-9.19, 8.15
Improved	17 (9.5%)	18 (10.4%)	
Not Assessed	11 (6.2%)	7 (4%)	
Failure	5 (2.8%0	6 (3.5%)	
MITT	N= 171	N = 160	
Success	156 (91.2%)	148 (92.5%)	- 7.76, 5.22
Failure All	15 (8.7%)	12 (7.5%)	
Cure	139 (81.3%)	132 (82.5%)	- 10.12, 7.69
Improved	17 (9.9%)	16 (10%)	
Not Assessed	11 (6.4%)	6 (3.7%)	
Failure	4 (2.3%)	6 (3.7%)	
PE	N= 143	N = 135	
Success	139 (97.2%)	130 (96.3%)	- 3.99, 5.8
Failure All	4 (2.8%)	5 (3.7%)	
Cure	125 (87.4%)	116 (85.9%)	- 7.23, 10.2
Improved	14 (9.8%)	14 (10.4%)	
Not Assessed	1 (0.7%)	-	
Failure	3 (2.1%)	5 (3.7%)	

CCF: Continuity Correction Factor

Comment: *The MO generated 95% CI for all populations showed non-inferiority for the POSA arm as compared to the FLU for the primary parameter of success (cure and improvement) well within the protocol specified delta of ± 15%. Additional analyses performed by the MO where CIs were generated for cures only again revealed non-inferiority between the treatment arms in all populations.*

Secondary endpoints:

Clinical Response at Day 7:

Comment: *There was also similarity in the results across populations with regards to the day 7 assessment with fewer subjects classified as cures and more improvements on both arms. Of note was the overall higher number of positive responses on both treatment arms at this timepoint whereas at the EOT fewer subjects went on to achieve success. There was again equivalence between posaconazole and fluconazole for both overall success for all populations and for "cures" only in the all treated and MITT populations. Posaconazole was numerically superior to the comparator in the PE population when only cures were assessed as successes suggesting that in the population of HIV subjects with documented Candida spp. OPC, posaconazole may lead to earlier clinical resolution.*

Table 19
Clinical Response at Day 7
All Populations per FDA criteria C/I97-331

	POSA	FLU	95% CI per MO with CCF
All Treated	N= 178	N = 172	
Success	171 (96%)	167 (97%)	- 4.83, 2.78
Failure All	7 (3.9%)	5 (7%)	
Cure	119 (66.8%)	112 (65.1%)	- 3.15, 7.05

Improved	52 (29.2%)	55 (32%)	
Not Assessed	6 (3.4%)	5 (2.9%)	
Failure	1 (0.5%)	-	
MITT	N= 171	N = 160	
Success	166 (97%)	155 (96.8%)	- 5.08, 5.47
Failure All	5 (2.9%)	5 (2.9%)	
Cure	115 (67.2%)	105 (65.6%)	- 4.07, 8.59
Improved	51 (29.8%)	50 (31%)	
Not Assessed	5 (2.9%)	5 (3.1%)	
Failure	5 (2.9%)	5 (3.1%)	
PE	N= 143	N = 135	
Success	141 (98.6%)	134 (99.2%)	- 5.83, 4.57
Failure All	2 (1.4%)	1 (0.7%)	
Cure	103 (72%)	91 (67.4%)	- 1.2, 13.31
Improved	38 (26.5%)	43 (31.8%)	
Not Assessed	2 (1.4%)	1 (0.7%)	
Failure	2 (1.4%)	1 (0.7%)	

CCF: Continuity Correction Factor

Relapse Rate:

Comment: *The clinical relapse rate observed 4 Weeks after the last dose of POSA was lower than that seen in the fluconazole treated subjects. Similar results were obtained for all populations analyzed.*

Table 20
Clinical Response at Follow-up
All Populations per FDA criteria C/I97-331

	POSA	FLU	95% CI per MO with CCF
All Treated	N= 149	N = 145	- 6.53, 16.58
Success	101 (67.8%)	91 (62.8%)	
Relapse	48 (32.2%)	54 (37.2%)	
MITT	N= 144	N = 136	-5.59, 18.17
Success	98 (68%)	84 (61.7%)	
Relapse	46 (32%)	52 (38.3%)	
PE	N= 129	N = 121	- 7.99, 17.36
Success	86 (66.7%)	75 (62%)	
Relapse	43 (33.3%)	46 (38%)	

CCF: Continuity Correction Factor

Clinical Response Rates After 14 Days of Treatment by Baseline Fluconazole Minimum Inhibitory Concentration – Microbiology (C/I97-331) as per the Applicant

For subjects in the MITT subset in Study C/I97-331, clinical response rates by baseline fluconazole MIC values were evaluated using the following breakpoints: susceptible (≤8 mcg/mL), dose dependent (>8 mcg/mL to ≤32 mcg/mL), and resistant (>32 mcg/mL). The breakpoints used in this analysis were based on the current Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) MIC breakpoints. Subjects were counted only once in the any *Candida* tally by their most resistant baseline isolate.

The majority of subjects in both treatment groups had baseline *Candida spp.* isolates that were microbiologically demonstrated to be susceptible to fluconazole.

Clinical response rates with posaconazole were similar to those achieved with FLU for all categories of isolates (sensitive, DD, and resistant). The clinical response rate on both treatment arms for isolates with high MICs is indicative of the difficulties in determining what determined resistant disease. In this study the subjects had relatively less advanced HIV disease and, fewer prior OPC episodes, and less exposure to prior azole antifungal therapy compared to subjects in the azole-refractory OPC studies.

Table 21
Clinical Response Rates: Number (%) of Clinical Responders by Baseline Fluconazole MIC Values Modified Intent-to-Treat Subset Protocol Nos. C/I97-331

		Posaconazole				Fluconazole			
		Any *Candida*		*Candida albicans*		Any *Candida*		*Candida albicans*	
MIC Breakpoints (µg/mL)a		**n**	**# responders**	**n**	**# responders**	**n**	**# responders**	**n**	**# responders**
Susceptible	≤8	137	135 (99)	144	141 (98)	129	125 (97)	138	134 (97)
Dose Dependent	>8 to ≤32	11	10 (91)	4	4 (100)	10	9 (90)	5	4 (80)
Resistant	>32	17	17 (100)	12	12 (100)	17	17 (100)	8	8 (100)

MIC = minimum inhibitory concentration.
a: Results other than a standard concentration value are assigned to the next higher standard concentration value. If a subject had multiple values within an organism, the maximum value within that species was used.

Mycologic Response at the EOT:

Comment: *The applicant provided analyses of mycologic response at the EOT by patient where eradication and/or superinfection were assessed as success and persistence or not assessed were classified as failures. CIs as per the MO revealed that posaconazole was non-inferior to fluconazole in these analyses as well as when only subjects with eradication were classified as successes.*

Table 22
Mycologic Response by Patient at the EOT All Populations per FDA criteria C/I97-331

	POSA	FLU	95% CI per MO with CCF
All Treated	N= 178	N = 172	
Success	107 (60.1%)	99 (57.5%)	-8.33, 13.44
Failure All	71 (39.8%)	73 (42.4%)	
Eradication	89 (50%)	80 (46.5%)	-7.55, 14.53
Superinfection	18 (10.1%)	19 (11%)	
Not Assessed	17 (9.5%)	17 (9.8%)	
Failure	54 (30.3%)	56 (32.5%)	
MITT	N= 171	N = 160	
Success	107 (62.5%)	99 (61.9%)	- 10.36, 11.76
Failure All	64 (37.4%)	61 (38.1%)	

Eradication	89 (52%)	80 (50%)	- 9.33, 13.43
Superinfection	18 (10.5%)	19 (11.9%)	
Not Assessed	10 (5.8%)	7 (4.4%)	
Failure	54 (31.6%)	56 (33.7%)	
PE	N= 143	N = 135	
Success	93 (65%)	89 (65.9%)	- 12.79, 11.01
Failure All	50 (35%)	46 (34%)	
Eradication	79 (55.2%)	72 (53.3%)	- 10.52, 14.35
Superinfection	14 (9.8%)	17 (12.6%)	
Not Assessed	2 (1.4%)	2 (1.5%)	
Failure	48 (33.6%)	44 (32.6%)	

CCF: Continuity Correction Factor

When mycologic response by patient was assessed by baseline MIC data, response rates were similar between the treatment arms for the susceptible isolates but numerically superior in favor of posaconazole or the DD and resistant isolates. Generally mycologic response was much lower than clinical response.

Table 23
Mycological Response Rates: Number (%) of Mycological Responders by Baseline Fluconazole MIC
Modified Intent-to-Treat Subset
Protocol Nos. C/I97-331

		Posaconazole				Fluconazole			
		Any *Candida*		*Candida albicans*		Any *Candida*		*Candida albicans*	
MIC Breakpoints (µg/mL)a		**n**	**# responders**	**n**	**# responders**	**n**	**# responders**	**n**	**# responders**
Susceptible	≤8	134	92 (69)	140	95 (68)	122	78 (64)	131	84 (64)
Dose Dependent	>8 to ≤32	10	4 (40)	4	2 (50)	10	7 (70)	5	2 (40)
Resistant	>32	12	6 (50)	8	4 (50)	15	6 (40)	7	3 (43)

MIC = minimum inhibitory concentration.
a: Results other than a standard concentration value are assigned to the next higher standard concentration value. If a subject had multiple values within an organism, the maximum value within that species was used.

When mycologic response was assessed at day 7, there were fewer failures across the populations in favor of posaconazole but there were also more superinfections.

Table 24
Mycologic Response by Patient at the Follow-up
All Populations per FDA criteria C/I97-331

	POSA	FLU	95% CI per MO with CCF
All Treated	N= 178	N = 172	
Success	83 (46.6%)	70 (40.7%)	-5.01, 16.95
Failure All	95 (53.3%)	102 (59.3%)	
Eradication	68 (38.2%)	59 (34.3%)	
Superinfection	15 (8.4%)	11 (6.4%)	
Not Assessed	16 (9%)	20 (11.6%)	
Failure	79 (44.4%)	82 (47.7%)	
MITT	N= 171	N = 160	
Success	83 (48.5%)	70 (43.7%)	- 7.93, 16.95
Failure All	95 (53.3%)	90 (56.2%)	

Eradication	68 (39.7%)	59 (36.8%)	
Superinfection	15 (8.7%)	11 (6.8%)	
Not Assessed	9 (5.3%)	9 (5.6%)	
Failure	79 (46.2%)	81 (50.6%)	
PE	N= 143	N = 135	
Success	70 (48.9%)	60 (44.4%)	- 6.55, 16.13
Failure All	73 (51%)	75 (55.5%)	
Eradication	57 (39.8%)	52 (38.2%)	
Superinfection	13 (9.1%)	8 (5.9%)	
Not Assessed	6 (5.3%)	4 (2.9%)	
Failure	67(46.8%)	71 (52.6%)	

CCF: Continuity Correction Factor

An analysis of mycologic response by patient and by pathogen at the EOT was also provided. *C. albicans* was isolated in 93% of subjects.

By pathogen eradication rates were similar between the treatment arms for *Candida albicans* and numerically superior in favor of POSA for *Candida glabrata* although there were too few isolates to draw any conclusions.

Table 25
Mycologic Response by Pathogen at TOC (Evaluable)
FDA Criteria
C/I97-331

	POSA		FLU	
Pathogen	# Isolated	# Eradicated	# Isolated	# Eradicated
All *Candida* Isolates	162	106 (65.4%)	147	9 (66.6%)
Candida albicans	138	94 (68%)	131	88 (67%)
Candida glabrata	11	4 (36.3%)	6	2 (25%)
Candida krusei	5	4 (80%)	6	6 (85.7%)
Candida norvegensis	1	1 (100%)	0	0
Candida spp.	4	1 (25%)	1	0
Candida tropicalis	3	2 (67%)	3	2 (67%)
Non-Candida spp.	1	1(100)	2	1 (50%)

Mycologic Relapse rate:

The applicant provided an analysis of mycologic relapse rate by patient at the follow-up visit.

"For subjects with follow-up data, the 95% confidence interval for the difference shows that the mycologic relapse rate 4 weeks after the last dose of POSA was statistically significantly smaller at the 0.05 level than that seen 4 weeks after the last dose of FLU in the MITT (59.4% vs. 73.6%, respectively) and protocol evaluable subsets (59.8% vs. 74.4%, respectively). This relapse rate for POSA versus FLU was consistent with that seen in the ITT (59.4% vs. 73.6%, respectively) and all-treated subsets (59.4% vs. 73.6%, respectively) for both treatments.

Comment: *There were a greater number of subjects on the fluconazole treatment arm who had mycologic relapse as compared to the posaconazole treated subjects. This difference extended across the populations.*

Table 26
Mycologic Relapse at Follow-up
All Populations per FDA criteria C/I97-331

	POSA	FLU
MITT	N = 95	N = 82
Relapse	61 (64.2%)	64 (78%)
PE	N = 85	N = 75
Relapse	55 (64.7%)	59 (76.6%)

When mycologic relapse was assessed by pathogen, there were 50 mycologic relapses in subjects with *Candida albicans* at baseline treated with POSA (40%) as compared to 59 (45%) on the FLU arm. There were 2 relapses on each arm in subjects with *C. glabrata* at baseline (18% POSA versus 33% FLU).

Mycologic eradication rates for the MITT population at TOC and F/U for All *Candida* isolates and *Candida albicans* were assessed. Mycologic evaluations were performed at follow-up in proportionately the same number of subjects in both arms.

Table 27
Mycologic eradication rates for the MITT population at TOC and F/U for All *Candida* isolates and *Candida albicans*

	Protocol specified criteria				FDA criteria			
	POS TOC	FLU TOC	POS F/U	FLU F/U	POS TOC	FLU TOC	POS F/U	FLU F/U
All Candida isolates	131/190 (69%)	121/175 (69%)	63/190 (33%)	34/175 (19%)	123/193 (64%)	111/175 (63%)	59/193 (31%)	28/175 (16%)
Candida albicans	116/162 (72%)	109/155 (70%)	49/162 (30%)	26/155 (17%)	108/165 (65%)	99/155 (64%)	44/165 (27%)	20/155 (13%)

• Using the FDA criteria for the MITT subset at TOC, similar proportions of isolates were eradicated at the test of cure (POSA 64%, N=123/193 and FLU 63%, N=111/175 of all baseline *Candida* isolates, the majority of which were *C. albicans*).
• Sustained eradication rates for FLU had a greater decrease from test of cure to post treatment follow-up than the eradication rates for POSA. Mycologic eradication for FLU decreased from approximately 63% to 16%, while the eradication rates for POSA dropped from 64% to 31%.

Comment: It should be noted that mycologic assessment was NOT preformed routinely in all subjects and the sponsor's conclusions were drawn only from the subset of subjects in whom culture was performed.

Therapeutic Response:

Therapeutic Success at test of cure (TOC) for the All Treated Subset by both the Protocol-defined and FDA-defined criteria demonstrated non-inferiority of the POSA regimen by both criteria. Similar analyses of therapeutic response for other subsets

(MITT, Protocol Evaluable) also demonstrated non-inferiority. This analysis was a post-hoc analysis.

Table 28
Therapeutic Response at the TOC
C/I97-331

Criteria for Therapeutic Success	Posaconazole 100mg n/N (%)	Fluconazole 100mg n/N (%)
Protocol Defined: Cure and <=20 CFU/ml	86/178 (48)	79 /172 (46)
95% CI for the difference (pos . flu): (-8.07, 12.84)		
FDA Defined: Cure and 0 CFU/ml	75/178 (42)	68/172 (40)
95% CI for the difference (pos . flu): (-7.69, 12.89)		

Other Analyses:

The applicant performed analyses of clinical response by sex, race, age, baseline sxs sum, region, country and site. There was consistency across the subgroups at the EOT. The applicant performed these analyses on the original MITT population of 169 POSA and 160 fluconazole subjects. These analyses can be found in APPENDIX A.

Study Comparisons:

The two treatment groups from studies 209 and 331were comparable with respect to age, sex, and race and disease characteristics evaluated at baseline for subjects in the MITT subset. In both studies, mean and median CD4 cell counts were comparable between the treatment groups, although t the mean counts were lower in subjects in study 209. In general, both study populations appeared to have less advanced HIV disease. The # of previous episodes was not collected in study 331 but the range was from 0 – 12 (mean = 2) in the subjects enrolled in study 209.

Table 29
Comparison of Demographics MITT
Study C/I97-331 and study C/I97-209

	C/I97-331		C/I97-209	
Demographic Characteristic	**Posaconazole 100 mg (n=169)**	**Fluconazole 100 mg (n=160)**	**Posaconazole 100 mg (n=91)**	**Fluconazole 100 mg (n=83)**
Age (yr)				
Mean ±sd	36.5 (8.0)	37.6±9.1	37.6 (9.2)	37.0 (8.2)
Median	35.0	36.0	38.0	37.0
Minimum-maximum	20 to 61	19-78	18 to 62	19 to 59
Sex, number.(%) subjects				
Female	44 (26)	41 (24)	16 (18)	20 (24)
Male	125 (74)	131 (76)	75 (82)	63 (76)
Race, number.(%) subjects				
Asian	16 (9)	16 (9)	4 (4)	3 (4)

Black	41 (24)	33 (19)	20 (22)	21 (25)
Caucasian	61 (36)	67 (39)	45 (49)	36 (43)
Hispanic	49 (29)	51 (30)	20 (22)	19 (23)
Other	2 (1)	5 (3)	2 (2)	4 (5)
CD4 count				
n	169	158	91	82
Mean ±sd	139±173.4	119 ±143.4	122 (146.2)	128 (174)
Median	82	71	65	54.5
Minimum-maximum	0-935	0-867	1 – 690	0 - 1050

Clinical Response Rates After 14 Days of Treatment:

The primary endpoint for both studies in subjects with azole-susceptible OPC was the clinical response (cured or improved) after 14 days of therapy. The clinical success rates achieved with posaconazole 100 mg QD were non-inferior to those achieved with fluconazole after 14 days of treatment in study 331. The results achieved in study 209 although lower were comparable to the rates achieved in study 331. This difference may have been due to the lower bioavailability of the capsule formulation used in study 209.

Table 30
Comparison of Clinical Response at the EOT
All Populations per FDA criteria

	Study C/I96-331		Study C/I96-209	
	POSA 100 QD	**FLU 100 QD**	**POSA 100 QD**	**FLU 100 QD**
MITT	N= 171	N = 160	N = 91	N = 83
Success	156 (91.2%)	148 (92.5%)	79 (86.8%)	74 (89.2%)
Cure	139 (81.3%)	132 (82.5%)	73 (80.2%)	69 (83.1%)
Improved	17 (9.9%)	16 (10%)	6 (6.6%)	5 (6.0%)
PE	N= 143	N = 135	N = 83	N = 77
Success	139 (97.2%)	130 (96.3%)	75 (90.4%)	72 (93.5%)
Cure	125 (87.4%)	116 (85.9%)	70 (84.3%)	67 (87.0%)
Improved	14 (9.8%)	14 (10.4%)	5 (6.0%)	5 (6.5%)

Clinical Response was also assessed in study 331 by # of previous OPC episodes. There appeared to be a trend towards a decrease in successful responses in the fluconazole treated subjects who had a greater # of previous episodes of OPC as compared to the POSA treated subjects but the numbers were too small to allow for valid conclusions.

Mycological Response Rates by Patient After 14 Days of Treatment (C/I96-209, C/I97-331)

In Study C/I96-209, mycological success rate by patient for subjects with any *Candida* species after 14 days of treatment (at Visit 3) was 37.4% (34/91) posaconazole 100 mg capsules and 50.6% (42/83) fluconazole. Mycological success was defined as growth ≤ 20 CFU/mL. This difference was **statistically significant** in favor of fluconazole.

In Study C/I97-331, the mycological success rates by patient were similar between the two treatment groups: MITT 62.5% (107/171) posaconazole and 61.9% (99/160)

fluconazole. In the PE population the rates were also similar (POSA 65% (93/143) and 65.9% fluconazole (89/135)

The mycological response by pathogen: In study 209 For *Candida albicans*, 37.9% (33/87) of subjects treated with posaconazole 100 mg capsules and 58.1% (43/74) of subjects treated with fluconazole 100 mg had a mycological response of eradication defined as ≤20 CFU/mL.

The mycological response rates of the other species isolated, *Candida glabrata*, other *Candida* species, and miscellaneous non-*Candida* species, were difficult to compare as these species occurred with a very low incidence (≤6 subjects in either treatment group).

In study 331, eradication rates for *Candida albicans* were similar at the TOC for evaluable isolates (as redefined by FDA criteria): posaconazole 94/138 (68%) as compared to 88/131 (67%) for the fluconazole arm. Rates were much lower on both arms versus *Candida glabrata* (posaconazole 4/11 (36.3%) versus 2/6 (25%). No conclusions could be drawn regarding the remaining isolates.

In Study C/I97-331, mycological assessments were performed 4 weeks after the last dose of study drug for 192 MITT subjects (101 treated with posaconazole and 91 treated with fluconazole; Using the FDA criteria for the MITT subset at TOC, similar proportions of isolates were eradicated at the test of cure (POS 64%, N=123/193 and FLU 63%, N=111/175 of all baseline *Candida* isolates, the majority of which were *Candida albicans*).

Sustained eradication rates for FLU dropped more from the test of cure to the post treatment follow-up with the refined FDA criteria than the eradication rates for POSA. Mycologic eradication for FLU decreased from approximately 63% to 16%, while the eradication rates for POS drop from 64% to 31%. It should be noted however that mycologic assessment was performed in a limited number of subjects.

Refractory OPC:

In support of the efficacy of posaconazole in azole-refractory OPC the Applicant submitted 2 open label non-comparative trials of posaconazole in the treatment of patients with refractory candidiasis in immunosuppressed HIV-infected subjects. There were 239 unique subjects enrolled in these trials. (199 unique subjects in C/I97-330 of which 60 treated subjects were rolled over into P0298 and 100 enrolled in P0298 including 40 unique subjects and the 60 rollovers). Because of the large number of rollovers and the lack of a fixed TOC, study P0298 was considered supportive only.

The primary efficacy parameter was the clinical success rate (cure or improvement) after 4 weeks (C/I97-330) or 3 months (P00298) of treatment among subjects in the MITT subset.

Studies C/I/97-330 Open-Label, Non-Comparative Trial of SCH 56592 in the Treatment of Azole Refractory Candidiasis in HIV-Infected Subjects:
C97-330 was submitted to IND 51,662 on December 9, 1997 (Serial No. 015)
I97-330 was submitted on April 14, 1998 (Serial No. 024)
Amendment #1: C/I97-330 April 1, 1999 (Serial No. 073)
Amendment #2: C/I97-330 July 7, 1999 (Serial No. 097)

Synopsis: Study C/I97- 330 was a Phase III, noncomparative, open-label, multicenter study of POSA in HIV-infected subjects with oral and/or esophageal candidiasis (EC) unresponsive to standard treatment with oral fluconazole (FLU) or itraconazole (ITZ).

During the acute treatment (days 1 – 28) period subjects received POS oral suspension, 400 mg twice daily for 3 days, followed by 400 mg once daily for 25 days (original Protocol) or 400 mg twice daily for 28 days (amended protocol). Following the acute treatment phase, subjects entered one of two maintenance phases; that included in the original protocol (400 mg twice daily, three times weekly for 3 months) or a long term treatment phase (protocol No. P00298, 400 BID for 1 year). The determination of which phase a patient entered depended on which protocol was in effect at the time and was not clinically determined. Thirty sites were involved (13 in the USA, 3 in Canada, 5 in South/Central America, 7 in Europe, and 2 in Australia).

Comment: The applicant was able to show that posaconazole at a dose of 100 mg QD was non-inferior to fluconazole in the treatment of OPC in an HIV population that had few risk factors for refractory disease. In Phase II study C/I97-209 it was shown that both the 100 mg and 400 mg doses of posaconazole had comparable efficacy to a standard fluconazole dose for the treatment of OPC. The use of increased doses of fluconazole in refractory OPC in profoundly immunosuppressed HIV infected subjects is well documented in the literature. It seems reasonable to use the maximum tested dose of posaconazole in a population of subjects with OPC clinically unresponsive to conventional treatment.

The primary efficacy analysis was performed on the clinical assessment at week 4 (after 28 days of treatment for the original subjects and on the last day of 28 days of treatment for the amended subjects). Patients who were missing data at week 4 and had no subsequent assessments of clinical response after week 4 were considered failures. If subjects had recorded assessments before and after week 4 indicating cure or improvement, the derived or imputed response was based on the later of the two assessments. Responses in the original protocol C/I97-330 were assessed by the investigator at Week 4 (day 28) and at three months; in the amended protocol, responses were assessed at the end of therapy (week 4, visit 5). When the clinical response was not assessed by the investigator at week 4, a response was derived according to the conventions included in the verification plan.

Follow-up assessments in C/I97-330 were to be performed at 30 days after the end of therapy; however, not all subjects had post treatment follow-up assessments performed and the actual assessment times in the post treatment follow-up varied.

Note: As indicated by the analysis plan, a true TOC assessment was extremely difficult in this study as most subjects were rolled over to a long term maintenance regimen.

Signs of mucositis/esophagitis (plaques or ulcers) were assessed using a scale taken from a modified AIDS Clinical Trial Group (ACTG) Protocol (see APPENDIX A).

Mycologic response and change in susceptibility pattern among isolates were secondary endpoints of this study. Quantitative cultures were performed, per protocol, in subjects at Baseline, Visit 3 (14 days), and Visit 5 (Week 4, End of Acute Treatment). Visit 6 (Follow-up) cultures were not required by protocol, though if a subject relapsed off therapy, it was requested that a culture be obtained. Cultures were also to be performed, according to protocol, in all subjects who were considered treatment failures prior to Visit 5.

Not all subjects who had a clinical evaluation at Week 4 or the End of Acute Treatment had cultures at that time, though mycologic response was never presumed in these subjects. (Two MITT subjects had neither a clinical nor a mycologic evaluation at Week 4 (C97330-017-001 and I97330-011-010 and 50 subjects who had a clinical evaluation at Week 4, but did not have Week 4 cultures, 34 TF)

Safety and tolerance assessments were based on laboratory evaluations, AE profiles, and discontinuations.

Subjects were instructed to swish and swallow study drug and to take it with food or immediately after eating. They were also instructed not to rinse their mouth for at least 30 minutes after taking study drug.

Comment: *The administration of the posaconazole dose with food led to increased bioavailability. The swish and swallow technique of administration as well as the instructions not to rinse post dose are indicative of the expectation that there is a topical effect as well as a systemic effect of POSA versus Candida spp.*

Dosage*: Subjects received one of two regimens during the initial 28 days of treatment ranging from 400 QD for 3 days followed by 400 BID for 25 days in the original protocol to 400 BID for 28 days in the amended protocol. Subjects in the original protocol could have been assessed at day 14 and changed to 400 mg BID for the remaining acute treatment phase.*

The rationale behind the dose change (increase) was not clearly stated. As per the protocol " The major reason had to do with simplifying the regimen, making the dosing uniform, and providing a fixed dosing regimen of 400 mg bid for 4 weeks, rather than beginning with 400 mg bid for 3 days, followed by 400 mg qd and then adjusting the regimen after 2 weeks as specified for subjects who were failing or not improving.

Pertinent **Inclusion Criteria** included the following
Note for all Inclusion criteria see Appendix A:

- History of failure to improve or worsening of candidiasis after a standard course of therapy with FLZ ≥100 mg/day for at least 10 consecutive days, or ITZ 200 mg/day for at least 10 consecutive days for oral candidiasis or ≥3 weeks for esophageal candidiasis.

Comment: *The above represent the standard dosing regimens for OPC. Fluconazole doses up to 400 mg/day may be used based on medical judgment of the patient's response to therapy. There is no firm definition of refractory OPC in the literature. Generally HIV infected subjects are diagnosed as refractory after one or two failed course of Fluconazole at standard or increased doses.*

Analyses of Response:

Clinical response at the end of 4-week treatment period was the primary efficacy endpoint for this study. Clinical evaluations included the assessment of mucositis/esophagitis by signs and/or symptoms at each visit.

Comment*: Subjects were assessed for clinical response while continuing on treatment. If a subject did not have a week 4 visit, the clinical response was imputed from the previous assessment. Although an assessment on treatment would be considered inadequate to support the primary OPC indication, it was considered acceptable for the population under study with refractory OPC.*

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 of candidiasis
• Clinical Failure: No improvement or worsening of signs or symptoms
• Relapse: Recurrence of signs or symptoms after initial improvement or cure at Visit 5, despite adherence to subsequent therapy (≥80% of doses), (Original Protocol and Amendment No. 1) or recurrence of signs or symptoms after initial improvement or cure at Visit 5 (Amendment No. 2).

Comment: *Subjects who were assessed after the initial 4 weeks of treatment were often on a maintenance regimen.*

Data Subset Populations: The MITT was the primary population used in this review with the EE as confirmatory. See Appendix A for further details.

Primary Endpoint

The primary protocol defined efficacy endpoint was the proportion of subjects who were clinically cured/improved (responders) after 4 weeks (28 days, Day 1 through Day 29) of therapy (actual window of days of therapy was 26 to 37). Any subject who discontinued the study or was identified as a treatment failure was analyzed as a clinical failure.

***Comment**: All MITT subjects were to be assessed after 28 days of initial treatment. If there was no visit an imputation rule was derived to estimate the missing clinical evaluation at Week 4.*

No formal test was planned to assess possible differences between the subset of subjects enrolled in the Original Protocol versus those enrolled in Amendments Nos. 1 and 2. An evaluation of results for subjects enrolled in these two subgroups were assessed independently.

Applicant's analysis

One hundred ninety nine subjects enrolled at 30 sites:

The All-Treated subset (N = 199) included all subjects with a diagnosis of OPC who received at least one dose of study drug. The Modified Intent-to-Treat population (MITT, N = 176) included the All-Treated subset with evidence of an azole-refractory *Candida* at Baseline. The Efficacy Evaluable (N = 158) subset comprised the subset of the All-Treated subjects that satisfied additional key inclusion criteria. To be included in this subset, subjects must have received at least 14 consecutive daily doses of study drug and had a clinical assessment at week 4 or at least 3 days of treatment before discontinuing study drug before week 4 due to treatment failure or an AE.

***Comment**: The MO considered the MITT population the primary population and the EE as confirmatory.*

Table 31
StudyC/I97-330 Analysis Populations

	Protocol Version Enrollment		
Subset of Subjects	**Original**	**Amended**	**Total**
All-Treated	103	96	199
Modified Intent-to-Treat	89	87	176
Efficacy Evaluable	81	77	158

Table 32
Reasons for Exclusion from the EE population
StudyC/I97- 330

	Number of Subjects
Reason for Exclusion	**n=199**
Total Number of Subjects Not Included in The Efficacy Evaluable Subset	**41**
No verifiable source documentation of enrollment dates or drug administration	4
Negative or no baseline culture	10
Resistance to FLZ/ITZ not documented	8
Non-candidal species on baseline culture	1
Less than 14 days of continuous therapy and/or no Visit 5 (Treatment Endpoint)	17
Adverse event (AE) occurring with less than 3 days of study drug administration	1

Disposition of subjects: See Appendix A for details

Seventy-four percent (148/199) of all subjects completed the acute treatment period of the study (Day 1 through Day 29 of the treatment period).

Twenty-four percent (47/199) of all subjects discontinued the acute treatment period of the study (23% (24/103O) and 24% (23/96A).

The status at the end of the **acute treatment period** was either missing or unknown for four subjects.

Reasons given for study discontinuation during the acute treatment period included: adverse events (9%, 18/199), treatment failure (3%, 6/199), lost to follow-up (1%, 2/199), subject did not wish to continue (2%, 3/199), non-compliance with protocol (6%, 11/199), did not meet protocol eligibility (2%, 3/199), and death (2%, 4/199).

Comment: All discontinuations for AEs were previously reviewed [redacted] The MO found no irregularities is the assessment of subjects. Deaths were not considered failures.

Demographics and Disease Characteristics:
(The MO provided demographics for the MITT population. The EE population demographics were similar).

The age range was 20 to 69 years, mean 39.1. The subjects were primarily males (11.9% were females) and 131 (74.4%) were Caucasian.

The mean CD4+ counts at Baseline were 32 with ranges of 1 to 492 and 0 to 271 cells/mm3. Eighty four percent (84%) of the MITT subjects were profoundly immunosuppressed with CD4+ counts ≤100 cells/mm3.

Forty nine percent of subjects were considered to have OPC refractory to fluconazole and 41% to both fluconazole and itraconazole.

Comment: *The demographic characteristics were consistent with those expected from an HIV infected population at the time these studies were performed. The CD4 counts were indicative of a profoundly immunosuppressed population in whom complete cure of their OPC was highly unlikely. Many subjects had failed previous courses of fluconazole and/or itraconazole and thus met the protocol definition of refractory disease. A large number of subjects had Candida spp. isolates with MICs between 32 – 64 mcg/mL versus fluconazole indicative of decreased effectiveness of that agent at the approved dose.*

Table 33
Demographics MITT Population
Study C/I97-330

Demographic Characteristic	Protocol Version Enrollment

	Original (n=89)	Amended (n=87)	Total (n=176)
Age (yr)			
Mean (sd)	39.2 (7.6)	39 (7.3)	39.1 (7.4)
Median	39.0	38.0	38.5
Min-Max	20 – 69	24 – 56	20 – 69
Weight (kg)			
Mean (sd)	63.1 (14.9)	60.5 (13.6)	61.8 (14.2)
Median	63.0	60.0	60.0
Min-Max	34 – 126	37 – 100	37 – 126
Missing	2	0	2
Gender (n, %)			
Female	10 (11.2)	11 (12.6)	21 (11.9)
Male	79 (88.7)	76 (87.3)	155 (88)
Race (n, %)			
Caucasian	70 (78.6)	61 (70.1)	131 (74.4)
Black	15 (16.8)	21 (24.1)	36 (20.4)
Asian	0	0	0
Hispanic	4 (4.4)	5 (5.7)	9 (5.1)
CD4 Count, cells/mm 3			
n	77	85	162
Mean (sd)	32 (63.8)	32 (54.3)	32 (58.8)
Median	12.0	10	10.5
Min-Max	1 – 492	0 – 271	0 – 492
CD4 Distribution, cells/mm^3 (n, % Subjects)			
≤100	71 (80)	77 (89)	148 (84)
>100	6 (7)	8 (9)	14 (8)
Missing	12 (13)	2 (2)	14 (8)
Refractory to Prior Antifungal Agents (n, % Subjects)			
Fluconazole	44 (49)	43 (49)	87 (49)
Itraconazole	8 (9)	2 (2)	10 (6)
Fluconazole & Itraconazole	37 (42)	35 (40)	72 (41)
Missing	0	7 (8)	7 (4)
Culture Resistant to Fluconazole (n, % Subjects)			
Candida albicans	50 (57)	50 (59)	100 (58)
Candida glabrata	11 (13)	14 (16)	25 (14)
Candida tropicalis	2 (2)	1 (1)	3 (2)
Candida krusei	5 (6)	5 (6)	10 (6)
Other *Candida* spp.	0	1 (1)	1 (1)
Fungal Culture (n, % Subjects)			
≤20 CFU/mL	1 (1)	0	1 (1)
>20 CFU/mL	88 (99)	85 (98)	173 (98)
Missing	0	2 (2)	2 (1)

Response Rates

See Appendix A and combined ISE.

Note: The MO confirmed the applicant's analyses using jump datasets.

Among subjects in the MITT subset, a 75% (132/176) clinical success rate (cure or improved) and a 36.5% (46/126) mycological response rate were achieved after 4 weeks of posaconazole treatment.

Clinical success rates ranged from 71% to 100%, inclusive, for all azole-resistant *Candida* species identified at Baseline, primarily *Candida albicans*.

Clinical success rates were similar for subjects in the original versus the amended protocols after 4 weeks of posaconazole treatment (MITT 75.3%, 67/89 and 74.7%, 65/87, respectively). Clinical relapse rates 4 weeks after the last dose of posaconazole were lower for subjects in the amended protocol (24.6%, 16/65) than for subjects in the original protocol (32.8%, 22/67), suggesting more sustained efficacy with the 800-mg daily dosing regimen compared to the 400-mg daily dosing or 800-mg/day intermittent (three times weekly) dosing regimens.

Conclusions:

This study supported the use of posaconazole 400 mg BID for 28 days in HIV infected subjects with refractory to other azoles OPC.

Additional MO analyses:

Response by dose:

33 subjects enrolled in the original protocol (All treated N = 103) were identified as having dose increases during acute treatment. Nine subjects increased their dose from 400 mg/day to 800 mg/day at the Week 2 (+7 days) assessment (C01-004, 02-002, 02-004, I01-002, 02-002, 02-004, 03- 003, 10-001, and 14-002). An additional 6 subjects had doses increased at Week 3 (C03-003, 03-005, I11-001, 11- 003, 12-002, and 14-001). Eleven subjects completed treatment at the original dose but had a dose increase when they rolled over into the maintenance phase. The following subjects had their dose increased for one day only: C02-001, I01-001, I02-001, I07-001, I12-003, I15-001, and I19-001. Of the 89 subjects included in the MITT population that received the original dose, 29 had their dose changed including 2 subjects that changed dose at the start of maintenance and 2 that changed during the study. Of the 29 subjects, the MO changed the outcome from cure or improvement at week 4 to failure in 16. With these changes, 38 subjects were cured, 36 failed and 14 improved. There was 1 UTD. A conservative analysis where only subjects considered cured were assessed as such led to a cure rate of 38/89 (42.6%) as compared to the sponsor's approximately 52% cured which was calculated independent of dose leading to the conclusion that the original dose was less effective in the treatment of a highly immunosuppressed population with previously treated OPC.

Therapeutic Response:

A therapeutic success analysis was performed by the sponsor for this study, but the results need to be interpreted cautiously due to missing evaluations (52 subjects not cultured). Therapeutic success for this study at Week 4 (End of Acute Treatment) was defined as clinical response of cure or improvement plus mycologic response, based on the ≤20 CFU/ml criteria. Mycologic response was documented at Week 4 in 124 of the 176 MITT subjects.

A 37% (46/124) mycological response rate was achieved after 28 days of posaconazole treatment among the MITT subset. Of the 124 MITT subjects with mycological assessments at Week 4, 116 subjects were clinical responders. Among these clinical responders, 40% (46/116) were also mycological responders.

Relapses:

Relapse rates were reassessed only in those MITT subjects with a clinical response of cure or improved at week 4 who had an assessment as opposed to an imputed response at that visit. Of the 176 MITT subjects, 132 were classified as cures at week 4 but only 80 met the above criteria. 59 (74%) of these subjects relapsed (32/40 (80%) original and 27/40 (68%) amended. The significance of this analysis is unclear as most subjects did not conclude their treatment after either acute treatment.

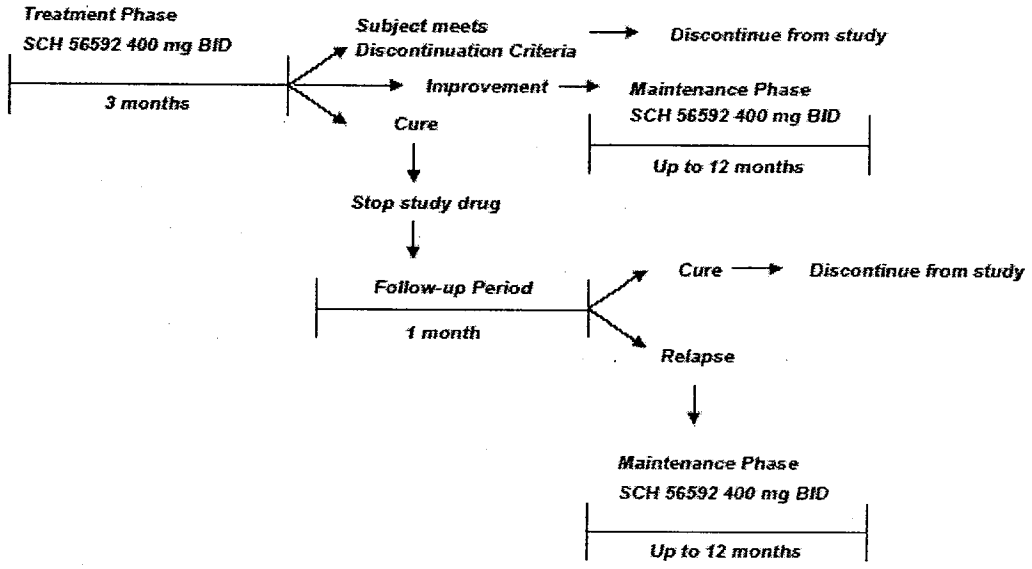
Response rates by baseline symptom score and CD4 counts can be found in Appendix A. Efficacy was consistent independent of severity of illness or CD4 count.

Study 0298: OPEN-LABEL RE-TREATMENT PROTOCOL FOR HIV-INFECTED PATIENTS WITH AZOLE-REFRACTORY CANDIDIASIS

Study 0298 was a Phase 3, non-comparative, open-label, multicenter study of POS in HIV-infected subjects with oral and/or esophageal candidiasis refractory to azole antifungal agents, specifically FLZ and ITZ. During the acute treatment phase, subjects received POS oral suspension, 400 mg BID, for up to 3 months. Subjects with a clinical response of cure at the end of acute treatment or who were discontinued prematurely were to have been observed for up to 1 month during an untreated follow-up period. However, subjects were allowed to proceed directly into the maintenance phase, continuing treatment with POS 400 mg BID for up to 12 months, if in the opinion of the investigator continued suppressive therapy was indicated. Subjects who remained cured at the end of follow-up were discontinued from the study. Subjects who relapsed during follow-up or who showed improvement at the end of the acute treatment phase were eligible for the maintenance phase, the latter group proceeding directly into maintenance. Study visits occurred monthly during the acute treatment and maintenance phases and at the end of the follow-up period. Clinical response was assessed monthly during the acute treatment phase and at the end of the follow-up period.

There were 2 general amendments subsequent to protocol finalization. The original protocol allowed for extended access to POS for up to 6 months in subjects with azole-refractory candidiasis treated with POS in study C/I97-330 and who relapsed

subsequently or for whom continued suppressive therapy was clinically warranted, defined as the POS-treated group. Amendment No. 1, dated 04 JUN 1999, changed the study to a retreatment protocol. The treatment period was reduced to 3 months, and subjects who had incomplete resolution of disease in study C/I97-330 were also allowed to enroll. Amendment No. 2, dated 18 JUL 2000, added the follow-up period and maintenance phase and allowed enrollment of subjects with azole-refractory candidiasis who had not been treated in study C/I97-330, defined as the POS-naïve group.



***Comment**: This study was primarily designed as a method to allow subjects with advanced HIV disease who had previously been treated with POSA after having failed a standard course of therapy with FLU or ITR or who had Candida isolates compatible with resistance to FLU or ITR to continue on posaconazole. This study was considered supportive only because of the lack of consistency amongst the enrolled subjects and the subjective nature of the decisions made by the investigators to continue treatment.*

Inclusion Criteria

Subjects with HIV diseases were eligible for inclusion in this study if they met the following specific to the indication criteria

Evidence of oropharyngeal candidiasis at time of enrollment, documented by KOH/fungal stain for yeasts, hyphae, or pseudohyphae consistent with *Candida* species confirmed by subsequent culture of oral lesions.
OR
Evidence of esophageal candidiasis documented by esophagoscopy or esophageal biopsy and culture.

History of prior therapy with POSA under Protocol No. **C/I97-330** with subsequent relapse or incomplete resolution of oropharyngeal candidiasis.
OR
History of failure to improve or worsening of oropharyngeal candidiasis after a standard course of therapy with fluconazole or itraconazole within 3 months prior to enrollment in this study. (A standard

course of therapy with fluconazole is ≥100 mg/day for at least 10 consecutive days for oral candidiasis or ≥3 weeks for esophageal candidiasis. A standard course of therapy with itraconazole is 200 mg/day for at least 10 consecutive days for oral candidiasis or ≥3 weeks for esophageal candidiasis.)

Exclusion Criteria:
Subjects who met any of the exclusion criteria listed below were not allowed to participate in this study.

Subjects with negative Baseline mycologic cultures for *Candida* species if such subjects had not received prior therapy with POSA.

Subjects with prior systemic antifungal therapy (eg, amphotericin B, flucytosine, azole antifungal agents) must have discontinued such therapy prior to study enrollment. There was no requirement for a washout period after terminating therapy with a systemic antifungal agent.

Concurrent or anticipated use of systemic antifungal agents (intravenous or oral) during the study period. Subjects who were clinical failures with previous SCH 56592 treatments.

POS oral suspension, 400 mg BID, was administered by having the subject swish and swallow the study medication with food or immediately after eating. Assessments were scheduled at Baseline (Visit 1), monthly during the treatment phase (Visits 2-4), at the end of the follow-up period (Visit 5), and monthly during the maintenance phase (Visits 6-17).

Signs and symptoms of oral candidiasis and esophagitis and the extent of plaques were assessed. Clinical response to therapy at the end of treatment (month 3) was the primary endpoint and was also assessed at all visits during the treatment phase and at the follow-up visit.
(For all definitions see study C/I97-330appendix A).

Data Subset Populations: see Appendix A

Comment: *The MO used the MITT population as the primary population and the EE as the for the confirmatory analyses. The primary focus of this study was to assess the chronic suppressive effect of posaconazole in a highly immunosuppressed population with refractory OPC/EC.*

Efficacy data was analyzed based on enrollment strata: POS-treated (subjects who received prior treatment with POS under Study C/I97-330) vs. POS-naïve (subjects not treated under C/I97-330). All subjects were to receive the same dose of POS (400 mg BID).

Subjects with a missing clinical response at the EOT were assigned as failures. Subjects with a missing mycological response at the end of treatment were assigned as failures (assumed persistent) if the subject had a *Candidal* isolate present at Baseline and during the follow-up period. Otherwise, missing mycological responses at follow-up were not changed.

Disposition of Subjects and Demographics:

One hundred subjects were enrolled at 19 sites. The All-Treated subset included all subjects with a diagnosis of OPC who received at least one dose of POS. The Modified Intent-to-Treat (MITT) population included the All-Treated subset with a positive *Candida* culture and evidence of an azole-refractory *Candida* culture at Baseline. The Efficacy Evaluable subset comprised the subset of the All-Treated subjects that satisfied additional key inclusion criteria. To be included in this subset, subjects must have received at least 60 days of study medication with no more than 7 consecutive days missed and had a clinical assessment at Visit 4. Twenty-five subjects in the All-Treated subset were not included in the Efficacy Evaluable subset

Table 34
Study P0298
Analysis Populations

Subset of Subjects	Enrollment Strata: Previously Treated	Enrollment Strata: Treatment Naive	Total
All-Treated	60 (60)	40 (40)	100
Modified Intent-to-Treat	59 (65.6)	31 (34.4)	90
Efficacy Evaluable	50 (66.7)	25 (33.3)	75

a: Included all subjects who received at least one dose of study medication. Also included Subject Nos. 01/007 and 02/015, who were known to have received treatment, but were missing dosing documentation.
b: Included All-Treated subset with a positive *Candida* culture and evidence of clinical or mycological *Candida* resistance at Baseline.
c: All-Treated subset who satisfied all key inclusion/exclusion criteria, received at least 60 days of study medication with no more than 7 consecutive days missed, and had a clinical assessment at Visit 4.
Treatment Naïve = NO previous POSA treatment

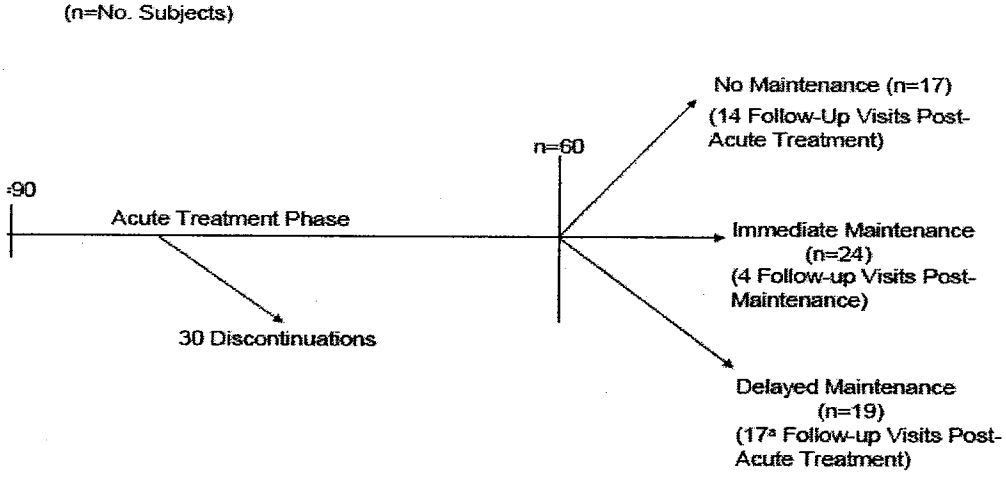
Table 35
Study P0298
Reasons for Exclusion

Reason for Exclusion	Number (%) of Subjects N = 100
All-Treated	**100 (100)**
Non compliance	2 (2)
Did not meet entry criteria (lack of positive culture or azole resistance)	8 (8)
MITT	**90 (90)**
Non compliance	8 (8)
Unacceptable concomitant medication	3(3)
No valid visit 4	2(2)
Administrative	1 (1)
Other	1(1)
Efficacy Evaluable	**75 (75)**
Non compliance	10 (10)
Lack of azole resistance	6 (6)

Unacceptable concomitant medication	3 (3)
Lack of positive baseline culture	2 (2)
No valid visit 4	2 (2)
Administrative	1 (1)
Other	1(1)

Sixty-five percent (65/100) of all treated subjects completed the acute treatment phase and 35% (35/100) discontinued the acute treatment phase of the study. Reasons for discontinuation during the acute treatment period included: adverse events (11%, 11/100), treatment failure (10%, 10/100), and subject did not wish to continue (6%, 6/100), lost to follow-up (4%, 4/100), non-compliance with protocol (3%, 3/100), and administrative (1%, 1/100). Forty-three percent (43/100) of all subjects entered follow-up either immediately following completion of acute treatment (49%, 32/65) or discontinuation from acute treatment (31%, 11/35), of which 81% (35/43) completed follow-up, and 19% (8/43) discontinued follow-up. Reasons for discontinuation during follow-up included: adverse events (9%, 4/43) and relapse/recurrence (9%, 4/43). Four subjects (4%, 4/100) considered to have missing follow-up status, actually had follow-up subsequent to maintenance therapy. Fifty-three percent (53/100) of all subjects never entered any follow-up; the majority either discontinued study during acute treatment or immediately entered maintenance following acute treatment.

In the MITT population, 30 subjects discontinued during the acute treatment phase and 60 completed that phase. 17 subjects did not undergo any maintenance, 24 went directly to maintenance and 19 entered maintenance after a follow-up drug free phase.



Subject Nos. 1/101 and 29/016 were considered to have delayed maintenance, despite the fact that they did not have a follow-up visit documented. According to dosing data, a gap in posaconazole administration occurred prior to initiation of maintenance treatment.

In the All-Treated subset, the mean and median duration of treatment, taking into account possible dosing interruptions and subject noncompliance, was 165.7 days and 112 days,

respectively. The duration of treatment exposure ranged from 1 to 516 days. In the MITT subset the mean duration of treatment was 196.3 days and the median was 117.

All subjects were between 25 and 61 years of age. Caucasian males comprised the majority of the study population. Positive fungal cultures were obtained for 83 subjects. The most common fungal organisms present on culture were *Candida albicans* (76/83; 92%) and *Candida glabrata* (24/83; 29%). CD4 counts were obtained on only 14 MITT subjects.

Table 36
Demographics MITT
Study P0298

Demographic Characteristic	All-Treated (n=100)	Modified Intent-to-Treat (n=90)	Efficacy Evaluable (n=75)
Age (yr)			
Mean (SD)	40.1 (6.6)	40.1 (6.7)	40.2 (7.2)
Median	40.0	40.0	40.0
Range	25-61	25-61	25-61
Sex (n[%])			
Female	16 (16)	14 (16)	9 (12)
Male	84 (84)	76 (84)	66 (88)
Race (n [%])			
Caucasian	73 (73)	65 (72)	57 (76)
Non-Caucasian	27 (27)	25 (28)	18 (24)
American Indian	1 (1)	1 (1)	0
Black	23 (23)	22 (24)	16 (21)
Hispanic	3 (3)	2 (2)	2 (3)
CD4 Count (cells/mm3)			
n	15	14	12
Mean (SD)	19.3 (24.4)	19.4 (25.3)	16.6 (21.5)
Median	7	6	6
Min - Max	0-72	0-72	0-68
Missing	85	76	63
CD4 Distribution (cells/mm3)			
≤100	15	14	12
>100	0	0	0
Missing	85	76	63
Fungal Culture[a] (n [%])			
Positive	83 (83)	75 (83)	65(87)
Negative	3 (3)	2 (2)	0
Missing	14 (14)	13 (14)	10 (13)
Fungal Culture Present (n [%])			
Candida albicans	76 (92)[b]	68 (91)[c]	58 (89)[d]
Candida glabrata	24 (29)[b]	24 (32)[c]	19 (29)[d]
Candida krusei	3 (4)[b]	3 (4)[c]	2 (3)[d]
Candida tropicalis	2 (2)[b]	2 (3)[c]	2 (3)[d]
Other *Candida* spp.	3 (4)[b]	2 (3)[c]	2 (3)[d]

a: Positive = at least one *Candida* isolate at Baseline was □20 CFU/mL or, if CFU was missing, an MIC reading was obtained. Negative = no growth, or all *Candida* isolates at Baseline were ≤20 CFU/mL.
b: Percentages based on 83 subjects with positive cultures. Some subjects may have had >1 isolate and may have been included in more than one culture category.
c: Percentages based on 75 subjects with positive cultures. Some subjects may have had >1 isolate and may have been included in more than one culture category.
d: Percentages based on 65 subjects with positive cultures. Some subjects may have had >1 isolate and may have been included in more than one culture category.

Protocol Deviations:
(For all see Appendix A)

During the acute treatment period (period under analysis for clinical response), 6 subjects took systemic anti-fungals other than study drug; (5/001, 9/100, 11/003, 16/011, 33/008, and 35/001). Of the 6 subjects, 3 were MITT only [11/003 (Cure), 33/008 (Treatment Failure, TF), 35/001 (TF)] and 3 were assigned to the EE population [5/001 (Improvement), 9/100 (TF), 16/011 (TF)].

Subjects 16/011 and 9/100 were analyzed in the EE subset since they met all inclusion criteria and were treatment failures. Subject 5/001 had already received 62 days of study drug in the acute treatment period with a clinical response of improvement before 1 week of ITZ was administered and so was considered eligible for analysis.

Primary efficacy endpoint analysis (clinical response at acute EOT) with the reassignment of the 3 subjects in the EE population to MITT and assignment of TF to all subjects receiving concomitant systemic antifungals did not substantially change the conclusions regarding the efficacy of posaconazole in azole-refractory OPC using the applicant's populations. (See Appendix A)

Applicant's Analysis

Clinical Response (see also Appendix A):

At the end of the acute treatment period (3 months), 88% (66/75) of all Efficacy Evaluable subjects were responders: 92% (46/50) of POS-treated subjects, and 80% (20/25) of POS-naïve subjects.

At the end of acute treatment, 86% (77/90) of all MITT subjects were responders: 88% (52/59) of POS-treated subjects, and 81% (25/31) of POS-naïve subjects. Similar clinical response rates were seen with the All-Treated subset.

Comment: *All subjects were assessed for clinical response by using the jump datasets and the CRFs. As per the MO analysis, of 92 discrete subjects who were assessed at the EOT, 46 were cured, 37 were improved and 9 were failures. The investigator assessments were the same.*

Response Rates at Monthly Visits during the Acute Treatment Period

Of the MITT subjects who were clinically evaluated, 98% (83/85) were responders at Month 1 Visit, 91% (64/70) at Month 2 Visit, and 96% (42/44) at Month 3 Visit. The majority of the treatment failures occurred within the first two months. By the Month 3 Visit, many of the subjects had already discontinued the study or had entered maintenance, thus accounting for the large number of subjects not clinically evaluated.

Clinical Relapse Rate at the Follow-Up Period Visit

Clinical relapse at the Follow-Up Month 1 Visit (defined as 8 through 37 days after the end of total acute treatment) was a secondary endpoint in this study. Relapse was defined as the recurrence of oral or esophageal candidiasis after discontinuation of therapy following a complete response or improvement. However, the majority of MITT subjects were not assessed for clinical relapse at the end of acute treatment because they either went immediately into maintenance or discontinued study during acute treatment.

Twenty-eight (31%, 28/90) MITT subjects were considered responders at the end of acute treatment and had a 1-month follow-up visit with an assessment for clinical relapse.

Of those, 46% (13/28) relapsed: 43% (9/21) of posaconazole-treated subjects and 57% (4/7) of POS-naïve subjects.

In addition, Subject Nos. 01/002, 18/002, 18/003, and 32/020 had follow-up assessments of relapse outside the Follow-up Month 1 Visit window on Days 148 (n=64), 99 (n=7), 113 (n=4), and 142 (n=76), respectively. All 4 subjects went on to receive long-term maintenance treatment.

Comment: Interestingly approximately half of the patients relapsed off treatment supporting the concept of continued suppressive treatment in this population.

Mycologic Response

Mycological cultures were obtained from subjects with oropharyngeal lesions who failed POS treatment or relapsed during follow-up or if clinically indicated. As in study 330 cultures were not routinely performed in responders or in subjects who remained on posaconazole treatment, thus 39 subjects were not cultured at this time point.

Cultures at the end of acute treatment were available in 57% (51/90) of subjects in the MITT population. At the end of the acute treatment period, 18% (9/51) of all MITT subjects were mycological responders (≤20 CFU/mL *Candida* species).

Mycological non-responders (>20 CFU/mL *Candida* species) comprised 82% (42/51) of the MITT population: 87% (27/31) of POS-treated subjects and 75% (15/20) of POS-naïve subjects.

Comment: 82% of subjects that were clinically failing had mycologic documentation of that failure at this timepoint.

An assessment of mycologic response by pathogen was not considered meaningful given the lack of an endpoint for all subjects. The applicant provided an analysis of clinical response at the end of the acute treatment period by *Candida* species isolated at Baseline for the MITT subset. In this assessment, subjects were allowed to have more than one isolate in their baseline culture.

There was a total of 99 *Candida* isolates among the 90 MITT subjects with an 86% (77/90) clinical response rate. Of these, the majority were *Candida albicans* (68/99) and *Candida glabrata* (24/99).

A clinical response was seen among 84% (83/99) of all Baseline *Candida* species: 85% (58/68) for *Candida albicans*, 79% (19/24) for *Candida glabrata*, 100% (3/3) for *Candida krusei*, 50% (1/2) for *Candida tropicalis*, and 100% for other *Candida* isolates (2/2).

Table 37
Clinical Response by Pathogen at the EOT
MITT study P0298

	Missing		Non-Responder		Responder		Total	
Pathogen.Isolate	N	%	N	%	N	%	N	%
Candida albicans	3	4.4	7	10.2	58	85.2	68	100.0
Candida glabrata	1	4.1	4	16.6	19	79.1	24	100.0
Candida krusei	-	-	-	-	3	100.0	3	100.0
Candida other isolates	-	-	-	-	2	100.0	2	100.0
Candida tropicalis	-	-	1	50.0	1	50.0	2	100.0
Total	4	4.0	12	12.1	83	83.8	99	100.0

Of the four missing/unknown clinical responders at end of treatment, three subjects (Subject Nos. 32/015, 33/008, and 36/002) discontinued acute treatment. One subject (Subject No. 33/007) completed acute treatment without an assessment and went directly into maintenance; this suggests that the subject was indeed responding to treatment.
Number of subjects who achieved a cure (absence of plaques or ulcers and no or minimal symptoms) plus number of subjects who improved (partial resolution of pre-treatment signs and symptoms of *Candidiasis*). At the end of the acute treatment period, 84% (63/75) of all Efficacy Evaluable subjects were responders. Three subjects (Subject Nos. 11/101, 32/007, 10/032) considered clinical responders based on an algorithm for determination of response or failure within certain time windows during acute treatment and follow-up were Treatment Failures at EOT, according to patient disposition/final status. Subject No. 11/101 received POS for 52 days, discontinuing due to treatment failure. Clinical assessment on Day 35 was improved. No clinical assessment was performed at discontinuation. Therefore, the Day 35 response was carried forward.
Subject No. 32/007 was considered a responder based on a Day 58 assessment of cure. A Day 99 assessment of failure concordant with the final status of Treatment Failure was outside the time window.
Subject No. 10/032 has been described previously.

Summary of Efficacy for Refractory OPC – a comparison of results across studies: (As per Applicant)

The study populations treated under protocols C/I97-330 and P0298 were similar. In both studies the subjects were primarily Caucasian males, mean age 38 – 40. In study 330 immunosuppression was well documented by baseline CD4 counts in approximately 95% of the patients. In 84% the counts were < 100 cells. Few patients underwent *de novo* CD4

count testing in study 0298 although CD4 counts were < 50 in those patients that were tested. Information regarding previous treatment for OPC and thus proof of refractoriness was not collected in study 0298 but was in study 330. These differences appeared to be due to the long term maintenance regimen nature of study 0298 and to the fact that 60% of the patients enrolled were previously treated with POSA in study 330. Fungal cultures were obtained at enrollment in both studies as were MIC data. Across both studies baseline MIC values of the primary isolate, *Candida albicans*, versus fluconazole and itraconazole were high.

Table 38
Demographics rOPC ISE MITT

	C/I97-330			
	Original Protocol[a] (n=89)	**Amended Protocol[a] (n=87)**	**Total (n=176)**	**P00298 (n=90)[b]**
Age (y)				
Mean (SD)	39.2 (7.6)	39.0 (7.3)	39.1 (7.4)	40.1 (6.7)
Median	39.0	38.0	38.5	40.0
Minimum to Maximum	20 to 69	24 to 56	20 to 69	25 to 61
Sex, n (%)				
Female	10 (11.2)	11 (12.6)	21 (11.9)	14 (16)
Male	79 (88.7)	76 (87.3)	155 (88.0)	76 (84)
Race, n (%)				
American Indian	0	0	0	1 (1)
Black	15 (16.8)	21 (24.1)	36 (20.4)	22 (24)
Caucasian	70 (78.6)	61 (70.1)	131 (74.4)	65 (72)
Hispanic	4 (4.4)	5 (5.7)	9 (5.1)	2 (2)
CD4 Cell Count, cells/mm3				
n	77	85	162	14
Mean (SD)	32 (63.8)	32 (54.3)	32 (58.8)	19.4 (25.3)
Median	12.0	10.0	10.5	6
Minimum to Maximum	1 to 492	0 to 271	0 to 492	0 to 72
CD4 Distribution, N (%)				
≤100 cells/mm3	71 (80)	77 (89)	148 (84)	14 (16)
>100 cells/mm3	6 (7)	8 (9)	14 (8)	0
Missing	12 (13)	2 (2)	14 (8)	76 (84)
Refractory to Prior Antifungal Agents				
Fluconazole	44 (49)	43 (49)	87 (49)	NA
Itraconazole	8 (9)	2 (2)	10 (6)	NA
Fluconazole + Itraconazole	37 (42)	35 (40)	72 (41)	NA
Missing	0	7 (8)	7 (4)	NA
Fungal Culture				
≤20 CFU/mL	1 (1)	0	1 (1)	2 (2)
>20 CFU/mL	88 (99)	85 (98)	173 (98)	75 (83)
Missing	0	2 (2)	2 (1)	13 (14)

a: Original Protocol = subjects enrolled under the Original Protocol (400 mg BID for 3 days, followed by 400 mg QD for 25 days, followed by 400 mg BID, three times weekly for 3 months);
Amended Protocol = subjects enrolled under Protocol Amendments 1 or 2 (400 mg BID for 28 days).
b: Fifty-nine of the 90 MITT subjects had received posaconazole under C/I97-330.

Three quarters of the subjects had documented receipt of antifungal therapy (181/239, 76%) prior to enrollment on study C/I97-330 (155/199, 78%) or study P00298 (26/40, 65%). FLU and ITR were the most common antifungal regimens used just prior to initiating POS.

Of the 199 subjects in C/I97-330, 136 (68%) had discontinued the previous course of therapy within 14 days of initiation of POS, 120 (60%) discontinued within 7 days and 86 (43%) within 1 day. Similar information was not available for study P0298.

Comment: The timing of the discontinuation or previous azole therapy is crucial to the differentiation of refractory disease versus relapse. Subjects who discontinued itraconazole of fluconazole treatment much before (> 14 days (before the start of POSA were more likely to have relapsing OPC as opposed to refractory disease. The 14 day cutoff has been used in previous applications.

8 subjects from study C/I97-330 were considered to be receiving ongoing antifungal therapy at the time of POS initiation. Four were receiving concomitant topical antifungals, but systemic drugs were discontinued on or within 3 days of initiation of POS.

Clinical Response Rates

Clinical Response Rates at the End of the Acute Treatment Period

In both azole-refractory studies, clinical responders were defined as subjects who achieved a clinical cure or improvement after 4 weeks (study 330) or 3 months of treatment (study P0298).

In Study C/I97-330, Clinical response at after the 4-week treatment period (week 4 visit) was the primary efficacy endpoint. Clinical evaluations included the assessment of mucositis/esophagitis by signs and/or symptoms at each visit.

Comment: Subjects were assessed for clinical response while continuing on treatment or if enrolled in the amended protocol on or around the last day of treatment. If a subject did not have this visit, the clinical response was imputed from the previous assessment. Although an assessment on treatment would be considered inadequate to support the primary OPC indication, it was considered acceptable for the population under study with refractory OPC.

In study 330, 75% (132/176) of MITT subjects and 81.6% (129/158) of efficacy-evaluable subjects were clinical responders (cure or improvement) at Treatment Endpoint (Week 4). Clinical response rates of cure or improvement for subjects treated under the original versus the amended protocols were similar for both the MITT (75.3% versus 74.7%, respectively) and efficacy evaluable (81.5% versus 81.8%, respectively) subsets.

Table 39